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REVIEW ARTICLE

Strategies to improve outcomes of autologous hematopoietic cell transplant in lymphoma

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Abstract

High-dose chemotherapy and autologous hematopoietic cell transplantation (HDT-AHCT) remains an effective therapy in lymphoma. Over the past several decades, HDT with BEAM (carmustine, etoposide, cytarabine, and melphalan) and CBV (cyclophosphamide, carmustine, and etoposide) have been the most frequently used preparatory regimens for AHCT in Hodgkin (HL) and non-Hodgkin lymphoma (NHL). This article reviews alternative combination conditioning regimens, as well as novel transplant strategies that have been developed, to reduce transplant-related toxicity while maintaining or improving efficacy. These data demonstrate that incorporation of maintenance therapy posttransplant might be the best way to improve outcomes.

Introduction

High-dose chemotherapy and autologous hematopoietic cell transplantation (HDT-AHCT) is an established therapeutic approach in lymphoma treatment, either as upfront therapy, or most commonly, in the relapsed or refractory (rel/ref) setting [1–5]. However, lymphoma recurrence continues to be the major cause for transplant failure. Efforts to develop more effective high-dose regimens include dose intensification of the regimens or integrating new agents into the combination regimens. In this article, we first review the traditional transplant approaches with established efficacy in lymphoma subtypes, followed by more novel conditioning regimens and transplant strategies to mitigate risk of relapse.

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History of HDT-AHCT

The concept of a steep dose–response relationship for anticancer drugs dates back to the 1960s when Skipper and coworkers predicted a log cell kill model for antineoplastic drugs. In this model, the relationship between tumor cell kill and drug dose was exponential, with the number of cells killed by a given dose of drug being proportional to both the dose of the drug and the number of cells exposed to the drug [6, 7]. HDT exploits the steepness of the dose–response relationship between chemotherapeutic drugs and fractional cell kill [8, 9]. The steepness of the dose–response curve implies that a disproportionately high number of cancer cells are killed when drug doses are increased.

Initial use of HDT followed by autologous bone marrow cell infusion for lymphomas was reported in 1959 and 1960s [10–13]. In 1978, investigators at the National Cancer Institute reported successful treatment of resistant malignant lymphoma and Burkitt lymphoma with HDT and AHCT [14, 15]. HDT-AHCT as a successful treatment for patients with relapsed Hodgkin lymphoma (HL) was first reported in the 1980s [16–18]. Subsequent trials have demonstrated HDT-AHCT as the standard of care for management of rel/ref lymphomas [5, 19–22] or as consolidation of a first remission for mantle cell and T cell lymphoma [2, 4, 23–31]. The Center for International Blood and Marrow Transplant Research (CIBMTR) has reported a marked increase between 1994 and 1995 and between 2004 and 2005 in the number of HDT-AHCT performed in North

America from 2573 to 3164 for non-Hodgkin lymphoma (NHL) and from 906 to 1302 for HL [32]. Interestingly, the proportion of patients aged ≥60 years who underwent AHCT during the same period rose from <7 to 35%, including an increase in those who are at least 70 years old from <1 to 5%. This increase may reflect changing demographics, patient selection, improved access, and safety of HDT-AHCT in this population, as well as better acceptance by the third-party payers because of its success.

HDT-AHCT in lymphoma subtypes

Hodgkin lymphoma

Durable remissions can be obtained using HDT-AHCT in HL patients whose disease has relapsed or was refractory to conventional therapy [33–36]. Two randomized trials have shown improvement in disease-free survival (DFS) with HDT-AHCT compared to conventional chemotherapy [19, 20]. Investigators in the British National Lymphoma Investigation trial prospectively randomized rel/ref HL patients to either chemotherapy or HDT-AHCT. The 3-year event-free survival (EFS) was 53% in transplanted patients, compared to 10% in the chemotherapy group ($p = 0.025$). The risk of disease progression was significantly lower ($p = 0.005$) in transplanted patients, although no significant differences in overall survival (OS) were observed. In the other randomized trial, conducted by the German Hodgkin Study Group and the European Society of Blood and Marrow Transplantation (EBMT), patients received two cycles of salvage chemotherapy with Dexa-BEAM (dexamethasone, carmustine, etoposide, cytarabine, melphalan). Responding patients then received either two additional cycles of Dexa-BEAM or high-dose BEAM-AHCT. The freedom from treatment failure at 3 years was 55% in subjects undergoing transplant, compared with 34% in patients who received Dexa-BEAM alone ($p = 0.019$). OS did not significantly differ between the two groups ($p = 0.331$). Both of these randomized clinical trials, however, were closed early because of poor accrual, mainly due to patient preferences, where they did not want to get randomized to chemotherapy-only arm. This issue has been a known challenge in executing and completing transplant vs no-transplant studies across many disease histologies.

Non-Hodgkin lymphoma

Diffuse large B cell lymphoma HDT-AHCT has become the standard consolidative therapy in rel/ref aggressive NHL [5]. This practice is based on the PARMA trial, a randomized, multicenter trial that compared HDT-AHCT vs chemotherapy in 215 patients who had relapsed but chemotherapy-sensitive intermediate-to-high-grade NHL [5]. All patients had achieved a first remission (complete remission 1 (CR1)) with an anthracycline-containing chemotherapy regimen. At the time of relapse, patients received two cycles of DHAP (dexamethasone, high-dose cytarabine, and cisplatin). Subsequently, they were randomized to receive either four more cycles of DHAP or HDT-AHCT. After a median follow-up of 63 months, the response rate was 84% after HDT-AHCT vs 44% after conventional therapy. At 5 years, EFS and OS were 46% and 53% in the transplant group compared to 12% ($p = 0.001$) and 32% ($p = 0.038$) in the chemotherapy only group, respectively. These differences might have been even larger in favor of transplant, were it not for the fact that patients whose disease progressed on the conventional arm could cross over to the transplant arm. This study demonstrated survival benefit in patients affected with relapsed chemotherapy-sensitive NHL who underwent HDT-AHCT as compared to conventional chemotherapy and therefore established this approach as the standard treatment.

Follicular lymphoma (FL) FL is frequently accompanied by bone marrow infiltration. Therefore, one of the concerns with HDT-AHCT in FL is the risk of reinfusing the lymphoma cells after HDT. Schouten and colleagues [3] designed a randomized trial to address two questions: (1) whether HDT-AHCT is more effective than standard treatment in improving survival in relapsed FL patients, and (2) whether ex vivo purging of the hematopoietic cell graft could positively impact progression-free survival (PFS) and OS. This randomized CUP trial (Chemotherapy vs Unpurged vs Purged arm) evaluated the role of HDT-AHCT vs conventional therapy in 140 patients who had rel/ref FL. The 4-year OS was 46% for the chemotherapy arm, 71% for the unpurged graft arm, and 77% for the purged graft transplant arm. There was a similar advantage for the transplant groups in 2-year PFS, which was 26, 58, and 55%, respectively ($p = 0.0037$). This trial showed that HDT-AHCT results in improved PFS and OS in patients with relapsed FL. It further showed that purging of the hematopoietic cell graft does not impact transplant outcomes.

