An application has been made to the European Accreditation Council for CME (EACCME) for Continuing Medical Education (CME) accreditation of this event. Through an agreement between the European Union of Medical Specialists and the American Medical Association, physicians may convert EACCME credits to an equivalent number of AMA PRA Category 1 Credits™. Information on the process to convert EACCME credit to AMA credit can be found at www.ama-assn.org/go/internationalcme.

This meeting is an European Society for Medical Oncology (ESMO) Supported meeting and is accredited with 25 ESMO-MORA cat. 1 point.

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SAVE THE DATE: 15-ICML—15th International Conference on Malignant Lymphoma
Lugano, Switzerland
June 18-22, 2019
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Management of Aggressive Lymphoma in Very Elderly Patients
C. Thieblemont, Paris (France)
Repeated on Friday, June 16, in Aula Magna, Lugano University

Clinical Applications of Genome Studies
A. Younes, New York, NY (USA)

Response-Adapted Therapy in HL
P. W. M. Johnson, Southampton (UK)

Aclc and PTCL: What Can Pediatric and Adult Oncologists Learn from Each Other?
L. Brugères, Villejuif (France) and F. D’Amore, Aarhus (Denmark)
Offered only once

Chemotherapy-Free Treatment of Indolent Lymphoma
J. W. Friedberg, Rochester, NY (USA)

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Role and Timing of New Drugs in CLL
M. Hallek, Cologne (Germany)

Room B

The Multiple Faces of Marginal Zone Lymphomas
M. Raderer, Vienna (Austria)

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The 2016 Updated WHO Classification of Lymphoid Neoplasms
L. Quintanilla-Martinez, Tuebingen (Germany)

Auditorium, Lugano University

Late Sequelae in Hodgkin Lymphoma Survivors
F. E. Van Leeuwen, Amsterdam (the Netherlands)
Offered only once

Aula Magna, Lugano University

Management of Aggressive Lymphoma in Very Elderly Patients
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This icon denotes presentations that will be available online, only for 14-ICML attendees, between July and September, 2017.

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Note: The articles published in the 14-ICML Educational Book represent the presentations made at the "Meet the Professor" sessions and "Educational Symposia" during the 14th International Conference on Malignant Lymphoma (14-ICML) held in Lugano, Switzerland from June 14 to 17, 2017.

All manuscripts submitted have been subjected to peer review, and authors have been requested to disclose any relationships with the companies whose products or services are discussed in their manuscripts.

Prof Michele Ghielmini, as guest editor, has reported no financial relationships with companies whose products are mentioned in this supplement.
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The costs of care in haematological cancers: Health economic issues

Martin F. Fey
University and Inselspital, Berne, Switzerland

Correspondence
Martin F. Fey, University and Inselspital, Berne, Switzerland.
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1 | MONEY MAKES THE CANCER WORLD GO ROUND ...

In most countries, expenditure for health care is on a steady rise, having reached, as it were, alarming levels. Cancer medicine contributes significantly to this phenomenon as cancers are frequent, and new expensive cancer diagnostics and therapeutics emerge. In addition, cancer patients tend to live longer and, hence, consume medical care for prolonged periods. Haematological cancers are no exception to this as costly diagnostic techniques are becoming routine in this field, and new high-price drugs flood the market.

To boil down the discussion of health care costs to the problem of unashamedly high-drug pricing would, however, not be comprehensive. Many types of expenditures need to be considered to obtain a complete picture of a spiralling financial cancer care burden (Table 1). In many health care systems, hospital care for in-patients yields the highest bills. This is particularly relevant for patients with haematological cancers as, for example, induction treatment for acute leukaemia, and allo- or auto-transplants often imply long periods of in-patient care. Add billing for new diagnostics to the basic costs of patient care and another money spending factor is identified. The days are long gone when a malignant lymphoma was simply diagnosed on an H&E-stained tissue section, with a limited array of immunohistochemistry tests thrown into the bargain. Although molecular diagnostic techniques and classical cytogenetic analyses have become somewhat cheaper (the costs for next generation sequencing have plummeted with respect to early days when this technique was first introduced into practice), they add net expenditure to the total money package billed to health care insurance companies and society.

Although a number of models have been developed to assess cancer care costs in relation to treatment success (for example, expenditure for quality-adjusted life years gained through effective therapy), indirect costs imposed by a cancer illness are often not considered (Table 1). Patients who are unable to return to their work (either transiently or permanently) fail to be productive, to the loss of their employer and of society. A lymphoma patient under treatment may formally be able to work, but perhaps in a less concentrated way and with reduced output with respect to his previous achievements during healthy days. These factors are very difficult to estimate, and therefore, they do not appear in many models of cost-for-cancer care assessment.

1.1 | Cancer drug pricing

In haematological oncology, where treatment relies heavily on drugs, pricing of the new compounds put on the market is a worrisome issue. “Old” drugs such as cyclophosphamide are sold for a few dozen Swiss francs, Euros, or US dollars per treatment cycle which looks almost dinky compared with the sums spent on monthly doses of a modern immune checkpoint inhibitor antibody, or a tyrosine kinase inhibitor. In fact, costs for the newest drugs may easily surpass the monthly income of a middle-class employee in a Western country. A number of reasons are often given to argue that there seems to be no easy escape from this troublesome spiral. Costs for the development of new drugs have been skyrocketing, and pharma company revenues from a few blockbuster drugs must compensate for huge financial investments into many compounds that never make it over the chemist’s counter.

An important reason for high pricing of new drugs are the costs of clinical trials. Clinical trials run to bring a new drug to the market are increasingly designed and conducted with neurotic worries about “drug safety.” Study protocols have grown into epic works of Dickensian length, and patients are asked to sign extensive “informed consent forms” geared more towards protecting the sponsor from law suits than providing simple and practical information for a potential trial participant. Frankly, one may express some doubt as to whether these legal requirements and constraints are really worth their money, as it is by no means certain that they translate directly into improved trial quality.
As clinical trials are essential to bring new cancer drugs to registration and sale one ought to look into the question of whether they are designed in a way to prove clinically relevant net benefit to the patients who receive these expensive drugs. Drugs that survive the hurdles of phase I and II trials commonly need to be tested in phase III for their practical everyday value in comparison with existing treatment standards. Put in simple terms, a new drug should add years to life (ie, prolong survival or even increase the hope for cure), or at least add "life" to years (ie, improve quality of life) in cancers where it is unlikely that palliative treatment would result in added life time. Such benefit would truly represent value for money spent on new drugs. The primary trial endpoints should therefore measure clinical benefit defined on this basis. Sadly, an inspection of pivotal trials in haematological oncology brings up a problematic picture (Tables 2 and 3).

Clinical trials run to improve chances of cure, for example, in aggressive B-cell non Hodgkin's lymphoma, or in Hodgkin's disease, usually explore event-free survival, or freedom from treatment failure as a primary endpoint (Table 2). This is acceptable provided that event-free survival or freedom from treatment failure are validated surrogate markers for cure or overall survival (OS). If so, increased financial burden caused by either drugs, or the costs for the treatment of drug toxicity, may be acceptable. In Hodgkin disease, BEACOPP yields similar OS in comparison with ABVD at the cost of increased BEACOPP toxicity that probably implies increased financial burden from BEACOPP (1). It would be interesting to obtain formal cost-effectiveness data comparing the 2 regimes, but I am not aware of such data in the literature.

The situation of diseases such as chronic lymphocytic leukaemia, multiple myeloma, or indolent non-Hodgkin lymphomas that are unlikely to be cured by current treatments (including new agents) appears more problematic. The endpoint almost invariably used to validate new drugs for these conditions in phase III trials is progression-free survival (Table 3). This endpoint reflects improvement of laboratory parameters and imaging findings, but it fails to mirror direct clinical benefit for the patients. It would, however, be important to demonstrate that new compounds provide patients with a longer life time without treatment and/or toxicity, and/or improved quality of life (QoL) to justify their high costs.

In many phase III trials on therapy for haematological cancers, QoL is studied as a secondary endpoint only (with insufficient power to draw firm conclusions), or totally neglected. For example, most trials on erythropoiesis-stimulating agents (ESA) to overcome treatment-induced anaemia in cancer chose an increase of haemoglobin levels as the primary endpoint, and data on QoL (anaemia-related symptoms) were also available only from subsets of patients. A large trial in Hodgkin disease on the treatment of therapy-related anaemia with ESA used QoL as a primary endpoint, and the conclusion was that there was no impact on patient-reported outcomes and fatigue.1 The (heavily industry-promoted) enthusiasm for the use of ESA has hopefully been dampened, even more so when it was shown, that patient mortality was higher under ESA.2 Not to give ESA therefore saves lives and money.

### Table 1
Types of health care costs. See separate file

<table>
<thead>
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<th>Direct</th>
<th>Indirect</th>
<th>Very indirect</th>
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<tr>
<td>Hospital in-patient care (charged per service item or blanket charge)</td>
<td>Loss of work power (unfit for work due to medical reasons)</td>
<td>Psychostress due to illness with reduced mental health (lack of concentration, memory loss, etc)</td>
</tr>
<tr>
<td>Hospital out-patient care</td>
<td>Unemployment due to illness</td>
<td>Loss of productiveness of company employing a cancer patient</td>
</tr>
<tr>
<td>Diagnostic tests (imaging, laboratory, etc)</td>
<td>No or reduced income</td>
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<tr>
<td>Interventions (surgery, radiological, etc)</td>
<td>... as above for family members and other carers</td>
<td>... as above for family members</td>
</tr>
<tr>
<td>Drugs</td>
<td>Costs for health care administration</td>
<td>Costs for quality assurance of medical services</td>
</tr>
<tr>
<td>Non–drug treatment (surgery and radiation-oncology)</td>
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<td>(certificates, interlaboratory comparisons, and &quot;round robin tests&quot;)</td>
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### Table 2
Primary endpoints in selected clinical trials testing lymphoma treatment with curative intent

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<th>Disease</th>
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<th>Primary endpoint</th>
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<td>Diffuse large B-cell NHL</td>
<td>R-CHOP</td>
<td>EFS</td>
<td>NEJM, 2002; 346: 235</td>
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<tr>
<td>Diffuse large B-cell NHL</td>
<td>R-ACVB</td>
<td>EFS</td>
<td>Lancet, 2011; 378: 1858</td>
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<tr>
<td>Diffuse large B-cell NHL in the elderly</td>
<td>Dose-dense R-CHOP</td>
<td>EFS</td>
<td>Lancet Oncol, 2013; 14: 525</td>
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<tr>
<td>Advanced Hodgkin's disease</td>
<td>BEACOPP</td>
<td>FFF</td>
<td>NEJM, 2003; 348: 2386</td>
</tr>
<tr>
<td>Advanced Hodgkin's disease</td>
<td>BEACOPP</td>
<td>FFF</td>
<td>NEJM, 2001; 365: 203</td>
</tr>
<tr>
<td>Burkitt's lymphoma</td>
<td>R-dose dense chemotherapy</td>
<td>3-year EFS</td>
<td>Lancet, 2016; 387: 2402</td>
</tr>
<tr>
<td>Primary CNS lymphoma</td>
<td>Whole brain radiotherapy</td>
<td>OS</td>
<td>Neurology, 2015; 84: 1242</td>
</tr>
</tbody>
</table>

Abbreviations: CNS, central nervous system; EFS, event-free survival; FFF, freedom from treatment failure; FFFP, freedom from first progression; OS, overall survival.
Progression-free survival in myeloma is based on response (defined through assessment of paraprotein levels, bone marrow morphology, and imaging) and its duration. Progression-free survival thus fails to reflect symptom control, better QoL, and overall longevity. The same holds true for chronic lymphocytic leukaemia (CLL) and other chronic incurable haematological cancers. It is rather astonishing, and frankly a bit irritating, that many experts in our field are happy with this type of evidence. To put it provocatively, treatment of myeloma with lenalidomide or pomalidomide means that almost CHF 10 000 are spent just to keep a monoclonal M-protein peak flattened and at the cost of sometimes considerable chronic toxicity. Progression-free survival is no direct evidence of clinical benefit, the proof of which should be mandatory before a lot of money is spent on costly new drugs. Clearly, the field of solid tumour oncology shows a better way to run such trials. A pivotal trial on metastatic pancreatic cancer proved the value of palliative treatment with gemcitabine, with the primary endpoint based on true clinical benefit parameters including stopping weight loss and improvement of pain, 2 central problems for these patients. This unique trial ought to serve as an example for rethinking the way new palliative treatments are validated in haematological oncology.

Haemat-oncology trialists often argue that OS cannot be reliably studied in myeloma or CLL, because subsequent treatment lines would blur the result. They ought to look across to metastatic breast or prostate cancer. In metastatic HER2-positive breast cancer, a chronic illness with many treatment lines open to the patients, a first line combination of 2 anti-HER2 monoclonal antibodies yielded an improvement of OS by more than 1 year with respect to treatment with trastuzumab alone, although the women certainly received sub-sequent lines of treatment upon progression. In metastatic castration-refractory prostate cancer where nowadays many treatment options are available, all new drugs (docetaxel, enzalutamide, and abiraterone) were validated with OS as the primary endpoint. Why then should this be impossible in haematological cancers?

In summary, phase III trial evidence used to pump new expensive drugs for leukaemia and lymphoma onto the market is partly unsatisfactory, as progression-free survival ill reflects the valuable (and necessary) gain in survival and high-quality life time. Clinical trialists in haematological oncology, drug registration authorities, and pharmaceutical companies should thoroughly rethink the way their trials are designed, as money spending should be limited to drugs that provide proven direct patient benefit.

### 1.3 Cost-effectiveness analyses

A number of techniques have been developed to assess the clinical value of new drugs in relation to their price. Best known are Incremental Cost-Effectiveness Ratios (ICERs) that are calculated on the basis of drug prices in a country of interest and interpreted in relation to clinical benefit produced by the treatment. Clinical benefit is defined as a quality-adjusted life years (QALY), and the price to be paid per QALY is then calculated. A widely used benchmark to define cost effectiveness is an ICER lower than US $50,000 per QALY. However, this benchmark is arbitrary, as no objectively “true” benchmark can be defined. Calculations of ICER per QALY saved are interesting, but in many countries, they have so far failed to have much impact on the drug market, on drug pricing, and on everyday prescription practices. In addition, these analyses are often performed retrospectively, and few trials if any try to collect economic data in a prospective fashion and as a compulsory part of the protocol (Table 3). Indirect costs are difficult to capture and are often neglected in these calculations. As a corollary, the literature in this field is prone to uncertainties, and it is difficult to interpret. For example, an analysis of the Tufts Medical Center Cost-Effectiveness Analysis Registry came to the conclusion that innovative treatments for haematological malignancies may provide reasonable value for money (most studies analysed in this survey fell below the US $50,000, or the US $100 000 ICER benchmark, respectively). However, a survey performed by an US group from the MD Anderson Cancer Centre in Houston found that the costs of most of new treatments for hematologic cancers were too high to be deemed cost effective in the United States. Although relevant,

### TABLE 3  Clinical validation of new therapeutic agents in randomised phase III trials to treat chronic lymphocytic leukaemia and multiple myeloma. See separate file

<table>
<thead>
<tr>
<th>Agent</th>
<th>Therapy line</th>
<th>Targeting subgroup mostly likely to benefit</th>
<th>Primary endpoint</th>
<th>Secondary endpoints</th>
<th>Assessment of QoL</th>
<th>Drug costs per cycle or month in CHF</th>
<th>Cost data collected per protocol and prospectively</th>
<th>Reference of relevant original article in peer-reviewed scientific journal</th>
</tr>
</thead>
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<tr>
<td>CLL</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Ibrutinib</td>
<td>1st line</td>
<td>No</td>
<td>PFS</td>
<td>OS and ORR</td>
<td>No</td>
<td>6600</td>
<td>No</td>
<td>NEJM, 2015; 373: 2425</td>
</tr>
<tr>
<td></td>
<td>≥2nd line</td>
<td>No</td>
<td>PFS</td>
<td>OS and ORR</td>
<td>No</td>
<td>6600</td>
<td>No</td>
<td>NEJM, 2014; 371: 213</td>
</tr>
<tr>
<td>Obinutuzumab</td>
<td>1st line</td>
<td>No</td>
<td>PFS</td>
<td>OS, ORR and molecular response</td>
<td>Patient-reported outcomes</td>
<td>4500 as of cycle 2</td>
<td>No</td>
<td>NEJM, 2014; 370: 1101</td>
</tr>
<tr>
<td>Myeloma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>≥2nd line</td>
<td>No</td>
<td>TTP</td>
<td>OS and ORR</td>
<td>No</td>
<td>8050</td>
<td>No</td>
<td>NEJM, 2007; 357: 2123</td>
</tr>
<tr>
<td>Pomalidomide</td>
<td>≥3rd line</td>
<td>No</td>
<td>PFS</td>
<td>OS and ORR</td>
<td></td>
<td>12 400</td>
<td>No</td>
<td>Lancet Oncol, 2013; 14: 1055</td>
</tr>
</tbody>
</table>

**Abbreviations:** CHF, Swiss francs; CLL, chronic lymphocytic leukaemia; PFS, progression-free survival; ORR, overall response rate; OS, overall survival; TTP, Time to progression.

aData on QoL in the obinutuzumab-chlorambucil trial not available in the main paper, published in the supplementary appendix only.

bThe Lancet Oncol paper on pomalidomide-dexamethasone claims that QoL data were collected (see section “statistical analysis”) but neither the technique of data harvesting (QoL questionnaire or scores) not QoL data are reported in the paper.

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**Table 3** Clinical validation of new therapeutic agents in randomised phase III trials to treat chronic lymphocytic leukaemia and multiple myeloma. See separate file.
provision and assessment of economic evidence are viewed by many as an additional (cumbersome) burden, ie, “the fourth hurdle” (the other 3 being the proof of efficacy, safety, and quality of drug manufacture).\(^8\)

1.4 | Solutions to the problem, if any ...

1.4.1 | Patient selection

A glance on Table 3 shows that none of the trials quoted made any effort to identify subpopulations of patients likely or unlikely to benefit from a particular drug, although they were all run under the label of “targeted treatment.” In this respect, some notable examples of solid tumours show a better way to go. The prime case in this respect is nonsmall cell lung cancer where somatic driver mutations are successfully targeted with increased efficacy. Clearly, there is a need for validated predictive markers in CLL or myeloma to select the best treatment in these heterogeneous disorders. It is sobering as well as irritating that few such efforts can be identified in our literature.

1.4.2 | Cheaper and simpler validation trials

Some authors argue that new drugs should be authority approved on the basis of much cheaper phase II data, chiefly reflecting favourable response rates in (molecularly) defined subpopulations. This is an interesting avenue. Nevertheless, a high-response rate may not be equalled with clinical benefit as defined earlier in this article. There is a need for new innovative endpoints amalgamating response as well as balancing QoL gain versus drug toxicity and disease symptoms.

1.4.3 | Revised reimbursement policies

“Pay-for-performance” is being discussed as a way of limiting payment for drugs to patients where treatment is successful whereas patients where a drug provides no benefit may not be billed or money refunded. Attractive as this may sound, it is difficult to put this system into practice in haematological oncology. How long must a patient with follicular lymphoma live to label rituximab maintenance therapy as a “success” (and pay)? Would a myeloma patient whose lab parameters improve transiently under carfilzomib, and who then needs to be switched to another drug after a few months, score as a “success” (where money is well spent) or as a “failure” (liable for no reimbursement of drug expenses). “Coverage with evidence development” may open an interesting avenue.\(^9\) In this system, health insurance would pay for new drugs with the condition that the price may be adjusted to prospectively collected outcome data.

2 | OUTLOOK

In an article well-worth reading,\(^10\) the authors concluded that “we all share responsibility for the international epidemic of dysfunctional regulation that increases health care costs and impedes development of and access to new therapies that could relieve suffering and prolong lives.” It is my firm personal view that if we continue to run clinical trials exposing unselected patients to so-called targeted agents in the area of refined molecular diagnostics, and if we continue to use progression-free survival as a primary endpoint, we are doing our present and future patients a disservice.

A fair number of doctors express the view that their job is to look well after their patients, to provide them with up-to-date care, and let politicians, health care officials, governments, and others worry about costs. Even worse (but rarely admitted) is the attitude that one should not interfere with the system for as long as good money can be gained from providing health care. In fact, in many health care systems (particularly in the private sector) neither doctors, hospitals, nor pharmaceutical companies have an interest in supplying less medical care for less money, hence less income. Competition in the health care market, often hailed as the best solution to bring down costs, fails in this respect, as the health care market is quite distinct from other markets in many ways.

There is, however, growing awareness of the problem. Recently, the ASCO Value Task Force published the conceptual framework for assessing value in cancer care.\(^11\) Almost in parallel, European Society of Medical Oncology (ESMO) created a similar task force, which produced the Magnitude of Clinical Benefit Scale.\(^12\) Quoting the example of tyrosine kinase inhibitors to treat chronic myeloid leukemia (CML), an expert consortium in CML stated that unsustainable prices for CML drugs may cause harm to patients who cannot afford them.\(^13\)

Drug prices should be based on objective measures of (I would like to add “direct clinical”) benefit, but they should not exceed values that harm patients and society. Price must reflect worth. The current situation in haematological oncology clearly has quite some way to go to reach this goal.

CONFLICT OF INTEREST

Dr Martin Fey is a Novartis and Nestlé shareholder. He holds a consultant contract with argenX.

REFERENCES


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Chemotherapy free treatment of indolent lymphoma

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1  |  INTRODUCTION

Advances in lymphoma biology have led to the identification of numerous new pathways and therapeutic targets that have the potential to significantly innovate treatment. The long natural history of indolent Non-Hodgkin lymphoma (NHL), waxing and waning pattern of disease, and repeated need for therapy over a patient’s lifetime provides an opportunity to use a precision approach to study new treatments with an important ultimate goal of preventing the toxicity and late effects of standard chemotherapy. Subsets of patients may be appropriate to treat without chemotherapy, with strategies including targeting the B cell receptor (BCR), CD20, the tumor microenvironment, epigenetic modifiers, and checkpoint inhibition at both the time of diagnosis, and at relapse. Moving forward, we expect that the development of novel clinic-pathologic biomarkers will facilitate the identification of patients with poor-risk disease who may be offered a targeted, risk-stratified approach to therapy, thereby addressing the needs of the most vulnerable patients.

Indolent NHLs comprise a heterogeneous group of diseases that include marginal zone lymphoma (MZL), lymphoplasmacytic lymphoma (LPL), small lymphocytic lymphoma/chronic lymphocytic leukemia (SLL/CLL), Waldenstrom macroglobulinemia (WM), select cases of mantle cell lymphoma (MCL), and follicular lymphoma (FL). Since a very detailed review of therapy in all these histologies is beyond the scope of this review, we will focus herein on FL.

The decision to treat patients with FL has historically relied on patient symptoms, disease tempo, stage and burden of illness.1 Patients with low-tumor-burden disease not meeting criteria for therapy have excellent survival without immediate treatment, and may be offered expectant observation or monotherapy with rituximab. For those with high-tumor burden in need of therapy, chemo-immunotherapy regimens such as rituximab-bendamustine (BR), or rituximab with cyclophosphamide, doxorubicin, oncovin, and prednisone (R-CHOP) provide excellent disease control, durable responses and remain the standard of care for most patients.2–4 In this review, we focus on scenarios where chemotherapy may be avoided, and look forward to integration of novel chemotherapy-free therapeutic paradigms (Table 1).

1.1  |  Anti-CD20 monoclonal antibodies

The anti-CD20 chimeric monoclonal antibody Rituximab revolutionized therapy of NHL with significant single agent activity, as well as improving overall survival when combined with standard chemotherapy regimens. Rituximab was first tested in a pivotal multicenter study of 166 patients with indolent lymphoma, demonstrating an overall response rate (ORR) of 48% after 4 doses in patients with relapsed disease.5 In patients with previously untreated indolent lymphoma, rituximab provided similar rates of disease control, which improved after a period of maintenance.6

The majority of patients with FL present with low tumor burden disease. In the SAAK 35/98 study by Ghielemini and colleagues, patients with either relapsed or treatment naive FL of any grade received 4 doses of rituximab weekly, and responding patients were subsequently randomized to either maintenance rituximab every 2 months for 4 doses, or observation.7 Long term follow up after a median of 9.5 years found that a high proportion of patients still had not progressed after several years, particularly those responding to rituximab induction. For these patients, it is clear that a chemotherapy approach was highly efficacious with minimal toxicity.

Ardessa and colleagues compared observation with 4 weekly doses of rituximab or 4 weekly doses of rituximab followed by maintenance every 2 months for years.8 Sixty percent of patients with just 4 doses of rituximab remained progression free at 3 years and overall survival (OS) was excellent in both arms at 97%. The US Eastern Cooperative Oncology Group (ECOG) RESORT study also evaluated the question of maintenance by treating low tumor burden FL with 4 weekly doses of rituximab.9 This was followed by randomization to either maintenance rituximab until failure of therapy or retreatment at the time of progression. No differences in time to treatment failure.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Setting</th>
<th>Mechanism of action</th>
<th>Response rate/Survival</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab</td>
<td>Front-line</td>
<td>Chimeric anti-CD20 monoclonal antibody</td>
<td>3 year PFS 60%</td>
<td>Ardeshna et al, Lancet Oncology 204</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3 year OS 97%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Median time to treatment failure 3.9 years; 4.3 years (maintenance rituximab)</td>
<td>Kahl et al, JCO 2015</td>
</tr>
<tr>
<td>Ofatumumab</td>
<td>Relapsed</td>
<td>Fully human anti-CD20 monoclonal antibody</td>
<td>ORR 22%. Median PFS 5.8 months</td>
<td>Czuczman et al, Blood 2010</td>
</tr>
<tr>
<td>Obinutuzumab</td>
<td>Relapsed</td>
<td>Type 2 humanized anti-CD20 monoclonal antibody</td>
<td>ORR 55%</td>
<td>Salles et al, JCO 2013</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Median PFS 11.9 months</td>
<td></td>
</tr>
<tr>
<td>Brutinib</td>
<td>Front-line FL</td>
<td>BTK inhibitor</td>
<td>ORR 75-85%</td>
<td>Fowler et al, ASH abstract 2015</td>
</tr>
<tr>
<td></td>
<td>Relapsed FL</td>
<td>BTK inhibitor</td>
<td>1 year PFS 77-87%</td>
<td>Bartlett et al, ASH abstract 2014</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ORR 20-30%</td>
<td></td>
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<tr>
<td>Ibelalisib</td>
<td>Relapsed</td>
<td>PI3 kinase delta inhibitor</td>
<td>ORR 57%</td>
<td>Gopal et al, NJEM 2014</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Median PFS 11 months</td>
<td></td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>Relapsed</td>
<td>Immunomodulator</td>
<td>ORR 53-76%</td>
<td>Leonard et al, JCO 2015</td>
</tr>
<tr>
<td></td>
<td>Front-line</td>
<td>Immunomodulator</td>
<td>Median time to progression 1.1-2 years</td>
<td>Fowler et al, Lancet Oncology 2014</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>87% CR</td>
<td></td>
</tr>
<tr>
<td>Venetoclax</td>
<td>Relapsed</td>
<td>BCL2 inhibitor</td>
<td>ORR 38% (FL)</td>
<td>Davids et al, JCO 2016</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>Relapsed</td>
<td>PD-1 inhibitor</td>
<td>ORR 40% (FL)</td>
<td>Lesokhin et al JCO 2016</td>
</tr>
</tbody>
</table>

Abbreviations: PFS: progression free survival OS: Overall survival ORR: Overall response rate BTK: Brutons tyrosine kinase PI3 kinase: phosphatidylinositol 3-kinase BCL2: B cell lymphoma 2.
were observed in either treatment arm, and consistent with the Ardesha data, OS was outstanding, with no difference in quality of life between groups. Taken together, monotherapy with short-course rituximab provides prolonged progression-free survival with minimal toxicity for the most common presentation of low tumor burden or slowly progressing FL.

The subsequent development of second-generation anti-CD20 monoclonal antibodies may further expand the treatment armamentarium of indolent lymphoma. Ofatumumab is a fully human anti-CD20 monoclonal antibody approved for the treatment of refractory CLL, but has modest efficacy in other indolent NHL. The type 2 anti-CD20 antibody obinutuzumab is also approved for relapsed CLL but in studies yielded more promising activity in indolent NHL, with ORR of 50% as a single agent. In combination with chemotherapy for previously treated and relapsed indolent lymphoma, obinutuzumab also results in superior progression free survival (PFS). Obinutuzumab has increased infusion toxicity and neutropenia compared with rituximab, and whether the improved outcomes with chemotherapy are observed when used as monotherapy is not yet known. We expect many future chemotherapy-free combinations under development for FL will include obinutuzumab rather than rituximab.

1.2 The B cell receptor and downstream targets

The BCR and its downstream signaling partners are imperative regulators of numerous cellular processes within the B cell. Subsequent therapeutic targeting of the BCR and phosphatidylinositol 3-kinase (PI3K) have made a significant impact in the treatment of indolent lymphomas and led to the European and American drug regulatory agency approval of ibrutinib (which inhibits BTK) for MCL, WM, CLL, and recently, MZL; while idelalisib (which inhibits PI3K delta isoform) has been approved for CLL and FL.

1.2.1 Bruton’s tyrosine kinase

In a multicenter phase I study of 56 patients with relapsed and refractory indolent lymphoma, ibrutinib was well tolerated and demonstrated an objective response rate of 60%, with CR in 16% of patients and PFS of almost 14 months. In the relapsed setting ibrutinib has had more modest responses in FL with ORR of approximately 20-30%. In the front-line setting, ibrutinib-rituximab combinations are generating interest. In a multicenter study, sixty patients with grade 1-3a FL were treated on 2 treatment arms. Arm 1 received 560 mg of ibrutinib daily until disease progression or toxicity. Rituximab was administered weekly for 4 doses at 375 mg/m². In arm 2 patients received 560 mg of ibrutinib daily for 8 weeks as a lead in treatment, then followed by the original schedule of arm 1. ORR for arm 1 was 85%; with 35% CR. For arm 2, ORR was slightly lower at 75%, with 35% CR. Median time to response was longer in arm 2 (4.3 months compared to 2.7 months). PFS at 1 year was 87% in arm 1 and 77% in arm 2. Grade 3 or higher rash occurred in 5-10% of patients; and grade 3 or higher diarrhea was observed in 10% of patients in arm 2. No formal disease criteria for therapy was required for entry to this study. In a disease as heterogeneous as FL, more nuanced risk stratified approaches to treatment will be required to understand who best will benefit from these novel approaches.

1.2.2 PI3 kinase

PI3K is a regulator of B cell function downstream of the BCR. Its activities are mediated through mammalian target of rapamycin (mTOR) and AKT pathways, ultimately influencing cell growth, survival, metabolism, and differentiation, and plays a large role in cancer development. In particular, the catalytic gamma and delta isoforms are largely limited to hematopoietic cells. As such therapeutic targeting of PI3K is actively being pursued in lymphoma treatment. Idelalisib is an oral inhibitor of PI3K delta and approved for relapsed and refractory FL based on a pivotal study in 156 patients with indolent NHL on the basis of ORR of 57% and median PFS of about 1 year. The enthusiasm for idelalisib has led to numerous studies using it in combination with other small molecule inhibitors for relapsed NHL. However major toxicities such as severe liver failure, life threatening opportunistic infections, and pneumonitis have eclipsed this effort, leading to early closure of early phase clinical trials. Second generation inhibitors of PI3K such as duvelisib and TGR1202 are actively under study and being pursued cautiously.

In the front line setting Casulo and colleagues presented encouraging data at the ASH 2016 meeting on pan PI3 kinase inhibitor duvelisib in combination with rituximab or obinutuzumab in previously untreated patients with FL. This international multicenter study included patients with FL in need of therapy based on high tumor burden. Response rates were encouraging (duvelisib/rituximab, 87%; and duvelisib/obinutuzumab, 91%) and toxicity profile was similar to that seen in idelalisib. Antimicrobial prophylaxis against pneumocystis pneumonia and routine monitoring for cytomegalovirus was recommended for all patients enrolled.

1.3 Targeting the microenvironment

Lenalidomide is an oral immunomodulatory drug with pleotropic effects on both the malignant B cell and its cellular milieu through anti-proliferative and anti-angiogenic action. There is robust clinical data on the use of lenalidomide in indolent lymphoma in both the relapsed/refractory and front-line setting. As a single agent lenalidomide has modest response rates (approximately 30%) but when added to rituximab, improves greatly (approximately 63-77%). In newly diagnosed patients with FL, CR was 87%. On the basis of this success the combination of lenalidomide and rituximab is undergoing evaluation in a multicenter phase III open label randomized study comparing lenalidomide and rituximab vs. rituximab-chemo, followed by rituximab maintenance in previously untreated FL patients (the “RELEVANCE” trial). We await with interest the results of this trial, as it is an important effort directly comparing a chemotherapy-free approach to standard chemoimmunotherapy in patients with high tumor burden FL. Triplet combinations using lenalidomide and rituximab with other targeted agents are in ongoing investigation.

1.4 Targeting apoptosis (BCL2)

The BCL2 family of proteins include both pro and antiapoptotic effectors. Venetoclax is a small molecule inhibitor of the anti-apoptotic BCL2 protein. It was the first inhibitor in this class receiving approval by the FDA in April 2016 for patients with relapsed CLL who have
17p deletion. Due to the possibility of life threatening tumor lysis, a slow dosing (ramp-up) approach is used in venetoclax to reduce this risk. More modest responses have been observed with venetoclax in other indolent NHL. Davids and colleagues observed response rates of approximately 38% in FL. Given the mechanism of action, combinations of venetoclax with chemotherapy and with novel agents has great appeal, and numerous trials are ongoing in this regard.

