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Supplement Article

I. Hodgkin lymphoma: special challenges and solutions

Joseph M. Connors*

British Columbia Cancer Agency Centre for Lymphoid Cancer, The University of British Columbia, Vancouver, BC, Canada

**Correspondence to:* Joseph M. Connors, British Columbia Cancer Agency Centre for Lymphoid Cancer, The University of British Columbia, 600 West 10th Avenue, V5Z 4E6 Vancouver, BC, Canada.
E-mail: jconnors@bccancer.bc.ca

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Introduction

In 2015 most patients who develop Hodgkin lymphoma (HL) will be cured, regardless of extent of disease at presentation. Basing treatment on more than five decades of careful clinical research, the oncologic specialist can offer treatment that is highly effective and usually acceptably tolerated by most patients. The high cure rate places a firm obligation on the treating specialist to craft a treatment strategy that maximizes the likelihood of cure while, at the same time, minimizing cost, inconvenience, toxicity and long-term ill effects. Fortunately, the appropriate and selective personalized use of multi-agent chemotherapy, localized radiation and, for a small carefully chosen minority, highly intensified treatment offers an efficient, cost effective, minimally toxic approach that meets the twin goals of high efficacy and low toxicity for almost all patients. There is wide, international agreement that the 30% of patients who present with limited stage HL should be treated with a brief course of chemotherapy and, among them, a selected subset should receive added radiation therapy. A more extended course of chemotherapy, usually six cycles, is recommended for the 70% of patients who present with advanced stage disease and, again, should be complemented by localized radiation for a selected minority. A small proportion of patients, approximately 5% to 8% of those presenting with limited stage disease and 15% to 20% of those with advanced stage disease, are not cured with primary treatment. Intensified chemo-radiotherapy, assisted by autologous hematopoietic stem cell transplantation, can cure at least 50% to 60% of such patients. Against this background of highly successful, generally well-tolerated treatment it is useful to identify special treatment strategies for subpopulations of patients who present with or develop special challenges to the successful delivery of effective, least toxic treatment for their HL such as patients presenting with underlying organ dysfunction, especially cardiac or pulmonary; patients with coincident pregnancy; human immunodeficiency virus (HIV) positive patients; or patients with highly favorable disease where the focus is not so much on cure as on minimizing toxicity. This Meet the Professor session will focus on these special subpopulations of patients.

Treatment of Hodgkin lymphoma patients with major pulmonary or cardiac compromise

Ideal treatment for HL requires multi-agent chemotherapy with combinations such as ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) or BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone and procarbazine). Patients with underlying pulmonary dysfunction, best assessed by careful questioning about exercise tolerance, smoking history and prior exposure to pulmonary toxins such as industrial dust and asbestos are NOT usefully assessed with pulmonary function tests and should have bleomycin omitted from their treatment if the specialist's clinical assessment is that they could not safely tolerate a drop in current lung function of about 1/3 of their current capacity. I choose 1/3 of current function because an occasional patient will experience that much of an acute drop from baseline. Emerging data concerning the effect of dropping bleomycin indicates that the agent can be safely omitted from further treatment cycles after an initial two cycles of treatment have induced a high quality response in the HL (see Johnson et al., presentation of RATHL data, this meeting).

Because doxorubicin can induce cardiac dysfunction it cannot be given safely to patients with pre-existing or emerging cardiac compromise, best assessed with estimation of ventricular ejection fraction using either multi-gated acquisition scanning (MUGA) or cardiac ultrasonography. An ejection fraction less than 50% or a history of documented congestive heart failure should prompt use of an alternative to doxorubicin. Patients over the age of 65 years or with any history of cardiac injury should be assessed with MUGA

scanning or echocardiography before and intermittently during chemotherapy. At our center, where ABVD is the standard combination, for patients with an ejection fraction less than 50% or history of cardiac failure, we substitute etoposide for the doxorubicin at a dose that causes roughly equivalent myelosuppression. Where BEACOPP or similar regimens are used the doxorubicin should be omitted.

Treatment of Hodgkin lymphoma patients with coincident pregnancy

The diagnosis of HL during pregnancy represents a unique clinical situation. The expectant mother's life is endangered and the developing fetus is at risk of injury. The mother, fetus and their family should be cared for by a multidisciplinary team including an oncologist specializing in lymphoma treatment, a high risk obstetrician and a high risk neonatologist. Staging should avoid ionizing radiation; thus, physical examination, blood tests, single posterior–anterior chest radiograph and abdominal ultrasonography suffice for staging. For patients with minimal or no symptoms chemotherapy should be avoided, especially in the first trimester. Delivery does not need to be premature, and the pregnancy should be carried to term. When necessitated by symptomatic or threatening progression, it is attractive to treat with intermittent single agent vinblastine every 2–4 weeks to stabilize the disease. For symptomatic HL resistant to single agent vinblastine, ABVD is the regimen of choice; its use appears to be safe for fetal development when used in any trimester; however, reported cases are few, and moderate levels of delayed toxicity in the child may well have been missed suggesting particular caution during the first trimester [1,2].