In a study by the GELA/GOELAMS group, 175 patients with rel/ref FL underwent either conventional chemotherapy or HDT-AHCT. At a median follow-up of 31 months, the 3-year OS was significantly higher in patients who received HDT-AHCT at first relapse (92% vs 63%; $p = 0.0003$) [37]. Furthermore, Casulo and colleagues [38] evaluated outcomes of FL patients experiencing early therapy failure within 2 years of frontline chemoimmunotherapy in 2 cohorts of patients: (1) non-transplant patients, from the National LymphoCare (NLCS) database and (2) patients who underwent HDT-AHCT, from the CIBMTR. There was no difference in 5-year OS between

the 2 groups (60% vs 67%, respectively; $p = 0.16$). However, patients receiving HDT-AHCT within 1 year of treatment failure had higher 5-year OS than those without transplant (73% vs 60%, $p = 0.05$). Results from the above studies support consideration of HDT-AHCT in patients with chemotherapy-sensitive relapsed FL, especially in those with early relapsed disease within 2 years of frontline therapy. Long-term outcomes of HDT-AHCT in FL demonstrating plateaus in PFS curves [39–41] suggest cure in a select group of patients with this therapy.

Mantle cell lymphoma (MCL) Several studies have shown improved outcomes with HDT-AHCT in MCL patients in first remission [2, 23–28, 42–44]. In a randomized trial, the European MCL Network compared consolidation with high-dose cyclophosphamide plus total body irradiation (TBI) and AHCT to maintenance therapy with alpha-interferon in 122 patients, after subjects achieved first remission using a CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone)-like induction therapy. A longer PFS in the transplant arm of 39 vs 17 months ($p = 0.01$) was observed, even though the 3-year OS was not significantly superior [28]. In a subsequent pooled analysis of three studies presented as an abstract form only, the median OS seemed to be superior in the AHCT arm after extended follow-up (90 vs 54 months, $p = 0.034$) [45]. In a phase 2 study by the Nordic Lymphoma Group (MCL-2) in 160 patients with MCL who received induction treatment with augmented CHOP [cyclophosphamide 1200 mg/m^2 (instead of 750 mg/m^2), doxorubicin 75 mg/m^2 (instead of 50 mg/m^2), vincristine, and prednisone] alternating with high-dose cytarabine combined with rituximab, followed by HDT-AHCT in responders, the 6-year OS, EFS, and PFS were 70, 56, and 66% respectively. In the intent-to-treat analysis, the 10-year OS and EFS for all 160 patients was 58% and 43%, respectively [27]. In a phase 2 trial using sequential R (rituximab)-CHOP/R-DHAP followed by HDT-AHCT, Delarue et al. reported an overall response rate (ORR) of 95% with median EFS of 83 months and a 75% survival rate at 5 years [43]. In a recent analysis of the CIBMTR data, 159 patients received HDT-AHCT or allogeneic hematopoietic cell transplant (allo-HCT) for MCL in first or subsequent remissions [46]. Both transplant strategies resulted in similar OS. However, the study suggests that the optimal timing for transplant is early in the disease course defined as first partial or CR, with no more than two prior lines of therapy. Freedman and colleagues reported outcomes of 28 patients who underwent HDT-AHCT for MCL at the completion of induction ($n = 8$) or salvage ($n = 20$) therapy [47]. The 4-year DFS and OS for all 28 patients were estimated to be 31% and 62%, respectively. The 8 patients transplanted in CR1 experienced better DFS than the 20 patients transplanted after relapse (49 vs 21 months, $p = 0.03$). In a large registry study of AHCT in 191 MCL patients, the 2- and 5-year OS were 76% and 50% and PFS were 55% and 33%, respectively. Patients with chemosensitive disease but not in first CR were 2.99 times (95% confidence interval (CI): 1.66–5.38, $P < 0.001$) more likely to die than patients transplanted in CR1 [48]. The above studies demonstrate that the outcomes of HDT-AHCT in MCL beyond CR1 is less favorable and associated with higher relapse rates.

T cell lymphoma

There are no randomized prospective studies in T cell lymphoma comparing HDT-AHCT to conventional therapy in first line or relapsed setting. However, favorable outcomes have been reported by employing HDT-AHCT as consolidation in first remission [4, 29–31, 49–52]. The largest phase 2 study of upfront HDT-AHCT [4] included 160 patients with peripheral T cell lymphoma (PTCL) who received CHOEP (cyclophosphamide, doxorubicin, etoposide, vincristine, and prednisone) for 6 cycles and those in CR or partial remission underwent HDT-AHCT ($n = 115$). By intent-to-treat analysis, the 5-year OS and PFS were 51% and 44%, respectively. In another prospective phase 2 study by Corradini and coworkers [50], the estimated 12-year OS, DFS, and EFS were 34, 55 and 30%, respectively, in 46 of the 62 patients who received upfront HDT-AHCT. OS and EFS were significantly better in patients with ALK-positive anaplastic large-cell lymphoma (ALCL), as compared with the remaining PTCL. Analyzing separately the subgroup of PTCL unspecified, the 12-year OS and EFS projections were 37% and 25%, respectively. A prospective German study [52] evaluated outcomes of 111 patients who were planned to undergo upfront HDT-AHCT for T cell lymphoma. Seventy-five (68%) patients received transplantation. By intent-to-treat analysis, the estimated 5-year OS, DFS, and PFS rates were 44, 54 and 39%, respectively. Several retrospective studies in patients with T cell lymphoma have shown promising outcomes of HDT-AHCT when employed in first remission, less favorable outcomes in second remission, and disappointing results in refractory setting [53–56]. One of the largest retrospective study performed by CIBMTR reported outcomes of 241 patients with T cell lymphoma undergoing AHCT ($n = 115$) or allo-HCT ($n = 126$) [55]. The 3-year PFS and OS of AHCT recipients beyond CR1 were 42% and 53%, respectively. Among allo-HCT recipients who received transplantations beyond CR1, the 3-year PFS and OS were 31% and 50% respectively. Of note, this study suggests that HDT-AHCT at relapse may be a potential option for select patients, particularly in those with ALCL histology. In the absence of randomized controlled studies, available evidence from retrospective and non-randomized prospective studies suggest that

HDT-AHCT offers greater effectiveness earlier in the disease course. In patients with rel/ref T cell lymphoma, while HDT-AHCT may be a potential option in select patients who achieve CR, allo-HCT remains a valuable treatment strategy for appropriately selected patients.

