Published in final edited form as:

Semin Hematol. 2016 July ; 53(3): 180–185. doi:10.1053/j.seminhematol.2016.05.010.

Treatment of relapsed and refractory Hodgkin Lymphoma

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Abstract

Despite the high first line cure rates in patients with Hodgkin Lymphoma (HL) still 10–20% of patients suffer from relapsed or refractory disease. High dose chemotherapy (HDCT) followed by autologous stem cell transplant (ASCT) is standard of care for suitable patients with relapsed or refractory HL and allows for cure in approximately 50%. Due to the poor prognosis of high risk patients even with HDCT and ASCT, consolidation strategies have been evaluated to improve the cure rates. For patients with recurrence after HDCT and ASCT, treatment is palliative in most cases. The anti CD30 antibody-drug conjugate brentuximab vedotin (BV) has been shown to induce high response rates in these patients; however, durable responses were reported in a small percentage of patients only. For carefully selected patients with multiple relapses, dose-reduced allogeneic transplant (RICallo) is a potentially curative option. The role of RICallo will have to be reevaluated in the era of anti-programmed death-1 (PD1) antibodies.

Introduction

More than 80% of patients with Hodgkin Lymphoma (HL) achieve long-term cure with current polychemotherapies and additional radiotherapy where indicated (1–4). Even approximately 50% of patients with relapsed or refractory disease after first line therapy can be cured with high dose chemotherapy (HDCT) and autologous stem cell transplantation (ASCT) followed by optional consolidation in high risk patients (5–7). After post-ASCT recurrence the antibody-drug conjugate (ADC) brentuximab vedotin (BV) has shown high efficacy and good tolerability (8); however, long-term remissions were observed in a small percentage of patients only. New combinations of BV with established drugs are currently

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Conflicts of interest:

BvT has received honoraria for consultancy, reimbursement of congress, travel, and accommodation costs and honoraria for preparation of scientific educational events from Takeda.

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being evaluated to further improve the outcome of patients with relapsed or refractory HL. This article summarizes the current standard of care and emerging data in the management of relapsed or refractory classical HL in patients eligible for HDCT and ASCT. The management of other subgroups and new drugs are discussed separately in this issue.

Standard of care in first relapsed and refractory HL

High dose chemotherapy (HDCT) - evidence from randomized trials

Because results with conventional chemotherapy were disappointing in patients with first relapsed or refractory HL, HDCT followed by ASCT was evaluated in this setting. Two prospective, randomized trials have defined the current standard of care in the treatment of relapsed and refractory HL (9, 10). The British National Lymphoma Investigation (BNLI) (9) trial randomized 40 patients who had not responded to first line chemotherapy to either conventional chemotherapy (mini-BEAM: 60 mg/m² carmustine, 300 mg/m² etoposide, 800 mg/m² cytarabine, 30 mg/m² melphalan q3wk for up to three cycles, standard group, 20 patients) or HDCT (BEAM: 300 mg/m² carmustine, 800 mg/m² etoposide, 1.600 mg/m² cytarabine, 140 mg/m² melphalan, experimental group, 20 patients) followed by ASCT support. The joint German Hodgkin Study Group (GHSG)/European Group for Blood and Marrow Transplantation (EBMT) HD-R1 trial (10) randomized 161 patients with relapse after polychemotherapy to either HDCT plus ASCT (88 patients) or to conventional chemotherapy (73 patients). All patients in this trial received two cycles of Dexamethasone-BEAM consisting of 240 mg dexamethasone, 60 mg/m² carmustine, 1000 mg/m² etoposide, 800 mg/m² cytarabine and 20 mg/m² melphalan. Chemosensitive patients were then randomized to either BEAM plus ASCT (300 mg/m² carmustine, 1200 mg/m² etoposide, 1600 mg/m² cytarabine and 140 mg/m² melphalan, 61 patients) or to two further cycles of Dexamethasone-BEAM (56 patients), each after at least partial remission (PR) and hematologic recovery was shown through restaging. In both the BNLI and the HD-R1 trial patients with residual masses were allowed to receive radiotherapy which was performed in 17 and 11 patients in the BNLI and HD-R1 trial, respectively. Both trials showed a significant superiority of HDCT in terms of event-free survival (EFS)/freedom from treatment failure (FFTF) but failed to show a significant overall survival (OS) benefit. Three year rates were 53% versus 10% (EFS, $p=0.005$) in the BNLI and 55% versus 34% (FFTF, $p=0.019$) in the HD-R1 trial. Recently, a meta-analysis of the two trials using updated follow-up information was performed by the Cochrane Group for Hematological Malignancies (CHMG) (11). With a median follow-up of 34 and 83 months for BNLI and HD-R1, respectively, progression free survival (PFS) was significantly improved in patients who were treated with HDCT plus ASCT compared to those treated with conventional chemotherapy (hazard ratio [HR] 0.55; 95% confidence interval [CI] 0.35–0.86, $p = 0.009$, Figure 1). However, the available evidence from the two trials was not sufficiently powered to show a statistically significant difference between HDCT plus ASCT and conventional chemotherapy in terms of OS (HR 0.67; 95%CI 0.41–1.07, $p = 0.1$, Figure 2). Nevertheless, the tendency towards an OS benefit of HDCT plus ASCT is considerable and the absence of a statistically significant OS benefit is most likely due to the small patient number in the two trials. Moreover, supportive care in patients receiving HDCT and ASCT has improved in the last years which presumably further

