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REVIEW ARTICLE

# Treatment strategies for Hodgkin lymphoma recurring following autologous hematopoietic stem cell transplantation

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Hodgkin lymphoma (HL) represents one of the great success stories in hematology going from a uniformly fatal disease, to one that is curable in the vast majority of cases. Despite this success, some patients experience relapse. To address this unmet need a variety of agents, classes of drugs, and strategies have demonstrated activity in HL recurring after autologous hematopoietic stem cell transplantation. These include chemotherapeutics (gemcitabine-based combinations, bendamustine), histone deacetylase (HDAC) inhibitors (panobinostat), immunomodulatory agents (lenalidomide), mTOR inhiobitors (everolimus), monoclonal antibodies (rituximab), and antibody-drug conjugates (brentuximab vedotin) as well the potential of long-term disease control via allogeneic transplantation. Such advances reflect our increased understanding of the biology of HL and hold promise for continued improved outcomes for those suffering with this condition.

**Key Words** Hodgkin lymphoma, Antibody drug conjugates, allogeneic transplant, HDAC inhibitor, IMID, mTOR

## INTRODUCTION

Hodgkin lymphoma (HL) newly presents in over 8,400 individuals per year in the United States (US), accounting for approximately 8.7% of all lymphomas in the US, and is diagnosed worldwide in approximately 635,000 individuals annually [1, 2]. Over the past half century with advancements in radiation and chemotherapy, HL has evolved from a disease that was nearly uniformly fatal, to one that reaches a cure rate approaching 70-90% with initial therapy [3, 4]. For patients who relapse after initial therapy, the current standard of care is high dose chemotherapy followed by autologous hematopoietic stem cell transplant (auto-HCT), which has been shown to yield long-term remissions in approximately 50% of patients with chemotherapy responsive disease [5, 6]. However, in the subset of patients with refractory disease or relapse after auto-HCT, prognosis remains poor. The purpose of this review will be to highlight current therapies in development for use in patients with relapsed/refractory HL who have failed auto-HCT, with an emphasis on novel combination chemotherapy regimens, biologic agents and the emerging role of reduced intensity conditioning allogeneic transplant (RIC allo-HCT).

## TRADITIONAL CHEMOTHERAPEUTICS

### 1. Gemcitabine-based regimens

The development of combination chemotherapeutic agents for use in relapsed/refractory HL has centered on gemcitabine (difluorodeoxycytidine), a drug that has been shown to have success as single agent therapy with an overall response rate (ORR) of 39% [7]. The combination of gemcitabine, vinorelbine and pegylated liposomal doxorubicin (GVD) for relapsed/refractory HL has been evaluated for safety and efficacy by the Cancer and Leukemia Group B (CALGB) in a phase I/II trial, which included 91 patients (Table 1) [8]. The median age was 33, with 89 patients having classic HL (2 patients with lymphocyte predominant disease), and

**Table 1.** Selected traditional chemotherapeutic regimens for relapsed Hodgkin lymphoma.

| Regimen | No. of patients | Median age in years | Number of prior treatments[a)] | Prior transplant | ORR% | CR% |
|---|---|---|---|---|---|---|
| GVD [8] | 91 | 33 | Transplant naïve: 79% one prior treatment<br>Prior transplant: 70% with 3 or more prior treatments | 40 (44%) | 70% | 19% |
| GDP [9] | 23 | 36.5 | At least 1 prior treatment; 26% refractory to ABVD | 0 | 69.5% | 17% |
| GCD [10] | 14 | 32 | 2 (range 1-5) | 4 | 86% | 50% |
| Bendamustine [11] | 18 | -- | -- | 12 with prior auto-HCT<br>2 with prior NMT | 75% | 38% |

[a)]Excluding auto-HCT.
Abbreviations: No., number; ORR, overall response rate; CR, complete response; auto-HCT, autologous stem cell transplant; NMT, non-myeloablative stem cell transplant; GVD, gemcitabine, vinorelbine and pegylated liposomal doxorubicin; GDP, gemcitabine, dexamethasone and cisplatin; GCD, gemcitabine, carboplatin, and dexamethasone; ABVD, adriamycin, bleomycin, vinblastine, dacarbazine; --, data not available.