Chemotherapeutic agents commonly used in AHCT

Treatment regimens prior to AHCT are administered for tumor cytoreduction and to ideally eradicate disease. The cornerstones in HDT are alkylating agents such as melphalan, busulfan, thiotepa, cyclophosphamide, and bendamustine. Alkylators do not generally show cross-resistance and have steep concentration–response [57]. Their activity is dependent on the extent of DNA damage and repair. Thus combination of alkylating agents with drugs known to inhibit DNA damage repair is expected to result in synergistic effect. In HDT, alkylators are frequently combined with other agents from the same or other classes to improve efficacy and overcome drug resistance. Etoposide, a topoisomerase II inhibitor, causes DNA break and cell-cycle arrest. This mechanism of action may promote synergistic cytotoxicity with alkylators [58]. The suggested mechanism of the synergistic cell killing of nucleoside analogs such gemcitabine is that they inhibit DNA synthesis and repair, which results in DNA damage, making it more accessible to DNA alkylation [59, 60]. Carmustine (BCNU) is a nitrosourea commonly used in HDT. However, in conventional doses, BCNU is limited by delayed marrow toxicity, pulmonary fibrosis, and hepatic renal dysfunction. When BCNU is used in combinations that include cyclophosphamide, there is an increased risk of pneumonitis and veno-occlusive disease (VOD) [61, 62]. Based on the synergism for antitumor effect of chemotherapeutic agents and their none or low overlapping toxicities, several combination regimens for HDT-AHCT in lymphoma have been developed. However, there are no prospective randomized studies to compare different conditioning regimens for AHCT in lymphoma. The most widely used high-dose conditioning regimens in HL and NHL are those based on a carmustine backbone, BEAM (carmustine, etoposide, cytarabine and melphalan) and CBV (cyclophosphamide, carmustine, and etoposide). This is demonstrated by the large retrospective registry study of patients with NHL and HL ($n = 4917$) who underwent AHCT from 1995 to 2008 [63]. The most common preparatory regimens used were BEAM ($n = 1730$), CBV ($n = 1853$), BuCy (busulfan, cyclophosphamide) ($n = 789$), and TBI-containing regimens ($n = 545$). The 1-year incidence of idiopathic pulmonary syndrome was the highest in recipients of CBV (hazard ratio (HR) 1.9) and TBI (HR 2.0) compared to BEAM. While the 1-year transplant-related mortality (TRM) was 4–8% and similar between regimens, in patients with diffuse large B cell lymphoma (DLBCL) and HL, BEAM was associated with lower mortality. A retrospective analysis of the EBMT database [64] comparing BEAC (carmustine, etoposide, cytarabine, and cyclophosphamide) to a matched cohort of NHL patient conditioned with BEAM showed no difference in toxicity or outcome. The 2-year PFS and OS were 63% and 78% for BEAC and 63% and 77% for BEAM-conditioned patients [$p =$ not significant (ns) for PFS and OS]. The 1-year cumulative incidence of non-relapse mortality (NRM) was 4% in the BEAC cohort and 3% in the BEAM group ($p =$ ns).

Novel carmustine-free HDT-AHCT in lymphoma

In recent years, owing to restricted availability, high drug acquisition cost, and toxicity concerns, investigators around the world have substituted carmustine with other agents (Table 1). Two retrospective studies evaluated replacement of carmustine in the BEAM regimen using thiotepa and cyclophosphamide, i.e., the TECAM regimen (thiotepa, etoposide, cyclophosphamide, cytarabine, and melphalan) [65, 66]. In 212 NHL and HL patients who had undergone TECAM-AHCT from 2000 to 2013, Grisariu and coworkers [65] reported no idiopathic pneumonitis, but 6 patients died of treatment-related toxicity during the first 100 days. The 3-year OS among DLBCL and HL patients was 61% (95% CI, 0.490–0.722) and 82% (95% CI, 0.701–0.904), respectively. The 3-year PFS was 49% (95% CI, 0.36–0.60) for DLBCL patients and 50% (95% CI, 0.37–0.61) for HL patients. Joffe and colleagues [66] compared outcomes of TECAM to BEAM in 125 consecutive patients affected with B cell lymphomas who underwent AHCT between. TECAM ($n = 65$) and BEAM ($n = 60$) had comparable results [3-year PFS 49% vs 62%, $p = 0.16$; 3-year OS 64% vs 71%, $p = 0.44$; TRM 1.6% vs 5%, $p = 0.35$] without a difference in toxicity or time to engraftment. In the EBMT registry-based retrospective study, thiotepa-containing preparative regimens were compared to BEAM [67]. No significant differences were identified between thiotepa-based and BEAM regimen for any survival end points. In a more detailed analysis, where 47 TEAM-treated patients were compared with 75 matched BEAM recipients, there were no significant differences between the two groups for any survival end points [67]. In addition, the frequency of common infectious and non-infectious complications including secondary malignancies was comparable between TEAM and BEAM. The above studies indicate that thiotepa-based HDT can be an alternative regimen to traditional BEAM, with comparable efficacy and safety profile. These results justify further evaluation of this regimen in a prospective, multicenter study.

Viani and colleagues substituted bendamustine for carmustine in BEAM (BeEAM) [68] in 43 NHL patients