increases the advantage of HDCT over conventional therapy. HDCT is widely accepted as standard of care in first relapsed and refractory HL.

Salvage chemotherapy

Conventional reinduction chemotherapy, often referred to as salvage therapy, is standard of care before administration of HDCT. It allows for a tumor reduction before ASCT and several reports have shown that the response to salvage therapy before ASCT is predictive for the final outcome (12, 13). From a straight evidence-based point of view, Dexamethasone-BEAM should be the standard salvage regimen because it was used in the randomized HD-R1 trial that established HDCT as standard of care in relapse or refractory HL (10). However, Dexamethasone-BEAM is hardly used today because it has a relatively high treatment related mortality (TRM) as compared to newer salvage combinations and is stem cell toxic leading to an inadequate stem cell harvest in many cases (14, 15). Owing to the lack of prospective, randomized trials comparing different salvage regimens the optimal choice of a salvage regimen is unclear. The ICE (5 g/m² ifosfamide, area under the curve [AUC] 5 carboplatin, 300 mg/m² etoposide) chemotherapy regimen which is regularly administered as an inpatient treatment for two cycles has become the standard salvage used in the US (16). In prospective clinical trials the complete response (CR) rate was approximately 50% and the overall response rate (ORR) was approximately 80%. For patients with unfavorable risk factors an augmented dosing has been evaluated (10 g/m² ifosfamide, AUC 5 carboplatin, 600 mg/m² etoposide) (16). Cytarabine-based regimens such as DHAP (160 mg dexamethasone, 4000 mg/m² high dose ara-C [=cytarabine], 100 mg/m² cisplatin) and ESHAP (160mg/m² etoposide, 2000 mg methylprednisolone, 2000 mg/m² high dose ara-C [=cytarabine], 100 mg/m² cisplatin) have demonstrated similar response rates as compared to ICE (17, 18). The GHSG and other European cooperative groups regard DHAP as standard salvage regimen. The optimal cycle length of platin-based salvage chemotherapies has not been analyzed in prospective trials, however, a recent retrospective analysis of the GHSG showed that dose density of DHAP induction therapy is an independent prognostic factor for PFS and OS in relapsed HL (19). Therefore, salvage chemotherapy should be administered in a dose dense way, where possible.

In the large randomized HD-R2 trial with 241 patients with relapsed HL, sequential high dose chemotherapy (SHDCT) after DHAP before BEAM was compared to conventional DHAP plus BEAM (20). However, PFS and OS were not different in the two groups whereas patients treated with SHDCT had longer treatment duration and experienced more toxicity. Therefore, SHDCT before HDCT and ASCT is not a suitable strategy in patients with relapsed HL.

Gemcitabine-based chemotherapy regimens have been evaluated as alternative salvage regimens. The advantages of gemcitabine-based regimens are good tolerability and easier outpatient administration. GVD (2000 mg/m² gemcitabine, 40 mg/m² vinorelbine, and 30 mg/m² pegylated liposomal doxorubicin in transplant naïve patients) was evaluated in 91 patients with relapsed or refractory HL and ORR was 70%, albeit with a modest 19% CR rate based upon CT imaging (21). Another program, IGEV (8000 mg/m² ifosfamide, 400mg prednisolone, 1600 mg/m² gemcitabine, and 20 mg/m² vinorelbine) was administered to 91

patients of which 49 (54%) achieved a CR and 25 patients (27.5%) had a PR for an ORR of 81.3%, based upon PET imaging (22). Lastly, Kuruvilla et al retrospectively compared GDP (2000 mg/m² gemcitabine, 40mg dexamethasone, and 75 mg/m² cisplatin) with mini-BEAM; response rates were similar but GDP was far less toxic (23).

