How I treat relapsed and refractory Hodgkin lymphoma

John Kuruvilla,1,2 Armand Keating,1,2 and Michael Crump1,2

Division of Medical Oncology and Hematology, 1 Princess Margaret Hospital, Department of Medicine, University of Toronto, 2 Toronto, Canada.

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Address correspondence to:

John Kuruvilla MD, FRCPC  
Princess Margaret Hospital  
Division of Medical Oncology & Hematology  
610 University Ave., Rm. 5-110  
Toronto, Canada M5G 2M9  
Tel: 416-946-2821  
Fax: 416-946-4563  
Email: john.Kuruvilla@uhn.on.ca
ABSTRACT

Relapsed or refractory Hodgkin lymphoma is a challenging problem for clinicians who treat hematological 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 prior to 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 survivors, hence 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.
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.¹ While 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.² 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.³⁴ Two randomized phase III clinical trials showed improved progression-free survival in patients receiving high-dose chemotherapy (HDCT), compared to those treated with standard-dose salvage chemotherapy, although there was no statistically significant difference in overall survival ⁵⁶.

While 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 non-responsive disease, assessing the role of prognostic factors and of functional imaging and provide a summary of the available treatment (including both stem cell transplant and non-transplant based strategies). We also highlight data on new treatments and novel agents currently in clinical trials.
DIAGNOSIS OF RELAPSED OR REFRACTORY HODGKIN LYMPHOMA

With the almost universal availability of computed tomography (CT) scanners and more recently, the increasing use of FDG-PET and CT-PET imaging, patients are often followed by serial imaging after completion of 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 are frequently used as the standard for surveillance imaging. The NCCN v2.2010 guideline on Hodgkin lymphoma (www.nccn.org) 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,7-10 and with limited data on outcome of patients with clinically versus radiologically detected relapse with modern imaging techniques.11,12

It has been suggested that all patients should have a repeat biopsy to establish the presence of refractory or relapsed HL. Repeat biopsy should be considered when the initial pathologic diagnosis was 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 feels 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 prior disease), we do not feel 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,\textsuperscript{11,12} the use of FDG-PET for assessment of response to primary therapy and in surveillance post-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),\textsuperscript{13} but post-therapy surveillance was felt 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 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) the Treatment section of this review titled “The role of functional imaging in response assessment prior to ASCT” following. In the context of post-therapy surveillance (as distinct from mid-therapy 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 feel that this can be the sole test 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 post-therapy. False positive scans may be due to rebound thymic hyperplasia in young
patients, local inflammation post-chemo or radiotherapy, sarcoidosis or deposition of brown fat. In a recent report that included 57 patients with mediastinal Hodgkin lymphoma, 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 10/21 had biopsies confirming persistent or recurrent HL; biopsies in the other cases showed only fibrosis or other benign etiologies. A study from Memorial Sloan Kettering Cancer Center in diffuse large cell lymphoma (DLBCL) 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 DLBCL. Patients with a positive post-treatment PET scan should proceed to biopsy whenever this can be done safely, or be reassessed with cross-sectional imaging, before initiating 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. Although early reports have lead some 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 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 to 95% who were FDG negative or with a CR by CT scan.
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 based on 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 remains an area worthy of additional prospective study. We recommend however, that patients undergo diagnostic re-biopsy 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 favoured. 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; prior to proceeding to salvage chemotherapy and ASCT.11,12

PROGNOSTIC FACTORS IN RELAPSED / REFRACTORY HODGKIN LYMPHOMA

Several studies have identified prognostic factors in cohorts of patients with RR-HL who undergo 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 German Hodgkin’s Lymphoma Study Group (GHSG). The first publication reported prognostic factors and outcomes in 206 patients enrolled on prospective clinical trials with primary refractory HL, defined as progressing while on primary treatment or within three months of completion.16 The significant adverse
prognostic factors identified from multivariate analysis were poor performance status (ECOG > 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. The significant adverse prognostic factors for overall survival identified in multivariate analysis were anemia (hemoglobin < 120 in male, < 105 in female), 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 as the GHSG primary refractory cohort had a 5 year OS of 26% compared to 46% for early relapse after chemotherapy (between 3-12 months) and 71% for late relapse (after 12 months) in the GHSG relapsed cohort. The lack of concordance between the reported studies with respect to other variables affecting outcome (for example, age, B symptoms, or relapse in a prior 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, or of the variables identified as 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.
While documenting 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 feel 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 enrolment when possible in prospective studies specifically in this group, as described below.