Table 1 Carmustine-free BEAM and CBV-like regimens

Reference	Conditioning regimen patients (n)	Histology	Median age (range)	Early TRM	PFS/OS	Comments
Grisariu et al. [65]	TECAM 212 2000–2013 Phase 2	NHL HL (DLBCL, FL, MCL, TCL)	46 (16–71)	6 by d100	3-y PFS/OS DLBCL 49/61% HL 50/82%	4 died of infection, 2 from MOF
Joffe et al. [66]	TECAM 65 (1999–2006) vs BEAM 60 (2007–2014)	NHL HL	55 (16–75) vs 43 (16–68)	1.6% vs 5% (p = ns)	3-y PFS/OS 49/64% vs 62%/71% (p = ns)	Comparable efficacy and safety
Sellner et al. [67]	TEAM 110 vs BEAM 199 (2003–2011)	NHL HL	44 (19–66) vs 44 (19–72)	1% vs 2%	30-mo PFS/OS 49/77 vs 62/77 (p = ns)	Comparable efficacy and toxicities
Visani et al. [68]	BeEAM 43	NHL HL	47(18–70)	0	30-mo DFS/OS 65/90%	Mucositis, diarrhea, liver enzyme/bilirubin
Chantepie et al. [69]	BeEAM 474	NHL HL	56 (17–71)	3.3%		ARF 132 (27.9%) (Gr ≥ 2; 12.3%)
Saleh et al. [106]	BeEAM 34 vs BEAM 68	NHL HL	49 (21–68) vs 52 (21–71)	0 for both	Comparable PFS OS not reached	Gr ≥ 3 diarrhea and fever higher in BeEAM
Tsang et al. [107]	BeEAM 26 vs BEAM 52 (2009–2016)	HL	34 (17–68)	0	2-y PFS/OS 63%/91% vs 56%/87%	Grade 3-4 mucositis more common with Be-EAM 35% than BEAM 10%
Boisjoly et al. [108]	BEAM/BEAC 96 vs BeEAM 50 (2012–2016)	NHL HL	55 (23–69) vs 57 (26–70)	0	OS comparable	Be-EAM more toxic (Plt recovery, ARF, TPN, infection, ICU), but cost-effective
Nathan et al. [109]	R-BeEAM 22 vs R-BEAM 36 (2011–2013)	B-NHL	60 (19–75)	1 sepsis death in BeEAM on d26	Similar 2-y PFS and OS	Grade 3–4 mucositis more in Be-EAM 59.1% vs 5.6%
Ninos et al. [110]	BEAM 40 vs BeEAM 40 (2012–2017)		54			Comparable engraftment outcomes
Jaimovich et al. [70]	Benda-CV 54	NHL HL	47 (18–74)	1.9%	6-mo OS 93%	Gr 3-4 fever, cardiac, nausea, diarrhea, mucositis respiratory
Jain et al. [111]	BACE 17 (2012–2014)	NHL HL		0		Neutropenic sepsis 14 Klebsiella 8 No pulmonay toxicity
Chakrabartty et al. [112]	BACE 12 (2014–2016)	NHL HL		0		No Gr 3-4 non-heme toxicity
Kim et al. [71]	NEAM 69	NHL	42 (20–66)	3%	EFS 17 mo 2-y OS 64%	Liver toxicity 10% Renal 3% Cardiac 3%
Sharma et al. [73]	LEAM 17 vs BEAM 34 (2001–2012)	NHL HL		12	2-y PFS/OS 41/62 vs 44/61 (p = ns)	Similar efficacy and toxicities
Kothari et al. [74]	LEAM 50 vs BEAM 50	NHL HL	52 (45–52) 51 (45–52)	4% vs 2% (p = ns)	3-y PFS/ OS 69/86% vs 75/86% (p = ns)	Comparable efficacy and toxicities
Sakellari et al. [113]	BuEM 50 vs BEAM 87	NHL HL		0% vs 3.4% p = ns	PFS/OS 65/78 vs 63/76 (p = ns)	
Berber et al. [114]	BuCyE 31 vs BEAM 11 (2010–2015)	NHL HL	26–54 24–46	6.5%		Comparable efficacy and toxicities

Table 1 (continued)

Reference	Conditioning regimen patients (n)	Histology	Median age (range)	Early TRM	PFS/OS	Comments
Zhang et al. [115]	BuCyE 294 (1999–2010)	NHL HL	47 (17–69)	2–3.5%	2-y OS 71% 5-y OS 63%	Hyperbili 38% No VOD No gr3–4 neurotoxicity
Kim et al. [116]	BuCyE 22 vs BEAM 43	NHL	46 (28–65) 46 (15–65)	9%	EFS/OS 11/22 mo vs 16/30 mo $p = \text{ns}$	Comparable efficacy and toxicities
Kim et al. [77]	BuCyE 64	NHL	43 (18–65)	3.1%	3-y PFS/OS 70/72%	4 VOD
Wadehra et al. [75]	BuCyE 127	HL	33 (14–67)	5.5%	5-y PFS/OS 48/51%	4 died from hepatic toxicity, 3 from pneumonitis Second malignancy 9% 3 MDS/AML, 1 bladder ca
Hanel et al. [117]	BuCyE 53 (1990–2000)	NHL HL	46 (18–64)	4%	3-y PFS/OS 31%/43%	VOD 6%, Liver tox mucositis
Copelan et al. [76]	BuCyE 382 (1992–1998)	NHL	16–72	10 (2.6%) in 1 year	3-y PFS 46%	11 VOD; 4 MDS/AML Cause of death: 4 respiratory failure 3 VOD 2 infection 1 bleeding

TRM treatment-related mortality, *PFS* progression-free survival, *DFS* disease-free survival, *EFS* event-free survival, *OS* overall survival, *d* day, *y* years, *mo* months, *NS* not significant, *NHL* non-Hodgkin lymphoma, *HL* Hodgkin lymphoma, *TCL* T cell lymphoma, *BEAM* [carmustine, etoposide, cytarabine, melphalan], *CBV* [cyclophosphamide, carmustine, etoposide], *R* rituximab, *TECAM* [thiotepa, etoposide, cyclophosphamide, cytarabine, melphalan], *BeEAM* [bendamustine, etoposide, cytarabine, melphalan], *Benda-CV* [bendamustine, cyclophosphamide, etoposide], *BACE* [bendamustine, cytarabine, cyclophosphamide, etoposide], *BEAC* [carmustine, etoposide, cytarabine, cyclophosphamide], *NEAM* [mitoxantrone, etoposide, cytarabine, melphalan], *LEAM* [lomustine, etoposide, cytarabine, melphalan], *BuCyE* [busulphan, cyclophosphamide, etoposide], *ARF* acute renal failure, *VOD* veno-occlusive disease, *AML* acute myeloid leukemia, *MDS* myelodysplastic syndrome, *MOF* multiorgan failure

undergoing AHCT. No grade III–IV nephrotoxicity, interstitial pneumonitis, idiopathic pneumonia, or cardiotoxicity were observed. No episode of hepatic VOD was reported. TRM at day 100 was 0%. In a French multicenter study of 474 lymphoma patients where BeEAM regimen was used, the observed grade 1–4 toxicities included mucositis (83.5%), gastroenteritis (53%), skin toxicity (34%), colitis (29%), liver toxicity (19%), pneumonitis (5%), and cardiac rhythm disorders (4%). Acute renal failure (ARF) was observed in 132 cases (27.9%). Organ toxicities and death were more frequent in patients who developed post-conditioning renal failure. In a multivariate analysis, pre-transplant chronic renal failure, bendamustine dose 160 mg/m^2 and age were independent prognostic factors for ARF [69]. Multiple other studies have compared BEAM to BeEAM retrospectively, showing comparable engraftment rates and survivals, but with a slight increase in BeEAM-associated toxic effects (Table 1). Other conditioning regimens using bendamustine are BACE (bendamustine, cytarabine, cyclophosphamide, and etoposide) and Benda-CV (bendamustine, cyclophosphamide, and etoposide). Jaimovich et al. [70] conducted a multicenter, prospective phase 2 study evaluating the safety and efficacy of Benda-CV. Toxicity profile was similar to that usually observed in the AHCT setting.