40 patients having had prior auto-HCT. Of the prior transplant patients, 70% had 3 or more prior chemotherapy regimens. GVD was given on days 1 and 8 of a 21-day cycle. The major dose limiting side effect in patients without prior transplant was mucositis and febrile neutropenia in those with prior transplant. Not surprisingly, grade 3 or 4 thrombocytopenia developed in 43% of prior transplant patients compared 14% of those without prior transplant. Three cases of AML/MDS occurred, all in patients with prior auto-HCT. The ORR was 70%, which included 51% with a partial response (PR) and 19% with a complete response (CR). At the maximum tolerated dose (MTD), ORR was 61% for the transplant naïve group (25/41) and 75% (27/36) for the prior transplant group. In terms of event free survival (EFS), the median had not been reached in the transplant naïve group with 52% of patients without evidence of disease progression at 4 years, and in the prior transplant group, the median EFS was 8.5 months. In the transplant naïve group, median overall survival (OS) had not been reached at 4 years, with 70% still alive, and in the prior transplant group median OS was 3.5 years. Progressive HL was the main cause of death in most patients, occurring in 27 of 36 that died [8]. Although outcomes were promising in the patients who had not undergone prior transplant, those had failed auto-HCT, despite a relatively high ORR, had a short median EFS, with progressive disease (PD) accounting for most deaths.

The combination of gemcitabine, dexamethasone and cisplatin (GDP) has also been evaluated for relapsed/refractory HL (Table 1). In a prospective phase II study published by Baetz *et al.*, 23 patients with relapsed/refractory HL were given gemcitabine 1,000 mg/m$^2$ IV on day 1 and 8, cisplatin 75 mg/m$^2$ IV following gemcitabine and dexamethasone 40 mg orally in divided doses on days 1-4 as part of a 21 day cycle [9]. The median age was 36.5, and at least 6 patients (26%) had failed to achieve a response with ABVD (Adriamycin, bleomycin, vinblastine and dacarbazine). ORR was 70%, including 17% (4 patients) with a CR and 52% (12 patients) with a PR. GDP was well tolerated, with no deaths secondary to treatment, no cases of cases of febrile neutropenia and no platelet transfusions were required, although 4 patients did require red blood cell transfusions. Since all patients went on to undergo auto-HCT, specific data with the regimen in the post-transplant setting cannot be derived from this study.

The combination regimen of gemcitabine, carboplatin, and dexamethasone (GCD) was evaluated by the Seattle group for use in relapsed/refractory HL (Table 1) [10]. In this prospective study, 51 patients with relapsed lymphoma were enrolled and evaluable, including 14 with HL. The median age of the HL patients was 32 and the median number of prior therapies was 2 (range, 1-5) with 4 relapsing after prior HCT (A. Gopal personal communication). Importantly, 12 patients (86%) responded (7 CR/5 PR) including all 4 patients with prior HCT (3 CR/1 PR). For those who attempted peripheral blood stem cell mobilization following this regimen (N=7), the median CD34 collection was $10.9\times10^6$/kg (range, 5.5-$18.8\times10^6$ CD34/kg). These studies and others indicate the tolerability and potential efficacy of gemcitabine-based regimens in patients with relapsed or refractory HL and the variety of effective combinations can allow the treating physician to tailor the added agents to a patient's specific needs and comorbidities (eg: neuropathy, renal insufficiency, marrow reserve, etc.).

## 2. Bendamustine

Bendamustine is a bi-functional alkylator that has been approved in the US and Europe for the treatment of relapsed indolent B-cell non-Hodgkin lymphoma (B-NHL) and chronic lymphocytic leukemia (CLL) [11]. *In vitro* data also suggest that bendamustine displays pro-apoptotic and anti-proliferative effects on cultured HL cells [12]. Based on these preclinical results, investigators at the Memorial Sloan Kettering Cancer Center evaluated the efficacy of bendamustine in a phase II study of patients with relapsed/refractory HL (Table 1) [13]. Preliminary data was reported on 18 patients (out of planned 37) of whom 16 were evaluable. Of these, 12 had failed prior auto-HCT and 2 had failed prior non-myeloablative transplant (NMT). Patients were treated with bendamustine at a dose of 120 mg/m$^2$ for two consecutive days every 28 days and pegfilgrastim was administered with each dose. Primary outcomes included re-

sponse rate and referral to NMT. The ORR was 75%, with 6 patients (38%) achieving a CR, 6 patients (38%) achieving a PR and one patient with stable disease (SD). Two patients died prior to first re-evaluation secondary to PD. Adverse events (AEs) reported were pyelonephritis, fungal pneumonia and grade 3 nausea. A total of 10 patients had either delays or reductions in treatment due to nausea, pneumonia, thrombocytopenia or neutropenia. Importantly, of the 12 patients who were potentially eligible for NMT, 6 (50%) were successfully referred, although 3 patients ultimately refused. These early results suggest the potential of bendamustine for use in heavily pre-treated HL patients, however the final peer-reviewed update from this trial and additional studies are needed to clarify the safety and efficacy of this approach. Future strategies including the incorporation of bendamustine into combination regimens for HL are underway at our center and others.