Brentuximab vedotin (BV) as salvage strategy

Recently, four studies have incorporated BV either sequentially or in combination with chemotherapy as part of a salvage strategy prior to ASCT (24–27). BV comprises an anti-CD30 antibody conjugated by a protease-cleavable linker to a microtubule-disrupting agent, monomethyl auristatin E (MMAE). BV demonstrated substantial efficacy, including an objective response rate of 75% and complete remission (CR) rate of 34%, in a pivotal phase two study of patients with CD30-positive HL who had failed HDCT and ASCT therapy and is approved in this setting (8). As a targeted therapy with minimal hematologic toxicity, BV may provide a unique opportunity to deliver therapy pre-ASCT.

Two studies, both peer reviewed and published, confirm a single agent response rate of > 80% as first salvage treatment, however the complete response rate is <40% (24, 25). Sequential treatment with platinum-based salvage treatment to patients lacking a PET negative response increases the CR rate to >80%. Three smaller studies have combined BV with either bendamustine, ICE or ESHAP and preliminary data suggests that the PET negative response is 75–90% (26, 27). Interestingly, patients achieving a CR to either single agent BV, sequential BV and chemotherapy or concomitant BV and chemotherapy all have similar two year PFS data post-ASCT: >80% of patients are progression-free. Clearly, single BV therapy will have the least side effects, but the lowest CR rate and likely prognostic factor analyses should determine the optimal salvage program.

In summary, several reasonable salvage options were evaluated in prospective non-randomized clinical trials and the clinician is left to choose based on the characteristics of the individual patient, personal experience, availability of drugs and the standards of a specific center.

Interim 18F-fluorodeoxyglucose-positron emission tomography (FDG-PET) during treatment for relapsed/refractory HL

As previously stated the current standard second-line treatment for relapsed or primary refractory HL is a multistep process that includes salvage chemotherapy, typically platinum-based, followed by HDCT and ASCT for patients with chemosensitive disease.

Approximately 45–55% of the transplanted patients are cured (5–7). Long term PFS is dependent upon prognostic factors determined prior to salvage chemotherapy (20, 28, 29), but more importantly, response to this chemotherapy whether complete or partial is the focal point in predicting outcome.

A number of years ago, we and others, determined that chemosensitive disease should be defined by the pre-transplant PET result (30). A negative scan after platinum-based therapy leads to a 5 year PFS rate of 75%. For patients with documented improvement on CT, but with a persistent PET-avidity, only 30% are cured. It is very clear that a post-salvage

chemotherapy PET scan is an interim evaluation, since definition of remission status is assessed at 90–100 days post-ASCT. Reporting should then be similar to that of untreated HL, scores 1–3 based upon Deauville or five point criteria are negative and 4 and 5 are positive. Investigators need to decide if patients with an abnormal, but chemosensitive scan, require a second attempt to achieve a CR, to improve upon a suboptimal 30% cure rate (31). Another option in this setting could be to adjust transplant-regimens or administer post-transplant therapy (32, 33).

Complicating that matter further, not all patients with a PET negative post-salvage chemotherapy response are equally curable. As discussed in this manuscript outcome for patients with nodal only disease is superior to that of patients with stage IV or non-contiguous extranodal involvement. For example patients with nodal only disease in remission at the time of ASCT have 90% cure rate compared to 67% for patients with extranodal disease. These results clearly have impact on the need or lack thereof for post-ASCT consolidative treatment. Lastly, as was discussed on the BV section, there is no difference in outcome comparing patients achieving a PET negative response with inpatient multiagent salvage chemotherapy compared to a simple outpatient approach.

Consolidation after high dose chemotherapy (HDCT)

Risk factors in HL patients receiving HDCT

It has been shown in several analyses that patients with certain adverse prognostic factors at recurrence have a poor prognosis even with HDCT (see also chapter 3 “Prognostic factors in Hodgkin Lymphoma” in this issue) (20, 28, 29). Especially the prognosis of patients with primary refractory disease is dismal with previously reported 5-year OS rates of 30% or less. Other factors that have been found to be associated with an inferior outcome are stage III/IV, extranodal disease, B-symptoms, anemia, poor performance status and bulky disease at relapse as well as early first relapse (< 12 months), in-field relapse after radiotherapy and non-response to salvage (14). Consolidation after HDCT has been evaluated in order to improve the results in patients with high risk disease.

