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Is It Time to Revisit the Role of Allogeneic Transplantation in Lymphoma?

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Abstract

Purpose of Review A multitude of new drug and cell therapy approvals for lymphoma has prompted questions about the role of allogeneic blood or marrow transplantation (allo-BMT). We sought to review the latest evidence examining the role of allo-BMT for lymphoma in this evolving landscape.

Recent Findings Despite several new drug classes, there remains a large unmet need, particularly in hard to treat subtypes of lymphoma and for patients with relapsed/refractory disease. Allo-BMT can provide an opportunity for cure due to a potent graft vs lymphoma effect in high-risk relapse/refractory follicular lymphoma, mantle cell lymphoma, and aggressive T cell lymphomas. Chimeric antigen receptor T cell therapy and checkpoint blockers have improved outcomes for patients with relapsed /aggressive B cell lymphomas and Hodgkin lymphoma respectively; the role of allo-BMT consolidation in the treatment algorithm for responders to these therapies is an evolving topic.

Summary Expanded donor availability including haploidentical relatives has improved access to allo-BMT. Non-myeloablative conditioning regimens and post-transplant cyclophosphamide prophylaxis have improved early transplant-related morbidity and rates of graft versus host disease and translated into long-term survival for patients with lymphoid malignancies. Patient selection remains key, but allo-BMT remains the only modality able to deliver durable long-term remissions across different types of lymphoma.

Keywords Allogeneic transplant · Lymphoma · Diffuse large B cell lymphoma · Graft-versus-lymphoma effect · Graft vs host disease · Hodgkin lymphoma · Mantle cell lymphoma · Non-Hodgkin lymphoma

Introduction

The last decade (2008–2018) has seen rapid growth in approvals of new drugs, novel drug classes, and unique modalities of therapy in oncology, and particularly in the hematological malignancies [1]. This expansion has been driven by targeted and immunotherapeutic drugs with the promise of a much-improved efficacy: toxicity ratio compared with traditional cytotoxics. The purpose of this review is to revisit the role of allogeneic blood or marrow transplantation (allo-BMT) in the rapidly evolving world of lymphoma therapeutics, especially where it currently fits into our treatment paradigms.

A majority of these new therapies are "palliative" rather than "curative," i.e., providing disease control and delaying relapse rather than durable remissions. Moreover, most of these agents have, when successful, achieved chronic suppression of disease and thus entail indefinite drug therapy (and

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toxicities, both medical and financial), with relapses off therapy being the norm.

The evidence of a graft-versus-lymphoma (GVL) effect of allo-BMT (independent of pre-transplant cytotoxic therapy) was initially recognized in the early 1990s; in patients with relapsed Hodgkin lymphoma or high-grade non-Hodgkin lymphoma, the actuarial probability of relapse was only 18% after allo-BMT compared with 46% after autologous BMT. But the event-free survival at 4 years was similar—47% versus 41% for both groups, as a result of higher transplant-related mortality resulting from graft-versus-host disease (GVHD) and immunodeficiency [2]. Multiple subsequent studies confirmed the similar outcomes between allo- and auto-BMT; relapse rates being lower with allo-BMT but eventually similar long-term survivals due to allo-BMT related non-relapse mortality [3–5].

Allo-BMT technologies have evolved vastly over the last decade, making it safer and more accessible. Early mortality has improved with non-myeloablative/reduced intensity conditioning (NMA/RIC). Alternate graft sources, especially from related HLA-haploidentical (haplo) donors, have dramatically improved the wait times and simplified the logistics of allo-BMT. Recent registry analyses demonstrated that haplo allo-BMT with post-transplantation cyclophosphamide (PTCy) was associated with similar rates of relapse and survival as both HLA-matched unrelated donor (MUD) and matched sibling donor (MSD) allo-BMT [6•, 7•]. A CIBMTR registry study comparing haplo with PTCy allo-BMT to MUD allo-BMT found the 100-day cumulative incidence of grades III–IV acute GVHD rate of just 8% and the 1-year rate of chronic GVHD of 13% in the haplo arm [6•]. Haplo with PTCy allo-BMT was compared with MSD allo-BMT in a separate CIBMTR analysis; cumulative incidence of grades II to IV acute GVHD at day 100 was similar between the two groups (27% vs 25%) while cumulative incidence of chronic GVHD at 1 year was significantly lower with haplo allo-BMT (12% vs 45%; $P < .001$). Most importantly, major outcomes were similar between haplo allo-BMT and MSD allo-BMT with the haplo arm showing 3-year rates of non-relapse mortality of 15%, relapse rate of 37%, progression-free survival of 48%, and overall survival of 61% [7•]. Thus, haplo with PTCy is a major breakthrough in transplant technology that has made allo-BMT much easier and faster to access with improvement in overall efficacy and safety of transplantation.

