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Reviews

Allogeneic Hematopoietic Cell Transplantation as Curative Therapy for Patients with Non-Hodgkin Lymphoma: Increasingly Successful Application to Older Patients



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A B S T R A C T

Non-Hodgkin lymphoma (NHL) constitutes a collection of lymphoproliferative disorders with widely varying biological, histological, and clinical features. For the B cell NHLs, great progress has been made due to the addition of monoclonal antibodies and, more recently, other novel agents including B cell receptor signaling inhibitors, immunomodulatory agents, and proteasome inhibitors. Autologous hematopoietic cell transplantation (auto-HCT) offers the promise of cure or prolonged remission in some NHL patients. For some patients, however, auto-HCT may never be a viable option, whereas in others, the disease may progress despite auto-HCT. In those settings, allogeneic HCT (allo-HCT) offers the potential for cure. Over the past 10 to 15 years, considerable progress has been made in the implementation of allo-HCT, such that this approach now is a highly effective therapy for patients up to (and even beyond) age 75 years. Recent advances in conventional lymphoma therapy, peritransplantation supportive care, patient selection, and donor selection (including the use of alternative hematopoietic cell donors), has allowed broader application of allo-HCT to patients with NHL. As a result, an ever-increasing number of NHL patients over age 60 to 65 years stand to benefit from allo-HCT. In this review, we present data in support of the use of allo-HCT for patients with diffuse large B cell lymphoma, follicular lymphoma, and mantle cell lymphoma. These histologies account for a large majority of allo-HCTs performed for patients over age 60 in the United States. Where possible, we highlight available data in older patients. This body of literature strongly supports the concept that allo-HCT should be offered to fit patients well beyond age 65 and, accordingly, that this treatment should be covered by their insurance carriers.

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INTRODUCTION

In many cases of high-risk non-Hodgkin lymphoma (NHL), the sole potentially curative option for patients (regardless of age) remains allogeneic hematopoietic cell transplantation (allo-HCT). With recent advances in pretransplantation, peritransplantation, and post-transplantation care, allo-HCT can now be successfully

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applied to a wider population of patients, including those with advanced age. Although it is true that advanced age does increase the risk of transplantation-related complications and nonrelapse mortality (NRM), allo-HCT still often represents the sole realistic option for cure in many older patients. After careful consideration of risks, benefits, and alternatives, an increasing number of patients into their 70s are electing to undergo allo-HCT.

In this report, we begin by reviewing 3 B cell NHL subtypes: diffuse large B cell lymphoma (DLBCL), follicular lymphoma (FL), and mantle cell lymphoma (MCL). These 3 lymphoma histologies accounted for 73% of allo-HCTs performed in patients over age 60 in the United States between 2010 and 2014 (Personal communication, Mehdi Hamadani, Center for International Blood and Marrow Transplant Research, April 18, 2016). For each subtype, we first provide a brief overview of the use of nontransplantation frontline therapies. We next briefly review outcomes for autologous hematopoietic cell transplantation (auto-HCT), and discuss the available data supporting the use of allo-HCT. Finally, we present data specifically supporting allo-HCT in elderly patients with lymphoma.

DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL)

Overview of DLBCL and Nontransplant treatment Options

The most common type of aggressive NHL, DLBCL encompasses several clinical-pathological entities. Although risk factors include HIV infection, solid organ transplantation, and autoimmune disorders, most cases are sporadic and occur predominantly in individuals age >60 years with no obvious predisposing factors. Overall, 60% of those affected will be cured with chemoimmunotherapy. Clinical factors such as the National Comprehensive Cancer Network (NCCN) International Prognostic Index (NCCN-IPI), however, delineate a wide range of results, identifying groups with a likelihood of 5-year survival ranging from as high as 96% to as low as 38% [1,2]. A greater understanding of biology and genetics has refined prognostic markers with potential therapeutic implications, such as the putative cell of origin (defined by gene expression profile or immunohistochemistry) [3,4], and translocation or overexpression of the *MYC* oncogene [5].

Despite these advances, several disease subsets represent high-risk disease, clinically defined by the NCCN-IPI

[1], or biologically identified, for example the “double-hit” and “triple-hit” lymphomas (ie, those with *MYC* and *BCL2* and/or *BCL6* translocations). Particularly for double- and triple-hit lymphomas, standard frontline therapies are ineffective for providing long-term remission, and cure is rarely achieved in the relapsed and refractory settings. Thus, selecting the optimal therapy for such patients remains a great challenge [5,6].