Kim and colleagues [71] replaced carmustine in BEAM with mitoxantrone (NEAM) in 69 patients harboring chemosensitive, aggressive NHL. Median EFS was 17.9 months, with an estimated 2-year OS of 64.2%. Febrile neutropenia was seen in 61 patients (88.4%). Grade 3 or 4 hepatic toxicity developed in 7 patients (10.1%), grade 3 or 4 renal toxicity in 2 patients (2.9%), and grade 3 or 4 cardiac toxicity in 2 patients (2.9%). Two patients (2.9%) developed TRM [71].

A large multicenter retrospective study conducted by Olivieri and colleagues [72] compared safety and efficacy of BEAM and FEAM (fotemustine, etoposide, cytarabine, and melphalan). FEAM conditioning resulted in higher rates of gastrointestinal and infectious toxicities. Mortality from infection was higher in the FEAM group (HR 1.99; 95% CI:1.02–3.88, $p = 0.04$). This study does not support fotemustine substitution for carmustine due to concerns of higher toxicity.

Lomustine has been used instead of carmustine in the BEAM regimen [73, 74]. The largest comparison of the LEAM (lomustine, etoposide, cytarabine, and melphalan) vs BEAM showed no significant differences in NRM, OS, PFS, and in any of the toxicity parameters between the two cohorts. The most common grade 3–4 toxicities observed in both approaches were stomatitis (30%), diarrhea (50%), and nausea (16% for LEAM and 6% for BEAM). Grade 3–4 hepatic and renal toxicity was infrequent [74].

Busulfan has replaced carmustine in several lymphoma conditioning regimens. Wadehra and co-workers reported the outcomes of 127 HL patients who underwent BuCyE (busulfan, cyclophosphamide, and etoposide)-AHCT [75]. The regimen was well tolerated, with 5.5% TRM at 100 days. At a median follow-up of 6.7 years, the 5-year PFS was 48%, and the 5-year OS was 51%. Five patients died between 5.3 and 9.3 years of late complications, including secondary myelodysplasia or acute myeloid leukemia (MDS/AML) (2%), bladder cancer (1%), pulmonary toxicity (1%), and an overall 9% 8-year risk of second solid malignancy. In the largest study involving 382 NHL patients using BuCyE conditioning [76], mucositis was the most common toxicity. Severe hepatic VOD occurred in 11 patients (2.9%) and MDS/AML (1%) [76]. In another study, Kim and colleagues [77] evaluated the efficacy and toxicity of BuCyE in 64 patients with rel/ref NHL. Hepatic VOD was observed in 4 patients, and 2 (3.1%) died from treatment-related complications. At a median follow-up of 16.4 months, 15 patients (23.4%) had progressed, while 13 subjects (20.3%) had died of disease. The estimated 3-year OS and PFS overall for all patients were 72% and 70%, respectively. Other studies of BuCyE regimen are listed in Table 1 [77].

Over the past years, several other regimens have been developed (Table 2). Tarella and coworkers [78] reported a 7-year OS and 6.7-year failure-free survival projection of 77% and 69%, respectively, with melphalan and mitoxantrone (Mito/Mel). The toxicities included grade 3–4 mucositis, cardiotoxicity, sepsis, colitis, and deep vein thrombosis. There was one fatal event due to severe pancytopenia following abdominal radiation.

Crump and colleagues [79] reported safety and efficacy of etoposide and melphalan (Eto/Mel) conditioning regimen in 73 patients with rel/ref HL. The most common toxicities were mucositis and diarrhea. However, cardiopulmonary toxicities and VOD were observed too. The 7 deaths related to AHCT were from infection ($n = 3$), interstitial pneumonitis ($n = 3$), and intracranial hemorrhage ($n = 1$). All cases of pneumonitis had received mantle and lung radiation immediately before AHCT.

Nieto and colleagues evaluated a combination of gemcitabine, busulfan and melphalan (GemBuMel) as conditioning regimen for AHCT in refractory NHL and HL [80–83]. Mucositis was the major toxicity. Two patients died from early posttransplant infections. Overall and complete response rates, respectively, were 87% and 62% (HL), 100% and 69% (B-NHL), 66% and 66% (T-NHL), and 71% and 57% (myeloma). At median follow-up of 24 months, the EFS and OS rates, respectively, were 54% and 72% (HL), 60% and 89% (B-NHL), 70% and 70% (T-NHL,) and 43% and 43% (myeloma). Furthermore, when this regimen was compared to BEAM conditioning, there were no transplant-related deaths in either cohort. Toxicities included mucositis, dermatitis, tranaminitis, and

Table 2 Other transplant conditioning approaches in lymphoma

Reference	Conditioning patients (*n*)	Histology	Median age (range)	Early TRM	PFS/OS	Comments
Nieto et al. [80]	GemBuMel 133 2007-11	HL 80 NHL 46 MM 7	41 (18–65)	2	2-y EFS/OS HL 54/72% BNHL 60/89% TNHL 70/70% MM 43/43%	Major toxicity was mucositis 2 died from infection
Nieto et al. [83]	GemBuMel 84 BuMel 39 BEAM 57 2005-10	HL	32 (17–65)	0	3-y EFS/OS 57/82 33/52 39/59	GemBuMel improved outcomes compared with BuMel and BEAM
Nieto et al. [82]	GemBuMel 80 vs BEAM 45	HL	31 (13–65) vs 38 (17–65)	0	2-y PFS/OS 65/89 vs 51/73	More mucositis, dermatitis, transaminase, Hyperbili in GemBuMel
Nieto et al. [118]	GemBuMel 32 vs BEAM 84	TCL	47 (16–67) vs 59 (14–78)	0	DFS/OS 76/75% vs 40/60%	GemBuMel appear superior
Davidson et al. [84]	Gem/mel 42	NHL HL	52 (38–66)	0	10-mo PFS 59%, OS 93%	Gr 3–4 non-hem events: mucositis (7), colitis (5), pneumonia (4), sepsis (2), diarrhea (1), esophagitis (1), emesis (1), transaminitis (1), pulmonary edema (1), stroke (1)
Tarella et al. [78]	Mito/Mel 113	DLBCL	48 (18–66)	4.5% infect	4-y EFS/OS 76/73%	Gr 3-4 mucositis, cardiac, sepsis, colitis, DVT
Villa et al. [119]	VP16/MEL 50	NHL	50 (29–63)	2% d100	3-y PFS/OS 42%/54%	
Ji et al. [120]	ChiCGB 43 2015-17	Poor-risk NHL HL	34 (22–62)	0	Median f/u 10 mo (3–26 mo) PFS 78% OS 89%	Grade 3 neutropenic fever, mucositis, dermatitis
Chahoud et al. [90]	R-BEAM 73 vs RIT-BEAM 40	DLBCL	52 (19–69)		5 y PFS/OS 62%/73% vs 65%/77%	Addition of 90YIT does not confer a further survival benefit
Bento et al. [89]	BEAM 1973 R-BEAM 207 RIT-BEAM 179	FL	56 (19–77) 55 (25–72) 55 (25–70)	3% in all	63/82% 63/88% 62/86% (p = ns)	No difference in relapse, TRM, EFS, OS
Chow Victor et al. [91]	RIT-CyE 108	NHL	52 (32–60)	d30 0 d100 2.8%	5-y PFS 50–60% OS 67–80%	2nd cancer in 5.6%

