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High-Dose Chemotherapy and Autologous Stem Cell Transplant in Older Patients with Lymphoma

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Abstract

High-dose chemotherapy followed by autologous hematopoietic stem cell transplant (HDT/ASCT) can improve survival in patients with lymphoma. Limited experience is available on the safety and efficacy of HDT/ASCT in elderly patients. In this article, we review the published data on the role of HDT/ASCT in management of lymphoma in older patients. Based on available data, evaluation of comorbidities, functional status, and comprehensive geriatric assessment (CGA) will help identify those who can benefit most from this intervention. Prospective clinical trials focusing on HDT/ASCT in older patients with lymphoma are needed to establish optimal management protocols in this select population.

Keywords

Lymphoma; Autologous; Hematopoietic; Stem; Cell; Transplant; Rescue; Elderly; Bone marrow; Aging

Introduction

As the global population is aging, the proportion of elderly patients with lymphoma has increased. It is projected that the incidence of lymphoma in individuals over 65 years of age in the USA will increase from 2010 to 2030 about 70 % for Hodgkin lymphoma (HL) and 67% for non-Hodgkin lymphoma (NHL) [1]. As such, it is essential to tailor optimal therapeutics in this age group.

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Compliance with Ethics Guidelines

Conflict of Interest Oscar B. Lahoud, Craig S. Sauter, Paul A. Hamlin, and Parastoo Bahrami Dahi declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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History of Autologous Stem Cell Transplant (ASCT) in Lymphoma

Initial use of high-dose chemotherapy (HDT) followed by autologous bone marrow cells for lymphomas was reported in 1959 and 1960s [2–5]. In 1978, investigators at the National Cancer Institute reported successful treatment of resistant malignant lymphoma and Burkitt's lymphoma with HDT and autologous stem cell transplant (ASCT) [6, 7]. HDT/ASCT as a successful treatment for patients with relapsed HL was first reported in the 1980s [8–10]. Subsequently, two randomized trials showed an improvement in disease-free survival in patients with relapsed or refractory HL who underwent HDT/ASCT compared to further conventional therapy [11, 12]. In NHL, HDT/ASCT has become the standard of care for management of relapsed or refractory aggressive lymphomas [13–15], or as consolidative treatment in first remission for mantle cell lymphoma [16–22] and T cell lymphoma [23–26]. Most studies of HDT/ASCT in lymphoma, however, have been performed on patients under the age of 60 years. Consequently, safety and efficacy of HDT/ASCT are not well established in the older age group.

The Center for International Blood and Marrow Transplant Research (CIBMTR) has reported a marked increase between 1994–1995 and 2004–2005 in the number of ASCT performed in North America from 2573 to 3164 for NHL and from 906 to 1302 for HL [27]. Interestingly, the proportion of patients 60 years of age or older who underwent ASCT during the same period rose from <7 % to 35 %, with among them, an increase in those who are at least 70 years old <1 % to 5 %. This increase may reflect changing demographics, as well as improved access and safety of HDT/ASCT in this population.

In this article, we review the published data on the use of HDT/ASCT in older patients with lymphoma, focusing on patient selection, treatment outcomes, and toxicities.

Patient Assessment and Prognostic Tools

There are no established eligibility criteria for HDT/ASCT, but overall age, functional status, comorbidities, and psychosocial support are the most important factors we tend to consider when evaluating a patient for HDT/ASCT, especially in the elderly [28].

Different prognostic tools have emerged to help predict transplant outcomes in patients with lymphoma. In HL, adverse outcomes have been identified to be associated with short remission duration (<12 months), extranodal disease, primary refractory disease, B symptoms, bulky disease at diagnosis, and detectable disease at transplantation [29–31]. Pretransplant functional imaging status has been identified as an independent predictor of outcome [32–34]. In NHL, chemosensitivity prior to HDT-ASCT carries the largest prognostic relevance [35, 36].