## BIOLOGICAL AGENTS AND SMALL MOLECULES

### 1. Panobinostat

A novel class of drugs under evaluation for use in refractory/relapsed HL are the histone deacetylase inhibitors, with most of the data are derived from experience with panobinostat. Panobinostat is an orally bioavailable pan deacetylase inhibitor (pan-DACi) that has been clinically evaluated multiple malignancies and also been shown to have *in vitro* activity against cultured HL cell lines [14]. In phase IA/II study published by Dickinson *et al.*, 13 patients with relapsed/refractory HL underwent treatment with panobinostat, with 58% (7/12) showing reduction in metabolic activity measured by PET response [15]. A large multi-center phase II trial, led by Sureda *et al.*, was initiated to further evaluate the safety and efficacy of panobinostat (Table 2) [16]. At the time of abstract publication (American Society Hematology, 2010), a total of 129 patients with relapsed/refractory HL had been enrolled and treated. The median age was 32 with a median of 4 (2-7) prior treatments, and 10% had prior allo-HCT. Panobinostat was dosed 40 mg orally three times a week in a 21-day cycle with response evaluated by CT/MRI. The ORR was 27%, with 5 patients achieving a CR and 30 patients achieving a PR. A preliminary analysis showed median progression free survival (PFS) was 5.7+ months, a disease control rate of 82% (PR, CR and SD) and a duration of response (DOR) of 6.9+ months. Grade 3/4 AEs included anemia, neutropenia and thrombocytopenia, typically reversible with holding or modifying the dose [16]. These results are encouraging, showing that Panobinistat in this heavily pre-treated population was not only tolerable, but also resulted in durable responses, suggesting that this class of agents may play a role in the management of HL in the future.

### 2. Lenalidomide

Lenalidomide, a pro-apoptotic, anti-angiogenic and immunomodulatory agent approved for the treatment of certain hematologic malignancies (multiple myeloma and myelodysplastic syndrome with del5q), is also being investigated for use in refractory/relapsed HL. In a small phase II trial led by Kuruvilla *et al.*, 15 patients, 14 of who were evaluable, were given 25 mg orally on days 1-21 of a 28-day cycle (Table 2) [17]. Grade 3-4 AEs included thrombocytopenia, anemia and neutropenia. Results showed PR in 2 patients and SD in 7 patients; unfortunately 5 patients discontinued therapy because toxicity and 6 discontinued therapy due to PD. Although this study was small, lenalidomide did show evidence of anti-tumor activity as evidenced by the patients with PR and SD [17]. In a larger multicenter phase II trial led by Fehniger *et al.*, 38 patients with relapsed or refractory HL were treated with lenalidomide 25 mg/day on days 1-21 of a 28-day cycle [18]. The primary endpoint was ORR, and treatment was continued until patients had either an unacceptable AE at the lowest dose (5 mg) or until developing PD. Of the 38 patients, 36 were evaluable, and of these, 7 patients had responses (1 CR and 6 PRs, ORR 19%) and 6 patients had SD (ORR cytostatic disease 33%). The most common grade 3-4 AEs included leukopenia, anemia, neutropenia, and thrombocytopenia. In the largest study evaluating lenalidomide in HL to date, led by Boll *et al.*, a total of 42 patients were given 25 mg lenalidomide daily for 21 days of a 28 day cycle [19]. Of the 42 patients enrolled patients, 24 were eligible for analysis, and 50% had responded (1 CR and 11 PR) at the time of re-staging CT scan. This study, along with the others mentioned, suggests that lenalidomide can be safely administered in heavily pre-treated HL patients similar to other relapsed lymphoma populations and holds promise as a single agent therapy in this patient

**Table 2.** Selected biologic agents and small molecules for relapsed Hodgkin lymphoma.

| Regimen | No. of patients | Median age | No. of prior treatments[a] | Prior transplant | ORR% | CR% |
|---|---|---|---|---|---|---|
| Panobinostat [16] | 129 | 32 | 4 | 10% prior allogeneic transplant | 27% | 4% |
| Lenalinomide [18] | 38 | 34 | 4 | 87% (29 prior auto-HCT, 1 syngeneic, and 3 both allo and auto-HCT) | 17% | 3% |
| Everolimus [21] | 19 | 37 | 6 | 84% | 47% | 5% |
| Rituximab [23] | 22 | 35 | 4 | 82% | 22% | 4% |
| Brentuximab Vedotin [30] | 102 | 31 | 4 | 100% | 75% | 34% |

[a]Excluding auto-HCT.
Abbreviations: No., number; ORR, overall response rate; CR, complete response; allo, allogeneic; auto-HCT, autologous stem cell transplant.

population.

