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## How I treat

# How I treat relapsed and refractory Hodgkin lymphoma

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**Relapsed or refractory Hodgkin lymphoma is a challenging problem for clinicians who treat hematologic malignancies. The standard management of these patients should include the use of salvage chemotherapy followed by autologous stem cell transplant (ASCT) in patients who are chemotherapy sensitive. Open issues in this area include the role of functional imaging, the specific chemotherapy regimen to be used before ASCT, and the role of consolidative radiotherapy.**

**Some patients will not be eligible for ASCT, and alternative approaches with conventional chemotherapy alone or with salvage radiotherapy should be considered. Prognostic factors for relapsed/refractory disease have been identified but generally are not used as a part of risk-adapted therapy. Allogeneic transplantation may offer the potential of a graft-versus-lymphoma effect, but this therapy has significant toxicity and results in few long-term disease-free survi-**

**vors; hence, it should only be offered in the context of disease-specific clinical trials. An expanding list of novel drugs has exhibited promising single-agent activity. Patients have effective options beyond primary therapy, and continued progress through controlled trials remains a tangible goal in the treatment of relapsed and refractory disease. (*Blood*. 2011;117(16):4208-4217)**

## Introduction

The treatment of limited-stage Hodgkin lymphoma (HL) has improved significantly with the adoption of combined modality therapy, with treatment failure occurring in approximately 10% of patients.<sup>1</sup> Although the therapy of advanced-stage HL has also improved, up to 10% of patients with advanced-stage HL will not achieve complete remission (CR), and 20%–30% of responding patients subsequently relapse after treatment.<sup>2</sup> Salvage chemotherapy followed by autologous stem cell transplantation (ASCT) is the treatment of choice in patients with relapsed HL or if the disease is refractory to initial chemotherapy.<sup>3,4</sup> The authors of 2 randomized phase 3 clinical trials showed improved progression-free survival (PFS) in patients receiving high-dose chemotherapy (HDCT) compared with those patients treated with standard-dose salvage chemotherapy, although there was no statistically significant difference in overall survival (OS).<sup>5,6</sup>

Although these randomized controlled trials form the basis for the management of patients with relapsed or refractory HL (RR-HL), the application of these and other data in the literature to patient care remains a challenge. Here, we focus on some of the difficult and controversial areas in patient management, including identification of progressive or nonresponsive disease, assessment of the role of prognostic factors and of functional imaging, and available treatments (including both stem cell transplantation and nontransplantation-based strategies). We also highlight data on new treatments and novel agents currently in clinical trials.

## Diagnosis of RR-HL

With the almost-universal availability of computed tomography (CT) scanners and more recently, the increasing use of fludeoxyglucose positron emission tomography (FDG-PET) and CT-PET imaging, patients are often followed by serial imaging after

completing primary therapy, with the result that the first sign of progressive disease may be an asymptomatic radiologic abnormality. Although institutional standards vary, the National Comprehensive Cancer Network (NCCN) Guidelines frequently are used as the standard for surveillance imaging. The NCCN v2.2010 guideline on Hodgkin lymphoma<sup>7</sup> recommends that surveillance imaging be performed routinely with chest imaging (chest x-ray or CT thorax) every 6-12 months (level of evidence grade 2A) and CT abdomen every 6-12 months (grade 2B). These recommendations are made despite several reports that serial imaging in asymptomatic patients in remission is of limited value in detecting disease recurrence<sup>8-11</sup> and with limited data on the outcomes of patients with clinically versus radiologically detected relapse via the use of modern imaging techniques.<sup>12,13</sup>

It has been suggested that all patients should have a repeat biopsy to establish the presence of RR-HL. Repeat biopsy should be considered when the initial pathologic diagnosis is ambiguous or unclear and is also important if the relapse is late in the disease course (beyond 3-5 years of primary therapy) or if the clinician believes another diagnosis may be likely. However, for most cases under consideration for second-line therapy (clear radiologic progression on therapy or early relapse within sites of previous disease), we do not believe it is justified to mandate an invasive test with its risk of complications.

Although data on the utility of routine PET scanning of patients in remission are not convincing,<sup>12,13</sup> the use of FDG-PET for assessment of response to primary therapy and in surveillance after remission has increased in popularity. The International Harmonization Project in Lymphoma consensus guidelines on FDG-PET imaging recommend scanning at the end of therapy (6-8 weeks after chemotherapy and 8-12 weeks after radiation),<sup>14</sup> but post-therapy surveillance was thought only to be appropriate for patients participating in clinical trials. In this context, the clinician must be

clear to define the rationale in pursuing a FDG-PET scan—is the scan being used to “identify” relapsed or refractory disease, or is it being used as a predictive biomarker suggesting a high likelihood of treatment failure? We will discuss the role of FDG-PET as a biomarker (part of response assessment) in the section “The role of functional imaging in response assessment before ASCT.” In the context of posttherapy surveillance (as distinct from midtherapy or end-of-therapy scans, which are used as part of response assessment), FDG-PET scans may be used to detect relapse, but we do not believe that this can be the only test used to detect recurrent HL given the positive predictive value of PET scans in this setting.