Emerging data also suggest younger donors (under age 40) may yield better allo-BMT outcomes than older donors [8•]. Therefore, not only have modern approaches whittled away many of the problems associated with allo-BMT including donor availability [9, 10] but early post allo-BMT may be a unique setting to optimize cure. Not only should this be a time of lowest tumor burden and tumor heterogeneity, but a new, active, non-tolerant immune system may cooperate with antitumor approaches. Thus, integrating novel therapeutics into post-transplant maintenance is an attractive future strategy to maximize the GVL effect.

Lymphomas are a heterogeneous group of malignancies with differing treatment paradigms and prognoses. Thus, the role of allo-BMT is likely to differ by subtype, particularly in view of all the new treatments for lymphoma. Below, we review the data around the role of allo-BMT for the major subtypes of lymphoma in this evolving landscape.

Follicular Lymphoma

Follicular lymphoma (FL) is the most common type of low-grade lymphoma and in most cases exhibits behavior of relapses sensitive to therapy—either chemotherapy, radiation, or targeted therapy. The plethora of new drug class FDA approvals for low-grade B cell lymphomas in the last decade has unfortunately not translated to more options for treating patients with FL, except for three PI3 kinase inhibitors (Table 1). Despite the overall favorable outlook for most patients with FL, there remains an unmet need for a substantial proportion of patients with treatment-resistant disease, those with early relapse < 2 years after chemo-immunotherapy and those with histologic transformation (which occurs at a rate of approximately 2–3% per year) [11–13].

Multiple trials have studied auto-BMT consolidation after response to frontline chemo-immunotherapy. Virtually, all these trials show a progression-free survival (PFS) benefit that has not translated to an improvement in overall survival (OS), as the median survival for patients with FL is now nearly 20 years. Moreover, patients continue to relapse after auto-BMT out to 20 years [14, 15]. Both pre and post-rituximab era studies showed a significant PFS benefit from auto-BMT consolidation in relapsed FL, but the benefit of just adding rituximab seemed to supersede the advantage from auto-BMT [16, 17].

To date, no randomized prospective trials comparing auto to allo-BMT have been completed successfully; thus, we are left with using retrospective data comparing unequally matched populations of patients. For example, a National Comprehensive Cancer Network (NCCN) study examined outcomes in 184 patients with relapsed/refractory FL who underwent auto or allo-BMT following disease relapse after prior rituximab-based therapy. Improvements in relapse rates with allo-BMT were far overshadowed by early transplant-related mortality [18]. A Canadian retrospective cohort study in patients with transformed FL—undoubtedly an extremely high-risk group—found similar 5-year OS and PFS between those treated with auto- and allo-BMT [19].

More recent studies have shown the converse in the auto vs allo-BMT debate. A registry study retrospectively evaluated the optimal first transplantation approach in relapsed/

Table 1 FDA-approved novel therapies for lymphoma 2008–2018 grouped by subtype of lymphoma and drug class

Lymphoma subtype	Low grade B cell		Aggressive B cell		Classical Hodgkin Lymphoma		T cell lymphoma	
Therapies by drug class	BTKi	Ibrutinib/Acalabrutinib	CART	Tisagenlecleucel/Axicabtagene ciloleucel	ADC	Brentuximab vedotin	ADC	Brentuximab vedotin
	Pi3Ki	Idelalisib/Copanlisib/Duvelisib			PD1	Nivolumab/Pembrolizumab	FA	Pralatrexate
	BCL2	Venetoclax					HDAC	Romidepsin /Belinostat
	IMID	Lenalidomide					AB	Mogamulizumab
	AB	Obinutuzumab						
	PI	Bortezomib						