Auto-HCT for DLBCL

High-dose chemotherapy with auto-HCT exploits the steep dose-response curve of some chemotherapy agents, by eradicating disease that could not be eliminated by conventional chemotherapy doses. Two decades ago, a randomized trial conducted in patients with relapsed aggressive lymphoma with chemosensitive disease showed a 53% 5-year survival with auto-HCT versus 32% with continuation of conventional chemotherapy [7]. Even in the rituximab era, some patients with disease relapse will be long-term survivors after proper second-line therapy and auto-HCT [8]; however, significantly worse results are expected in patients who never achieve complete response (CR) with frontline therapy, who have a short duration of CR, or relapse with a high IPI. For example, in the CORAL trial, fewer than 25% of patients who relapsed within 1 year of diagnosis achieved long-term disease-free survival with auto-HCT [9].

Investigations of strategies designed to improve on auto-HCT, such as modifying the transplant preparative regimen with the addition of radioimmunotherapy to the chemotherapy backbone [10] or the use of post-transplantation maintenance therapy [11], have not proven beneficial in relapsed/refractory (R/R) DLBCL. Auto-HCT remains the standard of care for chemosensitive R/R DLBCL, but better approaches are needed for patients who experience relapse after auto-HCT or for whom auto-HCT is not an option due to insufficient chemosensitivity.

Allo-HCT for DLBCL

Recent studies of allo-HCT involving at least 40 patients with DLBCL are listed in Table 1. Allo-HCT provides the theoretical advantage of a tumor-free graft and the benefit of a graft-versus-lymphoma (GVL) effect. This GVL effect has been well demonstrated by the fact that some patients who experience relapse after auto-HCT will attain cure with allo-HCT. Furthermore, the use of donor lymphocyte infusion,

Table 1
Recent Studies Reporting Outcomes of Allo-HCT for DLBCL (>40 Patients)

Study	No. of Patients	Previous Auto-HCT, %	Conditioning (%)	Median Age, yr (Range)	NRM/TRM, % (yr)	Relapse, % (yr)	OS, % (yr)
Thomson et al., 2009 [12]	48	69	RIC (100)	46 (23–64)	32 (4)	33 (4)	48 (4)
Sirvent et al., 2010 [13]	68	79	RIC (100)	48 (17–66)	23 (1)	41 (2)	49 (2)
Lazarus et al., 2010 [14]	79*	0	MAC (100)	46 (21–59)	43 (3)	33 (3)	26 (3)
van Kampen et al., 2011 [15]	101	100	MAC (37) RIC (63)	46 (18–66)	28 (3)	30 (3)	52 (3)
Rigacci et al., 2012 [16]	165	100	MAC (30) RIC (70)	43 (16–65)	19–32 (2)	NR	39 (5)
Bacher et al., 2012 [17]	396	32	MAC (42) RIC (58)	54 (18–66)	36–56 (5)	26–40 (5)	18–26 (5)
Hamadani et al., 2013 [18]	533†	25	MAC (58) RIC (42)	46 (19–66) 53 (20–70)	53 (3) 42 (3)	28 (3) 35 (3)	19 (3) 28 (3)
Fenske et al., 2015 [19]	503	100	MAC (25) RIC (75)	52 (19–72)	31 (5)	40 (5)	34 (5)

NR indicates not reported.

* Analysis restricted to patients undergoing MA allo-HCT as first transplantation.

† Included 85% DLBCL and 15% FL grade 3; all patients had chemoresistant disease pretransplantation.

withdrawal of immune suppression, or the combination provides a GVL effect in DLBCL after allo-HCT, leading to cure in some cases [12,20,21]. Allo-HCT, however, presents challenges including donor availability, the need for prolonged immunosuppression, and an increased risk of early treatment-related mortality (TRM) owing to toxicity of the conditioning regimen, graft-versus-host disease (GVHD), and infectious complications. Progress in addressing these challenges has been made in recent years.

In the past, allo-HCT used myeloablative conditioning (MAC) to eliminate maximal tumor and permit engraftment by eliminating the host immune system. No prospective trials comparing auto-HCT versus MAC allo-HCT for R/R DLBCL have been undertaken to date. A large retrospective analysis by the Center for International Blood and Marrow Transplant Research (CIBMTR) including 837 auto-HCTs and 79 allo-HCTs performed between 1995 and 2003 demonstrated higher TRM, NRM, and overall mortality in the allo-HCT group, with no decrease in the risk of disease progression [14]; however, the subjects who underwent allo-HCT were more likely to have high-risk disease features, including later disease stage, to have received more previous chemotherapy regimens, and to have resistant disease.

