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**REVIEW**

# Managing Hodgkin lymphoma relapsing after autologous hematopoietic cell transplantation: a not-so-good cancer after all!

MA Kharfan-Dabaja[1,2], M Hamadani[3], H Sibai[4] and BN Savani[5]

Hodgkin lymphoma (HL) relapsing after an autologous hematopoietic cell transplant (HCT) poses a therapeutic challenge. In this setting, salvage chemotherapy (for example, gemcitabine-based, ifosfamide-containing and others) or immunotherapy (for example, brentuximab vedotin) is essential as a bridging-cytoreduction strategy to an allogeneic HCT. Myeloablative allogeneic hematopoietic cell transplantation in relapsed HL is associated with high rates of non-relapse mortality. In carefully selected patients with chemosensitive disease, allografting following lower-intensity conditioning regimens can provide durable disease control rates of about 25–35%. Promising early results with haploidentical and umbilical cord transplantation are noteworthy and are expanding this procedure to patients for whom HLA-matched related or unrelated donors are not available. Unfortunately, a significant number of HL patients relapsing after an autologous HCT are not candidates for allografting because of the presence of resistant disease, donor unavailability or comorbidities. Brentuximab vedotin is approved for HL relapsing after a prior autograft. Rituximab and bendamustine are also active in this setting, albeit with short durations of remission. Histone deacetylase inhibitors (for example, panobinostat, mocetinostat), *mTOR* inhibitors (for example, everolimus) and immunomodulatory agents (lenalidomide) have shown activity in phase II trials, but currently are not approved for this indication. Second autologous HCT are rarely performed but this approach should not be considered standard practice at this time. The need for effective agents for post autograft failures of HL largely remains unmet. Continuous efforts to ensure early referral of such patients for allogeneic HCT or investigational therapies are the key to improving outcomes of this *not-so-good* lymphoma.

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## INTRODUCTION

High-dose therapy and autologous hematopoietic cell transplantation (auto-HCT) is considered the standard of care for chemosensitive relapsed Hodgkin lymphoma (HL).[1,2] Outcomes following auto-HCT are dependent on the presence of various prognostic factors[3–5] as well as demonstrating chemosensitivity beforehand.[6,7] $^{18}$Fluorodeoxy glucose–positron emission tomography (FDG-PET) to assess remission prior to auto-HCT is helping to better select subjects expected to benefit from the procedure; patients achieving a negative FDG-PET before autografting demonstrate better EFS (>80 vs 28.6%, $P<0.001$).[7] A high international prognostic score ($\geqslant 3$) before and persistent FDG-PET positivity after salvage therapy is associated with a higher risk of disease-specific death after auto-HCT.[8] Accordingly, achieving negative FDG-PET should be the main goal prior to auto-HCT. Conversely, Palmer *et al.*[9] failed to demonstrate a predictive benefit of performing an early FDG-PET, after auto-HCT, on post-transplant outcomes.

Brentuximab vedotin is proving efficacious when used to treat relapsed HL even after failing a prior auto-HCT.[10] A phase 2 study of brentuximab vedotin in relapsed/refractory HL showed an overall response rate (ORR) of 75% (CR = 34%) with a median PFS of 5.6 months.[11] Achieving a CR resulted in longer lasting responses of 20.5 months.[11] This suggests that effective salvage therapies in the setting of previous auto-HCT failure might create a window of opportunity for subsequent interventions such as an allogeneic HCT (allo-HCT) in eligible subjects. Below we summarize available literature related to the management of relapsed HL after a prior auto-HCT failure.

## SALVAGE THERAPIES FOR RELAPSED HL AFTER AUTO-HCT

Treating relapsed HL after an auto-HCT is a therapeutic challenge. In this setting, salvage chemotherapy or immunotherapy could be considered a bridging strategy to an allo-HCT provided an objective response is achieved. Unfortunately, a significant number of these patients are not eligible for allografting because of the presence of resistant disease, unavailability of a suitable donor, or suboptimal performance status or organ impairment, among other reasons. In this section, we discuss therapies with a potential for providing disease control after disease relapse following an auto-HCT (Table 1). It is important to highlight that randomized data in this setting are absent and evidence is based on uncontrolled single-arm studies or small institutional case series.

