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A review of autologous stem cell transplantation in Lymphoma

Umar Zahid, MD[1], **Faisal Akbar, MD**[2], **Akshay Amaraneni, MD**[3], **Muhammad Husnain, MD**[4], **Onyee Chan, MD**[5], **Irbaz Bin Riaz, MD, MSCE**[6], **Ali McBride, PharmD, MS**[7], **Ahmad Iftikhar, MBBS**[8], and **Faiz Anwer, MD, FACP**[9]

[1]Department of Medicine, University of Arizona, Tucson, Arizona. Graduate Student, College of Public Health, University of Arizona, Tucson, Arizona

[2]Department of Medicine, Wake Forest Baptist Medical Center, Winston Salem, North Carolina

[3]Department of Medicine, Hematology and Oncology, University of Arizona, Tucson, Arizona

[4]Internal medicine Residency program, Department of Medicine, University of Arizona, Tucson, Arizona

[5]Department of Medicine, Hematology and Oncology, University of Arizona, Tucson, Arizona

[6]Department of Medicine, University of Arizona, Tucson, Arizona

[7]College of Pharmacy, University of Arizona, Tucson, Arizona

[8]Research Volunteer, Department of Hematology and Oncology, University of Arizona, Tucson, Arizona

[9]Department of medicine, Hematology Oncology and Arizona Cancer Center, University of Arizona, Tucson, Arizona32

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

Corresponding Author: Faiz Anwer MD, FACP, Department of Medicine, Division of Hematology, Oncology, Blood & Marrow Transplantation, Multiple Myeloma Program. University of Arizona, Tucson, AZ, 85721, Phone: 520-626-3191, Fax: 520-626-8944, anwerf@email.arizona.edu.

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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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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

Introduction

In 2016, approximately over 80,000 cases of lymphoma were diagnosed in the United States 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 R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) [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. (1995) 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 [5,7]. In a study of chemosensitive HL patients in their first relapse, by Schmitz et al. (2002) showed 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 [8,9] but without OS advantage. For high-risk HD in the primary refractory setting, tandem transplant has been evaluated with limited success [10].

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. (2012), 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% [11]. Transplantation in first complete response (CR1) also appears to have better progression free survival (PFS) and OS [12]. In a T cell lymphoma study by Beitinjaneh et al. (2015) patients received ASCT or allogeneic transplant (Allo-SCT) in frontline setting and 76 patients received transplants after first relapse. The ASCT patients received BEAM (carmustine, etoposide cytarabine, and melphalan) 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 [13,14] as well as tandem transplantation [15] for aggressive lymphoma. In a study by Taverna and colleagues (2016) relapse prevention strategies after ASCT consolidation were reviewed in great detail [16]. 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. Diffuse large B-cell lymphoma (DLBCL) being the most common subtype [17]. 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 patient with Burkitt lymphoma [17]. While over 50% of patients with DLBCL can be cured with R-CHOP chemotherapy, another 30–40% can develop R/R disease [18]. Induction therapy for patients with DLBCL mainly is R-CHOP [19]. 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 DA-EPOCH-R (dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab). In a study by Wilson et al. (2012), investigators compared R-CHOP and DA-EPOCH-R in a phase II study and found DA-EPOCH-R compared favorably with R-CHOP especially for the treatment of germinal center B-cells (GCB) DLBCL [20]. A Phase III study (n=524) presented at 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 [21].

Role of Upfront high dose consolidation with ASCT for aggressive B Cell lymphoma—Stiff and colleagues (2013) explored HDT/ASCT as consolidation therapy for aggressive NHL patients (high-intermediate/high-risks 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 [22]. In a prospective study by Tarella et al. (2007) with 112 DLBCL patients with aaIPI score of 2 to 3 who received HDT/ASCT found over 80% of patients reached clinical remission with a 4-year OS projected at 76% and EFS of 73% [23]. A phase II study performed by Vitolo et al. (2009) compared the addition of rituximab to HDT/ASCT to those without rituximab in patients with untreated, IPI high-intermediate/high-risks DLBCL and found 4-year OS were 80% and 54%, respectively [24]. Kim et al. (2016) published a retrospective study to assess the effect of upfront ASCT in patients with advance-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 [25]. 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 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 [26]. This is a rapidly evolving area and future research studies will help clarify indications for frontline consolidation [27,28].

