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Supplement Article

XI. Management of paediatric and adult non-Hodgkin lymphoma: what lessons can each teach the other?

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Abstract

Is there anything that we can learn from each other regarding paediatric and adult non-Hodgkin Lymphoma (NHL) management? Do we treat the same patients? Are there differences in lymphoma biology in the different age groups? Are the procedures of decision making and the infrastructure comparable? Is the weighing of toxicity and outcome aspects in the benefit and risk assessments prior to treatment decisions comparable? Interestingly, the proportional distribution of the NHL subtypes and the spectrum of NHL occurring in children and adolescents differs significantly from that in adults. This observation might motivate biological studies aiming to elucidate the pathomechanisms of lymphomagenesis. Concerning NHL diagnosis and staging, the comparison of outcome data reported for paediatric and adult patient series is often impaired by the use of different staging systems. However, the impact of reference laboratories supporting correct subtyping and the advantages of population-based patient recruitment are experiences that might be transferable between paediatric and adult oncologists. Interestingly, the process of implementing new drugs into current treatment strategies and making these drugs available to patients varies substantially across patient's age groups. The far lower absolute number of patients, especially of relapsed patients, and the favorable outcome with current standard treatment may contribute to the marked differences in the kinetic of implementing new compounds comparing adult with paediatric NHL patients. Also, the basis for the conduction of cooperative clinical trials with pharmaceutical companies needs to be strengthened in paediatric clinical trial groups. In conclusion, both paediatric and adult oncologists benefit from the interdisciplinary discussion with each other, not only concerning results and experiences in clinical trials but also with respect to critical aspects of infrastructure.

Keywords: **Non-Hodgkin lymphoma; management; adult; pediatric**

Introduction

Before addressing the question 'Paediatric and Adult Non Hodgkin Lymphoma (NHL) Management: What Can We Learn from Each Other?', two open issues should be discussed: (1) is there any need to learn from each other and (2) is there anything that we can learn from each other? The first question is easy to answer. Indeed, there is substantial room for improvement of lymphoma management in both age groups. Current treatment regimens are associated with acute and long term toxicity and do not result in 100% event-free survival. The second question, whether there is any rational to assume that it could be beneficial for us to try to learn form each other, is even more critical. Are lymphoma patients in childhood and adulthood truly the same? Are there any differences in lymphoma biology in different age groups? Are the procedures of decision-making and all the (infra-) structure, for example, reference diagnostics, availability of clinical trials, sense of protocol adherence and so on comparable? Is the weighing of toxicity and outcome aspects in the benefit and risk assessments prior to treatment decisions comparable with paediatric and adult patients? Are common protocols, as successfully introduced in paediatric and adult lymphoma patients, as in other entities such as bone tumours?

Although the exemplarily raised aspects are unsolved, lymphoma management for paediatric and adult patients can benefit form interdisciplinary discussions and exchanges, as we will try to highlight in the following sections. We have

decided to focus on relevant examples, as covering all aspects of lymphoma management seems too ambitious in the context of this review.

Lymphoma classification and biology

For the different lymphoma other than Hodgkin's lymphoma, the current World Health Organization (WHO) classification defines four groups including 69 subtypes and uncounted numbers of variants of these subtypes. Although some of these subtypes and variants are mentioned to be rare, all were regarded relevant enough to be included in the WHO classification system. Interestingly, the proportional distribution of the NHL subtypes and the spectrum of NHL occurring in children and adolescents differ significantly from that in adults as schematically illustrated in Figure 1 [1,2]. As a consequence, it becomes obvious that among NHL patient populations, the overlap of histological subtypes treated by paediatricians and by adult physicians is limited. In children and adolescents, Burkitt lymphoma and leukaemia, lymphoblastic lymphoma (LBL), diffuse large B-cell lymphoma (DLBCL) and ALK positive anaplastic large cell lymphoma (ALCL) cover roughly 90% of all NHL patients. Except for DLBCL, all these typical paediatric NHL subtypes are regarded rare subtypes in adults, whereas other subtypes such as follicular lymphoma, chronic lymphocytic leukaemia and multiple myeloma are frequently observed histological subtypes.