### Conventional chemotherapy

*Gemcitabine-based*. Gemcitabine has single-agent activity in relapsed HL.[12] Various gemcitabine-containing regimens have

[1]Department of Blood and Marrow Transplantation, H. Lee Moffitt Cancer Center, Tampa, FL, USA; [2]Department of Oncologic Sciences, University of South Florida College of Medicine, Tampa, FL, USA; [3]Division of Hematology and Oncology, Medical College of Wisconsin, Milwaukee, WI, USA; [4]Department of Hematology-Oncology, Princess Margaret Hospital, Toronto, ON, Canada and [5]Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, USA. Correspondence: Dr MA Kharfan-Dabaja, Department of Blood and Marrow Transplantation, Moffitt Cancer Center, 12902 Magnolia Drive, FOB-3, Tampa, FL 33612, USA.
E-mail: Mohamed.Kharfan-Dabaja@Moffitt.org
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**Table 1.** Agents evaluated in HL relapsing after auto-HCT

| *Author* | *Therapeutic agent(s) and study design* | *N1* | *Median age, years (range)* | *N2* | *Response rate* | *Median duration of response* |
|---|---|---|---|---|---|---|
| Baetz *et al.*[15] | GDP<br>Phase II | 23 | 36 (19–57) | 0 | ORR = 69% | NR |
| Bartlett *et al.*[13] | GVD<br>Phase I/II | 91 | 33 (19–83) | 40 | ORR = 70%;<br>CR = 19% | EFS = 10% (4 years) |
| Gopal *et al.*[16] | GCD<br>Phase II | 14 | 32 | 4 | ORR = 86%;<br>CR = 50% | NR |
| Younes *et al.*[10] | Brentuximab vedotin<br>Phase I | 42 | 36 (20–87) | 33 | ORR = 38%;<br>CR = 24% | 9.7 months |
| Younes *et al.*[11] | Brentuximab vedotin<br>Phase II | 102 | 31 (15–77) | 102 | ORR = 75%;<br>CR = 34% | 20.5 months for patients in CR |
| Younes *et al.*[35] | Mocetinostat<br>Phase II | 51 | 34 (19–68) | 43 | ORR = 33% | |
| Younes *et al.*[34] | Panobinostat<br>Phase II | 129 | 32 (18–75) | 129 | ORR = 27%;<br>CR = 4% | 6.9 months |
| Kirschbaum *et al.*[36] | Vorinostat<br>Phase II | 25 | 42 (20–71) | 11 | ORR = 4% | NR |
| Younes *et al.*[29] | Rituximab<br>Phase II | 22 | 35 (17–66) | 18 | ORR = 22% | 7.8 months |
| Johnston *et al.*[41] | Everolimus<br>Phase II | 19 | 37 (27–68) | 16 | ORR = 47%;<br>CR = 5% | 7.2 months |
| Moskowitz *et al.*[21] | Bendamustine<br>Phase II | 35 | 34 (21–75) | 27 | ORR = 53%;<br>CR = 33% | 5 months |
| Corazzelli *et al.*[20] | Bendamustine<br>Retrospective | 41 | 33 (18–84) | 35 | ORR = 78%;<br>CR = 29% | 9.3 months<br>(for pts in CR) |
| Kuruvilla *et al.*[45] | Lenalidomide<br>Phase II | 15 | 37 (18–74) | 10 | PR = 13% | NR |
| Böll *et al.*[46] | Lenalidomide<br>Phase II | 42 | NR | NR | ORR = 46% | NR |
| Fehniger *et al.*[44] | Lenalidomide<br>Phase II | 38 | 34 (25–63) | 33 | ORR = 19%;<br>CR = 16% | 15 months |
| Fehniger *et al.*[47] | Lenalidomide<br>Phase II | 42 | 38 (20–83) | 31 | ORR = 30% | 8.2 months |
| Christian *et al.*[39] | Panobinostat + Lenalidomide<br>Phase I | 7 | 31 (24–72) | 3 | ORR = 33% | NR |

Abbreviations: CR = complete remission; GCP = gemcitabine, carboplatin and dexamethasone; GDP = gemcitabine, dexamethasone and cisplatin; GVD = gemcitabine, vinorelbine and pegylated liposomal doxorubicin; N1 = total number of subjects; N2 = number of subjects who received prior autologous HCT; NR = not reported; ORR = overall response rate; PR = partial remission.

