Where does transplant fit in the age of targeted therapies?

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The role of hematopoietic cell transplantation (HCT) for indolent lymphoma has evolved over the last 5 years with the availability of novel low-toxicity therapies and a better understanding of the prognosis of these entities. However, despite numerous treatment options for patients with follicular lymphoma, none are thought to be curative, and many require ongoing therapy with chronic toxicity. Historical trials indicate that autologous HCT as initial consolidation leads to improved progression-free survival, but not overall survival (OS) and, thus, is not typically recommended. However, autologous HCT for chemosensitive relapse can be carried out with ~1% early mortality risk, affording disease control lasting a median of 3 to 5 years and the potential to improve OS. These results may compare favorably in efficacy, toxicity, and cost vs multiple sequential novel therapies with shorter durations of benefit. Recent data indicate that autologous HCT in follicular lymphoma patients with early initial progression will result in more than one third being alive and without relapse at 5 years, leading to improved OS when used within a year of the first recurrence. Unlike other available therapies, allogeneic HCT has the potential to cure up to one half of those transplanted with indolent B-cell non-Hodgkin lymphoma, although the risks need to be recognized and appropriate patient and donor selection is critical to ensure the best outcomes. HCT continues to remain a viable option in the current era of multiple targeted agents.

Learning Objectives

- Ascertain the timely use of autologous and/or allogeneic stem cell transplantation in relapsed or refractory follicular lymphoma
- Understand the role of transplant in the context of current treatment options for indolent lymphoma

Case 1

K.M. is a 62-year-old woman who presented to her primary care physician with several months of waxing and waning adenopathy. Biopsy revealed grade 1-2 follicular lymphoma (FL), and staging studies showed multifocal adenopathy with multiple nodes above and below the diaphragm. Complete blood count was notable for mild anemia and thrombocytopenia. Follicular Lymphoma International Prognostic Index score was 3. She was treated with 6 cycles of bendamustine plus rituximab, which she tolerated well, but with some delayed count recovery during cycles 5 and 6. Posttherapy positron emission tomography–computed tomography (PET-CT) showed a complete response (CR) with residual non–fluorodeoxyglucose-avid nodes up to 2 cm. One year after completing therapy (19 months after diagnosis), she again developed adenopathy and progressive fatigue. Understanding the poor risk of her early relapse and her desire for episodic therapy, she is treated with 4 cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone (R-CHOP) and achieved a second CR. She is referred to a transplant center to receive high-dose carmustine, etoposide, cytarabine, melphalan (BEAM), followed by autologous hematopoietic cell transplantation as consolidation.

Introduction

Indolent non-Hodgkin lymphomas (NHLs) are a heterogeneous class of diseases including FL, lymphoplasmacytic lymphoma/Waldenström macroglobulinemia (WM), marginal zone lymphoma (MZL), and small lymphocyte lymphoma. Because FL accounts for the majority of all indolent NHLs, the outcomes and impacts of therapeutic options are more frequently reported for this histologic subtype and then extrapolated to the other entities. The World Health Organization evaluated lymphoma incidence patterns and survival trends based on Surveillance, Epidemiology, and End Results data, reporting a relatively high 2-year survival rate in FL between 88% and 93%.[1] However, a high short-term survival is less relevant in a disease that is characterized by a relapsing and remitting pattern with a median survival surpassing 2 decades. Early relapse within 2 years of chemoimmunotherapy or progression of disease within 2 years of diagnosis (POD24) occurs in roughly 20% of patients and portends inferior survival, with 50% overall survival (OS) at 5 years compared with 90% for those without POD24.[2,3] Similar data suggest that if one has not suffered relapse within 12 months of diagnosis, survival is similar to age-matched controls.[4] Even in those with later relapses, remission durations are thought to become shorter over time with standard therapy and, in most cases, advanced disease is not curable.[5] An association between POD24 and inferior OS was also found in

