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A Review of Autologous Stem Cell Transplantation in Lymphoma

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Abstract
Purpose of Review Chemotherapy remains the first-line therapy for aggressive lymphomas. However, 20–30% of patients with non-Hodgkin lymphoma (NHL) and 15% with Hodgkin lymphoma (HL) recur after initial therapy. We want to explore the role of high-dose chemotherapy (HDT) and autologous stem cell transplant (ASCT) for these patients.
Recent Findings There is some utility of upfront consolidation for-high risk/high-grade B-cell lymphoma, mantle cell lymphoma, and T-cell lymphoma, but there is no role of similar intervention for HL. New conditioning regimens are being investigated which have demonstrated an improved safety profile without compromising the myeloablative efficiency for relapsed or refractory HL.
Summary Salvage chemotherapy followed by HDT and rescue autologous stem cell transplant remains the standard of care for relapsed/refractory lymphoma. The role of novel agents to improve disease-related parameters remains to be elucidated in frontline induction, disease salvage, and high-dose consolidation or in the maintenance setting.

Keywords High-dose chemotherapy · Autologous stem cell transplantation · Relapsed/refractory · Lymphoma · Salvage chemotherapy · Novel agents

This article is part of the Topical Collection on *B-cell NHL, T-cell NHL, and Hodgkin Lymphoma*

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Introduction

In 2016, approximately over 80,000 cases of lymphoma were diagnosed in the USA with just over 20,000 lymphoma-related deaths during the same period [1]. Chemotherapy remains the first-line standard of care for aggressive lymphomas. Roughly 20–30% of patients with non-Hodgkin lymphoma (NHL) will not be able to achieve a complete remission (CR) with standard induction like rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) [2]. For relapsed or refractory (R/R) NHL patients, use of a salvage chemotherapy (ST) regimen and high-dose chemotherapy (HDT) consolidation with use of autologous stem cell transplant (ASCT) can be curative [3, 4]. Evidence for the utility of HDT comes from a study by Philip et al. comparing ST to HDT followed by ASCT in patients with high-grade lymphoma of both B-cell and T-cell subtypes. After a 5-year follow-up, overall survival (OS) was 53% in the HDT/ASCT group compared to 32% in the ST group (P value =0.038) [3]. Several investigators have looked at the use of upfront ASCT

consolidation in aggressive NHL [5, 6]. In a study of chemosensitive HL patients in their first relapse, Schmitz et al. showed that 55% patients randomized to ASCT were disease-free at 3 years compared to 34% of patients who received aggressive conventional chemotherapy (CHT) alone, but there was no difference in OS [4]. Upfront consolidation was attempted in advanced HL [7, 8] but without OS advantage. For high-risk HD in the primary refractory setting, tandem transplant has been evaluated with limited success [9].

The role of ASCT in T-cell lymphoma (TCL), however, is less defined due to lack of sufficiently powered randomized controlled trials (RCTs). In a prospective phase II study by D'Amore et al., systemic peripheral T-cell lymphoma (PTCL) patients were treated with CHOEP-14 (CHOP with the addition of etoposide) or CHOP-14 (for patients older than 60). Patients consolidated with HDT/ASCT on intention-to-treat analysis showed a 5-year OS of 51% [10]. Transplantation in first complete response (CR1) also appears to have better progression-free survival (PFS) and OS [11]. In a T-cell lymphoma study by Beitinjaneh et al., patients received ASCT or allogeneic transplant (allo-SCT) in frontline setting and 76 patients received transplants after first relapse. The ASCT patients received carmustine, etoposide cytarabine, and melphalan (BEAM) conditioning while the allo-SCT patients received various conditioning regimens and found a higher 4-year OS and PFS in patients who received stem cell transplant (SCT) (either autologous or allogeneic) in CR1. Patients with chemotherapy-sensitive disease who achieved a CR with ASCT had an 84% 4-year survival compared to 44% with patients who had partial response (PR). There are several trials that continue to evaluate the role of ASCT or allo-SCT [12, 13] as well as tandem transplantation [14] for aggressive lymphoma. In a study by Taverna and colleagues, relapse prevention strategies after ASCT consolidation were reviewed in great detail [15]. In this brief review, we will focus on the current trends and evidence for the use of HDC and ASCT for NHL, HL, and PTCL.