### 3. Everolimus

Inhibiting the mammalian target of rapamycin (mTOR) pathway has also been supported by preclinical data as a potential strategy for the treatment of HL. Most clinical data regarding mTOR inhibition and HL comes from studies with everolimus (RAD001), currently approved in the US for treating relapsed renal cell carcinoma [20, 21]. The activity of everolimus in relapsed/refractory HL was recently evaluated in a phase II trial published by Johnston *et al.*, in which 19 patients with relapsed/refractory HL were given 10 mg po Everolimus daily in a 4 week cycles. In this study, the median age was 37, patients had a median of 6 prior therapies, and 84% had prior auto-HCT (Table 2) [21]. The median duration of therapy was 7 months. The ORR was 47%, including 8 patients with a PR and1 CR. Additionally, SD was reported in 8 patients. The median PFS was 7.2 months, and OS was 25.2 months (from study entry). Grade 3 or higher hematologic AE was experienced in 11 patients, including 6 patients with grade 3 anemia and 4 patients with grade 4 thrombocytopenia. Grade 3 or higher non-hematologic AEs were experienced in 11 patients, including 3 patients with grade 3 pulmonary toxicity and 1 with grade 4 pulmonary toxicity. The high ORR shown with Everolimus in HL supports the hypothesis that the mTOR pathway may play an important role in the progression of HL, and that further studies investigating the safety and efficacy of these agents are warranted.

### 4. Rituximab

Rituximab, a monoclonal antibody directed against the cell-surface marker CD20 used extensively in NHL, has also been shown to have activity in HL. In a study published by Rassidakis *et al.*, classic HL Reed-Sternberg (RS) cells expressed CD20 in 22% of 598 patients studied [22]. The use of rituximab in relapsed/refractory HL was evaluated by the M.D. Anderson Cancer Center, in a study that included 22 patients, of whom all had nodular sclerosing type of HL (Table 2) [23]. The median age was 35 years, and 82% had prior transplant. Rituximab was given IV weekly (375 mg/m$^2$) in the outpatient setting for 6 consecutive weeks. ORR was 22% (5 of 22 patients), including one CR and median remission duration was 7.8 months. Interestingly, objective response was seen regardless of CD20 expression on RS cells. Moreover, of the 7 patients with B symptoms, 6 had resolution, and declines in serum IL-6 were seen after therapy. Because RS cells make up only approximately 5% of total tumor bulk in HL, it is thought that perhaps rituximab's effect *in vivo* may not be due to killing of RS cells, rather may be secondary to eliminating surrounding reactive B cells, leading to a decrease in cytokine and chemokine secretion [24]. Nevertheless, rituximab could be considered for those patients whose RS cells express CD20 and had exhausted other options.

### 5. Brentuximab vedotin

A cell surface marker that has attracted significant attention due to its role in the development of targeted monoclonal antibody therapies has been CD30, which is expressed in low levels in some normal tissues and abundantly in HL and anaplastic large cell lymphoma (ALCL) [25]. One of the first of such novel agents directed against this antigen is SGN-30, a chimerized IgG1 monoclonal antibody specific for CD30 [26]. Two phase I dose escalation trials of SGN-30 demonstrated that drug was well tolerated and had anti-tumor activity [27, 28]. Based on these results, a phase II trial was conducted by Forero-Torres *et al.*, evaluating 38