shown encouraging activity (Table 1). The Cancer and Leukemia Group B (CALGB) 59804 study evaluated a gemcitabine-based regimen in 91 (40 had undergone prior auto-HCT) patients with relapsed/refractory HL.[13] The ORR was 70% (CR = 19%). Median EFS was not reached in the transplant-naïve group, and it was 8.5 months in previously autografted patients.[13] Notably in patients who relapsed after an auto-HCT, despite high response rates, the median EFS was shorter with disease progression accounting for most deaths.[14] Other promising gemcitabine-based combinations are summarized (Table 1).[15,16] In medically fit patients, gemcitabine-based regimens represent a reasonable option to cytoreduce disease before an allo-HCT. Reports of serious pulmonary toxicity after combining gemcitabine and brentuximab vedotin preclude prospective investigation of this combination.[17]

## Bendamustine

Bendamustine is approved for treatment of CLL and indolent B-cell NHL.[18] Previous data suggested activity of bendamustine in HL.[19] A retrospective study reported an ORR of 78% using bendamustine in relapsed HL.[20] The Memorial Sloan-Kettering Cancer Center group conducted a phase 2 study of bendamustine in 36 (75% had relapsed after a prior auto-HCT) patients with relapsed/refractory HL.[21] The ORR was 53% (CR = 33%).[21] Responses were seen in cases with prior auto-HCT failure provided they did not relapse within 3 months of autografting. Ongoing clinical trials are currently investigating bendamustine in combination with gemcitabine (NCT01535924) or lenalidomide (NCT01412307) in relapsed/refractory HL.

## Monoclonal antibodies

*Brentuximab vedotin*. Expression of CD30 on Reed Sternberg (RS) cells has been explored as a target for MoAb therapy.[22,23] Brentuximab vedotin is a CD30 Ab conjugated to a potent anti-microtubule agent, monomethylauristatin E (MMAE). It is approved for treatment of HL after failing an auto-HCT and for relapsed/refractory anaplastic large cell lymphoma.[10] In a phase 1 study, brentuximab vedotin was administered to 45 patients with relapsed/refractory CD30-positive hematologic malignancies (primarily HL), including 73% who had undergone a prior auto-HCT.[10] Objective responses, including 11 CR, were observed in 17 patients (Table 1).[10] These observations were confirmed in a phase 2 study of 102 relapsed/refractory HL cases after auto-HCT: ORR was 75% (CR = 34%), median PFS was 5.6 months, and median duration of response (those in CR) was 20.5 months.[11] Activity of brentuximab vedotin makes it ideal for treatment of HL relapsing after prior auto-HCT. Single-institution retrospective data also suggest that it can successfully bridge these patients to a potentially curative reduced-intensity conditioning (RIC) allo-HCT, without adversely affecting engraftment kinetics.[24] Ongoing clinical trials are assessing the role of brentuximab vedotin as a maintenance/consolidation following auto-HCT (NCT01100502, AETHERA Trial).

### Rituximab

Rituximab has documented activity in nodular lymphocyte predominant HL.[25,26] It is active in relapsed/refractory classical HL regardless of subtype or degree of CD20 expression on RS cells.[27] Rationale of using rituximab in classic HL includes elimination of CD20+ reactive B cells supporting RS cells, hence depriving malignant cells of survival signals and potentially increasing host immune responses.[28] Single-agent rituximab was associated with an objective response of 22% in nodular sclerosis histology.[29] Responses occurred only in nodal or splenic sites irrespective of degree of CD20 expression on RS cells.[29] Rituximab is not approved for treatment of HL.