A. B-Cell Non-Hodgkin Lymphoma

In 2016, 86% of all lymphoid malignancies diagnosed were expected to be B-cell NHL, with diffuse large B-cell lymphoma (DLBCL) being the most common subtype [16]. Depending on the specific subtype, survival rates vary from 5-year survival of 83–91% for patients with marginal zone lymphoma down to 44–48% for patients with Burkitt lymphoma [16]. While over 50% of patients with DLBCL can be cured with R-CHOP chemotherapy, another 30–40% can develop R/R disease [17]. Induction therapy for patients with DLBCL mainly is R-CHOP [18]. A subset of patients with aggressive DLBCL (i.e., "double-hit" lymphomas, dual expression of MYC and BCL2) may benefit from an alternative intensive regimen like dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab (DA-EPOCH-R). In a study by Wilson et al., investigators compared R-CHOP and DA-EPOCH-R in a phase II study and found that DA-EPOCH-R compared favorably with R-CHOP especially for the treatment of germinal center B-cell (GCB) DLBCL [19]. A phase III study (n = 524) presented at the 2016 American Society of Hematology (ASH) annual meeting, comparing these regimens, found no difference in event-free survival (EFS) or OS; however, further molecular analysis among subtypes is still pending [20].

Role of Upfront High-Dose Consolidation With ASCT for Aggressive B-Cell Lymphoma Stiff and colleagues explored HDT/ASCT as consolidation therapy for aggressive NHL patients (high-intermediate/high-risk defined by the age-adjusted International Prognostic Index (aaIPI), performance status 2 to 4, stage III or IV, and elevated LDH) in a randomized phase III trial and did not find any benefits in OS albeit improvement in PFS [21]. A prospective study by Tarella et al. with 112 DLBCL patients with an aaIPI score of 2 to 3 who received HDT/ASCT found that over 80% of patients reached clinical remission with a 4-year OS projected at 76% and EFS of 73% [22]. A phase II study performed by Vitolo et al. compared the addition of rituximab to HDT/ASCT to those without rituximab in patients with untreated, IPI high-intermediate/high-risk DLBCL and found 4-year OS to be 80 and 54%, respectively [23]. Kim et al. published a retrospective study to assess the effect of upfront ASCT in patients with advanced-stage DLBCL of different molecular classification (GCB versus non-GCB) and found significant OS and PFS benefits within the ASCT group compared to the non-ASCT group [24]. In the non-ASCT group, patients had poorer outcome in the non-GCB subtype while there were no significant differences between the two subtypes in the ASCT group. The authors suggest that upfront ASCT consolidation may be superior for treatment of selected non-GCB-subtype high-risk lymphomas. Upfront HDT/ASCT for high-risk DLBCL in CR1 may provide better outcomes [25]. This is a rapidly evolving area, and future research studies will help clarify indications for frontline consolidation [26, 27].

Role of High-Dose Chemotherapy Consolidation With ASCT for Relapse and Refractory Non-Hodgkin Lymphoma In patients with R/R DLBCL, the standard of care is salvage chemotherapy followed by HDT/ASCT. The PARMA study found a significant 5-year OS benefit (53 versus 32%, P = 0.038) in patients who were chemotherapy-sensitive and received consolidation with ASCT compared to those without consolidation [3]. Dexamethasone, high-dose cytarabine, and cisplatin (DHAP) ST was used prior to consolidation. Studies using various ST regimens such as rituximab plus DHAP (R-DHAP) [28]; ifosfamide, carboplatin,

and etoposide (ICE) [29]; rituximab plus ICE (R-ICE) [30]; gemcitabine, dexamethasone, and cisplatin (GDP) [31•]; and rituximab, gemcitabine, and oxaliplatin (R-GEMOX) [32] were done in order to maximize response rate and potential gain in OS. In the multicenter phase III, CORAL study, R-ICE and R-DHAP were tested against each other, and R-ICE failed to show superiority over R-DHAP. A follow-up study using a subset of the CORAL data by Thieblemont et al. showed cell-of-origin (COO) influence response to ST; specifically, they found that R-DHAP is superior to R-ICE in GCB-subtype DLBCL [33]. In a study by Crump et al., GDP was found to be non-inferior to DHAP in terms of response and survival rates with less toxicity [31•].