BTKi, Bruton's tyrosine kinase inhibitor; *Pi3ki*, phosphoinositide 3-kinase inhibitor; *BCL2*, B cell lymphoma-2 inhibitor; *IMID*, immunomodulator; *AB*, antibody; *PI*, proteasome inhibitor; *ADC*, antibody-drug conjugate; *PD1*, programmed cell death protein-1 inhibitor; *FA*, folate analog antimetabolite; *HDAC*, histone deacetylase inhibitor

refractory grade 3 FL patients; within the first 11 months post BMT, auto- and allo-BMT had similar risks of relapse/progression and PFS. Beyond 11 months, auto-BMT was associated with a higher risk of relapse/progression (RR = 21.3; $P = 0.003$) and inferior PFS (RR = 3.2; $P = 0.005$) [20]. Similar results have been obtained in grades 1–2 relapsed/refractory FL with an early survival advantage for auto-HSCT in the first 24 months, but an inferior OS beyond 24 months. A landmark analysis of patients alive and progression-free at 2 years after BMT showed a significantly higher risk of relapse/progression (RR, 7.3; $P < .0001$) and inferior PFS (RR, 3.2; $P < .0001$) and OS (RR, 2.1; $P = .04$) after auto-HSCT [21].

The largest study of allo-BMT in FL is a European Society for Blood and Marrow Transplantation (EBMT) and the Center for International Blood and Marrow Transplant Research (CIBMTR) combined analysis of 1567 relapsed FL patients who underwent allo-BMT from 2001 to 2011 with a HLA-matched donor. A prognostic score incorporating age, lines of prior therapy, disease status, and performance status stratified patients into three groups—low, intermediate, and high risk—with 5-year PFS rates of 68%, 53%, and 46%, and 5-year OS rates of 80%, 62%, and 50%, respectively. The group concluded that RIC allo-BMT should be considered for relapsed FL as it remains the only potentially curative treatment option [22•]. Our practice is to consolidate fit patients with high-risk relapse/refractory FL with non-myeloablative allo-BMT, including often using haplo donors. Although no randomized data exist to support this approach, there is clear evidence that a strong GVL effect exists and the rates of early non-relapse mortality (NRM) and GVHD are substantially better with modern transplant regimens. Moreover, emerging data suggest that the addition of rituximab as maintenance may reduce the relapse rate of FL [23] and other B cell lymphomas after allo-BMT [24].

Mantle Cell Lymphoma

Mantle cell lymphoma (MCL) is unique with features of both indolent and aggressive lymphomas. Although MCL can sometimes present indolently and not require therapy at diagnosis, relapsing MCL is a relentless disease characterized by chemo-resistance. Despite several novel drug classes (Bruton's tyrosine kinase inhibitors—Ibrutinib and Acalabrutinib, proteasome inhibitor Bortezomib, Bcl-2 inhibitor Venetoclax, and Lenalidomide) showing activity against relapsed MCL, response durations are short-lived compared with other B cell malignancies such as CLL [25, 26].

In one of the largest prospective randomized controlled trials of young (< 65 years old), fit patients with MCL, the addition of high-dose cytarabine to first-line chemo-immunotherapy and auto-BMT consolidation showed improvement in

PFS from a median of 4.3 years to 9.1 years. Despite these impressive results in the cytarabine group, late relapses were common even after long-lasting remissions and therefore even maximal intensity first-line therapy is unlikely to result in a cure of patients with MCL [27]. Smaller studies have shown similar late relapses after aggressive frontline therapy with auto-BMT consolidation [28]. A CIBMTR retrospective review of 519 MCL patients compared auto- and RIC allo-BMT outcomes at different times in the disease course. In both early and late transplantation cohorts, progression/relapse was lower and NRM was higher in the allo-BMT group [29]. Other real-world analyses of auto- vs allo-BMT in MCL have shown similar trends; patients undergoing auto-BMT had improved outcomes in the short run but had a continuing risk of relapse years post therapy, whereas survival curves plateaued in patients undergoing allo-BMT indicating a curative GVL effect [30].

Allo-BMT in Patients Aged > 65 Years

Some have suggested that allo-BMT may not be appropriate in older patients and since the average age of patients newly diagnosed with MCL is between 65 and 70 years, allo-BMT may not be generally applicable [31]. However, whereas end-organ toxicities limit the role of auto transplant in older patients, non-myeloablative allo transplant is a gentler procedure and we regularly transplant patients up to the age of 80 years. In patients 70–75-year age group, we have shown PFS and OS indistinguishable from that seen in cohorts of patients in their 50s and 60s [32•]. Chemo-responsiveness appears to be more important than the number of prior lines of therapy at the time of allo-BMT consolidation; a French retrospective study showed a median PFS after RIC allo-BMT of 34 months and median OS of 63 months for patients who achieved at least a partial response, compared with 4 months and 6 months respectively for patients with progressive disease at the time of transplant [33].