This age-dependent preference of most NHL subtypes raises the question whether the biology of NHL subtypes occurring in all age groups is constant or variable with respect to patient age. Limited studies on lymphoma biology pay attention to this aspect. One of the largest series covering diffuse large B-cell lymphoma reported the association of biologic and genetic features with patients' age, but no cut-offs between age groups could be defined [3]. Such results should motivate additional biological studies as advanced knowledge on age-dependent biological characteristics may play a key role in the process of elucidating the pathologic mechanisms of lymphomagenesis.

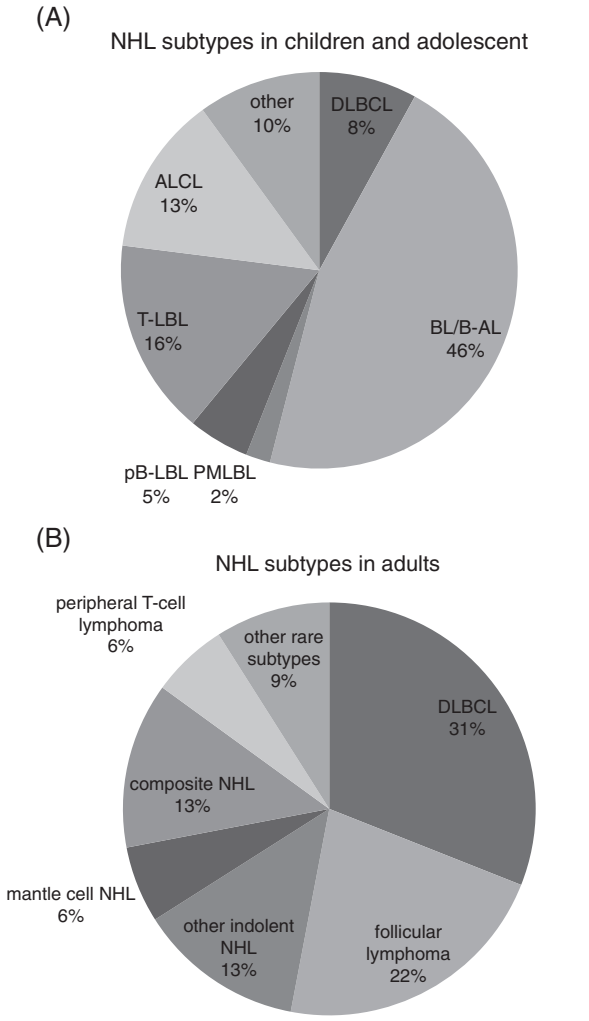

Figure 1. Distribution of histological subtypes in children and adolescents compared with adult non-Hodgkin lymphoma patients. (A) Non-Hodgkin lymphoma (NHL) subtypes in children and adolescents [1]. Distribution of histological subtypes among 2084 paediatric and adolescent NHL patients registered in a population-based fashion in Germany, Austria and Switzerland [1]. (B) NHL subtypes in adults [2]. Distribution of histological subtypes among 1403 adult NHL patients diagnosed in nine institutions in eight countries. T-LBL, lymphoblastic T-cell lymphoma; pB-LBL, lymphoblastic B-cell lymphoma; BL/B-AL, Burkitt lymphoma and Burkitt leukaemia; DLBCL, diffuse large B-cell lymphoma; PMLBL, primary mediastinal large B-cell lymphoma; ALCL, anaplasticlarge cell lymphoma; other, rare subtypes and NHL not further classified

Diagnosis and staging

Unfortunately, the comparison of outcome data reported for paediatric and adult patient series is often impaired by the use of different staging systems. For children and adolescents, the St. Jude staging system [4] is standard while NHL in adults is usually staged according to the Ann Arbor staging system [5]. The two systems are depicted in Table 1. Most relevant differences refer to the definition of advanced stage diseases. In many paediatric clinical trials, the diagnosis of NHL and the subtyping are centrally monitored by the respective study centre and supported by reference laboratories that are routinely or even mandatorily involved to establish the correct diagnosis. The implementation of reference pathology significantly reduced the number of paediatric patients misdiagnosed and mistreated, which is obviously of great clinical relevance as the treatment regimens used for paediatric NHL patients significantly differ according to NHL subtypes.