Conditioning regimen and its impact on outcome is an area of great interest [34]. Historically, BCNU, etoposide, cytarabine, and melphalan (BEAM) regimen is commonly used in USA. A study by Chen et al. with 4917 patients and their HDT regimens included BEAM, cyclophosphamide, carmustine less than 300 mg/m^2, and etoposide (CBV^{low}); carmustine greater than 300 mg/m^2 (CBV^{high}); and busulfan and cyclophosphamide (Bu/Cy) prior to ASCT [35•]. In patients with DLBCL, CBV^{high} had worse outcomes compared to the other regimens and also had increased rates of toxicities such as idiopathic pulmonary syndrome (IPS). Another study combined a radioactive conjugate iodine-131 tositumomab and BEAM (B-BEAM) and compared it to rituximab plus BEAM (R-BEAM) and found a similar 2-year PFS and OS in patients with chemotherapy-sensitive relapsed DLBCL [36]. A meta-analysis by Auger-Quittet et al. looking at Zevalin (yttrium-90 ibritumomab tiuxetan) (Z-BEAM) showed a 2-year OS of 84.5% [37].

Role of Upfront ASCT With HDT for Double- and Triple-Hit Lymphoma

High-grade B-cell lymphomas with MYC and BCL2 and/or BCL6 oncogene rearrangement (*MYC/8q24*, *BCL2/18q21*, and/or *BCL6/3q*27detected by FISH, or cytogenetics) are termed double-hit (DT) or triple-hit (TH) (for three rearrangements) lymphomas, and have poor prognosis with R-CHOP induction (median OS 12 months or less). The role of intensive induction such as rituximab, cyclophosphamide, vincristine, doxorubicin, methotrexate/ifosfamide, and etoposide cytarabine (R-CODOX-M/IVAC); rituximab, cyclophosphamide, vincristine, doxorubicin, dexamethasone/methotrexate, and cytarabine (R-hyper CVAD/MA); rituximab with dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (DA-EPOCH-R); and high-dose consolidation was explored in a retrospective study by Petrich et al. DA-EPOCH-R resulted in significantly higher rates of CR, and with respect to R-CHOP, intensive regimens showed significantly improved PFS. In patients who achieved CR to frontline therapy, median OS was similar for observed versus consolidation SCT of any type (median OS not reached; $P = 0.14$) [38]. In a study by Landsburg et al., patients who were not treated with intensive induction appear to benefit from high-dose consolidative ASCT, while patients who receive intensive induction did not show benefit from upfront consolidative ASCT [39].

Role of Upfront ASCT With HDT for Mantle Cell Lymphoma

Intensive induction and upfront consolidation are routinely offered to patients with aggressive mantle cell lymphoma (MCL). Dreyling et al. reported data on a prospective randomized study with an advanced MCL cohort, and after induction with CHOP-like regimen, patients received either HDC/ASCT or maintenance with interferon (IFN). Patients in the HDC/ASCT arm who got chemotherapy-based mobilization and total body irradiation (TBI) 12 Gy/cyclophosphamide (Cy)-based pretransplant conditioning experienced a significantly longer PFS (median of 39 versus 17 months) [40]. A long-term follow-up of this study was reported at ASH 2009 by Hoster et al. which included the Dreyling et al. trial and two other trials studying mantle cell patients. They evaluated 180 patients with MCL, 80 treated with R-CHOP, and 78 treated with ASCT (56 received CHOP without ASCT, 46 CHOP with ASCT, 44 R-CHOP without ASCT, 34 R-CHOP with ASCT). Of the patients analyzed, 71% were low risk, 22% were intermediate risk, and 6% were high risk, with a median follow-up duration of 63 months. Median overall survival was 54 months with CHOP without ASCT, 66 months after R-CHOP without ASCT, and 90 months after CHOP with ASCT, and median OS was not reached in R-CHOP with ASCT with a hazard ratio for OS for rituximab of 0.7 ($P = 0.14$) and 0.63 for ASCT ($P = 0.0379$). They concluded that the addition of ASCT and rituximab increased the response duration and overall survival [41]. Hermine et al. randomized 500 MCL patients to R-CHOP versus R-CHOP alternating with R-DHAP and showed better disease control in the cytarabine-containing induction group after a 6-year median follow-up. Unlike data on DH lymphoma, R-CHOP-based inferior induction response was not neutralized by the use of upfront high-dose consolidation with TBI/Cy-based consolidation [42]. The Nordic Lymphoma Group MCL2 study updated results (2012) of upfront intensive induction and ASCT using BEAM or carmustine, etoposide, AraC, and cyclophosphamide (BEAC) regimen showed a median EFS of 7.4 years, but ongoing relapse was reported to be beyond 5 years [43].