International Prognostic Index (IPI)

The International NHL Prognostic Factors members identified five independent factors at diagnosis that could affect survival in NHL—age >60 years, serum lactate dehydrogenase (LDH) greater than upper limit of normal, performance status (PS) >2, Ann Arbor Stage 3 or 4, and extranodal involvement—to create the International Prognostic Index (IPI) scoring system, which became the backbone for trial designs and selected therapeutic interventions

in NHL [37]. In the same study, a simplified model for younger patients factoring stage, serum LDH and PS only, referred to as age-adjusted IPI (aa-IPI) was found to be predictive of response and survival outcomes in patients 60 years or less. Gradually, specific scoring systems have been developed for various NHL subtypes, including the follicular lymphoma IPI (FLIPI) score [38] and the mantle cell lymphoma IPI (MIPI) score [39]. Moreover, the IPI scoring system was first revised to account for the improvements in immunochemotherapy in the rituximab era into the revised IPI (R-IPI) [40] and was further enhanced in recent years by the National Comprehensive Cancer Network (NCCN-IPI) [41]. All of these scoring systems incorporate age as a contributing factor to poor prognosis, with the MIPI and NCCN-IPI attributing up to 3 additional risk points for each age bracket, respectively.

Age

In view of the importance of age in prognosticating outcomes in NHL, the US Intergroup Study E4494 investigated the significance of age within an older population of NHL patients over 60 years old treated with Rituximab-CHOP (R-CHOP), in order to ultimately generate an elderly IPI (E-IPI) with 70 years as the cutoff point for the IPI [42].

All these scoring systems emphasize the prognostic value of age to predict outcome of patients with NHL at presentation. Hamlin et al. evaluated the role of the IPI and age-adjusted IPI at the initiation of second-line therapy (sIPI and sAAIPI, respectively) as predictors of ASCT outcomes in 150 patients with relapsed and primary refractory DLBCL [43]. Patients were between 16 and 86 years of age (median 49 years old), and 25 of them were 60 years or older; all 150 patients received salvage chemotherapy with ifosfamide, carboplatin, and etoposide (ICE), and 108 (72 %) responded to treatment. Interestingly, when the components of the sIPI were assessed in univariate analysis by log rank, age was not predictive of PFS, whereas extranodal status, PS, LDH, and stage predicted both PFS and OS. In a multivariate analysis using a Cox regression model, only 3 factors, PS, LDH, and stage, remained predictive by intent to treat. Accordingly, the sAAIPI was predictive of both PFS and OS, but generated similar outcomes in the high-intermediate and high-risk groups, which were therefore united into one faction, ultimately resulting in the identification of three distinct risk categories: low risk (0 factor), intermediate risk (1 factor), and high risk (2 or 3 factors). These data allow us to risk stratify patients with NHL being evaluated for HDT/ASCT irrespective of age, with estimated 4-year PFS and OS of 70 and 74 % in low-risk, 39 and 49 % in intermediate risk, and 16 and 18 % in high-risk sAAIPI, respectively [43]. The clinical impact of sAAIPI was confirmed in the prospective multicenter CORAL trial where 398 patients aged 19 to 65 with relapsed DLBCL underwent HDT/ASCT [44]. In that study, sAAIPI score (low-to-intermediate vs high-risk) was one independent factor affecting response rate (70 vs 51 %, $p < 0.001$), 3-year event-free survival (EFS) (40 vs 18 %, $p < 0.001$), PFS (data not shown), and OS (62 vs 32 %, $p < 0.001$).

HCT-CI

The Hematopoietic Cell Transplantation Comorbidity Index (HCT-CI) was designed to assess patients undergoing allogeneic stem cell transplant with respect to their pulmonary, cardiac, hepatic, and renal function, taking into account a history of prior malignancy,

psychiatric disturbances, peptic ulcer disease, autoimmune, or other inflammatory conditions (e.g., infection, obesity) and with its overall score being predictive for nonrelapse-related mortality and survival [45, 46]. It was subsequently investigated as a potential prognostic value for HDT/ASCT eligibility and outcome in patients with relapsed or refractory aggressive NHL in a Dutch study [47], which showed that high HCT-CI scores at relapse were associated with significantly less chance of ultimately receiving ASCT and inferior OS. Notably, the study also reproduced the results obtained by Hamlin et al. [43], confirming the role of sAAIPI scores at predicting OS, with similar 5-year OS of 62, 30, and 17 % for the low, intermediate, and high risk, respectively.