Despite such limitations, reviewing the literature on allo-HCT reveals a consistent message that long-term overall survival (OS) in the 20% to 50% range is possible (Table 1). The 25% to 30% rate of NRM remains the greatest drawback. Less-intensive preparative regimens (termed reduced-intensity conditioning [RIC]) have been implemented in recent years. Retrospective comparisons between MAC and RIC show reduced NRM, at the expense of some increase in disease relapse, but producing long-term OS rates comparable to those for MAC [17,18]. Most allo-HCTs for DLBCL are now performed using lower-intensity regimens, which also permits the use of this procedure in older patients who are otherwise good candidates but previously would have been excluded from MAC allo-HCT because of age [17]. The expanding use of allo-HCT in older patients is evidenced by the fact that the more recent studies listed in Table 1 include patients 65 to 72 years of age. One recent study focusing on the use of allo-HCT in patients with NHL in their 60s and early 70s found no major increase in NRM for such patients [22].

Allo-HCT for DLBCL following failed auto-HCT

Roughly 30% to 40% of DLBCL auto-HCT recipients ultimately will experience relapse or progression of DLBCL and cannot be cured with intensification of chemotherapy. As noted above, because of the GVL effect in DLBCL, such patients are often considered for allo-HCT after a failed previous auto-HCT [15,16,19,23]. These studies report TRM/NRM rates of 17% to 31% but 3- to 5-year OS rates of 34% to 52%. In the most recent and largest study, from the CIBMTR, 503 patients were analyzed. At 3 years, NRM was 30%, with a progression/relapse rate of 38% and OS of 37%, a reasonable result given that the median survival typically seen in this population is in the 3- to 10-month range [24,25]. In multivariate analysis, advanced age was not a prognostic factor, indicating that chronologic age should not be the key factor used to determine allo-HCT eligibility. A prognostic model was constructed using Karnofsky Performance Status <80, time from auto-HCT to allo-HCT of <1 year, and chemo-resistant disease as adverse factors. This CIBMTR model facilitates the identification of high-risk patients unlikely to benefit from allo-HCT (3-year OS of 14%), as well as low-risk

patients who have good potential to benefit from allo-HCT (3-year OS of 43%) [19].

Summary: DLBCL

These data indicate that medically appropriate patients with DLBCL whose disease relapses after auto-HCT have the clearest indication for allo-HCT and potentially can be cured. In this setting, patients should receive RIC preferentially, ideally after conventional debulking therapy. Other subsets of patients who may benefit from allo-HCT are patients known to have a low chance of cure with auto-HCT, as identified by use of the second-line IPI, failure to attain CR using initial therapy, relapse <12 months after chemotherapy, or NHL refractory to second- and third-line chemotherapy [9,18,20,26]. The recently developed CIBMTR prognostic model described above can guide decision making [19]. Other appropriate indications include (1) patients in whom auto-HCT is not feasible, either by failure to obtain an adequate autologous graft for transplantation or coexistence of intrinsic bone marrow disease, particularly myelodysplastic syndrome; (2) DLBCL transformed from an indolent B cell malignancy relapsing after anthracycline-containing therapy, or a failed auto-HCT; and (3) double-hit DLBCL.

FOLLICULAR LYMPHOMA (FL)

Overview of FL and Nontransplant treatment Options

FL is the most common subtype of indolent NHL, accounting for roughly 20% of all cases of NHL. Unlike patients with aggressive NHL, nearly all patients who complete induction therapy will eventually relapse and require additional lines of therapy. Furthermore, although OS is prolonged for many patients, with standard therapies FL remains incurable for the vast majority. The Follicular Lymphoma International Prognostic Index (FLIPI) incorporates clinically based features and identifies a subgroup at high risk for early disease-related death [27]. Approximately one-quarter of all patients with FL fall into this poor-risk category (ie, ≥ 3 risk factors), which has an estimated 5-year OS of only 53%.