### Histone deacetylase inhibition

Histone deacetylase (HDAC) inhibitors are epigenetic therapies that exert antitumor activity from increased tumor suppressor gene transcription, growth inhibition, cell cycle regulation and apoptosis.[30,31] HDAC inhibitors inhibit STAT6-mediated T-helper 2 cytokine and TARC (thymus and activation-regulated chemokine) production and induce cell death in HL cell lines.[32] Panobinostat is an oral pan-deacetylase inhibitor which in a phase 1 study demonstrated promising activity (ORR ~35%) in relapsed HL.[33] Single-agent activity was confirmed in a phase 2 study showing an ORR in 27% (CR = 4%) and a median PFS of 6.1 months.[34] Table 1 summarizes other HDAC inhibitors with single-agent activity in relapsed HL.[35,36]

Considering the synergistic activity of HDAC inhibitors with other therapies,[37,38] development of trials of HDAC inhibitors combined with chemotherapy, MoAbs and small molecule inhibitors is warranted. A phase 1 study of panobinostat combined with lenalidomide in relapsed HL is ongoing.[39]

### Inhibiting the mammalian target of rapamycin (mTOR)

Everolimus is approved for treatment of various solid tumors. RS cells contain active, phosphorylated Akt and display greater phosphorylation of known target Akt proteins. Inhibition of Akt in HL cell lines leads to apoptosis, suggesting that the PI3K–Akt–mTOR pathway has a role in growth and survival of RS cells.[27,40] Johnston *et al.*[41] provided a proof-of-concept phase 2 trial enrolling 19 (84% had undergone prior auto-HCT) patients with relapsed HL showing an ORR of 47% and a median time-to-progression of 7.2 months (Table 1). Everolimus is also synergistic with other agents.[38,42,43]

### Immunomodulatory therapy

Lenalidomide is an immunomodulatory agent with several mechanisms of action.[27] Limited data suggest that lenalidomide has modest clinical activity in relapsed/refractory HL (Table 1). A multicenter phase 2 study evaluated the efficacy of lenalidomide, in 38 patients with relapsed/refractory HL (87% had prior auto-HCT).[44] Lenalidomide was administered until disease progression or if unacceptable toxicity occurred.[44] Of the 36 evaluable patients, responses were: CR = 1, PR = 6 and stable disease = 5, resulting in an objective response of 19% and a cytostatic ORR of 33%.[44] This and other studies suggest that lenalidomide is active in heavily pretreated HL.[39,45–47]

## ALLOGENEIC HCT

Use of myeloablative preparative regimens for allo-HCT resulted in prohibitive non-relapse mortality (NRM), discouraging its widespread application as salvage treatment especially in the setting of prior auto-HCT failure. Introduction of reduced intensity conditioning (RIC) regimens lowered NRM in HL and other diseases, allowing allo-HCT to be offered to a higher proportion of heavily pretreated cases.[48–51]

### Myeloablative regimens

A NRM exceeding 50% was reported after myeloablative allo-HCT for relapsed HL.[52–54] Although many factors influence outcome, such as high number of prior therapies, hence late referrals for allografting, and suboptimal performance status, another reason for such a high mortality rate could be partly attributed to using myeloablative regimens in patients with comorbidities. Myeloablative conditioning studies were predominantly offered in the past when supportive care was less effective.[55,56]

An analysis from the European Group for Blood and Marrow Transplantation (EBMT) showed a higher NRM (52% at 4 years) in allo-HCT for HL compared with other lymphomas, underlying the frailty of these patients.[57] A continuous pattern of relapse and no clear *plateau* in survival curves was reported, limiting referral of HL for myeloablative allo-HCT.[57]

### RIC regimens

The past two decades witnessed a fundamental change in allo-HCT.[48] Previously, high-dose conditioning, using chemotherapy or chemo-radiation, was thought necessary for preventing graft rejection, making marrow space and providing anti-tumor activity. Recognition of the benefits of adoptive immunotherapy, mediated by donor T cells, provided the basis to develop less toxic regimens, so called non-myeloablative or RIC regimens. This allowed allo-HCT to be considered in older patients, or those with comorbidities.

A wide variety of RIC regimens has been used, varying in intensity from truly non-myeloablative to RIC regimens approaching the intensity of standard conditioning.[58,59] More intensive conditioning regimens (melphalan-based, discussed below) reduce relapse rates when compared (non-randomized) with less-intensive RIC regimens using low-dose TBI.[60] Currently, no consensus exists on the optimal RIC allo-HCT regimen for HL or other diseases.