Geriatric Assessment

In the elderly patients, some characteristics not taken into account within the above scoring systems but present in other tools, such as the Comprehensive Geriatric Assessment (CGA), may impact feasibility of HDT/ASCT and outcomes and could potentially be utilized to identify elderly-frail patients at higher risk of post-HDT/ASCT mortality [48]. By evaluating cognitive status, socioeconomic issues and support, depression, polypharmacy, nutrition, ability to perform specific daily tasks independently, comorbidities, and other geriatric syndromes, the CGA may help recognize the older patients who are at increased risk for morbidity, mortality, and chemotherapy toxicity [49, 50]. Although the CGA has yet to be validated in this setting, a multidisciplinary team approach that includes a geriatrician, nutritionist, pharmacist, social worker, psychiatrist/psychologist in addition to the hematology/transplant team might ultimately be of benefit when evaluating older patients for HDT/ASCT [51].

Stem Cell Mobilization and Conditioning Prior to ASCT

Stem Cell Mobilization and Collection

Hematopoietic stem/progenitor cell (HSPC) mobilization is achieved either using cytokine-alone or cytokine following myelosuppressive chemotherapy (chemo-cytokine mobilization) to increase the circulating HSPC. Chemo-cytokine mobilization results in superior HSPC yields overall [52–54]. Two randomized trials show that autologous peripheral blood HSPC are associated with more rapid engraftment and have a similar treatment outcome when compared to bone marrow-derived HSPC [55, 56]. The relative ease of collecting peripheral blood-derived HSPC has made this the standard collection approach.

Both filgrastim (10 mcg/kg daily) and Pegfilgrastim have been used in successful mobilization. Numerous groups published equivalent mobilization efficiency between a single injection of 6 or 12 mg pegfilgrastim compared with multiple daily doses of filgrastim when these agents are used after mobilizing chemotherapy [57–59]. Plerixafor, the CXCR4 antagonist, provides a promising chemotherapy-free mobilization regimen that improves the rates of successful mobilization in older adults over granulocyte colony-stimulating factor alone [60].

Although HSPCs tend to increase and persist throughout life via self-renewal mechanisms, emerging preclinical studies suggest that they are impacted by aging, with aging-associated

dysfunction through various intrinsic and extrinsic molecular mechanisms within the stem cell niche resulting in altered HSPC self-renewal, heterogeneity, differentiation, localization, polarization, and other regulatory pathways [61]. These changes may lead to clinical differences in hematopoietic cell mobilization and engraftment between older and younger patients. In a French retrospective study, lymphoma patients over 65 years of age yielded a statistically significant lower number of CD34-positive cells/patient than their younger counterpart as well as a lower number of CD34-positive cells harvested/apheresis [62]. However, in both groups, a similar rate of successful harvesting was achieved, as the number of CD34-positive cells collected in the elderly population was sufficient to perform one or more ASCT. A new strategy aimed to optimize the mobilization of HSPC has been the upfront use of plerixafor, a CXCR4 antagonist, with granulocyte colony stimulating factor (G-CSF) in patients over 60 years of age, which was shown a significantly higher number of elderly patients achieving target stem cell collection in the plerixafor+G-CSF compared to G-CSF+placebo [60]. Treatment was well-tolerated and resulted in similar efficacy as in the younger age group.

Data suggest that increasing age seems to have limited impact on the phenotype and functional in vitro and in vivo properties of human HSPCs. One study by Woolthuis et al. compared in vitro function of CD34-positive cells derived from young (<35 years) and older (>60 years) adult bone marrow and demonstrated no functional differences [63]. In the same study, hematopoietic regeneration was compared between 64 patients aged 50 years or less with 55 older patients at least 60 years old after ASCT. Although mobilization, apheresis yield, colony-forming potential, and short-term regeneration did not differ significantly between younger and older patients, complete recovery of all three hematopoietic cell lineages 1 year after transplantation was much lower in the elderly, with only 29 % achieving full count recovery compared to 56 % in younger patients ($p=0.009$). When evaluated for other potential confounding factors, age at transplantation and diagnosis were the only independent prognostic variables for complete recovery of peripheral blood counts 1 year after ASCT.