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 a significant 5-year OS benefit (53% vs. 32%, P = 0.038) in patients who were chemotherapy-sensitive and received consolidation with ASCT compared to those without consolidation [3]. DHAP (dexamethasone, high-dose cytarabine, and cisplatin) ST was used prior to consolidation. Studies using various ST regimens such as R-DHAP (rituximab plus DHAP) [29], ICE (ifosfamide, carboplatin, and etoposide) [30], R-ICE (rituximab plus ICE) [31], GDP (gemcitabine, dexamethasone, and cisplatin) [32•] and R-GEMOX (rituximab, gemcitabine, and oxaliplatin) [33] 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. (2011) showed cell-of-origin (COO) influence response to ST and specifically they found R-DHAP is superior to R-ICE in GCB subtype DLBCL [34]. In a study by Crump et al. (2014), GDP was found to be non-inferior to DHAP in terms of response and survival rates with less toxicity [32•].

Conditioning regimen and its impact on outcome is an area of great interest [35]. Historically, BEAM (BCNU, etoposide, cytrabine, melphalan) regimen is commonly used in USA. A study by Chen et al. (2015) with 4917 patients and their HDT regimens included BEAM, CBV^{low} (cyclophosphamide, carmustine less than 300 mg/m2, and etoposide), CBV^{high} (carmustine greater than 300 mg/m2), and Bu/Cy (busulfan and cyclophosphamide) prior to ASCT [36•]. In patients with DLBCL, CBV^{high} had worse outcomes compared to the other regimens and also had increase rates of toxicities such as Idiopathic pulmonary syndrome (IPS). Another study combined a radioactive conjugate B-BEAM (iodine-131 tositumomab and BEAM) and compared it to R-BEAM (rituximab plus BEAM) and found a similar 2-year PFS and OS in patients with chemotherapy-sensitive relapsed DLBCL [37]. A meta-analysis by Auger-Quittet et al. (2014) looking at Z-BEAM (Zevalin (yttrium-90 ibritumomab tiuxetan)) showed a 2-year OS of 84.5% [38].

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* 27 detected by FISH, or Cytogenetics) is termed Double-hit (DT) or Triple-hit (TH) (for three rearrangements) lymphoma, and have poor prognosis with R-CHOP induction (median OS 12 months or less). Role of intensive induction such as R-CODOX-M/IVAC (rituximab, cyclophosphamide, vincristine, doxorubicin, methotrexate/ifosfamide, etoposide cytarabine), R-Hyper CVAD/MA (rituximab, cyclophosphamide, vincristine, doxorubicin, dexamethasone/methotrexate, cytarabine) DA-EPOCH-R (Rituximab with dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) and high dose consolidation was explored in a retrospective study by Petrich et al. (2014). DA-EPOCH-R resulted in significantly higher rates of CR and with respect to R-CHOP, intensive regimens showed significantly improved PFS. Those patients who achieved CR to frontline therapy, median OS was similar for observed vs consolidation SCT of any type (median OS not reached; P = .14) [39]. In a study by Landsburg et al. (2016) patients who were not treated with intensive induction, they

appear to benefit from high dose consolidative ASCT, while patients who receive intensive induction did not show benefit from upfront consolidative ASCT [40].

Role of upfront ASCT with HDT for Mantle cell lymphoma (MCL)—Intensive induction and upfront consolidation is routinely offered to patients with aggressive MCL. Dreyling et al. (2005) reported data on prospective randomized study with advanced MCL cohort and after induction with CHOP like regimen; patients received either HDC/ASCT or received maintenance with interferon (IFN). Patients in the HDC/ASCT arm who got chemotherapy based mobilization and total body irradiation (TBI) 12 Gray (Gy)/Cy (cyclophosphamide) based pre-transplant conditioning experienced a significantly longer PFS (median of 39 months vs. 17 months) [41]. A long-term follow-up of this study was reported at ASH 2009 by Hoster, et al (2009) that included the Dreyling et al. (2005) trial and two other trials studying Mantle cell patients. They evaluated 180 patients with MCL, 80 treated with R-CHOP, 78 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, median follow up duration was 63 months. Median overall survival was 54 months with CHOP without ASCT, 66 months after R-CHOP without ASCT, 90 months after CHOP with ASCT, and median OS was not reached in R-CHOP with ASCT with the hazard ratio for OS for rituximab was 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 [42]. Hermine et al. (2016) randomized 500 MCL patients to R-CHOP vs R-CHOP alternate with R-DHAP and showed better disease control in cytarabine containing induction group after six-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 [43]. Nordic Lymphoma Group MCL2 study updated results (2012) of upfront intensive induction and ASCT using BEAM or BEAC (carmustine, etoposide, araC, cylcophosphamide) regimen showed median EFS of 7.4 years but ongoing relapse were reported beyond 5 years [44].