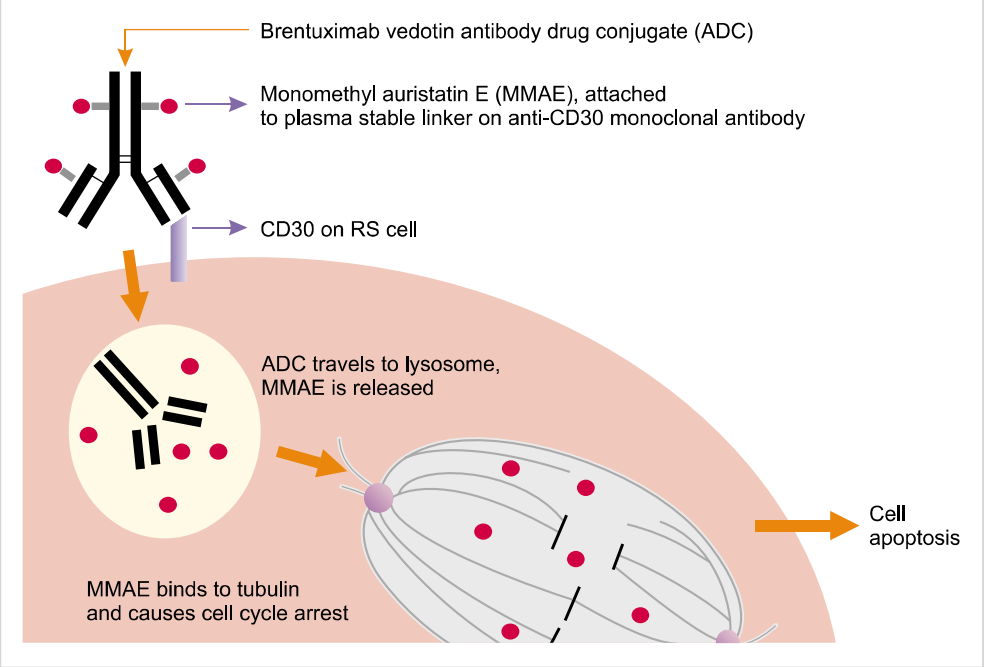


**Fig. 1.** Proposed Mechanism of Action of Brentuximab Vedotin Antibody Drug Conjugate (ADC). Depiction of CD30 ligation by ADC followed by CD30-ADC internalization, lysosomal cleavage of linker and intracellular release of anti-tubulin agent MMAE leading to cell cycle arrest and apoptosis. Abbreviation: RS, Reed-Sternberg.

HL and 41 ALCL patients who underwent 6 weekly IV infusions of SGN-30, followed by a 14-day break [29]. Of the 38 patients with HL, 11 patients (29%) had SD, however, no objective responses were observed. Although the ORR was 0% in HL patients who received with SGN-30, this work provided the foundation for the subsequent development of brentuximab vedotin (SGN-35).

Brentuximab vedotin (SGN-35) is comprised of the previously described SGN-30, with the addition of a dipeptide linker that enables the attachment of Monomethyl auristatin E (MMAE), a potent anti-microtubule agent [26]. Specifically, brentuximab vedotin binds to CD30 on malignant RS cells, releases MMAE inside the cell via lysosomal degradation and once inside the cell, MMAE binds to tubulin within the cell and induces cell cycle arrest leading to apoptosis of the RS cell (Fig. 1) [30]. In a phase I open label trial published by Younes *et al.*, 45 patients with relapsed or refractory CD30+ lymphomas (42 patients with HL, 2 with ALCL and 1 with CD30+ angioimmunoblastic T Cell Lymphoma) were given brentuximab vedotin (0.1-3.6 mg/kg) every 3 weeks [31]. The AEs reported included peripheral neuropathy (16%) as well as nausea, diarrhea, fatigue, pyrexia and neutropenia. Of patients evaluated, 17 patients had objective responses (including 11 CRs) and 50% (6 of 12) of patients who received the MTD of 1.8 mg/kg had an objective response. The median duration of remission was 9.7 months. For patients with relapsed/refractory HL who had undergone previous therapies, 50% (13 of 26) had an objective response, including 9 CRs and 4 PRs. This response rate is particularly striking when compared with results with the un-conjugated SGN-30, in which no responses were observed [29, 31]. These encouraging phase I results led further studies investigating the safety and efficacy of brentuximab vedotin.

In a large, multi center phase II trial presented by Chen *et al.*, the safety and efficacy of brentuximab vedotin were evaluated in patients with HL recurring after auto-HCT. A total of 102 patients were enrolled and given 1.8 mg/kg IV brentuximab vedotin every 21 days as outpatient 30 minute infusions (Table 2) [30]. Patients had a median of 3.5 (1-13) prior systemic chemotherapy treatments (excluding auto-HCT). Over 70% of patients had primary refractory disease, and 42% had not responded to most recent prior therapy. The primary endpoint of the study was ORR per an independent review facility (IRF) in accordance with the Revised Response Criteria for Malignant Lymphoma [32]. Per the IRF, the ORR was 75% (76 of 102 patients), with CR in 34% (35 of 102). For patients with CR, the median DOR had not been reached (0.3+ to 61.4+ weeks). The major AEs occurring in $\geq$15% of patients were peripheral sensory neuropathy, fatigue, nausea, diarrhea and neutropenia. Grade 3 AEs occurring in more than 5% of patients were anemia, thrombocytopenia, neutropenia and peripheral sensory neuropathy. These results demonstrating an ORR of 75% in the relapsed/refractory HL population led to the approval of this agent in the US for HL recurring after auto HCT or for those with relapsed disease after $\geq$2 regimens who are not auto-HCT candidates.