Our practice is to consolidate eligible (defined by functional age and comorbidities) patients with relapsed MCL after response to salvage therapy, with non-myeloablative allo-BMT in line with international guidelines [34]. As with follicular lymphoma, most MCL patients undergoing allo-BMT at our center use younger related haplo donors rather than older matched sibling donors because of evidence that outcomes with younger donors are better.

Aggressive B Cell Lymphoma

About 60% of patients with aggressive B cell lymphomas, diffuse large B cell lymphoma (DLBCL) being the most common subtype, are curable with chemo-immunotherapy. However, relapses are frequent, especially in patients with subtypes of aggressive lymphoma such as non-germinal center, double-hit, and double-expresser lymphomas. These relapsed lymphomas are also recalcitrant to salvage cytotoxics and auto-BMT consolidation [35]. In relapsed DLBCL patients who are transplant eligible and responsive to salvage chemotherapy, auto-BMT consolidation is clearly better than chemotherapy alone [36]. However, a significant proportion of patients either relapse post-auto or have chemo-refractory disease, predictive of a dismal 20% 2-year survival [37]. Moreover, the biology of DLBCL unresponsive to RCHOP appears to be worse than DLBCL refractory to CHOP alone, such that auto-BMT outcomes in the RCHOP era do not appear as favorable compared with the pre-rituximab era [38]. CAR-T cell therapies (Table 2) have offered the potential for a durable remission for patients with these very hard to treat aggressive lymphomas, but the limited follow-up period for these novel therapy trials makes long-term success hard to ascertain [40, 41]. Nevertheless, the current practice of most institutions is to not use allo-BMT consolidation for patients in complete response to CAR-T therapies.

There also remain a substantial proportion of patients with aggressive lymphoma unresponsive to or relapsing after CAR-T cell therapy. The role of allo-BMT in patients who relapse after auto-BMT is well established. A retrospective analysis by the CIBMTR analyzed data from 396 recipients of allotransplants for DLBCL receiving myeloablative (MAC; $n = 165$), reduced intensity (RIC; $n = 143$), or non-myeloablative conditioning (NMA; $n = 88$) regimens showed similar five-year PFS (15 to 25%) and OS (18 to 26%) rates across the three arms. The lower rates of NRM with RIC or NMA were balanced out by the lower risk of lymphoma progression/relapse with myeloablative conditioning [42].

Table 2 FDA-approved agents that have shown evidence of durable benefit off chronic therapy without allogeneic blood or marrow transplant

Drug/therapy	Indication for type of Relapse/refractory lymphoma	Results
Brentuximab vedotin	Classical Hodgkin lymphoma	9% patients in long-term remission without allo-HSCT [39]
Tisagenlecleucel	Aggressive B cell	42% complete response rate at median follow-up of 28.6 months [40]
Axicabtagene ciloleucel	Aggressive B cell	58% complete response rate with a median follow-up of 27.1 months [41]

Another EBMT study showed similar results, with RIC regimens showing a trend toward lower NRM, higher relapse rate, with no differences in PFS and OS [43].

In transplant-naïve patients with relapsed DLBCL, comparisons between auto- and allo-BMT in the 1990s showed lower relapse rates with allo-BMT but the benefit of the GVL effect on lymphoma relapse was offset by NRM associated with allo-BMT [44]. Our institutional experience published a decade ago was similar—auto- and allo-BMT produced similar OS for patients with relapsed DLBCL. For patients with chemo-sensitive disease, allo-BMT seemed to provide longer survival with less relapse; however, this was achieved at the cost of greater NRM [45]. The CIBMTR constructed a model using performance status, auto-BMT to allo-BMT interval and chemosensitivity to help identify a group of patients who might benefit the most from an allo-BMT after failing auto-BMT. Being identified as low risk in this model predicted a 3-year PFS of 40% and 3-year OS of 43% [46•]. Improvements in NRM with RIC conditioning have come alongside dramatic reductions in GVHD rates with PTCy. Our practice is to consolidate patients with high-risk relapsed aggressive lymphomas (such as double-hit lymphomas or those with a short disease-free interval after CR) in second remission with allo-BMT rather than auto-BMT.