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MZL, as recently reported by the FIL-NF10 study that evaluated >1300 registered cases in Europe and South America between 2010 and 2018. With a median follow-up of 43 months, 5-year progression-free survival (PFS) was 64%, and OS was 88%. POD24 was identified in 59 (18%) patients, with 3-year OS for patients with POD24 reported to be 53% (hazard ratio [HR], 19.5; 95% confidence interval [CI], 8.4-45) vs 88% in patients without POD24.[6]

Thus, with a wide spectrum of outcomes when caring for patients with FL and other indolent NHL subtypes, an overall "life strategy" should be used to best incorporate standard chemoimmunotherapy, novel agents, and transplant in the treatment algorithm, keeping in mind the goals of improving survival and quality of life, which may include time off therapy.

Hematopoietic cell transplantation (HCT), utilizing autologous stem cell transplantation (auto-HCT) and allogeneic stem cell transplantation (allo-HCT), has been an effective option for relapsed or refractory (R/R) FL but is not recommended for initial consolidation. Defined indications are published by the American Society for Blood and Marrow Transplantation.[7] These modalities take advantage of the antilymphoma effect of high-dose chemotherapy (HDT) with or without total body irradiation (TBI), followed by autologous stem cell rescue in chemosensitive disease, as well as the immune-related effects of graft-versus-lymphoma (GVL) in allo-HCT. With the advent of multiple targeted agents in the past decade, patients are faced with a variety of new options, which may cloud the role and timing of HCT. Factors to consider when deciding upon HCT vs a targeted agent in the R/R setting include duration of therapy, intermittent vs continuous dosing, upfront toxicities, long-term or late effects, and cost. Here, we aim to better define the role of HCT in R/R FL in the age of targeted therapies.

Indications for auto-HCT

Initial consolidation

Multiple prospective randomized controlled trials done largely in the prerituximab era evaluated the role for auto-HCT as consolidation following first-line therapy.[8-11] Although these studies did show dramatic improvements in PFS and event-free survival (EFS) with the incorporation of auto-HCT, all failed to show a benefit in OS; therefore, auto-HCT is currently not indicated as consolidation after first-line therapy outside of a clinical trial. One example is the GOELAMS 064 study that randomized patients with newly diagnosed untreated FL to chemotherapy vs HDT and auto-HCT. The chemotherapy arm consisted of 6 cycles of cyclophosphamide, doxorubicin, vepeside, and prednisone, followed by a maintenance phase for 1 year with concomitant interferon α-2b administered subcutaneously 3 times per week for 18 months. The auto-HCT arm received vindesine, cyclophosphamide, doxorubicin, and prednisone, followed by stem cell harvesting and auto-HCT after the second or third cycle. After a median follow-up of 9 years, the OS was not statistically different between the 2 arms: 76% for auto-HCT and 80% for chemotherapy ($P = .55$). Although the 9-year PFS was higher in the auto-HCT arm compared with the chemotherapy arm (64% vs 39%; $P = .004$), more secondary malignancies were seen following a TBI-based regimen, further arguing against auto-HCT as initial consolidation.[10] Provocative observations from these trials do show infrequent late relapses beyond 5 to 8 years and the potential for lower rates of secondary malignancies with non-TBI–based approaches. One could hypothesize that there may be subsets of patients identified using modern prognostic tools who could enjoy a survival benefit from auto-HCT in the first remission, although such an approach requires evaluation in prospective trials.[12-14]