Treatment of Hodgkin lymphoma patients with coincident HIV infection

HL is five- to ten-fold more common in patients with human immunodeficiency virus (HIV) infection than in the general population [3–5]. HIV-associated HL is much more likely to be widespread at presentation, pursues a more aggressive natural history and is much more likely to be of mixed cellularity or lymphocyte depleted histology. More than 80% of patients present with advanced stage, frequently in the bone marrow, which has a negative impact on treatment tolerance and prognosis and the incidence of multiple extranodal sites and B symptoms is much higher than with classical HL.

The treatment of HL coincident with HIV infection is challenging because of the frequency of opportunistic infections, likelihood of coincident organ dysfunction because of HIV or other viral infections such as hepatitis and necessity to employ an array of anti-HIV and other antibiotics and supportive medications all of which may interact with the necessary chemotherapeutic agents. Successful treatment combines vigorous supportive care consisting of antiviral and antifungal agents and neutrophil stimulating growth factors with highly active anti-retroviral agents (HAART) together with standard multi-agent chemotherapy. With appropriate supportive care standard regimens such as ABVD [6–8] and BEACOPP [9] can be delivered. Greater than normal toxicity must be anticipated. Disappointingly, even with intensive supportive care and proper chemotherapy, response and cure rates are lower than in the non-HIV-infected population; however, much progress has been made and 5-year overall survival of 60% to 70% can be achieved [4]. The major innovation in treating HIV-associated HL in recent times has been the widespread use of HAART before, during and after management of the lymphoma. Recent studies have demonstrated that the prognosis of such patients has dramatically improved [3,8]. Much progress still needs to be made, however. Even in the most recent era, when HAART has lowered the incidence of coincident infectious complications of the HIV infection and suppresses the retrovirus itself, cure rates for HL remain lower than those achieved in patients without HIV infection.

Treatment of patients with highly favorable prognosis Hodgkin lymphoma

By the 1990s foundational observations incorporating computed tomographic staging followed by treatment employing brief chemotherapy with two to four courses of ABVD plus radiation demonstrated that combined modality treatment can cure most HL patients who present with limited stage disease [10,11]. With the ABVD effectively addressing micro-metastatic systemic lymphoma a series of carefully crafted clinical trials showed that the radiation field size could be successfully reduced from wide to involved field, as definitively demonstrated by the German Hodgkin Study Group [12], and finally involved nodal [13,14]. By the mid-2000s we knew that 90% to 95% of patients with limited stage HL can be cured with two cycles of ABVD followed by small field radiation [12]. We had reached the crucial goal of curing almost all of the patients. The stage was set to broaden the definition of 'best' treatment by searching for therapy that cures almost all patients with the most efficient, cost effective, least toxic approach. Functional imaging with fluorodeoxyglucose positron emission tomography (PET) has provided the tool needed to reach that goal.

The ingredients that must be in place to successfully rely on interim PET to guide treatment of limited stage HL are listed in Table 1. It is important to remember that all of these ingredients must be available to optimize the outcome including accurate diagnosis based on modern immunohistochemistry; second and third generation CT/PET scanners; mature teams of radiologists and nuclear medicine specialists with extensive experience interpreting

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Table 1. Essential resources for interim PET guided management of limited stage Hodgkin lymphoma

Resource	Justification
Expert hematopathology review	Accurate diagnosis is fundamental
Modern CT/PET scanner	Integration of CT and PET images is essential for accurate staging and interpretation of interim evaluation
Experienced radiologist/nuclear medicine specialist	Accurate interpretation of CT/PET scans is a learned skill dependent on experience
Reproducible, internationally accepted PET interpretation criteria = Deauville score	Reproducibility over time and across multiple treatment settings crucially depends on strict, well-understood criteria
Experienced chemotherapy and radiation oncology teams	Both modalities require careful administration by experienced, well-supported physician-led but technician-dependent teams
Experienced hematopoietic stem cell transplant team	Secondary treatment for the small minority of relapsing patients requiring it must be highly effective and associated with minimal risk of severe toxicity
Long-term commitment to accurate follow-up of patients	Events crucially defining major late toxicity emerge much later than disease-control related events, typically after the first decade of follow-up

CT/PET scans; an internationally accepted, reproducible scoring system, the Deauville criteria [15]; and well-established teams of hematologists, medical oncologists, radiation oncologists and hematopoietic stem cell transplant experts.