A large series from EBMT, consisting of 285 patients with HL who received a RIC allo-HCT, mostly with chemosensitive disease (80% had prior auto-HCT) showed low rates of NRM but disease relapse remained frequent (Table 2).[61] Sarina *et al.*[62] performed a retrospective donor-versus-no donor analysis of 185 patients with relapsed HL after prior auto-HCT. In their series, 66% had a suitable donor (matched-related (MRD), unrelated (URD) or haploidentical). Patients with an available donor had better OS and PFS (66 vs 42% and 39 vs 14%, respectively; $P < 0.001$).[62] This suggests that RIC allo-HCT is superior to conventional salvage therapy in HL patients who failed previous auto-HCT.[62,63]

EBMT compared RIC ($n = 89$) with myeloablative ($n = 79$) allo-HCT in relapsed/refractory HL.[60] Of the RIC group, 62% have had a prior auto-HCT compared with 41% in the myeloablative group.[60] Results demonstrated a nearly twofold higher incidence of relapse (57 vs 30%), but higher 5-year OS (28 vs 22%, $P = 0.003$) in the RIC group.[60] One-year NRM was lower in the RIC group (23 vs 46%, $P = 0.001$).[60]

In addition, a small study demonstrated encouraging results for RIC allo-HCT in HL using fludarabine-based conditioning in 14 young patients (MRD = 11, URD = 3) with progressive/refractory HL after auto-HCT.[64] All engrafted and achieved full donor chimerism without reported NRM.[64] One- and 2-year OS were 93% and 73%, respectively. Two-year survival was 100% for those with prior chemosensitive disease.[64] One-year PFS was 36% (chemosensitive = 62%, chemoresistant = 0%).[64] Table 2 summarizes these and other studies. Considering a RIC allograft in medically fit relapsed HL patients, with available donor and clear evidence of chemosensitive disease is reasonable.

### Adding melphalan to fludarabine

Three prospective trials evaluated allo-HCT using a RIC regimen of fludarabine plus melphalan in relapsed/refractory HL

**Table 2.** RIC allo-HCT for HL relapsing after auto-HCT

| *Author* | *Conditioning regimen and number of patients* | *Prior auto-SCT, n (%)* | *Transplant period* | *Outcome* | *Comments* |
|---|---|---|---|---|---|
| Sureda *et al.*[60] | RIC = 89; MAC = 79 | RIC = 55 (61.8%); MAC = 32 (40.5%) | 1997–2001 | PFS = 18% (RIC), 20% (MAC), OS = 28% (RIC), 22% (MAC) (5-year) | Prior auto-HCT was independently associated with poor outcome |
| Robinson *et al.*[61] | RIC = 285 | 80% (25% had refractory disease before allo-HCT) | 1995–2005 | PFS 25%, OS 29% (3-year) | Relapse within 6 months of auto-HCT associated with poor outcome |
| Sarina *et al.*[62] | RIC = 104 vs conventional non-transplant treatment | Total number of patients = 185 104 of 122 with available donor underwent RIC allo-HCT (all relapsed after auto-HCT) compared with 63 with no donor (no allo-HCT) | 1999–2008 | PFS 39.3% (RIC allo-HCT) vs 14.2% (no allo-HCT); OS 66% (RIC allo-HCT) vs 42% (no allo-HCT) (2-year) | Patients with donor had better PFS and OS |
| Thomson *et al.*[63] | RIC = 38 vs conventional non-transplant treatment | All patients relapsed following auto-HCT | 1998–2004 | 10-year OS (from diagnosis) 48% (RIC allo-HCT) vs 15% (no allo-HCT) 5-year OS from RIC allo-HCT 51% and PFS 42% | RIC allo-HCT superior to non-transplant therapy |
| Todisco *et al.*[64] | RIC = 14 | 14 (100%) | 1999–2005 | PFS 36%; OS 73% (2-year) | |
| Peggs *et al.*[65] | RIC = 49 | 44 (90%) had prior auto-HCT | 1997–2003 | PFS 39%; OS 55.7% (4-year) | 16 (33%) received DLI from 3 months after allo-HCT for residual disease or progression |
| Alvarez *et al.*[66] | RIC = 40 | 29 (73%) had prior auto-HCT | 1999–2004 | PFS 32%; OS 48% (2-year). Patients with late relapse (>1 year) after auto-HCT. PFS 70 vs 18%. OS 75 vs 16% | 11 (25%) patients received DLI for disease relapse |
| Anderlini *et al.*[67] | RIC = 58 | 48 (83%) had prior auto-HCT | 2001–2005 | PFS 32%. OS 64% (2-year) | No significant differences in OS, PFS, progression/ relapse rate between MRD and URD allo-HCT |
| Majhail *et al.*[68] | RIC = 21 | UCB 9 (7 (78%) had prior auto-HCT. MRD 12 (7 (58%) had prior auto-HCT | 2000–2005 | PFS 25% (UCB), 20% (MRD) (2-year) | Improved outcome for patients in CR >12 months from auto-HCT |
| Burroughs *et al.*[69] | RIC = 90 (MRD 38, URD 24, haploidentical 28) | 92% had prior auto-HCT | 1998–2007 | *MRD*: PFS 23%, OS 53%. *URD*: PFS 29%, OS 58%. Haploidentical: PFS 51%, OS 58% (2-year) | |
| Devetten *et al.*[70] | 143 | 89% had prior auto-HCT | 1999–2004 | PFS 20%; OS 37% (2-year) | Extranodal disease and KPS <90% were significant risk factors for poor outcome |
| Johansson *et al.*[71] | 23 | 20 (87%) had prior auto-HCT | 2000–2007 | PFS 27%; OS 59% (3-year) | |