### 1.5 Immune checkpoint inhibition

Among the latest and most exciting developments in cancer therapy is targeting tumor immune escape through checkpoint inhibitors. In lymphoma, interference with the engagement between the programmed-death (PD) receptor and its ligand (PD-L1) has demonstrated very encouraging activity, particularly in relapsed Hodgkin lymphoma. In other indolent NHL, results are promising but highly preliminary as very small numbers of patients have been reported. In relapsed FL, PD-L1 inhibitor pembrolizumab was among the first checkpoint inhibitors studied in combination with rituximab. ORR was 66%, with a 52% CR and response duration of 18 months. A phase I study of PD1 inhibitor nivolumab resulted in ORR of 40% in ten patients with FL. Other immune checkpoint inhibitors including pembrolizumab, durvalumab and atezolizumab are being actively investigated, and again these agents may be able to be combined with chemotherapy and with targeted agents.

### 2 CONCLUSIONS: WHEN AND HOW SHOULD A CHEMOTHERAPY FREE REGIMEN BE USED IN INDOLENT LYMPHOMA?

At present, the majority of patients with FL present with low tumor burden disease. These patients are candidates for observation, or short-course rituximab, without chemotherapy. A significant proportion of these patients experience prolonged progression-free survival, and can be retreated with rituximab at symptomatic relapse. If these patients ultimately become refractory to rituximab, presuming disease continues to behave in an indolent manner, they may be excellent candidates for a continued chemotherapy-free approach with approved agents such as lenalidomide or ibrutinib.

Patients with other indolent histologies such as marginal zone lymphoma and lymphoplasmacytic lymphoma have lower response rates to single agent monoclonal antibody therapy. Still, we consider approaching selected patients with marginal zone lymphoma and indolent behavior of disease with single agent rituximab. For patients with lymphoplasmacytic lymphoma, we generally utilize single agent ibrutinib as a chemotherapy-free approach for most patients.

Given the favorable outcomes enjoyed by most patients with FL, vigilance to avoid overtreatment of asymptomatic patients with favorable risk disease is an important goal. At present, most patients with high tumor burden disease should still receive chemoimmunotherapy as initial treatment, based upon observed prolonged progression-free survival. Selected patients with significant co-morbidities, and elderly, frail patients may not tolerate chemotherapy well, and for these symptomatic high tumor burden patients, chemotherapy-free approaches such as lenalidomide and rituximab may be considered a reasonable therapeutic option. Moving forward, we feel that evaluation of novel treatment approaches in patients with newly diagnosed FL should occur along with prospective testing of predictive clinic-pathologic biomarkers. We expect this will yield further integration of rational chemotherapy-free regimens into the treatment paradigm of selected subsets of patients with high tumor burden disease. Such substitution for chemotherapy will need to consider efficacy, unique short- and long-term toxicities, cost, quality of life, and duration of therapy in addition to response rates. It is imperative that future trials of chemotherapy-free regimens incorporate these endpoints, including patient-reported outcomes for patients with indolent B-cell lymphomas.

### CONFLICT OF INTEREST

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### REFERENCES


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The role of stem cell transplant for lymphoma in 2017

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1 | INTRODUCTION

The risks and benefits of high dose therapy (HDT) and autologous stem cell transplantation (ASCT) or allogeneic stem cell transplant (alloSCT) must always be weighed against the outcome in any disease setting compared with standard therapy. This is a constantly changing risk benefit and in diseases such as chronic myeloid leukemia or chronic lymphocytic leukemia, the role of alloSCT has been displaced by successful treatment with the targeted therapies imatinib for chronic myeloid leukemia and ibrutinib, idelalisib, and venetoclax for chronic lymphocytic leukemia. No targeted therapies have yet displaced the use of SCT in lymphomas, and this modality maintains a major role in the treatment of relapsed disease. Similarly, comparative studies exploring the role of AlloSCT versus ASCT have suggested a higher risk of nonrelapse mortality, a lower probability of disease relapse, but often similar overall survival (OS) in relapsed or refractory non-Hodgkin lymphoma. Careful patient selection and usage of reduced intensity conditioning (RIC) AlloSCT may allow reduction in nonrelapse mortality. Criteria for optimal patient selection, timing of SCT and the use of ASCT versus AlloSCT remain clinical questions that are best evaluated within well conducted clinical trials and are reviewed here. The indications for each of the major subtypes of lymphoma, diffuse large B cell lymphoma, follicular lymphoma, mantle cell lymphoma and T cell lymphoma are shown in Tables 1–4 respectively.

1.1 | The role of transplant in diffuse large B cell lymphoma

Diffuse large B cell lymphoma (DLBCL) comprises multiple molecular and biological subtypes, and this results in a broad range of clinical outcomes. Standard front-line chemo-immunotherapy with R-CHOP can be curative in ~50% of patients. Transplantation has a major role, particularly for relapsed patients who are sensitive to relapse therapy and in this setting, HDT and ASCT have been shown to improve outcome in randomized clinical trials. The role of HDT and ASCT was first established in a randomized trial of 109 patients who responded to dexamethasone, high dose Ara-C and Cisplatin (DHAP) salvage chemotherapy who were randomized to receive further cycles of DHAP or HDT and ASCT.1 The HDT and ASCT group had improved event free and OS. Disease sensitivity to salvage chemotherapy and longer time from first remission to relapse are associated with improved outcome after ASCT. Patients who undergo ASCT when the disease is resistant to salvage chemotherapy have higher treatment-related mortality (TRM), and the probability of long term durable disease-free survival is less than 20%. Positron emission tomography (PET) is strongly recommended for pretreatment evaluation and for final response assessment and a negative PET scan following induction chemotherapy is associated with improved outcome. A positive PET scan at the end of induction chemotherapy identifies patients with primary refractory disease but HDT and ASCT remains an option for this group of patients.

There is a move towards targeted therapies to increase this cure rate, for those subgroups of patients who have poorer outcome, notably activated B cell DLBCL, double-hit lymphoma (DHL) defined by the dual translocation of MYC and BCL2 genes, and dual protein-expressing lymphomas defined by the overexpression of MYC and BCL2 protein. Primary refractory disease is common in double hit lymphomas that exhibit rearrangements of MYC and BCL2 genes. However, in the absence of successful targeted therapies, it was reasonable to attempt to improve the outcome in these patients by escalating chemotherapy and this remains the focus of much clinical research. The role of HDT and ASCT as part of initial therapy remains highly contentious and has been tested in many randomized trials, and the results have been often contradictory. Four randomized trials have been presented using HDT and ASCT in the rituximab era and none have shown an OS advantage. A meta-analysis of 15 randomized trials including more than 3000 patients has been reported.2 Thirteen of these studies including more than 2000 patients showed that HDT and ACST was associated with higher complete remission (CR) rates, but there was no OS benefit for HDT and ACST. High dose therapy with ASCT in first line is therefore not recommended outside of clinical trials.

Allogeneic SCT (AlloSCT) has also been explored in DLBCL, and the use of reduced intensity conditioning regimens has opened up this approach for patients who have relapsed after prior ASCT. The use of alloSCT in place of ASCT for those with high risk features remains a clinical trial question.
### TABLE 1  Indications for stem cell transplantation in diffuse large B cell lymphoma

<table>
<thead>
<tr>
<th>Diffuse large B cell lymphoma</th>
<th>Autologous SCT</th>
<th>Allogeneic SCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>First relapse sensitive</td>
<td>S</td>
<td>CO</td>
</tr>
<tr>
<td>Primary refractory sensitive</td>
<td>S</td>
<td>CO</td>
</tr>
<tr>
<td>Later relapse</td>
<td>S</td>
<td>CO</td>
</tr>
<tr>
<td>CR1 PET +ve</td>
<td>CO</td>
<td>NGR</td>
</tr>
<tr>
<td>Relapse after autologous</td>
<td>NGR</td>
<td>CO</td>
</tr>
<tr>
<td>First line high risk</td>
<td>D</td>
<td>NGR</td>
</tr>
<tr>
<td>Primary refractory resistant</td>
<td>NGR</td>
<td>CO</td>
</tr>
<tr>
<td>First relapse resistant</td>
<td>NGR</td>
<td>CO</td>
</tr>
</tbody>
</table>

S, Standard of care. This category includes indications that are well defined and generally supported by evidence in the form of high quality clinical trials and/or observational studies.

CO, Clinical option. This category includes indications for which large clinical trials and observational studies are not available. However, hematocrit (HCT) has been shown to be an effective therapy with acceptable risk of morbidity and mortality in sufficiently large single- or multicenter cohort studies. Hematocit is considered a treatment option for individual patients after careful evaluation of risks and benefits.

NGR, Not generally recommended. Transplantation is not currently recommended for these indications where evidence and clinical practice do not support the routine use of HCT. This recommendation does not preclude investigation of HCT as a potential treatment for these indications, but transplantation should be pursued best in the context of clinical trials.

D, Developmental. Transplantation should be considered only in the context of clinical trials.

### TABLE 2  Indications for stem cell transplantation in follicular lymphoma

<table>
<thead>
<tr>
<th>Follicular lymphoma</th>
<th>Autologous SCT</th>
<th>Allogeneic SCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR1</td>
<td>D</td>
<td>NGR</td>
</tr>
<tr>
<td>Primary refractory sensitive</td>
<td>S</td>
<td>S/CO</td>
</tr>
<tr>
<td>Primary refractory resistant</td>
<td>NGR</td>
<td>S/CO</td>
</tr>
<tr>
<td>First relapse sensitive</td>
<td>S</td>
<td>CO</td>
</tr>
<tr>
<td>First relapse resistant</td>
<td>N</td>
<td>CO</td>
</tr>
<tr>
<td>Later relapse</td>
<td>S</td>
<td>S/CO</td>
</tr>
<tr>
<td>Relapse after autologous</td>
<td>NGR</td>
<td>CO</td>
</tr>
<tr>
<td>Transformation to high grade</td>
<td>S</td>
<td>CO</td>
</tr>
</tbody>
</table>


### TABLE 3  Indications for stem cell transplantation in mantle cell lymphoma

<table>
<thead>
<tr>
<th>Mantle cell lymphoma</th>
<th>Autologous SCT</th>
<th>Allogeneic SCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR1/PR1</td>
<td>S</td>
<td>C</td>
</tr>
<tr>
<td>Primary refractory sensitive</td>
<td>S</td>
<td>S/C</td>
</tr>
<tr>
<td>Primary refractory resistant</td>
<td>NGR</td>
<td>S/C</td>
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<tr>
<td>First relapse sensitive</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>First relapse resistant</td>
<td>NGR</td>
<td>C</td>
</tr>
<tr>
<td>Later relapse</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>Relapse after autologous</td>
<td>NGR</td>
<td>C</td>
</tr>
</tbody>
</table>

Abbreviations: S, standard of care; D, developmental; NGR, not generally recommended; CO, clinical option.

### TABLE 4  Indications for stem cell transplantation in T cell lymphoma

<table>
<thead>
<tr>
<th>T cell lymphoma</th>
<th>Autologous SCT</th>
<th>Allogeneic SCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR1/PR1</td>
<td>CO</td>
<td>CO</td>
</tr>
<tr>
<td>Primary refractory sensitive</td>
<td>S</td>
<td>CO</td>
</tr>
<tr>
<td>Primary refractory resistant</td>
<td>NGR</td>
<td>CO</td>
</tr>
<tr>
<td>First relapse sensitive</td>
<td>S</td>
<td>CO</td>
</tr>
<tr>
<td>First relapse resistant</td>
<td>NGR</td>
<td>CO</td>
</tr>
<tr>
<td>Later relapse</td>
<td>C</td>
<td>CO</td>
</tr>
<tr>
<td>Relapse after autologous</td>
<td>NGR</td>
<td>CO</td>
</tr>
</tbody>
</table>

Abbreviation: S, standard of care; D, developmental; NGR, Not generally recommended; CO, clinical option.

### 1.2  The role of transplant in follicular lymphoma

Unlike aggressive lymphomas, the use of HDT with ASCT in the treatment of follicular lymphomas (FL) has not yet been as fully established. The rational for considering transplantation is that the disease is incurable using standard approaches, young patients with FL will die of their disease, and promising results have been observed in a number of phase II studies. Detection of MRD has been a useful surrogate marker for tracking long-term progression-free survival (PFS) in patients examining the autologous stem cells or in serial samples after transplantation. A major concern relates to the risk of development of secondary myelodysplasia/acute myeloid leukemia. The European Bone Marrow Transplant Registry sponsored CUP study (conventional chemotherapy, unpurged, purged autograft) is the only prospective randomized trial to assess the role of autologous SCT in patients with relapsed FL. The results of the study suggest a PFS and OS advantage of ASCT over conventional chemotherapy, with 4 years OS of 46% for the chemotherapy arm, versus 71% for the unpurged, and 77% for the purged ASCT arms. However, it should be remembered that this study was closed early because of slow accrual with 140 of the planned 250 patients accrued and only 89 randomized.

The role of HDT and ASCT in FL patients during first remission was also explored in a number of phase II trials, and in 3 phase III randomized trials. The German Lymphoma Study Group (GLSG) trial recruited 307 previously untreated patients up to 60 years of age and patients who responded after induction chemotherapy with 2 cycles of CHOP or mitoxantrone-chlorambucil-prednisone were randomized to autologous SCT or IFN-alpha maintenance. Among 240 evaluable patients, the 5-year PFS was 64.7% for ASCT, and 33.3% in the IFN-alpha arm (P < .0001). Acute toxicity was higher in the ASCT group, but early mortality was below 2.5% in both study arms. Longer follow-up is necessary to determine the effect of ASCT on OS. In the Groupe Ouest Est des Leucemies Aigues et des Maladies du Sang study, 172 newly diagnosed advanced FL patients were randomized either to cyclophosphamide, doxorubicin, teniposide, prednisone, CHVP, and IFN-alpha or to HDT followed by purged ASCT. Patients treated with HDT had a higher response rate than patients who received chemotherapy and IFN-alpha (81% versus 69%, P = .045) and a longer median PFS (not reached versus 45 months), but this did not translate into a better OS due to an excess of secondary malignancies after transplantation. A subgroup of patients with a significantly higher event-free survival rate ASCT could be identified using the follicular lymphoma international prognostic index (FLIPI). The GELF94 study enrolled 401
previously untreated advanced stage FL patients who were randomized to receive CHVP plus IFN-alpha compared with 4 courses of CHOP followed by HDI with total body irradiation (TBI) and ASCT and OR rates were similar in both groups (79% and 78% respectively) and 87% of eligible patients underwent ASCT. Intent-to-treat analysis after a median follow-up of 7.5 years showed no difference between the 2 arms for OS (P = .53) or PFS (P = .11). Long-term follow-up demonstrated no statistically significant benefit in favor of first-line ASCT in patients with FL, which the investigators conclude should be reserved for relapsed patients. A meta-analysis concluded that that high-dose therapy and ASCT does not improve OS in FL. In view of these results, ASCT should be used in first remission only in the setting of clinical trials.

There is a trend towards increasing use of allogeneic SCT in the management of indolent lymphomas. In a report of the International Bone Marrow Transplant Registry, results after SCT are described for 904 patients with FL. Among these patients, 176 patients underwent allogeneic SCT, 131 patients underwent autologous SCT using purified stem cells and 597 using unpurged autologous stem cells. The TRM in these 3 groups was 30%, 14%, and 8%, respectively, disease recurrence occurred in 21%, 43%, and 58%, and 5 years overall survival was 51%, 62%, and 55%, respectively. The use of TBI containing regimens was associated with increased TRM but decreased risk of relapse. The use of allogeneic SCT was associated with increased TRM, but significantly lower risk of disease recurrence in keeping with a graft versus lymphoma effect in this disease. Trends suggest that outcomes are improving and this is highly likely to continue with the use of reduced intensity conditioning regimens that have become used increasingly since the time this registry data was collated. Long term PFS has been observed after allogeneic SCT even in patients with refractory FL. In 29 FL patients, 11 of whom had refractory disease, the nonrelapse mortality was 24% and there was a 23% incidence of relapse. The 5-year OS was 58% with 53% event-free survival. A group of patients with very poor outcome are those patients who have relapsed after previous autologous SCT. The treatment-related mortality following myeloablative alloSCT was 22% and the probability of disease progression was 52% at 3 years in a study from the International Bone Marrow Transplant Registry. The use of TBI conditioning regimens and achievement of CR at the time of allogeneic SCT were associated with improved outcome. The use of reduced intensity conditioning regimens appears to be associated with improved outcome. The outcome following reduced intensity conditioning transplant regimen incorporating T cell depletion using alemtuzumab immunosuppressive therapy has been reported for 81 patients with lymphoma including 41 with low grade, 37 with high/intermediate grade, and 10 patients with mantle-cell lymphoma (MCL), 31 of whom had relapsed following previous autologous SCT. Patients received a conditioning regimen consisting of alemtuzumab, fludarabine, and melphalan, and received short course cyclosporine as graft-versus-host disease (GVHD) prophylaxis. The use of this conditioning regimen was associated with a low incidence of GVHD, and the TRM was notably decreased in patients with low grade compared to higher grade histology. The 3 years progression-free survival was 65% for patients with low grade lymphoma, 50% for patients with MCL, and 34% for high grade lymphoma (P = .002). Donor lymphocyte infusion (DLI) was given to 36 patients, 21 for relapsed or persistent disease, and 15 for persistence of mixed chimerism. The use of DLI to treat relapse after alloSCT is solely dependent upon the existence of a graft versus lymphoma effect. In seven patients with FL and SLL who had relapsed after prior allogeneic SCT, six patients responded and with four the CRs were maintained for 43-89 months. The effectiveness of DLI to treat relapse after allogeneic SCT provides perhaps the strongest evidence for a graft versus lymphoma effect that can be exploited in indolent lymphomas. The role of RIC allogeneic SCT has been evaluated by Cancer and Leukemia Group B in a phase II study to evaluate the safety and efficacy in patients with recurrent low-grade B cell malignancies, including 16 patients with FL. The 3-year TRM was 9%, and the 3-year OS was 81%. The incidence of grade II-IV acute GVHD was 29%, and extensive chronic GVHD was 18%.

Transformation of FL to high grade histology is associated with poor outcome and the role of SCT has been explored. A multicenter study of 172 patients with transformation of FL concluded that ASCT was associated with improved outcomes than those treated with chemotherapy alone, but this was not seen with AlloSCT because of the high TRM.

### 1.3 Mantle cell lymphoma

Mantle-cell lymphoma is characterized by poor prognosis with a median survival historically of only 3 to 4 years, although this is improving with newer therapies. The European MCL Network initiated a randomized trial comparing consolidation with myeloablative radiochemotherapy followed by ASCT to maintenance with alpha-interferon in first remission in 122 patients up to the age of 65 years of age or younger with advanced-stage MCL who achieved complete or partial remission after CHOP-like induction therapy. Sixty-two patients proceeded to ASCT and 60 received IFN alpha. Patients in the ASCT arm had a significantly longer PFS (median of 39 months compared with 17 months for patients in the IFN alpha arm P = .0108). However, the 3-year OS was only 83% after ASCT versus 77% in the IFN group (P = .18). They concluded that early consolidation by myeloablative radiochemotherapy followed by ASCT is feasible and results in a significant prolongation of PFS in advanced-stage MCL, but that longer follow-up is needed to determine the effect on OS.

Following publication of this and other phase II studies suggesting improved outcome for ASCT in first remission, this approach has become standard in most centers. The role of ASCT in later lines of treatment remains much more controversial and alloSCT is more commonly offered. The role of alloSCT is less established, but its role is supported by a number of single center studies, usually using RIC alloSCT.

The role of both ASCT and alloSCT remains to be clarified in MCL and has been reviewed recently by the EBM/European MCL network who have published their guidelines. The panel concluded that ASCT is the standard of care for younger fitter patients in first remission. The role of alloSCT to consolidate first response, even in high-risk patients, is not yet established and is associated with significant toxicity and the panel did not support the use of alloSCT for first-line consolidation in such high-risk patients. A number of single-center prospective studies and retrospective registry studies have been reported with conflicting data regarding both toxicity and efficacy of RIC alloSCT with many of these patients having failed a previous ASCT. There was a partial
consensus among the experts in support of alloSCT for relapse after ASCT. It was felt that the benefit of an RIC alloSCT in this setting will likely depend upon a number of factors notably the time from ASCT to relapse.

1.4 | T-cell lymphomas

Peripheral T-cell lymphoma (PTCL) comprises a heterogeneous group of mature T-cell tumors with a generally poor prognosis; ASCT and alloSCT offer a potential cure for these patients though the optimal type and timing of SCT remains to be defined. The Nordic Lymphoma Group (NLG) conducted the largest prospective phase II study in 160 untreated systemic PTCL patients to evaluate the efficacy of a dose-dense approach consolidated by up-front HDT and ASCT.15 The authors concluded that HDT and ASCT were well tolerated and led to long-term PFS in 44% of treatment-naïve patients with PTCL. This represents an encouraging outcome, particularly considering the high median age and adverse risk profile of the study population. They concluded that HDT and ASCT are a rational up-front strategy in transplantation-eligible patients with PTCL.

The role of ASCT has been less well-defined in relapsed disease although several retrospective studies have been published on the use of ASCT as salvage treatment. Taken together, the data from published studies show that the ASCT as salvage strategy appears feasible and safe with a low morbidity and mortality.15 As in other disease settings, the most important prognostic factor is the remission status of the patients at the time of ASCT, with better long-term survival in patients transplanted in CR, compared to patients with other disease status. It must be noted that all data in this setting are generated retrospectively and this requires further confirmation.

Studies investigating the role of alloSCT as part of first-line therapy in poor-risk T-cell lymphomas are ongoing. Data are not yet sufficient to recommend alloSCT outside of clinical trials. Patients with relapsed or refractory anaplastic lymphoma kinase–negative anaplastic large cell lymphoma, angioimmunoblastic T-cell lymphoma (AITL), or peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS) achieve long-term survival in 35%-50% of cases after alloSCT and survival in patients with less frequent subtypes also seems promising. These results appear significantly better than those of any other treatment modality, including the new drugs. Therefore, alloSCT should be considered in patients with relapsed/refractory T-cell lymphoma. Because of low patient numbers and lack of comparative studies, the optimum conditioning regimen prior to transplantation as well as other details of the transplant procedure remain unknown and require further study.16

2 | CONCLUSIONS

Stem cell transplantation has an established role in the management of lymphomas. Randomized clinical trials showing a benefit for SCT must always be interpreted in light of advances in standard treatments since the time of publication of the studies. The role of SCT in rarer circumstances is often circumstantial and SCT and particularly the role of ASCT versus alloSCT must always be considered in the setting of the needs of an individual patient. Chemosensitivity to last treatment, duration of last response, and overall fitness for transplants appear the most important factors for consideration.

CONFLICT OF INTEREST

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REFERENCES


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Role and timing of new drugs in CLL

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1 | NOVEL INSIGHTS INTO THE BIOLOGY OF CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

Signaling through the B-cell receptor (BCR) has emerged as a potential key mechanism in CLL pathogenesis. It has been suggested that the BCR may induce antigen-independent cell-autonomous signaling in CLL. The importance of BCR signaling for CLL pathogenesis is underscored by the prognostic value of the IGVH mutational status or the restricted repertoire of IGVH gene usage (stereotypy). In addition, the use of whole exome sequencing and large, annotated clinical CLL databases has allowed describing the genomic landscape in CLL. Recurrent mutational patterns suggest that BCR and inflammatory pathways, NOTCH signaling, Wnt signaling, DNA damage control, chromatin modification, and RNA and ribosomal processing are frequently altered in CLL. In addition, the interaction of CLL cells with their microenvironment is essential for CLL pathogenesis. In knock-out models, leukemia-associated macrophages were shown to be important components of the microenvironment of CLL cells. Even conventional therapeutics such as chemotherapy with alkylators and monoclonal antibodies mediate their effects through compartment-restricted interactions with macrophages. Finally, agents supposed to exclusively target BCR-associated kinases such as Lyn or Bruton tyrosine kinase seem to exert essential effects through the modulation of the leukemic microenvironment, since targeted deletions of these kinases reduce the capacity of macrophages to "feed" CLL growth. These insights have allowed to create a strongly improved understanding of the pathogenesis of this leukemia and to establish new, less toxic principles of therapies by using kinase inhibitors or Bcl2 antagonists.

2 | PREDICTORS OF PROGNOSIS AND THEIR POTENTIAL IMPACT ON THE CHOICE OF THE INITIAL TREATMENT

The clinical course of CLL is highly variable but can be predicted today by a plethora of clinical, biological, genetic, and molecular factors. The challenge is to define a limited set of meaningful tests to predict the prognosis and/or response to treatment with reasonably high reliability. Therefore, we have teamed up with an international consortium of study groups to create the CLL International Prognostic Index (CLL-IPI). Data of 3472 treatment-naïve patients from France, Germany, UK, United States, and Poland were used, and multivariate analyses were performed using 27 baseline factors and overall survival (OS) as endpoint. Two separate datasets of 838 patients from the Mayo Clinic and 416 from a Scandinavian population-based cohort were added for external validation. Five independent prognostic factors were identified: TP53 deletion and/or mutation (collectively called TP53 dysfunction), IGHV mutational status, serum β2-microglobulin, clinical stage, and age. By using a weighted grading of the independent factors, a prognostic index was derived separating 4 risk groups with significantly different OS at 5 years (P < .001; C-statistic, c = 0.723) (See Table 1). These risk groups were confirmed by all validation datasets. The CLL-IPI also allows to propose a practical approach when treatment is indicated (Table 1). It needs to be stressed that patients at early stages or with low CLL-IPI or with asymptomatic disease do not require treatment even in the era of novel agents.

3 | CURRENT THERAPIES

Chlorambucil was the standard treatment for CLL for several decades. In the 1990s, combinations of purine analogues (fludarabine) and cyclophosphamide were found to improve the quality and duration of response in younger patients. Building from these combinations, the addition of the anti-CD20 monoclonal antibody rituximab to fludarabine and cyclophosphamide created the first CLL treatment regimen that was shown to prolong OS, and rituximab to fludarabine and cyclophosphamide became the standard of care for patients able to tolerate this treatment. Subsequently, the addition of a novel-humanized, glycoengineered anti-CD20 antibody obinutuzumab to chlorambucil also led to a prolonged survival in elderly patients with comorbidities. Thus, chemoimmunotherapy using anti-CD20 monoclonal antibodies has become the standard treatment for most CLL patients, independently of age.
More recently, a growing understanding of CLL pathogenesis has fostered the development of drugs targeting pathways that appear essential for leukemic cell survival. Two kinase inhibitors, ibrutinib and idelalisib, which respectively target Bruton tyrosine kinase and phosphatidylinositol-3-kinase, have demonstrated efficacy and were recently approved. While the broadest current application is in relapsed patients, these agents have specifically improved the care for patients with TP53 dysfunction in the first-line setting. Ibrutinib is recommended as a first-line therapy for all patients with TP53 dysfunction in the absence of a contraindication. Idelalisib in combination with rituximab is recommended for patients with TP53 dysfunction not suitable for alternative first-line treatment options. Other agents targeting kinases in the BCR signalling and related pathways, as well as antibodies targeting surface antigens, such as CD37, are currently being tested in clinical trials. The BCL-2 antagonist venetoclax has recently shown an impressive therapeutic efficacy, which appears to be independent of adverse prognostic parameters, such as a TP53 dysfunction or refractoriness to fludarabine. Venetoclax was recently approved for treatment of relapsed patients with TP53 dysfunction.

Today, we need to create optimized therapeutic combinations to obtain long-lasting remissions, if not cure for CLL patients. One of these concepts uses sequential targeted therapies to eradicate residual disease. The treatment intensity is tailored by assessing minimal residual disease. First results obtained by this approach have been promising.

4 | SEQUENCE AND TIMING OF THERAPIES IN THE ERA OF NOVEL AGENTS

Overall, the current recommendations for therapy have become less standardized than a few years ago. For many situations, there are multiple options, and the definitive choice depends on the comorbidity or expected toxicity profile of the drugs applied. On the basis of the current knowledge, we have proposed a treatment algorithm that is constantly updated and shown in Tables 2 and 3. By using this algorithm, the choice of the best treatment depends on the disease activity, molecular risk of the leukemia (p53 dysfunction indicating high-risk), and first-line versus second-line therapies. The choice of the best inhibitors or agents depends also on the typical side effects of some of these agents (e.g., ibrutinib inducing a relative contraindication for patients with atrial fibrillation).

5 | SUMMARY AND OUTLOOK

Like in other hematologic malignancies, the management of CLL is currently undergoing a dynamic and rapid change. Targeted and nonchemotherapeutic drugs such as obinutuzumab, ibrutinib, idelalisib, or venetoclax when used in combinations, will continue to change current treatment recommendations very dramatically. Therefore, it is important that we contribute to the impressive and historically unique chance by offering our time and commitment to include our patients into current clinical trials.
REFERENCES


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Response-adapted therapy in Hodgkin lymphoma

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1  |  INTRODUCTION

The outlook for patients with classical Hodgkin lymphoma (HL) has improved dramatically over the last 60 years, and it is now considered one of the most curable forms of cancer through the use of highly effective chemotherapy, with radiotherapy in a proportion of cases. The improvements in survival rates in this relatively young patient group have exposed the problem of long-term treatment-related toxicity and prompted us to look beyond a cure-at-all-costs approach. There is a drive towards individually tailored treatment, designing therapy based upon individual prognostic variables and biomarkers, with the aim to achieve the best possible outcome whilst minimising the associated toxicity. Much attention has focused on the early assessment of response to treatment, which offers a case-specific, adaptive approach, enabling identification of patients whose treatment can safely be attenuated, and the minority with more resistant disease who could benefit from escalation to more effective, but potentially more toxic, therapy.

2  |  THE RATIONALE FOR ADAPTED THERAPY

It is only in the last 40 years, with the dramatic improvement in Hodgkin’s survivorship, that the full extent of long-term toxicity in this particular group has emerged (Table 1). Studies of mortality following HL treatment show that deaths from other causes outweigh those directly related to HL and second malignancies are the leading cause of death among HL survivors. The increased risk of breast cancer in patients previously treated with extended field radiotherapy has been consistently reported. One cohort study reported a 5.6-fold increased risk of invasive breast cancer in women treated with radiotherapy for HL compared with the general population. The risk is known to be sustained for at least 30 years after completion of treatment and is higher for women receiving radiotherapy before the age of 40, particularly where higher doses are used and larger volumes of breast tissue are irradiated. There is also evidence that radiotherapy and alkylating chemotherapy (AC) are linked to higher rates of lung and gastrointestinal malignancy in HL survivors. The risk of lung cancer is directly related to radiation dosage and the number of cycles of AC received, and prognosis for these patients is very poor, with median survival of less than 1 year following diagnosis. Acute myeloid leukaemia, peaking within 5 years of exposure to AC, is another well-recognised complication of treatment and also carries a poor prognosis. However, the relative risk is considerably lower with ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) than with earlier regimes such as MOPP (mechlorethamine, vincristine, procarbazine, and prednisolone) or the more intensive escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisolone), which entail higher cumulative AC doses. Alkylating agent-related infertility is known to occur with more intensive regimes such as eBEACOPP. The German Hodgkin Study Group reported severe menopausal symptoms in one-third of women, and oligospermia in 89% of men, following treatment with 6 cycles of eBEACOPP. There is also increased morbidity and mortality from ischaemic heart disease, valvular heart disease, conduction abnormalities, and anthracycline-related cardiomyopathy in survivors of HL treated with radiotherapy. The risk of bleomycin pulmonary toxicity is well documented and is associated with a significant decrease in 5-year overall survival (OS) from 90% in unaffected patients to 63% in those with confirmed toxicity.

As these risks have emerged, clinicians are confronted with the question of how to reduce toxicity without losing disease control. Some measures have already been tested, including reducing radiation volumes and even omitting consolidation radiotherapy altogether following complete responses determined by standard cross-sectional imaging. A meta-analysis assessing breast cancer risk in HL survivors demonstrated an odds ratio of 3.25 for extended field versus involved field radiotherapy, without evidence of any increase in recurrence rates with field reduction.

Given this precedent, the next logical question was whether the same could be done with systemic treatment. Prospective trials comparing ABVD with the more intensive eBEACOPP have found that in those receiving ABVD alone, fertility was largely preserved and the subsequent risks of secondary malignancy and leukaemia were negligible. However, there is also evidence of reduced efficacy with less...
intensive treatment. ABVD is associated with a 10% to 15% lower probability of failure-free survival than eBEACOPP, but it is important to highlight that this does not appear to lead to higher rates of mortality, with individual studies showing no significant difference in OS, due in part to effective salvage with second-line chemotherapy.

Optimising the outcome for each patient with HL requires the selection of therapy to maximise the probability of durable remission, whilst keeping the risk of long-term toxicity to a minimum. With cure rates above 80% using current treatment, it is clear that treating all patients with intense, toxic therapy from the outset will benefit only a minority with more chemoresistant disease. This calls for an approach that enables identification of those requiring more intensive therapy, and those in whom treatment can be safely de-escalated, confining the risk of toxicity to those likely to benefit the most.

The historical approach to such stratification has been the use of the prognostic features at presentation. For anatomically early stage disease (Ann Arbor I and II), the groups have been divided into favourable and unfavourable according the presence of bulk, systemic symptoms, and the erythrocyte sedimentation rate. In advanced disease, the International Prognostic Score (IPS) is the accepted measure of prognosis at baseline, consisting of 7 independent risk factors based on analysis of 5000 patients under 65 years old treated before 1990. It therefore does not take into account subsequent improvements in survival, particularly in the poorer risk groups. As a result, a reanalysis of the IPS in 2012 has shown that the difference in 5-year freedom from progression between the low-risk (IPS 0-3) and high-risk (IPS≥4) groups has reduced from more than 30% to 15%. The IPS is therefore unsatisfactory for identifying the group of patients at greatest risk of treatment failure, who would benefit most from early intensification.