Time to neutrophil engraftment, antibiotic use, and length of hospitalization are similar for younger and older patients undergoing ASCT for lymphoma [64–67]. One notable exception is platelet count recovery, which may be slightly delayed in older patients with lymphoma [65, 67].

Conditioning Regimen

Conditioning regimens prior to ASCT are used for tumor cytoreduction and ideally disease eradication. The choice of regimen has been based on institutional experience, and several regimens are considered standard and routinely used for patients with lymphoma. There have been efforts to develop nontotal body irradiation (TBI)-containing transplant regimens to avoid short-term and long-term risks associated with TBI, including fatigue, nausea, vomiting, parotiditis, xerostomia, xerophthalmia, mucositis, esophagitis, diarrhea, alopecia, organ toxicities, interstitial pneumonitis, cataracts, sterility, second malignancies, and myelodysplasia [68–70].

BEAM (carmustine, etoposide, cytarabine, and melphalan) and CBV (cyclophosphamide, carmustine, and etoposide) are the two most frequently used regimens for patients with lymphoma undergoing ASCT. Studies have reported lower risk of progression and longer survival associated with use of BEAM versus CBV [71, 72]. Low rates of transplant-related morbidity (TRM) rate have been reported with BEAM [73].

Similarly, a conditioning regimen with dose-reduced busulfan and cyclophosphamide appeared to be well tolerated in 34 patients with relapsed NHL who were at least 60 years old and underwent HDT/ASCT at the Massachusetts General Hospital [74]. None of these patients experienced early TRM, and the 2-year OS and PFS were 67 and 54 %, respectively. Other investigators have used myeloablative radioimmunotherapy with or without chemotherapy and have shown these modalities to be safe and effective in older patients with NHL [75, 76].

As seen in Table 1, various transplantation modalities have been used, with various efficacy and tolerability. The optimal conditioning regimen in older lymphoma patients has yet to be identified, and prospective comparative trials are lacking.

Toxicities of HDT/ASCT in Older Patients with Lymphoma

Each HDT regimen is associated with its own unique toxicities. Commonly seen are hematologic, gastrointestinal, and cardiopulmonary toxicities causing infection, bleeding, nausea, vomiting, diarrhea, mucositis, arrhythmia, and pneumonitis. Older adults may be at greater risk for some toxicities, such as gastrointestinal complications (45 vs 23 %; $p=.06$) after ASCT [66]. One particular concern in this population is an increased risk for cardiovascular toxicity. In an Australian retrospective study of recipients of HDT/ASCT for multiple myeloma and NHL, 40 patients aged 60 or above were compared to younger controls [64]. While all other clinical outcomes and toxicities were similar and treatments were overall well tolerated in both groups, there was a markedly increased rate for grade 3 or 4 cardiovascular toxicities in the older population, with 50 % of patients affected, compared to only 10 % in the younger group ($p<0.0001$). The most common grade 3 or 4 cardiovascular toxicities in the older patients were atrial fibrillation (9/40), followed by hypotension (7/10) and edema (4/40). Of note, in this study, 14 (35 %) patients in the older group had pre-existing cardiac comorbidities compared to only 7 (17.5 %) patients in the younger group, but this baseline disparity was not found to be statistically significant ($p=0.075$) though a trend was appreciated. Out of these 14 older patients with pre-existing cardiac condition, 3 of them already had atrial fibrillation. These few discrepancies in baseline characteristics, however, certainly cannot fully account for the difference in cardiovascular complication rates of HDT/ASCT between the elderly and younger patients. Older patients should be aware for their increased risk for cardiac toxicities with HDT/ASCT, with atrial fibrillation being the most common grade 3 or 4 cardiovascular complication. However, these age-related increases in toxicities have not been reported across all studies.