B. Hodgkin lymphoma (HL)

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 United States and 1120 were expected to die of disease [1]. Approximately 80% cases of newly diagnosed HL are curable with combination chemotherapy ABVD (Doxorubicin, Bleomycin, Vinblastine, Dacarbazine) followed by 20–30 Gy involved field radiation in selected subset of patients [45]. Despite highly active frontline treatment, 5–10% of HL patients are primary refractory or 10–30% HL patients relapse after achieving an initial CR [46].

Role of Upfront Consolidation in Hodgkin Lymphoma—In a study by Federico, M. et al. (2003) [9], the role of HDT (BEAM and CVB) followed by ASCT vs. CHT (four additional courses of the same CHT used in induction phase) as frontline therapy for advance HL patient (according to Strauss-derived system) was evaluated [47] and found no benefit of early intensification with HDT/ASCT. In a study by Carella, A.M. et al (2009) [48], the results of extended follow up of above mentioned study showed 10-year OS were

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). 10-year relapse free survival (RFS) and failure free survival (FFS) were 88% (95% CI, 81–95), 79% (95% CI, 72–85) vs. 89% (95% CI, 83–93), 75% (95% CI, 67–82) for HDT/ASCT and CHT respectively (p=0.7–0.8). Authors concluded that 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 (ST) for relapsed Hodgkin Lymphoma—ST followed by HDT/ASCT has been the standard of care for R/R HL. Outcome of consolidation ASCT depends on response to ST, assessed by 18F-fluorodeoxyglucose (FDG) PET/CT scan. Pre-transplantation PET negativity is one of the strongest predictor of HDT/ASCT outcome [49]. Choice of optimal ST is unclear and is chosen on the bases of individual patient [50•]. Salvage ICE has shown overall response rate (ORR) of 80% and CR of 50% [51]. Other options for ST include DHAP and ESHAP (etoposide, methylprednisolone, high dose ara-C, cisplatin) with comparable responses to ICE chemotherapy. GVD (gemcitabine, vinorelbine, and doxorubicin) showed ORR of 70% with 19% CR [52]. IGEV (ifosfamide, prednisolone, gemcitabine, and vinorelbine) demonstrated ORR 81.3% with 54% CR and 27.5% PR [53].

Two landmark RCTs, the British National Lymphoma Investigation (BNLI) in 1993 [54] 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/m2 carmustine) followed by ASCT vs. CHT (mini-BEAM: 60 mg/m2 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. In a meta-analysis of above two trials by Rancea et al. (2013) [55] 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 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 = .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 conditioning regimen since HDT/ASCT showed superiority over CHT in R/R setting [4,54]. Prior studies showed that higher doses of BCNU increase risk of pulmonary toxicity as high as 35% [56,57]. In an effort to reduce pulmonary toxicity, Arai et al. (2010) conducted a phase I/II study of conditioning regimen using gemcitabine along with vinorelbine (gemcitabine maximum tolerated dose 1250 mg/m2) [58]. The incidence of BCNU-related toxicity was 15% with this regimen (CI 9 to 24%). Two-year freedom from progression (FFP) and OS were 71% (CI 6 to 81%) and 83% (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 [36•]. In that study, three-year PFS/OS were 62/79%, 60/73% and 57/68% for BEAM, CBV^{low} and CBV^{high} respectively. IPS incidence after one

year of ASCT was 3% for BEAM/CBV^{low} and 6% for CBV^{high}. In a prospective study by Musso et al. (2016), conditioning with FEAM (fotemustine substituted for BCNU, etoposide, cytarabine, melphalan) for R/R HL [59] 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 was no reported pulmonary toxicity, hepatic/renal adverse events or secondary malignancies.

Role of Tandem ASCT for Relapsed Hodgkin Lymphoma—In H96 trial by Morschhauser et al. (2008) [10], which looked at the risk adopted ST with single or tandem ASCT for 245 R/R HL patients, randomized to poor risk group (n 150, intensified ST and double ASCT) and intermediate risk group (n 95, standard ST and HDT/ASCT). Intent 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 compares favorably with the previously reported OS of 30%. In 2016, 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 [60]. Tandem ASCT remains an option for poor risk patients but more prospective studies need to look at this strategy with use of PET CT imaging.

Role of antibody drug conjugate Brentuximab vedotin (BV) 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 study by Moskowitz et al. (2015) 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 [61]. In study by Chen et al. (2015), BV was used as second line agent prior to ASCT (n 37, R/R HL) and showed ORR of 68% (13 CR, 12 PR), and 32 patients (86%) proceeded to ASCT [62]. In AETHERA trial (2015), a cohort of 329 patients with R/R HL was randomized to receive HDT/ASCT followed by maintenance BV treatment (n 165) or to placebo group (n 164). BV significantly improved post-transplantation PFS (HR .57; 95% CI, .40 to .81; P = .001). Median PFS by independent review showed significant improvement with BV treatment versus placebo (42.9 versus 24.1 months, P = .0013). Two-year PFS rates were 63% versus 51%, respectively [63].