Unfortunately, the positive predictive value of a PET scan for detecting residual active disease is quite variable and generally lower than the negative predictive value of PET posttherapy. False-positive scans may be because of rebound thymic hyperplasia in young patients, local inflammation after chemotherapy or radiotherapy, sarcoidosis, or deposition of brown fat. In a recent report that included 57 patients with mediastinal HL, the majority with stage I or II disease and 25 with bulky mediastinal masses, 21 had a positive FDG-PET scan at the end of treatment or in early follow-up. On biopsy, only 10 of 21 had biopsies confirming persistent or recurrent HL; biopsies in the other cases showed only fibrosis or other benign etiologies.<sup>13</sup>

A study from Memorial Sloan Kettering Cancer Center in diffuse large B-cell lymphoma after primary therapy similarly provides a cautionary tale for decision-making informed by PET in HL: only 5 of 38 biopsies of FDG-PET–positive lesions at the end of therapy demonstrated diffuse large B-cell lymphoma.<sup>15</sup> Patients with a positive posttreatment PET scan should proceed to biopsy whenever this can be done safely or be reassessed with cross-sectional imaging before beginning salvage therapy in conjunction with progressive or new lesions detected by conventional imaging that are in keeping with HL. The diagnosis would appear clear, but we recommend either serial imaging if the site of disease is difficult to access or a biopsy to obtain definitive evidence of disease.<sup>12,13</sup> Although early reports have led some researchers to conclude that the presence of FDG-PET–positive imaging abnormalities at the end of primary chemotherapy is a biomarker for subsequent treatment failure and requires intensification and ASCT, not all studies of end-of-treatment PET support this conclusion. For example, early follow-up from the German Hodgkin Lymphoma Study Group (GHSG) HD15 study suggests that radiotherapy applied to FDG-positive residual masses may be an effective alternative: 86% of such patients remained progression free, compared with 95% who were FDG negative or with a CR by CT scan.<sup>16</sup>

In summary, we do not recommend ongoing serial imaging of asymptomatic patients in remission after primary treatment. The NCCN guideline of serial imaging every 6-12 months is determined by data that we believe are not compelling enough to expose patients to further diagnostic radiation and additional unnecessary costs. Given the resource and patient care implications, this area remains worthy of additional prospective study. We recommend, however, that patients undergo diagnostic rebiopsy to confirm progressive disease if the primary diagnosis was unclear, if the relapse is late or unusual in pattern, or, in particular, if an alternative diagnosis is favored. We also recommend the biopsy of FDG-PET–positive lesions to clarify the presence of active HL whenever feasible or close serial monitoring with conventional imaging until disease progression before proceeding to salvage chemotherapy and ASCT.<sup>12,13</sup>

**Table 1. Poor prognostic factors in relapsed or refractory Hodgkin lymphoma**

Patient group	Factor
Relapsed	Time to relapse < 1 year <sup>18,21-24</sup>
	Stage III-IV (IV: Lohri, Martin) <sup>18,19,21,22,24</sup>
	Anemia <sup>18</sup>
	B symptoms <sup>21,24</sup>
Refractory	Poor performance status <sup>23</sup>
	Poor performance status <sup>17,23</sup>
	Age > 50 y <sup>17</sup>
	Failure to attain a temporary remission <sup>17</sup>
	B symptoms <sup>21</sup>
ASCT	Stage III-IV (IV: Martin) <sup>19,21</sup>
	Previously untreated relapse <sup>23</sup>
	Response to chemotherapy <sup>19</sup>
	Low serum albumin <sup>25</sup>
	Anemia <sup>25</sup>
	Age <sup>25</sup>
	Lymphocytopenia <sup>25</sup>
	B symptoms <sup>26</sup>
	Extranodal disease <sup>26</sup>
	Time to relapse < 1 year <sup>26</sup>
Disease status at ASCT <sup>20</sup>	
Disease relapse in previous radiation field <sup>20</sup>	

ASCT indicates autologous stem cell transplant.

## Prognostic factors in RR-HL

Several authors<sup>17-26</sup> have identified prognostic factors in cohorts of patients with RR-HL who have undergone subsequent salvage chemotherapy and ASCT (summarized in Table 1). The largest studies of prognostic factors in patients not specifically selected for ASCT have been performed by the GHSG. In the first publication, investigators reported prognostic factors and outcomes in 206 patients enrolled in prospective clinical trials with primary refractory HL who were defined by the presence of lymphoma that progressed while on primary treatment or within 3 months of completion.<sup>17</sup> The significant adverse prognostic factors identified from multivariate analysis were poor performance status (Eastern Cooperative Oncology Group score > 0), age > 50 years, and failure to obtain a temporary remission to initial therapy. A subsequent GHSG publication reported prognostic factors and outcomes in 422 patients with relapsed HL.<sup>18</sup> The significant adverse prognostic factors for overall survival identified in multivariate analysis were anemia (hemoglobin < 120 in men, < 105 in women), advanced clinical stage (III or IV), and time to treatment failure of < 12 months.

The prognostic factors summarized in Table 1 show that time to relapse after initial therapy, advanced stage at relapse, and poor performance status have consistently been demonstrated to be predictors of poor outcome. Time to relapse appears to be of particular importance because the GHSG primary refractory cohort had a 5-year OS of 26% compared with 46% for early relapse after chemotherapy (between 3 and 12 months) and 71% for late relapse (after 12 months) in the GHSG-relapsed cohort.<sup>17,27</sup> The lack of concordance between the reported studies with respect to other variables affecting outcome (for example, age, B symptoms, or relapse in a previous radiation field) likely reflects underlying variability in disease biology insufficiently captured by available clinical parameters, and the relatively small sample sizes of these series. Prospective validation of the predictors of outcome identified by Josting et al and others<sup>17,27</sup> or of the variables identified as