R/R disease

Historical data. The utility for auto-HCT in the relapsed setting is supported largely by a single small randomized trial, performed in the prerituximab era, known as the CUP Trial. Patients with chemosensitive relapsed FL after a median of 1 prior regimen were treated with cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP), and those who achieved a CT-defined CR or partial response were randomized to cyclophosphamide plus TBI conditioning, followed by auto-HCT (with a second randomization to a purged vs unpurged graft). After a median follow-up of 5.8 years, the investigators reported an improved 4-year OS of 71% to 77% for patients with chemosensitive disease receiving HDT, followed by purged or unpurged stem cell support, compared with 46% for patients receiving 3 additional cycles of chemotherapy ($P = .079$); however, this difference was not statistically significant.[15] Two-year PFS also improved for patients receiving auto-HCT (55-58%) compared with patients receiving chemotherapy (26%; $P = .0037$). Since the publication of the CUP Trial, additional multicenter and registry trials performed in the rituximab era have reported 3- to 5-year PFS/EFS between 36% and 57% and 3- to 5-year OS between 59% and 87% following auto-HCT in the R/R setting (Table 1). Based on these data, auto-HCT is an accepted route of salvage therapy for patients with FL manifesting chemosensitive disease in the primary refractory, first relapse, second relapse, or subsequent relapse setting, although the best results are seen when used prior to the third relapse.[7] Similar recommendations are made for auto-HCT in patients with WM or MZL, although data on the use of these approaches following failure of BTK inhibitors are lacking.[16-18] For WM, the mSMART guidelines published in 2016 cite a nonrelapse mortality (NRM) of 3.8% and estimated 5-year PFS and OS rates of 40% and 69%, respectively, attesting to the tolerability and efficacy of auto-HCT for younger patients with relapsed chemosensitive disease.[17] Similarly, 5-year EFS and OS were reported to be 53% and 73%, respectively, for MZL patients undergoing auto-HCT between 1994 and 2013 although the NRM was higher (9%).[18]

Factors associated with outcomes. Multiple variables come into play when considering auto-HCT for R/R FL; however, chemosensitive disease, or lack thereof, likely plays the largest role in outcomes. Data from our center indicate that chemosensitivity defined as a CT-assessed partial response or CR prior to transplant, as well as pretransplant Follicular Lymphoma International Prognostic Index score, is independently associated with survival.[19] Patients entering transplant in remission had twofold greater survival compared with those who did not. We also retrospectively evaluated the impact of rituximab sensitivity and noted that this was the most important predictor of PFS (HR for progression or death, 0.35; $P = .006$) and OS (HR for death, 0.24; $P = .01$), when evaluated in the context of other available factors.[20] Fluorodeoxyglucose–positron emission tomography has also been shown to be associated with outcomes in this setting. A French series of 59 patients with chemosensitive relapsed FL found that those with residual fluorodeoxyglucose-avid disease with a Deauville score ≥ 3 had a 3-year PFS of 42.8% vs 74.9% in the other patients ($P = .02$).[21] The HCT-Comorbidity Index (HCT-CI) has also been widely used to help evaluate the appropriateness of HCT for an individual patient.[22]

Use in specific high-risk populations. As noted above, patients relapsing early following chemoimmunotherapy have been defined as a group with inferior survival and in whom alternative strategies may be warranted. Casulo et al evaluated FL patients with POD24

Table 1. Selected studies of auto-HCT in relapsed follicular lymphoma

Study	Design	Patients, n	PFS, % (follow-up, y)	OS, % (follow-up, y)
"CUP" Trial; Schouten et al[15]	Prospective randomized	65	55-58 (2)	71-77 (4)
NCCN Lymphoma Outcomes; Evens et al[28]	Multicenter	135	57 (3)	87 (3)
CIBMTR; Kluchnikov et al[46]	Registry	250	41 (5)	74 (5)
CIBMTR; Kluchnikov et al[47]	Registry	136	36 (5)	59 (5)
EBMT Lymphoma Working Party; Robinson et al[48]	Registry	726	48 (5)	72 (5)

CIBMTR, Center for International Blood and Marrow Transplant Research; EBMT, European Society for Blood and Marrow Transplantation; NCCN, National Cancer Care Network.