Abbreviations: MAC = myeloablative conditioning regimen; MRD = matched related donor; OS = overall survival; RIC = reduced-intensity conditioning; UCB = umbilical cord blood transplantation; URD = unrelated donor.

(Table 2).[65–67] Peggs *et al.*[65] reported on 49 patients (90% failed prior auto-HCT) who received conditioning with fludarabine, melphalan and alemtuzumab prior to allo-HCT. Donor source consisted of MRD in 31 and URD in 18 patients.[65] Planned DLI starting 3 months after transplantation, for residual disease/ progression, were administered in 33% of cases.[65] The NRM was 16% (MRD = 7%, URD = 34%) at 2 years.[65] Projected 4-year OS was 56%.[65] Similarly, Alvarez *et al.*[66] described outcomes of 40 relapsed/refractory HL (73% had prior auto-HCT and 33% had chemoresistant disease) patients, median age of 35 years, who underwent allo-HCT using fludarabine plus melphalan. Two-year PFS and OS were 32% and 48%, respectively. Also, 100-day NRM was 13 and 25% at 1 year.[66] Patients who experienced remission lasting 12 months or longer after prior auto-HCT had better PFS

(70%) and OS (76%).[66] Anderlini *et al.*[67] studied 40 patients with chemosensitive or stable relapsed/refractory HL. The first 14 patients received conditioning with fludarabine and CY with or without antithymocyte globulin.[67] Because of early progression, the subsequent 26 patients received fludarabine plus melphalan.[67] Use of melphalan resulted in a higher OS rate at 18 months (73 vs 39%, $P = 0.03$) and lower NRM (18 vs 30%).[67] This study demonstrates the effect of conditioning regimen on outcome. We, however, caution about drawing conclusions due to small sample size and non-randomized nature of this comparison.

### Impact of donor source

Separate retrospective analyses did not show any significant impact of donor type on outcome of HL treated with RIC allo-HCT.[60,61,67] Three recent publications focused on the use of alternative donors and contributed to outline the role of HLA matching on outcome.[68–70] These data underline the feasibility of RIC allo-HCT and suggest searching for a suitable donor, either a MRD or an alternative one, as soon as relapse after an auto-HCT occurs.

A published study compared outcomes by donor source in 58 HL patients (83% failed prior auto-HCT) who underwent RIC allo-HCT from a MRD ($n = 25$) or URD ($n = 33$).[67] All received fludarabine and melphalan as the preparative regimen.[67] The 2-year NRM was 15%.[67] Incidence of acute (grade II–IV) and chronic GVHD were lower in recipients of MRD (12 vs 39%, $P = 0.04$ and 57 vs 85%, $P = 0.006$).[67] Projected 2-year PFS and OS were 32 and 64%, respectively, with 2-year disease progression/relapse of 55%. There were no statistically significant differences in OS or disease progression/relapse between MRD and URD recipients.[67]

A Swedish study of 23 heavily pretreated HL patients who received a RIC allo-HCT (20 had prior auto-HCT and a median of 5 prior therapies) reported a high incidence (17%) of post-transplant lymphoproliferative disorders.[71] Larger studies are needed to confirm this worrisome finding.