Brentuximab vedotin has also been evaluated in a number of other settings, including for longer-term use, in combination with chemotherapeutic agents and for improved disease control prior to RIC allo-HCT. Forero-Torres *et al.*, in a recent retrospective analysis, evaluated 15 patients who had received more than 16 consecutive cycles of brentuximab vedotin, dosed at either 1.2 or 1.8 mg/kg of brentuximab vedotin every 3 weeks, and found that the safety profile did not meaningfully change [33]. Studies evaluating the combination of this agent with standard chemotherapeutic regimens, such as ABVD and AVD (Adriamycin, vinblastine and dacarbazine) are currently underway [34]. Brentuximab-vedotin also has potential use for improving disease control in patients with relapsed/refractory HL prior to transplant, and is currently being evaluated for this purpose. A retrospective analysis by Chen *et al.*, described 16 patients from the Fred Hutchinson Cancer Research Center (FHCRC)/ Seattle Cancer Care Alliance (SCCA) (N=4) and the City of Hope National Medical Center (COH) (N=12) with relapsed/refractory HL who underwent RIC allo-HCT following treatment with brentuximab vedotin [35]. At COH, the 1-year OS was 100% and PFS was 90% with 1 relapse, at the FHCRC/SCCA all 4 patients were progression free at a follow up at 7.2 months. There appeared to be no increased risk of EBV/CMV infections, no delay in engraftment and no grade III-IV acute graft-versus-host disease (GVHD) though one patient experienced extensive chronic GVHD to date. These results imply that brentuximab vedotin has the potential to improve pre-transplant disease control prior to RIC allo-HCT that hypothetically could translate into improve long-term disease-free survival (DFS), without incurring added risk of infection or delayed engraftment. The full potential of brentuximab vedotin for use in HL is still emerging, and future trials will be needed to fully define the optimal use of this agent in HL.

## ALLOGENEIC TRANSPLANT

Achieving lasting cure in patients with relapsed/refractory HL following auto-HCT remains difficult, and while novel single agent therapies have shown promise, traditional thinking suggests that these therapies do not have the same potential for cure as allo-HCT. However, an allo-SCT still poses multiple challenges, including identification of a donor, short and long-term toxicity, and continued risk of relapse [36]. Fully myeloablative allo-HCTs have also been evaluated, but an association with early transplant related mortality (TRM) have limited their appeal [37, 38]. An alternative allo-HCT strategy that is more commonly employed in this setting is RIC allo-HCT. The following section will review recent advances and challenges of RIC allo HCT in patients with relapsed/refractory HL.

### 1. Conditioning intensity

In an informative paper published by Sureda *et al.* in 2008, RIC allo HCT was compared with full myeloablative

**Table 3.** Selected series of reduced intensity allogeneic transplant for relapsed Hodgkin lymphoma.

| First author | No. of patients | Donor type | Conditioning regimen | Med. age | No. of prior Rx | Prior trans-plant[a)] | Chemo-Ref. disease | NRM | PFS | OS |
|---|---|---|---|---|---|---|---|---|---|---|
| Sureda *et al.* [39] | 89 (RIC) | 86.5% MRD<br>13.5% MUD | RIC regimens[b)] | 30 | 84%≥3 | 62% | 55% | 24% at 3 yrs | 18% at 5 yrs | 28% at 5 yrs |
| Anderlini *et al.* [40] | 40 | 50% MUD<br>50% HLA haplo | RIC: 35% Flu/Cy +ATG; 65% Flu-M | 31 | 5 | 75% | 35% | 22% at 18 mos | 32% at 18 mos | 61% at 18 mos |
| Anderlini *et al.* [41] | 58 | 57% MUD<br>43% MRD | RIC: Flu-M | 32 | 5 | 83% | 48% | 15% at 2 yrs | 32% at 2 yrs | 64% at 2 yrs |
| Burroughs *et al.* [36] | 90 | 27% MUD<br>42% MRD<br>31% HLA haplo | NMT: TBI 2Gy +/- Flu; TBI/Flu/Cy (haplo only) | 32 | 5 | 92% | 21-43% | 8-21% at 2 yrs | 23-51% at 2 yrs | 53-58% at 2 yrs |
| Robinson *et al.* [42] | 285 | 33% MUD<br>3% MMUD<br>60% MRD<br>4% MMRD | RIC: 79.5% Flu based; 16% TBI based | 31.2 | 4 | 80% | 25% | 21.1% at 3 yrs | 25% at 3 yrs | 29% at 3 yrs |