A proportion of patients may be safely observed without treatment until the development of symptomatic progressive disease, bulky adenopathy, cytopenia, organ obstruction, or malignant fluid collection [28]. Patients who require therapy but otherwise have a low tumor burden may be managed with single-agent rituximab [29]; however, many patients require combination chemoimmunotherapy. Currently, bendamustine-rituximab may be a preferred frontline approach in FL with a high tumor burden, with improved progression-free survival (PFS) (median, not reached versus 41 months; $P = .0072$) and decreased toxicity compared with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) [30].

There is no standard therapy for R/R FL; readily available options include anti-CD20 immunotherapies, combination chemotherapy, radioimmunotherapy, the oral PI3 kinase idelalisib, immunomodulatory drugs (lenalidomide), and the Bruton tyrosine kinase inhibitor ibrutinib [31]. More intensive treatments often are considered for high-risk patients, especially those who relapse early after induction therapy, because relapse within 2 years of initial therapy is associated with a 5-year OS of only 50% [32]. In this context, auto-HCT and allo-HCT can provide for long-term survival in R/R FL.

Auto-HCT for FL

Auto-HCT for FL in first remission

The data to support auto-HCT for FL in first remission are limited. Prospective randomized trials comparing chemotherapy with auto-HCT in first complete remission have generally shown a PFS benefit, but not an OS benefit, in favor of up-front auto-HCT [33–36]. Benefit in terms of improved lymphoma-specific survival appears to be offset by a decrease in survival owing to secondary malignancies, such as myelodysplastic syndrome and acute myelogenous leukemia. As a result, auto-HCT is not recommended for consolidation of remission after first-line therapy for low-grade FL.

Auto-HCT for R/R FL

Although auto-HCT can produce prolonged remissions, it typically is not viewed as curative therapy in R/R FL. Prospective studies are lacking, although a randomized study ($n = 89$) from the pre-rituximab era, which closed early due to poor accrual, showed improved 2-year PFS and 4-year OS in auto-HCT recipients compared with patients receiving standard chemotherapy [37]. A review of 2 French studies demonstrated that rituximab at relapse appeared to have a more prominent impact on event-free survival and OS compared with receipt of auto-HCT [38]. At least 9 additional single-center retrospective studies and large registry studies of R/R FL have demonstrated PFS in the 30% to 60% range at 5 to 10 years, although not all of the patients in these series were treated with rituximab [39]. Considering that a large majority of patients with FL relapse after auto-HCT, this approach cannot be considered a curative intervention for most patients with FL. However, auto-HCT is a reasonable consideration and may provide prolonged disease control in high risk FL patients who are not candidates for allo-HCT.

Allo-HCT for FL

There are no randomized prospective trials or retrospective studies to support the application of allo-HCT as consolidation therapy for FL in first remission. However, numerous prospective as well as retrospective studies support the use of allo-HCT in R/R FL. Outcomes reported by selected studies investigating allo-HCT in R/R FL are presented in Table 2.

Allo-HCT for R/R FL: prospective studies

Shea et al. [50] reported a prospective study of 16 patients receiving RIC allo-HCT conditioned with fludarabine/

cyclophosphamide and a matched related donor graft. The 3-year event-free survival was 75%, and 3-year OS was 81%; 3 subjects relapsed. A second prospective study of 47 patients conducted at M.D. Anderson Cancer Center used RIC conditioning with fludarabine, cyclophosphamide, and rituximab [51]. The median 5-year PFS and OS were both 85%; 7 patients died, most from infectious complications. Another report combined 2 prospective multicenter Spanish trials in 37 patients who received fludarabine/melphalan RIC regimen [42]. The relapse incidence was only 8%, but NRM was as high as 71% in patients with active disease before allo-HCT. For patients in CR before transplantation, the 4-year OS was 71%, comparable to those reported in other studies. In a prospective study from the United Kingdom that enrolled 82 consecutive patients with FL treated with fludarabine, melphalan, and alemtuzumab RIC, NRM was 15%, relapse rate was only 26% at 4 years, and OS was 76% at 4 years [43]. Finally, another prospective multicenter study in 46 patients with FL coordinated by the Fred Hutchinson Cancer Research Center [40] reported a high 42% rate of NRM, driven in large part by the use of mismatched unrelated allografts. The relapse rate at 3 years was low, at 14%.