### Haploidentical or umbilical cord blood transplantation

Haploidentical or umbilical cord blood transplantation has shown encouraging results in various diseases including HL.[72,73] Burroughs *et al.*[69] retrospectively compared outcomes of HL who received RIC allo-HCT from MRD ($n = 38$), URD ($n = 24$) or haploidentical-related donors ($n = 28$); 92% had failed prior to auto-HCT. Conditioning consisted of 2 Gy TBI alone (MRD = 15) or combined with either fludarabine 90 mg/m$^2$ in MRD ($n = 19$) and all URD recipients, or fludarabine 150 mg/m$^2$ in all haploidentical-related donor recipients.[69] All the latter received also CY before and after transplantation.[69] Of the patients with measurable disease before transplantation, 41% MRD, 63% URD and 86% of haploidentical donor recipients achieved a CR or PR.[69] Two-year rates of disease progression were 56% in MRD, 63% in URD and 40% in haploidentical recipients.[69] The 2-year OS and PFS were 53 and 23% for MRD, 58 and 29% for URD and 58 and 51% for haploidentical recipients.[69] There was no significant difference between the groups in grade III–IV acute or chronic GVHD.[69] This demonstrates that a haploidentical donor is reasonable to consider when no MRD or URD are available.[69]

Majhail *et al.*[68] examined 21 patients with HL who were conditioned with TBI and either fludarabine plus BU or CY followed by MRD ($n = 12$; median age, 42 years) or umbilical cord blood grafts ($n = 9$; median age 28 years). With a median follow-up of 17 months (umbilical cord blood recipients) and 24 months (MRD recipients), the 2-year OS and PFS were comparable between the groups: 51 and 25% for umbilical cord blood recipients, and 48 and 20% for MRD recipients, respectively.[68] There was also no difference in 180-day NRM (umbilical cord = 22%, MRD = 25%).[68] Alternative donor sources are viable options for HL in need of an allo-HCT. Other details of these studies are summarized in Table 2.

## A SECOND AUTOLOGOUS HCT AS A SALVAGE STRATEGY

Data supporting use of second auto-HCT in post-autograft relapsed HL is limited, mostly based on small case series. Vose *et al.*[74] described outcomes of three patients who received a second auto-HCT ($n = 2$) or a syngeneic allo-HCT ($n = 1$) at 7,8 and 17 months, respectively, after their first auto-HCT. Two (auto-HCT = 1, syngeneic allo-HCT = 1) died from sepsis, whereas the third progressed.[74] Vandenberghe *et al.*[75] reported 12 relapsed HL post auto-HCT cases who received a second auto-HCT ($n = 10$) or an allo-HCT ($n = 2$). Median age of subjects (male = 8, 80%) who received a second auto-HCT was 21 years.[75] Median time from first-to-second auto-HCT in patients ($n = 4$) who achieved a CR was 29 months and in those who died from progression of HL ($n = 4$) or other causes ($n = 2$ (cardiac event = 1, secondary AML = 1)) was only 11 months.[75] Longer intervals between the first and second auto-HCTs result in better outcomes, but the number of subjects is too small to draw any solid conclusions. Benefit of a second auto-HCT in subjects with longer time intervals between autografts was also described by Lin *et al.*[76] Smith *et al.*[77] reported a series of 35 patients (HL = 21, NHL (diffuse large B cell or follicular large cell) = 19) with median age of 38 years who received a second auto-HCT using BEAM in 48% of cases. The second auto-HCT was performed more than 1 year from the first auto-HCT in 82% of cases.[77] Authors reported a high 100-day and 1-year NRM of 11% and 18%, respectively.[77] Five-year PFS and OS were 30% and 30%, respectively. A longer time interval from first to second auto-HCT results in better outcomes but toxicity is concerning.

In the absence of solid data, a second autograft for salvage of relapsed HL is not recommended as standard of care.