There is some evidence that more-sophisticated biological stratification by gene expression profiling might help identify the worst prognostic groups. One model using 23 genes to predict OS demonstrated a 29% difference in 5-year OS between high- and low-risk groups (63 vs 92%), although these findings have not been replicated in other similar studies. Other studies have examined circulating biomarkers with the potential to predict disease response. The thymus and activation-related chemokine is highly expressed by Reed-Sternberg cells, and elevated levels were shown to correlate with tumour burden as well as other prognostic variables such as Ann Arbor stage. Studies of other factors such as IL6, ILR2, and soluble CD30 have also demonstrated an association between elevated levels and adverse outcomes, but larger prospective trials are required to validate these as predictive markers.

In summary, the means to discriminate better from worse prognostic groups based on characteristics at presentation are unsatisfactory, and it is for this reason that a more dynamic measurement of prognosis has been sought.

### 3 | POSITRON EMISSION THERAPY AS A PROGNOSTIC TOOL

Response to treatment is clearly important in predicting long-term outcome. Patients who fail to reach complete remission with first line treatment have a much worse prognosis, and much attention has focused on the use of imaging to identify these at an early stage. Computed tomography (CT) is certainly useful in assessing morphological response, but an interim reduction in tumour size has not been shown to predict accurately long-term prognosis. This may relate to the fact that malignant cells represent only a small proportion of total tumour volume, so tumour shrinkage can lag behind response at a cellular level and may not occur until the latter stages of treatment, or beyond.

Functional imaging with positron emission tomography (PET) and PET-computed tomography (PET-CT) with 2-(18F) fluoro-2-deoxy-D-glucose (FDG) has been extensively studied and, in early retrospective studies, was shown to be superior to CT and IPS in predicting durable remissions. Interim PET-CT (iPET) after 2 cycles of ABVD was associated with a high predictive value, with a 3-year failure-free survival of 95% in those with a negative iPET and 18% in the iPET positive group. In this setting, IPS was shown to have no significant independent prognostic value, with iPET positive patients categorised as low risk by IPS at equally high risk of relapse as those in high IPS groups.

Positron emission tomography imaging relies on the increased uptake of labeled FDG by actively metabolising tissues, including those affected by active HL. One confounding factor is that numerous other tissues such as myocardium, liver, kidney, brain, brown fat, inflamed lung tissue, and regenerating bone marrow are also "FGD avid." This has resulted in efforts to establish a standardised method of interpretation, to reduce the variability of qualitative visual assessment. The 5-point Deauville scale was developed in 2009 and grades areas of abnormally high FDG uptake by comparison with normal physiological uptake in different tissues (Table 2). The scale allows the cutoff point to be adjusted based on trial design, but as a general rule, a score of 1 to 3 is reported as negative, and 4 to 5 as positive. In an international validation study involving 6 independent reviewer, there was complete concordance in differentiating a positive from a negative scan in 82% of cases.

The high predictive value of iPET in tandem with the

### TABLE 1  Summary of long-term toxicities following treatment for HL

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epithelial malignancies (eg, breast and lung)</td>
<td>Radiotherapy, alkylating agents&lt;sup&gt;2,3&lt;/sup&gt;</td>
</tr>
<tr>
<td>Myelodysplasia and acute leukaemia</td>
<td>Alkylating agents&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>Mediastinal radiotherapy anthracyclines&lt;sup&gt;7&lt;/sup&gt;</td>
</tr>
<tr>
<td>Infertility</td>
<td>Alkylating agents&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
<tr>
<td>Pulmonary fibrosis</td>
<td>Bleomycin&lt;sup&gt;8&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Abbreviation: HL, Hodgkin lymphoma.

### TABLE 2  The 5-point Deauville scale for evaluation of interim PET scans

<table>
<thead>
<tr>
<th>Score</th>
<th>Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No uptake</td>
</tr>
<tr>
<td>2</td>
<td>Uptake less than or equal to mediastinum</td>
</tr>
<tr>
<td>3</td>
<td>Uptake greater than mediastinum but less than or equal to liver</td>
</tr>
<tr>
<td>4</td>
<td>Modestly increased uptake compared with liver</td>
</tr>
<tr>
<td>5</td>
<td>Markedly increased uptake compared with liver and/or new lesions</td>
</tr>
<tr>
<td>X</td>
<td>New areas of uptake unlikely to be related to lymphoma</td>
</tr>
</tbody>
</table>

Abbreviation: PET, positron emission tomography.
validated Deauville scale\(^{12}\) led to its inclusion in international guidelines as the standard for response assessment in HL.\(^{13}\)

### 4 | RESPONSE-ADAPTED THERAPY: CURRENT EVIDENCE

With iPET appearing to offer reliable prognostic stratification early on during treatment, a number of prospective trials have been undertaken to assess intensification and de-escalation of therapy based on iPET results, both in early stage and advanced disease.

### 5 | EARLY STAGE DISEASE

#### 5.1 | De-escalation after a negative iPET

In early stage disease, studies have focused on the omission of radiotherapy following a negative iPET. In the UK NCRI RAPID trial, patients with nonbulky stage IA or IIA HL with a Deauville score of 1 to 2 on iPET after 3 cycles of ABVD (n = 420, 74.6%) were randomised to either receive Involved field radiotherapy (IFRT) or no further treatment.\(^{14}\) Similarly, the European EORTC H10 study compared standard therapy with PET-guided treatment, in which patients with a negative iPET after 2 cycles of ABVD did not go on to receive Involved node radiotherapy (INRT).\(^{15}\) Their findings were similar, each showing a small increase in the risk of recurrence following the omission of radiotherapy, but without an associated worsening of OS. RAPID reported a 3-year PFS of 94.6% in the radiotherapy group and 90.8% for those not treated. In the H10 trial, PFS at 1 year for “unfavourable risk” patients was 97.3% in the “standard therapy” group and 94.7% in the iPET-directed cohort. After 5 years, the PFS values for these groups were 92% and 90%, indicating that IFRT delayed rather than preventing recurrence in a proportion of cases, with a significant number of relapses occurring outside the radiotherapy field. A modest improvement in PFS is offset by exposing all patients to radiation, most of whom gain no benefit and are put at risk of significant toxicity. From the published trials, the number needed to treat with radiotherapy to prevent 1 recurrence is between 25 and 30. Overall, these findings show that patients with early stage disease have an excellent prognosis with or without consolidation radiotherapy, but longer term follow-up is needed to determine the extent to which second malignancies and cardiovascular disease are avoided by this approach.

#### 5.2 | Intensifying therapy after a positive iPET

EORTC H10 is the only prospective randomised study to have reported on escalation of therapy. Of the 19% of patients in the unfavourable group who were iPET-positive following 2 cycles of ABVD, 5-year PFS for those randomised to continue ABVD followed by INRT was 77%, compared with 91% in those who went on to receive eBEACOPP and INRT (hazard ratio 0.42, \(P = 0.002\)). Remissions were significantly more durable with escalation of treatment, but it is noteworthy that adverse events such as grade 3 to 4 febrile neutropenia were more common in the eBEACOPP group (23.9% vs 1.1%), and OS was not significantly different, despite a trend favouring eBEACOPP: 89% vs 96%, \(P = 0.062\).\(^{15}\)

### 6 | ADVANCED DISEASE

#### 6.1 | De-escalation after a negative iPET

The international Response-adapted therapy in Hodgkin lymphoma (RATHL) and Italian Gruppo Italiano Terapie Innovative nei Linfomi (GITIL) studies have both assessed treatment reduction following 2 cycles of ABVD. In RATHL, patients with a negative iPET were randomised to either continue ABVD or de-escalate to Doxorubicin, vinblastine, bleomycin (AVD).\(^{16}\) Three-year PFS was 85.7% and 84.4% for the ABVD and AVD groups, respectively, with a difference of 1.6 percentage points (95% CI, −3.2 to 5.3). Overall survival after 3 years was also similar (97.2% for ABVD and 97.6% for AVD). Thus, after a negative iPET, the omission of bleomycin did not lead to higher rates of recurrence or mortality, a finding that was replicated across all subgroups including stage, disease bulk, and IPS. Furthermore, there were lower rates of pulmonary adverse events in the AVD subgroup, and significantly better preservation of lung diffusion capacity up to 1 year after treatment. Whilst indicating that iPET can be used to safely de-escalate therapy, the RATHL study also echoed an observation of other prospective trials: that the negative predictive value of iPET is less than that reported in earlier retrospective studies. This finding was more pronounced in more advanced cases, with a 3-year PFS of 79.6% in stage IV disease, compared with 90% in stage II. It is interesting to compare these observations with the LYSAGAH2011 study, in which patients with a negative iPET after 2 cycles of eBEACOPP went on to complete 4 cycles of ABVD.\(^{17}\) Two-year PFS was 92% in the de-escalated ABVD group, and 94% for those remaining on eBEACOPP, indicating that this represents another safe de-escalation strategy. It also suggests that iPET is more reliable in patients treated with more intensive chemotherapy. Hence, the need to improve the negative predictive value of iPET in advanced disease, as highlighted by the RATHL study, could be met by using more intensive regimens from the outset in the especially high-risk group.

#### 6.2 | Intensifying therapy after a positive iPET

Escalation of treatment to eBEACOPP following 2 cycles of ABVD has been evaluated by the GITIL 0607 study, the US Intergroup Study and the RATHL trial.\(^{16,18,17}\) The results of these studies are strikingly similar, reporting a 3-year PFS of 65% to 70% in the patients with a positive iPET. It is important to note when interpreting these trials that there was no control arm, owing to the previously reported poor prognosis for iPET-positive patients who continued to receive ABVD. However, by comparison with earlier retrospective studies, which reported durable remissions in less than 30% of this particular group, it is plausible to conclude that escalation of therapy to eBEACOPP is an effective measure, a conclusion supported by the results in early stage disease in the H10 study. This still leaves a third of iPET-positive patients needing further treatment for relapse within 3 years, so clearly there is room for improvement, especially among the small number with an iPET score of 5, where the failure rate after BEACOPP was 50% in RATHL. More intensive regimens have been considered for this
group, as exemplified in the Italian Lymphoma Group HD0801 phase II trial, in which patients with a positive iPET after 2 cycles of ABVD went on to receive 4 cycles of salvage therapy with ifosfamide, gemcitabine, and vinorelbine followed by myeloablative chemotherapy and autologous stem cell transplantation. The 2-year PFS was 76% for iPET-positive patients, although in this study the iPET-positive group included those with a score of 3 on the 5-point Deauville scale, which may have improved the PFS figure significantly.

7 | CONCLUSION

With the dangers of treatment-related toxicity and the association between positive iPET and worse outcomes, a strong case can be made for response-adapted therapy, both de-escalating treatment in those responding well to limit long-term toxicity and intensifying therapy in nonresponders to try and achieve durable remissions. The data on early disease suggest that a decision can be taken based on the outcome of iPET for the safe omission of consolidation radiotherapy or appropriate escalation of chemotherapy. In advanced disease, iPET must be interpreted carefully, since its negative predictive value diminishes in those with the worst disease and those treated with less intensive chemotherapy. There is an argument to treat patients with very bad baseline prognostic features with more intensive therapy prior to iPET. The studies performed have identified safe methods for the de-escalation of both ABVD and eBEACOPP, as well as effective means of intensifying therapy to achieve better outcomes following positive iPET.

Finding the right balance between efficacy and toxicity remains a significant challenge in treating HL. Although not perfect, iPET offers an early assessment of response to treatment, which allows a tailored approach to be taken with each patient, and is rapidly becoming the standard of care. In the future, gene expression and biomarker analysis may prove useful for further stratifying patients, and novel agents such as brentuximab vedotin and PD-1/PDL-1 checkpoint inhibitors can be integrated into the response-adapted approach to further individualise therapy and improve outcomes.

CONFLICT OF INTEREST

Dr Johnson needs to declare that he has undertaken remunerated consulting for Takeda and Bristol-Myers Squibb. Dr Broadfoot has no conflicts to declare.

REFERENCES


The 2016 updated WHO classification of lymphoid neoplasias

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KEYWORDS
2016 revision of the WHO classification, non-Hodgkin lymphomas

1 | INTRODUCTION

The World Health Organization (WHO) is preparing a revised and updated edition of the 2008 classification of tumors of the hematopoietic and lymphoid tissue to be released in 2017.1 The aim of this revised version of the 4th edition of the WHO classification is to incorporate the new scientific and clinical information to refine diagnostic criteria for previously described lymphomas, in some cases, change nomenclature to convey better the clinical features of the disease, and to introduce newly recognized disease entities. Much has been learned about non-Hodgkin lymphomas (NHL) after the 2008 WHO classification and monograph was published, as a consequence of new information coming from translational and basic research and improved techniques used for routine diagnosis. The list of genetic aberrations that are present in NHL and that are useful either for diagnosis or for understanding the pathogenesis of different diseases has been growing continuously. Some discoveries found using molecular techniques have been rapidly incorporated into daily diagnostic practice such as immunohistochemical stains for SOX11 or BRAF used to help in the diagnosis of mantle cell lymphoma (MCL) or hairy cell leukemia (HCL), respectively. Molecular detection of the recurrent MYD88 or RHOA or IDH2 mutations are helping to delineate the morphological spectrum of lymphoplasmocytic lymphoma (LPL) and angioimmunoblastic T-cell lymphoma (AITL), respectively. Nevertheless, the prognostic and diagnostic value of mutational analysis in daily practice and its role in targeted therapy remains to be determined. Although the goals of the WHO classification are to identify well-defined entities, as we move forward some challenges in the WHO classification still continue. The borders between some of the disease entities remain ill-defined for example nodular lymphocyte predominant Hodgkin lymphoma with diffuse growth pattern versus T-cell/histiocyte rich large B-cell lymphoma.

2 | SMALL B-CELL LYMPHOID NEOPLASMS

Small B-cell lymphomas are composed mainly of small lymphocytes and are often referred as “low-grade” B-cell lymphomas. The WHO classification intentionally does not divide lymphomas by grade, and because they are not necessarily indolent, the preferred name used is “small B-cell lymphomas” (SBL). They include chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), follicular lymphoma (FL), nodal marginal zone lymphoma (MZL), MALT lymphoma, HCL, LPL, and MCL.2 The changes in the revised WHO classification are summarized in Table 1.

2.1 | Precursor lesions

Monoclonal B-cell lymphocytosis (MBL) is now divided in “low-count” and “high-count” defined as less than or greater than 0.5 × 10⁹/L CLL cells in peripheral blood (PB). High-count MBL is now recognized as a precursor lesion of CLL/SLL. In FL and MCL, the—in situ—lesions have been renamed as “in situ neoplasias” to avoid a lymphoma diagnosis. These are considered precursor lesions with relatively low rate of progression.
2.2 | Follicular lymphoma

Follicular lymphoma is clinically and morphologically a rather heterogeneous disease with complex cytogenetic and molecular abnormalities. Several variants are now recognized including duodenal-type FL, a rather localized disorder with low risk of dissemination, and predominantly diffuse FL with 1p36 deletion that often presents as a localized inguinal mass and lacks BCL2 rearrangement.

2.3 | Pediatric-type FL

Pediatric-type FL (PTFL) is now a definite entity. It has been renamed because similar cases may occur in adults. The criteria for this diagnosis should be strictly applied to avoid misdiagnosis especially with conventional FL grade 3B that is considered a more aggressive disease, and with conventional FL grade 1-2, BCL2 negative. Pediatric-type FL has excellent prognosis and a conservative watch-and-wait approach is recommended.
2.4 | Large-B-cell lymphoma with IRF4 rearrangement

Large-B-cell lymphoma with IRF4 rearrangement is a new provisional entity that most commonly affects children and young adults. It involves mainly the Waldeyer’s ring and cervical lymph nodes and is usually low stage disease at presentation. These lymphomas may have a follicular, follicular/diffuse, or diffuse growth pattern. They are characterized by the strong expression of IRF4/MUM1 and BCL6, and approximately 50% of the cases express BCL2 and CD10. Most cases have IGH/IRF4 rearrangement and BCL6 alterations (Figure 1). Despite the strong expression of IRF4/MUM1, these cases have a germinal center signature by gene expression profiling (GEP). Most cases have shown good response to chemotherapy.4

2.5 | Mantle cell lymphoma

Mantle cell lymphoma usually presents with advanced stage and rapid progression, and historically, it has been considered an aggressive disease. However, now it is recognized that there are 2 pathogenetic ways to develop MCL. The classical MCL originate from a B cell with unmutated IGHV and expression of SOX11, whereas the leukemic, nonnodal subtype develops from IGHV mutated, SOX11+B cells. The latter involves mainly PB, bone marrow and spleen. Although these cases have an indolent behaviour, secondary alterations in TP53 may occur and can result in very aggressive disease.1

2.6 | Molecular/cytogenetic changes in SBL

The main changes in SBL are due to the impact of new molecular/cytogenetic information obtained mainly by next generation sequencing. Hairy cell leukemia is defined in almost all cases by the BRAF V600E mutation, which is not detected in HCL-variant.7 In contrast, 50% of HCL-variant carry mutations in MAP2K1, which encodes MEK1 downstream of BRAF. Another specific genetic alteration found in >90% of LPL/Waldenström macroglobulinemia is MYD88 L265P mutation.6 This mutation is also found in 50% of IgM monoclonal gammapathy of undetermined significance, 30% of diffuse large B-cell lymphoma (DLBCL) of nongerminal center type, 50% of primary cutaneous DLBCL, leg type, and rare cases of MZL both splenic and in lymph nodes. It has also been described in 3% of CLL cases defining a specific group of young patients with good prognosis. This mutation is not found in plasma cell myeloma. Another mutation found in 30% of LPL/Waldenström macroglobulinemia and 20% of IgM MGUS is CXCR4 gene mutation, which seems to impact the clinical presentation and overall survival.

There is a plethora of mutations that are not disease-defining mutations but have prognostic and biological implications. These include TP53, NOTCH1, SF3B1, and BIRC3 in CLL or TP53, ATM,
NOTCH 1 and 2 in MCL. In FL, next generation sequencing studies have shown frequent mutations in chromatin regulator/modifier genes. Early driver mutations seem to include mutations in genes such as CREBBP, KMT2D (MLL2), and EZH2.

3 DIFFUSE LARGE B-CELL LYMPHOMA

The 2008 WHO classification of lymphoid malignancies recognizes within the group of DLBCL, several subtypes characterized by unique clinical and pathological features including primary DLBCL of the central nervous system, primary cutaneous DLBCL, leg type, T-cell/histiocyte-rich large cell lymphoma, and EBV positive DLBCL of the elderly. Nevertheless, most cases of DLBCL fall into the "not otherwise specified" (NOS) category. The recommended cutoff for MYC is

3.1 Cell of origin

On the basis of GEP studies, DLBCLs have been divided into 2 main subgroups; germinal center B cell-like (GCB) and activated B cell-like (ABC)–DLBCL. These molecular subgroups reflect either the stage in B cell development from which the disease originates or the activity of different biological programs. Gene expression profiling, which is considered the gold standard to assign the molecular subtypes, is not routinely available and is not cost-effective in routine diagnosis. Several studies have attempted to recapitulate the molecular subgroups (GCB vs. non-GCB) using a limited panel of antibodies available in most pathology laboratories. The Hans algorithm has been the most widely used in clinical trials. Although most studies have found that immunohistochemical algorithms correlate with prognosis in DLBCL, everybody agrees that these algorithms are an imperfect substitution for GEP. Nevertheless, because of the potential prognostic value of cell of origin and the increasing efforts to tailor therapy on the basis of molecular characteristics of DLBCL, the revised WHO classification requires the identification of these 2 subtypes and the use of immunohistochemistry algorithms is now acceptable.

3.2 MYC and BCL2 expression

The prognostic importance of simultaneous MYC and BCL2 protein expression, so called "double-expressor" (DE) has been stressed in the revised WHO classification. The recommended cutoff for MYC is >40% positive tumor cells, and the cutoff for BCL2 expression is >50%. MYC and BCL2 DE have been reported to occur in 19–40% of DLBCL patients, and to have a worse prognosis than patients who do not express any or only 1 protein, but better prognosis than double hit (DH) or triple hit (TH) DLBCL (see below), which have a dismal outcome. Interestingly, the DE cases appear more commonly in the ABC subtype, and it has been suggested that this may largely contribute to the known inferior survival of the ABC subtype.

3.3 EBV+ large B-cell lymphoma

The EBV+ large B-cell lymphoma is now recognized as a definite entity; however, the term "elderly" has been substituted by NOS because these lymphomas can present in younger patients as well. It is important to distinguish this entity from other well-characterized EBV+ lymphomas.

3.4 EBV+ mucocutaneous ulcer

The EBV+ mucocutaneous ulcer has been added as a new recognized entity and is characterized by a limited growth despite the aggressive morphological features, and good outcome with conservative approach. It is usually associated with iatrogenic immunosuppression and age-related immunosenescence.

3.5 Burkitt-like lymphoma with 11q aberrations

The Burkitt-like lymphoma with 11q aberrations is a rare disorder that has been added as a provisional entity. Morphologically, these cases resemble Burkitt lymphoma but lack the MYC rearrangement. Instead, they have a very characteristic 11q chromosomal alteration with proximal gains and telomeric losses. In contrast to Burkitt lymphoma, they have a more common nodal presentation and broader morphological spectrum; however, they show similar aggressive clinical behaviour.

4 HIGH-GRADE B-CELL LYMPHOMAS

The morphological distinction between BL and DLBCL has been problematic for pathologists. Gene expression profiling studies have shown that BL has a characteristic signature but that there are cases within the spectrum of DLBCL and aggressive B-cell lymphomas, which have a molecular signature similar to BL or fall into an intermediate category. The 2008 WHO classification recognized this problem as an added provisional category of B cell lymphoma, unclassifiable, with features intermediate between DLBCL and BL (BCLU) (Table 2). The MYC rearrangements are detected in 30% to 50% of the cases and are usually associated with additional chromosomal aberrations. In this group, the incidence of DH/TH involving MYC and BCL2 and/or BCL6 has been reported to be high (32%-78%). Because the precise morphological boundaries of this category was not well defined, and therefore, lacked reproducibility among pathologists, it was decided to put all DH/TH in 1 group regardless of the morphology of the tumor cells and designate this group as high-grade B-cell lymphoma with DH/TH rearrangements. Nevertheless, the morphology should be described in the report (DLBCL vs BCLU vs blastoid). The majority of these cases have a GCB phenotype. Cases with high-grade morphology, BCLU or blastoid morphology but which lack MYC, BCL2, and/or BCL6 rearrangements should be grouped as high-grade B-cell lymphoma, NOS. High-grade B-cell lymphoma is a disease of older patients presenting with nodal or extranodal disease usually in an advanced clinical stage, high lactate dehydrogenase, and frequent bone marrow and central nervous system infiltration with a dismal prognosis.
<table>
<thead>
<tr>
<th>2008 WHO classification</th>
<th>2016 revision</th>
<th>Comments</th>
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<tr>
<td>Diffuse large B-cell lymphoma (DLBCL), NOS</td>
<td>Diffuse large B-cell lymphoma, NOS</td>
<td>- cell of origin is required. Use of IHC algorithm is acceptable</td>
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<tr>
<td>- germinal center B-cell type&lt;sup&gt;a&lt;/sup&gt;</td>
<td>- coexpression of MYC and BCL2 (DE) is prognostically relevant.</td>
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</tr>
<tr>
<td>- activated B-cell type&lt;sup&gt;a&lt;/sup&gt;</td>
<td>T-cell/histocytic rich large B-cell lymphoma</td>
<td>- no major changes</td>
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<tr>
<td>T-cell/histocytic rich large B-cell lymphoma</td>
<td>T-cell/histocytic rich large B-cell lymphoma</td>
<td>- no major changes</td>
</tr>
<tr>
<td>Primary CNS lymphoma</td>
<td>Primary CNS lymphoma</td>
<td>- frequent MYD88 L265P mutations</td>
</tr>
<tr>
<td>Primary cutaneous DLBCL, leg type</td>
<td>Primary cutaneous DLBCL, leg type</td>
<td>- MYD88 L265P mutations in ~50% of cases</td>
</tr>
<tr>
<td>EBV&lt;sup&gt;+&lt;/sup&gt; DLBCL of the elderly</td>
<td>EBV&lt;sup&gt;+&lt;/sup&gt; DLBCL, NOS&lt;sup&gt;a&lt;/sup&gt;</td>
<td>- change in nomenclature because it occurs also in younger patients - should be distinguished from other well-characterized EBV-associated lymphomas</td>
</tr>
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<td>EBV&lt;sup&gt;+&lt;/sup&gt; mucocutaneous ulcer&lt;sup&gt;a&lt;/sup&gt;</td>
<td>EBV&lt;sup&gt;+&lt;/sup&gt; mucocutaneous ulcer&lt;sup&gt;a&lt;/sup&gt;</td>
<td>- new entity associated with iatrogenic immunosuppression and age-related immunosenescence</td>
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<tr>
<td>DLBCL associated with chronic inflammation</td>
<td>DLBCL associated with chronic inflammation</td>
<td>- no major changes</td>
</tr>
<tr>
<td>Lymphomatoid granulomatosis</td>
<td>Lymphomatoid granulomatosis</td>
<td>- no major changes</td>
</tr>
<tr>
<td>Primary mediastinal large B-cell lymphoma</td>
<td>Primary mediastinal large B-cell lymphoma</td>
<td>- no major changes</td>
</tr>
<tr>
<td>Intravascular large B-cell lymphoma</td>
<td>Intravascular large B-cell lymphoma</td>
<td>- no major changes</td>
</tr>
<tr>
<td>ALK+ large B-cell lymphoma</td>
<td>ALK+ large B-cell lymphoma</td>
<td>- no major changes</td>
</tr>
<tr>
<td>Plasmablastic lymphoma</td>
<td>Plasmablastic lymphoma</td>
<td>- MYC rearrangement in ~50% of cases - 70% EBV&lt;sup&gt;+&lt;/sup&gt; with latency I or II</td>
</tr>
<tr>
<td>Primary effusion lymphoma</td>
<td>Primary effusion lymphoma</td>
<td>- no major changes</td>
</tr>
<tr>
<td>Large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease</td>
<td>HHV8&lt;sup&gt;+&lt;/sup&gt; DLBCL, NOS&lt;sup&gt;a&lt;/sup&gt;</td>
<td>- change in nomenclature</td>
</tr>
<tr>
<td>Burkitt lymphoma</td>
<td>Burkitt lymphoma</td>
<td>TCF3 or ID3 mutations in up to 70% of cases</td>
</tr>
<tr>
<td>Burkitt-like lymphoma with 11q aberration&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Burkitt-like lymphoma with 11q aberration&lt;sup&gt;a&lt;/sup&gt;</td>
<td>- new provisional entity - resembles Burkitt lymphoma but lacks MYC translocation</td>
</tr>
<tr>
<td>B-cell lymphoma unclassifiable with features intermediate between DLBCL and Burkitt lymphoma (BCLU)</td>
<td>High grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements&lt;sup&gt;a&lt;/sup&gt;</td>
<td>- new category for all double or triple hit lymphomas excluding transformed FL, lymphoblastic lymphoma and MCL</td>
</tr>
<tr>
<td>High grade B-cell lymphoma, NOS&lt;sup&gt;a&lt;/sup&gt;</td>
<td>High grade B-cell lymphoma, NOS&lt;sup&gt;a&lt;/sup&gt;</td>
<td>- include cases with BCLU and blastoid morphology without gene rearrangements</td>
</tr>
</tbody>
</table>

Provisional entities are written in italics.

<sup>a</sup>Changes in nomenclature or new provisional or definite entities
## TABLE 3  Mature T and NK-cell neoplasms within the 2008 and revised 2016 WHO classification

<table>
<thead>
<tr>
<th>2008 WHO classification</th>
<th>2016 revision</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-cell prolymphocytic leukemia</td>
<td>T-cell prolymphocytic leukemia</td>
<td>- no major changes</td>
</tr>
<tr>
<td>T-cell large granular lymphocytic leukemias</td>
<td>T-cell large granular lymphocytic leukemias (T-LGL)</td>
<td>- STAT3 and STAT5B mutations in a subset of cases</td>
</tr>
<tr>
<td>Aggressive NK-cell leukemia</td>
<td>Aggressive NK-cell leukemia</td>
<td>- no major changes</td>
</tr>
<tr>
<td>Systemic EBV+ T cell lymphoproliferative disorder (LPD) of childhood</td>
<td>Systemic EBV+ T cell lymphoma of childhood*</td>
<td>- change in nomenclature due to the fulminant clinical course and monoclonal proliferation</td>
</tr>
<tr>
<td>Hydroa vacciniforme-like lymphoma</td>
<td>Chronic active EBV infection*</td>
<td></td>
</tr>
<tr>
<td>Adult T-cell leukemia/lymphoma</td>
<td>Adult T-cell leukemia/lymphoma</td>
<td>- no major changes</td>
</tr>
<tr>
<td>Extranodal NK/T-cell lymphoma, nasal type</td>
<td>Extranodal NK/T-cell lymphoma, nasal type</td>
<td>- no major changes</td>
</tr>
<tr>
<td>Enteropathy-associated T-cell lymphoma, type I</td>
<td>Enteropathy-associated T-cell lymphoma</td>
<td>- no major changes</td>
</tr>
<tr>
<td>Enteropathy-associated T-cell lymphoma type II</td>
<td>Monomorphic epithelioid intestinal T-cell lymphoma*</td>
<td>- change in nomenclature</td>
</tr>
<tr>
<td>Indolent T-cell LPD of the GI tract*</td>
<td>- new provisional entity</td>
<td></td>
</tr>
<tr>
<td>Hepatosplenic T-cell lymphoma</td>
<td>Hepatosplenic T-cell lymphoma</td>
<td>- no major changes</td>
</tr>
<tr>
<td>Subcutaneous panniculitis-like T-cell lymphoma</td>
<td>Subcutaneous panniculitis-like T-cell lymphoma</td>
<td>- no major changes</td>
</tr>
<tr>
<td>Mycosis fungoides</td>
<td>Mycosis fungoides</td>
<td>- no major changes</td>
</tr>
<tr>
<td>Sezary syndrome</td>
<td>Sezary syndrome</td>
<td>- no major changes</td>
</tr>
<tr>
<td>Primary cutaneous CD30+ LPD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Lymphomatoid papulosis (LyP)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- anaplastic large cell lymphoma</td>
<td>Primary cutaneous CD30+ LPD</td>
<td></td>
</tr>
<tr>
<td>- Lymphomatoid papulosis (LyP)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- anaplastic large cell lymphoma</td>
<td>- new morphological subtypes</td>
<td></td>
</tr>
<tr>
<td>Primary cutaneous γδ T-cell lymphoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary cutaneous acral CD8+ T-cell lymphoma*</td>
<td>- new provisional entity</td>
<td></td>
</tr>
<tr>
<td>Primary cutaneous CD4+ small/medium T-cell lymphoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary cutaneous CD4+ small/medium T-cell LPD*</td>
<td>- change in nomenclature. Indolent disorder indistinguishable from clonal drug reactions</td>
<td></td>
</tr>
<tr>
<td>Peripheral T-cell lymphoma, NOS</td>
<td>Peripheral T-cell lymphoma, NOS</td>
<td>- molecular subgroups recognized</td>
</tr>
<tr>
<td>Angioimmunoblastic T-cell lymphoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Follicular T-cell lymphoma*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- PTCL with TFH phenotype*</td>
<td>- frequent TET2, RHOA and IDH2 mutations</td>
<td></td>
</tr>
<tr>
<td>- new subgroups with THF phenotype</td>
<td>(Continues)</td>
<td></td>
</tr>
</tbody>
</table>
4.1 Fluorescence in situ hybridization

Which cases should be analyzed by fluorescence in situ hybridization (FISH) is a matter of debate. Whether all DLBCL should be analyzed for MYC, BCL2, and BCL6 or only those with GCB phenotype or whether to preselect the cases using a 2-step approach (>40% MYC expression, >50% BCL2 expression) should be decided in the different institutions. Nevertheless, only 6% of GCB DLBCL will have DH/TH. Using the 2-step approach will reduce the costs considerably and DH lymphomas missed by this approach will be enriched by cases harbouring MYC and BCL6 and those cases without dual expression, whose clinical significance is unclear.

5 MATURE T AND NK-CELL NEOPLASMS

Mature T and natural killer cell neoplasms comprise a heterogeneous group of disorders that account for approximately 15% of all NHL. In contrast to B-cell lymphomas, most T-cell lymphomas lack defining genetic alterations, and its classification relies on a combination of morphological and immunophenotypical features. The recognition that T-cell lymphomas are related to the innate and adaptive immune system, as well as enhanced understanding of T-cell subsets such as follicular helper T-cells (TFH) has contributed to improve the classification of T and natural killer cell neoplasms (Table 3). We have learned that the morphological spectrum of AITL is broader than previously thought. The importance of the EBV+ lymphoproliferative disorders of childhood has resulted in the addition of chronic active EBV infection—systemic and cutaneous forms—and changes in nomenclature in the revised 2016 WHO classification. The better understanding of T-cell lymphomas with cutaneous presentation has resulted in new provisional entities—primary cutaneous acral CD8+ T-cell lymphoma—and change in nomenclature in primary cutaneous CD4+ small/medium LPD to stress the indolent behaviour of this disease. Furthermore, in the last years molecular studies have shed light onto the molecular signatures and chromosomal alterations in peripheral T-cell lymphoma (PTCL), NOS. All these findings add increasing evidence that cell lineage is a major determinant in mature T-cell lymphomas biology and help to better delineate established and new entities.