Allo-HCT for R/R FL: retrospective studies

The NCCN compared outcomes in 48 allo-HCT and auto-HCT recipients [45]. The allo-HCT recipients had a 3-year NRM of 26%; in a multivariable analysis, allo-HCT was associated with an increased risk of death compared with auto-HCT ($P = .002$). These data should be interpreted with caution, however, as the group of FL allo-HCT recipients were a highly select and high-risk group. In contrast, a recent and larger analysis by the CIBMTR indicates that long-term remission is feasible in a significant number of R/R FL patients who receive allo-HCT, and that patients who do not die early in the post-transplantation course have prolonged survival compared with patients receiving auto-HCT. Among 268 relapsed patients with grade 1 to 2 FL who underwent RIC allo-HCT, the 5-year NRM was 26%, the probability of disease progression at 5 years was 20%, and the 5-year PFS was 41%, representing a subset of patients who are likely cured of their disease. The 5-year OS was 66%, and among 24-month survivors, the subsequent risk of death was decreased in patients undergoing allo-HCT compared with those undergoing auto-HCT (RR, 2.09; $P = .04$) [47]. A recent retrospective study from Memorial Sloan-Kettering compared outcomes for patients with R/R FL undergoing auto-HCT versus allo-HCT in the post-

Table 2
Studies Evaluating Allo-HCT in Relapsed/Refractory FL (>30 Patients)

Study	No. of Patients	Conditioning (%)	Age, yr, Median (Range)	TRM/NRM, % (yr)	Relapse, % (yr)	OS, % (yr)	Comments
Rezvani et al., 2008 [40]	46	RIC	54 (33–66)	42 (3)	14 (3)	52 (3)	Prospective
Hari et al., 2008 [41]	208	MAC (58) RIC (42)	44 (27–70)	23 (1)	8–17 (3)	62–71 (3)	Retrospective (CIBMTR)
Piñana et al., 2010 [42]	37	RIC	50 (34–62)	37 (4)	8 (4)	57 (4)	Prospective
Thomson et al., 2010 [43]	82	RIC	45 (26–65)	15 (4)	26 (4)	76 (4)	Prospective
Khouri et al., 2012 [44]	47	RIC	53 (33–68)	15 (8)	4 (8)	85 (8)	Prospective; 45/47 MRD
Evens et al., 2013 [45]	48	NR	50 (27–64)	24 (3)	16 (3)	61 (3)	Retrospective (NCCN)
Robinson et al., 2013 [46]	149	RIC	51 (33–66)	22 (3)	20 (5)	67 (5)	Retrospective (EBMT)
Klyuchnikov et al., 2015 [47]	268	RIC	52 (27–74)	26 (5)	20 (5)	66 (5)	Retrospective (CIBMTR); grade 1 and 2 FL
Klyuchnikov et al., 2015 [48]	70	RIC	53 (36–64)	27 (5)	20 (5)	54 (5)	Retrospective (CIBMTR); grade 3 FL
Yano et al., 2015 [49]	46	RIC	48 (34–66)	23 (5)	15 (5)	81 (5)	Retrospective (Japan)

MRD indicates matched related donor.

rituximab era. In a subgroup analysis performed in patients with a remission duration of <12 months before salvage therapy, 3-year event-free survival was 42% with auto-HCT versus 80% with allo-HCT, suggesting that patients with a very short first remission (<1 year) may be better served with an allo-HCT approach [52].

Allo-HCT for grade 3 FL

A recent report from the CIBMTR examined the outcomes of 61 patients who underwent RIC allo-HCT for grade 3 FL [48]. At 5 years, NRM was 27% and OS 54%, indicating that grade 3 histology should not be an exclusion factor for allo-HCT, and that RIC can offer long-term survival for patients with grade 3 histology.

Summary: FL

Although auto-HCT is not considered a curable intervention for most patients, a subset (~30% to 35%) may enjoy long-term (>5-year) remissions with this therapy, justifying its use in second or third remission. Furthermore, given the development of less-toxic novel therapeutic strategies in the modern era, the use of auto-HCT may decline in the coming years. It should be noted that these novel strategies are not currently known to be curative. In contrast, allo-HCT repeatedly has been shown to be a curative therapy for a significant subset of patients with R/R FL. Although the rate of early death is increased in patients with FL receiving allo-HCT owing to increased NRM, the studies cited above demonstrate excellent long-term outcomes in those surviving the early period. With the increasing application of RIC allo-HCT, and continued improvement in supportive care, NRM rates likely will continue to decline for well-selected patients with FL who receive expert supportive care. Such patients can expect a reasonable chance of being cured. These observations apply to patients over age 65 years, for whom outcomes with RIC are comparable to, or only minimally less favorable than, those in the 55- to 64-year age group [22].