Tandem autologous stem cell transplant (ASCT)

In the prospective Société Française de Greffe de Moelle (SFGM) and Groupe d’Étude des Lymphomes de l’Adulte (GELA) H96 trial 150 high risk patients (primary refractory disease [n=77] or 2 of the following risk factors at first relapse: early relapse, stage III or IV at relapse, in-field relapse after radiotherapy [n=73]) and 95 intermediate risk patients (one risk factor at relapse) received tandem or single HDCT plus ASCT, respectively (6). The results of the recently published long-term follow-up of this trial compare favorably to historical data: with a median follow-up of 10.3 years, median FFTR and OS were 64% (95% CI, 54% to 74%) and 70% (95% CI, 61% to 80%) for the intermediate-risk group, and 41% (95% CI, 33% to 49%) and 47% (95% CI, 39% to 55%), for the poor-risk group (34). Three other analyses also suggested a benefit of a second ASCT as consolidation in high-risk relapsed/refractory HL patients (32, 35, 36); however, evidence from a randomized controlled trial comparing single versus tandem ASCT in high risk patients is lacking.

Post-transplant maintenance strategy

There is one recent study addressing the issue of post-transplant consolidative therapy, the AETHERA trial (33). Patients had primary-refractory or relapsed HL and were treated with BV or placebo starting 30–45 days after HDCT and ASCT. The objective of the study was to compare PFS between the two treatment arms. The study achieved its primary objective, demonstrating a significant PFS benefit for patients in the BV arm versus placebo (HR = 0.52, $p = 0.001$). Based upon investigator review there is an 18% improvement in PFS at three years post-ASCT (Figure 3) (37). There is no difference in OS at this time point, which is almost certainly due to the availability BV for the placebo patients that progressed; these patients were enrolled on a companion protocol to receive BV free of charge. In this randomized, placebo-controlled study of HL patients with pre-salvage risk factors for progression, remission duration < 1 year, primary refractory disease or extranodal disease, were eligible to receive consolidative treatment with BV provided a statistically and clinically significant improvement in PFS per independent review facility (IRF) and per investigator, compared to placebo. In multivariate analysis besides three risk factors just stated B symptoms at salvage, less than a CR to salvage therapy or needing > 1 salvage regimen to achieve chemosensitive disease predicted for outcome. Greater than 50% of patients on study had at least three risk factors and in this cohort patients receiving BV had a three year PFS of 60% versus only 30% for patients receiving placebo (Figure 4). Only 2/3 of patients had a PET scan pre-ASCT since this test was not required, however in an ad hoc analysis it appears that if complete response was evident, only patients that had two or more risk factors benefited from consolidation; this will need to be confirmed in subsequent studies. Clinical trials are underway evaluating checkpoint inhibitors as consolidation post-ASCT.

Standard of care in patients with recurrence after ASCT

Chemotherapy and radiotherapy

Treatment of patients with recurrence after ASCT is palliative in most cases. Several trials have evaluated conventional chemotherapy in this setting and single agents as well as combinations of cytotoxic drugs have shown activity in multiple relapsed HL. Gemcitabine, vinorelbine, bendamustine and GVD are some of the potential options (21, 38–40). However, long-term remissions are very uncommon with conventional chemotherapy and approximately 70–80% of patients died within the first five years after post-ASCT relapse according to analyses from the pre-BV era (41, 42). Radiotherapy has been shown to induce durable remissions in selected patients with localized relapse and should be considered where possible (43).

Brentuximab vedotin (BV)

In August 2011, the anti-CD30 ADC BV was the first pharmacotherapy for the treatment of patients with HL approved by the US food and drug administration (FDA) since approximately 30 years (44). In a pivotal phase II prospective trial with 102 patients with relapsed HL after HDCT and ASCT BV as single agent (1.8 mg/kg q3wk) induced a high ORR of 75% and a CR rate of 34% (8). Of note, 71% of patients in the trial had disease refractory to prior treatments which underlines the high single agent activity of BV. Overall,