5.1 Peripheral T-cell lymphoma (PTCL), NOS

Peripheral T-cell lymphoma is a diagnosis of exclusion with broad morphological spectrum presenting mainly as a nodal disease. Gene expression profiling studies have discovered that there are 3 distinct molecular subgroups in PTCL, NOS defined by the overexpression of the transcription factors GATA3 and TBX21 or expression of cytotoxic genes. GATA3 and TBX21 are master regulators of T helper (TH) cells, skewing TH polarization into TH2 and TH1 differentiation pathways, respectively. Importantly, these subgroups have biological and clinical implications. The GATA3 group has an inferior prognosis and overall survival than cases with the TBX21 signature. GATA3 and T-bet antibodies are reliable surrogates to the molecular signatures.

<table>
<thead>
<tr>
<th>2008 WHO classification</th>
<th>2016 revision</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaplastic large cell lymphoma, ALK+</td>
<td>Anaplastic large cell lymphoma, ALK+</td>
</tr>
<tr>
<td>- no major changes</td>
<td>- 6p25 rearrangement (DUSP22) subgroup has good prognosis</td>
</tr>
<tr>
<td>Breast implant−associated anaplastic large cell lymphoma</td>
<td></td>
</tr>
<tr>
<td>“Changes in nomenclature or new provisional or definite entities. Provisional entities are written in italics.”</td>
<td></td>
</tr>
</tbody>
</table>

TABLE 3 (Continued)
5.2 | Nodal T-cell lymphomas with TFH phenotype

AITL, the prototype of this group, is characterized by recurrent mutations in TET2, RHOA, IDH2, and DNMT3A in a significant proportion of cases. These mutations have been found also in PTCL, NOS with TFH phenotype suggesting that all these lymphomas represent different morphological manifestations of the same disease. Follicular T-cell lymphoma (FTCL) is also included in this group, but often presents with localized disease and less symptoms. For designation of TFH phenotype, at least 2 to 3 TFH-related antigens should be expressed by the tumor cells including ICOS, CXCL13, CD279/PD1, CD10, BCL6, SAP, and CCR5.

5.3 | Anaplastic large-cell lymphomas (ALCL)

In contrast to the 2008 WHO classification, anaplastic large-cell lymphomas (ALCL) ALK+ is recognized as a definite entity with different cytogenetic prognostic subgroups. The subgroup with DUSP22/IRF4 rearrangements on chromosome 6p25 usually lacks cytotoxic granules and seems to have a better prognosis (Figure 2). ALCL ALK- is also associated with breast implants. This subgroup has been incorporated in the revised classification as a provisional entity designated as breast implant–associated ALCL.

5.4 | Primary intestinal T-cell lymphoma

In primary intestinal lymphomas, 2 distinct entities are now recognized; enteropathy-associated T-cell lymphoma (EATL), previously known as EATL type I and monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL), previously known as EATL type II. MEITL is not associated to celiac disease and is characterized by a monomorphic proliferation of lymphoid cells with CD8 and CD56 expression and mostly derived from γδ T-cells. STAT5B mutations were reported in 36% of cases, all with a γδ T-cell phenotype.

6 | CONCLUSIONS

The 2016 revision of the WHO classification maintains the same principles of the 2008 edition, which is to recognize distinct entities on the basis of morphology, immunophenotype, genetic changes, and clinical features. The main changes in this revision include modification in the nomenclature of some diseases mostly to convey better the clinical features of the entity. Lymphoma designation was changed either to “neoplasia” or “lymphoproliferative disorder” to denote either the low risk of progression to a full-blown lymphoma in precursor lesions or to stress the indolent behaviour of the disease, respectively. New provisional entities have been recognized and new scientific and clinical research resulted in upgrading some provisional entities to definite entities. The major contribution of molecular studies that has shed light onto the molecular pathways and chromosomal alterations of many disease entities has also been incorporated.

CONFICT OF INTEREST

The author have no competing interest.
REFERENCES


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The multiple faces of marginal zone lymphomas

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1 INTRODUCTION

According to the recent WHO classification, marginal zone lymphomas (MZL) are divided into 3 principal clinical entities comprising extranodal marginal zone B-cell lymphoma of the mucosa-associated lymphoid tissue (MALT-lymphoma), nodal MZL, and splenic MZL. Mucosa-associated lymphoid tissue lymphoma accounts for 7% to 8% of all newly diagnosed lymphomas, while both nodal and splenic MZLs are much rarer with both being diagnosed at a comparable rate; ie, 1% of newly diagnosed lymphomas.1

While initially thought to represent different ends of a spectrum of a certain lymphoid malignancy arising from a relatively mature, postgerminal B-cell related to the plasma cells, more recent data are increasingly suggesting these MZLs to be distinct different entities. The objective of this article is therefore to shortly summarize and highlight the clinical properties and respective differences of these 3 lymphoma subtypes.

1.1 Aetiology

One of the most striking properties of the initially described MZL, ie, MALT lymphoma, was the high association of MALT lymphomas with antigenic drives such as bacterial infections and autoimmune diseases. While the architecture of the disease was shown to resemble the Peyer’s patches rather than recapitulating the features of lymph nodes, MALT lymphoma is hardly ever diagnosed at the site of physiologically occurring MALTs, but rather arises in “acquired” MALT. Following the initial description of gastric MALT lymphoma by British pathologists Isaacson and Wright,2 a high rate of association with the gram-negative rod Helicobacter pylori (HP) was reported. As a consequence, a high percentage of patients has been reported to be positive for HP, and the WHO classification still states that up to 90% of gastric MALT lymphomas occur in individuals harbouring HP. More recent data, however, appear to challenge this assumption, with an increasing rate of patients being diagnosed with HP-negative gastric MALT lymphomas.

While the association between HP infection and gastric MALT lymphoma has become the role model for MALT lymphoma development, virtually, any organ in the human body may acquire MALT in the course of chronic antigenic stimulation and—as a consequence—may give rise to MALT lymphoma. Various terms, including bronchus-associated lymphoid tissue, skin-associated lymphoid tissue, or nasal-associated lymphoid tissue have been coined. This has also engendered the search for infections other than HP in different organs, but the association is still not as clear cut, although, eg, Chlamyaphila psittaci has been found in ocular adnexal, Borrelia Burgdorferi in cutaneous, and Achromobacter xylosoxidans in pulmonary MALT lymphomas. Nevertheless, the association between these bacteria and MALT lymphoma appears to widely differ between various geographic regions3 and could not be reliably reproduced.

In keeping with the concept of chronic antigenic stimulation in the pathogenesis of MALT lymphoma, the association between MALT lymphoma and autoimmune diseases has repeatedly been highlighted. Especially, the increased risk for parotid lymphoma in patients with Sjogren syndrome as well as chronic autoimmune thyroiditis with thyroid (and probably also gastric) MALT lymphoma has been reported, with the risk for lymphoma development being thought to be up to 70-fold elevated over healthy individuals. In total, up to 40% of patients diagnosed with MALT lymphoma are thought to have an underlying autoimmune disease, with patients being younger at diagnosis and predominately female (79%), with a higher rate of extragastric MALT lymphomas (especially salivary gland lymphomas) than patients without an autoimmune background. Apart from this, however, there appears to be no significant clinical difference or disadvantage in clinical course.3

As opposed to these data, there appears to be no association between bacterial infection or autoimmune disease and both nodal and splenic MZL. However, while the association between MALT lymphoma and hepatitis C virus (HCV) is not clear cut, it was shown to be play a causative role in other types of MZL, with reports of lymphoma regression following successful elimination of HCV in up to 73% of patients.4

1.2 Clinical presentation

While most patients with MZL will be asymptomatic or with excellent performance status at diagnosis, there is a marked difference in
clinical presentation and localization between the 3 types of MZL, which is reflected by the terminology used in the WHO classification.

The stomach still remains the most commonly involved organ in patients with MALT lymphoma (amounting for 35%-60% of newly diagnosed MALT lymphomas in larger cohorts), followed by the ocular adnexa and lung and salivary glands.

Only little data exist on nodal MZL, and this diagnosis if usually made by excluding a mucosal or splenic origin of the disease, as little or no molecular or pathological hallmarks to distinguish nodal MZL exist, and some overlap with follicular lymphoma (FL) has been described. In one of the most extensive series so far, 20 cases of nodal MZL were compared with 73 patients with MALT lymphoma, and a higher rate of stage III/IV disease (71% versus 34%), peripheral lymph node involvement (100% versus 8%), and involvement of para-aortal lymph nodes (56% versus 14%) was found.5

In addition, there appears to be a relevant difference in bone marrow involvement between splenic MZL and nodal as well as MALT lymphoma, with the latter being virtually absent (<5%) in large series on MALT lymphoma.

The predominant involvement of mucosal sites in patients with MALT lymphoma has initially been described in gastric MALT lymphomas, but these mucosal homing properties were soon extended also to other localizations. Various homing molecules including alpha4beta7-integrins and MAdCAM-1 interacting with mucosal high-endothelial venules or the CXCR4 and CXCR7 chemokine receptors have been defined as being operative in MALT lymphomas. For us to further complicate things, the homing properties have been described to differ according to the initial mucosal environment of the lymphoma cells, with different patterns of spread for gastric as opposed to pulmonary or salivary gland lymphomas and a distinct crosstalk between orbital and mammary MALT lymphomas with subcutaneous tissues due to a common embryological origin.6,7

In clinical terms, the propensity of MALT lymphoma for (subclinical) mucosal multiorgan involvement has consequences for staging procedures, as local treatment is highly effective in case of localized disease. As opposed to initial data, which had rated up to 90% of MALT lymphomas as being diagnosed in stage I, more recent evaluations have defined the rate of multiorgan involvement to be higher than expected with extensive staging procedures.1,2 Interestingly, the rate of dissemination appeared to be different between gastric and nongastric MALT-lymphomas at 25% and up to 50% in recent series. In addition, also (subclinical) secondary gastric spread, especially in patients with manifest pulmonary MALT lymphoma, has been described. As opposed to splenic MZL, where bone marrow biopsy is still an integral part of staging, the necessity for this procedure has been questioned in recent publications because of the extremely small likelihood of involvement3 and the absence of a prognostic value of bone marrow involvement reported in gastric MALT lymphoma.

While the necessity for extensive staging remains, the use of 18F-FDG-PET/CT does not appear to be helpful in patients with MALT lymphoma because of the low sensitivity of roughly 50% in these patients as opposed to nodal MZL, where PET/CT will detect most of involved lymph nodes. Experimental approaches currently include the use of tracers others than 18F-FDG for PET imaging, or combination of 18F-FDG-PET with diffusion weighted magnetic resonance imaging. In patients with a positive 18F-FDG-PET result, however, this imaging modality may be used for prognostication and assessment of therapeutic approaches.

### 1.3 | Therapeutic aspects

In therapeutic approaches, MALT lymphoma appears to be the most diverse, as treatment varies depending on the localization of the disease.8 However, in spite of the various approaches and different localizations, the prognosis of MALT lymphoma is thought to be the most favourable of all 3 types of MZL.

In a direct comparison between nodal and extranodal MZL, the 5-year OS was 56% for nodal MZL as opposed to 81% for MALT lymphoma, with the 5-year failure-free survival being 28% and 65%, respectively.9 Because of the close clinical resemblance of nodal MZL to FL, treatment in fact resembles FL, with rituximab-based immunochemotherapy being the cornerstone of management. A recent retrospective analysis of 56 patients with nodal MZL could confirm the high rate of disseminated disease upon diagnosis (78.6%), but found a better prognosis than in the older Nathwani series, with most of patients being alive at 120 months.9 In this retrospective series, the median progression free survival (PFS) was 42.2 months, with the median OS not being reached after a median follow-up of 38.2 months. The rate of transformation to DLBCL nevertheless was 12.5% in this series, which appears similar to splenic MZL, as a recent analysis of 107 patients from British Columbia has reported a 10-year transformation rate of 18%.10 In this study, splenectomy was again confirmed as highly effective management also in patients with disseminated disease, while immunochemotherapy had historically been reserved for patients thought unfit for surgery. Nevertheless, conservative management including the use of the anti-CD20-antibody rituximab or immunochemotherapy using rituximab plus bendamustine are increasingly being studied.

As opposed to this, the risk of transformation in MALT lymphoma appears low at 2% to 5% in larger series. In addition, an excellent prognosis for both gastric and nongastric MALT lymphomas has been repeatedly been reported irrespective of therapy, with 5-year overall survival higher than 90% and a 10-year survival of 75% to 80%.3 Interestingly, also "wax-and-wane" phenomena have been reported, especially in patients with pulmonary and ocular adnexal MALT lymphoma, suggesting that patients do not require immediate therapy in the absence of symptoms.

However, the propensity for late relapses in both the initially involved organ (60%) and distant spread has also been reported in up to 30% to 50% of patients after therapy, with the median time to relapse being 5 years.

While treatment of MZL, and especially MALT lymphomas, is highly heterogeneous, one of the peculiar features of MALT lymphoma is the prominent role of antibiotic therapy for initial management of these patients, while the only widely applied anti-infective therapy in nodal MZL (and in anecdotal reports also splenic MZL) is anti-HCV therapy.

The high rate of association between HP infection and gastric MALT lymphoma have encouraged early trials of HP eradication for gastric MALT lymphoma, and antibiotic therapy has in fact become
standard for all patients with gastric MALT lymphoma and HP infection, irrespective of stage. Detection of HP infection, however, may be difficult on histological assessment of biopsy samples, as only a small percentage of patients will have direct evidence of the bacteria. In view of this, also, alternative methods including breath test and serology should be used. Antibiotic therapy targeting HP will result in 75% to 80% of responses in patients with gastric MALT lymphoma, and patients responding to therapy do not require further treatment, even in the absence of complete remission. This is based on the fact that the clinical course of patients with (minimal) residual disease in the stomach is favourable, with 30% developing complete remissions with prolonged follow-up and more than 60% remaining stable for years.

An interesting—and clinically challenging—phenomenon in gastric MALT lymphoma is the increasing rate of patients who are apparently negative for HP. While the rate of HP-negative gastric MALT lymphomas was thought to be in the range of 5% to 10%, it is steadily increasing, with the percentage being between 35% and 50% in more recent studies. While the exact reason for this remains speculative, it does not appear to change current management practice for gastric MALT lymphoma, as even HP-negative patients have been shown to benefit from antibiotic therapy as sole management, and this is also advocated in recent various guidelines. This may be based on the presence of as yet undiscovered infectious agents, but is more likely a result of direct antineoplastic efficacy of some antibiotics, especially clarithromycin. Prolonged therapy with clarithromycin has consequently been reported to be effective also in heavily pretreated individuals with MALT lymphoma, resulting in prolonged responses in up to 50% of patients.

The role of antibiotic therapy in nongastric MALT lymphoma has been a matter of more debate, as initial data on HP-eradication in extragastric MALT lymphoma had been negative. However, the discovery of a potential role of other infectious agents including Chlamydia psittaci (CP) in orbital MALT lymphoma has raised new interest in antibiotic therapy. However, conflicting data in infection rate for CP in ocular adnexal MALT lymphomas have been reported, with the percentage ranging from 0% to 100%, with an average of 23% in the literature. As a matter of fact, response to treatment to either doxycycline or clarithromycine in ocular adnexal MALT lymphoma was seen both in CP-positive and CP-negative cases, and regression in 33% to 65% can be expected with the use of antibiotics in ocular adnexal MALT lymphoma.

In view of this, primary antibiotic therapy appears reasonable in patients with ocular adnexal MALT lymphomas who do not need prompt shrinkage of the tumor.

2 CONCLUSIONS

In spite of the 3 types of MZL are still summarized as different ends of a common spectrum, increasing data have been accumulating that suggest pronounced differences between nodal, splenic, and extranodal MZL in pathogenesis, pathology, and treatment.

CONFLICT OF INTEREST

The authors have no competing interest.

REFERENCES


Management of aggressive lymphoma in very elderly patients

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1 INTRODUCTION

The age defining “very elderly” patients has been determined according to the type of treatment administered, on the basis of the outcome of clinical trials. R-CHOP can be administered until the age of 80. Beyond this, specific considerations should be taken into account, and this threshold has thus been used to define this population. Lymphoma in very elderly patients is common because approximately half of all lymphoma cases occur in patients more than 65 years old and one-third of reported cases are aged over 75 years.

The incidence of lymphoma in older patients has increased in recent years, probably more than that of young patients, as the population aged over 60 years is continuously expanding. Although recent results showed a trend during the nineties towards stabilization of lymphoma incidence for young patients, this is not the case for older patients simply because humans are living longer and the number of older patients is consequently increasing.

Very few differences have been described between young and elderly lymphoma patients in morphology and clinical presentation. However, the outcome of elderly patients with lymphoma is worse, particularly for those with aggressive subtypes, because of the difficulties encountered during treatment and the difficulties related to the presence of other diseases, diminished organ functions, and altered drug metabolism. Until recently, very elderly patients were systematically considered too frail to receive an appropriate treatment and were thus treated with low-dose regimens. Recent studies have concluded that the best way to improve the survival of very elderly patients with lymphoma is to choose treatment based on objective scales for the disease and the patient’s general status.

2 INCIDENCE OF LYMPHOMA IN VERY ELDERLY PATIENTS

Life expectancy has increased dramatically over the past 50 years, with the greatest increase since the 1960s occurring between 2000 and 2015 (by 5 years). This naturally results in an increase in the number of elderly patients. Current estimates indicate that the number of people older than 65 years has more than doubled compared to 100 years ago. Individuals aged over 75 years will triple by 2030, and the group aged 85 years or older will double in the same period. This is associated with an increase in the incidence of cancer, which has been the leading cause of death, ahead of heart disease, for individuals younger than 85 years since 1999.

An increase in the incidence of lymphoma between 8% to 10% per year has been documented in Europe and the United States, particularly for patients older than 65 years, who represent half of all newly examined lymphoma patients. For the last 25 years, lymphoma incidence has increased by more than 50%, and even more than this in patients more than 60 years old, with 15 to 17 new cases a year for every 100 000 inhabitants in the United States. Several epidemiologic studies have been performed to understand this rise, in particular attempting to associate it with occupational exposures, which have changed a lot over the past 25 years. Although these analyses have not differentiated causes between young and old patients, they reveal a strong association with environmental exposure, particularly with dioxins emitted by incinerators and tobacco, with the role of pesticides being uncertain but probable, while association with sun exposure

Summary article of Meet the Professor and Educational Symposia presentations of the 14-ICML.
remains controversial. Recent studies linked the occurrence of lymphoma to different infectious agents, but why such infections are increasing is not known.

3 \ | AGGRESSIVE LYMPHOMAS: THE MOST FREQUENT HISTOLOGICAL SUBTYPES IN VERY ELDERLY PATIENTS

All lymphoma subtypes are observed in elderly patients but with some differences compared to those encountered in younger patients. Most large epidemiologic studies done with the Working Formulation for Clinical Usage, the Revised European-American Lymphoma classification, and the World Heath Organization classification found a higher percentage of aggressive lymphomas in the elderly. In 1997, a large study defined the differences between young and elderly patients; all cases included were reviewed by 5 expert pathologists. The study revealed some differences between the 8 referral centers worldwide: elderly patients more frequently had diffuse large B-cell lymphoma (DLBCL), peripheral T-cell lymphoma, and lymphocytic/lymphoplasmocytic lymphoma, and less frequently anaplastic large cell lymphoma, lymphoblastic lymphoma, and Burkitt lymphoma. Smaller analyses confirmed these data particularly that for patients aged over 80, DLBCL being the most common lymphoma.2

4 \ | VARIATIONS IN BIOLOGY OF DLBCL BETWEEN YOUNG AND VERY ELDERLY PATIENTS

Since the last decade, DLBCL biology has been increasingly understood; it is known to be highly heterogeneous, the germinal center B-cell like/activated B-cell like (ABC) signature being considered the major biological determinant. Remarkably, several arguments are present in the literature showing that the biology of aging has a major impact on lymphoma biology. This includes not only the germinal center B-cell like/ABC signature, the ABC being overrepresented in patients over 80 years compared with patients aged 50 to 60 years (54% vs 33% ABC, \( P = .04 \)), but also BCL2 expression or cytogenetic complexity, which increases with age at diagnosis.3,4 Similarly, various genetic features, such as IRF4 translocations, 1q21, 18q21, 7p22, and 7q21 gains, as well as changes in 3q27, including gains and translocations affecting the BCL6 locus differently are significantly associated with patient age, although no cutoffs between age groups have been defined.5 For MYC gene rearrangement, it has been shown that the partner gene, an immunoglobulin (IG) K, L or H gene or not an IG, has greater prognostic value than the break itself; of importance, the median age of MYC-IG patients is almost a decade older than MYC-non-IG patients (median age, 69 vs 60.5 years; \( P = .027 \)).5 Recurrent somatic mutations in CD79B, KMT2D, and MYD88 have been significantly correlated with age.6 This different biology according to age may reflect changes in the B-cell population during aging. Another hypothesis relates to the putative pathologic specificity of DLBCL occurring in elderly patients such as the Epstein–Barr virus (EBV)-related DLBCL almost exclusively reported in elderly or very old patients, despite being rare in Western countries.

5 \ | STAGING: SPECIAL MENTION IN VERY ELDERLY PATIENTS

Given the biological complexity of these tumors, a biopsy is an essential step in the management of aggressive lymphoma in very elderly patients. Immunohistochemistry is mandatory before starting treatment, while Fluorescent in situ hybridization (FISH) and genomic analyses should only be done for research purposes, as the role of these parameters is not yet clearly defined for the choice of treatment.

Relative to young patients, clinical and biological characteristics of very elderly patients with lymphoma at presentation are similar considering the main characteristics for lymphoma.2,7 Staging to evaluate lymphoma disease should then be conducted in the same way with clinical examination, body CT scan, other examinations for clinical symptoms, blood counts, bone marrow biopsy, LDH and \( \beta _2 \)-microglobulin measurements, human immunodeficiency virus, and hepatitis B and C virus serology. 18_FDG_PET = 2-deoxy-2-[F-18]fluoro-D-glucose-positron emission tomography (FDG-PET)/CT is now the recommended standard for posttreatment assessment in DLBCL, irrespective of age in the last ESMO guidelines published in 2015 (Table 1).

Specific attention must be paid to comorbidities and organ dysfunction to assess the age-related factors. Very elderly patients frequently have comorbidities including diminished cardiac and renal function, as well as alterations in drug absorption, distribution, activation, detoxification, metabolism, and clearance, which modify the pharmacodynamics of the therapeutics. Decreases in the glomerular filtration rate and tubular reabsorption delay drug excretion, such that doses may have to be tailored to creatinine clearance. Because of decreased liver function, the metabolism of certain drugs such as cyclophosphamide or anthracyclines may be altered. However, adjustment for hepatic function was not associated with better tolerance. Hematopoietic reserve capacity may also be altered, and myelotoxicity is thus increased with standard treatment doses compared to younger patients.8 However, decreasing dosages because of a putative increased toxicity was proven to be associated with poorer therapeutic results. The presence of a comorbidity is associated with decreased dose intensity and decreased overall survival (OS).9 Details of this staging are presented in Table 1.

Evaluation of lymphoma and the geriatric assessment are performed in most centers by a hematologist. It is rare to find a concerted evaluation between a geriatrician and a hematologist due to the lack of geriatric specialists. Reliable and simple questionnaires, such as the activities in daily living and instrumental activities in daily living, are available and are adapted for routine practice to assist the hematologist to personalize the treatment strategy based on objective data.

6 \ | TREATMENT

There is currently no standard treatment for very elderly patients because the most important point in this scenario is to define how to adapt treatment to the patient’s specificities rather than to apply a unique regimen. However considerable progress has been made over the last decade, with retrospective and prospective studies placing median OS in this population in the range of 2.0 to 2.5 years.7,10,11 A classical approach to treat these patients has been to place them into
3 groups as defined by Balducci in 2000: fit, unfit, and frail. However, the definition of these groups for lymphoma are highly dependent on the type of treatment proposed and its expected toxicities and risks, notably febrile neutropenia, cardiopathy, number and duration of hospitalizations, neuropathy, diabetes, and osteoporosis inducing early death and functional decline.

### Table 1: Staging in very elderly patients with aggressive lymphoma

<table>
<thead>
<tr>
<th>Lymphoma</th>
<th>Geriatric assessment</th>
<th>Physiological status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical examination (performance status, lymphoma clinical extension)</td>
<td></td>
<td>- Renal function</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Cardiac function</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Nutrition: albumin level, weight loss, body mass index (BMI), risk of infection</td>
</tr>
<tr>
<td>LDH levels, biochemical assessment</td>
<td></td>
<td>Global health status, “comprehensive geriatric assessment” (CGA)</td>
</tr>
<tr>
<td>HBV, HCV, HIV serology</td>
<td></td>
<td>Assessment of comorbidities including classification according to severity grades</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Listing of medications</td>
</tr>
<tr>
<td>Bone marrow assessment&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td>Evaluation of geriatric factors = dependencies with the ADL (Activities in Daily Living) and IADL (Instrumental Activities in Daily Living) questionnaires</td>
</tr>
<tr>
<td>CT scan of the body (extension)</td>
<td></td>
<td>Mood evaluation with the GDS15 (Geriatric Depression scale) auto-questionnaire</td>
</tr>
<tr>
<td>18FDG/PET&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td>Geriatric syndromes (including vision and hearing problems, bladder problems, dizziness, falls, delirium (a kind of temporary confusion) and dementia mainly)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Evaluation of life expectancy</td>
</tr>
</tbody>
</table>

<sup>a</sup>Bone Marrow biopsy (BMB) is not anymore recommended in the staging of diffuse large B-cell lymphoma (DLBCL) in the most recent ESMO guidelines. However, the absence of bone marrow evaluation may lead to underevaluate a specific complication associated with decreased bone marrow reserves that may lead to an increased risk of febrile neutropenia. Bone marrow puncture may be proposed if BMB is not feasible.

<sup>b</sup>under evaluation.

### 6.1 The prephase

The use of prephase treatment associating oral vincristine (1 mg total dose 1 week before cycle 1 [day -7]) and oral prednisone (60 mg/m<sup>2</sup> for 1 week) has been advocated, allowing a reduction in induction therapy-associated toxicities.<sup>10,12</sup> Vincristine appears to be the least...
6.2 | Chemotherapy adapted to fit patients with DLBCL

Delivery of standard dose R-CHOP was felt to be unrealistic in the fit population, and although rituximab use was associated with decreased mortality, 1-year OS was better when anthracycline dose intensity was <85% versus >85%, perhaps related to baseline performance status. Few prospective trials integrate a search for optimal treatment. Peyrade et al performed a multicenter single-arm phase II trial in 150 patients aged more than 79 years old with DLBCL at diagnosis, evaluating the efficacy and safety of 6 cycles of a combination of a low-dose CHOP chemotherapy with a standard dose of rituximab given at 3-week intervals. (R-miniCHOP; rituximab 375 mg/m²; 400 mg/m² of cyclophosphamide, 25 mg/m² doxorubicin, 1 mg vincristine, and 40 mg/m² prednisolone for 5 days). Overall response rates were 73%, and the complete or unconfirmed complete response rate was 62%. With a median follow-up of 20 months, median OS was 29 months and the 2-year OS rate was 59%. The R-miniCHOP regimen was well tolerated, allowing administration of the full planned dose in 72% of patients. The very low number of hospital admissions and deaths (12) were attributed to treatment toxicity. The most frequent toxicities were hematologic with grade 3 or 4 neutropenia in 59 patients and febrile neutropenia in 11 cases. Considering these promising results, R-miniCHOP could be considered as the standard of care in very elderly patients with DLBCL, representing a good compromise between efficacy and safety.

6.3 | Which regimen in patients with contraindication to anthracyclines?

To avoid cardiotoxicity associated with doxorubicin, this agent may be replaced by a nonpegylated liposomal doxorubicin (Myocet) (R-COMP regimen). Luminari et al conducted a phase II study in 75 elderly patients (median 72 years, range 61 to 83) with newly diagnosed DLBCL and left ventricular ejection fraction (LVEF) greater than 50%. Planned treatment was 8 courses of R-COMP. Overall response rate was 71% with 57% complete response (CR), 3-year progression-free survival 69%, and 3-year OS 72% with an acceptable safety profile. R-COMP appears to result in reduced cardiotoxicity compared to standard doxorubicin (21% cardiac event, with 4% of patients having grades 3-4. Similarly in 2011, Corazzelli and colleagues applied a dose-dense R-COMP14 regimen to elderly poor-risk patients with DLBCL. Fridrik et al conducted a phase III trial, randomizing 88 DLBCL patients to receive R-CHOP or R-COMP. Patients were stratified for N-terminal pro-brain natriuretic peptide (NT-proBNP) serum levels and for international prognostic index (IPI) score. Only 1 patient presented a LVEF less than 50% at diagnosis and received R-CHOP therapy at randomization. The investigators concluded that in patients with normal cardiac function at diagnosis, nonpegylated liposomal doxorubicin did not reduce cardiotoxicity, although cardiac safety signals were increased in R-COMP compared with R-CHOP. during treatment, LVEF measurements were less than 50% in 4.6% of patients in the R-COMP arm, compared with 15.8% in the R-CHOP arm (P < .001) and NT-proBNP levels were less than 400 pg/mL during and at the end of treatment in 90% patients in the R-COMP arm, but in only 66.7% in the R-CHOP arm (P = .013). Efficacy was similar in the R-COMP and R-CHOP arms; however, this trial was not powered to detect differences in response outcome between the 2 arms.14

6.4 | Chemotherapy adapted to unfit very elderly patients

Alternative regimens, investigated in very elderly patients or patients ineligible for anthracyclines, may be proposed. R-CEOP, substituting etoposide (50 mg/m² intravenously on day 1 and 100 mg/m² orally on days 2 and 3 in the standard CHOP regimen) for doxorubicin was reported by Moccia and colleagues in 2009 and compared the results with a historical cohort treated with R-CHOP, with similar 5-year time to progression (57% vs 62%, respectively), but a lower 5-year OS rate in patients who received R-CEOP (49% vs 64%, P = .02). R-bendamustine may also be proposed. However, results are worse, with only a 52% rate of complete response and short survival.

6.5 | Growth factors and febrile neutropenia

In this patient population, optimal use of myeloid growth factors remains an important means of minimizing myelosuppression and subsequent infectious complications, not only to reduce morbidity and mortality but also to allow delivery of full adapted-dose therapy which in turn impacts disease outcome. Administration should be based on ASCO and EORTC guidelines. Randomized phase III trials have confirmed the potential benefit of these agents in elderly patients. Epoetin should be used with caution in these patients with comorbidities such as hypertension.

6.6 | Central Nervous System (CNS) prophylaxis

A recent retrospective evaluation was performed of CNS relapse in very elderly DLBCL patients aged 80 years or older treated in 2 prospective LYS study with miniCHOP therapy, associated with either rituximab or ofatumumab, another anti-CD20 monoclonal antibody. This study showed a very low incidence of CNS relapse (1.8% at 2 years) despite the lack of CNS prophylaxis. This led to the conclusion that the absence of prophylaxis does not have a dramatic impact on incidence of CNS relapse and that prophylaxis can be avoided in the very elderly given the potential for the negative impact of the associated toxicities.15

6.7 | Therapeutic strategies for other lymphoma subtypes

While therapeutic strategies for treating very elderly DLBCL patients are becoming clearer, very few specific propositions have been made for the treatment of other aggressive lymphoma subtypes. Burkitt lymphoma is a major problem given the poorer results obtained with classical CHOP and the near impossibility of increasing the dose intensity except in “young elderly” patients, ie, between 60 and 65 or 68 years. R-CHOP is recommended, and if patients fail it, palliative treatment is
improvement in patient outcomes. The poorer results seen in the very elderly patients may reflect, at least partially, the use of lower doses of chemotherapeutic agents. However, once a complete remission is reached, disease-free survival of very elderly patients does not differ from that of younger patients, emphasizing the critical importance of achieving this response outcome. As the adapted dose-CHOP plus rituximab regimen is very well tolerated, it is currently considered standard treatment in fit patients. New immunochemotherapy agents in first-line should help increase the complete remission rate.

7 | CONCLUDING REMARKS

Age has been described as an adverse prognostic factor for survival of lymphoma patients, especially when other diseases are also present. The poorer results seen in the very elderly patients may reflect, at least partially, the use of lower doses of chemotherapeutic agents. However, once a complete remission is reached, disease-free survival of very elderly patients does not differ from that of younger patients, emphasizing the critical importance of achieving this response outcome. As the adapted dose-CHOP plus rituximab regimen is very well tolerated, it is currently considered standard treatment in fit patients. New immunochemotherapy agents in first-line should help increase the complete remission rate.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES


Disease-oriented treatment of T-cell lymphoma

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KEYWORDS
ATL, extranodal NK/T-cell lymphoma, JCOG, mogamulizumab, T-cell lymphoma

1 | INTRODUCTION

Natural killer (NK)/T-cell lymphomas are relatively rare lymphoid malignancies, and their incidence accounts for 10% to 20% of non-Hodgkin lymphomas (NHLs). According to the International T-cell Lymphoma Project, extranodal NK/T-cell lymphoma, nasal type (ENKL) and adult T-cell leukemia-lymphoma (ATL) had the 2 worst prognoses among the various types of peripheral T-cell lymphoma (PTCL). Here, we describe recent advances in the management of PTCLs, focusing on ENKL and ATL.