from registry data who did (n = 175) or did not (n = 174) undergo auto-HCT.[23] The investigators did not observe any difference in 5-year survival between the groups as a whole, but they did note that survival was better in the auto-HCT group for patients who were transplanted within a year of early treatment failure (70% vs 63%, $P = .05$). The potential benefit of early auto-HCT was also identified in a multivariable analysis of this data set, noting major limitations and potential unaccounted imbalances from retrospective data. Jurinovic et al evaluated FL patients in 2 prospective trials and showed that 77% of those with POD24 who underwent auto-HCT had a 5-year survival, from the start of second-line therapy, compared with 59% of those who did not ($P = .031$).[24] Although one has to acknowledge the challenges in comparing nonrandomized transplant data with nontransplant data, these results continue to support auto-HCT as an option for FL patients with chemosensitive POD24.

Novel strategies. No data to date have indicated that 1 conditioning regimen is clearly superior to another. Retrospective data evaluating the addition of radioimmunotherapy with ^{90}Y-ibritumomab tiuxetan (Zevalin) to standard BEAM or rituximab-BEAM conditioning did not show a benefit to either approach, although the potential benefit of adding radioimmunotherapy may have been obscured by the fact that only 1% to 2% of patients were noted to have active disease before transplant.[25] Rituximab maintenance after auto-HCT is generally not recommended in rituximab-exposed patients, although novel post–auto-HCT maintenance strategies with agents, such as idelalisib, are currently being evaluated (NCT03133221).[26]

Case 2

L.R., a 54-year-old chef diagnosed at age 37 years with stage IV FL, was treated with consecutive lines of chemotherapy and rituximab, with progressively shorter times to progression. He eventually had his third remission consolidated with high-dose therapy, followed by auto-HCT, resulting in a 6-year remission. After a period of initial observation following his third relapse, he was treated with bendamustine and rituximab, which yielded a good partial remission, although prolonged cytopenias after the fourth cycle prohibited additional chemotherapy. He had no fully HLA-matched sibling donor (HLA-MSD) or HLA-matched unrelated donor (HLA-MUD) available. Thus, he underwent reduced intensity allo-HCT using posttransplant cyclophosphamide graft-versus-host disease (GVHD) prophylaxis from his haploidentical brother and remains in remission without active GVHD 4 years after allo-HCT.

Indications for allogeneic stem cell transplantation

Allogeneic stem cell transplantation offers potential long-term disease control for relapsed chemosensitive FL, but it is generally not considered unless auto-HCT fails or patients are otherwise unable to undergo or are unlikely to benefit from auto-HCT. When performed in first relapse or beyond, retrospective data would suggest that, although the GVL effect may confer a disease-free survival (DFS) advantage compared with auto-HCT, higher NRM and treatment-related mortality (TRM) abrogate much of the differences in OS. However, comparisons of outcomes following allo-HCT with other therapies can be challenging based on varied patient and disease characteristics.

Myeloablative conditioning

The first large registry trial performed in the prerituximab era evaluated 904 patients reported to the International Bone Marrow Transplant Registry between 2000 and 2009. It compared the outcomes of 131 (14%) patients receiving purged auto-HCT, 597 (67%) patients receiving unpurged auto-HCT, and 176 (19%) patients receiving myeloablative allo-HCT for FL.[27] Although myeloablative allo-HCT conferred a 5-year DFS advantage of 45% vs 31% to 39% for auto-HCT, this was offset by higher 5-year TRM of 30% vs 8% to 14% for auto-HCT. Therefore, no survival benefit was seen in this study, with 5-year OS rates of 51% (allo-HCT) vs 55% to 62% (auto-HCT).