**TREATMENT**

1. **Salvage chemotherapy - prior to ASCT**

Despite a multitude of published phase II studies reporting results of salvage regimens for RR-HL,\textsuperscript{18-28} there are no direct comparisons of different combinations, and thus no consensus on the “gold-standard” second-line chemotherapy. The published RCTs of ASCT for RR-HL employed mini-BEAM or dexa-BEAM 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 hematological and non-
hematological toxicity, and not impair the ability to mobilize and collect peripheral blood
stem cells for ASCT. Although the RCTs described above would argue for the use of
multidrug regimens including carmustine (BCNU), etoposide, cytarabine and melphalan
(miniBEAM), we have found these regimens to have significant hematologic toxicity,
requiring frequent hospitalization for febrile neutropenia, and a high incidence of
transfusion support. Stem cell mobilization appears to be compromised following
treatment with miniBEAM.²⁹

Several published and widely used salvage chemotherapy regimens are summarized in
Table 2. These trials report overall response rates (ORR) between 60 – 87%, with
overlapping 95% confidence intervals. Although these single arm phase II 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 GI toxicity (nausea and vomiting) is also common. While the Dexa-BEAM
regimen had an ORR of 81% in the GHSG/EBMT phase III ASCT trial, TRM from
salvage chemotherapy in that study was 5%. Other trials have reported TRM between
0–2%, a more acceptable level given the young age and lack of co-morbidity typically
seen 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 give two 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 most series likely unable to demonstrate significant differences in response to salvage therapy due to a lack of statistical power. Patients with primary refractory HL have an inferior response rate to second-line chemotherapy (51% versus 83%, p<0.0001); the wide range of response rates (between 32-84% reported in other series) likely reflects relatively small sample sizes and imbalances of this and other prognostic factors.

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 PR with an alternative regimen and proceeded with ASCT.34 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.35 A UK series reported that patients with an inadequate response to first salvage (n=6), defined as persistent bulk or residual marrow disease, derived the greatest benefit from second salvage, compared to those achieving SD (n=6) or PD (n=5). Second salvage allowed
the first group to proceed with stem cell transplantation (3 allo-SCT, 3 ASCT), which resulted in long-term remission in 5 patients.\textsuperscript{36}

We have recently reviewed our experience in patients that did not achieve a CR or PR to salvage chemotherapy with gemcitabine, dexamethasone, cisplatin (GDP) (D. Villa,–manuscript submitted) using more modern response criteria.\textsuperscript{37} Based on 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 $> 5 \text{ cm}$.\textsuperscript{38} 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 $> 5 \text{ cm}$ 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 five year PFS post-ASCT in these patients is 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 non-curative 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 high-dose chemotherapy. 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 studies report that regimens containing melphalan such as Dexa-BEAM or mini-BEAM may result in reduced stem cell mobilization.\textsuperscript{39-41} Available results for PBSC mobilization after treatment with these salvage chemotherapy regimens are presented in Table 3. Optimal timing for PBSC mobilization will vary based on the regimen employed and may vary substantially between patients based on disease and treatment factors. Given these issues and a desire to standardize PBSC mobilization, we employ an efficient PBSC mobilizing regimen consisting of 2 g/m\textsuperscript{2} of cyclophosphamide day 1, etoposide 200 mg/m\textsuperscript{2} day 1-3 and filgrastim 10 μg/kg/day starting on day +6 with serial CD34+ 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 or GDP are reasonable options.\textsuperscript{29,42} Based on our experience in patients who are non-responders 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 based on our experience described above) should be employed in patients with PD, larger volume disease or lesions that remain positive by functional imaging. While the need for alternative salvage therapy identifies a group with a poor prognosis
compared to patients responding to their initial regimen, approximately 50% may proceed to ASCT and a minority remains in remission.

2. The role of functional imaging in response assessment prior to ASCT

FDG-PET is increasingly employed 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 higher rate of relapse post-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 functional imaging) but significantly inferior if positive (65%).