Similarly, other complications may be more common in older adults with lymphoma who undergo ASCT, such as nausea, mucositis, and neurologic complications may be more

frequent; however, not all studies have consistently shown an increased risk for these complications [64–67]. Infections, sinusoidal obstruction syndrome, and pneumonitis, which were major concerns in earlier studies, are not more frequent in recent studies of older patients with lymphoma [64–67].

Outcomes of HDT/ASCT in Older Patients with Lymphoma

The outcomes of HDT/ASCT in elderly patients with lymphoma have essentially been reported in retrospective series. Table 1 summarizes the clinical data from 26 of those studies. The largest studies are those from the CIBMTR program [14], the European Blood and Marrow Transplant (EBMT) registry [88], the Transplant Registry Unified Management Program (TRUMP) registry database of the Japanese Society for Hematopoietic Cell Transplantation [92•], and Memorial Sloan Kettering (MSKCC) database [93•]. In these studies, the cutoff age used to define elderly population is heterogeneous, with minimum age set as low as 55 [14] and as high as 69 or 70 [89, 90].

Transplant-Related Mortality

Early studies suggested that older adults undergoing ASCT were at greater risk for transplant-related mortality (TRM) with estimated 1-year TRM for older patients (age ≥ 55 years) to be 25 to 38 % [96–98]. However, these older studies frequently included patients who were conditioned with high-dose TBI. With the adoption of better supportive care and reduction in the use of TBI-based conditioning, TRM rates for older adults undergoing ASCT have substantially improved (Table 1). The researchers from CIBMTR compared patients with NHL who are at least 55 years of age with those under 55 undergoing HDT/ASCT [14]. In this large database, with a TRM of 15 %, the older patients with aggressive NHL were 1.86 times more likely to experience TRM than their younger counterparts with similar aggressive pathology (95 % confidence interval [CI] 1.43–2.43, $p < 0.001$). Likewise, the relative death risks were higher in the older group for both low grade and aggressive NHL subtypes. The authors reported that the impact of age on disease-related outcomes appeared to remain the same when cutoff age was set at 60 years old or more for the older population. Within the older population, conditioning with TBI and use of peripheral blood as source of HSPC resulted in higher early TRM compared with non-TBI containing conditioning regimens and bone marrow source of HSC, respectively. Taken together, these data suggest that although older patients might appear to be at increased relative risk for TRM, the absolute TRM risk remains somewhat small in light of potentially curative therapy.

Recent studies report 1-year TRM rates for older patients (age ≥ 55 years) of 4 to 12 %, which are similar or slightly higher than those reported for younger patients. [13, 14, 64–66, 87, 88, 91•]. These studies suggest that risk factors associated with increased TRM include poor performance status, high comorbidity index, multiple prior therapies, and advanced or chemotherapy-resistant disease.

In an analysis of 202 patients age 60 or above who underwent HDT/ASCT for NHL, Dahi et al. reported an early TRM (day +100) of 4 % [93•], which is comparable to those reported in other earlier series [66, 87, 88, 91•]. Eight patients (4 %) experienced TRM within the first

100 days after transplantation. Five died from infections and 3 from treatment-related organ toxicity. TRM remained the same at 1 year after HDT-ASCT.

In an analysis of 484 patients aged 60 years or over who received ASCT for relapsed/refractory DLBCL, the nonrelapse mortality (NRM) at day 100, 1 year, and 2 years was 4.1, 5.9, and 7.7 %, respectively [92•]. The major cause of early NRM was infection (11 patients, 55 %), followed by multiorgan failure (5 patients, 25 %), and interstitial pneumonia (3 patients, 15 %). The major cause of late NRM (after day 100) was secondary malignancy (7 patients, 25 %), followed by interstitial pneumonia (5 patients, 18 %), infection (4 patients, 14 %), and hemorrhage (4 patients, 14 %).