Reduced-intensity and nonmyeloablative conditioning

Because of the high rates of NRM and TRM seen in earlier studies using myeloablative conditioning regimens, increased efforts were undertaken to decrease toxicities and expand treatment options for older less-fit patients. Most allo-HCTs now use reduced-intensity conditioning (RIC) or nonmyeloablative (NMA) conditioning regimens. In the rituximab era, a comprehensive analysis from the National Cancer Care Network Lymphoma Outcomes Project evaluated the outcomes of 184 patients with R/R FL, of whom 136 (74%) received an auto-HCT and 48 (26%) received an allo-HCT.[28] RIC was the conditioning regimen used for most allo-HCTs. The 100-day NRM for auto-HCT and allo-HCT was 1% and 6%, respectively ($P < .0001$), whereas 3-year NRM was 3% and 24%, respectively ($P < .0001$). For auto-HCT and allo-HCT, cumulative rates of relapse, progression, and/or transformation were 32% vs 16%, respectively ($P = .03$), and 3-year OS rates were 87% vs 61%, respectively ($P < .0001$).

Another multicenter study evaluated 62 patients with R/R or transformed indolent NHL treated with RIC allo-HCT between 1998 and 2002. The 3-year estimated OS was 52% and PFS was 43% for patients with indolent disease, 87% of whom had FL. These rates increased to 67% and 54% if a related donor was used; however, the 3-year cumulative NRM was still high (42%) for the entire study population, and it was 23% for indolent patients receiving a related allograft.[29]

More recently, data from the Center for International Blood and Marrow Transplant Research (CIBMTR), comparing cohorts of older patients (age ≥ 65 years) and younger patients (age 55-64 years), examined the outcomes of 1629 patients undergoing a RIC or NMA allo-HCT between 2008 and 2015. The 4-year adjusted probabilities of NRM, PFS, and OS of the younger (n = 1183) and older (n = 446) cohorts were 24% vs 30% ($P = .03$), 37% vs 31% ($P = .03$), and 51% vs 46% ($P = .07$), respectively.[30]

Table 2. Selected studies of allo-HCT in relapsed follicular lymphoma

Study	Design	Patients, n	Conditioning regimen	NRM, % (follow-up, y)	GVHD	PFS/DFS, % (follow-up, y)	OS, % (follow-up, y)
van Besien et al[27]	Registry	176	100% HLA-MSD, 68% TBI based, 32% non-TBI based.	30 (5)	—	45 (5)	51 (5)
NCCN Lymphoma Outcomes; Evens et al[28]	Multicenter	48	63% HLA-MSD; 37% HLA-MUD; 31% fludarabine, melphalan; 29% TBI based; 23% busulfan, fludarabine; 17% other.	24 (3)	—	52 (3)	63 (3)
Rezvani et al[29]	Multicenter	62	55% related, 45% unrelated; 2 Gy fludarabine.	42 (3)	Acute GVHD: grade 2, 45%; grade 3, 8%; grade 4, 10%.	54 (3)	67 (3)
CIBMTR; Shah et al[30]	Registry	1629	HLA-MSD, HLA-MUD, mm-URD, RIC, or NMA.	24-30 (4)	Grades 2-4, 35-38% (180 d).	31-37 (4)	46-51 (4)
Tombyln et al[31]	Prospective*	8	HLA-MSD, RIC (fludarabine, cyclophosphamide, rituximab).	0 (3)	Grades 2-4, 0%.	86 (3)	100 (3)

mm-URD, mismatched unrelated donor; NCCN, National Cancer Care Network.
*Early closure from low accrual.

RIC allo-HCT vs auto-HCT

The Blood and Marrow Transplant Clinical Trials Network did attempt to prospectively compare outcomes of patients with relapsed chemotherapy-sensitive FL assigned to receive RIC allo-HCT vs auto-HCT, but slow accrual led to early study closure. However, after a median follow-up of 3 years, the reported OS in the 8 patients receiving RIC (fludarabine, cyclophosphamide, rituximab) allo-HCT was 100% compared with 73% in the 22 patients receiving an auto-HCT. The 3-year PFS was also superior in the allo-HCT cohort (86% vs 63%). Interestingly, the investigators found a higher 1-year and 3-year TRM for auto-HCT compared with prior studies (15% and 21.8%, respectively); however, given the premature closure of this study and the small number of enrolled patients, definitive conclusions could not be drawn.[31] Cumulatively, these studies show allo-HCT as a potentially curative option for relapsed FL because of the lower disease relapse rates compared with auto-HCT (Table 2); however, TRM rates >30%, even with RIC or NMA, in some series may offset this benefit. Furthermore, multiple pre-HCT factors, logistics, and donor availability often dictate whether auto-HCT or allo-HCT is considered at the time of relapse.