Recently, a large series studying FI after ICE chemotherapy reported similar results with a five year EFS of 31% for FI positive disease compared to 75% if negative. A small Italian series of 24 patients that underwent FDG-PET scanning after two cycles of salvage chemotherapy reported 2-year PFS of 93% for PET negative and 10% for PET positive patients. Schot et al reported that post-salvage 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 while 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.

3. ASCT High Dose Therapy Regimens and Strategies

The role of aggressive second-line therapy in HL has been defined by two published phase three RCTs. The GHSG/EBMT assigned 161 patients with relapsed HL to receive two cycles of dexa-BEAM chemotherapy, and randomized responding patients to either two additional cycles of dexa-BEAM or high dose therapy and ASCT. Although there was no difference in overall survival, freedom from treatment failure at three years was significantly improved in the ASCT group (55 versus 34%, p=0.02). Neither of these trials of ASCT included chemorefractory patients, and only cohort and registry data address the benefit of ASCT in these patients.

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 post ASCT demonstrates 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 which patients were transplanted as these protocols were conducted between 1986-2005.

Similar to the situation with salvage therapy pre-transplant, direct comparisons of high-dose regimens are lacking and choice of agents and doses is quite variable. The toxicity and anti-lymphoma efficacy of these regimens also varies (see Table 4 following), 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 two randomized trials of ASCT for RR-HL used BEAM (BCNU, etoposide, Ara-C, melphalan) HDCT. Other single institution studies report outcomes with regimens such as CBV (cyclophosphamide, BCNU, VP-16), CBVP (cyclophosphamide, BCNU, VP-16, cisplatin), etoposide and melphalan, single agent high dose melphalan, CCV (cyclophosphamide, CCNU, VP16), and total lymphoid irradiation (TLI) with VP-16 carboplatin and cyclophosphamide. 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 non-hematological toxicity (GI, pulmonary and hepatic toxicity) as well as proven anti-tumour activity. The latter has been difficult to demonstrate, since many patients are transplanted in complete or near complete response following 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 prior to transplant) has not been well defined.

While further intensification of high dose regimens has met with limited success,\textsuperscript{50} there may be opportunity to further refine the autograft platform. Intensification using augmented-dose mobilization regimens\textsuperscript{47}, or additional therapy after stem cell collection\textsuperscript{52}, have been reported to improve outcome. The Cologne high-dose sequential (HDS) protocol begins with an induction phase of two cycles of standard DHAP chemotherapy followed by a response assessment. Responders proceed to HDS which consists of 4g/m\textsuperscript{2} of cyclophosphamide followed by G-CSF and subsequent PBSC collection, 8 g/m\textsuperscript{2} of methotrexate with vincristine 1.4 mg/m\textsuperscript{2}, etoposide 2 g/m\textsuperscript{2} with G-CSF and an optional second PBSC collection and finally BEAM high dose therapy and ASCT. The GHSG reported a multi-center phase II pilot trial showing HDS to be feasible with acceptable toxicity.\textsuperscript{50} Recently, the GHSG and EBMT reported the HD-R2 trial, a randomized comparison of high dose sequential therapy (HDS) followed by ASCT to standard DHAP and ASCT.\textsuperscript{51} 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, progression-free or overall survival were observed.\textsuperscript{52}

An additional intensification strategy that has been tested is the use of tandem autologous transplants.\textsuperscript{53} While controlled trials are lacking, this strategy was tested prospectively in a large cohort study by the GELA investigators. The GELA multi-center H96 trial tested a risk-adapted approach in which patients were assigned to a single or
tandem autograft based on the presence of risk factors at initiation of savage therapy. Those with primary refractory disease or at least two poor risk factors – time to relapse < 12 months, relapse in a prior 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. 54 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 to a standard single autograft to assess survival advantage.