MANTLE CELL LYMPHOMA (MCL)

Overview of MCL and Nontransplant treatment

Options

MCL comprises ~6% of newly diagnosed cases of NHL. The median age at diagnosis is in the late 60s, with a 4:1 male predominance. Patients often present in an advanced disease stage, along with extranodal involvement. Modern chemotherapies alone, or as induction followed by auto-HCT in first remission, undoubtedly have improved patient outcomes; however, disease relapse eventually occurs in most patients [53].

Although variables such as histology (eg, blastoid morphology), tumor proliferation index, cytogenetics, and gene expression profiling have prognostic value in MCL, their clinical applications for risk-adapted treatment remains limited [45]. The MCL International Prognostic Index (MIPI) is a commonly used risk-stratification score based on patient age, performance status, serum lactate dehydrogenase, and white blood cell count at diagnosis, with/without Ki-67 proliferation index, that classifies MCL into low-, intermediate-, and high-risk groups, with median OS ranging from 29 months to > 5 years [54]. This index also has been validated to predict outcomes after auto-HCT [55], but has not yet been validated as a tool to direct optimal consolidation therapies in patients responding to frontline therapies.

Historically, using conventional frontline therapy such as R-CHOP, the median duration of remission was only 12 to 18 months [56]. Recently, however, incorporation of such agents as bortezomib, bendamustine, and lenalidomide into first-line therapy have improved on this result, with PFS in the 27- to 35-month range or longer [30,57–59]. Intensive regimens like R-Hyper-CVAD (rituximab, fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with methotrexate and cytarabine) without subsequent consolidation led to impressive PFS in some reports, but toxicity concerns have dampened enthusiasm for this approach [60–62].

Given the relatively short remissions observed in MCL, investigators have tested the concept of maintenance rituximab after conventional frontline therapies. The median duration of first remission has improved to the 3- to 5-year range. As a result, rituximab maintenance is a reasonable option for elderly patients with MCL who are not candidates for HCT [63,64].

Auto-HCT for MCL

Auto-HCT for MCL in first remission

In the pre-rituximab era, the poor prognosis seen in relapsed MCL motivated the European MCL Network to conduct a randomized, prospective postremission trial comparing auto-HCT with IFN α maintenance [65]. Auto-HCT demonstrated superior PFS; however, no OS benefit was seen, possibly due to crossing over of the IFN α -treated patients to subsequently receive auto-HCT off protocol. Although similar prospective randomized data in the rituximab era are not available, several large prospective phase 2 trials applying up-front auto-HCT after various intensive induction regimens have yielded median PFS durations in the 5- to 7-year range [66–71]. Despite the lack of randomized, controlled data demonstrating a survival benefit with auto-HCT as consolidation in first remission, many clinicians have adopted this approach. Certain patients, such as those not in CR at the time of up-front auto-HCT [72], those with minimal residual disease pretransplantation [73], or those with a high-risk MIPI score [55,68,74], fare considerably less well with upfront auto-HCT consolidation, underscoring the need for novel modalities to consolidate first remission for such patients.

Auto-HCT for relapsed/refractory MCL

Initial retrospective studies, including a European Society of Blood and Marrow Transplantation (EBMT) study [75], have suggested that auto-HCT may have limited value in relapsed and refractory patients. More recent studies, however, including a large retrospective study from the CIBMTR, have indicated that durable remissions in the 2- to 4-year range may be seen in selected patients with MCL whose disease remains chemosensitive [72,76]. Therefore, in patients with relapsed chemosensitive MCL who are not candidates for potentially curative allo-HCT (due to comorbidities, donor availability, etc), consolidation with an auto-HCT can be offered, with the understanding that this therapy is not curative. It remains to be seen whether auto-HCT will remain part of the treatment paradigm for R/R MCL in the era of new and novel agents.