**Table 2. Salvage chemotherapy regimens in relapsed or refractory Hodgkin lymphoma**

Chemotherapy regimen	No. of patients	CR (%), 95% CI	PR (%), 95% CI	ORR (%), 95% CI	Grade 3/4, NEUT (%)	Grade 3/4, TCP (%)	Grade 3/4, VOM (%)	Toxic deaths (%), 95% CI
Dexa-BEAM <sup>6</sup>	144	27, 20-34	54, 46-62	81, 75-87	NS	NS	NS	5, 1-9
Mini-BEAM <sup>19</sup>	55	49, 35-63	33, 21-47	82, 69-91	86	60	NS	2, 0.1-10
ICE <sup>21</sup>	65	26, 16-39	59, 46-71	85, 74-92	NS	NS	NS	0, 0-5
DHAP q2wk <sup>30</sup>	102	21, 13-29	68, 59-77	89, 83-95	88	69	26	0, 0-4
GDP <sup>32</sup>	23	17, 5-39	52, 31-73	69, 47-87	9	13	13	0, 0-15
GVD <sup>38*</sup>	91	19	51	70	63	14	0	0
IEV <sup>35</sup>	51	76, 60-88		84, 71-93	100†	NS	NS	0
MINE <sup>34</sup>	157	NS	NS	75, 64-84	NS	NS	NS	5‡
IV <sup>36, 39</sup>	47	45, 30-60	38, 25-54	83, 69-92	65	0	2	NS

ASCT indicates autologous stem cell transplant; BEAM, BCNU, etoposide, ara-C, melphalan; CI, confidence interval; CR, complete response; DHAP, dexamethasone, ara-C, cisplatin; GDP, gemcitabine, dexamethasone, cisplatin; GVD, gemcitabine, vinorelbine, doxil (liposomal doxorubicin); ICE, ifosfamide, carboplatin, etoposide; IEV, ifosfamide, etoposide, vinorelbine; IV, ifosfamide; MINE, mitoguazone, ifosfamide, vinorelbine; etoposide; NEUT, neutropenia; NS, not stated; ORR, overall response rate; PR, partial response; q2wk, every 2 weeks; TCP, thrombocytopenia; and VOM, vomiting.

\*Mucositis reported in 9%.

†All patients experienced grade IV neutropenia.

‡The 5% toxic death rate included patients undergoing ASCT.

determinants of outcome with primary therapy, should be performed, but an international collaborative effort is needed to determine the key predictive factors in these patients.

Although the documentation of these factors may allow the clinician to prognosticate on outcome and provide informed consent to patients undergoing therapy, few therapeutic strategies actually incorporate a risk-adapted approach in the management of RR-HL. Given the wealth of clinical prognostic factor data available, we believe that time to relapse (< 3 months identifying primary refractory disease and 3-12 months identifying early relapse of disease associated with poor outcome), advanced stage, and poor performance status are robust predictors of outcome and should be used to test risk-stratified approaches to treatment. Primary refractory disease has a particularly poor outcome, and we recommend enrollment when possible in prospective studies specifically in this group of patients.

## Treatment

### Salvage chemotherapy: before ASCT

Despite a multitude of published phase 2 studies reporting results of salvage regimens for RR-HL,<sup>27-36</sup> there are no direct comparisons of different combinations and thus no consensus on the gold-standard second-line chemotherapy. The published randomized controlled trials (RCTs) of ASCT for RR-HL used mini-BEAM (ie, BCNU [bis-chloronitrosourea], etoposide, ara-C, melphalan) or dexa-BEAM (dexamethasone, BCNU, etoposide, ara-C, melphalan), so these regimens should be considered standard regimens in this setting. If the ultimate goal of salvage chemotherapy is to enable patients to proceed to ASCT, the ideal salvage regimen should produce a high response rate with acceptable hematologic and nonhematologic toxicity and not impair the ability to mobilize and collect peripheral blood stem cell (PBSC) mobilization for ASCT. Although the authors of the aforementioned RCTs would argue for the use of multidrug regimens, including mini-BEAM, we have found these regimens to have significant hematologic toxicity, to require frequent patient hospitalization for febrile neutropenia, and to have a high incidence of transfusion support. Stem cell mobilization appears to be compromised after treatment with mini-BEAM.<sup>37</sup>

Several published and widely used salvage chemotherapy regimens are summarized in Table 2.<sup>6,19,21,31-36,38,39</sup> These trials

report overall response rates between 60% and 87%, with overlapping 95% confidence intervals. Although these single-arm phase 2 trials enrolled different patient populations, there is no evidence to demonstrate that one is superior over others. Calculated confidence intervals are also presented for treatment-related mortality (TRM) rates. The reported toxicity in these trials is largely hematologic, although gastrointestinal toxicity (nausea and vomiting) is also common. Although the dexa-BEAM regimen had overall response rates of 81% in the GHSG/European Group for Blood and Marrow Transplantation (EBMT) phase 3 ASCT trial, TRM from salvage chemotherapy in that study was 5%. Other trials have reported TRM between 0% and 2%, a more acceptable level given the young age and lack of comorbidity typically found in patients with HL. The optimal number of cycles of salvage chemotherapy to administer is not known; typically, 2-3 cycles of treatment are given, but there is a balance between further toxicity (including potential impact on collecting stem cells for ASCT) and potential efficacy by improving response. We routinely administer 2 cycles of GDP and assess response—if adequate response is achieved, we proceed to stem cell collection.

Published reports often include a mixture of patients with primary refractory and relapsed disease, with the authors of most series likely unable to demonstrate significant differences in response to salvage therapy because of a lack of statistical power. Patients with primary refractory HL have an inferior response rate to second-line chemotherapy (51% vs 83%,  $P < .0001$ )<sup>40</sup>; the wide range of response rates (between 32% and 84% reported in other series) likely reflects relatively small sample sizes and imbalances of this and other prognostic factors.<sup>4,17,34,41-43</sup>

Unfortunately, lack of response to salvage chemotherapy is not uncommon, and clinicians are left with a therapeutic dilemma. The randomized GHSG trial only randomized responding patients and thus RCT evidence does not support proceeding to ASCT in this setting. Our group has published previously on delivering second-line salvage chemotherapy; in an older cohort study of 37 patients with RR-HL receiving DHAP as first salvage therapy, 6 of 10 patients who had a suboptimal response achieved at least a partial response (PR) with an alternative regimen and proceeded with ASCT.<sup>44</sup> A subsequent series in patients with DHAP failure reported that mini-BEAM was successful in 8 of 11 patients who were able to proceed to ASCT.<sup>45</sup> The authors of a United Kingdom series reported that patients with an inadequate response to first salvage ( $n = 6$ ), defined as persistent bulk or residual marrow