The randomized trials of ASCT in RR-HL employed 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 favourable 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 to regimens such as CBV which add high-dose carmustine. We do not recommend the routine usage of alternate ASCT strategies (HDS or tandem ASCT) due to 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. While 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 post-ASCT in patients with adverse risk factors prior to salvage therapy.
4. Standard Dose Therapy Approaches

While most patients with relapsed or refractory HL will be recommended to receive aggressive salvage and ASCT due to young age and lack of co-morbidity, alternative options are available. There are few published reports of salvage radiotherapy alone in relapsed or refractory HL (Table 5). Most of these patients were treated before anthracycline-based primary chemotherapy became the standard of care in North America, and prior to the emergence of early phase III 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 1999.55 Eighty-five percent of the patients had progressed after COPP-ABVD (cyclophosphamide, vincristine, procarbazine, prednisone with ABVD) or similar regimens, while 8% had received standard or escalated BEACOPP. The remaining patients had received radiotherapy alone. The five-year freedom from treatment failure and overall survival 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.42,56-60 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 twelve months, the presence of extra-
nodal disease and poor performance status are predictors of worse outcomes with salvage radiotherapy.

Combined modality therapy incorporating multi-agent chemotherapy followed by radiotherapy has become the standard of care for primary treatment of limited stage HL based on multiple trials.\textsuperscript{61-63} While radiotherapy alone at relapse is felt to be largely palliative, the role of combined modality therapy using 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 prior 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 employing radiotherapy, but this is unlikely to happen due to the large number of patients required to do such a trial and the acceptance of adding radiotherapy to a transplant-based strategy based on cohort data and its inclusion in the phase III GHSG trial.\textsuperscript{6,42,64}

The data supporting re-treatment with standard dose chemotherapy alone following 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,\textsuperscript{65} 8 year freedom from second progression and overall survival were 53% and 62%, respectively, for patients re-treated with MOPP-ABVD following a CR
lasting more than 12 months. Separate analyses of patients with relapsed HL enrolled in adult\textsuperscript{17} or pediatric\textsuperscript{66} cooperative group trials demonstrate that time to initial treatment failure is a strong predictor of survival for patients receiving salvage therapy, independent of high-dose chemotherapy and ASCT (although assignment to therapy in these reports was not randomized and prognostic factors were not controlled).

To summarize, we feel that non-ASCT based strategies can be considered in limited, specific clinical scenarios. As 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 employed in primary treatment or if relapse has occurred in non-irradiated 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 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 centre, more than five years) following 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 when patients relapse after receiving non-anthracycline-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 biological 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.

5. Intensive Strategies including Allografting and Second Autograft

Allogeneic stem cell transplantation (Allo-SCT) continues to be a treatment option in advanced HL due to the relatively young age of many of these patients. Myeloablative allo-SCT has been employed in advanced phases of the disease but with dampened enthusiasm because TRM often exceeded 50% and relapses were not uncommon. The role of myeloablative allo-SCT in HL appeared limited; while dose intensity can be delivered in the context of a myeloablative allograft and donor stem cells are free of tumour 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 anti-tumour effect following donor lymphocyte infusion. In addition to this anti-tumour 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 due to decreased rates of early treatment-related mortality. Despite early favourable outcomes, mature results of RIC-allo available in the literature consistently demonstrate a lack of long-term disease control with progression-free survival estimates of approximately 25-30% and overall survival estimates of 35-60% at least two years post-SCT.
A large prospective study completed by the GEL/TAMO and EBMT has been recently reported. Over a seven year span, 78 patients ultimately proceeded through a RIC-allo transplant with a preparative regimen consisting of fludarabine 150 mg/m², melphalan 140 mg/m² and GVHD 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 GVHD was associated with a reduced rate of relapse post transplant and in patients with relapse after allo-SCT, DLI alone generate an overall response rate of 40%. These results suggest the presence of a GVHL effect in a prospective multi-center 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 to retrospective cohorts by two groups. Both the UK Cooperative Group and Italian studies demonstrated an overall survival advantage favouring allografting. Unfortunately, both studies suffer from the routine problems of retrospective cohort comparisons and have a relatively small sample size. Thus these results, while 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 prior ASCT. In this 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 CIBMTR reported a series that included 21 HL patients who underwent a second autograft. 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 were re-transplanted within one year of the initial autograft (5 year PFS of 0% versus 32%, p=0.001).

Based on current data, we recommend RIC-allo for Hodgkin lymphoma only in the context of prospective clinical trials as 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 employed. The role of a second autograft remains unclear but can be considered in patients with a time to relapse of greater than one year (five 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 post ASCT outside of clinical trials testing strategies to improve outcomes, and only
recommend second ASCT in chemosensitive patients that have been in remission for five years following first ASCT.