In some countries, a system of population-based recruitment of all newly diagnosed paediatric and adolescent

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Table 1. St. Jude and Ann Arbor staging system for non-Hodgkin lymphoma

Stage	St. Jude (Murphy)	Ann Arbor
I	A single extranodal tumour or a single anatomic nodal area with the exclusion of mediastinum and abdomen	A single lymph node region or a single extralymphatic organ or site (IE)
II	A single extranodal tumour with regional node involvement ≥2 nodal areas or ≥2 extranodal tumours with or without regional nodal involvement on the same side of the diaphragm A completely resected primary gastrointestinal tract tumour with or without involvement of associated mesenteric nodes	≥2 nodal regions or localized involvement of extralymphatic organ or site (IIE) on the same side of the diaphragm
III	≥2 nodal or extranodal tumours on opposite sides of the diaphragm Primary intrathoracical or unresectable primary intra-abdominal tumour Any paraspinal or epidural tumour, regardless of other tumour site(s)	Involvement of nodal or localized extralymphatic organ (IIIE) on both sides of the diaphragm
IV	Involvement of bone marrow or central nervous system	Diffuse or disseminated involvement of one or more extralymphatic sites or organs

NHL patients into clinical trials provide an excellent data base for analyses on the incidence of NHL, the distribution of histological subtypes, associations of patient characteristics with NHL subtypes and outcome. In addition, the data on these population-based registered patients serve as stable and sufficient historical control groups for newly implemented clinical trials and allow the reduction of required patient numbers to prospectively answer clinical questions.

Lymphoma treatment

Standard therapy for paediatric patients with LBL are regimens similar to those used for the treatment of acute lymphoblastic leukaemia (ALL), consisting of a 9-week eight drug induction, a consolidation with high-dose methotrexate and a re-induction followed by oral maintenance for a total treatment duration of 24 months [6]. Both, T-cell and B-cell LBL are treated according to that regimen and achieve event-free survival probabilities of about 80%. Prior to an envisioned international clinical trial for paediatric LBL patients, several clinical trial groups agreed to prospectively evaluate the prognostic relevance of molecular markers to establish an optimized risk stratification system. Interestingly, a first proposal of such a molecular-based risk stratification system not only had certain overlap with a recently published genetic classifier for adult T-cell ALL patients but also showed significant differences [7,8]. For adult LBL patients, similar strategies were reported concerning the optimal treatment strategy. The use of ALL-type treatment regimen improved the disease-free survival to 45–72% [9]. In addition to ALL-type chemotherapy, mediastinal radiotherapy and high-dose chemotherapy with autologous transplant are included in some protocols for patients with advanced disease. Both treatment modalities are not part of paediatric protocols [6]. Mediastinal radiotherapy for bulky T-LBL disease had been part of French paediatric protocols but was omitted because of the lack of effectiveness and the risk of secondary cancers.

Mature B-cell NHL represents more than 50% of NHL cases in paediatric and adolescent patient populations with Burkitt lymphoma/leukaemia and DLBCL being the most common subtypes. In many paediatric clinical trials, the treatment is identical for both subtypes and consists of dose intense 5 to 7 days of multi agent chemo-courses based on high-dose methotrexate and high-dose cytarabine for advanced stage disease, but not rituximab [10,11]. The most frequently used regimens are the French-American-British Lymphomes Malins B (FAB-LMB) regimen and the German Berlin-Frankfurt-Münster (NHL-BFM) regimen. Both result in event-free survival probabilities of ~90% in all stages [12,13]. The treatment is associated with significant acute toxicity while data on long-term toxicity are lacking. As Burkitt lymphoma and DLBCL are usually registered in the same trial and treated according to the same protocol, the clinical need to differentiate one from the other is limited and mostly academic. This is in clear contrast to adult B-NHL patients. Another difference between paediatric and adult NHL management is the fact that rituximab, which is an inherent part of B-NHL treatment of adult patients since several years, is not yet prospectively tested in children and adolescents. This might in part be due to the favourable outcome achieved with the current standard chemotherapy and the lack of systematic data concerning infectious complications and the immune reconstitution after rituximab treatment in children [14].