**Table 3. Efficacy of PBSC mobilization after salvage chemotherapy for relapsed or refractory Hodgkin lymphoma**

Regimen	n	% CD34 ≥ 2 × 10 <sup>6</sup> /kg	% CD34 ≥ 5 × 10 <sup>6</sup> /kg	% undergoing marrow harvest
GDP <sup>37</sup>	34	97	97	3
MB <sup>37</sup>	34	82	57	18
ICE <sup>21</sup>	65	86	67	14

GDP indicates gemcitabine, dexamethasone, cisplatin; ICE, ifosfamide, carboplatin, etoposide; MB, mini-BEAM; and PBSC, peripheral blood stem cell.

disease, derived the greatest benefit from second salvage, compared with those achieving stable disease (SD; n = 6) or progressive disease (PD; n = 5). Second salvage allowed the first group to proceed with stem cell transplantation (3 allogeneic stem cell transplantation [allo-SCT], 3 ASCT), which resulted in long-term remission in 5 patients.<sup>46</sup>

We have recently reviewed our experience in patients who did not achieve a CR or PR to salvage chemotherapy with gemcitabine, dexamethasone, cisplatin (GDP; D. Villa, manuscript in preparation) using more modern response criteria.<sup>47</sup> On the basis of our experience with RR-HL, our policy is to proceed with ASCT in patients who have not achieved CR/PR if patients have stable disease after salvage therapy but have negative functional imaging (typically by gallium scan) and no residual masses of > 5 cm.<sup>20</sup> Five-year PFS was similar in the 99 patients undergoing ASCT in CR/PR to the 13 patients transplanted with SD (61% and 69%, respectively). In patients with PD, residual functional imaging abnormalities or presence of disease > 5 cm after receiving GDP, we proceeded with a cycle of mini-BEAM. Of these 19 patients with an inadequate response to GDP, the response rate to mini-BEAM was 32%, although given our criteria, 47% of patients could proceed to ASCT. The 5-year PFS after ASCT in these patients was disappointing at 22%. In our series, 10 of 131 patients (8%) did not have adequate response to chemotherapy to proceed to ASCT and went on to receive noncurative treatment.

An important issue related to salvage chemotherapy is the potential for second-line therapy to impair the ability to mobilize peripheral blood stem cells to support potentially curative HDCT. The efficacy of salvage chemotherapy for HL must be balanced by toxicity and the impact on subsequent PBSC mobilization. Success rates for PBSC mobilization have not been consistently reported in the trials listed in Table 2. Some investigators report that regimens containing melphalan, such as dexamethasone-BEAM or mini-BEAM, may result in reduced stem cell mobilization.<sup>48-50</sup> Available results for PBSC mobilization after treatment with these salvage chemotherapy regimens are presented in Table 3.<sup>21,37</sup> Optimal timing for PBSC mobilization will vary on the basis of the regimen used and may vary substantially between patients on the basis of disease and treatment factors. Given these issues and a desire to standardize PBSC mobilization, we use an efficient PBSC-mobilizing regimen consisting of 2 g/m<sup>2</sup> cyclophosphamide on day 1, etoposide 200 mg/m<sup>2</sup> on days 1-3, and filgrastim 10 μg/kg/d starting on day +6 with serial CD34<sup>+</sup> blood testing starting on day +13.

We recommend the use of a standard salvage therapy regimen with which clinicians are comfortable that results in high response rates, acceptable toxicity, that does not impair stem cell mobilization, and ideally, that can be delivered in the outpatient setting. Regimens such as ICE (ie, ifosfamide, carboplatin, and etoposide) or GDP are reasonable options.<sup>21,37</sup> On the basis of our experience in patients who are nonresponders to a platinum-containing regimen, patients with SD with small-volume disease that is negative

by functional imaging can safely proceed to ASCT, with similar PFS as those who achieve a PR. An alternate regimen (we use mini-BEAM on the basis of our experience described previously) should be used in patients with PD, larger volume disease, or lesions that remain positive by functional imaging. Although the need for alternative salvage therapy identifies a group with a poor prognosis compared with patients responding to their initial regimen, approximately 50% may proceed to ASCT, and a minority remains in remission.

### The role of functional imaging in response assessment before ASCT

FDG-PET is increasingly used as part of response assessment in second-line therapy despite a lack of large prospective datasets to guide decision-making. One may also think of functional imaging as a biomarker with a positive test after salvage therapy suggesting a greater rate of relapse after ASCT. Retrospective institutional series suggest that abnormal functional imaging (FI; either gallium or FDG-PET scan) after salvage therapy and before ASCT are predictive of poor outcome (3-year OS of 58% vs 87% if negative FI). In particular, patients who had achieved a PR with CT imaging could be discriminated by FI—in those with negative FI, outcome was similar to patients in CR (3-year OS of 90% in CR, 80% in PR with negative FI) but significantly inferior if positive (65%).<sup>51</sup>

Recently, the authors of a large series studying FI after ICE chemotherapy reported similar results, with a 5-year EFS of 31% for FI-positive disease compared with 75% if negative.<sup>52</sup> A small Italian series of 24 patients who underwent FDG-PET scanning after 2 cycles of salvage chemotherapy reported 2-year PFS of 93% for PET-negative and 10% for PET-positive patients.<sup>53</sup> Schot et al<sup>54</sup> reported that postsalvage therapy PET results were independent of clinical risk score in predicting outcome in 101 patients undergoing ASCT, but only 20 had HL, and the results of assessment of response by PET in that study appeared generally achievable with CT scan response criteria.