What have we learned from trials and center experiences in which those essential resources have been employed? The modern body of evidence most relevant to the choice of treatment for limited stage HL emerged starting with the HD6 trial conducted by the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) and the Eastern Cooperative Oncology Group (ECOG). This study compared a strategy of radiation-based treatment with one employing chemotherapy with ABVD alone [16]. Because the control arm of this study employed obsolete radiation the study's real value for the management of patients today lies in what was achieved in the experimental arm especially the remarkably good outcomes that followed initial treatment with chemotherapy alone—the best outcomes ever reported for limited-stage HL. On the experimental arm of the HD6 study patients with limited-stage HL were treated with ABVD alone. With a median follow-up duration of 11.3 years, the estimated 12-year overall survival of those assigned to the experimental ABVD alone arm was 94%. It is useful to compare the HD6 results with those of the German Hodgkin Study Group (GHSG) HD10 clinical trial [16]. This trial established that, for a more favorable subset of patients with limited stage HL than was enrolled in the HD6 study, brief ABVD (either two or four cycles) plus involved-field radiation (either 20 Gy or 30 Gy), produced a 95% overall survival rate at 8 years. Thus, the strategy of ABVD alone, as given in the HD6 study, matched or exceeded the strategy of combined-modality treatment (HD6: 12-year OS = 94%; HD10 8-year OS = 95%).

Two additional large datasets addressing limited stage HL have been at least partially reported and, because they employed CT/PET scanning in staging and for interim assessment and took place in an era when high dose chemotherapy had become widely and readily available, conditions not present for either the HD6 or GHSG HD10 studies described above; they are more useful to explore the utility of interim PET scanning. The NCIC CTG/ECOG HD6 study established that approximately 80% of patients with limited stage HL can be cured with ABVD chemotherapy alone [16]. What was needed, therefore, was a test that can identify that 80% as early as possible in treatment so they can be spared exposure to radiation. Both the PET-response adapted RAPID trial conducted in the United Kingdom [17] and the H10 trial by the European Organization for Research and Treatment of Cancer, Group d'Etude des Lymphomes de l'Adulte and Fondation Italiana Lymphomi (EORTC/GELA/FIL) [18] have provided useful guidance. With an aggregate population of over 850 patients with favorable limited stage HL enrolled in those two trials it becomes clear that approximately 80% achieve a PET-negative response after two to three cycles of ABVD. The negative predictive value of the PET scan, using eventual relapse as the measure of efficacy and four cycles of chemotherapy as the planned treatment, is above 90%. These two trials nicely complement the observations from the NCIC CTG/ECOG HD6 study and the GHSG HD10 trial allowing identification of a treatment strategy for limited stage HL that neatly preserves very high efficacy but minimizes exposure to unnecessary, potentially toxic radiation.

A useful thought experiment illustrates why the approach of PET-tailored assignment of radiation is so desirable. Consider 100 patients given two cycles of ABVD followed by involved field radiation. Projecting from data from the GHSG HD10 and the EORTC/GELA/FIL H10 study 95 will be cured with primary treatment and at least four of the five who relapse will be cured with secondary autologous hematopoietic stem cell transplant (ASCT). However, all 100 patients will have been exposed to radiation and 5 to high dose chemotherapy. For comparison, consider the same 100 patients treated with two cycles of ABVD and then assessed with PET scan. Using data from

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the NCIC CTG/ECOG HD6, the RAPID and the EORTC/GELA/FIL H10 trials (over 1200 patients) 80 will have a negative PET scan and complete treatment with one or two more cycles of ABVD. The 20 with a positive PET scan will complete treatment with involved field radiation. From the entire 100 patients, nine will relapse, eight from the 80 treated without radiation (10% of 80) and one from the 20 given radiation (5% of 20). All nine will then be treated with ASCT. Compare the total treatment burden visited on the two patient populations. The former 100 patients received a total of 200 cycles of ABVD, 100 involved fields of radiation and five ASCTs. The latter was given 360 cycles of ABVD ($80 \times 4 + 20 \times 2$), 20 involved fields of radiation and nine ASCTs. In both groups 99% of patients were cured so the choice between them must be based on relative toxicity, cost and impact on quality of life. After patients have tolerated two cycles of ABVD the marginal additional toxicity of two more cycles is quite modest, and there is no evidence that this added chemotherapy contributes any meaningful addition to late toxicity. The former strategy results in five ASCTs and the latter nine. However, with the first strategy 80 of the 100 patients were exposed to radiation entirely unnecessarily. The ABVD alone approach exposes very few patients to radiation (20%), while the combined-modality approach exposes every patient to radiation (100%). Costs are difficult to assign because they vary remarkably from country to country; however, omitting radiation for 80% of the patients always drives costs lower in the PET guided group. Risks and costs of second neoplasms remain unclear because how much lower a risk of second cancer, if any, can be expected with current best radiation treatment is unknown. One must ask, however, why any additional risk should be visited on the patient and higher cost on society when doing so carries no net benefit. Interim PET-guided management of limited stage Hodgkin lymphoma is here to stay, for very good reasons.

Most patients with Hodgkin lymphoma can be cured, even those with the special challenges to successful treatment described above.

Conflict of interest

The authors have no competing interest.

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