6. Non-curative Treatment of Relapsed / Refractory HL

Despite the aggressive strategies outlined above, 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 that 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 (patient and physician preference, donor availability, lack of sensitive disease), and thus the treatment plan will not be curative. In the non-curative setting, there are many conventional agents that may be employed in sequence or combination to provide disease control, gemcitabine and vinblastine being frequently employed.\textsuperscript{83,84} It would be more appealing to use novel agents that exploit alternative mechanisms of action as 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 favourable results when combined with standard drugs.\textsuperscript{83-88} Recent reports of novel therapeutics have described new agents with favourable single agent activity.\textsuperscript{89} A pilot study of the monoclonal anti-CD20 antibody rituximab has shown a response rate
of 22% in classical HL, and was associated with resolution of B symptoms. Recent studies of a conjugated anti-CD30 antibody (brentuximab vedotin or SGN-35) have shown impressive activity in heavily pre-treated patients (tumour reduction in 86% of patients in the phase 1 trial and objective responses in 6 of 12 patients treated and the MTD). Emerging data suggests several classes of agents – histone deacetylase inhibitors, mTOR inhibitors and immunomodulatory agents are potentially worthy of further study in RR-HL.

The challenge remains how best to manage patients who progress or relapse after ASCT given the variety of standard treatment options (single and multi-agent 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 favour enrolment of patients in prospective studies as 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 favour the use of involved or extended field radiation. Patients that have not responded adequately to salvage chemotherapy prior to ASCT and those who have early progression after ASCT (within 3-6 months) should be offered investigational agents if possible, as 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 co-morbidities may not 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 favour enrolment in studies of investigational agents, as 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 failed trials of novel agents or if trials are not available, but combination regimens can have significant toxicity and the improvement in outcome compared to single agents would appear to be very modest at best. Patient preference should also be an important factor in clinical decision making.
CONCLUSIONS

Despite two 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. While autografting may successfully cure a proportion of these patients, they remain under-represented in prospective trials, and the biology underlying the nature of resistance remains unclear. Clearly, this is an area where translational research could lead to significant improvement in patient outcome.

Another challenge for clinicians is how best to integrate the varied data outside of the RCTs to direct care for these patients. A number of 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. While 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 employ 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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Table 1: Poor Prognostic Factors in Relapsed or Refractory Hodgkin Lymphoma

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapsed</td>
<td>Time to Relapse &lt; 1 year&lt;sup&gt;17,42,96-98&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Stage – III/IV (IV-Lohri, Martin)&lt;sup&gt;17,20,42,96,98&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Anemia&lt;sup&gt;17&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>B Symptoms&lt;sup&gt;42,98&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Poor Performance Status&lt;sup&gt;97&lt;/sup&gt;</td>
</tr>
<tr>
<td>Refractory</td>
<td>Poor Performance Status&lt;sup&gt;16,97&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Age &gt; 50 years&lt;sup&gt;16&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Failure to Attain a Temporary Remission&lt;sup&gt;16&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>B Symptoms&lt;sup&gt;42&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Stage III-IV (IV-Martin)&lt;sup&gt;20,42&lt;/sup&gt;</td>
</tr>
<tr>
<td>ASCT</td>
<td>Previously Untreated Relapse&lt;sup&gt;97&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Response to Chemotherapy&lt;sup&gt;20&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Low Serum Albumin&lt;sup&gt;99&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Anemia&lt;sup&gt;99&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Age&lt;sup&gt;99&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Lymphocytopenia&lt;sup&gt;99&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>B Symptoms&lt;sup&gt;100&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Extranodal disease&lt;sup&gt;100&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Time to Relapse &lt; 1 year&lt;sup&gt;100&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Disease Status at ASCT&lt;sup&gt;38&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Disease Relapse in Prior Radiation Field&lt;sup&gt;38&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
Table 2 – Salvage Chemotherapy Regimens in Relapsed or Refractory Hodgkin Lymphoma