B. Hodgkin Lymphoma

HL is a rare malignancy of B-lymphocytes and accounts for 0.5% of all malignancies. According to 2016 projections, 8500 cases were diagnosed with HL in USA and 1120 were

expected to die of disease [1]. Approximately 80% cases of newly diagnosed HL are curable with combination chemotherapy doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) followed by 20–30 Gy involved field radiation in a selected subset of patients [44]. Despite highly active frontline treatment, 5–10% of HL patients are primary refractory or 10–30% of HL patients relapse after achieving an initial CR [45].

Role of Upfront Consolidation in Hodgkin Lymphoma

In a study by Federico et al. [8], the role of HDT (BEAM and CVB) followed by ASCT versus CHT (four additional courses of the same CHT used in the induction phase) as frontline therapy for advanced HL patients (according to the Strauss-derived system) was evaluated [46], but no benefit of early intensification with HDT/ASCT was found. In a study by Carella et al. [47], the results of the extended follow-up of the abovementioned study showed 10-year OS to be 85% (95% CI 78–90) and 84% (95% CI 77–89) for patients who underwent HDT-ASCT or CHT, respectively, without significant difference ($P = 0.7$). Ten-year relapse-free survival (RFS) and failure-free survival (FFS) were 88% (95% CI 81–95), 79% (95% CI 72–85) versus 89% (95% CI 83–93), and 75% (95% CI 67–82) for HDT/ASCT and CHT, respectively (P = 0.7–0.8). The authors concluded that, in patients responding to initial CHT, the consolidation with HDT/ASCT is not superior; most importantly, findings confirm that consolidation therapy should not be offered.

Salvage Chemotherapy for Relapsed Hodgkin Lymphoma

ST followed by HDT/ASCT has been the standard of care for R/R HL. Outcome of consolidation for ASCT depends on response to ST, assessed by 18F-fluorodeoxyglucose (FDG) PET/CT scan. Pretransplantation PET negativity is one of the strongest predictors of HDT/ASCT outcome [48]. Choice of optimal ST is unclear and is chosen on the basis of individual patients [49•]. Salvage ICE has shown an overall response rate (ORR) of 80% and CR of 50% [50]. Other options for ST include DHAP and etoposide, methylprednisolone, high-dose AraC, and cisplatin (ESHAP) with comparable responses to ICE chemotherapy. Gemcitabine, vinorelbine, and doxorubicin (GVD) showed an ORR of 70% with 19% CR [51]. Ifosfamide, prednisolone, gemcitabine, and vinorelbine (IGEV) demonstrated an ORR of 81.3% with 54% CR and 27.5% PR [52].

Two landmark RCTs, the British National Lymphoma Investigation (BNLI) in 1993 [53] and the joint German Hodgkin Study Group (GHSG)/European Group for Blood and Marrow Transplantation (EMBT) HD-R1 trial in 2002 [4], compared the HDT (BEAM with 300 mg/m^2 carmustine) followed by ASCT versus CHT (mini-BEAM with 60 mg/m^2 carmustine in BLNI, dexa-BEAM in HD-R1) and showed significant benefit of HDT/ASCT for EFS and freedom from treatment failure (FFTF); however, there was no significant OS benefit. A meta-analysis of the above two trials by Rancea et al. [54] utilizing the median follow-up of 34 and 83 months from BNLI and HD-R1, respectively, showed significant improvement of PFS in patients who were treated with HDT/ASCT compared to the CHT group (hazard ratio [HR] 0.55; 95% CI 0.35–0.86, P value =0.009). However, data failed to show a statistically significant difference for OS between HDT/ASCT and CHT (HR 0.67; 95% CI 0.41–1.07, $P = 0.1$). There was a trend towards better OS, but data was not sufficiently powered.