Current reports of the ability of functional imaging using gallium or FDG PET scanning to predict outcome post-ASCT are contradictory, and although information from such scans may provide some prognostic information for patients and physicians, the results are not robust enough to determine who should proceed to transplant or to direct risk-adapted therapy outside of a clinical trial designed to test this concept.

### ASCT high-dose therapy regimens and strategies

The role of aggressive second-line therapy in HL has been defined by 2 published phase 3 RCTs.<sup>5,6</sup> The GHSG/EBMT assigned 161 patients with relapsed HL to receive 2 cycles of dexamethasone-BEAM chemotherapy and randomized responding patients to either 2 additional cycles of dexamethasone-BEAM or high-dose therapy and ASCT. Although there was no difference in OS, freedom from treatment failure at 3 years was significantly improved in the ASCT group (55% vs 34%, *P* = .02).<sup>6</sup> Neither of these trials of ASCT included chemorefractory patients, and only cohort and registry data address the benefit of ASCT in these patients.<sup>3,4,17</sup>

There are limited modern data on the role of ASCT in lymphoma overtly refractory to chemotherapy. Data from Seattle in 64 chemoresistant (defined as less than a partial remission) HL patients at a median follow-up of 4.2 years after ASCT demonstrate a 5-year PFS and OS of 17% and 31%, respectively. These results appear inferior to outcomes of ASCT in chemosensitive patients but also are likely to be influenced by issues related to the era in

**Table 4. High-dose chemotherapy regimens used with ASCT in relapsed or refractory Hodgkin lymphoma**

Regimen	N	Early TRM (%)	OS, %	PFS/DFS, %	Secondary AML/MDS	Comment
BEAM <sup>6</sup>	56	1/56 (2)	44/61	FFTF-3: 55	1/56	OS not clearly reported
CBV <sup>57</sup>	128	3/26 (8)	OS-4: 45	FFS-4: 25	5/128	
CBVP <sup>58</sup>	68	5/68 (7)	NS	50	1 (total n of 96)	
VP-16/MEL <sup>20</sup>	73	3/73 (4)	NS	DFS-4: 39	NS	
BEAM <sup>34</sup>	101	NS	71	FFTF-5: 67	1 AML (unknown if in ASCT group)	
TLI + VP-16/CY <sup>21</sup>	22	2/22 (9)*	81	61	NS	
CCV <sup>56</sup>	59	5/59 (8)	OS-3: 57	EFS-3: 52, FFP-3: 68	1	21 deaths, 11 NRM, high pulmonary toxicity 63%
HDM <sup>55</sup>	46	0	OS-5: 57	EFS-5: 52	0	Estimated 5-year results, short FU

AML, acute myeloid leukemia; BEAM, BCNU, etoposide, ara-C, melphalan; CBV, cyclophosphamide, BCNU, VP-16; CBVP, cyclophosphamide, BCNU, VP-16, and cisplatin; CCV, cyclophosphamide, CCNU (lomustine), VP16; DFS, disease-free survival; EFS-3/-5, 3- or 5-year event-free survival; FFP-3, 3-year freedom from progression; FFTF-5, 5-year freedom from treatment failure; FFTF-10, 10-year freedom from treatment failure; FU, follow-up; HDM, high-dose melphalan; MDS, myelodysplastic syndrome; MEL, melphalan; NRM, nonrelapse mortality; NS, not stated; OS-3/-4/-5, 3-, 4-, or 5-year overall survival; PFS, progression-free survival; TLI, total lymphoid irradiation; TRM, treatment-related mortality.

\*Unknown if in CBV or TLI group reported.

which patients were transplanted; these protocols were conducted between 1986 and 2005.

Similar to the situation with salvage therapy pretransplant, direct comparisons of high-dose regimens are lacking, and the choice of agents and doses is quite variable. The toxicity and antilymphoma efficacy of these regimens also varies (Table 4),<sup>6,20,21,34,55-58</sup> which may be a reflection of the agents and doses used, the characteristics of the patients treated, or, most likely, both of these factors.

The 2 randomized trials of ASCT for RR-HL used BEAM (ie, BCNU, etoposide, Ara-C, and melphalan) HDCT. Other single-institution studies report outcomes with regimens such as CBV (ie, cyclophosphamide, BCNU, VP-16), CBVP (cyclophosphamide, BCNU, VP-16, and cisplatin),<sup>59</sup> etoposide and melphalan,<sup>20</sup> single-agent high-dose melphalan,<sup>55</sup> CCV (ie, cyclophosphamide, CCNU [lomustine], VP16),<sup>56</sup> and total lymphoid irradiation with VP-16, carboplatin and cyclophosphamide.<sup>60</sup> The lack of randomized comparisons of HDCT regimens makes it difficult to conclude that there is an optimum regimen in terms of toxicity and efficacy. Characteristics of an attractive HDCT regimen include low incidence of nonhematologic toxicity (gastrointestinal, pulmonary, and hepatic toxicity) as well as proven antitumor activity. The latter has been difficult to demonstrate because many patients are transplanted in complete or near-complete response after salvage chemotherapy, and few report correlation of a high percentage of patients converting from PR to CR with improved long-term EFS. Later effects, including fatigue, cognitive deficits, as well as secondary cancers remain important considerations, but the impact of HDCT on these outcomes (as distinct from the effects of exposure to salvage chemotherapy and radiation before transplant) has not been well defined.