<table>
<thead>
<tr>
<th>Regimen</th>
<th>No. of Patients</th>
<th>CR% 95% CI</th>
<th>PR% 95% CI</th>
<th>ORR% 95% CI</th>
<th>Grade 3/4 NEUT %</th>
<th>Grade 3/4 TCP %</th>
<th>Grade 3/4 VOM %</th>
<th>Toxic deaths %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexa-BEAM</td>
<td>144</td>
<td>27 (20-34)</td>
<td>54 (46-62)</td>
<td>81 (75-87)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>5 (1-9)</td>
</tr>
<tr>
<td>Mini-BEAM</td>
<td>55</td>
<td>49 (35-63)</td>
<td>33 (21-47)</td>
<td>82 (69-91)</td>
<td>86 (60 NS)</td>
<td>NS</td>
<td>NS</td>
<td>2 (0.1-10)</td>
</tr>
<tr>
<td>ICE</td>
<td>65</td>
<td>26 (16-39)</td>
<td>59 (46-71)</td>
<td>85 (74-92)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>0 (0-5)</td>
</tr>
<tr>
<td>DHAPq2wk</td>
<td>102</td>
<td>21 (13-29)</td>
<td>68 (59-77)</td>
<td>89 (83-95)</td>
<td>88 (69 26)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>GDP</td>
<td>23</td>
<td>17 (5-39)</td>
<td>52 (31-73)</td>
<td>69 (47-87)</td>
<td>9 (13 13)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>GVD</td>
<td>91</td>
<td>19 (5-39)</td>
<td>51 (31-73)</td>
<td>70 (47-87)</td>
<td>63 (14 0)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>IEV</td>
<td>51</td>
<td>76 (60-88)</td>
<td>52 (31-73)</td>
<td>69 (47-87)</td>
<td>100 (84 100)</td>
<td>NS</td>
<td>NS</td>
<td>0</td>
</tr>
<tr>
<td>MINE</td>
<td>157</td>
<td>NS</td>
<td>NS</td>
<td>75 (64-84)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>5 (3)</td>
</tr>
<tr>
<td>IV</td>
<td>47</td>
<td>45 (30-60)</td>
<td>38 (25-54)</td>
<td>83 (69-92)</td>
<td>65 (0)</td>
<td>2</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

KEY:
- NS – Not stated, NEUT – neutropenia, TCP – thrombocytopenia, VOM-vomiting
- 1 – mucositis reported in 9%
- 2 – all patients experience grade IV neutropenia
- 3 – 5% toxic death rate included patients undergoing ASCT

CHEMOTHERAPY REGIMENS:
- BEAM: BCNU, etoposide, ara-C, melphalan; ICE: ifosfamide, carboplatin, etoposide,
- DHAP: dexamethasone, ara-C, cisplatin, GDP: gemcitabine, dexamethasone, cisplatin
- GVD: gemcitabine, vinorelbine, doxil (liposomal doxorubicin); IEV: ifosfamide,
etoposide, vinorelbine; MINE: mitoguazone, Ifosfamide, vinorelbine; etoposide; IV:
Ifosfamide; vinorelbine
Table 3 – Efficacy of PBSC Mobilization following Salvage Chemotherapy for Relapsed or Refractory Hodgkin Lymphoma

<table>
<thead>
<tr>
<th>Regimen</th>
<th>N</th>
<th>% CD34 ≥ 2 X 10^6/kg</th>
<th>% CD34 ≥ 5 X 10^6/kg</th>
<th>% undergoing marrow harvest</th>
</tr>
</thead>
<tbody>
<tr>
<td>GDP</td>
<td>34</td>
<td>97</td>
<td>97</td>
<td>3</td>
</tr>
<tr>
<td>MB</td>
<td>34</td>
<td>82</td>
<td>57</td>
<td>18</td>
</tr>
<tr>
<td>ICE</td>
<td>65</td>
<td>86</td>
<td>67</td>
<td>14</td>
</tr>
</tbody>
</table>

Table 4 – High Dose Chemotherapy Regimens used with ASCT in Relapsed or Refractory Hodgkin Lymphoma