Allo-HCT for MCL

Allo-HCT for MCL in first remission

Although adoptive immunotherapy in the form of allo-HCT is a potentially curative option for patients with MCL, there are no prospective data assessing this approach in first

Table 3
Studies Evaluating Allo-HCT in Relapsed/Refractory MCL (>30 Patients)

Study	No. of Patients	Conditioning (%)	Age, yr, Median (Range)	TRM/NRM, % (yr)	Relapse, % (yr)	OS, % (yr)
Maris et al., 2004 [77]	33	RIC (100)	53 (33–70)	9 (2)	16 (2)	65 (2)
Cook et al., 2010 [78]	70	RIC (100)	52 (25–69)	18 (3)	65 (5)	37 (5)
Le Gouill et al., 2012 [79]	70	RIC (100)	56 (33–67)	32 (2)	18 (2)	53 (2)
Hamadani et al., 2013 [80]*	202	MAC (37) RIC (63)	54 (27–69) 59 (42–75)	38–43 (1)	32–33 (3)	25–30 (3)
Fenske et al., 2014 [72]†	88	RIC (100)	58 (26–75)	17 (1)	38 (5)	31 (5)
Krüger et al., 2014 [81]	33	MAC (21) RIC (79)	59 (33–69)	24 (5)	15 (5)	73 (5)

* Included only patients with refractory disease.

† Excluded patients with refractory disease.

remission. Registry data from the CIBMTR examining the role of allo-HCT versus auto-HCT in first CR or partial remission showed no benefit in terms of PFS (55% versus 52% at 5 years) or OS (62% versus 61% at 5 years); however, early allograft was associated with a significantly higher NRM (25% versus 3% at 1 year) [72]. As a result, the use of allo-HCT in chemosensitive patients with MCL in first remission generally is not recommended. Early use of allo-HCT can be considered in selected patients for whom the chance for success with auto-HCT is poor, such as those with high MIPI score or not in CR before transplantation. It has been hypothesized that in such patients, outcomes might be improved by early allografting. This approach would not yet be considered standard care by most clinicians, but warrants prospective investigation.

Allo-HCT for R/R MCL

As shown in Table 3, evidence from several single-center studies and large transplantation registries have established that allo-HCT is the sole potentially curative modality for R/R MCL, with 35% to 45% of patients disease-free (and likely cured) at 3 years post-transplantation [72,77–81]. Chemosensitive disease and adequate performance status are predictive of improved allo-HCT outcomes. In recent years, the wider adoption of RIC regimens has extended the availability of allo-HCT to elderly patients and patients with medical comorbidities. Nonetheless, the prognosis remains particularly poor in the challenging subset of patients with chemotherapy-unresponsive MCL. A large CIBMTR analysis restricted to such chemorefractory patients showed that approximately one-quarter gain durable disease control with allo-HCT, likely due to a clinically relevant GVL effect [80]. No benefit of MAC was seen even in this high-risk cohort of patients. Thus, in otherwise healthy patients with relapsed or refractory MCL and an available sibling or adult unrelated donor, RIC allo-HCT with curative intent is a reasonable therapeutic option. In medically fit patients without significant comorbidities, advanced age should not be considered a contraindication.

Summary: MCL

Currently, both auto-HCT and allo-HCT play important roles in the management of MCL. Auto-HCT is not considered curative therapy for MCL, although an intensive induction and consolidation from auto-HCT may provide many patients with remissions that can last 6 to 8 years or longer. Selected patients with MCL who did not undergo auto-HCT as part of frontline therapy also may benefit from auto-HCT later in the disease course. Despite the recent emergence of several exciting new agents, for the vast majority of patients with R/R MCL, allo-HCT remains the sole treatment option

with curative potential. With the widespread implementation of RIC, properly selected patients with MCL who receive expert supportive care have a reasonable chance of being cured with allo-HCT. This also applies to patients over age 65, in whom outcomes with RIC are comparable to those in the 55- to 64-year age group [22].

ALLO-HCT IN OLDER PATIENTS WITH LYMPHOMA

Tables 1–3 list numerous key studies of allo-HCT in DLBCL, FL, and MCL, several of which include patients up to age 70 to 75 years. A recent registry study by McClune et al. [22] specifically analyzed outcomes in 82 patients age ≥ 65 undergoing allo-HCT for NHL. Although 100-day NRM was not significantly different, NRM at 1 year was higher in this older age group (34%) compared with 2 younger populations, 40 to 54 years (27%) and 55 to 64 years (22%). Relapse rates at 3 years were similar across the 3 age groups (28% to 33%). Not surprisingly, OS was highest in the 40- to 54-year age group; however, the ≥ 65 -year age group fared reasonably well, with a 3-year OS of 39%. Nonetheless, it should be emphasized that in individual patients over age 65, the real question should be not whether allo-HCT outcomes are comparable to those in patients under age 65, but rather *whether allo-HCT offers the best reasonable chance for long-term remission or cure for that patient*, when considering all treatment options.