Although further intensification of high-dose regimens has met with limited success,<sup>59</sup> there may be opportunity to further refine the autograft platform. Intensification with the use of augmented-dose mobilization regimens<sup>55</sup> or additional therapy after stem cell collection<sup>61</sup> has been reported to improve outcome. The Cologne high-dose sequential (HDS) protocol begins with an induction phase of 2 cycles of standard DHAP (dexamethasone, high-dose ara-C, cisplatin) chemotherapy followed by a response assessment. Responders proceed to HDS which consists of 4 g/m<sup>2</sup> cyclophosphamide followed by granulocyte colony-stimulating factor and subsequent PBSC collection, 8 g/m<sup>2</sup> methotrexate with vincristine 1.4 mg/m<sup>2</sup>, etoposide 2 g/m<sup>2</sup> with granulocyte colony-stimulating factor and an optional second PBSC collection, and finally, BEAM high-dose therapy and ASCT. The GHSG reported a multicenter phase 2 pilot trial in which they demonstrated HDS to be feasible

with acceptable toxicity.<sup>59</sup> Recently, the GHSG and EBMT reported the HD-R2 trial, a randomized comparison of HDS therapy followed by ASCT to standard DHAP and ASCT.<sup>62</sup> Mature follow-up of the randomized study was recently published, and with a median follow-up of 42 months, no significant differences in freedom from treatment failure, PFS, or OS were observed.<sup>61</sup>

An additional intensification strategy that has been tested is the use of tandem autologous transplants.<sup>63</sup> Although controlled trials are lacking, this strategy was tested prospectively in a large cohort study by the Groupe d'Etude des Lymphomes de l'Adulte (GELA) investigators. The GELA multicenter H96 trial tested a risk-adapted approach in which patients were assigned to a single or tandem autograft on the basis of the presence of risk factors at initiation of salvage therapy. Those with primary refractory disease or at least 2 poor risk factors—time to relapse < 12 months, relapse in a previous radiation field or stage III/IV disease at the time of relapse were considered high risk and were planned to receive tandem ASCT; all others received a single transplant.<sup>64</sup> With 6% TRM and 5-year OS of 46% in the poor-risk group, this trial demonstrated feasibility, but the approach should be tested prospectively compared with a standard single autograft to assess survival advantage.

The randomized trials of ASCT in RR-HL used BEAM as the high-dose therapy regimen and thus BEAM could be considered the standard. We would stress that ASCT programs should use a regimen with which they have experience and report favorable toxicity results. We use etoposide and melphalan and have observed a very low incidence of pulmonary toxicity and virtually no episodes of veno-occlusive disease, compared with regimens such as CBV, which add high-dose carmustine. We do not recommend the routine use of alternate ASCT strategies (HDS or tandem ASCT) because of a lack of RCT evidence. Patients with high-risk disease (primary refractory HL, for example) should be enrolled in prospective trials of novel strategies aimed to improve cure rates. Although it is appealing to consider risk-adapted therapy as part of routine standard of care, prospective RCT evidence is necessary—to that end, we would strongly recommend that patients be enrolled in trials such as those testing maintenance therapy with brentuximab vedotin (SGN-35) or panabinostat after ASCT in patients with adverse risk factors before salvage therapy.

#### Standard-dose therapy approaches

Although most patients with relapsed or refractory HL will be recommended to receive aggressive salvage and ASCT because of

**Table 5. Results of salvage radiotherapy alone in relapsed or refractory Hodgkin lymphoma**

Reference	N	OS	Relapse-free survival	Prognostic
Josting et al <sup>65</sup>	100	OS-5: 51%	FFTF-5: 26%	B symptoms Advanced stage Poor performance status
Campbell et al <sup>67</sup>	81	OS-10: 46%	FFTF-10: 33%	B symptoms Age > 50 years Extranodal disease < CR to previous chemotherapy Male sex
Leigh et al <sup>68</sup>	28	Median:97 mo	Median RFS: 46 mo	Initial CR to chemotherapy
Pezner et al <sup>69</sup>	10	OS-5: 60%	RFS-5: 30%	Disease-free interval < 1 y
Brada et al <sup>66</sup>	44	OS-10: 40%	PFS-10: 23%	Age > 40 y Extranodal disease Disease-free interval < 1 y
MacMillan and Bessell <sup>70</sup>	11	OS-10: 90%	DFS-10: 44%	NS
Uematsu et al <sup>71</sup>	28	OS-7: 36%	RFS-7: 36%	NS

CR indicates complete remission; DFS-10, 10-year disease-free survival; FFTF-5, 5-year freedom from treatment failure; FFTF-10, 10-year freedom from treatment failure; NS, not stated; OS-5, 5-year overall survival; OS-10, 10-year overall survival; PFS-10, 10-year progression-free survival; RFS-5, 5-year relapse-free survival; and RFS-7, 7-year relapse-free survival.

young age and lack of comorbidity, alternative options are available. There are few published reports of salvage radiotherapy alone in relapsed or refractory HL (Table 5).<sup>65-71</sup> Most of these patients were treated before anthracycline-based primary chemotherapy became the standard of care in North America and before the emergence of early phase 3 data showing the superiority of ASCT over conventional chemotherapy.

The largest modern series is a retrospective review from the GHSG reporting the outcome of 100 patients enrolled in trials between 1988 and 1999.<sup>65</sup> Eighty-five percent of the patients had progressed after COPP-ABVD (ie, cyclophosphamide, vincristine, procarbazine, prednisone with ABVD [adriamycin, bleomycin, vinblastine, and dacarbazine]) or similar regimens, whereas 8% had received standard or escalated BEACOPP (ie, bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone). The remaining patients had received radiotherapy alone. The 5-year freedom from treatment failure and OS rates for the entire cohort were 29% and 51%, respectively. In multivariate analysis, the presence of B symptoms and advanced stage (III, IV) at relapse were adverse predictors of overall survival. Poor Karnofsky performance status (< 90%) was identified as a poor prognostic factor for freedom from treatment failure.

Review of other studies demonstrates similar results.<sup>20,65-70</sup> Long-term disease control with salvage radiotherapy is achieved in only 23%-44%. Patients with B symptoms, response duration to initial therapy of less than 12 months, the presence of extranodal disease, and poor performance status are predictors of worse outcomes with salvage radiotherapy.