BV was well tolerated; the most common grade 3 or grade 4 adverse events (AEs) were peripheral sensory neuropathy (8%), fatigue (2%), neutropenia (20%) and diarrhea (1%). In the recently presented 5-year follow-up of the trial (45), the median overall survival (OS) was 40.5 months (95% CI: 28.7, 61.9 [range, 1.8 – 72.9+ months]) and the estimated 5-year survival rate was 41% (95% CI: 31, 51%). At a median of 35.1 months (range, 1.8 – 72.9 months) since first dose of BV, the median PFS was 9.3 months overall, but was not reached in CR patients. At the time of presentation, 15 patients remained in remission and were still being followed at study closure; of the 15 patients, 6 received consolidative allogeneic stem cell transplant (alloSCT) and 9 have had no treatment following BV. These data suggest that a small proportion of patients might be cured with BV even after post-ASCT relapse.

Allogeneic transplant (alloSCT) in Hodgkin Lymphoma (HL) patients with recurrence after autologous stem cell transplant (ASCT)

In most centers, alloSCT is exclusively performed in patients with HL recurrence after ASCT and even at relapse after ASCT, alloSCT is an option for carefully selected patients only. The reduced relapse rate associated with a potential graft-versus-tumor effect is offset by lethal graft-versus-host toxicity. Data on alloSCT in HL are limited to phase II or retrospective studies, randomized trials are lacking. Myeloablative conditioning in HL led to poor results because of the exceedingly high non-relapse mortality (46); however, several analyses showed that dose-reduced allogeneic transplant (RIC-alloSCT) might be an option for patients relapsing after ASCT (47, 48). The largest prospective trial with RIC-alloSCT in relapsed or refractory HL was performed by the Grupo Español de Linfomas/Trasplante de Médula Osea (GEL/TAMO) and the Lymphoma Working Party of the EBMT (49). In this phase II study, 92 patients were planned to receive salvage therapy followed by RIC-alloSCT (conditioning regimen: fludarabine 150 mg/m², melphalan 140 mg/m²). Of those, 79 had prior ASCT and 78 patients proceeded to RIC-alloSCT. Anti-thymocyte globulin was additionally used as graft-versus-host-disease prophylaxis for recipients of grafts from unrelated donors (23 patients). The PFS rate was 47% and 18% at 1 and 4 years from trial entry, respectively. For the allografted population, the PFS rate was 48% and 24% at 1 and 4 years, respectively, and the OS rate was 71% and 43% at 1 and 4 years, respectively. Patients allografted in CR had a significantly better outcome. In summary, RIC-alloSCT is an option for selected HL patients with post-ASCT relapse achieving a remission to salvage chemotherapy. Recent data also suggest that haploidentical alloSCT may be an effective approach for cHL patients with relapse after ASCT (50, 51). Lately, BV was evaluated as potential salvage therapy prior alloSCT and several retrospective reports yielded promising results (52, 53). The role of alloSCT in HL will have to be reevaluated in the era of programmed death 1 (PD-1) checkpoint inhibitors that will be reviewed separately in this issue.

Acknowledgments

CM has received research support from Merck and Seattle Genetics.

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Figure 1.

Meta-analysis of trials comparing conventional chemotherapy (CT) with high dose chemotherapy (HDCT) followed by autologous stem cell transplant (ASCT) in relapsed Hodgkin Lymphoma: Forest plot of comparison of progression-free survival (PFS).

Figure 2.

Meta-analysis of trials comparing conventional chemotherapy (CT) with high dose chemotherapy (HDCT) followed by autologous stem cell transplant (ASCT) in relapsed Hodgkin Lymphoma: Forest plot of comparison of overall survival (OS).

Figure 3. A randomized, double-blind, placebo-controlled, phase 3 trial of brentuximab vedotin (BV) as consolidation therapy after autologous stem cell transplant in patients with high risk Hodgkin Lymphoma (AETHERA): Progression-free survival (PFS) per investigator 3 years since last patient randomized. Includes clinical assessments of lymphoma.

Risk factors:

- Relapsed < 12 months or refractory to frontline therapy
- Best response of PR or SD to most recent salvage therapy
- Extranodal disease at pre-ASCT relapse
- B symptoms at pre-ASCT relapse
- 2 or more prior salvage therapies

Figure 4.

A randomized, double-blind, placebo-controlled, phase 3 trial of brentuximab vedotin (BV) as consolidation therapy after autologous stem cell transplant in patients with high risk Hodgkin Lymphoma (AETHERA): Risk factors associated with poor outcomes.