TRM treatment-related mortality, *PFS* progression-free survival, *DFS* disease-free survival, *OS* overall survival, *EFS* event-free survival, *d* day, *y* years, *mo* months, *NS* not significant, *NHL* non-Hodgkin lymphoma, *HL* Hodgkin lymphoma, *TCL* T cell lymphoma, *BNHL* B cell non-Hodgkin lymphoma, *TNHL* T cell non-Hodgkin lymphoma, *MM* multiple myeloma, *BEAM* [carmustine, etoposide, cytarabine, melphalan], *CBV* [cyclophosphamide, carmustine, etoposide], *R* rituximab, *GemBuMel* [gemcitabine, busulphan, melphalan], *MITO* mitoxantrone, *ChiCGB* [chiamide, cladribine, gemcitabine, busulfan], *CyE* [cyclophosphamide, etoposide], *ARF* acute renal failure, *VOD* veno-occlusive disease, *RIT* radioimmunotherapy, *DVT* deep venous thrombosis

hyperbilirubinemia. At a median follow-up of 34.5 months, GemBuMel was associated with a better 2-year PFS (65% vs 51%; $p = 0.008$) and overall survival (89% vs 73%; $p = 0.0003$). GemMel regimen in NHL and HL [84] resulted in several grade 3–4 nonhematologic toxicities, including mucositis, infectious colitis, pneumonia, sepsis, non-infectious diarrhea, esophagitis, emesis, transaminitis, pulmonary edema, and stroke.

Taken together, the above studies show that the substitution of carmustine with other chemotherapy agents such as thiotepa, bendamustine, lomustine, mitoxantrone, and busulfan in HDT is safe, with comparable engraftment and survival outcomes. While the incidence of pulmonary complications in the carmustine-free regimens is lower, other non-hematologic complications such as renal and gastrointestinal toxicities with bendamustine, VOD with busulfan, and cardiologic and liver toxicities with mitoxantrone need to be taken into consideration when choosing an alternative regimen. Although GemBuMel seems to be a reasonable alternative conditioning regimen in refractory disease, one cannot discount investigator bias in choosing the approach.

Alternative and innovative transplant strategies in lymphoma

Radioimmunotherapy (RIT)-based conditioning regimen

Incorporation of RIT into a conditioning regimen for B cell NHL to increase transplant efficacy have been evaluated. Studies have shown this approach to be safe and associated with encouraging results [85, 86]. In a phase 1 study, Vose and colleagues [85] evaluated 23 patients with rel/ref B-NHL who underwent AHCT with BEAM combined with the radioimmunoconjugate iodine-131 tositumomab. The complete response rate after transplantation was 57%. Short- and long-term toxicities were similar to historic control patients treated with BEAM alone. With a median follow-up of 38 months, the OS and EFS were 55% and 39%, respectively. A phase 2 study conducted by Krishnan and co-workers [86] evaluated safety and efficacy of yttrium-90 ibritumomab tiuxetan combined with BEAM and AHCT in 41 B-NHL patients. At a median follow-up of 18.4 months, the estimated 2-year OS and PFS were 88.9% and 69.8%, respectively. Adverse events were similar to those seen historically with use of BEAM-AHCT alone and included grade 3–4 pulmonary toxicity in 10 patients. A randomized study of ibritumomab tiuxetan (RIT)-BEAM vs BEAM in rel/ref aggressive lymphoma showed that RIT-BEAM is safe and possibly more effective than BEAM alone [87]. The multicenter phase 3 trial, conducted by the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) where patients with chemosensitive, relapsed DLBCL were randomized to either rituximab (R)-BEAM ($n = 113$) or ^{131}I-tositumomab (RIT)-BEAM ($n = 111$), showed no significant differences in 2-year PFS (48.6% vs 47.9%, $p = 0.97$) and 2-year OS (66% vs 61%, $p = 0.38$). TRM also was comparable (4.1% vs 4.9%, $p = 0.97$), although the RIT arm had a significantly higher mucositis score [88]. In FL, the effect of the addition of RIT or rituximab to BEAM was evaluated using data obtained from the EBMT registry. In that study, 3 cohorts of patients were compared: BEAM ($n = 1973$) [78], Y-Ibritumomab (RIT)-BEAM ($n = 207$), and R-BEAM ($n = 179$). The cumulative incidences of relapse at 2 years were 34, 34, and 32% for RIT-BEAM, R-BEAM, and BEAM, respectively. By multivariate analysis, there were no significant differences with RIT-BEAM or R-BEAM compared with BEAM for relapse, NRM, EFS, or OS [89]. Two other recent studies involving RIT-based conditioning are summarized in Table 2 [90, 91]. Of note, there is an ongoing phase 1 study evaluating escalating doses of ^{131}-I monoclonal antibody BC8 (anti-CD45 antibody) followed by HDT-AHCT in rel/ref HL and NHL (ClinicalTrials.gov Identifier: NCT00860171). The published evidence, thus far, does not support routine addition of RIT to HDT-AHCT.

Tandem transplantations

Another approach to improve transplant outcomes in lymphoma have included the use of tandem transplants, i.e., two stem cell transplantations within a period of <6 months. Several retrospective and prospective studies suggest that tandem HDT-AHCT may improve the outcome of patients with high-risk rel/ref HL [92–96]. The prospective H96 trial conducted by the Lymphoma Study Association and Société Française de Greffe de Moell (LYSA/SFGM-TC) assessed the long-term results of this strategy. This multicenter phase 2 trial evaluated a risk-adapted strategy with single or tandem AHCT in 245 HL patients. Poor-risk patients ($n = 150$) received tandem AHCT, whereas intermediate-risk patients ($n = 95$) received a single AHCT. At a median follow-up of 10.3 years, 10-year freedom from second failure and OS rates were 64% (95% CI, 54–74%) and 70% (95% CI, 61–80%) for the intermediate-risk group and 41% (95% CI, 33–49%) and 47% (95% CI, 39 to 55%) for the poor-risk group, respectively. The 15-year cumulative incidences of second primary malignancies were higher in patients with tandem AHCT (24% vs 2%). In another phase 2 study performed by the US intergroup [96], 82 patients with rel/ref HL underwent tandem transplant. There were no TRM in the first year after AHCT. With a median follow-up of 6.2 years, the 5-year PFS and OS were 55% (95% CI: 44–64%), and 84% (95% CI: 74–90%), respectively. Deau and coworkers [97] evaluated the tolerance and efficacy of double AHCT or AHCT followed by allo-HCT in 120 rel/ref HL patients

prospectively. Of those, 115 (96%) patients underwent a single AHCT, 44 (60%) had tandem AHCT, and 29 (40%) had AHCT followed by allo-HCT. The 2-year PFS rate for the whole population and for patients receiving tandem transplant was 56% (95% CI: 46–65%) and 71% (95% CI: 49–84%), respectively. Among tandem transplants, 20 deaths (17%) were observed, 10 of which were transplant related (6 allo-HCT and 4 AHCT). This study suggests that tandem HCT is effective in high-risk rel/ref HL patients, although TRM remains high. In the era of immunotherapies and targeted therapies, this strategy is less well defined. The role of tandem AHCT in NHL has not been established [98, 99].