[a)]Excluding auto-HCT, [b)]Included regimens under RIC definition: carmustine 300 mg/m$^2$ IV, etoposide 600-800 mg/m$^2$ IV, cytarabine 800-1,600 mg/m$^2$ IV, melphalan 100-140 mg/m$^2$ IV (BEAM regimen); Flu plus 2-4 Gy TBI or 1-2 low dose alkylating agents.
Abbreviations: RIC, reduced intensity chemotherapy; No., number; Ref., refractory; NRM, non-relapse mortality; PFS, progression free survival; OS, overall survival; yrs, years; NMT, nonmyeloablative therapy; TBI, total body irradiation; mos, months; MUD, matched unrelated donor; MMUD, mis-matched unrelated donor; MRD, matched related donor; MMRD, mis-matched related donor; HLA haplo, HLA haploidentical donor; Flu, fludarabine; Cy, cyclophosphamide; ATG, antithymocyte globulin; Flu-M, fludarabine-melphalan.

allo-HCT (Table 3) [39]. In this retrospective study, a total of 168 patients with relapsed/refractory HL were evaluated, with 89 receiving RIC and 79 receiving myeloablative conditioning. Patients in the RIC group had improved non-relapse mortality (NRM) compared with the conventional group: at 3 months NRM was 15% (RIC) vs. 28% (conventional), and at 1 year was 23% (RIC) vs. 46% (conventional). In terms of relapse, the two groups were similar: at 5 years, OS was 28% (RIC) vs. 22% (conventional), and 5 year PFS was 18% (RIC) vs. 20% (conventional). Factors in both groups associated with an increased in NRM were chemorefractory disease (relative risk, RR=1.64), conventional conditioning regimen (RR=2.85) and previously failed auto-HCT (RR=1.9). NRM was especially high in those patients who had failed prior auto-HCT who underwent full myeloablative transplant (RR=3.7). These data imply that myeloablative preparative regimens, especially in patients who have undergone prior auto-HCT, are associated with higher toxicity and that for most patients, may not be of added benefit. Overall results from both arms indicate that only about 1 in 5 patients will achieve long-term DFS regardless of conditioning regimen, and that relapse is problematic in both groups.

## 2. Choice of RIC regimen

A number of groups have focused on identifying a regimen for RIC allo-HCT that could improve outcomes and to date, no firm conclusions can be drawn. Anderlini *et al.* published a small, single institution retrospective analysis comparing fludarabine-cyclophosphamide (Flu-Cy)+ATG with a more intensive regimen with fludarabine-melphalan (Flu-M) in patients with relapsed/refractory HL undergoing RIC allo-HCT (Table 3) [40]. In this study, 40 patients received either a matched unrelated donor (MUD, N=20) or HLA-identical sibling donor (N=20), and patients received one of the two previously described RIC regimens. Short term TRM was promising for the groups overall: 5% at day 100 and 22% at 18 months. Of the original 40 patients, a total of 8 patients died from TRM and another 8 patients died from PD. Flu-M was shown to have a better OS than the Flu-Cy+ATG regimen (73% vs. 39% at 18 months) [40]. This same investigator published a prospective study further evaluating the outcome of Flu-M as a RIC regimen in allo HCT for patients with relapsed/refractory HL. In this study, 58 patients underwent RIC allo HCT with Flu-M with both MUD (N=33) and matched related donor (MRD, N=25) [41]. TRM was 7% at day 100 and 15% at 2 years. Of the 58 patients, 20 had died, including 14 from PD and 3 from GVHD. Interestingly, no significant differences were found in OS, PFS, PD or TRM between the MUD vs. MRD groups. Though the non-randomized nature of these comparisons must be acknowledged, these studies showed that Flu-M based RIC regimens for allo-HCT may be superior to Flu-Cy+ATG based RIC regimens and that there do not appear to be inferior outcomes when an MUD is employed. Short of these data, substantial formal comparisons of RIC regimens are limited for HL, and, thus, most patients are treated with approaches that are standard for a given institution.

## 3. Donor source

Determining whether donor source affects outcome in patients with relapsed/refractory HL undergoing RIC allo-HCT has been a clinically important question. As described above, Anderlini was not able to show a difference between MRD and MUD [41]. To specifically address this question, Burroughs *et al.* conducted a single institution retrospective analysis that evaluated differences in donor type and outcome