In the past decade, the highest reported early TRM of 18 and 19 % was seen in the “very elderly” patients, those over 70 years of age [89, 90]. Andorsky et al. compared patients 65–69 years to those over the age of 70 and found an increased nonrelapse mortality in the older group that was nonstatistically significant at 100 days (17.65 vs 5.13 %, $p=0.0158$) but statistically significant at 1 year (35.29 vs 7.69 %, $p=0.017$) [89]. The most common cause of deaths also differed in both groups, with lymphoma recurrence being the most frequent cause in patients 65–69 years of age (58 %) as opposed to infection in those 70 years or older (27 %). Interestingly, the study highlighted that in-hospital falls were more frequent in older patients (29 vs 8 %) and were associated with higher mortality. This finding not only reinforces the importance of a CGA screening approach as we mentioned above, but also indicates the potential need for ongoing geriatric follow-up and fall prevention. Overall survival was also lower in the older patients (median OS 2.62 vs 6.03 years), but it is difficult to ascertain whether this might only be due to lead-time bias, since the effective median age at death would be estimated around 74.62 years for the older patients versus 73.03 years in the younger group.

Efficacy of HDT/ASCT

Response to HDT-ASCT is dependent on the subtype, stage, and grade of lymphoma [14]. Similar to younger patients, adverse risk factors for OS and PFS in older adults include poor performance status, multiple prior therapies, chemotherapy-resistant disease, high LDH, and male gender [13, 14, 65, 88, 91•]. Some retrospective studies suggest that older adults with NHL undergoing ASCT may have a slightly increased risk of relapse, and modestly decreased OS, or PFS [13, 14, 88], although these findings have not been demonstrated in all studies [65, 91•]. Dahi et al. demonstrated that HDT/ASCT is safe and effective in select older patients with a 3-year OS and PFS of 73 and 60 %, respectively [93•]. Other groups have reported similar results on elderly patients undergoing HDT/ASCT [87, 88, 91•]. Chihara et al. ($n=484$) showed a 2-year PFS and OS of 48 and 58 %, respectively [92•].

Taking all studies together (Table 1), HDT-ASCT in older patients with NHL was generally feasible, well-tolerated and effective therapeutically. These data suggest that HDT/ASCT in some elderly patients with lymphoma might improve survival. However, prospective clinical trials to formally assess this are lacking.

The data supporting HDT/ASCT in older patients with HL is much more limited. Although some of the studies mentioned above and in Table 1 occasionally included few patients with

HL, there has only been one single-institution Canadian retrospective study focusing specifically on this population [67]. Puig and colleagues identified 15 patients with chemosensitive relapsed/refractory HL 60 years or older, who received conditioning with melphalan and etoposide followed by ASCT. When compared to a matched younger cohort, the 3-year PFS and OS were similar in both groups (73 and 88 %, respectively, in older group; 56 and 84 % in younger group; $p=0.45$ and $p=0.80$, respectively). TRM was not seen in any patients in the study. This suggests that HDT/ASCT is feasible in older patients with HL, possibly leading to similar outcomes as in younger patients.

Conclusion

This review aims to summarize the role of HDT/ASCT in management of older patients with lymphoma. While there is extensive data demonstrating survival benefit in younger patients with NHL and HL, the evidence supporting its use in the elderly is limited. Pretransplant assessment in elderly patients should include evaluation of comorbidity indices such as the HCT-CI and sAAPI, and a CGA. In-hospital falls in individuals older than 70 years of age have been linked to increased mortality after HDT/ASCT. Applying the CGA to older patients undergoing HDT/ASCT was recommended by the National Comprehensive Cancer Network (NCCN) in recently published guidelines [99••]. Preclinical and clinical studies suggest that older patients do not mobilize as many CD34-positive stem cells as younger patients. However, this does not appear to clinically impact the success rate of apheresis. In addition, G-CSF with plerixafor was shown to further enhance HSPC collection when compared to G-CSF with placebo. There does not appear to be a preferred conditioning regimen or dosing in older patients with lymphoma undergoing HDT/ASCT: BEAM-like conditioning regimens have shown feasibility and tolerability. TBI-based regimens appear to be associated with increased TRM compared with non-TBI containing regimens. Older patients undergoing HDT/ASCT are at a higher risk for grade 3 or 4 cardiovascular toxicity.