Owing in part to the advances in patient selection, donor selection, pretransplantation lymphoma therapy, and peri-transplantation supportive care, older patients are increasingly undergoing allo-HCT. As shown in Figure 1, data from the CIBMTR show increasing use over time of allo-HCT for NHL in patients age >60 years. For example, the percentage of patients age >60 undergoing allo-HCT for DLBCL, FL, and

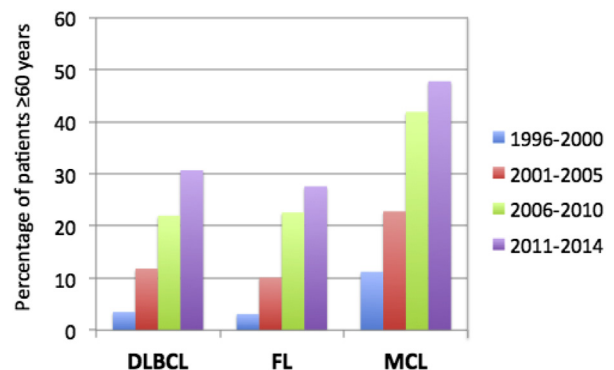


Figure 1. Increase in proportion of NHL patients over age 60 undergoing allo-HCT in the United States between 1996 and 2014. Data provided by the Center for International Blood and Marrow Transplant Research.

MCL rose from 12%, 10%, and 23%, respectively, in 2001 to 2005 to 31%, 28%, and 48%, respectively in 2011 to 2014 (personal communication, CIBMTR). These figures clearly show that allo-HCT is an important therapeutic option for DLBCL, FL and MCL, even in older patients. In recent years, alternative donor transplantation (umbilical cord blood or haploidentical marrow) has become more widespread, with recent studies reporting outcomes that compare favorably to those using matched unrelated donors [82,83]. The haploidentical approach, with post-transplantation cyclophosphamide, has been successfully applied to patients with lymphoma up to age 75, with a reported 1-year NRM of 10% to 15% across all age groups from 50 to 75 years, and a 3-year survival of approximately 50% [82,84]. With the growing use and success of alternative donor transplantation, it is expected that an even larger number of older patients will be allo-HCT candidates, because in many cases such patients do not have a matched sibling in sufficiently good health to serve as a donor.

Based on the foregoing data, it is becoming increasingly clear that allo-HCT is in fact feasible in older patients. Thus, transplantation clinicians will be increasingly challenged to consider allo-HCT for these older patients. On an individual patient level, the decision to proceed to transplantation requires a careful consideration of patient issues (comorbidities, performance status), disease factors (histology and biological features of the lymphoma, clinical aggressiveness, disease burden), donor factors, and psychosocial factors. These considerations are of particular importance in older patients, in whom the therapeutic window for transplant may be narrow and the risk for toxicity and disability post-transplantation may be higher. With this in mind, it will be very important to prospectively collect quality of life data in elderly patients undergoing allo-HCT for NHL, if allo-HCT becomes a covered indication in these patients.

SUMMARY AND CONCLUSIONS

Ideally, there would be more prospective randomized clinical trial data available to prove superior survival with allo-HCT for FL, DLBCL, and MCL compared with alternative approaches. No such studies have been successfully completed to date, however. One such study was attempted in FL, but was not completed because of poor accrual [85]. Although it is true that a number of exciting targeted, biological, and immunological therapies are emerging in NHL, how these new therapies might enhance or replace allo-HCT is unclear. High-quality studies comparing novel agents with allo-HCT, or integrating such agents with allo-HCT, are needed to answer such questions. In the meantime, based on the extensive literature currently available and summarized in this review, it is clear that for many patients with NHL, allo-HCT is the sole currently available therapy that offers cure.

Advances in the HCT field have enabled the successful application of this therapy in patients age >65 years. Access to allo-HCT in the United States historically has been quite limited owing to a lack of insurance coverage. Despite this limitation, there is now a body of evidence showing that patients with lymphoma in their 60s and 70s can in fact tolerate and benefit from allo-HCT. Based on this evidence, we strongly assert that allo-HCT now represents a standard of care for older patients with NHL, and thus the associated costs should be covered by insurance carriers.

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