2 | DISEASE-ORIENTED TREATMENT OF ENKL

NK/T-cell lymphoma, nasal type is a predominantly extranodal lymphoma that is associated with Epstein-Barr virus (EBV). The most frequently involved site at presentation is the nasal cavity, and 75% of patients have localized nasal disease. The incidence of ENKL is less than 1% of all NHL in Western countries, while it is 3% to 9% in East Asian countries. Therefore, several prospective clinical trials of ENKL have been conducted mainly in Asian countries.

The therapeutic outcomes of patients with ENKL treated with CHOP-like chemotherapy alone were insufficient, with a complete remission (CR) rate being of 25% to 50% and 5-year overall survival (OS) rate of 0% to 34%. ENKL tumor cells express P-glycoprotein derived from the multidrug resistance (MDR) 1 gene, which is thought to be one reason why CHOP-like regimens are inadequately active against ENKL. In contrast, radiotherapy (RT) is one of the most reliable treatments against ENKL; the CR rates of RT alone in patients with localized ENKL are 66% to 100% and 5-year OS rates are 40% to 70%. However, the high rates of relapse remain problematic.

To explore a more effective treatment for localized nasal ENKL, the Lymphoma Study Group of the Japan Clinical Oncology Group (JCOG-LSG) conducted a phase I/II study of concurrent chemoradiotherapy for newly diagnosed localized nasal ENKL (JCOG0211). The protocol treatment consisted of concurrently used RT (50-50.4 Gy) and 3 cycles of dexamethasone, etoposide, ifosfamide, and carboplatin (DeVIC) (Figure 1A). This regimen is comprised of MDR-non-related agents (ifosfamide and carboplatin) and etoposide. In the phase I part of the study, the safety of 2-dose levels of DeVIC was evaluated under the concurrent use of RT. Three patients who received a two-third dose of DeVIC (2/3DeVIC) did not develop dose-limiting toxicities (DLTs), while 4 of 6 patients receiving full-dose DeVIC developed DLTs. Therefore, 2/3DeVIC was chosen as the recommended dose for the subsequent phase II study. In total, 27 patients were treated with RT-2/3DeVIC and the efficacy was assessed in 26 patients: The CR rate was 77% (20/26) and overall response rate (ORR) was 81% (21/26). The 5-year OS rate was 70% and progression-free survival (PFS) rate was 63%, with a median follow-up of 67 months. Seventy percent of patients achieving CR had long-term remissions without any consolidative therapy such as autologous hematopoietic stem cell transplantation (HSCT). No treatment-related death was observed. Recently, Yamaguchi et al reported the outcomes of 149 localized nasal ENKL patients undergoing RT-DeVIC in clinical practice. With a median follow-up of 4.9 years, the 5-year OS and PFS rates of the 149 patients were 71% and 60%, respectively. These results validate the efficacy of RT-DeVIC in a large number of patients with long-term follow-up. The Korean group also reported the efficacy of similar treatment strategy for localized nasal disease (Table 1). Based on the results, concurrent chemoradiotherapy with MDR-non-related agents is thought to be the most suitable treatment for patients with localized nasal ENKL (Figure 2).

Patients with newly diagnosed advanced or non-nasal ENKL have previously shown very poor outcomes; the 1-year OS rate of those...
undergoing anthracycline-containing regimens was less than 20%. This is also the case for relapsed/refractory patients. To overcome these poor outcomes, investigators in Japan and in other Asian countries designed a novel combination chemotherapy regimen named SMILE (dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide) (Figure 1B). After a dose-finding phase I study, a phase II study in patients with newly diagnosed stage IV or relapsed/refractory ENKL was conducted. Thirty-eight eligible patients were treated with 2 cycles of SMILE, followed at the physician’s choice by additional SMILE cycles and/or autologous/allogeneic HSCT. Because 2 patients died of grade 5 infections, the protocol was amended to include more careful assessment of infection and to incorporate a lymphocyte count of 500/μL or more into the eligibility criteria. There were no subsequent treatment-related deaths. Overall response rate in the 38 eligible patients was 79%, and the CR rate was 45%. The 5-year OS and PFS rates were 47% and 39%, respectively, with a median follow-up duration of 74 months. These results indicate the high efficacy of SMILE in this unfavorable patient population, and this regimen is now widely used in clinical practice (Figure 2).

### Table 1

<table>
<thead>
<tr>
<th>Disease</th>
<th>Study group</th>
<th>Treatment</th>
<th>Study design</th>
<th>No. of patients</th>
<th>CR rate, %</th>
<th>OS, %</th>
<th>PFS, %</th>
<th>Median follow-up duration, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localized nasal-disease</td>
<td>JCOG-LSG</td>
<td>RT + 2/3DeVIC</td>
<td>Phase I/II</td>
<td>27</td>
<td>77</td>
<td>70 (5 y)</td>
<td>63 (5 y)</td>
<td>67</td>
</tr>
<tr>
<td></td>
<td>CISL</td>
<td>CCRT-VIPD</td>
<td>Phase II</td>
<td>30</td>
<td>80</td>
<td>86 (3 y)</td>
<td>85 (3 y)</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>CISL</td>
<td>CCRT-VIDL</td>
<td>Phase II</td>
<td>30</td>
<td>87</td>
<td>60 (5 y)</td>
<td>73 (5 y)</td>
<td>44</td>
</tr>
<tr>
<td>Advanced disease or R/R disease</td>
<td>Yamaguchi et al.</td>
<td>SMILE</td>
<td>Phase II</td>
<td>38</td>
<td>45</td>
<td>55 (1 y)</td>
<td>53 (1 y)</td>
<td>24</td>
</tr>
</tbody>
</table>

Abbreviations: CCRT, concurrent chemoradiotherapy; CISL, Consortium for Improving Survival of Lymphoma; CR, complete remission; DeVIC, dexamethasone, etoposide, ifosfamide, and carboplatin; RT, radiotherapy; SMILE, dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide.

### 3 | NEW AGENTS FOR ENKL

Few clinical trials have examined novel agents in ENKL. As ENKL is associated with EBV infection, cell therapy targeting EBV-related antigen such as latent membrane protein (LMP) is an expected novel treatment. Bollard et al reported the efficacy of autologous LMP-specific cytotoxic T lymphocytes. Fifty patients with EBV-positive lymphoma including 6 with active ENKL received LMP-specific cytotoxic T lymphocyte infusion. Four of the 6 patients achieved CR, and 3 showed durable responses. Although ENKL is an entity of T/NK-cell...
lymphomas, effective novel agents for PTCLs sometimes show different toxicity profiles in patients with ENKL. For example, Kim reported severe EBV reactivation in ENKL patients treated with romidepsin, a histone deacetylase inhibitor. Considering its unique pathophysiology and clinical features, the management of ENKL should be investigated separately from other PTCLs.

4 DISEASE-ORIENTED TREATMENT OF ATL

Adult T-cell leukemia-lymphoma is a distinct entity of PTCL that is associated with human T-lymphotropic virus type-I (HTLV-1). The clinical course of ATL is heterogeneous, and 4 clinical subtypes (acute, lymphoma, chronic, and smoldering types) have been proposed. Acute, lymphoma, and unfavorable-chronic types are considered to be aggressive, while the favorable-chronic and smoldering types are indolent. While more than half the patients with indolent ATL survive for 5 years or longer without therapeutic intervention, patients with aggressive ATL have poor prognosis.

The disappointing results with conventional CHOP-like chemotherapies in the 1980s and the proposal for a subtype classification of ATL have led to a search for new active treatments against aggressive ATL (Table 2). In the 1990s, a phase II trial (JCOG9303) was conducted to investigate a multiagent chemotherapeutic regimen (LSG15; VCAP-AMP-VECP) consisting of vincristine, cyclophosphamide, doxorubicin, and prednisolone; RT, radiotherapy; SMILE, dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide; VIDL, etoposide, ifosfamide, dexamethasone, and L-asparaginase; VIPD, etoposide, ifosfamide, cisplatin, and dexamethasone.

TABLE 2 Selected prospective clinical trials for aggressive ATL

<table>
<thead>
<tr>
<th>Disease</th>
<th>Study group/author</th>
<th>Treatment</th>
<th>Study design</th>
<th>No. of patients</th>
<th>CR rate, %</th>
<th>ORR (%)</th>
<th>MST, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated aggressive ATL</td>
<td>JCOG8101</td>
<td>VEPA vs VEPA + methotrexate</td>
<td>Phase III</td>
<td>54</td>
<td>17</td>
<td>NA</td>
<td>7.5</td>
</tr>
<tr>
<td>JCOG9303</td>
<td>VCAP-AMP-VECP</td>
<td></td>
<td></td>
<td>96</td>
<td>35.5</td>
<td>80.6</td>
<td>13.0</td>
</tr>
<tr>
<td>JCOG9801</td>
<td>CHOP-14 vs VCAP-AMP-VECP</td>
<td></td>
<td></td>
<td>61</td>
<td>24.6</td>
<td>65.6</td>
<td>10.9</td>
</tr>
<tr>
<td>Ishida, et al</td>
<td>VCAP-AMP-VECP</td>
<td></td>
<td></td>
<td>57</td>
<td>40.4</td>
<td>72.0</td>
<td>12.7</td>
</tr>
<tr>
<td>VCAP-AMP-VECP vs VCAP-AMP-VECP plus Mogamulizumab</td>
<td>Randomized phase II</td>
<td>24</td>
<td>33</td>
<td>75</td>
<td>NR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>29</td>
<td>52</td>
<td>86</td>
<td>NR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R/R ATL</td>
<td>Ishida, et al</td>
<td>Mogamulizumab</td>
<td>Phase II</td>
<td>26</td>
<td>30.7</td>
<td>50</td>
<td>13.7</td>
</tr>
<tr>
<td>Ishida, et al</td>
<td>Lenalidomide</td>
<td>Phase II</td>
<td>26</td>
<td>15</td>
<td>42</td>
<td>20.3</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ATL, adult T-cell leukemia-lymphoma; AMP, doxorubicin, ranimustine, and prednisone; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisolone; CR, complete remission; JCOG, Japan Clinical Oncology Group; MST, median survival time; NA, not applicable; NR, not reached; ORR, overall response rate; VECP, vindesine, etoposide, carboplatin, and prednisone; VEPA, vincristine, cyclophosphamide, prednisolone, and doxorubicin; VCAP, vincristine, cyclophosphamide, doxorubicin, and prednisone.
system involvement occurs in 10% to 20% of patients with ATL, intrathecal prophylaxis was incorporated. Among 93 evaluable patients, 75 responded (81%) and 33 patients obtained a CR (35%). The OS rate at 2 years was 31%. Despite considerable hematologic toxicities, LSG15 showed promising response and survival rates (Table 2). Subsequently, a phase III study to compare VCAP-AMP-VECP with CHOP-14 was conducted. A longer survival rate at 3 years (24% vs 13%) and a higher CR rates (40% vs 21%) was observed with VCAP-AMP-VECP were obtained compared to CHOP-14. These results suggest that VCAP-AMP-VECP is a more effective regimen at the expense of greater toxicities, providing a basis for future investigations for the treatment of aggressive ATL.

The outcome of patients treated with VCAP-AMP-VECP remains unfavorable compared to those with other PTCLs. Allogeneic HSCT (allo-HSCT) is recommended for younger patients with aggressive ATL, based on the results of several registry studies, although robust evidences based on prospective studies are lacking. To evaluate the efficacy of allo-HSCT more accurately, a prospective multicenter phase II study of VCAP-AMP-VECP chemotherapy followed by allo-HSCT is currently underway (JCOG0907, UMIN000004147) (Figure 3). However, to perform allo-HSCT, it is essential to obtain sufficient tumor controls before transplantation. Therefore, further investigations to improve these regimens are required.

In Western countries, interferon-α and zidovudine have been used to treat ATL. A recent meta-analysis suggested the effectiveness of this therapy for ATL, particularly leukemic forms such as acute and chronic types. However, caution is needed because of the potential selection bias in this type of retrospective studies, and the optimal role of this combination treatment should be carefully evaluated in prospective trials. Currently, JCOG-LSG is conducting a phase III study comparing interferon-α and zidovudine while observing for indolent ATL (JCOG1111, UMIN000011805) (Figure 3).

5 | NOVEL AGENTS FOR ATL

5.1 | Mogamulizumab

Mogamulizumab is a humanized monoclonal antibody that recognizes the N-terminal region of human CC chemokine receptor-4 (CCR4). It is a defucosylated antibody, prepared by glycoengineering, and augments antibody-dependent cell-mediated cytotoxicity. CC chemokine receptor-4 is a 7-transmembrane G-protein-coupled receptor that is selectively expressed on Th2 cells and regulatory T cells. Tumor cells from about 90% of patients with ATL express CCR4. Based on the promising results of a phase I study of mogamulizumab for CCR4-positive PTCLs (including ATL), a pivotal phase II study (1.0 mg/kg/day, once per week for 8 weeks) for CCR4-positive relapsed ATL was conducted. The best ORR was 50% (13/26), including 8 CRs. The median PFS and OS were 5.2 and 13.7 months, respectively.

![Figure 3](https://example.com/figure3.png)

**Figure 3** Two ongoing trials for ATL conducted by JCOG-LSG. (A) JCOG1111 is a phase III study comparing interferon-α plus zidovudine with watchful waiting for indolent ATL (pII: JCOG 1111). (B) JCOG0907 is a phase II study of intensive chemotherapy followed by allogeneic hematopoietic stem cell transplantation for aggressive ATL. Protocol was amended incorporating reduced-intensity stem cell transplantation and elderly patients up to 65 years old. Protocol was amended to allow mogamulizumab use. Subsequently, it was omitted considering the potential increase of risk in graft-versus-host disease. Allo-HSCT, allogeneic hematopoietic stem cell transplantation; AMP, doxorubicin, ranimustine, and prednisone; ATL, adult T-cell leukemia-lymphoma; AZT zidovudine; IFN, interferon; JCOG-LSG, the lymphoma study Group of the Japan Clinical Oncology Group; JMDP, Japan marrow donor program; VCAP, vincristine, cyclophosphamide, doxorubicin, and prednisone; VECP, vindesine, etoposide, carboplatin, and prednisone.
common adverse events were lymphocytopenia (96%), neutropenia (52%), thrombocytopenia (52%), acute infusion reaction (89%), and skin eruption (63%). Notably, skin eruption occurs partly because m ogamulizumab eliminates effector regulatory T cells. Most adverse cutaneous reactions are manageable with immediate corticosteroid use. Based on these results, mogamulizumab was approved for relapsed/refractory ATL in March 2012 in Japan. To explore a more suitable regimen for untreated aggressive ATL, a randomized phase II study of VCAP-AMP-VECP with or without mogamulizumab was conducted.\textsuperscript{12} A higher CR rate was obtained in the antibody-containing arm (52% vs 33%), suggesting that VCAP-AMP-VECP in combination with mogamulizumab is a more effective option. Based on these results, mogamulizumab was approved in Japan in December 2014 also for untreated ATL. In contrast, Fuji et al reported that mogamulizumab treatment prior to allo-HSCT may increase the risk of severe acute graft-versus-host disease.\textsuperscript{13} Therefore, conventional induction chemotherapy without mogamulizumab is nowadays recommended in transplant-eligible patients in Japan.

### 5.2 Lenalidomide

A phase I study of lenalidomide for relapsed ATL and PTCLs was conducted, and 25 mg daily for 28-day cycle was regarded as the maximum tolerated dose.\textsuperscript{14} Among the 9 patients with ATL, 3 achieved partial responses, with a hematological CR in 2 patients. Subsequently, a phase II study of lenalidomide for ATL was conducted.\textsuperscript{15} Objective responses were noted in 11 of 26 patients (ORR, 42%), including 5 CRs. The median PFS and OS were 3.8 and 20.3 months, respectively. We expect that lenalidomide will be a promising treatment option for aggressive ATL.

### 5.3 Histone deacetylase inhibitors

Histone deacetylase (HDAC) is an enzyme involved in the remodeling of chromatin and plays an important role in the epigenetic regulation of gene expression. Several HDAC inhibitors, such as vorinostat, romidepsin, and panobinostat have been investigated in T-cell lymphomas. However, most have not been adequately evaluated in patients with ATL. Recently, a novel HDAC inhibitor, chidamide (HBI-8000), showed promising efficacy in a phase II study for relapsed/refractory PTCLs in China and was approved by the Chinese FDA with a dose of 30 mg twice weekly. Chidamide shows antitumor activity in ATL-derived cell lines. In Japan, a phase I study of chidamide for relapsed/refractory NHL was conducted, and the safety of 2-dose levels (twice weekly 30 and 40 mg) was evaluated (NCT02697552). Although 2 DLTs were observed in the 40-mg cohort, both were asymptomatic and reversible. Furthermore, 5 of 6 patients in the 40-mg cohort achieved objective responses. Notably, among 5 patients with ATL in this study, 4 patients receiving 40 mg twice weekly achieved partial response. Based on these results, 40 mg twice weekly was chosen as a recommended phase II dose. Subsequently, 2 pivotal phase II studies of HBI-8000 to evaluate the efficacy in patients with relapsed/refractory ATL (NCT02955589) and PTCLs (NCT02953652) were recently initiated.

### 5.4 Enhancer of zeste homolog inhibitor

Zeste homolog 1 (EZH1) and EZH2 function as a histone methyltransferase and trimethylate histone H3 lysine 27 (H3K27me3), respectively. Since H3K27me3 is a repressive histone modification, EZH1/2 overexpression induces epigenetic gene silencing. According to studies in ATLe derived cell lines, EZH2 overexpression appeared to be associated with the oncogenesis and progression of ATL. Therefore, EZH1/2 is expected to be a novel therapeutic target for ATL. Several EZH2 selective inhibitors are being evaluated in clinical trials for B-NHLs. It is expected that an EZH1/2 dual inhibitor will show more potent antitumor activity because it can inhibit both pathways involved in H3K27 trimethylation. In Japan, the first-in-human phase I study of DS-3201b, a first-in-class EZH1/2 dual inhibitor, for relapsed/refractory NHL including ATL is currently underway (NCT02732275).

### 6 CONCLUSION

We summarized recent clinical investigations of the management of T/NK-cell lymphomas, focusing on ATL and ENKL. Considering their rarity and endemic character of these cancers, well-designed prospective trials for T/NK-cell lymphomas are difficult to conduct. Clinical investigators are recommended to collaborate internationally to accomplish the challenging goals of achieving further improvements in the treatment of T/NK-cell lymphomas, including ENKL and ATL.

### ACKNOWLEDGEMENT

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### CONFLICT OF INTEREST

SM has received travel fee from Celgene; and honoraria from Chugai.

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### REFERENCES


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Late sequelae in Hodgkin lymphoma survivors

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1 INTRODUCTION

Since the introduction of modern radiotherapy and combination chemotherapy in the 1960s, Hodgkin lymphoma (HL) has become a highly curable malignancy with 5-year survival rates of more than 80%.1 However, the life expectancy and quality of life of HL survivors are reduced by the occurrence of late adverse treatment effects.2-5 Most of the HL survivors experiences 1 or more physical and/or psychosocial problems. Common late effects include second and subsequent malignant neoplasms, several cardiovascular diseases (CVDs), thyroid dysfunction, subfertility, premature menopause, and fatigue.2,3,5,9 In addition to this wide range of physical late effects, many HL survivors face psychosocial problems that may or may not be linked to specific treatments, but significantly reduce their quality of life. These include impaired memory and concentration, depression and anxiety, sexual problems, and problems with employment and insurances.

2 RISK OF SECOND MALIGNANCY

Increased risks of solid tumors in irradiated HL patients and of leukemia in chemotherapy-treated patients have been reported consistently in the literature.3,5 In a recent study that included HL patients treated from 1965 to 2000,7 the excess risk of second malignancy remained significantly increased beyond 35 years after HL treatment (Figure 1), with a 40-year cumulative incidence of second cancer estimated at 43.6% (Figure 2). The largest standardized incidence ratios (SIRs) are observed for leukemia (SIR = 10-30), followed by connective tissue, pleura and thyroid cancer, and non-Hodgkin lymphoma (SIR = 6-20).5,7

Moderately, increased risks (SIR = 2-7) are observed for a large number of solid tumors, such as cancers of the lung, breast, stomach, esophagus, colon/rectum, cervix, mouth and pharynx, and melanoma.3,5-7 Absolute excess risk (AER) is the best risk measure to express burden of disease. Hodgkin lymphoma patients experience an excess of about 85 to 125 malignancies per 10 000 patients per year, over and above the background rate. Solid tumors account for most of the excess cancers (60-100 per 10 000 patients per year), and, of those, breast and lung cancers account for the largest proportion of excess malignancies.3,5-7

The SIR of solid tumors is minimally elevated in the 1 to 4 year follow-up period, but becomes significantly increased from 5 to more than 30 years since first treatment.5,7,10 For several tumor sites (breast, thyroid, and esophagus), the excess risk does not become apparent until after 10 to 15 years of observation. Hodgson et al6 modeled relative risks (RRs) and found no indication for increasing or decreasing RRs beyond 10 years of follow-up. Because of the rising background incidence of cancer with age, long-term survivors experience strongly increasing AERs of solid malignancy. In a recent report with very long-term follow-up, HL survivors in their 60s or 70s experienced 1.7 and 3.1 excess cancers per 100 patients per year, on top of a background cancer incidence of 1.3 and 2.1 per 100 patients/year, respectively.7

The literature uniformly shows that the SIRs of various solid tumors increase strongly with younger age at first treatment.3,5-7 The effect is strongest for breast cancer. For both breast and nonbreast solid malignancies, AERs strongly increase with older attained age, indicating the increasing burden of excess cancers with advancing age of HL survivors. Thirty years after treatment, at attained ages of younger than or equal to 51 years, the cumulative incidence of breast cancer in survivors treated before age 21 is as high as 26% that is comparable to the risk of BRCA mutation carriers.3,5,10

While alkylating chemotherapy is the main cause of acute myeloid leukemia after HL,3,5 elevated risks of solid cancers following HL have been largely attributed to radiation therapy (RT).3,5-7 For a number of solid malignancies (lung, breast, stomach, and pancreas), the risk has been shown to increase strongly and linearly with higher radiotherapy doses.3,5,11,12 For example, compared with a dose of less than 4 Gy to affected breast site, the RR of breast cancer rises from 4.1 for 7 to
23 Gy to an 8.0-fold increase for more than 40.5 Gy. For lung cancer, the increased RRs from smoking appeared to multiply the elevated risks from radiotherapy (Table 1), implying that there are large absolute excess risks for lung cancer among irradiated patients who smoke, while nonsmokers experience little excess risk from radiation. It was estimated that 9.6% of all lung cancers after HL were due to treatment, 24% were due to smoking, and 63% were due to treatment and smoking in combination.

Radiation field size is an important risk factor for solid cancer risk. For breast cancer, it has been shown that smaller radiation volumes than mantle field are associated with substantially lower risk, which is important in view of the smaller field sizes currently used in HL treatment. Furthermore, alkylating chemotherapy and pelvic radiotherapy appear to reduce the risk of radiotherapy-associated breast cancer, because of the high frequency of premature menopause after chemotherapy. A long versus short duration of intact ovarian

**TABLE 1** Risk of lung cancer in patients with Hodgkin lymphoma according to type of treatment and smoking category

<table>
<thead>
<tr>
<th>Treatment for hodgkin disease</th>
<th>RR (95% CI) by smoking category (no. of case patients; control patient)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiation ≥ 5 Gy</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.0^e</td>
</tr>
<tr>
<td>Yes</td>
<td>7.2 (2.9–21.2)</td>
</tr>
<tr>
<td>No</td>
<td>4.3 (1.8–11.7)</td>
</tr>
<tr>
<td>Yes</td>
<td>7.2 (2.8–21.6)</td>
</tr>
</tbody>
</table>

Abbreviations: RR, relative risk; 95% CI, 95% confidence interval.

Data adapted from Travis et al. Data represents estimated tobacco smoking habit 5 years before diagnosis date of lung cancer and corresponding date in control patients, with the use of information recorded up to 1 year before these dates. This group includes nonsmokers, light current cigarette smokers (less than 1 pack per day), former cigarette smokers, smokers of cigar and pipes only, and patients from whom tobacco smoking habit was not stated. Moderate (1 or 2 packs per day) and heavy (2 or more packs per day) current cigarette smokers. Reference group.
function after radiation was a strong predictor of subsequent breast cancer risk. Women with less than 10 years of intact ovarian function after radiotherapy had a 70% decreased risk of breast cancer compared with women with 10 to 20 years of ovarian function after irradiation, while those with more than 20 years of intact ovarian function after radiotherapy had 5.3-fold increased risk of breast cancer. These results indicate that ovarian hormones are a crucial factor to promote breast tumorigenesis once radiotherapy has produced an initiating event.

Several studies have observed that not only radiotherapy but also alkylating chemotherapy can substantially increase the risk of solid malignancy, in particular, risks of lung, stomach, and pancreatic cancers. Lung cancer risk after HL is increased 2 to greater than 4-fold with increasing number of cycles of alkylating agent-containing chemotherapy, particularly nitrogen mustard, vincristine, procarbazine, and prednisolone. For stomach cancer risk, a strong association with cumulative procarbazine dose was observed. While additive effects of chemotherapy and radiotherapy have been observed for lung cancer, supramultiplicative effects were recently reported for stomach cancer. Radiation doses to the stomach of greater or equal to 25 Gy combined with exposure to high-dose procarbazine (≥5600 mg/m²) were associated with a 78-fold increased risk of stomach cancer, compared with RRs of 2.8 and 1.2 for exposure to greater than or equal to 25 Gy of radiation alone and exposure to high-dose procarbazine (≥5600 mg/m²) alone, respectively.

A recent Dutch study examined whether HL patients treated in the 1989 to 2000 period, when less toxic treatments had been introduced and had a lower risk of second malignancy than patients treated in 1965 to 1988. While the cumulative incidence of leukemia was significantly lower in the most recent treatment era, no such decrease was observed for solid malignancies, even though smaller radiotherapy volumes were associated with lower risk in multivariable analysis, especially for breast cancer. The surprising absence of a declining overall risk of solid malignancy was attributed to a number of factors, such as later than expected wide application of changes in radiotherapy policy, screening for breast cancer, and changes in chemotherapy regimens.

3 | RISK OF CARDIOVASCULAR DISEASE

Both radiotherapy involving the heart and anthracycline-containing chemotherapy can increase the risk of CVD in HL survivors. Radiation-induced CVD includes coronary heart disease (CHD), valvular heart disease (VHD), myocardial dysfunction, electrical conduction abnormalities, and pericardial disease. Anthracyclines can, depending on the cumulative dose, lead to both acute cardiomyopathy and chronic cardiac complications (especially heart failure [HF]). Radiation- and anthracycline-associated cardiac damage have a different pathogenesis, which also appears to differ from the general population. Radiation may damage the endothelium of blood vessels. In large arteries, this damage may lead to accelerated atherosclerosis and an increased risk of vascular stenosis and thromboembolism. Animal studies have shown that radiation predisposes to the formation of unstable plaques that are more likely to rupture and cause a fatal heart attack or stroke. Cardiotoxicity following anthracyclines is typically associated with loss of myocardial mass, leading to progressive cardiac remodelling and dysfunction.

Prospective screening studies among HL survivors demonstrate that clinically significant cardiovascular abnormalities, like coronary artery stenosis, coronary artery calcifications, reduced left ventricular dimensions, VHD, and conduction defects, are very common, even in asymptomatic survivors. Large cohort studies of HL survivors show a 2- to 7-fold increased risk of cardiac death (mainly myocardial infarction), depending on the age of the patients (stronger risk increases for radiotherapy at younger ages), treatment regimens used, and follow-up time. Furthermore, 3- to 6-fold increased SIRs of CHD, VHD, and HF are observed in patients treated for HL relative to the general population, also after long-term follow-up. The persistence of increased SIRs over prolonged follow-up times is of concern because they imply increasing AERs over time, because of the rising incidence of CVDs with age.

Van Nimwegen et al recently examined long-term CVD risk in 2524 five-year survivors of HL who were treated in the Netherlands between 1965 and 1996. After 35 years of follow-up, HL survivors still had a 4- to 6-fold increased SIR of CHD or HF compared with the general population, corresponding to 857 excess events of CHD and HF per 10 000 person-years. Within the cohort, 40-year cumulative incidence of CVD was 50%. In patients treated before 25 years of age, the highest RRs were seen (for CHD, VHD, and HF), but substantial absolute excess risks were also observed for patients treated at older ages. Mediastinal radiotherapy increased the risks of developing CHD (2.7-fold), VHD (6.6-fold), and also HF (2.7-fold), as first cardiovascular events. Anthracycline-containing chemotherapy increased the risks of VHD (1.5-fold) and HF (3.0-fold) as first cardiovascular events. Patients treated with mediastinal radiotherapy had a 40-year cumulative incidence of any CVD of 54.6% compared with 24.7% in patients not treated with mediastinal radiotherapy or anthracyclines. The cumulative incidence of CVD after HL according to treatment exposure is shown in Figure 3. After 20 years of follow-up, anthracycline-associated risks of VHD and HF (as first events) were still significantly elevated.

Data on possible interaction between chemotherapy and radiotherapy and risk of cardiac diseases are scarce. Several studies suggest that anthracycline-containing chemotherapy further increases the radiotherapy-related risk of VHD and HF by 2- to 3-fold compared with radiotherapy alone. This effect was additive in a recent report and more than additive in another study.

Three recent case-control studies addressed the shape of the radiation dose-response curve for CHD and VHD after HL treatment. The first study included 325 patients diagnosed with CHD as their first cardiovascular event after HL. Radiation charts and simulation radiographs were used to estimate mean heart dose for all cases and 1204 matched controls. The median interval between HL and CHD was 19 years. Risk of CHD increased linearly with increasing mean heart dose (excess RR per Gy, 7.4%), with 2.5-fold increased risk for patients receiving a mean heart dose of 20 Gy (compared with no mediastinal RT). In the study of risk factors for VHD after HL, the radiation dose-response relationship was linear with upward curvature. A recent case-control study of cardiomyopathy and HF after HL
showed a linear relationship with the mean left ventricular dose (MLVD). Anthracycline-containing chemotherapy increased HF rate by a factor of 2.83, and there was no significant interaction with MLVD. Twenty-five year cumulative risks of HF following MLVDs of 0 to 15, 16 to 20, and greater than or equal to 21 Gy were 4.4%, 6.2%, and 13.3%, respectively, in patients treated without anthracycline-containing chemotherapy and 11.2%, 15.9%, and 32.9%, respectively, in patients treated with anthracyclines. The establishment of a clear radiation dose response for different CVDs implies substantially lower CVD risks for more recently treated HL patients who received involved-node or involved-site radiotherapy and lower radiation doses.

An important question is whether conventional cardiovascular risk factors influence CVD risk in survivors who received cardiotoxic treatments and whether such factors modify treatment-related risk of CVD. Several studies show that hypertension, hypercholesterolemia, diabetes, and recent smoking do increase CVD risk in HL and childhood cancer survivors,\textsuperscript{2,16–18} but few studies could examine risk modification. Two recent reports show additive effects of smoking on the risks of CVD from mediastinal radiotherapy and anthracyclines.\textsuperscript{9,16} The above case-control study of risk factors for CHD after HL treatment showed that hypertension was an independent risk factor for CHD (RR = 1.85), which added to the radiotherapy-associated risk but did not modify it.\textsuperscript{16} However, a recent study in childhood cancer survivors showed that the combined effect of chest radiotherapy plus hypertension resulted in potentiation of risk for major cardiac events beyond that anticipated on the basis of an additive effect.\textsuperscript{17} Two studies examined the effects of physical inactivity on CVD risk after HL.\textsuperscript{16,18} Jones et al found a lower risk of treatment-related cardiac events in childhood HL survivors who reported greater than or equal to 9 metabolic equivalent hours per week, which is equivalent to approximately 2 to 2.5 hours of cycling or walking.\textsuperscript{18} Van Nimwegen and colleagues also showed that patients with a high level of physical activity (≥4 hours a week of walking, cycling, or sports) had a considerably lower risk of developing CHD than patients who were inactive (<1 hour a week) (RR = 0.52).\textsuperscript{16}

The above findings underline the importance of control of conventional CVD risk factors, including maintenance or adoption of a healthy lifestyle after HL treatment. Both additive and supra-additive effects of conventional CVD risk factors and treatment imply that early diagnosis and appropriate management of CVD risk factors may substantially reduce the risk of premature cardiac disease.