Similar data have been reported in small series of WM and MZL patients receiving allo-HCT. A retrospective analysis of WM patients receiving myeloablative conditioning (n = 37) or RIC (n = 49) allo-HCT reported a 3-year NRM of 23% but a higher relapse rate in RIC patients (25%) compared with myeloablative conditioning patients (11%); however, 5-year PFS and OS were similar for both groups, 49% and 64% for RIC and 56% and 62% for myeloablative conditioning, respectively.[32] With regard to MZL, a very small analysis of 6 patients receiving both myeloablative conditioning and RIC allo-HCT between 2001 and 2017 reported a median PFS and OS of 23 months and a 5-year OS of 44%, suggesting potential curative effects of GVL in both of these indolent etiologies, but careful selection of patients is needed.[33]

Factors associated with outcomes

The European Society for Blood and Marrow Transplantation and the CIBMTR conducted a retrospective analysis of 1567 patients, the largest cohort ever studied, to ascertain the role for allo-HCT in relapsed FL treated between 2001 and 2011 and to determine the factors associated with outcomes.[34] Despite differences in clinical practice between European and US transplant centers, the adjusted 5-year PFS was 52% for both; OS was 62% and 61%, respectively, for the European Society for Blood and Marrow Transplantation and CIBMTR patients; and 5-year cumulative incidence of TRM was 29%. After multivariate analysis, grade 3 histology, age at transplantation (continuous variable), prior lines of chemotherapy, chemorefractory disease, poor performance status, and myeloablative conditioning regimens were found to be adverse prognostic factors. There was no difference in outcomes found between HLA-MSDs and HLA-MUDs in this large cohort of patients. The investigators concluded that allo-HCT should be considered earlier in a patient's FL course, particularly before multiple lines of chemotherapy are administered, chemorefractoriness develops, or performance status declines.

The contribution of rituximab-containing RIC regimens has also been described in 2 recent publications. The first analyzed the outcomes of >1400 transplanted patients (histologies included diffuse large B-cell lymphoma, FL, mantle cell lymphoma, and MZL) between 2008 and 2014 in the CIBMTR database. A 3-year PFS benefit was identified for individuals receiving a rituximab-containing RIC regimen compared with a nonrituximab-based approach (56% vs 47%, $P = .005$), even after multivariate analysis; however, no difference in OS was identified after multivariate analysis (risk ratio, 0.84; 95% CI, 0.69-1.02; $P = .08$).[35] A subsequent analysis limited to FL patients did not identify this PFS benefit when comparing fludarabine, cyclophosphamide, and rituximab (FCR) conditioning with fludarabine and busulfan conditioning (3-year PFS, 74% vs 71%, respectively; $P = .65$).[35] The 3-year OS rate was higher in the FCR group but the difference was not statistically significantly different (81% v. 73%, $P = .18$) because both regimens afforded excellent survival; however, the risk of chronic GVHD was reduced with FCR compared with fludarabine and busulfan (risk ratio, 0.52; 95% CI, 0.36-0.77; $P = .001$).[36] Taken together, these studies suggest a PFS benefit

Table 3. Considerations for use of auto-HCT and allo-HCT for indolent NHL

Auto-HCT	Allo-HCT
Both of the following: 1. Chemosensitive disease 2. Medically fit for high-dose therapy AND one of the following: 1. Relapse within 24 mo of initial chemoimmunotherapy 2. No more than third relapse 3. Desire for time off therapy 4. Short remission period after last therapy	All of the following: 1. Ability to achieve low disease burden before transplant, may be following novel nonchemotherapy agents. 2. Appropriate donor available 3. Medically fit/"younger" age AND one of the following: 1. Not eligible or have received prior auto-HCT 2. At least second relapse 3. Short remission period after last therapy

for rituximab-containing RIC for NHL as a disease group; however, this benefit is not seen when restricted to FL as a subtype. The OS data are still reassuring and compare favorably with selected studies (Table 2).