Role of Conditioning Chemotherapy Consolidation With ASCT for Relapsed Hodgkin Lymphoma

BEAM was adopted as a conditioning regimen since HDT/ASCT showed superiority over CHT in the R/R setting [4, 53]. Prior studies showed that higher doses of BCNU increase the risk of pulmonary toxicity as high as 35% [55, 56]. In an effort to reduce pulmonary toxicity, Arai et al. conducted a phase I/II study of conditioning regimen using gemcitabine along with vinorelbine (gemcitabine maximum tolerated dose, 1250 mg/m^2) [57]. The incidence of BCNU-related toxicity was 15% with this regimen (95% CI 9 to 24%). Two-year freedom from progression (FFP) and OS were 71% (95% CI 6 to 81%) and 83% (95% CI 75 to 91%), respectively. According to the Center for International Blood and Marrow Transplant Research (CIBMTR) large retrospective registry data of 4917 lymphoma patients (HL = 1012, NHL = 3905), BEAM and CBV continued to be two most commonly used conditioning regimens before ASCT [35•]. In that study, 3-year PFS/OS was 62/79, 60/73, and 57/68% for BEAM, CBV^{low}, and CBV^{high}, respectively. IPS incidence after 1 year of ASCT was 3% for BEAM/CBV^{low} and 6% for CBV^{high}. In a prospective study by Musso et al., conditioning with fotemustine substituted for BCNU, etoposide, cytarabine, and melphalan (FEAM) for R/R HL [58] resulted in 2-year PFS of 73.8% (95% CI .64–.81) and adjusted 2-year risk of progression of only 19.4% (95% CI .12–.27). There were no reported pulmonary toxicity, hepatic/renal adverse events, or secondary malignancies.

Role of Tandem ASCT for Relapsed Hodgkin Lymphoma

The H96 trial by Morschhauser et al. [9], which looked at the risk, adopted ST with single or tandem ASCT for 245 R/R HL patients, randomized to the poor-risk group (n = 150, intensified ST and double ASCT) and the intermediate-risk group (n = 95, standard ST and HDT/ASCT). Intention-to-treat analysis showed 5-year freedom from second failure (FF2F) and OS rates of 46 and 57% in the high-risk group and 73 and 85% in the intermediate-risk group. Outcomes were similar for

primary refractory and poor-risk/relapsed HL. For patients with chemotherapy-resistant disease, the 46% 5-year OS rate was achieved with tandem ASCT compared favorably with the previously reported OS of 30%. In 2016, a long-term follow-up analysis was published and relatively favorable results were confirmed: 10-year FF2F and OS in the high-risk patients were 40 and 47%, respectively [59]. Tandem ASCT remains an option for poor-risk patients, but more prospective studies need to look at this strategy with the use of PET CT imaging.

Role of Antibody Drug Conjugate Brentuximab Vedotin for Hodgkin Lymphoma

Brentuximab vedotin, an antibody drug conjugate (ADC) directed against CD30, approved for R/R HL, is also approved for use after ASCT as maintenance. In a study by Moskowitz et al., the role of BV as a second-line therapy was evaluated in PET-adopted sequential ST for R/R HL. ORR was 76% (PET negativity) either with BV alone or followed by augmented ICE (aug-ICE). At 2 years, EFS was better after ASCT for patients who achieved PET negativity compared to patients who remained PET-positive prior to ASCT [60]. In study by Chen et al., BV was used as a second-line agent prior to ASCT (n = 37, R/R HL) and showed an ORR of 68% (13 CR, 12 PR), and 32 patients (86%) proceeded to ASCT [61]. In the AETHERA trial (2015), a cohort of 329 patients with R/R HL were randomized to receive HDT/ASCT followed by maintenance BV treatment (n = 165) or to a placebo group (n = 164). BV significantly improved post-transplantation PFS (HR .57; 95% CI .40 to .81; P = 0.001). Median PFS by independent review showed significant improvement with BV treatment versus placebo (42.9 versus 24.1 months, P = 0.0013). Two-year PFS rates were 63 versus 51%, respectively [62].