Most adult patients with DLBCL are treated with the Rituximb Cyclophosphamid Hydroxydaunorubicin Vincristin

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Predniso(lo)n (R-CHOP) regimen, or its variants consisting of six to eight courses of rituximab, cyclophosphamide, doxorubicine, vincristine and prednisone usually administered outpatient [15]. The outcome data reported with this regimen are markedly influenced by the inclusion criteria of the respective trial. For young adults with low or limited risk profile, R-CHOP achieves similar results as mentioned earlier for paediatric DLBCL patients while outcome data worsen for elderly patients or patients with high-risk disease [16]. The most relevant pros and cons concerning R-CHOP for DLBCL patients are the outpatient treatment and the moderate acute toxicity on the one hand but high cumulative doses of anthracyclines and the risk of cardiac long term toxicity on the other hand [13]. In contrast, diagnosis of Burkitt lymphoma requires more intensive treatment regimens [17], and therefore, a correct distinction between DLBCL and Burkitt lymphoma is mandatory in order for the patient to receive the most appropriate treatment.

For paediatric patients with ALCL, six courses of chemotherapy with intermediate high-dose methotrexate are accepted as standard and result in 90% overall survival probability [18]. In Europe, biological parameters like minimal disseminated disease assessment and the immunity to NPM-ALK antigen are about to become standard for risk stratification [19]. Importantly, ALCL in children and adolescents are ALK positive in most of the cases while ALCL in adults is ALK negative in roughly 40% of the cases. Novel drugs such as the anti-CD30 immunoconjugate brentuximab vedotin and ALK inhibitors like crizotinib are about to change the treatment for paediatric and adult ALCL patients.

Burkitt and LBL relapses in children and adolescents after frontline treatment with current chemotherapeutic protocols are associated with very poor prognosis. Most patients do not achieve a stable second remission and therefore do not reach the indicated high-dose chemotherapy and allogeneic haematopoietic stem cell transplant [20]. Similar observations of poor prognosis are reported for adult patients with relapsed Burkitt or LBL [9,17]. Independent of patients' age, it is widely agreed that these patients are subjected to clinical trials whenever available.

Systematic treatment optimization

For all the discussed histological subtypes, novel drugs are on the way or already approved. Many of these new compounds such as ibrutinib or idelalisib have the advantage of targeting specific pathways that play an important role in lymphomagenesis. Thus, these novel compounds can potentially be combined with current standard chemotherapy to improve patient outcome. Alternatively, these novel drugs might serve as a substitute for more toxic current treatment elements and might reduce toxicity without impairment of disease-free survival. Interestingly, the process of implementing new drugs into current treatment strategies and making these drugs available to patients varies substantially across patient's age groups. Rituximab might be mentioned exemplarily: after consistent clinical trials with successful improvement of outcome, the drug was part of the standard of care and the best clinical practice for virtually all adult B-cell lymphoma patients for years [21]. Today, several clinical trials evaluating optimized successor compounds are open for recruitment for adult patients. In contrast, the role of rituximab in the treatment of paediatric patients with NHL is still unknown. Two phase II trials were published, and the first phase III trial opened patient recruitment in 2012 with final results expected only in several years [14].

The far lower absolute number of patients especially of relapsed patients and the favourable outcome with current standard treatment may contribute to the marked differences in the kinetic of implementing new compounds comparing adult and paediatric NHL patients. Also, the basis for the conduction of cooperative clinical trials with pharmaceutical companies needs to be strengthened in paediatric clinical trial groups.

In conclusion, both paediatric and adult oncologist benefit from the interdisciplinary discussion with each other, not only concerning results and experiences in clinical trials but also with respect to critical aspects of infrastructure.

Conflict of interest

The authors have no competing interest.

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