Novel approaches to allo-HCT

When HLA-MSDs are unavailable, HLA-MUDs are relied upon; however, availability is often driven by racial/ethnic background and timing. Haploidentical related donors can overcome potential barriers in identifying HLA-MUDs, but initial concerns were raised regarding the higher risk for NRM, disease relapse, and delayed immune reconstitution from efforts used to mitigate rejection and potential GVHD.[37] Posttransplantation cyclophosphamide (PT-Cy) helps to mitigate the morbid effects of GVHD, and this approach was evaluated in a group of 987 lymphoma patients receiving an allo-HCT from a haploidentical related donor (Haplo-HCT, n = 180) or an HLA-MSD (n = 807), of whom 232 were treated for FL.[38] All Haplo-HCT patients received PT-Cy, with or without a calcineurin inhibitor and mycophenolate mofetil; compared with their HLA-MSD counterparts, the 3-year PFS and OS were not significantly different between the groups: 48% vs 48% (P = .96) and 61% vs 62% (P = .82) for Haplo-HCT and HLA-MSD, respectively. The cumulative incidence of grade 2 to 4 acute GVHD at day 100 also did not differ: 27% for Haplo-HCT and 25% for HLA-MSD (P = .84). However, the cumulative incidence of chronic GVHD at 1 year after Haplo-HCT was reduced to 12% compared with 45% in HLA-MSD (P < .001), suggesting that Haplo-HCT followed by PT-Cy may decrease the risk for chronic GVHD and remains a viable approach to transplant should HLA-MSD or HLA-MUD be unavailable.

RIC using ^{90}Y-ibritumomab tiuxetan has also been evaluated in a number of phase 1/2 trials prior to allo-HCT for B-cell lymphoma. The intended goal is to provide early cytoreduction, even in patients with chemoresistant disease, thereby allowing time for the establishment of the GVL effect. In aggregate, these data suggest that ^{90}Y-ibritumomab tiuxetan can be safely added to a variety of RIC regimens without significant additional toxicity; perhaps the greatest benefit is seen in patients who had chemoresistant disease or otherwise could not achieve a CR prior to transplant, with 3-year PFS of 70% to 80% in this subset.[39,40]

When to refer for transplant

The decision to transplant R/R indolent NHL can be challenging in light of multiple targeted agents now approved in this setting and the rapid evolution of treatment options in this field. These approaches also have to be balanced with the short- and long-term toxicities of transplant. Table 3 lists scenarios in which an auto-HCT or allo-HCT should be considered. Auto-HCT would be appropriate for fit patients with chemosensitive disease (ideally in complete remission following salvage chemotherapy) suffering early progression (POD24), those with up to a third relapse, or potentially for those achieving a short remission (<6 months) following their last therapy.

For allo-HCT recipients, one must be cognizant of timing and logistics surrounding the referral and treatment process, because HLA typing, donor searches, and caregiver coordination may add weeks to months to the transplant process. Ideally, initiation of the transplant process should be synchronized with attainment of best response to pretransplant therapy. Likewise, comorbidity indices and risk calculators have been developed to help predict outcomes and NRM following HCT, but these should not negate the recommendations by a transplant specialist. Ultimately, referrals to and recommendations by a major transplant center will dictate whether a patient receives an allo-HCT, after taking into consideration multiple factors. Generally, patients who are 65 years or younger with relatively few or well-controlled comorbidities who desire longer-term remission or the potential for cure and are willing to take on the risks should be referred. Unlike auto-HCT, RIC allo-HCT does not rely on chemotherapy for long-term disease control, offering the opportunity of using novel nonchemotherapeutic agents to achieve a pretransplant remission.