Combined modality therapy incorporating multiagent chemotherapy followed by radiotherapy has become the standard of care for primary treatment of limited-stage HL on the basis of multiple trials.<sup>72-74</sup> Although radiotherapy alone at relapse is thought to be largely palliative, the role of combined modality therapy with the use of conventional-dose chemotherapy as part of a second-line treatment strategy has only been studied retrospectively. This type of strategy would be particularly appealing if patients have not received radiotherapy with previous treatment or have relapsed with disease in sites that have not been previously irradiated. Prospective, randomized trials would be required to determine the role of any salvage therapy using radiotherapy, but this is unlikely to happen because of the large number of patients required to do

such a trial and the acceptance of adding radiotherapy to a transplant-based strategy on the basis of cohort data and its inclusion in the phase 3 GHSG trial.<sup>6,21,75</sup>

The data supporting retreatment with standard-dose chemotherapy alone after relapse after anthracycline-based chemotherapy are similarly limited. Reports from single centers suggest that some patients with late relapse (defined as more than one year after completion of induction chemotherapy) may achieve long-term disease control with standard-dose second line regimens. In the series from Milan reported by Bonfante et al,<sup>76</sup> 8-year freedom from second progression and OS was 53% and 62%, respectively, for patients retreated with MOPP (meclorothamine, vincristine, procarbazine, prednisone)-ABVD after a CR lasting longer than 12 months. Separate analyses of patients with relapsed HL enrolled in adult<sup>18</sup> or pediatric<sup>77</sup> cooperative group trials demonstrate that time to initial treatment failure is a strong predictor of survival for patients receiving salvage therapy, independent of HDCT and ASCT (although assignment to therapy in these reports was not randomized and prognostic factors were not controlled).

To summarize, we believe that non-ASCT-based strategies can be considered in limited, specific clinical scenarios. Because these cases are rare, management decisions should include clinicians experienced in the field of lymphoma and transplantation. It is important to include radiotherapy in the treatment plan for relapsed disease when radiotherapy was not used in primary treatment or if relapse has occurred in nonirradiated areas. Salvage radiotherapy alone may be considered reasonable treatment, especially for older patients with relapsed HL who lack B symptoms, have a good performance status, and have limited stage disease at relapse. In selected patients not eligible for ASCT, salvage radiotherapy remains an important option. We believe that some patients with very late relapse (at our center, > 5 years) after primary therapy who experience localized relapse without B symptoms can be treated successfully with standard-dose chemotherapy and involved (or occasionally extended) field radiation. In the rare circumstance in which patients relapse after receiving nonanthracycline-based primary treatment, we would recommend a standard-dose therapy regimen, including doxorubicin, and the use of radiation therapy for limited stage or bulky disease. Ideally, identification of biologic predictors of favorable outcome after late relapse would aid clinical decision-making and potentially spare



those patients who are curable with standard dose second-line therapy the risks and toxicity of ASCT.

### **Intensive strategies including allografting and second autograft**

Allo-SCT continues to be a treatment option in advanced HL because of the relatively young age of many of these patients. Myeloablative allo-SCT has been used in advanced phases of the disease but with tempered enthusiasm because TRM often exceeded 50% and relapses were not uncommon.<sup>78-81</sup> The role of myeloablative allo-SCT in HL appeared limited; whereas dose intensity can be delivered in the context of a myeloablative allograft and donor stem cells are free of tumor cell contamination, the presence of a clinically significant graft-versus-Hodgkin lymphoma (GVHL) effect has never been clearly demonstrated.

More recently, reports have demonstrated signs of antitumor effect after donor lymphocyte infusion.<sup>82-85</sup> In addition to this antitumor effect, the safety of allogeneic transplantation has improved with the use of reduced-intensity allogeneic stem cell transplantation (RIC-allo). These approaches have become increasingly popular because of decreased rates of early treatment-related mortality.<sup>86-89</sup> Despite early favorable outcomes, mature results of RIC-allo available in the literature consistently demonstrate a lack of long-term disease control with PFS estimates of approximately 25%-30% and overall survival estimates of 35%-60% at least 2 years after SCT.<sup>84,86-89</sup>

A large prospective study completed by the el Grupo Español de Linfomas/Trasplante Autólogo de Médula Ósea (GEL/TAMO) and EBMT has been recently reported.<sup>90</sup> During a 7-year span, 78 patients ultimately proceeded through a RIC-allo transplant with a preparative regimen consisting of fludarabine 150 mg/m<sup>2</sup>, melphalan 140 mg/m<sup>2</sup>, and graft-versus-host disease prophylaxis of cyclosporine and short course methotrexate. With a median follow-up of 38 months, 3-year outcomes included a relapse rate of 59%, PFS of 25%, and OS of 43%. Although post-SCT outcomes were similar in matched sibling and unrelated donors, patients with chemorefractory disease had an inferior PFS (25% vs 64% at 1 year). Chronic graft-versus-host disease was associated with a reduced rate of relapse after transplantation, and in patients with relapse after allo-SCT, donor lymphocyte infusion (DLI) alone generate an overall response rate of 40%. These results suggest the presence of a GVHL effect in a prospective multicenter trial but highlight the high relapse rate and not-insignificant toxicity with this approach.

In the absence of randomized comparisons with standard therapy, RIC-allo transplant has been compared with retrospective cohorts by 2 groups.<sup>91,92</sup> Both the United Kingdom Cooperative Group and Italian studies demonstrated an overall survival advantage favoring allografting. Unfortunately, both studies suffer from the routine problems of retrospective cohort comparisons and have a relatively small sample size. Thus these results, although provocative, remain only hypothesis-generating. Patient selection remains a potential confounding issue in all allo-SCT reports (particularly in retrospective institutional or registry reviews), and the benefit of RIC-allo to patients with RR-HL remains open to debate. Future trials may focus on strategies designed to reduce relapse after allo-SCT but allo-SCT itself should be tested in controlled trials to clarify these issues.