## MANAGING RELAPSE AFTER AN ALLO-HCT

### Donor lymphocyte infusion

Relapsing after an allo-HCT is generally considered ineligibility for enrollment in clinical trials. Peggs *et al.*[65] reported a response rate of 56% after DLI in the setting of persistent disease or progression after RIC allo-HCT employing *in vivo* T-cell depletion with alemtuzumab. Administration of DLI started 3 months after allo-HCT and resulted in a 2-year NRM of 16% and a 4-year PFS and OS of 39% and 56%, respectively.[65] In the T-cell replete setting, Anderlini *et al.* demonstrated a response rate of 37% after DLI.[78] Median duration of response was 7.5 months and all responders developed GVHD.[78] A recent meta-analysis showed a pooled proportion of CR of 37% after DLI in T-depleted or T-replete allo-HCT.[79]

Brentuximab vedotin combined with DLI for early relapse after allo-HCT induces tumor-specific immunity and sustained clinical remission.[80] This approach is interesting to explore in a prospective clinical trial. Although DLI is required more frequently after T-cell-depleted allo-HCT, it can also be considered in persistent/relapsed disease after a T-cell replete allo-HCT provided there is no active ongoing GVHD.

## DISCUSSION

Durable remissions in post auto-HCT failure in HL remain a therapeutic challenge. Availability of less toxic RIC regimens has undoubtedly widened applicability and improved outcomes of allo-HCT in relapsed HL. Although there are no prospective randomized trials that compare allo-HCT to conventional chemotherapy or immunotherapy or chemoimmunotherapy in the treatment of prior auto-HCT failures, a retrospective comparative

analysis based on donor availability suggests superior outcomes when an allo-HCT is offered.[62]

Encouraging results of haploidentical transplantation *albeit* based on a small non-randomized comparison shows future promise of this modality. It is important to keep in mind that outcomes after allo-HCT appear to be related to duration of remission achieved after prior auto-HCT. Patients who relapse within $<1$ year from a prior autograft appear to have worse outcomes when offered an allo-HCT.[66] Emergence of novel therapies such as MoAbs or inhibitors of key signal transduction pathways are demonstrating promising activity in treating patients who are being considered for an allo-HCT after failing prior high-dose therapy and autografting. Offering these subjects enrollment in clinical trials remains the most desirable option whenever possible. Also, demonstration of tumor chemosensitivity, preferably by achieving a CR, is a prerequisite prior to proceeding with an allo-HCT in our opinion.

To date, no RIC allo-HCT conditioning regimen is considered standard of care. The choice of a particular RIC conditioning regimen appears to be dictated mostly by physician and center preference and familiarity. Further studies are needed to identify the optimal regimen for RIC allografting for relapsed HL after an auto-HCT failure.

Management of disease relapse after an allo-HCT is very difficult, especially when relapse occurs in the setting of active GVHD. Unfortunately, most clinical trials would exclude this population from participation. Administration of DLI induces responses in half of the cases when used in the T-cell depleted setting.[65] Administration of DLI for relapsed after a T-cell replete allo-HCT is more challenging; but yet capable of inducing responses in over one-third of cases provided that active GVHD is absent.[78,79]

## FUTURE DIRECTIONS

Earlier application of auto-HCT in high-risk HL, destined to do poorly with standard chemotherapies and before emergence of chemoresistance warrants prospective investigation. This strategy could potentially be explored with either high CD68+ tumor infiltrating macrophages or positive mid- or end- front-line therapy PET scans.[81] Moreover, development of post auto-HCT maintenance or consolidation strategies in HL has lagged behind. Unfortunately the PATH trial evaluating role of panobinostat maintenance in post autograft setting (NCT01034163) was prematurely terminated. Outcomes of the ATHERA trial (NCT01100502) are eagerly awaited, that will hopefully clarify the role of brentuximab vedotin consolidation in patients with persistent residual disease after auto-HCT. Other candidate agents for examination in the setting of post autograft maintenance/consolidation setting include lenalidomide, novel HDAC inhibitors and mTOR inhibitors.

For cases of relapsed HL after an auto-HCT, integrating novel therapies whether as part of preparative regimens or as a maintenance strategy post-allografting or as cytoreductive therapy prior to DLI, are important research questions that need to be addressed in future clinical trials.

## CONFLICT OF INTEREST

The authors declare no conflict of interests.

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