Upfront and late adverse effects should also be taken into account when considering HCT. In addition to the expected, but manageable, short-term effects of myeloablative therapy, the major long-term consideration centers on secondary malignancies, primarily treatment-related myelodysplastic syndrome (MDS) or acute myelogenous leukemia (AML). Older studies have reported rates of 8% to 21% up to 10 years and >30% at 15 years after auto-HCT, with risk factors being radiation-based conditioning, extensive prior therapies, alkylating agents, topoisomerase inhibitors, and fludarabine.[41,42] A recent large Surveillance, Epidemiology, and End Results registry data evaluation suggests that MDS/AML rates in the modern era are 6% (95% CI, 5-7) at 10 years, with adverse risk factors that can be used for patient selection or treatment modification, including age > 55 years, ≥3 prior chemotherapy regimens, and TBI or busulfan-based conditioning.[43] These data suggest that, although secondary MDS/AML must be considered, the risk may be lowest in young less heavily pretreated patients conditioned with BEAM. Upfront risks for allo-HCT are generally related to acute GVHD and infectious complications, both of which can have a lifelong impact on quality of life. NRM ranges from 20% to 40% at 3 to 5 years in various studies (Table 2); these data should be made clear to patients relative to donor source and comorbidities prior to this undertaking.[27-31]

Treatment trends and cost

Data gathered by the CIBMTR as far back as the year 2000 show that ~2500 to 5000 auto-HCTs are performed annually for NHL/Hodgkin lymphoma, with an increase from 2500 to 4000 by the year 2009 and largely plateauing around 4500 annually since 2014. The number of auto-HCTs, specifically for FL and as measured by the CIBMTR, ranged from 130 to 180 annually between 2006 and 2018 (Mehdi

Hamadani, Medical College of Wisconsin, written communication, 19 May 2019). Between 2006 and 2015, ~500 to 1000 allo-HCTs were performed annually for NHL/Hodgkin lymphoma, with a clear decline since 2014 in the numbers of HLA-MRD and HLA-MUD for FL specifically. The declining trend in the use of HCT in R/R FL in the past decade may be due, in part, to a better recognition of prognosis, based on time to initial relapse, as well as a preference for continuously administered targeted therapies. However, in comparison with novel agents, HCT remains a potentially cost-effective episodic approach. Inpatient and outpatient direct medical costs from time of HCT to 100 days post-HCT were evaluated using a single longitudinal administrative claims database representing a national commercially insured population. During the study period from 2007 to 2009, the median total cost for an auto-HCT in lymphoma was $102 458, with 75% incurred during the transplant hospitalization.[44] Costs for allo-HCT in lymphoma were not available, although for other hematologic malignancies (AML, MDS, acute lymphoblastic leukemia) the median total cost was $191 142.[44] More recent data from the national inpatient sample database estimate the cost for auto-HCT and allo-HCT to be $121 514 and $314 513 for lymphoma in the United States, with only 1% and 7% early TRM rates, respectively.[45] If one expects an ~50% 5-year PFS for patients with POD24 undergoing auto-HCT based on registry data, the costs and safety of transplant may compare favorably with the expenses, risks, and chronic toxicity of many of the continuous therapies that typically cost >$10 000 per month and often yield a PFS of only 1 to 2 years.[24]

Summary

The introduction of multiple targeted agents for indolent NHL has complicated the role of transplant. Despite the wealth of treatment options, specific subsets of patients, including those with chemosensitive early relapse, short remission durations, or even a desire for episodic therapy over chronic therapy, may benefit from auto-HCT. Allo-HCT can be considered for select patients who are unable to receive or have suffered relapse after an auto-HCT, and it offers the potential for cure. Furthermore, HCT may be economically sound compared with costly chronic treatments. Improvements in conditioning regimens, donor options, and GVHD prevention have the potential to further improve outcomes.

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