Role of Checkpoint Inhibitors

Programmed death 1 (PD1) is an inhibitory regulator of T-cell activation and function [63]. HRS cells express high levels of PD1 ligands (PD-L1 and PD-L2) which, after engaging with a PD1 receptor on activated T-cells, leads to decrease in function and survival of immune cells. Nivolumab and pembrolizumab are checkpoint inhibitors being studied extensively for the treatment of HL. In a phase I study of 23 heavily pretreated HL patients who received nivolumab at a dose of 3 mg/kg every 2 weeks, 24-week PFS was 86% and ORR was 87% (CR 17%, PR 70%, 95% CI = 66 to 97%) with a median follow-up of 40 weeks [64]. In a phase I study of pembrolizumab for relapsed HL [65], an ORR of 53% was seen (CR 20%, PR 33%). Updated data of extended follow-up of both agents was presented at the 2015 ASH meeting, and approximately 50% responses were durable [66, 67]. A follow-up multicenter phase II study (KEYNOTE-087) was presented at ASH 2016 in 210 patients with an R/R disease that included three cohorts of patients with R/R disease alone, relapsed after ASCT or relapsed after BV. They found that the ORR was greater than 65% in all three cohorts and over 20% of patients in all cohorts had a CR. OS data was not provided for the study; however, these data led to the approval of pembrolizumab for HL in the R/R setting [68]. Patients treated with nivolumab enrolled in the CheckMate study showed an ORR of 66% (PR 57.5%, CR 8.8%), with a 6-month PFS of 77% [69]. The KEYNOTE study with pembrolizumab randomized R/R HL to two cohorts, and the ORRs were 70% (CR 20%, PR 50%) and 80% (CR 27%, PR 53%) for cohorts 1 and 2, respectively [70]. The response rate with nivolumab for HL patients who progressed after auto-SCT and BV was replicated in other trials as well [71, 72].

C. Peripheral T-Cell Lymphoma and Natural Killer/T-Cell Lymphoma

Peripheral T-cell lymphoma (PTCL) arises either from clonal proliferation of mature post-thymic T-cells [73] or from mature skin-resident T-cells [74]; nearly all PTCLs will express a T-cell receptor (TCR). PTCLs tend to be aggressive lymphomas with very poor prognosis. PTCL-NOS or angioimmunoblastic T-cell lymphomas (AITLs) have the worst prognosis with a 5-year OS of 32%. Anaplastic large-cell lymphoma (ALCL), anaplastic lymphoma kinase (ALK)-positive, demonstrated the best 5-year OS of 70%. ALCL, ALK-negative, had an intermediate 5-year OS (49%). Reported OS is 42% for extranodal natural killer/T-cell lymphoma (NK/TCL), nasal type, 20% for enteropathy-associated T-cell lymphoma (EATL), 14% for adult T-cell lymphocytic leukemia (ATLL), and only 7% for hepatosplenic γδ T-cell lymphoma (γδ HSTCL) [75]. Due to the rarity of the disease and the lack of RCTs, there is no consensus regarding first-line therapy in PTCLs and NKTCL. Even with combination chemotherapy, 5-year OS is poor and depends on the IPI score and type of TCL [76]. Given the poor outcome with CHT, there has been a shift towards aggressive strategies such as ASCT or radiation therapy as consolidation. There is no general consensus regarding the preferred induction chemotherapy; usually, a CHOP or CHOEP-like regimen is considered the standard of care in front-line treatment. A large retrospective study showed similar survival between the two approaches with 3-year OS of 62% for CHOP therapy versus 56% for the intensive therapy group. The French GOELAMS group (2010) prospectively compared the etoposide, ifosfamide, cisplatin/doxorubicin, bleomycin, vinblastine, and dacarbazine (VIP/ABVD) regimen to CHOP but found no difference in terms of EFS or OS [77]. The GELA group (2003) RCT comparing standard CHOP to doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone (ACVBP) in poor-prognosis aggressive (B- and T-cell) NHL showed ACVBP to be superior to CHOP in older patients (60–70 years

old) but failed to show any difference in younger patients [78]. Seven high-grade NHL studies by the German study group showed that young good-risk patients had improved 3-year EFS (71 versus 50%) if etoposide was added to CHOP [79]. The Swedish Lymphoma Registry, which identified 252 patients with enteropathy-associated T-cell lymphoma or nodal PTCL other than ALK-positive ALCL, also showed that addition of etoposide to CHOP was associated with superior response rates and PFS but not OS [80]. CHOP or CHOEP therefore remains the standard first-line therapy outside the setting of a clinical trial.