Maintenance therapy after HDT-AHCT

Recurrent disease after HDT-AHCT remains the main cause of treatment failure in patients with rel/ref HL and NHL. The post-AHCT setting is characterized by a minimal disease state and a state of immune remodeling with gradual reconstitution of a full immune system. It represents the last effective intervention point for cure of rel/ref lymphoma. A variety of maintenance therapy approaches post-AHCT have been explored to decrease the risk of disease relapse, with varying success (Table 3).

Anti-CD20 monoclonal antibody Rituximab, has been evaluated for maintenance treatment post-HDT-AHCT in B cell NHLs. In a prospective, phase 3 study, the Collaborative Trial in Relapsed Aggressive Lymphoma, 396 patients with rel/ref DLBCL were randomized to salvage chemotherapy with R-ICE (rituximab, Ifosfamide, carboplatin, and etoposide) or R-DHAP [100, 101]. Responding patients proceeded to HDT-AHCT and underwent a second randomization after transplant to either observation or rituximab maintenance for 1 year. There was no difference in response rates between the R-ICE and R-DHAP arms, 63.5% vs 62.8%, respectively, or in EFS, 26% vs 35%, respectively. Maintenance rituximab did not impact the EFS, PFS, or OS in DLBCL [100]. However, in a subset analysis based on sex that compared the rituximab and observation groups, the 3-year EFS was 43% (95% CI, 31–54%) in men and 69% (95% CI, 53–81%) in women ($p = 0.1$). This was attributed to higher rituximab clearance and hormone-related pharmacokinetic variations in males. Thus the impact of an increased dose of rituximab on survival requires further investigation. In FL, a randomized phase 3 study by EBMT evaluated the role of rituximab in vivo purging and maintenance therapy in patients with rituximab-naive, chemosensitive rel/ref FL. Patients were randomly assigned to in vivo purging with weekly rituximab 375 mg/m^2 for 4 doses or observation prior to hematopoietic cell collection. After HDT-AHCT, patients underwent a second randomization to receive maintenance rituximab once every 2 months for a total of 4 doses. There was no difference in PFS between the purging group and observation group. Although rituximab maintenance was associated with a longer PFS (10-year PFS 54% vs 37%, $p = 0.01$), it did not impact OS [39]. Although While in DLBCL, maintenance rituximab after HDT-AHCT is not supported by published data, its use in FL is based on improvement in PFS. In MCL, a phase 3 trial examined induction chemo-immunotherapy followed by R-BEAM: 240 patients were randomized to either rituximab maintenance (once every 2 months for 3 years) or observation (120 patients per group). The rate of EFS, PFS, and OS at 4 years were 79, 83 and 89%, respectively, in the rituximab group, vs 61, 64 and 80% in the observation group ($p = 0.001$) [102]. This study established rituximab maintenance therapy after HDT-AHCT in MCL.

Anti-CD30 antibody–drug conjugate

Brentuximab vedotin (BV), an anti-CD30 antibody–drug conjugate is a microtubule-disrupting agent leading to cell-cycle arrest and apoptosis. In a phase 2 trial in patients with rel/ref HL after AHCT, the ORR was 75%, with 34% achieving a CR [103]. In HL, the phase 3 randomized ATHERA trial [104] randomized patients with rel/ref disease to maintenance BV or placebo every 3 weeks for up to 16 cycles. The most common toxicities were peripheral neuropathy and neutropenia. The median PFS was 43 months for the BV group compared with 24 months for the placebo group. Based on this study, BV was approved by the US Food and Drug Administration for early consolidation after HDT-AHCT in patients with high-risk rel/ref HL. Pro and coworkers demonstrated safety and efficacy of BV in 58 patients with rel/ref ALCL in a phase 2 study. Of the 38 patients who achieved CR, 16 received a consolidative AHCT with median PFS not reached [105].

In an effort to further improve transplant outcomes in lymphoma and to reduce relapse rate, ongoing clinical trials are investigating a multitude of novel targeted agents for post-AHCT maintenance. These ongoing studies are summarized in Table 4.

Transplant timing along with established and investigative maintenance agents in lymphoma are summarized in Fig. 1.

In summary, in the era of personalized and targeted treatments in lymphoma, HDT-AHCT still plays an important role in disease control. Lymphoma recurrence, however, continues to be the major cause for treatment failure. Patients whose disease recurs after HDT-AHCT generally are considered incurable, with the exception of a small proportion who may be cured with an allo-HCT or with novel targeted agents. Various strategies have been

Table 3 Established and investigative maintenance strategies after autologous stem cell transplant

Intervention	Study phase	Studies
Anti-CD20 monoclonal antibody: Rituximab	Phase III Phase III Phase III	DLBCL [100]: No impact on DFS or OS FL [39]: maintenance rituximab once every 2 months×4 doses is associated with a longer PFS (10-year PFS 54% vs 37%, $p = 0.01$), but no impact on OS MCL [102]: maintenance rituximab once every 2 months×3 years. 4-year EFS, PFS, and OS were 79, 83, and 89%, respectively, in the rituximab group, vs 61, 64, and 80% in the observation group ($p = 0.001$)
Anti-CD30 antibody drug conjugate: Brentuximab vedotin	Phase III	HL (high-risk rel/ref) [104]: maintenance BV every 3 weeks, for up to 16 cycles. Median PFS was 43 months for the BV group compared with 24 months for the placebo group
Anti-PD-1 monoclonal antibody: Pidilizumab	Phase II	DLBCL [121]: 3 doses of pidilizumab after AHCT: 16-month PFS and OS were 72 and 85%, respectively. Among patients who had measurable disease post-AHCT, ORR was 51%
Proteasome inhibitors: Bortezomib	Phase II Phase II	MCL [122]: bortezomib 1.3 mg/m^2 weekly×4, every 3 months and rituximab 375 mg/m^2 weekly×4 every 6 months for a total of 2 years. 2-year DFS and OS: 90.2% (95% CI 66–97), and 94.7% (95% CI 68–99), respectively MCL [44, 123]: After two doses of posttransplant rituximab, patients were randomized to bortezomib consolidation (1.3 mg/m^2 on days 1, 4, 8, and 11 for four cycles) or bortezomib maintenance (1.6 mg/m^2 weekly 4 of 8 weeks for 18 months) on day 90 after transplant. The 2-year PFS rates were similar in both arms (84 and 89%, respectively). 5-year PFS rates compared to historical control (72.7% vs 51.5%, $p = 0.0006$) suggest a PFS benefit for post-autologous SCT bortezomib maintenance in MCL
Immune modulators: Lenalidomide	Phase I/II	DLBCL and HL [124, 125]: No dose-limiting toxicities in phase 1, and dose of 10 mg daily was determined appropriate for phase 2. At a median follow-up of 24 months, PFS and OS were 62% and 75%, respectively
Histone deacetylase inhibitor: Vorinostat	Phase I	HL and NHL [126]: starting day 60 post-AHCT for 21 consecutive days followed by a week off for up to 11 cycles. Of the 23 enrolled patients, 11 completed maintenance vorinostat treatment plan per protocol. Four patients were removed owing to progressive disease, and 7 were removed owing to toxicities. One patient developed lung cancer after 6 cycles. Given the toxicities observed, vorinostat at this schedule is not optimal for prolonged maintenance therapy