Treatment for HL has changed dramatically over time. The risk of radiotherapy-related CVD after HL is expected to decrease significantly over time since fewer patients receive combined modality treatment and radiotherapy policies have changed.\textsuperscript{2,13} If radiotherapy is applied, the target volumes are smaller, 3-dimensional conformal radiotherapy planning is used, and the applied dose is lower. Additional advanced techniques such as deep-inspiration breath-hold and intensity-modulated radiation therapy with butterfly techniques further significantly reduce doses to the heart and cardiac substructures.\textsuperscript{2} The risk of anthracycline-related HF, however, likely increases because of the increased use of anthracyclines. A recent report showed that cumulative incidence curves of CVD were similar for HL patients treated 1965 to 1974, 1975 to 1984, and 1985 to 1995, implying that a large population of survivors remains at increased CVD risk for many years to come.\textsuperscript{7}
TABLE 2 Summary of follow-up recommendations for HL survivors according to NCCN, COG, and the Dutch BETER consortium according to types of major late effects

<table>
<thead>
<tr>
<th>Treatment Exposure</th>
<th>NCCN</th>
<th>COG</th>
<th>Dutch BETER Consortium</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Second malignancy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Breast cancer:</td>
<td>Annual breast self-examination beginning at puberty until age 25, then every 6 mo</td>
<td>Breast cancer: Screening only recommended for women with history of RT to chest and/or axillae before age 40: Age 25-30: annual clinical breast examination and MRI Age 30-60: annual clinical breast examination, mammography and MRI Age 60-70: biennial clinical breast examination and mammography Age 70-75: biennial mammography through population screening Thyroid nodule/cancer: See screening for thyroid dysfunction</td>
</tr>
<tr>
<td></td>
<td>Annual mammography and breast MRI screening, to start 8 to 10 y post treatment, or at age 40, whichever comes first, for women with history of chest RT between ages 10 and 30</td>
<td>Annual mammogram and breast MRI, beginning 8 y after radiation or at age 25, whichever occurs last Lung cancer: Imaging and surgery and/or oncology consultation as clinically indicated Colorectal cancer: Colonoscopy every 5 y, beginning at 10 y after radiation or at age 35, whichever occurs first, for patients with RT of ≥30 Gy to the abdominal and/or pelvic region Thyroid nodule/cancer: Yearly thyroid exam Skin cancer: Annual dermatologic examination and monthly skin self-examination in patients with prior RT exposures</td>
<td>At this moment screening for lung cancer, colorectal cancer and skin cancer are not recommended, as evidence is lacking that this is effective in reducing morbidity or mortality.</td>
</tr>
<tr>
<td></td>
<td>Consider chest imaging for survivors with &gt;30 pack-y history of smoking.</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Colonoscopy every 10 y for survivors age ≥50. or by age 40 for survivors at increased risk for colorectal cancer due to treatment history.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Skin cancer: Counseling on skin cancer risks.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cardiovascular disease</strong></td>
<td>Cardiac disease:</td>
<td>Periodic echocardiogram and ECG with frequency dependent on age at treatment exposure and cumulative doses in patients with history of treatment with anthracyclines or chest RT Carotid disease: Examination for diminished carotid pulses or carotid bruits in patients treated with neck RT</td>
<td>Screening only recommended after: Cardiotoxic CT with cumulative doses equivalent to doxorubicin ≥300 mg/m² Chest RT only or combined with cardiotoxic CT, independent of dose Cardiovascular disease: Echocardiogram every 5 y if treated with cardiotoxic CT; only once, 15 y after diagnosis, when treated with RT only Every 5 y, up to age 70: physical examination (eg, blood pressure), lipids, glucose, biomarkers (BNP or NTproBNP) ECG once 5 y after diagnosis</td>
</tr>
<tr>
<td></td>
<td>Consider stress test and echocardiogram at 10-y intervals after treatment for patients with history of chest RT Carotid disease: Consider carotid ultrasound at 10-y intervals in patients with history of neck RT Cardiovascular disease risk factors: Annual blood pressure, lipids, and aggressive management of cardiovascular risk factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Endocrinopathies</strong></td>
<td>Hypothyroidism:</td>
<td>Annual TSH, free T4 Infertility: Periodic follicle-stimulating FSH, LH and estradiol screening in patients with exposure to alkylating agents or pelvic RT</td>
<td>Thyroid dysfunction: For patients with history of neck RT: Every 1-3 y palpation of thyroid gland Annual TSH, if abnormal: free T4 Infertility: When treated with alkylating CT or RT to gonadal region (before age 40 in women): Counseling about reduced fertility span Men: testosterone if hypogonadism is suspected, women: LH, FSH, and estradiol</td>
</tr>
<tr>
<td></td>
<td>Annual TSH for patients with history of neck irradiation Infertility: Reproductive counseling</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: BETER, Better care after Hodgkin lymphoma: Evaluation of long-term Treatment Effects and screening Recommendations; COG, Children’s Oncology Group; CT, chemotherapy; ECG, electrocardiogram; FSH, follicle-stimulating hormone; LH, luteinizing hormone; MRI, magnetic resonance imaging; NCCN, National Comprehensive Cancer Network; RT, radiation therapy; TSH, thyroid stimulating hormone.
4 | RISK OF OTHER LATE EFFECTS

4.1 | Pulmonary dysfunction

Both mediastinal RT and bleomycin are associated with acute lung toxicity, but can also lead to persistently reduced pulmonary function and long-term pulmonary fibrosis. Several studies have documented decline in pulmonary function in HL patient after adriamycin, bleomycin, vinblastine, dacarbazine (ABVD) chemotherapy and mediastinal irradiation.

A prospective study evaluated the pulmonary function of 67 survivors of HL patients (21 with ABVD and 46 with bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisolone [BEACOPP] and 34 with mediastinal irradiation to a median dose of 28.95 Gy). At a median follow-up of 61 months posttreatment, abnormal pulmonary function tests were found in 13.4% of patients, although only 4.5% had functional dyspnea. Prior history of bleomycin pulmonary toxicity was significantly associated with chronic respiratory impairment (75% vs 10%, P = .007).

4.2 | Endocrinopathies

4.2.1 | Thyroid dysfunction

The long-term risk of hypothyroidism can be as high as 60% after neck RT for HL. In a study of 1677 HL patients, the 20- and 26-year actuarial risks of thyroid diseases were 52% and 67%, respectively, with most of the cases being hypothyroidism. The risk of hypothyroidism is related to radiation doses, and a significant dose-volume effect has also been observed. The risk of developing hypothyroidism in HL survivors was only 11.5% if the percentage of the thyroid gland volume receiving 30 Gy (V30) was 62.5% or lower, but the risk was significantly higher at 70.8% if the thyroid gland V30 was greater than 62.5% (P < .0001).

4.2.2 | Infertility

Both RT and chemotherapy can have temporary or permanent effect on the fertility of men and women, depending RT dose, age at treatment, the type of drugs, and total dose of chemotherapy.

In men, radiation doses of 1.2 Gy and higher are associated with a reduced chance of recovery of spermatogenesis. In women, ovarian dysfunction from radiation exposure depends strongly on age at treatment, total dose, and fractionation. Ovarian doses of less than 1.5 Gy rarely leads to sterility in women younger than 40 years. After doses of 2.5 to 5.0 Gy, 30% to 40% of women treated between 15 and 40 years of age will experience permanent ovarian failure, whereas over 90% of the women older than or equal to 40 years of age will be permanently sterilized at these doses.

The risk for infertility after chemotherapy depends on the cumulative doses of alkylating agents. Regimens such as nitrogen mustard, vincristine, procarbazine, and prednisolone, cyclophosphamide, vincristine, procarbazine, and prednisone (COPP), or BEACOPP carry a much higher risk for infertility as compared with regimens without alkylating agents, such as ABVD, which rarely lead to permanent sterility in men or in women. Both escalated and baseline BEACOPP are associated with risk of azoospermia in over 90% of male HL patients. Half of women who received escalated BEACOPP reported continuous amenorrhea in 1 study, and the risk is significantly associated with advanced-stage disease, age over 30 at treatment, and lack of oral contraceptive use during treatment. However, the risk of amenorrhea was lower with baseline BEACOPP.

4.2.3 | Diabetes, muscular atrophy, fatigue

Increased risk of diabetes, muscular atrophy, and fatigue are discussed in a recent review.

5 | CURRENT GUIDELINES FOR SURVEILLANCE

Several organizations offer surveillance guidelines for HL survivors, with special attention to key late effects such as second malignancy and cardiovascular disease. The National Comprehensive Cancer Network provides guidelines for monitoring for late effects specifically for HL survivors 5 years after initial treatment, including types of testing and their timing. The long-term follow-guidelines from Children’s Oncology Group present detailed recommendation according to specific treatment exposures and potential impact to body sites. Many of the follow-up guidelines could be relevant to HL survivors. Summarized in Table 2 are surveillance recommendations from the 2 groups according to late effect types.

CONFLICT OF INTEREST

The authors have no competing interest.

REFERENCES


8. van der Kaaij MAE, Heutte N, Le Stang N, et al. Gonadal function in women older than or equal to 40 years of age will be permanently sterilized at doses of 30 Gy (V30) was 62.5% or lower, but the risk was significantly higher at 70.8% if the thyroid gland V30 was greater than 62.5% (P < .0001).

The authors have no competing interest.


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Clinical applications of genome studies

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1 INTRODUCTION

In 2017, it is estimated that 80,000 new patients will be diagnosed with non-Hodgkin lymphoma (NHL) in the United States.1 The NHLs are classified into more than 60 histologically, phenotypically, and genetically defined subsets, with diffuse large B-cell lymphoma (DLBCL) being the most common histologic subtype in adults.2 With the exception of a handful of drugs approved by the FDA, treatment of most types of Non-Hodgkin lymphoma (NHL) has not changed in more than 2 decades. For example, patients with advanced stage DLBCL are uniformly treated with a combination regimen of rituximab, cyclophosphamide, adriamycin, vincristine, and prednisone (RCHOP), which is based on a 40-year-old CHOP regimen.

The discovery of a variety of genetic alterations led to the identification of numerous potential therapeutic targets and to the development of more than 800 compounds that are being examined in clinical trials or in preclinical experiments for the treatment of cancer, including lymphoma.3 However, based on past experience, the development of most of these compounds is unlikely to succeed owing to the lack of anticancer benefit, excessive toxicity, poor understanding of the optimal dose and schedule, limited understanding of the patient subsets that benefit, or a combination of these reasons. Furthermore, although the number of studies enrolling lymphoma patients has increased, many of them lack focus, do not advance the field, and compete for a relatively small pool of eligible patients.

A common outcome of clinical trials that test novel agents in unselected populations is a modest clinical activity with a reasonable safety profile.4 Such outcomes are not sufficient for securing approval by regulatory agencies, such as the FDA, for affecting clinical practice. Moreover, an increasing number of costly phase 3 studies fail to meet their end points because these trials continue to use traditional randomization designs and frequently compare empirical combination regimens with standard regimens in unselected patient populations. It is not surprising that only a handful of drugs have been approved in recent years by the FDA for the treatment of lymphoma. These failures underline the importance of developing novel strategies that can translate the recent molecular and genetic discoveries into successful treatment regimens.5 With the recent success of new targeted agents for biomarker-selected patients with melanoma and non–small-cell lung cancer, the search for predictive biomarkers that may guide therapy for other cancers, including lymphoma, has become a focus in drug development.

2 BIOMARKER SELECTION AND NOVEL TRIAL DESIGNS

Molecular analysis of DLBCL tumors together with functional interrogation of cell lines models has uncovered a wealth of therapeutic targets for which targeted agents are available for clinical testing. One prevalent oncogenic pathway in DLBCL is constitutive B-cell receptor signaling.6 An initial phase 2 clinical trial in relapsed or refractory DLBCL of the B-cell receptor pathway inhibitor ibrutinib revealed significant clinical activity in the activated B-cell–like subtype, but most patients developed resistant disease within 10 months.7 Based on this observation, ibrutinib was rapidly combined with RCHOP chemotherapy in a phase 1 trial.8 Once the safety of this combination was established, it was evaluated in a randomized study in patients with newly diagnosed nongerminai center B-cell–like DLBCL (Figure 1).

For many years, cancer patients were selected for specific therapy based on diagnostic tests that were simple and frequently lacked precision, such as immunohistochemical-staining methods and polymerase chain reaction.5 In DLBCL, gene expression-profiling analysis identified 2 major distinct “cell of origin” subtypes; germinal center B–cell–like, and activated B–cell–like.9,10 However, gene expression-profiling studies never gained traction because of its complexity and the need to standardize it as a clinical assay. Subsequently, a simplified nanostring-based assay (Lymph2Cx) was used to identify DLBCL subsets that can be used in clinical diagnostic laboratories.11 While the Lymph2Cx assay will facilitate patients’ selection for clinical trials, its use is limited to DLBCL as it cannot be applied to the remaining NHL patients.

Recent DNA- and RNA-sequencing studies have identified recurrent actionable genetic alterations that cross the boundaries of
the cell of origin classification of DLBCL. Some of these genetic alterations are detected across different lymphoma histologies and even across different cancers. Functional genomics studies revealed that some of these genetic alterations are involved in tumor pathogenesis and/or involved in promoting tumor cell growth and survival, and therefore, they are considered as "actionable" alterations. Many importantly, several recurrent genetic alterations frequently converge on common oncogenic "pathways" that could potentially guide therapy. However, the significance of most of these genetic alterations remain unknown. Despite these limitations, clinical trials have been initiated to select patients based on these "actionable" genetic alterations. Importantly, clinical assays were recently developed to detect these genetic alterations in clinical diagnostic laboratories, with relatively fast readouts. Accordingly, new designs of clinical trials have emerged. Basket trials typically capture patients with different cancers based on the presence of the same genetic alterations across tumor types (such as BRAF or PI3K mutations). Umbrella trials, typically, enroll patients with the same tumor type but subdivided based on different genetic alterations or biomarkers.

As many genetic alterations occur across different NHL subtypes to a variable degrees, basket trials can be designed to treat patients with different lymphoma histologic subtypes based on actionable genetic alterations or oncogenic pathways. Alternatively, lymphomas can be divided based on several genetic alterations or pathways and, therefore, can be offered different treatments using an "umbrella" trial design (Figure 1). At the present time, most umbrella trials stratify patients based on the presence of alterations in 1 gene, such as EZH2, or TP53 (Figure 1). Because some patients may not have actionable genetic alterations in their lymphoma cells, alternative treatments can be offered to such patients, such as immune therapy-based approaches.

Future trials designs will focus on grouping several genetic alterations that converge on functional oncogenic pathway (Figure 2). For each basket, one could use a backbone drug and combine it with a second drug based on solid preclinical data. Alternatively, an agent that demonstrates activity in a specific basket can be randomized against other "standard of care agents" or can be combined with front-line regiments.
3 CONCLUSIONS AND FUTURE DIRECTIONS

As our diagnostic tools continue to improve and become more widely applicable in the clinical setting, precision medicine is becoming a reality. With time, more actionable genetic alterations will be identified in a smaller subset of patients, and therefore, most cancers will become rare diseases as they are defined by these genetic biomarkers. Accordingly, new and more efficient clinical trial designs will need to be adopted. Both "basket" and "umbrella" designs are being explored in oncology. For these type of trials to succeed, multicenter collaborations will be critical.

CONFLICT OF INTEREST
Anas Younes received honorarium from foundation medicine.

REFERENCES

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Anaplastic large-cell lymphoma and peripheral T-cell lymphoma: What can pediatricians and adult oncologists learn from each other?

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1 INTRODUCTION

Mature T and NK cell lymphomas are a heterogeneous group of diseases derived from post-thymic T/NK cells at diverse stage of differentiation. In the 2016 revision of the WHO classification, 29 different entities have been described. There are major differences in the repartition of subgroups according to age. Whereas in adults angio-immunoblastic and peripheral T-cell lymphoma not otherwise specified (PTCL NOS) are the most frequent subtypes, in children and adolescents, most peripheral T-cell lymphomas are ALK+ anaplastic large-cell lymphomas (ALCL), which account for 10% to 12% of all non-Hodgkin lymphoma (NHL) occurring in this age group and the non-ALK PTCL represent only 1% of all childhood NHL. Despite the rarity of these entities, a lot of data has been accumulated since several years through national and international collaboration of pediatric groups and especially the European Intergroup for Childhood non-Hodgkin Lymphoma (EICNHL).

2 ANAPLASTIC LARGE-CELL LYMPHOMA

Anaplastic large-cell lymphoma is a rare, aggressive, CD30-positive NHL affecting mostly children/adolescents and young adults. Three ALCL entities have been described: ALCL, ALK positive; ALCL, ALK negative; and primary cutaneous ALCL. More than 90% of pediatric cases are primary systemic ALCL ALK positive (ALK+ ALCL).

ALK+ ALCL results from chromosomal translocations involving the ALK gene and different partners, most frequently the nucleophosmin (NPM) gene associated with the (2;5)(p23;q35). More than 10 other partners have been described so far such as TPM3 resulting in the t(1;2)(q25;p23), ATIC (inv)(2)(p23q35), or clathrin t(2;22)(p23;q11). The translocation results in the oligomerization of the fusion protein leading to a constitutive phosphorylation of ALK. This leads to the activation of multiple pathways such as JAK/STAT3, AKT/Pi3K, RAS/ERK leading to growth-factor independent cell proliferation and inhibition of apoptosis.

ALK- ALCL account for less than 5% of systemic ALCL in children and adolescents. It is an heterogeneous group of lymphoma also shown to be associated with JAK/STAT pathway activation either through mutations or by kinase fusions. The most frequent translocation involves the DUSP22-IRF4 region which is present in 30% of ALK- ALCL in adults. The incidence of this translocation in pediatric ALK negative ALCL is still unknown.

ALK+ and ALK- ALCL have been recently shown to share a common methylation profile in genes involved in T cell differentiation and immune response.

Primary cutaneous ALCL is regarded by the WHO as a different disease and belongs to the spectrum of primary cutaneous CD30-positive lymphoproliferations (CD30+LPD), a group that additionally includes lymphomatoid papulosis. This entity is rare in children with only 33 cases of primary cutaneous ALCL (27 ALK negative and 6 ALK positive) among 487 patients included in the large European ALCL99 trial between 1999 and 2006. Of note, only ALK- ALCL are considered as primary cutaneous ALCL in the WHO classification. Given the overlapping histologic and phenotypic features between lymphomatoid papulomatosis and cutaneous ALCL, differential diagnosis between these entities may be difficult.

3 PATHOLOGY

Anaplastic large-cell lymphomas are characterized as a proliferation of large and pleomorphic lymphoid cells with abundant cytoplasm, often horseshoe-shaped nuclei referred to as "hallmark cells," that
preferentially involve lymph nodes sinuses. Neoplastic cells strongly express CD30 and, in most cases, Epithelial Membrane Antigen (EMA) is positive in most cases. Most case express cytotoxic granule-associated proteins (TIA1, granzyme B, and perforine). Several pan T antigens, such as CD2, CD3, CD5, CD7, or CD8, are lost in a large proportion of cases. However, a major TCR rearrangement is evidenced in most cases.

The expression of ALK fusion protein can be detected by immunostaining with a heterogeneous pattern of staining according to ALK fusion partner. In cases carrying the classic NPM/ALK translocation, ALK expression can be detected in the cytoplasm, the nucleus and nucleoli whereas variant translocations are associated with a cytoplasmic or membranous staining.

The 2008 WHO classification recognizes 5 morphological patterns of ALK-positive: common, small-cell, lymphohistiocytic, Hodgkin-like, and composite patterns. These different subtypes must be recognized by the pathologist. Diagnosis could be difficult in some cases as in the lymphohistiocytic form, microenvironment masks the tumor proliferation, that localizes in a perivascular topography. CD30 and ALK immunohistochemistry is very useful in these cases.

4 | CLINICAL PRESENTATION

Most patients with systemic ALCL present with lymph node involvement, frequently associated with B symptoms, mediastinal mass, and extra-nodal spread including skin, liver, lung, soft tissue, and bone localization. Less than 15% of patients have initial bone marrow involvement detected by cytology but minimal disseminated disease can be detected in more than 50% of the patients by PCR against the ALK fusion product performed on blood and/or bone marrow. In addition, a few cases present with a leukemic presentation. Central nervous system involvement is rare and mostly represented by brain tumors rather than cerebrospinal fluid involvement. Hemophagocytic lymphohistiocytosis syndrome may be present at diagnosis or even precede the diagnosis of ALCL.

Most cases have an advanced disease with stage III-IV using the St Jude’s classification for Childhood non-Hodgkin’s lymphoma. The international prognostic index used in adults has not been validated in children and adolescents.

Cutaneous ALCL are characterized by papulo-nodular skin lesions and/or subcutaneous nodules, often ulcerated without extra-cutaneous lymphoma dissemination. Most patients present with a single lesion. In some cases, it may be difficult to distinguish a reactive draining lymph node infiltrated by a few reactive CD30+ positive lymphocytes from a partial infiltration of a local lymph node by an ALK negative ALCL. In these cases, differentiating a primary cutaneous ALCL from a skin localization of a systemic ALCL is challenging.

5 | TREATMENT

ALK+ ALCL is a chemosensitive disease, leading to high response rates with diverse chemotherapy regimens at front line and relapse. In the late 1990s, several national groups have published the results obtained in previous therapeutic studies with diverse first-line chemotherapy regimens. With diverse therapeutic regimen in term of number of chemotherapy agents, dose, and duration of treatment, most regimens allow to achieve event-free survival (EFS) rates of 65% to 75% (Table 1). The large ALCL99 trial performed by the EICNHL group, included more than 350 patients and led to 2-year EFS and overall survival (OS) of 73% and 92%, respectively with a chemotherapy derived from a BFM B NHL protocol. Following this trial, the ALCL 99 protocol is now the reference chemotherapy for pediatric ALCL by most pediatric groups considering the good results in overall and event-free survival and the low cumulative dose of drugs associated with long-term toxicities, such as alkylating agents and anthracyclines. Several factors have been shown to be associated with a higher risk of treatment failure in children and adolescents (Table 2).

6 | TREATMENT OF RELAPSE

There is still no consensus for the treatment of relapse. Several retrospective studies describing approaches based on a wide variety of reinduction chemotherapy combined in most publications with autologous or allogeneic hematopoietic stem cell transplantation (HSCT) have demonstrated that 50 to 60% of patients suffering from relapsed ALCL, ALK+ can be rescued (Table 3).

The efficacy of a risk-adapted strategy for pediatric ALCL relapses has been evaluated through a prospective trial run by the EICNHL between 2004 and 2013. The 3-year EFS and OS of 118 patients included in this trial were 58 ± 5% and 76 ± 4%, respectively. In this trial, therapeutic strategy was adapted to risk factors with allogeneic HSCT after reinduction with multiagent chemotherapy for patients with high risk relapses (progression during treatment or CD3 positive), autologous HSCT in intermediate risk relapses and weekly vinblastine for 2 years without any HSCT in patients with low-risk relapses (occurring after 1 year).

Following these results, given the poor results obtained in the intermediate risk group with autologous HSCT, the EICNHL group recommends allogeneic HSCT for all high-risk relapses and vinblastine for intermediate and low-risk relapses.

High survival rates are still achievable in patients with second and further relapses. In the experience of EICNHL, the 5-year OS were 57% and 52% for patients included in ALCL99 trial who experienced a second or third recurrences, respectively.

The availability of new targeted therapy will now increase again the cure rate of such patients and may lead to a complete change in the strategy in the treatment of this disease.

7 | NEW THERAPIES FOR ANAPLASTIC LARGE-CELL LYMPHOMA

7.1 | Brentuximab vedotin

Brentuximab vedotin is an anti-CD30 drug conjugated to an anti-microtubule agent, auristatin. In the pivotal phase 2 including 58 patients with ALCL (16 ALK+ ALCL), an overall response of 81% and a CR rates of 69% in AKL+ ALC were achieved with a median duration of response was 13 months. On the basis of these results, brentuximab vedotin was approved in the USA and Europe for the treatment of relapsed ALCL in
### TABLE 1 Main reports on front line treatment in anaplastic large cell lymphomas

<table>
<thead>
<tr>
<th>Author year of publication</th>
<th>Study group</th>
<th>Period of recruitment</th>
<th>Treatment strategy</th>
<th>Treatment duration</th>
<th>No. of patients</th>
<th>2- to 5-y EFS</th>
<th>2- to 5-y OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brugieres Blood 1998</td>
<td>SFOP/SFCE</td>
<td>1989-1997</td>
<td>B-cell regimen (COPADM + maintenance)</td>
<td>7-8 m</td>
<td>82</td>
<td>66%</td>
<td>83%</td>
</tr>
<tr>
<td>Seidemann Blood 2001</td>
<td>BFM</td>
<td>1990-95</td>
<td>B-cell regimen (BFM-B)</td>
<td>2-5 m</td>
<td>89</td>
<td>76%</td>
<td>-</td>
</tr>
<tr>
<td>Williams BJH 2002</td>
<td>UKCCSG</td>
<td>1990-98</td>
<td>B-cell regimen (LMB)</td>
<td>4.5 m</td>
<td>72</td>
<td>59%</td>
<td>65%</td>
</tr>
<tr>
<td>Rosolen Cancer 2005</td>
<td>AIEOP</td>
<td>1993-97</td>
<td>T-cell regimen</td>
<td>24 m</td>
<td>34</td>
<td>65%</td>
<td>85%</td>
</tr>
<tr>
<td>Laver JCO 2009</td>
<td>POG</td>
<td>1994-2000</td>
<td>APO ± IMTX-HIDAC</td>
<td>12 m</td>
<td>86</td>
<td>72%</td>
<td>88%</td>
</tr>
<tr>
<td>Lowe PBC 2009</td>
<td>CCSG</td>
<td>1996-2001</td>
<td>Compressed T-cell regimen</td>
<td>11 m</td>
<td>86</td>
<td>68%</td>
<td>80%</td>
</tr>
<tr>
<td>Brugieres JCO 2009</td>
<td>EICNHL</td>
<td>1999-2006</td>
<td>B-cell regimen ± vinblastine</td>
<td>4-12 m</td>
<td>352</td>
<td>73%</td>
<td>92%</td>
</tr>
<tr>
<td>Alexander JCO 2010</td>
<td>COG</td>
<td>2004-2008</td>
<td>APO ± vinblastine</td>
<td>12 m</td>
<td>125</td>
<td>74%</td>
<td>84%</td>
</tr>
</tbody>
</table>

### TABLE 2 Main reports on prognostic factors

<table>
<thead>
<tr>
<th>Pg factors</th>
<th>Authors/Year of publication</th>
<th>Study group</th>
<th>No. of patients</th>
<th>Risk group</th>
<th>No. 5-y PFS</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td>Ledley Blood 2008</td>
<td>EICNHL</td>
<td>235</td>
<td>Mediastinal and/or skin and or visceral lesion</td>
<td>144</td>
<td>61%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>None of these risk factor</td>
<td>81</td>
<td>89%</td>
</tr>
<tr>
<td>Histologic subtype</td>
<td>Lamant JCO 2011</td>
<td>EICNHL</td>
<td>375</td>
<td>Histologic subtype with SC/LH component</td>
<td>247</td>
<td>42%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No SC/LH component</td>
<td>114</td>
<td></td>
</tr>
<tr>
<td>MDD</td>
<td>Damm-Welk Blood 2007</td>
<td>BFM</td>
<td>80</td>
<td>MDD positive</td>
<td>38</td>
<td>38%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MDD negative</td>
<td>42</td>
<td>82%</td>
</tr>
<tr>
<td>MRD</td>
<td>Damm-Welk Blood 2014</td>
<td>BFM/AEIOP</td>
<td>180</td>
<td>MDD positive MRD positive</td>
<td>26</td>
<td>19%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MDD positive MRD negative</td>
<td>26</td>
<td>69%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MRD negative</td>
<td>77</td>
<td>82%</td>
</tr>
<tr>
<td>Anti ALK AB titer</td>
<td>Mussolin Leukemia 2013</td>
<td>BFM/AEIOP</td>
<td>128</td>
<td>Low antibody titer (&lt;1/750)</td>
<td>39</td>
<td>42%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>High antibody titer (&gt;1/750)</td>
<td>89</td>
<td>79%</td>
</tr>
<tr>
<td>Combined MDD/AB titer</td>
<td></td>
<td></td>
<td></td>
<td>Low antibody titer and positive MDD</td>
<td>28</td>
<td>26%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Low antibody titer or positive MDD</td>
<td>62</td>
<td>68%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>High antibody titer and negative MDD</td>
<td>40</td>
<td>93%</td>
</tr>
</tbody>
</table>

Abbreviations: AB, antibody; EICNHL, European Intergroup for Childhood non-Hodgkin Lymphoma; HR, Hazard Ratio; MDD, minimal disseminated disease detected by PCR against the fusion transcript on blood and/or bone marrow at diagnosis; MRD, minimal residual disease detected by PCR against the fusion transcript on blood before the second therapy course; PFS, progression-free survival; SC/LH, small cell and/or lymphohistiocytic component.

### TABLE 3 Main reports on relapsed/refractory anaplastic large-cell lymphomas

<table>
<thead>
<tr>
<th>Author Year of publication</th>
<th>Study group</th>
<th>Period of treatment</th>
<th>No. of patients</th>
<th>No. of patients in CCR after relapse according to therapeutic strategy</th>
<th>3-y EFS</th>
<th>3-y OS</th>
<th>Prognostic factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brugieres Ann Onc 2000</td>
<td>SFOP</td>
<td>75-97</td>
<td>41</td>
<td>Chemotherapy alone 11/20 Autologous HSCT 9/15 Allogeneic SCT 0/1</td>
<td>44%</td>
<td>69%</td>
<td>Time to relapse &lt;1 y (EFS: 28%)</td>
</tr>
<tr>
<td>Woessmann JCO 2011</td>
<td>BFM</td>
<td>90-03</td>
<td></td>
<td>Chemotherapy alone 1/6 Autologous HSCT 21/39 Allogeneic HSCT 11/16</td>
<td>57%</td>
<td></td>
<td>Progression during treatment CD3 positivity</td>
</tr>
<tr>
<td>Mori BJH 2005</td>
<td>Japan</td>
<td>89-03</td>
<td>26</td>
<td>Chemotherapy alone 6/10 Autologous HSCT 3/8 Allogeneic HSCT 6/6</td>
<td>51%</td>
<td>61%</td>
<td>None</td>
</tr>
<tr>
<td>Ruf 2015 (abstract)</td>
<td>EICNHL</td>
<td>2004-</td>
<td></td>
<td>Risk adapted strategy Vinblastine 21 Autologous HSCT 31 Allogeneic HSCT 45</td>
<td>59%</td>
<td>78%</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: CCR, continuous complete remission; EICNHL, European Intergroup for Childhood non-Hodgkin Lymphoma; HSCT, hematopoietic stem cell transplantation.
adults following failure of at least 1 multiagent chemotherapy protocol. An update of the pivotal study provided 4-year follow-up of the patients included in the phase 2 study, the median progression-free survival (PFS) was 20 months (25.5 m for ALK+ ALCL) and 4-y OS was 64%. The median PFS for the patients who achieved a CR and did not receive a posttreatment HSCT (n = 21) was 37.7 months and the median PFS was not reached for the patients who achieved a CR and received a subsequent HSCT (n = 15).9

Several trials are on-going in children and adults to evaluate the role of this drug in combination with conventional chemotherapy or with another targeted therapy for front-line treatment in adults and children.

7.2 | Crizotinib, an ALK- and multikinase inhibitor

Crizotinib is an orally available anti-ALK/MEK inhibitor that has been shown to induce high response rates in relapsed/refractory ALK+ ALCL: CR in 6/8 ALCL patients included in a pediatric phase 1 trial and in all 9 ALCL patients treated with crizotinib in a retrospective report in adults.2 Only few progressions have been described for ALCL during crizotinib treatment so far, all occurring within 2 to 5 months of treatment initiation.

Even though it induces responses in most cases, crizotinib has not yet proven curative since abrupt relapses following crizotinib discontinuation have been described,10 and no successful reported case of continuous CR after discontinuation of treatment has been reported. Thus, crizotinib is currently used to induce second remission in relapsed/refractory ALK+ ALCL patients before allogeneic or autologous HSCT or as life-long therapy.

7.3 | Ceritinib, a second generation ALK inhibitor

In the pediatric and adult phase 1 trials with ceritinib, a second-generation potent ALK inhibitor, a very high response rate has also been observed in ALK+ ALCL.11 After a dose-escalation of ceritinib, an expansion phase is ongoing in children/adolescents. However, similar to crizotinib, no successful discontinuation has been reported so far, and thus, ceritinib is also mostly used to induce remission in relapsed/refractory ALK+ ALCL patients before allogeneic HSCT.

7.4 | Anti-PD1 immunotherapy

Multiple data indicates that the immune system plays a major role in the control of ALK+ ALCL. Antibodies against ALK and cytotoxic T cell and CD4 T-helper responses to ALK have been detected in patients with ALK+ ALCL both at diagnosis and during remission with a significant inverse correlation between ALK-antibody titers and the incidence of relapses. Moreover, vaccination using trunked cDNA ALK has been reported to induce long-lasting protection from lymphoma growth in mice models. It has also been shown that ALK+ ALCL cells strongly express the immunosuppressive cell-surface protein PD-L1 (B7-H1) which can be detected by immunostaining. All patient tissue samples reported so far showed a strong PD-L1 expression.12 PD-L1 expression is induced by the chimeric NPM1/ALK tyrosine kinase, by activating STAT3, confirming a unique function for NPM/ALK as a promoter of immune evasion by inducing PD-L1. This provides a solid rationale to test PD1 inhibitors in ALCL.2

Two cases of a dramatic and durable response with PD1 inhibitors in patients with a refractory ALK+ ALCL after allograft13 and in an ALK-negative ALCL have been already reported.

The role of these new therapies in the frontline treatment of ALCL still has to be assessed. Given the rarity of this lymphoma and the good outcome obtained with conventional treatment, this evaluation requires a large worldwide collaboration and raises methodological and financial issues which have hampered the development of these new drugs in this indication so far.

7.5 | Non-anaplastic peripheral T-cell lymphoma

Peripheral T-cell lymphoma is an heterogeneous group of disease accounting for less than 2% of all childhood NHL. Among the 29 entities described in the 2016 revised WHO classification,1 only a few have been described in children and adolescents.

7.6 | Diagnosis

Diagnosis of non-anaplastic PTCL in children and adolescents is challenging given its low incidence, changes in classification over time and the heterogeneity of this entity. Indeed, on the 69 cases diagnosed as non-ALCL PTCL by the BFM group between 1986 and 2012, only 38 were confirmed as PTCL after histologic review.14 Several cases were reclassified as ALCL in its small cell variant subtype, Hodgkin disease or autoimmune lymphoproliferative syndrome.