Role of Upfront Consolidation With ASCT for T-Cell Lymphoma

Poor outcomes in certain subgroups of PTCL after CHT have led to the trend of consolidation with HDT/ASCT [81, 82, 83–84]. In a study by Reimer et al., ASCT used as first-line therapy in patients with PTCL showed that estimated 3-year OS and PFS were 48 and 36%, respectively. The estimated 3-year OS was 71% for patients who underwent HDT/ASCT compared to 11% for patients who did not. Corradini and colleagues studied the role of autologous or allogenic SCT as first-line therapy in newly diagnosed PTCL patients after intensified chemo-immunotherapy with CHOP and alemtuzumab showing that frontline allogenic SCT or ASCT was effective in prolonging disease-free survival in patients <60 years of age. Guidelines for management of PTCL by British Committee for Standards in Haematology (2011) recommend consideration for consolidation with HDT/ASCT (grade C). Prior to 2009, CHTs were the only options for R/R PTCL, other than hematopoietic transplants. However, chemotherapy only improves survival by about 1 month compared with palliation [85]. Four additional drugs are now approved in the USA to treat R/R PTCL, and these include pralatrexate, romidepsin, belinostat, and BV. Response rates with pralatrexate, romidepsin, and belinostat range from 25 to 54% in mixed R/R PTCL populations [86], while 86% of ALCL patients respond to BV [87]. Extranodal NK/T-cell lymphoma (ENKL), nasal type, is associated with Epstein-Barr virus (EBV) and has poor prognosis. Localized disease is treated with combination of chemotherapy and radiation therapy, and the asparaginase-containing dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide (SMILE) regimen is recommended for induction with advanced or R/R disease followed by ASCT or allo-SCT [88, 89].

Conclusion

The use of HDT with autologous rescue remains very important in the treatment of R/R lymphoma. High-dose consolidation advantage is seen in the form of longer EFS, PFS, higher cure rates, and OS [53]. The role of novel agents to improve disease-related parameters remains under vigorous testing either in the frontline induction, disease salvage, and high-dose consolidation or in maintenance setting. Some variations of commonly used BEAM conditioning regimens were studied such as in Visani et al.'s phase I/II study looking at bendamustine, etoposide, cytarabine, and melphalan (BeEAM) conditioning [90]. In a study by Ramzi et al., oral lomustine in place of bendamustine (CEAM conditioning) was used [91]. High-dose thiotepa, etoposide, and carboplatin combination was also studied (2012) in high-risk lymphoma as a form of conditioning prior to ASCT, and an OS rate of 79.3% with a 5-year survival of 77.6% [92] was found. The CORAL cohort was once again analyzed in 2016 by Van Den Neste et al. [93•], and they found three independent factors predictive of improved outcomes (low to low-intermediate tertiary International Prognosis Index (tIPI) at relapse, progression after more than 6 months from ASCT, and chemosensitivity to third-line salvage). One salvage modality with ongoing interest is allo-SCT in patients who relapse after ASCT; the advantage of graft versus tumor (GvT) effect is undeniable, but the procedure has higher non-relapse mortality (NRM). Advances in understanding about disease biology and use of molecular technology such as gene expression profiling (GEP) have enabled better understanding and characterization of distinct molecular subtypes, i.e., germinal center B-cell-like (GCB) and activated B-cell (ABC).

Promising novel agents are on the horizon; the list includes, but not limited to, lenalidomide, ibrutinib, bortezomib, CAR T-cells, ADC antibodies, Bi-specific antibodies, immune checkpoint inhibitors like PD1 and PD-L1, CTLA4-blocking antibodies, and many more under investigation. With the continuous refinement of targeted, personalized agents, it is foreseeable that outcomes for patients with aggressive lymphoma will continue to improve.

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Compliance With Ethical Standards

Conflict of Interest Umar Zahid, Faisal Akbar, Akshay Amaraneni, Muhammad Husnain, Onyee Chan, Irbaz Bin Riaz, Ali McBride, and Ahmad Iftikhar each declare no potential conflicts of interest.

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