AHCT autologous hematopoietic cell transplantation, *NHL* non-Hodgkin lymphoma, *HL* Hodgkin lymphoma, *DLBCL* diffuse large B cell lymphoma, *FL* follicular lymphoma, *MCL* mantle cell lymphoma, *DFS* disease-free survival, *OS* overall survival, *EFS* event-free survival, *ORR* overall response rate, *BV* brentuximab vedotin

Table 4 Ongoing investigative maintenance strategies after autologous stem cell transplant

Intervention	Study phase	Disease	Identifier	Clinical trial
Lenalidomide	Pilot Study	HL	NCT01207921	Lenalidomide maintenance therapy post-AHCT
Lenalidomide	Phase 1/2	NHL	NCT01035463	Lenalidomide maintenance after high-dose BEAM with or without rituximab
Lenalidomide	Phase 1/2	DLBCL	NCT01241734	Lenalidomide with RICE with lenalidomide maintenance post-AHCT
Lenalidomide	Phase 1/2	HL and NHL	NCT01575860	Maintenance lenalidomide in lymphoma after AHCT
Lenalidomide	Phase 3	MCL	NCT02354313	Lenalidomide vs observation after AHCT
Bortezomib	Phase 2	MCL	NCT00310037	Bortezomib after combination chemotherapy, rituximab, and AHCT
Bortezomib	Phase 2	MCL	NCT01267812	Weekly maintenance bortezomib and rituximab in MCL Post-AHCT
Bortezomib+vorinostat	Phase 2	HL and NHL	NCT00992446	Bortezomib+vorinostat as maintenance after AHCT
Ixazomib+Rituximab	Phase 1/2	MCL	NCT02632396	Ixazomib and rituximab after AHCT
Everolimus+Rituximab	Phase 2	HL and NHL	NCT01665768	Maintenance rituximab with mTOR inhibition after AHCT
Ibrutinib	Phase 3	MCL	NCT02858258	AHCT after a rituximab/ibrutinib/Ara-c induction and ibrutinib maintenance
Ibrutinib	Phase 3	DLBCL (ABC subtype)	NCT02443077	Ibrutinib during and following AHCT vs placebo
Romidepsin	Phase 2	T-NHL	NCT01908777	Maintenance therapy with romidepsin for T cell NHL after AHCT
Nivolumab	Phase 2	HL	NCT03436862	Nivolumab as maintenance therapy after AHCT
Pembrolizumab	Phase 2	HL, DLBCL, T-NHL	NCT02362997	Pembrolizumab after AHCT

AHCT autologous hematopoietic cell transplantation, *NHL* non-Hodgkin lymphoma, *HL* Hodgkin lymphoma, T-NHL T cell non-Hodgkin lymphoma, *MCL* mantle cell lymphoma, *DLBCL* diffuse large B cell lymphoma, *ABC* activated B cell

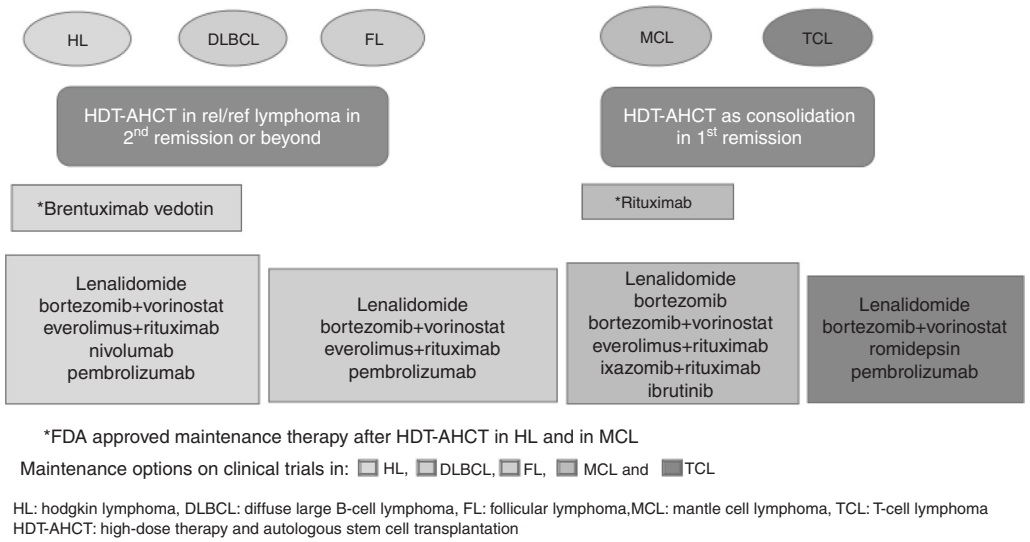

Fig. 1 Schema for transplant and maintenance strategies in lymphoma. Transplant timing and maintenance options in lymphoma

investigated to improve outcomes of HDT-AHCT and reduce relapse, including advancements in supportive care, intensification of the conditioning regimen, incorporation of novel agents into the combination regimens, and innovative maintenance strategies after HDT-AHCT. The use of maintenance therapies appears to hold the greatest promise for leading future direction. While awaiting mature data on the currently accruing clinical trials, it is important to recognize the associated potential toxicities, logistic concerns, and potentially higher financial cost when selecting patients who may benefit from further treatment post-HDT-AHCT.

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Compliance with ethical standards

Conflict of interest HML has been a consultant and promotional speaker for Seattle Genetics. The other authors declare that they have no conflict of interest.

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