Although clinical outcomes reported in older patients may not have been as impressive as those in younger patients, a significant number of elderly patients do appear to tolerate and benefit from HDT/ASCT, with 3-year PFS and OS as high as 60 and 73 %, respectively, in some studies. Although data in older patients with HL is more limited, these patients appear to have similar promising outcomes as younger patients. As the population ages and novel targeted therapies emerge, the optimal management approaches for older patients with lymphoma considering HDT/ASCT have yet to be identified. Prospective, phase III clinical trials are lacking, and additional studies examining this growing patient population further are needed.

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Table 1

Studies of HDT/ASCT in elderly patients with lymphoma

Reference	Patients	Histology, grade	Median age (range)	Conditioning protocol	Early TRM	PFS	OS
Stamatoullas 1997 [77]	13	NHL; HG 2, IG 11	62 (61–72)	BEAM	7.7 %	NA	NA
Moreau 1998 [78]	14	IG or HG NHL	63 (61–65)	BEAM	0	50 % at 3.5 yrs	45.7 % at 3.5 yrs
Leger 2000 [79]	21	LG 4, IG 15	62 (60–73)	CBV; BEAM	10%	NA	67 % at 19 mths
Jantunen 2000 [80]	13	DLBCL 7, MCL 5	63 (60–70)	BEAC; BEAM	8%	NA	62 % at 16 mths
Gopal 2001 [81]	53	DLBCL 29, PTCL 4, MCL 3, LG FL 8, Others HG 8, LG 1	62 (60–67)	Bu/Mel/TT; Cy/TBI +/-VP16; CBV; Bu/Cy; BEAC	9%	24 % at 4 yrs	33 % at 4 yrs
Olivieri 2001 [82]	21	HG NHL 14, LG NHL 6, HL 1	63 (60–78)	BEAM; Mel+other; Bu/Cy; TBI	1.8 %	NA	NA
Zallio 2002 [83]	20	DLBCL 10, FL 4, MCL 3, SLL 3	67 (61–80)	Mel +/- MITOX	5%	51 % at 4.5 yrs	59 % at 5 yrs
Bitran 2003 [84]	11	DLBCL	66 (65–78)	Cy/TBI/VP16; BEAM	9%	44 % at 4 yrs	44 % at 4 yrs
Magagnoli 2003 [85]	12	NHL; stage III–IV 11, stage I 1	65 (60–71)	Mel+other; Mel	0	NA	NA
Villela 2003 [86]	13	NHL	63 (60–71)	BEAM; CBV	0	NA	NA
Buadi 2006 [13]	93	DLBCL 57, MCL 6, T-cell 4, Transformed FL 24, Others 2	66 (60–76.5)	BEAM; BEAC	5.4 %	38 % at 4 yrs	mOS 2 yrs
Jantunen BMT 2006 [66]	88	DLBCL 29, MCL 27, FL 15, PTCL 12	63 (60–70)	BEAM; BEAC; Cy/TBI	11 %	62 % at 2 yrs	63 % at 2 yrs
Gopal 2007 [75]	24	DLBCL 9, MCL 8, FL 6, MZL 1	64 (60–76)	RIT	0	51 % at 3 yrs	59 % at 3 yrs
Hosing 2008 [87]	99	NHL	68 (65–82)	BEAM 90 %; Cy/TBI +/- Rituximab	3%	48–64 % at 3 yrs	61 % at 3 yrs
Jantunen 2008 [88]	463	DLBCL	63 (60–74)	73 % BEAM; others	4.4 %	51 % at 3 yrs	60 % at 3 yrs
Lazarus 2008 [14]	805	173 FL LG	60 (55–72)	BEAM/BEAC; TBI; Cy/VP16; Others	7%	29 % at 5 yrs	54 % at 5 yrs
		632 FL HG, DLBCL, Immunoblastic NHL	61 (55–73) HG		15%	19 % at 5 yrs	30 % at 5 yrs
Lazarus 2008 [14]	149	128 HG NHL, 21 LG FL	67 (65–73)	BEAM/BEAC; TBI; Cy/VP16	11 %	21 % at 3 yrs	35 % at 3 yrs
Yusuf 2009 [74]	34	DLBCL 22, FL10, MCL 2	66 (60–78)	Bu/Cy	0	54 % at 2 yrs	67 % at 2 yrs
Andorsky 2011 [89]	39	DLBCL 26, FL 3, MCL 5, HL 1, T or NK 4	67 (65–69)	TBI-containing 5, non-TBI-containing 34	5%	NA	mOS 6.03 yrs
Andorsky 2011 [89]	17	DLBCL 12, MCL 3, HL 1, T-cell or NK 1	72 (70–78)	TBI-containing 3, non-TBI containing 14	18%	NA	mOS 2.62 yrs
Puig 2011 [67]	15	HL	64 (60–67)	Mel/VP16	0	73 % at 3 yrs	88 % at 2.5 yrs
Elsrom 2012 [90]	21	DLBCL 13, Burkitt 2, Transformed 2, PTCL 1, FL 1, HL 1	71 (69–86)	BCV; BEAM	19%	mPFS 8 mths	mOS 18 mths
Jantunen 2012 [91•]	79	MCL	67 (65–73)	72 % BEAM; others	3.8 %	29 % at 5 yrs	61 % at 5 yrs