(Table 3) [36]. In this study, 90 patients with HL received an allo-HCT from either a MUD (N=24), HLA-haploidentical related donor (N=28) or MRD (N=38). Most patients had failed prior high dose autologous/syngeneic HCT (92%), had undergone radiation (83%), and had a median of 5 (2-10) prior regimens. Nonmyeloablative preparative regimens included 2 Gy total body irradiation (TBI) alone (MRD), or 2 Gy TBI combined with Flu 30 mg/m$^2$/day on days -4, -2 (MRD, MUD) or finally Cy 14.5 mg/kg/day on days -5, -6 (HLA haploidentical related recipients) combined with Flu 30 mg/m$^2$/day and 2 Gy TBI. This was followed by post-grafting immunosuppression with either cyclosporine/tacrolimus or mycophenolate mofetil (MMF). At 25 months median follow up, OS ranged from 53-58%, PFS ranged from 23-51%, and relapsed/PD ranged from 40-63%. HLA-haploidentical related recipients had significantly lower NRM compared with MRD recipients. Moreover, HLA-haploidentical related recipients also had significantly decreased risk of relapse compared with the other groups. The incidence of acute GVHD (grades III-IV) and chronic GVHD was 16% and 50% respectively in the MRD group, 11% and 35% in the HLA-haploidentical related group and 8% and 63% in the MUD group [36]. This study further supports that RIC/NMT regimens are associated with lower NRM, and also suggests that alternative donor sources can be considered an option in these heavily pre-treated patients who may have a limited time frame to proceed to HCT. Disease progression, however, remains a challenge regardless of donor type [36].

### 4. Factors associated with outcome

Identifying prognostic factors that predict outcome in patients with relapsed/refractory HL undergoing RIC allo-HCT is especially important given the high reported relapse rates. A retrospective analysis published by Robinson *et al.*, evaluated 285 patients, 25% with chemorefractory disease and 80% who had prior auto-HCT (Table 3) [42]. At a median follow up of 26 months, 55% of patients had died (159 of 285), and relapse rates were high with 41% at 1 year, 53% at 2 years and 59% at 5 years. At 3 years, PFS was 25% and OS was 29%. Improved OS was seen in patients who had chemosensitive disease, had good performance status, entered allo-HCT in CR, and had transplants other than sex mismatched male recipients and CMV-/- transplants. Improved PFS was associated with similar factors affecting OS, including CR at the time of allo-HCT, chemosensitive disease, good performance status and transplant other than sex mismatched male recipients. Additionally, patients who had relapsed within six months of prior auto-HCT were also associated with lower PFS and higher relapse rate. Acute GVHD developed in 49% of patients, and was associated with worse outcomes: higher NRM, lower PFS and OS, and no improvement in risk of relapse. At 100 days, 38% (87) patients developed chronic GVHD, although 13% (5 patients) were unable to be evaluated [42]. Data from this study and others can be used to help predict post-transplant outcomes and assist in deciding which patients may achieve the most benefit from this procedure.

### 5. Relapse after RIC allo-HCT

As shown by prior studies reported in this review, there are some patients with relapsed/refractory HL who achieve lasting cure with RIC allo-HCT, although many patients unfortunately suffer PD. To better counsel patients in this situation and to evaluate specific management strategies in this setting, Ram *et al.* described 101 patients with lymphoma who had relapses after RIC and allo-HCT [43]. This group included 26 patients with relapsed/refractory HL, 50% (13 patients with HL) of whom had prior auto-HCT. HL patients tended to relapse later than those with other lymphoma histologies (6.3 months vs. 3.4 months for indolent NHL and 1.3 m for aggressive NHL). Relapse occurred much sooner in the HL group with prior auto-HCT (median 4.6 months) compared with patients who did not have prior auto-HCT (median 12 months). The estimated 3 year OS after relapse in HL patients was 47%. Patients with HL, despite a longer time to initial relapse relative to indolent NHL, were shown to have the greatest risk of PD even after response to initial therapy for post RIC allo-HCT relapse. Thus, further strategies to achieve lasting remission following RIC allo-HCT are needed. One potential option that has been evaluated includes brentuximab vedotin (discussed earlier in this review), which was shown by Gopal *et al.*, in a multicenter series of 25 patients with HL recurring following allo-HCT, to yield a 50% response rate in evaluable patients [44]. Nevertheless, despite interest in this area, improved strategies are still need for management of post allo-HCT relapse.

## CONCLUSIONS

In summary, the treatment of relapsed/refractory HL has seen the development of significant advances in the last decade. The development of novel primarily gemcitabine-based chemotherapeutic combinations as well as demonstration of activity of varied classes of agents including HDAC inhibitors (panobinostat), immunomodulatory agents (lenalidomide), mTOR inhiobitors (everolimus), novel cytotoxics (bendamustine), monoclonal antibodies (rituximab), and antibody-drug conjugates (brentuximab vedotin) hold promise that the natural history of this challenging clinical situation can be improved. To date, most data suggest that long-term DFS for HL recurring after auto-HCT can be obtained in a minority of patients following allo-HCT, though even with this procedure toxicity and continued relapse remains a major hurdle. Future directions will likely include moving these agents earlier into the treatment paradigm with the hopes to reduce the fraction of patients with relapse and to optimize the use of these and forthcoming strategies to best improve outcomes of those who continue to suffer disease progression.

## DISCLOSURES

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