<table>
<thead>
<tr>
<th>Regimen</th>
<th>N</th>
<th>Early TRM</th>
<th>OS (%)</th>
<th>PFS/DFS (%)</th>
<th>Secondary AML/MDS</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>BEAM</td>
<td>56</td>
<td>1/56 (2%)</td>
<td>44/61</td>
<td>FFTF-3: 55</td>
<td>1/56</td>
<td>OS not clearly reported</td>
</tr>
<tr>
<td>CBV</td>
<td>128</td>
<td>3/26 (8%)</td>
<td>OS-4: 45</td>
<td>FFS-4: 25</td>
<td>5/128</td>
<td></td>
</tr>
<tr>
<td>CBVP</td>
<td>68</td>
<td>5/68 (7%)</td>
<td>NS</td>
<td>50</td>
<td>1 (total N of 96)</td>
<td></td>
</tr>
<tr>
<td>VP16/MEL</td>
<td>73</td>
<td>3/73 (4%)</td>
<td>NS</td>
<td>DFS-4: 39</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>BEAM</td>
<td>101</td>
<td>NS</td>
<td>71</td>
<td>FFTF-5: 67</td>
<td>1 AML (unknown if in ASCT group)</td>
<td></td>
</tr>
<tr>
<td>TLI + VP16/CY</td>
<td>22</td>
<td>2/22 (9%)</td>
<td>81</td>
<td>61</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>CCV</td>
<td>59</td>
<td>5/59 (8%)</td>
<td>OS-3: 57</td>
<td>EFS-3: 52</td>
<td>1</td>
<td>21 deaths, 11 NRM high pulm tox 63%</td>
</tr>
<tr>
<td>HDM</td>
<td>46</td>
<td>0</td>
<td>OS-5: 57</td>
<td>EFS-5: 52</td>
<td>0</td>
<td>Est 5 year results, short FU</td>
</tr>
</tbody>
</table>

Key
OS-3,4,5 – 3,4, or 5 year overall survival
FFP-3 – 3 year freedom from progression
FFTF-5 – 5 year freedom from treatment failure
FFTF-10 – 10 year freedom from treatment failure
EFS-3,5 – 3 or 5 year event-free survival
NS – Not stated
(1) unknown if in CBV or TLI group reported
Table 5. Results of Salvage Radiotherapy Alone in Relapsed or Refractory Hodgkin Lymphoma

<table>
<thead>
<tr>
<th>Reference</th>
<th>N</th>
<th>Overall Survival</th>
<th>Relapse-Free Survival</th>
<th>Prognostic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Josting</td>
<td>100</td>
<td>OS-5: 51%</td>
<td>FFTF-5Y: 26%</td>
<td>B Symptoms&lt;br&gt;Advanced Stage&lt;br&gt;Poor Performance Status</td>
</tr>
<tr>
<td>Campbell</td>
<td>81</td>
<td>OS-10: 46%</td>
<td>FFTF-10: 33%</td>
<td>B Symptoms&lt;br&gt;Age &gt; 50&lt;br&gt;Extra-nodal disease&lt;br&gt;&amp; CR to previous Chemo&lt;br&gt;Male gender</td>
</tr>
<tr>
<td>Leigh</td>
<td>28</td>
<td>Median: 97 mos</td>
<td>Median RFS: 46 mos</td>
<td>Initial CR to chemo</td>
</tr>
<tr>
<td>Pezner</td>
<td>10</td>
<td>OS-5: 60%</td>
<td>RFS-5: 30%</td>
<td>Disease Free Interval &lt; 1 year</td>
</tr>
<tr>
<td>Brada</td>
<td>44</td>
<td>OS-10: 40%</td>
<td>PFS-10: 23%</td>
<td>Age &gt; 40&lt;br&gt;Extranodal disease&lt;br&gt;Disease-free interval &lt; 1 year</td>
</tr>
<tr>
<td>MacMillan</td>
<td>11</td>
<td>OS-10: 90%</td>
<td>DFS-10: 44%</td>
<td>NS</td>
</tr>
<tr>
<td>Uematsu</td>
<td>28</td>
<td>OS-7: 36%</td>
<td>RFS-7: 36%</td>
<td>NS</td>
</tr>
</tbody>
</table>

Key

OS-5 – 5 year overall survival <br>OS-10 – 10 year overall survival <br>FFTF-5 – 5 year freedom from treatment failure <br>FFTF-10 – 10 year freedom from treatment failure <br>RFS – Relapse free survival <br>NS – Not stated