A second autograft has been considered an option for patients who relapse after a previous ASCT. In these cases, stem cells must be available from the initial procedure or need to be collected a second time. There are limited institutional and registry data to support

such a strategy. The Center for International Blood and Marrow Transplant Research reported a series that included 21 HL patients who underwent a second autograft.<sup>93</sup> With day 100 TRM of 11%, 5-year PFS and OS were 30% for the entire cohort, with no difference in outcome between NHL and HL cases. Outcomes were inferior in patients who underwent another transplantation within 1 year of the initial autograft (5-year PFS of 0% vs 32%,  $P = .001$ ).

On the basis of current data, we recommend RIC-allo for HL only in the context of prospective clinical trials because allo-SCT trials continue to report disappointing relapse rates. However, if clinicians feel strongly about proceeding with this strategy, patients with refractory disease should be excluded and opportunities to exploit the GVHL effect should be used. The role of a second autograft remains unclear but can be considered in patients with a time to relapse of greater than 1 year (5 years at our center) after the initial transplant. We support prospective trials that test either new strategies to reduce relapse rates after allograft or prospectively compare RIC-allo to conventional therapy. In our practice currently, we do not recommend allografting for HL after ASCT outside of clinical trials testing strategies to improve outcomes and only recommend second ASCT in chemosensitive patients who have been in remission for 5 years after first ASCT.

### **Noncurative treatment of RR-HL**

Despite the aggressive strategies outlined in this work, up to 50% of patients will ultimately relapse after ASCT. These patients (along with those that did achieve adequate chemosensitivity to proceed to ASCT, elderly patients, or patients with significant comorbidities who may not tolerate intensive therapy) are likely incurable with standard therapies. A minority of these patients may be eligible for RIC-allo, but many factors may pose obstacles to this type of treatment (eg, patient and physician preference, donor availability, lack of sensitive disease), and thus the treatment plan will not be curative. In the noncurative setting, there are many conventional agents that may be used in sequence or combination to provide disease control; gemcitabine and vinblastine frequently are used.<sup>94,95</sup> It would be more appealing to use novel agents that exploit alternative mechanisms of action because patients have frequently been exposed to multiple standard agents by the time they may relapse after ASCT.

Unfortunately, the first trials of novel agents in RR-HL were largely unsuccessful; anti-CD30 antibodies, bortezomib, and thalidomide failed to show promising single-agent activity or favorable results when combined with standard drugs.<sup>94-99</sup> Recent reports of novel therapeutics have described new agents with favorable single-agent activity.<sup>100</sup> A pilot study of the monoclonal anti-CD20 antibody rituximab has shown a response rate of 22% in classic HL and was associated with resolution of B symptoms.<sup>101</sup> Recent studies of a conjugated anti-CD30 antibody (brentuximab vedotin or SGN-35) have shown impressive activity in heavily pretreated patients (tumor reduction in 86% of patients in the phase 1 trial and objective responses in 6 of 12 patients treated at the maximum tolerated dose).<sup>102</sup> Emerging data suggest several classes of agents—histone deacetylase inhibitors, mammalian target of rapamycin inhibitors, and immunomodulatory agents are potentially worthy of further study in RR-HL.<sup>103-105</sup>

The challenge remains how best to manage patients who progress or relapse after ASCT given the variety of standard treatment options (single and multiagent chemotherapy, radiation therapy), intensive treatment strategies (second autografts, RIC-allo transplants), or drug development trials that are currently available. Because no comparative prospective data are available to



inform this decision, clinicians and patients will have to make careful choices. We favor the enrollment of patients in prospective studies because these strategies will ultimately advance the field.

We use the following principles to guide our treatment approach in the palliative setting. If disease is localized, we favor the use of involved or extended field radiation. Patients who have not responded adequately to salvage chemotherapy before ASCT and those who have early progression after ASCT (within 3-6 months) should be offered investigational agents if possible because the likelihood of response to conventional agents in this setting is low and toxicity should be expected. However, patients with advanced age and/or significant comorbidities may not be eligible for clinical trials, and the intensive follow-up and travel required for these studies needs to be considered. For these patients, simple treatment with sequential single-agent chemotherapy would be reasonable. For the majority of cases, we favor enrollment in studies of investigational agents because accrual to prospective trials remains a priority and will hopefully lead to improvements in patient outcome. Standard agents can be considered in patients who have not responded to trials of novel agents or if trials are not available, but combination regimens can have significant toxicity and the improvement in outcome compared with single agents would appear to be very modest at best.<sup>38</sup> Patient preference should also be an important factor in clinical decision making.

## Conclusion

Despite 2 RCTs forming the basis of the treatment of RR-HL, there are many areas that remain controversial and open to debate. Looking forward, one of the key challenges in the management of relapsed and refractory HL is the management of chemorefractory disease. Although autografting may successfully cure a proportion of these patients, they remain underrepresented in prospective trials, and the biology underlying the nature of resistance remains unclear. Clearly, this is an area in which translational research could lead to significant improvement in patient outcome.

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Another challenge for clinicians is how best to integrate the varied data outside of the RCTs to direct care for these patients. Several important clinical decisions such as the selection of second-line chemotherapy and the high-dose therapy regimen, as well as the roles of functional imaging and radiation peri-ASCT remain somewhat unclear. Although the success of the management of RR-HL lies in a durable cure rate of approximately 50%, RCTs have not improved on the standard ASCT platform. Strategies that exploit adoptive immunotherapy (such as DLI in the allo-SCT setting) or that use active novel agents in the pre-ASCT setting to improve response or as maintenance post-ASCT will hopefully be tested in well-designed controlled trials. International collaboration will be essential to translate early encouraging results into the standard therapies of the future for patients with HL.

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