In the retrospective analysis of pediatric experience published so far, the incidence of the different subtypes varied a lot among the different study groups, underlining the interest of a review at a multinational level. The most common subtype was PTCL not otherwise specified (NOS) accounting for 30% to 68% of the pediatric cases, followed by extra-nodal NK/T-cell lymphoma accounting for 15% to 47% of the cases and subcutaneous panniculitis like lymphoma (5% to 15% of the cases). The incidence of other subtypes varied from a series to another probably because of differences in the registration process of these rare entities in pediatric lymphoma databases.

Another striking feature is the large proportion of pediatric PTCL with an associated predisposing condition or a previous malignancy (25% of all cases in the largest series from EICNHL/IBFM group).15

In adults, PTCL NOS is an heterogeneous group of diseases characterized by the proliferation of malignant cells mostly CD4+/CD8– with frequent loss of CD5 and CD7 expression and clonal rearrangement of TCR. GEB analysis led to the identification of 3 subtypes characterized by the expression of GATA3, TBX21, and cytotoxic genes.1 Data on pediatric PTCL are not mature enough to know whether all these subtypes can be seen in young patients. The outcome of PTCL NOS in children and adolescents is clearly better than in adults with survival around 56% to 61% in pediatric series published so far but comparison between pediatric and adult PTCL NOS has not been performed so far and it may be quite different entities.

Besides PTCL NOS, several subtypes of mature T- and NK-cell lymphomas are associated with EBV. The most common is the extranodal NK/T-cell lymphoma, nasal type (ENTKLN), accounting for
Abbreviation: NA, not available.

15% to 40% of all PTCL reported in children so far. The incidence seems to be higher in Asia than in European countries.

In addition to ENTKL, the 2016 revision of the WHO classification individualizes 2 subtypes of EBV-associated T- and NK-cell lymphoproliferative disorders in children: chronic active EBV infection with a broad range of manifestations from indolent chronic lymphoproliferation to a systemic EBV+ T-cell lymphoma of childhood, characterized by a fulminant course often associated with hemophagocytic syndrome.1

The diagnosis spectrum of childhood PTCL NOS is different from adults with quite reduced after exclusion of the more frequent entities: mainly anaplastic large adults and quite reduced after exclusion of the more frequent entities:

- careful exclusion of these other entities based on a study of T-cell lymphoproliferation EBV+/
- delta T-cell rearrangement in cases of B-cell lymphoproliferation EBV+/
- and NK-cell lymphoma of childhood, characterized with homologous therapy courses according to protocols designed for B-cell lymphomas seems to be as efficient as prolonged semi-continuous chemotherapy according to regimen. The role of allogeneic HSCT in first cr is still unclear and many new drugs are being tested in adults and may be available in children for relapsed/refractory PTCL.

Given the rarity of these entities in children, only worldwide collaboration with, extensive biological and pathological characterization, homogeneous therapeutic strategies among the different study groups and prospective registration of all cases in specific databases for rare lymphomas will allow us to collect enough data to design optimal treatment for these cases, such a project is on-going in the rare lymphoma subgroup of EICNHL.

### CONFLICT OF INTEREST

The authors have no competing interest.

### REFERENCES


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Molecular genetics of aggressive B-cell lymphoma

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1 | INTRODUCTION

Aggressive B-cell non-Hodgkin lymphomas (B-NHLs) comprise a spectrum of genetically, phenotypically, and clinically distinct malignancies, which, according to the updated 2016 WHO classification, include 7 major subtypes comprising 16 disease entities. In particular, all these tumors derive from mature B cells that have transited through the germinal center (GC), but display heterogeneous phenotypes that reflect both their derivation from distinct phases of B-cell physiology during the GC reaction, and the occurrence of genetic lesions that lead to the alteration of distinct cellular pathways. This chapter will focus on the cell of origin and pathogenesis of Burkitt lymphoma (BL) and diffuse large B-cell lymphoma (DLBCL), which together account for approximately 80% of aggressive B-NHL.

1.1 | Cell of origin

Most B-NHLs, including all aggressive B-NHL, are derived from GC, the histological structure dedicated to the generation and selection of B cells that produce high affinity antibodies. Germinal centers are made of a dark zone (DZ), including highly proliferating B cells that undergo Immunoglobulin Somatic Hypermutation (SHM), and a light zone (LZ) where B cells are selected based on their affinity for the antigen and perform class-switch recombination (CSR). Based on their gene expression profiles, BLs appear to derive from DZ B cells, whereas follicular lymphoma and DLBCL correspond to B cells arrested by transformation events that occur at various stages of the GC-transit. In particular, follicular lymphoma and the germinal center B-cell (GCB)-like subtype of DLBCL resemble LZ B cells, while activated B-cell (ABC)-like DLBCLs seem to derive from GC cells arrested during the early stages of post-GC plasma-cell differentiation (plasmablasts). Primary mediastinal B-cell lymphoma represents a distinct subtype that originates from post-GC thymic B cells in the mediastinum.

1.2 | Mechanisms of genetic lesions in the GC

Analogous to most tumors, the coding genomes of B-NHL carry genetic aberrations including amplifications, deletions, and nonsynonymous point mutations associated with gain- or loss-of-function consequences. In addition, B-NHLs display chromosomal translocations and aberrant somatic hypermutation, both of which are dependent on immunoglobulin remodeling mechanisms including V(D)J recombination, SHM, and CSR.

1.2.1 | B-cell non-Hodgkin lymphoma–associated translocations

B-NHL-associated translocations do not generate fusion genes and chimeric proteins, typical of acute leukemias, but rather lead to the juxtaposition of heterologous promoters and/or enhancers to an oncogene, leading to its dysregulated or ectopic expression. Although the immunoglobulin loci represent the most frequently targeted sequences, they can be replaced by a variety of regulatory regions in so-called promiscuous translocations (eg, translocations involving BCL6). The mechanism involved in these translocations has not been clarified yet. B-NHL-associated translocations can be broadly divided into 3 groups corresponding to distinct mechanisms of generation: translocations derived from mistakes of the recombination-activating gene–mediated V(D)J recombination process (eg, the t(14;18) translocations involving IGH and BCL2 in follicular lymphoma); translocations mediated by errors in the activation-induced cytidine deaminase (AID)-dependent CSR process (immunoglobulin-MYC translocations in sporadic Burkitt lymphoma [sBL]); translocations occurring as by-products of the AID-mediated SHM mechanism, which also generates DNA breaks (immunoglobulin-MYC translocations in endemic Burkitt lymphoma [eBL]).

1.2.2 | Aberrant somatic hypermutation

Aberrant somatic hypermutation is uniquely associated with B-NHL, in particular with DLBCL, and appears to derive from a malfunction in the physiological SHM process, which leads to the aberrant targeting of multiple nonimmunoglobulin loci. In GC B cells, SHM introduces mutations only in the rearranged immunoglobulin variable (igV) genes, as well as in the 5′ region of a few other genes, including BCL6. Conversely, multiple mutational events targeting >10% of the transcribed genes can be found in over half of DLBCL cases and, at
lower frequencies, in few other lymphoma types. Mutations may affect untranslated as well as coding regions, thus possibly altering the regulation and/or the function of the target genes. In the case of MYC, a significant number of amino acid substitutions have proven to carry functional consequences in activating its oncogenic potential, but a comprehensive understanding of the functional consequences of aberrant somatic hypermutation is still lacking.

2 | BURKITT LYMPHOMA

Burkitt lymphomas include sBL, eBL, and HIV-associated (HIV-BL) forms, all of which deriving from GC DZ B cells, as suggested by the presence of mutated IgV sequences and transcriptional signature. All eBL and one third of sBL and HIV-BL cases are infected by the Epstein-Barr virus, although the pathogenetic role of this virus remains controversial. The genome of all BL is characterized by the invariable presence of chromosomal translocations involving the MYC oncogene and one of the immunoglobulin loci. The common consequence of these translocations is the ectopic and constitutive expression of the MYC proto-oncogene due to escape from the BCL6-mediated transcriptional repression that normally prevents MYC expression in DZ B cells. MYC is a nuclear phosphoprotein that functions as a sequence-specific DNA-binding transcriptional regulator to control proliferation, cell growth, differentiation, and apoptosis, all of which are implicated in carcinogenesis. In addition, MYC controls DNA replication independently of its transcriptional activity, a property that may promote genomic instability by inducing replication stress, a function particularly dangerous when activated in highly proliferative DZ B cells.

Approximately 70% of BL cases display either mutations of the TCF3 transcription factor—which seem to enable escape from its negative regulator ID3—or inactivating mutations in ID3 that prevent its modulatory function on TCF3. The resulting dysregulated activity of TCF3 appears to promote antigen-independent "tonic" B cell receptor (BCR) signaling and, as a consequence, to activate the PI3K pathway, which is a key component of tonic BCR signaling and is not active in normal DZ B cells. In addition, TCF3 affects cell proliferation by transactivation of CCND3, a D-type cyclin that regulates the G1-S phase transition and is necessary for GC formation and expansion. Interestingly, mutations that increase CCND3 protein stability are also found in approximately 40% of sBL.

The relevance of the combined MYC and PI3K dysregulation in DZ B cells is supported by the fact that transgenic mice engineered to activate both pathways in mature B cells develop lymphomas faithfully resembling human BL, including the acquisition of CCND3 mutations. However, these tumors are clonal, indicating that additional lesions are necessary for lymphomagenesis. Accordingly, one-third of human BL cases display inactivating mutations of several tumor suppressors including TP53, PTEN and CDKN2A. The Gα13-dependent pathway that is involved in modulating GC B-cell migration and confinement, appears also to be frequently disrupted in BL similarly to GCB-DLBCL (discussed in the Section 4).

3 | DIFFUSE LARGE B-CELL LYMPHOMA

Diffuse large B-cell lymphomas include cases that arise de novo, as well as cases that derive from the clinical evolution of various, less aggressive B-NHLs, such as follicular lymphoma and chronic lymphocytic leukemia. Gene expression profile analyses have identified 2 major subtypes of DLBCL: GCB-DLBCL, deriving from GC LZ B cells, and ABC-DLBCL originating from a later stage of GC differentiation when B cells are committed to plasmablastic differentiation. These DLBCL subtypes display subtype-specific genetic aberrations, as well as common ones, including those involving chromatin modifiers, BCL6 dysregulation, and immune escape.

3.1 | Dysregulation of the BCL6 proto-oncogene

Dysregulation of the BCL6 proto-oncogene plays a critical role in lymphomagenesis by enforcing the proliferative phenotype of GC B cells, by suppressing proper DNA damage responses, and by blocking terminal differentiation. The tumorigenic properties of dysregulated BCL6 in the pathogenesis of DLBCL have been confirmed in mouse models. The BCL6 locus is targeted by chromosomal translocations that place the intact protein coding sequence of BCL6 downstream of heterologous regulatory regions provided by the partner chromosomes. These regions comprise the IGH locus, as well as the promoters of a variety of genes, which are characterized by a broader spectrum of expression throughout the B-cell development including the post-GC stages. Thus, this "promoter substitution" mechanism prevents the down regulation of BCL6 expression that is normally associated with post-GC differentiation. In addition, the binding of BCL6 or IRF4 to the BCL6 promoter can be impaired by mutations that contribute to dysregulate BCL6 expression by interfering with its auto-regulatory circuit, or the CD40-induced, IRF4-mediated repression. Overall, genetic alterations that affect the BCL6 locus and lead to its dysregulated expression are common events in DLBCL (approximately 30%). Dysregulated BCL6 expression and/or activity is also sustained by indirect mechanisms, including loss-of-function alterations in the acetyl-transferases CREBBP and EP300, which are involved in the acetylation-mediated inactivation of BCL6, gain-of-function mutations in its positive regulator MEF2B, and inactivation of FBXO11, a specific adaptor for BCL6 ubiquitylation and degradation.

3.2 | Alterations in genes encoding chromatin modifiers

Alterations in genes encoding chromatin modifiers are common in DLBCL, independently of the subtype. They are represented by genetic inactivation of the acetyl-transferases EP300 and/or CREBBP in about 40% of DLBCL and of the histone methyltransferase MLL2 (approximately 30% of cases). These alterations consistently target only 1 allele whereas the other remains intact, suggesting a haploinsufficient tumor suppressor role of these genes, as recently shown in mouse models. These lesions favor lymphomagenesis by reprogramming the cancer epigenome, but their precise consequences on gene expression remain to be elucidated. Nonetheless, inactivation of CREBBP and/or EP300 has been shown to hamper acetylation-
mediated activation of the TP53 tumor suppressor and inactivation of the BCL6 proto-oncogene, thus contributing to lymphomagenesis. Of note, these lesions may occur early during lymphomagenesis as suggested by their presence in common cell precursors before their divergent progression toward DLBCL or follicular lymphoma.

### 3.3 | Immune escape

Immune escape may be caused in over 60% of DLBCL cases due to lacking cell-surface expression of the Major Histocompatibility Complex (MHC) class-I complex, which is necessary for the recognition by cytotoxic T cells. This defect is due to inactivation of the gene encoding β-2 Microglobulin (B2M), inactivation of the genes encoding Human Leukocyte Antigen (HLA)-A, HLA-B and HLA-C and defective transport of B2M or HLA-I molecules on the cell surface by presently unknown mechanisms. Defective HLA-I cell surface expression is often coselected with genetic inactivation or defective transport of the CD58 molecule, which is involved in the immune surveillance by natural killer cells. Thus, in most DLBCL cases, tumor cells appear to be invisible to both cytotoxic T cells– and natural killer cell–mediated immune recognition. Genetic-based escape from immune surveillance appears to be relatively specific for DLBCL among B-NHLs, since the same aberrations are rare in other lymphoma types. Interestingly, loss of B2M and therefore inability to express HLA-I on the cell surface, is one of the events recurrently associated with the progression of follicular lymphoma toward DLBCL.

### 4 | GERMINAL CENTER B CELL–DLBCL

Chromosomal translocations involving MYC and BCL2, analogous to the ones that characterize BL and follicular lymphoma, are detected in approximately 10% and approximately 40% of GCB-DLBCL, respectively. The co-occurrence of lesions affecting MYC and BCL2 genes is associated with poor prognosis. The following 3 programs appear to be affected with some specificity in GCB-DLBCL.

#### 4.1 | Mutations of the EZH2 gene

Mutations of the EZH2 gene are found in about 20% of GCB-DLBCL and result in a gain-of-function phenotype. While the EZH2 gene encodes a methyltransferase involved in the transcriptional repression of CDKN1A, PRDM1, and IRF4, suggesting a role in promoting proliferation and impairing differentiation, GCB-DLBCL-associated mutant proteins appear to be more efficient in converting mono- or di-methylated H3K27 to tri-methylated H3K27 (H3K27me3). Mice engineered to express the lymphoma-associated mutant protein develop GC hyperplasia, validating a contribution of EZH2 mutations toward lymphomagenesis. Indeed, lymphoma development was induced when the mutant EZH2 protein was expressed in the presence of dysregulated BCL2 expression in mouse B cells, consistent with the co-occurrence of these genetic lesions in GCB-DLBCL.

#### 4.2 | Altered GC B-cell migration

Several chemokines and their receptors, including S1PR2 and P2RY8, are involved in modulating the cell migrations occurring in the GC. Approximately 30% of GCB-DLBCL and a fraction of BLs have been shown to carry mutations (S1PR2, GNA13, ARHGEF1, and P2RY8 genes) inactivating the Ga13-dependent pathway, which control the confinement of B cells within the GC. Loss of Ga13-mediated signaling in mouse B cells led to disruption of the GC architecture and release of GC B cells in the lymph and blood circulation, thus providing an explanation for the ability of GCB-DLBCL cells to leave their tissue of origin and travel to distant sites.

### 4.3 | Mutations altering the tumor microenvironment

The HVEM receptor (TNFRSF14) gene is mutationally inactivated in GCB-DLBCL. HVEM inactivation in mice drives the development of GC lymphomas and induces a tumor-supportive microenvironment marked by exacerbated lymphoid stroma activation and increased recruitment of T follicular helper cells. These changes result from the disruption of inhibitory cell-cell interactions between the HVEM and BTLA (B and T lymphocyte attenuator) receptors.

### 5 | ACTIVATED B CELL–DLBCL

#### 5.1 | Constitutive NF-κB signaling

A variety of genetic alterations converge on the activation of the NF-κB transcription complex in ABC-DLBCL. In about 20% of cases, mutations in the CD79A/B genes that encode components of the BCR complex contribute to chronic BCR signaling by preventing endocytosis of the receptor and/or by blunting the activity of src family tyrosine kinase LYN, a negative regulator of the pathway. Activating mutations targeting the CARD11 gene in approximately 10% of ABC-DLBCL lead to hyper-responsiveness of the signal transduction complex CARD11-BCL10-MALT1 to activate NF-κB independently of upstream signals, including BCR. About 35% of cases carry mutations of the MYD88 gene, encoding an adaptor protein that mediates the TLR- and IL1R-mediated activation of IL1R-associated kinase 2 (IRAK2) and NF-κB. These mutations promote cell survival by altering the MYD88 function to gain the ability of spontaneously assembling a complex containing IRAK1 and IRAK4, which leads to activation of NF-κB. In addition, MYD88 mutations induce transcriptional signatures associated with JAK-STAT3 and type-I interferon signaling, suggesting that alterations of MYD88 affects multiple pathways. The TNFAIP3 gene, encoding A20, a key negative modulator of the NF-κB pathway, is genetically inactivated in 30% of ABC-DLBCL, thus preventing termination of NF-κB responses. Activated B cell–DLBCLs are dependent upon NF-κB activation as demonstrated by their death upon NF-κB inhibition in vitro.

#### 5.2 | Block in terminal differentiation

Two mechanisms that are largely mutually exclusive converge on the negative regulation of the plasma-cell master regulator PRDM1/BLIMP1. Bi-allelic inactivation of the PRDM1 gene is observed in about 30% of ABC-DLBCL cases. Alternatively, BCL6 dysregulation by chromosomal translocations, that are more frequent in ABC-DLBCL
than in GCB-DLBCL, also leads to constitutive repression of PRDM1 by BCL6. This repression of PRDM1 may be even more common in DLBCL cases considering the variety of genetic lesions that have been shown to affect BCL6 expression and activity.7 Finally, approximately 25% of ABC-DLBCL display gain-of-function alterations of SPIB, a transcription factor that can form a complex with IRF4 and contributes to PRDM1 inactivation by directly repressing its transcription. PRDM1 genetic inactivation in GC B cells in mice leads to ABC-DLBCL development. These tumors display constitutive NF-κB activation, demonstrating the requirement of both pathways for ABC-DLBCL pathogenesis.

CONFLICT OF INTEREST

The author have no competing interest.

REFERENCES


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Pathology and classification of aggressive mature B-cell lymphomas

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1 | INTRODUCTION

The aggressive mature B-cell lymphomas are a heterogeneous group of tumors with different biological and pathological characteristics that are associated with a broad spectrum of clinical manifestations. Some of the subtypes are relatively common whereas others are less frequent and occur in particular subsets of patients. The response to therapy and the outcome are also diverse among entities. Although current therapies may cure large proportion of patients, still around 30% of them develop an incurable disease. The recent genetic and molecular studies are increasing the understanding of the mechanisms underlying the clinical and biological diversity of these tumors and are providing valuable information for new therapeutic opportunities.

The recent update of the World Health Organization (WHO) classification of lymphoid neoplasms includes different entities of aggressive mature B-cell lymphomas with well-defined diagnostic criteria (Table 1). The most common subtype accounting for approximately 80% of all these neoplasms is diffuse large B-cell lymphoma, not otherwise specified (DLBCL, NOS), a category that includes tumors, which cannot be classified in any of the other more specific entities. The other diseases are less common but have distinctive features. T-cell/histiocyte-rich large B-cell lymphoma (THRLBCL) is a subtype in which the tumor cells are overrun by an exuberant stromal response. Some large B-cell lymphomas (LBCLs) are originated in particular topographic sites suggesting their relationship to specific cell subsets of these sites or the influence of the microenvironment in their pathogenesis. A group of LBCL are associated with Epstein-Barr virus (EBV) infection and occur in patients that may have a certain immunological impairment in controlling the viral infection. Most LBCL have a mature B-cell phenotype, but some tumors acquire a terminal B-cell differentiation phenotype loosing mature B-cell markers and expressing proteins related to plasma cell differentiation. Some of these tumors are associated with HHV8 and/or EBV infection. Burkitt lymphoma (BL) is a well-defined aggressive neoplasm that can be cured in most patients but certain aspects regarding the presence of MYC translocation in all cases still remain controversial. Finally, the updated WHO classification has revised the concept of aggressive B-cell lymphomas with features intermediate between DLBCL and BL and tumors with MYC and BCL2 and/or BCL6 translocations. This review will address the pathology of all these entities emphasizing the new aspects included in the updated WHO classification (Table 1).

1.1 Diffuse large B-cell lymphoma, NOS

Diffuse large B-cell lymphoma, NOS is clinically and biologically very heterogeneous. One of the major advances understanding its diversity was the recognition of 2 molecular subtypes based on their gene expression profiling (GEP). These 2 subtypes are related to a different cell of origin either in normal germinal center B-cells (GCB) or in activated B-cells (ABC). In addition to the GEP, these 2 molecular subtypes differ in the activation of different molecular pathways, profile of chromosomal alterations, and somatic mutations. These biological differences translate into different outcome of the patients with most of the studies showing worse prognosis for ABC than GCB-DLBCL. Germinal center B-cell tumors rely preferentially on the activation of the PI3K pathway and BCL6 overexpression whereas ABC tumors have a constitutive activation of the nuclear factor-κB pathway through different mechanisms. Genetic alterations in GCB include BCL2 and BCL6 rearrangements and mutations in histone modifiers (EZH2, KMT2D, and CREBB) whereas ABC tumors have frequent mutations in MYD88 and CD79a. The distinctive molecular pathogenesis of these tumors is expected to lead to more precise therapeutic strategies targeting the specific molecular alterations. For these reasons, the recognition of these 2 molecular subtypes by the pathologists is now recommended in the clinical practice. The considered gold standard for this molecular classification is the differential GEP detected by microarrays. However, this approach requires frozen tissues and it is not currently used in the clinics. The initial alternative approach to identify these molecular subtypes in routine practice has
TABLE 1  Aggressive mature B-cell lymphomas in the updated 2016 WHO classification

<table>
<thead>
<tr>
<th>Classification</th>
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<tbody>
<tr>
<td>Diffuse large B-cell lymphoma, not otherwise specified (NOS)</td>
</tr>
<tr>
<td>Germinal center B-cell type</td>
</tr>
<tr>
<td>Activated B-cell type</td>
</tr>
<tr>
<td>T-cell/histiocyte–rich large B-cell lymphoma</td>
</tr>
<tr>
<td>DLBCL, topographic site related</td>
</tr>
<tr>
<td>Primary mediastinal (thymic) large B-cell lymphoma</td>
</tr>
<tr>
<td>Primary DLBCL of the CNS</td>
</tr>
<tr>
<td>Primary cutaneous DLBCL, leg type</td>
</tr>
<tr>
<td>Intravascular large B-cell lymphoma</td>
</tr>
<tr>
<td>DLBCL, EBV-related</td>
</tr>
<tr>
<td>EBV-positive DLBCL, NOS</td>
</tr>
<tr>
<td>EBV-associated with chronic inflammation</td>
</tr>
<tr>
<td>Lymphomatoid granulomatosis</td>
</tr>
<tr>
<td>LBCL with terminal B-cell differentiation</td>
</tr>
<tr>
<td>Plasmablastic lymphoma</td>
</tr>
<tr>
<td>ALK-positive large B-cell lymphoma</td>
</tr>
<tr>
<td>Primary effusion lymphoma</td>
</tr>
<tr>
<td>HHV8+ DLBCL, NOS</td>
</tr>
<tr>
<td>Burkitt lymphoma</td>
</tr>
<tr>
<td>Burkitt-like lymphoma with 11q aberrations</td>
</tr>
<tr>
<td>High grade B-cell lymphoma</td>
</tr>
<tr>
<td>High-grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements</td>
</tr>
<tr>
<td>High-grade B-cell lymphoma, NOS</td>
</tr>
</tbody>
</table>

Abbreviations: ALK, anaplastic lymphoma kinase; CNS, central nervous system; DLBCL, diffuse large B-cell lymphoma; EBV, Epstein-Barr virus; NOS, not otherwise specified.

been the use of a small number of distinctive biomarkers by immuno-histochemistry (IHC). Different algorithms have been proposed with relative good concordance with GEP classification in around 80–90% of the cases. However, they have also limitations related to standardization and reproducibility among pathologists. In addition, they may lack precision to identify the ABC subgroup since most IHC algorithms call for a dual classification between GCB and non-GCB tumors. However, there is a small subgroup of cases (10%) that cannot be classified by GEP (unclassified) and IHC algorithms force their inclusion in one of the 2 subtypes. A recent developed assay based on GEP of 20 genes (Lymph2Cx) based on Nanostring technology reliably identifies the 2 molecular DLBCL subtypes on RNA extracted from formalin-fixed and paraffin-embedded tissues with excellent concordant result when compared to the microarrays GEP. The assay is also highly reproducible among different laboratories and confirms the different clinical outcome of the 2 subtypes. The WHO classification recommends the identification of the cell of origin of all DLBCL, NOS and considers the IHC acceptable. However, gene expression-based assays may be a promising more precise methodology.

1.2 T-cell/histiocyte–rich large B-cell lymphoma

T-cell/histiocyte–rich large B-cell lymphoma is an aggressive and relatively uncommon lymphoma histologically characterized by scattered, large, atypical B cells embedded in a microenvironment with abundant T cells and histiocytes. Patients are frequently diagnosed at higher clinical stages with liver, spleen, and bone marrow involvement. The aggressive behavior of these tumors has been attributed to the advanced stage and high International Prognostic Index (IPI) that the patients usually have at diagnosis. Some cases with identical morphology and phenotype may arise from nodular lymphocyte predominant Hodgkin lymphoma (NLPFL) and are considered as a THRLBCL-like transformation from NLPHL. The term “like” is used due to still some uncertainties regarding the relationship between de novo THRLBCL and transformed cases. However, recent studies have shown similarities in the GEP and genetic alterations of the tumor cells in THRLBCL and NLPFL supporting the idea of a closer relationship.

1.3 DLBCL, topographic site related

Several LBCLs are classified mainly, but not exclusively, based on the topographic site of their origin (Table 1). Although these entities do not have a specific phenotype or molecular hallmark, they have particular features.

1.3.1 Primary mediastinal (thymic) LBCL

Primary mediastinal large B-cell lymphoma usually presents in young females with a large mediastinal mass that may infiltrate surrounding structures. The tumor may affect regional lymph nodes but when it disseminates outside of the thorax, it tends to involve solid organs. Histologically, the tumor cells may have an abundant clear cytoplasm and fibroblasts are common. Thymic remnants may be seen, as the tumor seems to originate from mature thymic B cells. Phenotypically, the tumor cells may express PDL1, PDL2, CD30, and CD23, and are usually negative for Ig and HLA class I and II. Gene expression profiling has identified a specific signature that may be useful to differentiate primary mediastinal large B-cell lymphoma from DLBCL, NOS involving the mediastinum or to recognize these tumors in locations outside of the thorax. The genetic profile differs from DLBCL, NOS with frequent translocations inactivating class II major histocompatibility complex transactivator (CIITA), activation of the nuclear factor–κB, and JAK/STAT pathways due to several genetic alterations in regulatory genes such as TNFAIP3 and SOCS1, and PTPN1, respectively.

1.3.2 Other lymphomas related to specific topographic sites

Other large B-cell entities related to specific sites are Primary DLBCL of the central nervous system (CNS), Primary cutaneous DLBCL, leg type, and intravascular LBCL. All these tumors are uncommon. The Primary DLBCL of the CNS should be distinguished from other brain LBCL occurring in the context of immunodeficiency. Primary DLBCL of the CNS has frequent deletions and negative expression of the HLA genes and mutations of MYD88, CARD11, and CD79, which may have therapeutic implications. A certain relationship with lymphomas of the testis exists since rare cases with extracranial dissemination may involve the testes, and vice versa, some lymphomas of the testes may relapse in the brain. Primary cutaneous DLBCL, leg type is an aggressive tumor presenting in the skin of the lower extremities although it may also occur in other cutaneous locations. It has an ABC phenotype and strong expression of BCL2. Intravascular LBCL is
very aggressive, usually with systemic intravascular dissemination at diagnosis. Some improvement in the outcome has been reported with immunochemo-therapy. Random skin or transbronchial biopsies, even when these sites appear unaffected, have been proposed for an early diagnosis and treatment of this tumor.

### 1.4 DLBCL, EBV related

A group of LBCL is associated with EBV infection and has different clinical and pathological features. They occur in apparently immuno-deficient patients but appear to have predisposing conditions, which decrease EBV immune surveillance. The most common is the EBV-positive DLBCL, NOS. The term NOS refers to the fact that there are other LBCL EBV positive with distinct clinical and pathologic features. This entity was previously named EBV-positive DLBCL of “the elderly” because of the higher frequency in patients older than 50 years. However, recent studies have recognized this tumor in younger patients. Histologically, the large atypical B cells may have Reed-Sternberg-like features and are accompanied by a variable amount of inflammatory cells including CD8-positive T cells. Areas of necrosis are frequent. Cases in young patients resemble THCRLBCL with abundant T cells. The histological features may suggest the diagnosis and trigger the study of EBV by in situ hybridization. The virus must be present in most if not all tumor cells and usually express latency II or III antigens. The prognosis is significantly worse in elderly than young patients. Other LBCL EBV positive are DLBCL associated with chronic inflammation and lymphomatoid granulomatosis. The first occur in the context of long lasting inflammation, particularly in confined sites, such pleura (pyothorax), bone or joints. Lymphomatoid granulomatosis is an angiocentric and angiodestructive lymphoproliferative disease that involves extranodal sites. The lesion is composed of a variable number of EBV-infected large atypical cells intermingled with reactive T cells. The clinical behavior has been related to the proportion of tumor cells.

### 1.5 LBCL with terminal B-cell differentiation

Large B-cell lymphoma with terminal B-cell differentiation is a heterogeneous group of aggressive lymphomas characterized by a immunoblastic or plasmablastic morphology and the acquisition of a plasma cell phenotype with downregulation of mature B-cell markers (CD20 and PAX5) and expression of plasma cell antigens (BLIMP1, CD38, and CD138) (Table 1).

Plasmablastic lymphoma mainly presents in extranodal sites, particularly of the head and neck, but the disease is usually disseminated at diagnosis. Some cases have bone involvement and features overlapping with plasma cell myeloma. The differential diagnosis should consider the clinical context of plasmablastic lymphoma in immunodeficient patients and EBV infection. Epstein-Barr virus is positive with latency I in approximately 70% of the cases. MYC translocations are detected in 50%, usually with an IG partner. The clinical course is very aggressive with a median overall survival of 6 to 11 months.

HHV8 induces a spectrum of lymphoproliferative diseases with 2 subtypes of lymphomas, Primary effusion lymphoma (PEL) and HHV8 + DLBCL, NOS. PEL occurs mainly in cavities without a tumor mass. Some patients subsequently develop a solid tumor with similar pathologic features, and finally, rare cases initially present as solid tumor masses indistinguishable from PEL and have been termed extracavitary PEL. Most cases are EBV positive with latency I although some cases are negative, mainly in the elderly and in areas of endemic HHV8. HHV8+ DLBCL, NOS has similar morphology and phenotype but is EBV negative an expresses IgM, lambda. IGHV are unmutated. These tumors usually arise in HHV8+ multicentric Castleman disease but also in the absence of this disease in immunodeficient patients. Anaplastic lymphoma kinase-positive LBCL is a very aggressive tumor occurring in immunocompetent young adults. The tumors present with generalized lymphadenopathy and advanced stage. The plasmablastic phenotype seems induced by the anaplastic lymphoma kinase activation due to translocations mainly with Clathrin (CLTC) although other partners are also found. STAT3 seems an important downstream target.

### 1.6 Burkitt lymphoma

Burkitt lymphoma is a well-defined entity genetically characterized by MYC rearrangements. In the last years, Next generation sequencing (NGS) have revealed the profile of somatic mutations with frequent mutations in TCF3 and I3D that are very uncommon in DLBCL. CCND3 is also mutated in 30% of the tumors. An unresolved issue is the existence of true BL without MYC translocation. Recent studies have identified cases with similar morphology and phenotype but negative for MYC rearrangements that have 11q alterations with proximal gains and telomeric losses. These cases have been named Burkitt-like lymphoma with 11q aberrations and have more frequent nodal presentation and complex karyotypes. The information on these cases is still limited.

### 1.7 High-grade B-cell lymphoma

The updated 2016 WHO classification has considered high-grade B-cell lymphomas (HGBLs) as a provisional category that emphasizes the relevance of genetic information for its recognition. All LBCL with MYC and BCL2 and/or BCL6 rearrangements are included in the category of HGBL with MYC and BCL2 and/or BCL6 rearrangements. These cases have been also named "double hit" HGBL (HGBL-DH). The relevant criteria for the diagnosis are the genetic alterations independently of the morphology of the tumor that may be DLBCL, plasmablastic, or with features intermediate between DLBCL and BL. The specific morphology should be noted because it may have prognostic impact. Cases with blastoid morphology or with features intermediate between DLBCL and BL without translocations are considered HGBL, NOS. Diffuse large B-cell lymphoma with high expression of MYC and BCL2 protein without genetic alterations have been called "dual-expressors." This dual-expressors is considered an adverse prognostic factor, but these tumors are not included in the HGBL category since the outcome does not seem so adverse, and the biological consequences of having a genetic alteration may also be different.