Reference	Patients	Histology, grade	Median age (range)	Conditioning protocol	Early TRM	PFS	OS
Chihara 2014 [92•]	484	DLBCL	64 (60–78)	MCEC; MEAM; LEED; others	4.1 %	48 % at 2 yrs	58 % at 2 yrs
Gopal 2014 [76]	36	MCL 23, DLBCL 8, indolent B-NHL 5	65 (60–76)	RIT+augmented Flu	0	53 % at 3 yrs	54 % at 3 yrs
Dahi 2014 [93•]	202	DLBCL 74, MCL 69, FL 12, CNSL 13, TCL 25, Others 9	65 (60–74)	BEAM +/- Rituximab, RIT-BEAM, other	4%	60 % at 3 yrs	73 % at 3 yrs
Frosch 2015 [94]	38	MCL	65 (61–74)	BEAM	0	3.2 yrs RCHOP+ASCT; 4.0 yrs R-HyperCVAD; 1.6 yrs R-CHOP; 0.9 yrs R-HyperCVAD +ASCT	mOS 6 yrs
Martin 2015 [95]	73	MCL 12, DLBCL 34, PCNSL 2, FL 13, Transformed 6, Others 12	67 (65–74)	72 BEAM; 1 Z-BEAM	2.7 %	67 % at 2 yrs	79 % at 2 yrs

HDT/ASCT high-dose therapy/autologous stem cell transplant, *TRM* treatment-related mortality, *PFS* progression-free survival, *OS* overall survival, *mPFS* median PFS, *mOS* median OS, *yrs* years, *mtls* months, *NA* not available, *NHL* non-Hodgkin lymphoma, *HG* high-grade, *IG* intermediate-grade, *LG* low-grade, *DLBCL* diffuse large B cell lymphoma, *PTCL* peripheral T cell lymphoma, *MCL* mantle cell lymphoma, *FL* follicular lymphoma, *SLL* small lymphocytic lymphoma, *MZL* marginal zone lymphoma, *HL* Hodgkin lymphoma, *NKC* natural killer cell, *CNSL* central nervous system lymphoma, *PCNSL* primary CNS lymphoma, *TCL* T cell lymphoma, *BEAM* BiCNU (Carmustine), Ara-C (Cytarabine), Melphalan, *CBV* cyclophosphamide, carmustine, etoposide (VP16), *BEAC* BiCNU (Carmustine), Etoposide, Ara-C (Cytarabine), Cyclophosphamide, *Bu* busulfan, *MeI* melphalan, *TT* thiotepa, *Cy* cyclophosphamide, *TBI* total body irradiation, *MITOX* mitoxantrone, *RIT* radioimmunotherapy, *MCEC* ranimustine, carboplatin, etoposide, cyclophosphamide, *MEAM* ranimustine, etoposide, cytarabine, melphalan, *LEED* cyclophosphamide, etoposide, melphalan, vincristine, doxorubicin, dexamethasone alternating with high-dose methotrexate and cytarabine