Role of Checkpoint inhibitors—Programmed death 1 (PD1) is an inhibitory regulator of T-cell activation and function [64]. HRS cells express high levels of PD1 ligands (PD-L1 and PD-L2) which after engaging with PD-1 receptor on activated T-cell lead to decrease 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 dose of 3 mg/kg every 2 weeks, 24 weeks PFS was 86% and ORR was 87% (CR 17%, PR 70%, 95% CI = 66% to 97%) with median follow up of 40 weeks [65]. In a Phase I study of Pembrolizumab for relapsed HL [66], 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 [67,68]. A follow up multi-center Phase II study (KEYNOTE-087) was presented at ASH 2016 in 210 patients with R/R disease that included 3 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 [69]. Patient treated with Nivolumab enrolled in CheckMate study showed ORR of 66% (PR 57.5%, CR 8.8%), with a six- month PFS of 77% [70]. The Keynote study with Pembrolizumab randomized R/R HL to 2 cohorts and ORR was 70% (CR 20%, PR 50%) and 80% (CR 27%, PR 53%) for Cohort 1 and 2 respectively [71]. The response rate with Nivolumab for HL patients who progressed after auto SCT and BV was replicated in other trials as well [72,73].

C. Peripheral T-Cell Lymphoma (PTCL) and Natural Killer/T-Cell Lymphoma (NKTCL)

PTCL either arises from clonal proliferation of mature post-thymic T cells [74] or mature skin resident T cells [75], nearly all PTCL will express a T-cell receptor (TCR). PTCLs tend to be aggressive lymphomas with very poor prognosis. PTCL-NOS or angioimmunoblastic T-cell lymphoma (AITL) have the worst prognosis with 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, have an intermediate 5-year OS (49%). Reported OS is 42% for Extranodal natural killer/T-cell lymphoma, nasal type (NK/TCL), 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) [76]. 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 depend on the IPI score and type of TCL [77]. 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 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 62 % for CHOP therapy vs 56% for intensive therapy group. The French GOELAMS group (2010) prospectively compared the VIP/ABVD regimen (etoposide, ifosfamide, cisplatine/doxorubicin, bleomycin, vinblastine, dacarbazine) to CHOP but found no difference in terms of EFS or OS [78]. The GELA group (2003) RCT comparing standard CHOP to ACVBP (doxorubicine, cyclophosphamide, vindesine, bleomycin, prednisone) 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 [79]. Seven high grade NHL studies by the German study group showed that young good risk patients had improved 3-year EFS (71% vs. 50%) if etoposide was added to CHOP [80]. 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 [81]. 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 [82–85•]. In a study by Reimer et al. (2009), 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 (2014) 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 one month compared with palliation [86]. Four additional drugs are now approved in the US 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 [87], while 86% of ALCL patients respond to BV [88]. Extranodal NK/T-cell lymphoma, nasal type (ENKL) is associated with Epstein-Barr virus (EBV) and have poor prognosis. Localized disease is treated with combination of chemotherapy and radiation therapy and the asparaginase-containing SMILE (dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide) regimen is recommended for induction with advanced or R/R disease followed by ASCT or Allo-SCT [89,90].

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 [54]. 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 variation of commonly used BEAM conditioning regimens were studied such as in Visani et al. (2011) phase I/II study looking at BeEAM conditioning (Bendamustine, etoposide, cytarabine, melphalan) [91]. In study by Ramzi et al. (2012) oral lomustine in place of bendamustine (CEAM conditioning) was used [92]. High dose thiotepa, etoposide and carboplatin combination was also studied (2012) in high risk lymphoma as a form of conditioning prior to ASCT and found an OS rate of 79.3% with a 5-year survival of 77.6% [93]. The CORAL cohort was once again analyzed in 2016 by Van Den Neste et al. [94•] and found 3 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 chemo-sensitivity to third-line salvage). One salvage modality with ongoing interest is allo-SCT in patients who relapse after ASCT, advantage of graft versus tumor (GvT) effect is undeniable but procedure has a higher non-relapse mortality (NRM). Advances in understanding about disease biology, use of molecular technology such as gene expression profiling (GEP) has enabled better understanding and characterization of distinct molecular subtypes i.e. germinal center B-cell-like (GCB), 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, PD-L1, CTLA4 blocking antibodies and many more under investigation. With the continuous refinement of targeted, personalized agents, it is foreseeable that outcomes for patient with aggressive lymphoma will continue to improve.

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References

• Important

•• Very important

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