The expansion of fluorescence in situ hybridization (FISH) studies in aggressive lymphomas is showing that the clinical impact of the DH seems more variable than suggested in the initial studies but the reasons for this diversity are not well known. The biology of HGBL-DH
is complex and not yet well understood.\textsuperscript{12} The presence of MYC rearrangements is the determinant factor, but there are several additional elements that seem to modulate their biological relevance (Table 2).\textsuperscript{12,14} The association with BCL2 translocations usually confers an adverse prognosis, but the role of BCL6 is still controversial.\textsuperscript{14,15} Other modulators of MYC rearrangements are associated with higher levels of MYC expression than non-IG partners, and this may explain the worse prognosis of the former. The MYC and BCL2 protein expression levels may be also different in cases with translocation probably due to additional phenomena such as amplification of the translocated allele, mutations of MYC, or others. The cell context may also be a modifier with DLBCL cases having a better outcome than tumors with blastoid or DLBCL/BL intermediate morphology. The clinical context of the patients seems also to be important since patients with high-risk clinical features have more adverse evolution than patients with low-risk factors.\textsuperscript{15} Therefore, further studies evaluating all these aspects are needed to better understand the significance of this new category. Independently of all these variables, the recognition of HGBL-DH is clinically relevant because most of the tumors have a very aggressive behavior and standard DLBCL treatments are considered insufficient.

The importance of recognizing HCBL-DH challenges the current diagnostic practice of aggressive B-cell lymphomas since the use of FISH in all cases may confer a workload and economic burden difficult to be confronted in most centers. Although no consensus still exists, a selection of cases for FISH analysis based on morphological and phenotypic criteria seems an acceptable compromise.\textsuperscript{1} Virtually, all HGBL-DH with MYC and BCL2 translocations are of the GCB subtype and cases with these rearrangements usually have high protein expression. Therefore, a reasonable strategy would be to perform FISH in all GCB-DLBCL with high MYC and BCL2 protein expression.\textsuperscript{15} In addition, FISH should be performed in cases with blastoid or intermediate DLBCL/BL morphology given the high frequency of the translocations (approximately 50%) in these tumors. This strategy would miss some DH cases with low protein expression, but the clinical significance of both situations is still controversial.\textsuperscript{14,15}

### REFERENCES

The 2016 WHO update highlights the heterogeneity of aggressive perspective, DLBCL has emerged as an extremely diverse disease. (IPI) have cure rates of approximately 50% (Table 1). From a biologic perspective, elderly patients and patients with a high International Prognostic Index (IPI) are not cured (Figure 1). From a clinical perspective, efforts to improve upon CHOP as the standard of care.

Since its introduction in 1976, CHOP has been the backbone of treatment in aggressive lymphomas. Efforts to improve upon CHOP have included shortening the cycle length (14 days versus 21 days), adding more cytotoxic agents, or delivering chemotherapy in an infusional regimen (ie, DA-EPOCH-R). However, a pivotal US intergroup study showed that "more" chemotherapy does not improve survival and only added toxicity, and serial European trials have shown that any benefit from added etoposide or shortening of the treatment cycle disappeared once rituximab was introduced.1 The major advance in diffuse large B-cell lymphoma (DLBCL) came with the addition of rituximab to CHOP, which improved survival by approximately 15% to 20% across age groups, and established R-CHOP as the standard of care.

Despite the overall success of R-CHOP, it is clear that many patient subsets are not cured (Figure 1). From a clinical perspective, elderly patients and patients with a high International Prognostic Index (IPI) have cure rates of approximately 50% (Table 1). From a biologic perspective, DLBCL has emerged as an extremely diverse disease. The 2016 WHO update highlights the heterogeneity of aggressive B-cell lymphomas via the following changes: the requirement for cell-of-origin (COO) testing, the elimination of B-cell lymphoma, unclassifiable (BCLU), and replacement by high-grade lymphomas with shared genetic lesions (ie, dual MYC and BCL2 or BCL6 rearrangements, "double hit lymphoma [DHL]") as a separate entity and the acknowledgement of dual expression of MYC and BCL2 (double expressor lymphomas [DEL]) as an adverse prognostic feature.

With these updates in mind, should the treatment of aggressive B-cell lymphomas be altered? Unfortunately, as the discussion below illustrates, there are many more questions than answers at this time. However, a number of ongoing and emerging trials will hopefully help individualize treatment options in the near future.

1 | INTRODUCTION

The treatment of aggressive B-cell lymphomas is in evolution, largely based on the recognition of major genetic and biologic subtypes harboring distinct pathogenetic lesions. In this review, we will consider current treatment options with the caveat that many trials do not address some of the high-risk subsets with enough power to conclude on definitive approaches.

Before discussing specific biologic subsets of DLBCL, it is worth presenting the results of several recent large-scale, phase III randomized trials. As mentioned above, infusional delivery of chemotherapy, such as DA-EPOCH-R, has been proposed as an improvement over R-CHOP. Several single center and multicenter phase II trials support high-response rates, superior progression-free survival (PFS) and overall survival (OS) compared with historical results with R-CHOP (reviewed in Sehn and Gascoyne3). Based on these promising results, CALGB 50303 was designed to prospectively test R-CHOP vs DA-EPOCH-R in treatment-naive DLBCL. However, when evaluating all 524 patients, there was no difference in the primary endpoint of event-free survival (EFS) (3-y EFS 0.81 vs 0.79, P = NS).3 Similarly, the GOYA trial compared R-CHOP against obinutuzumab-CHOP (G-CHOP) in over 1400 patients with newly diagnosed DLBCL and found no difference in response, PFS, or OS.4 The Southwest Oncology Group randomized chemosensitive high-risk patients clinically defined via an IPI 3 to 5, to consolidative autologous stem cell transplant (autoSCT) or observation.5 With the exception of the subset of patients with high-risk disease (mixture of R-CHOP and CHOP induction), there was no PFS or OS advantage to autoSCT. The PRELUDE trial took a different approach; patients with an IPI 3 to 5 who were in remission at the end of R-CHOP were randomized to 3 years of oral enzastaurin vs placebo.6 Again, no differences in outcome were found.

There are many logistic explanations for not finding a difference in these well-designed and well-intentioned but seemingly negative trials. First, they likely included a mixture of DHL, DEL, germinal center B-cell (GC)-DLBCL, and activated B-cell (ABC)-DLBCL, among other yet-to-be-defined biologic groups. While some have performed subset analyses, the studies were not powered to test for differences...
Clinical impact of heterogeneity on curative potential

Time to move beyond R-CHOP for all

FIGURE 1 The effectiveness of R-CHOP declines in high-risk subgroups. GC, germinal center B-cell; IPI, International Prognostic Index.

TABLE 1 High-risk subsets and expected outcomes with R-CHOP therapy

<table>
<thead>
<tr>
<th>Subset</th>
<th>Freq.</th>
<th>CR, %</th>
<th>PFS, %</th>
<th>OS, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABC-DLBCL</td>
<td>30-50</td>
<td>NR</td>
<td>2 y, 28</td>
<td>2 y, 46</td>
</tr>
<tr>
<td>Double hit lymphoma</td>
<td>3-12</td>
<td>40</td>
<td>1 y</td>
<td>&lt;1 y</td>
</tr>
<tr>
<td>Double expressor lymphoma</td>
<td>21</td>
<td>NR</td>
<td>5 y, 27</td>
<td>5 y, 30</td>
</tr>
<tr>
<td>Elderly DLBCL, 60 y</td>
<td>50</td>
<td>70-80</td>
<td>5 y, 50</td>
<td>5 y, 58</td>
</tr>
<tr>
<td>High IPI</td>
<td>45</td>
<td>NR</td>
<td>4 y, 53</td>
<td>4 y, 55</td>
</tr>
</tbody>
</table>

Abbreviations: ABC, activated B-cell; CR, complete response; DLBCL, diffuse large B-cell lymphoma; IPI, International Prognostic Index; OS, overall survival; PFS, progression-free survival.

between groups. A second potential issue is the time required to confirm biology and assign a treatment arm; these delays inadvertently contribute to selection bias whereby only the fittest patients within high-risk subgroups are enrolled. Thus, for DLBCL-NOS, R-CHOP remains the standard of care at this time.

1.2 Treatment based on cell-of-origin

The dichotomy of DLBCL into 2 prognostic groups based on gene expression profiling (GEP) was identified over 15 years ago; patients with a GCB (GC-DLBCL, GCB) phenotype have superior survival compared with patients with an ABC (ABC-DLBCL, non-GCB) phenotype. The prognostic relevance of COO has been validated in R-CHOP treated patients and has spurred a generation of trials attempting to individualize treatment based on COO. Many trials have focused on targets and pathways that are differentially expressed between GCB and non-GCB. Many have adopted an "R-CHOP + targeted agent X" approach in a randomized setting, with the hope of changing COO from a prognostic factor to a predictive factor.

An important consideration when basing treatment on COO is the method of assessment. The initial publication used GEP on frozen material. Unfortunately, GEP is not routinely available, and frozen samples are not typically collected. This challenge prompted the development of several immunohistochemical algorithms as surrogates for GEP (reviewed in Meyer et al7); while this approach is much simpler and can be performed on paraffin-embedded tissues, there is an approximate 20% to 30% error rate. Furthermore, there is significant variability amongst pathologists. Most recently, nanostaining technology has been proposed as a more accurate means of assessing COO.9 This is being incorporated into a number of trials, but is not yet the standard means of assessing COO in clinical practice.

Based on superior single agent activity of lenalidomide and ibrutinib in relapsed/refractory non-GCB DLBCL, there are several prospective trials adding these agents to R-CHOP specifically in this subset. The Mayo Clinic group found an improved PFS (72% vs 39%) and OS (95% vs 61%) in non-GCB favoring lenalidomide plus R-CHOP ("R2-CHOP") against historical control non-GCB patients receiving R-CHOP.9 Similarly, an Italian multicenter study reported a 24-month EFS and OS of 59% and 78%, respectively, in elderly non-GCB patients.10 Of note, both of these trials used immunohistochemistry to determine COO. The potential ability to overcome negative prognosis of non-GCB DLBCL have prompted an ongoing US intergroup trial (E1412) as well as an international phase III (ROBUST) trial that are comparing R-CHOP against R2-CHOP prospectively. Importantly, the use of nanostring hopes to improve the precision of COO determination. Similar to lenalidomide, there is an ongoing trial of R-CHOP with or without ibrutinib (PHOENIX) in non-GCB DLBCL.

Unfortunately, data so far targeting subsets based on COO have been largely negative. Two phase II randomized trials tested the inclusion of bortezomib to CHOP specifically in non-GCB DLBCL11,12 Notably, COO was determined by an immunohistochemistry (IHC) algorithm. A randomized phase III trial (ReMoDL) also tested the inclusion of bortezomib to R-CHOP, and the preliminary data do not show any benefit of the added drug in neither subgroup by COO, even when determined by GEP. Thus, altering treatment based on COO is not yet standard of care although we await results of ongoing trials.

1.3 Double hit lymphoma

MYC rearrangements occur in 10% to 15% of DLBCL, making this numerically more common than all cases of Burkitt lymphoma (BL). While MYC rearrangements confer a negative prognosis, it is the dual rearrangements of MYC (strong proliferative gene) with BCL2 (strong apoptotic gene) that leads to clinical resistance to therapy and minimal long-term survival. Double-hit lymphomas are relatively uncommon, accounting for 5% to 7% of all DLBCL. Clinically, patients with DHL tend to have higher LDH, more frequent GCB phenotype, and higher IPI.

The bulk of data guiding treatment in DHL is retrospective. Results with R-CHOP are very poor, with limited long-term survival (reviewed in Nowakowski et al7). A British Columbia Cancer Agency analysis found less than one-third long-term survival, whereas another large study found essentially no survivors beyond 2 years. There are several single-center and multicenter retrospective reports suggesting that augmented regimens, including EPOCH-R and R-HyperCVAD, are superior to R-CHOP. An NCI-based study is prospectively testing
DA-EPOCH-R in MYC-associated high-grade lymphoma (NCT01092182). Of note, only half of patients have DHL via FISH/cytogenetics. Early results are promising, with overall survival approximately 75% with short follow-up.

It is unclear if consolidative autologous stem cell transplant can overcome the negative significance of DHL. Retrospective series have not found a significant benefit for transplant, particularly if patients achieve a complete remission. However, a major problem is inherent chemoresistance and inability to even get to transplant. The Southwest Oncology Group 9701, a prospective trial randomizing patients to transplant consolidation versus observation after CHOP/R-CHOP, performed a retrospective analysis and found that all patients with DHL died irrespective of consolidative transplant. At the time of relapse, autoSCT does not successfully salvage most of the patients. A Bio-CORAL analysis found that patients with an MYC rearrangement had a significantly lower 4-year PFS and OS (18% vs 42%, P = .03; 29% vs 62%, P = .01, respectively), with no impact of the preceding salvage regimen. Recently, a large retrospective review from 2 high-volume institutions found similar findings: patients with DHL had an inferior 4-year PFS and OS (28% vs 57%, P = .013; 25% vs 61%, P = .002, respectively). Thus, while 25% to 30% of chemosensitive DHL patients may benefit from autoHCT at relapse, this is clearly a highly selected subset of patients, and most of the patients do not benefit.

The elimination of morphologic categories such as BCLU and alignment of diseases harboring similar genetic abnormalities will be helpful in future trial design for this high-risk and poor-prognosis subgroup. For now, the overwhelming body of data is retrospective in nature and confirms limited long-term survival with R-CHOP-like regimens. A clinical trial should be the first choice for any patient.

### 1.4 | Dual expressor lymphomas

While most of the patients with DHL have protein overexpression of their respective genes, the converse is not necessarily true. Based on large reviews, up to 30% of DLBCL or high-grade lymphoma patients will have protein overexpression of MYC (≥40%) and BCL2 (≥50%) because of mechanisms other than classic translocations. Double expressor lymphomas is recognized as a poor prognostic marker by the 2016 WHO classification.

While not as dismal as DHL, patients with DEL have decreased survival following R-CHOP compared with patients without DEL. The International DLBCL R-CHOP Consortium Program found 5-year OS 30% vs 50% (P < .0001) for DEL vs non-DEL patients (reviewed in previous studies). Similarly, Green and colleagues found a lower complete response rate, shorter OS, and inferior PFS with only one-third of patients achieving long-term disease control.

The optimal treatment of DEL is unknown. One recently presented phase I trial tested escalating doses of lenalidomide plus DA-EPOCH-R. All 10 patients with DEL had a complete response, and the phase II portion of the trial is ongoing to further evaluate safety and efficacy. The US intergroup is targeting BCL2 with venetoclax and adding this to a DA-EPOCH-R backbone. For now, similar to DHL, the best option is to consider a clinical trial.

### 1.5 | Burkitt lymphoma

Burkitt lymphoma is an uncommon mature B-cell malignancy clinically characterized by an extremely rapid onset and growth phase and predilection for younger patients. Non-HIV associated/sporadic cases are most common in European and North American countries, but remain relatively rare with an estimated incidence of 0.4 per 100,000, translating to fewer than 1500 US cases in 2016. There is an unexplained increase in males. Burkitt lymphoma affects mainly children and adolescents, but there is a secondary peak in adults. Major advances for newly diagnosed patients, notably the addition of rituximab and improved supportive care, have improved cure rates and survival substantially. Unfortunately, relapsed and refractory disease has dismal outcomes with few long-term survivors.

The backbone of management is the delivery of intensive multiagent chemotherapy with rituximab and CNS prophylaxis. There are several commonly used regimens, including COHDOX-M/IVAC, HyperCVAD/H-MTX/Ara-C, CALGB/Alliance 10002, and DA-EPOCH-R. In general, the addition of rituximab seems to improve outcomes although there is also more toxicity. There is only 1 prospective randomized trial that compares the French LMB regimen with or without rituximab, with a median follow-up of 38 months, the study met its prespecified endpoint of 3-year EFS and showed an advantage for the rituximab-containing arm (75% vs 62%, HR, 0.59, P = .024). The largest noncomparative prospective trial of 363 patients from 98 centers found that rituximab added to chemotherapy was associated with a 5-year OS of 80%, although age significantly impacted outcomes. The CALGB/Alliance added rituximab to a previously piloted chemotherapy regimen (CALGB 9251) and reported improved complete remission rates, EFS, and OS with the use of a short-duration but intensive regimen.

Age and functional status are important additional clinical considerations in management. Adults tend to have inferior outcomes partly related to toxicity. In the German multicenter experience, the 5-year overall survival for adolescents (ages 15–25 years), adults, and elderly (≥55 years) patients declined from 90% to 84% to 62%, respectively; notably, patients over age 55 years also received less intensive treatment. A multivariate analysis of 105 patients treated on a prospective Italian study found age and performance status as the only significant factors; patients over the age of 60 years and with a poor performance had an approximate 20% long-term survival.

One of the key difficulties in interpreting the literature is directly related to new insights raised by the 2016 WHO update in lymphoid malignancies. As highlighted previously in this session, many cases morphologically resembling BL may, in fact, now be classified as high-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements since most of the clinical trials did not systematically assess for these rearrangements. Furthermore, there may be a number of "atypical BL" included in these trials that had the more favorable BL with 11q aberrations but were not recognized since this entity had yet to be described.

### 2 | CONCLUSION

As our understanding of aggressive B-cell lymphoma biology evolves, it is clear that the disease is quite complex and each of the high-risk
groups aforementioned interact and overlap. For example, there is a concentration of DHL in patients with GC-DLBCL and a concentration of DEL in patients with ABC-DLBCL. However, as the biologic underpinnings of aggressive lymphoma are teased apart, we may be able to target specific subsets with new treatments and eventually move towards the promise of more individualized treatment.

CONFLICT OF INTEREST
Sonali M. Smith: Consultant for Celgene, Pharmacyclics.

REFERENCES
1 | INTRODUCTION

A multitude of studies have investigated why the immune system fails to develop an effective response against cancer and how to mobilize a successful immune therapeutic attack against cancer cells. Lymphomas are tumors of the immune system that develop from the cells devoted to the body defense within permissive specialized and well-vascularized tissue microenvironments, such as bone marrow and secondary lymphoid organs. Malignant lymphoid cells entail a bidirectional dialogue with a host of nonmalignant immune cells of both innate and adaptive immunity. This cross-talk not only favors malignant cell growth, survival, and drug resistance but also prevents antitumour response through resistance to cytotoxicity, compromised cytotoxic cell activity, and altered tumour-identifying ligand expression or secretion. Improving the understanding of the mechanisms that underlie the deficiency of an adequate antitumour immune response is now allowing manipulation of the immune system for the purpose of lymphoma eradication.

2 | THE MECHANISMS OF IMPAIRMENT OF AN ADEQUATE ANTITUMOUR IMMUNE RESPONSE IN LYMPHOMA

The first question to address is through which mechanisms malignant cells subvert normal cells of the immune system to protect themselves from attack. A number of different mechanisms have been ascertained. As an example, diffuse large B cell lymphoma (DLBCL) cells commonly fail to express cell-surface molecules necessary for the recognition of tumour cells by immune-effector cells. This may occur because of mutations and deletions that inactivate either the β2-Microglobulin gene, thus preventing the cell-surface expression of the HLA class-I (HLA-I) complex that is necessary for recognition by cytotoxic T lymphocytes (CTL) or the CD58 gene, which encodes a molecule involved in T and natural killer cell-mediated responses.

Lymphoma cells divert the classical activation of the innate immune system and subvert the antitumour immune response exerted by T helper (Th) cells, CTL, and macrophages. The apposition of lymphoma cells with T cells within involved tissues induces a dysfunction of the T-cell immunological synapse, the complex molecular structure that represents the site where the T-cell receptor (TCR) is triggered by the peptide–HLA complex. This dysfunction has been described initially in B-cell chronic lymphocytic leukemia (CLL) and subsequently also in follicular lymphoma (FL) and DLBCL. It is due to inhibitory ligand-induced impairment of T-cell actin dynamics and prevents the lysis of tumour cells through CTL.

Notably malignant lymphoid cells may also secrete cytokines such as IL-12 that induce T cell "exhaustion," a reversible condition that occurs when T cells are exposed to prolonged stimulation with antigen and leads to a profound inability of T cells to respond to activation signals. Moreover, lymphomatous tissues are enriched with immune cell subsets that suppress an efficient immunological response against the tumour such as FoxP3 regulatory T cells (Tregs). Tregs suppress the proliferation and activity of both CD4+CD25– and CD8+ T cells, and their enrichment is contributed to by lymphoma cells that allow the preferential conversion of T helper cells into Tregs by proteins such as TGF-β or CCL22.

A number of studies have suggested a critical role for monocyte/macrophage cells in chronic lymphoid malignancies. Their accumulation is favoured by the inflammatory microenvironment within infiltrated tissues that attracts monocytes/macrophages and cooperates with IL-10 to promote the M2 polarization of tumour associate macrophages. M2-polarized tumour associate macrophages promote tumour growth by stimulating angiogenesis and inducing an immunosuppressive Th2 response.

A major achievement has been the understanding that the homeostasis of antigen-specific lymphocytes requires multiple different signals. Lymphocyte activation is triggered by specific antigen recognition through the TCR and costimulatory signals. Coinhibitory signals delivered through specialized receptors that function as immune checkpoints maintain self-tolerance and promote the
resolution of inflammation during immune responses thereby preventing the development of autoimmunity. The molecular family of checkpoint inhibitors classically represented by the B7–CD28–CTLA-4 family has been enriched by the identification of the programmed cell death 1 (PD-1)/programmed death–ligands 1 and 2 (PD-L1 and PD-L2) immune checkpoint inhibitory receptor and ligands. The functional and biochemical properties of PD-1 are not limited to but have been best studied in T cells where PD-1, induced upon activation through the TCR and cytokine receptors, is necessary for the termination of the immune response. Programmed death–ligand 1 is constitutively expressed at low levels on both professional and nonprofessional antigen presenting cells as well as on a wide variety of nonhematopoietic cell types and its expression is also induced by proinflammatory cytokines.

A key mechanism by which cancer cells limit the host immune response is the upregulation of PD-1 ligands and their ligation to PD-1 on tumour-specific CD8+ T cells. In the tumour microenvironment inflammatory mediators, among which interferon-γ produced by tumour-infiltrating T cells that are capable of recognizing tumour antigens is the most potent, can induce expression of PD-L1 and PD-L2 not only on cancer cells but also on other cell types such as macrophages, dendritic, and stromal cells. The expression of PD-1 ligands on tumour cells can have a genetic basis as best exemplified by classical Hodgkin lymphoma where chromosome 9p24.1/CD274(PD-L1)/PDCD1LG2(PD-L2) alterations have been shown to increase the abundance of PD-1 ligands. JAK2-STAT signalling further increases PD-1 ligand expression. Notably, Epstein-Barr virus (EBV) infection can increase expression of PD-1 ligands in EBV+ HL. Levels of PD-L1 expression in cancer cells are also regulated by epigenetic mechanisms.

Lymphoma cells protect themselves from attack by the immune system through several different mechanisms. These observations have paved the way to the development of new therapeutic avenues of cancer immunotherapy. The use of genetically modified chimeric antigen receptor (CAR)-T-cells that overcome the mutational landscape of cancers and the blockade of immune checkpoint receptors that inhibit the immune response convincingly show that the possibility to eradicate lymphoid malignancies with immunotherapeutic approaches is more realistic than ever before.

3 IMMUNE CHECKPOINT INHIBITORS IN LYMPHOMA

Two immune checkpoints have been targeted in lymphoma and antibodies that block signaling via these receptors have resulted in therapeutic benefit for patients. CTLA-4 is commonly expressed on T-cells after activation and specifically functions to down regulate T-cell activity through a variety of mechanisms. These mechanisms include preventing costimulation by outcompeting CD28 for its ligand B7 and also by inducing T-cell cycle arrest. Blocking CTLA-4 prevents down regulation of T-cell function and promotes the persistence and activation of intratumoural T-cells. Similarly, PD-1 is a negative regulator of T-cell activity and limits T-cell activation when stimulated by 1 of its 2 ligands, PD-L1 and PD-L2. Activation of this receptor typically down regulates T-cell activity and PD-1 is commonly expressed on activated and immunologically exhausted T-cells. Persistent stimulation via PD-1 results in an ineffective immune response and blocking signaling through PD-1 using an anti–PD-1 antibody allows for reactivation of suppressed or exhausted T-cells. Targeting these 2 immune checkpoints is therefore a rational therapeutic approach.

Initial clinical studies utilized an anti–CTLA-4 antibody ipilimumab in B-cell lymphoma with a goal of enhancing antitumour T-cell responses. In an initial phase II clinical trial, 18 patients were treated and 2 responses were seen—1 patient with DLBCL had a complete response and 1 patient with FL had a partial response. Correlative studies showed that T-cell proliferation in response to recall antigens increased in most patients confirming activation of the immune system. Subsequent clinical trials were done using ipilimumab in patients with relapsed hematological malignancies post autologous stem cell transplant. In these studies, responses were seen in lymphoma patients including 2 complete responses in patients with HL and a partial response in patients with mantle cell lymphoma (MCL). Ipilimumab has subsequently been combined with nivolumab, an anti–PD-1 antibody, and the combination has shown significant clinical responses in HL.

While targeting CTLA-4 has resulted in modest clinical benefit, clinical trials testing PD-1 blockade have shown significant promise in patients with lymphoma, particularly HL. Initial trials used an anti–PD-1 antibody pidilizumab, and while there is some controversy as to whether pidilizumab specifically targets PD-1, the initial trial of pidilizumab postautologous stem cell transplant did show a significant impact of this agent on progression free survival. A subsequent clinical trial of pidilizumab in combination with rituximab in FL showed a high complete response rate of 52% in the 32 patients treated. Additional clinical trials of other anti–PD-1 antibodies have been performed. Studies using nivolumab that targets PD-1 showed dramatic responses in patients with HL. In the initial phase I trial of nivolumab, the 23 patients in the HL cohort had an overall response rate of 87%. The responses seen in this trial have been durable and with longer-term follow-up, a significant proportion of patients have remained in remission. A subsequent confirmatory phase II study of nivolumab in HL patients confirmed an overall response rate of 68%. These responses have remained durable and with a median follow-up of 14 months, the median duration of response has not yet been reached. The response rates in other lymphomas have been lower but responses have been seen in patients with FL, DLBCL, and T-cell non-Hodgkin lymphoma. In general, responses in these histologies have been in the 20% to 40% range and responses have not been as durable. Similar results have been seen with pembrolizumab, a further antibody targeting interactions between PD-1 and its ligands. Data with this agent in classical HL have confirmed high response rates and good tolerability. In an initial phase I clinical trial, the overall response rate for the 31 patients treated was 58% and these responses have also been durable with longer-term follow-up. A subsequent phase II trial of pembrolizumab, including patients who progressed after autologous stem cell transplant as well as patients ineligible for a transplant, confirmed a high response rate of 68% with the responses varying between 64% and 74% depending on the subset analyzed. Correlative studies from the Hodgkin cohort in both the pembrolizumab and nivolumab studies have confirmed high expression...
of PD-1 ligands on the malignant cells and the majority of the overexpression is due to amplification or copy number gain at chromosome 9p24.1.

The significant clinical results of particularly pembrolizumab and nivolumab in HL and other lymphomas have led to a plethora of combination studies. An initial study combining ipilimumab and nivolumab, so as to have dual immune checkpoint blockade, resulted in a 74% response rate in a cohort of 31 HL patients. Of note, however, responses have been significantly lower even with dual checkpoint blockade in other lymphoma histologies. Similarly, combination studies of immune checkpoint therapy with antibody drug conjugates such as brentuximab vedotin have been conducted. Recent reports of the results of combining brentuximab vedotin with nivolumab showed an overall response rate of 90% in HL patients in first relapse and 100% in patients who had progressed posttransplant. Further studies using multiple combinations in various lymphoma histologies are currently in progress. Clearly, targeting immune checkpoints is a promising approach to optimizing the antitumour immune response in both Hodgkin and non-Hodgkin lymphoma.

4 | ADOPTIVE T-CELL THERAPIES (CAR-T)

A further option to overcome tumour resistance is to adoptively transfer large numbers of expanded or genetically reprogramed T-cells specific for a tumour expressed antigen. Approaches include the use of tumour infiltrating lymphocytes, cells transfected with TCR specific for tumour antigens in the context of the patient’s HLA, or chimeric antigen receptor gene-modified T cells (CAR-T). Chimeric antigen receptor gene-modified T cells specific for the B cell lineage antigens CD19, CD20, and CD22 have shown the greatest promise in patients with acute lymphoblastic leukemia, NHL, and CLL. For NHL, the most encouraging antitumour activity has been with second-generation CAR constructs that have used a murine scFv specific for CD19 and linked to either the 41BB or CD28 costimulatory domains and a CD3zeta signaling sequence. Typically, cells are collected from the patient via leukapheresis and then either separated into subsets (CD4 and CD8 cells) or bulk lymphocytes directly stimulated through CD3 and CD28 and transfected with either a lentiviral or retroviral vector. Using this approach, cells are produced rapidly (<7 days), but may be comprised of widely variable T cell subsets.

In the initial report, they treated 15 patients (9 with DLBCL, 2 indolent NHL, and 4 CLL) with 8 CR and 4 PR. In patients with DLBCL, 4/7 evaluable patients had a CR and 3 were ongoing between 9 and 22 months. The CRS and neurotoxicity was the most significant toxicity and 1 patient without known CRS had sudden death at day 16 post-CAR-T cells. Patients had extensive prior therapy, and the achievement of CR’s in this population represents a significant finding. In addition, this was feasible in patients who had relapsed following allogeneic transplantation, without any apparent increase in graft-vs-host disease or graft rejection. Kite Pharmaceuticals is planning to commercialize this approach (KTE-C19) in relapsed/refractory DLBCL and reported early results from the pivotal ZUMA-1 at ASH 2016. In 62 patients with DLBCL (n = 58) or transformed FL or PBMC (n = 11), the overall response rate was 79% with a 52% initial CR rate to a targeted dose of 2 × 10^9 cells/kg after low-dose Cy/Flu conditioning. At 3 months, the ORR was 44% with a CR rate of 39%. Data have not yet been released for 6- and 9-month follow-up, but this compares favorably to historical data for patients with relapsed/refractory DLBCL (8% CR from the SCHOLAR-1 study). Grade 3 or greater CRS was observed in 18% and neurotoxicity in 34% of patients. Two patients died of related side effects.

The Seattle group has taken a different approach by creating a more uniform CAR-T cell product by selecting CD4 and CD8 T cell populations and administering a CAR-T cell product containing CD4: CD8 cells in a defined 1:1 ratio in 32 patients with NHL. In this phase I/II trial, we observed that the dose of CAR-T cells was important as well as the type/intensity of lymphodepletion. Patients treated with Cy alone had a high incidence of immunologic rejection of the modified T cells that limited the duration of response. The addition of fludarabine decreased this immune rejection and resulted in more robust CAR-T cell expansion, which required a 1 log reduction in the administered T cell dose to limit toxicity. By using a defined ratio of cells, we were able to identify dose response and dose toxicity relationships. The overall response rate was 63% with a 33% CR rate. However, using Cy/Flu lymphodepletion the ORR was 72% with a 50% CR and with a longer duration of remission. This was correlated with greater CAR-T cell expansion and persistence. We were able to release of inflammatory mediators including IL-6, TNF-alpha, and gamma interferon and manifest as fever, hypotension, capillary leak, and coagulopathy. This may require ICU-level care. For grading, see Lee et al. In most studies, an unexplained neurotoxicity with delirium and somnolence or even seizures and/or stroke like phenomena can occur in a subset of patients. Fortunately, even if significant, these neurotoxicities are usually fully reversible. Moderate-to-severe CRS can be treated by anti–IL-6 protein or receptor antibodies (tocilizumab or siltuximab) often in combination with a short course of dexamethasone. Tumour responses are usually quite rapid and occur in the first 1 to 2 months. Hospitalization is often required for supportive care, but approximately 30% of patients in the Seattle series were treated entirely as outpatients.

Kochenderfer at the NCI has reported the longest outcomes for patients with NHL. This approach uses a murine scFv and a CD28 costimulatory domain that is transfected into bulk-stimulated T cells using a retroviral vector. Using this approach, cells are produced rapidly (<7 days), but may be comprised of widely variable T cell subsets.
observe complete remission of disease in the blood, bone marrow, nodal and extra nodal tissues, and CNS. Severe CRS was observed in 13% and severe neurotoxicity in 28%, and 2 patients died of toxicity (both treated above the eventual MTD). Importantly, measurement of serum biomarkers 1 day after CAR-T cell infusion was correlated with the development of severe CRS or neurotoxicity suggesting an avenue for early intervention. Juno Therapeutics has developed this approach further (UCAR-17) in an ongoing multicenter phase I/II trial that also reported encouraging results at ASH 2016 with 82% OR and 73% CR in the first 11 evaluable patients with DLBCL. Of interest, 1 patient with a parenchymal brain lesion also responded with a CR and without CRS or CNS toxicity.

At this time, it is difficult to compare these very different CAR-T cell products, but both approaches appear to be generating response rates and CR rates that are vastly superior to the current standards of care in this difficult to treat patient population (relapsed refractory DLBCL). The duration of remissions and the causes of disease relapse will be important to the field. However, this is likely just the beginning of a new treatment era because combination therapy with CAR-T cells and checkpoint inhibitors are a logical extension and clinical trials are ongoing.

**CONFLICT OF INTEREST**

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**REFERENCES**


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