T Cell Lymphomas

The mature T—and natural killer (NK)—cell lymphoma category encompasses a variety of different types of disease varying in aggressiveness, disease behavior, and prevalence. Peripheral T cell lymphoma, not otherwise specified (PTCL-NOS), angioimmunoblastic T cell lymphoma (AITL), and anaplastic large cell lymphoma (ALCL) are the most common subtypes of T cell lymphoma and therefore a majority of available allotransplant data is for these entities [47].

The major therapeutic advances in cell therapy for aggressive B cell lymphoma have not translated to the T cell lymphomas. Anthracycline-based cytotoxic therapy (with or without etoposide) remains the cornerstone of frontline therapy for most advanced T cell lymphomas, but long-term cure rates are poor with this strategy except in patients with ALK + ALCL [48]. Patients with CD30-expressing PTCL, especially ALCL, benefit from the addition of brentuximab vedotin (BV) to first-line therapy, but most patients with PTCL do not meet the > 10% CD30 expression eligibility criteria for addition of this antibody-drug conjugate [49]. Auto-BMT for younger, fit patients in first response has cemented its place in most guidelines, but without supportive data from prospective randomized controlled trials [50]. Doubts about the efficacy of auto-BMT have been cast by a recent multicentric study that aimed to correct for sample selection bias by stringent matching for potential confounding factors between patients allocated or not to auto-BMT. Neither the Cox multivariate model nor the propensity score analysis found a survival advantage in favor of auto-BMT as consolidation for patients in first response after induction [51]. Our current practice is to not recommend auto-BMT consolidation in first complete responders with PTCL-NOS, ALCL, or AITL.

Multiple retrospective studies have shown the benefit of allo-BMT in patients with relapsed T cell lymphomas [47]. The earliest was a 2004 study showing a 51% 5-year PFS for patients with chemo-sensitive relapse consolidated with allo-BMT [52]. In a large retrospective multicenter analysis of patients who underwent an allo-BMT for non-cutaneous PTCL between 2006 and 2014 in 34 French centers, 1 year and 2 year overall survivals were 68% and 64% with a low cumulative incidence of relapse of 22% at 2 years. The strongest signal for a GVL effect in T cell lymphoma is among the 30 patients transplanted in progressive disease (PD), 50% of whom reached CR after allo-BMT; 2 year-OS was 51% in this subgroup [53]. Another study reported outcomes in patients with relapsed T cell lymphoma who received an allo-BMT from years 2000–2017 at six centers in the USA. With a median follow-up for survivors of 49.17 months, the OS and PFS rates were 60.1% and 47.8% at 2 years [54].

Subtypes such as enteropathy-associated T cell lymphoma (EATL), hepatosplenic T cell lymphoma (HSTL), acute/lymphoma type adult T cell leukemia/lymphoma (ATLL), and gamma-delta subcutaneous panniculitis-like T cell lymphoma are rarer and present an even greater unmet need due to virtually non-existent cures with chemotherapy alone. Although most are case-reports or small retrospective case series, many long-term remissions after allo-BMT have been reported in each of these highly aggressive T cell lymphomas [54–56]. The 2017 Guidelines Committee of the American Society for Blood and Marrow Transplantation (ASBMT) recommended allo-BMT consolidation in patients with relapsed/refractory EATL, HSTL, ATLL, and subcutaneous panniculitis-like T cell lymphoma, especially in the setting of chemo-sensitive relapse. In addition, allo-BMT is recommended as consolidation in first-line responders with acute/lymphoma type ATLL and HSTL [57].

Cutaneous T cell lymphoma (CTCL) is a particularly challenging disease to treat; survival in advanced stages (IIB and beyond) is poor, and relapsing disease in the skin provides a constant nidus for systemic infections. Despite these challenges, several groups have reported positive long-term outcomes of allo-BMT in CTCL. The EBMT reported on 60 patients with mycosis fungoides (MF) ($n = 36$) and Sezary syndrome (SS) ($n = 24$) with a median of four prior treatments; the OS was 48%, and PFS was 33% after allo-BMT at 5 years [58]. Similar results were seen in a retrospective study by MD Anderson, but outcomes in patients with SS without large cell transformation (LCT) (four-year PFS of 73%) was dramatically better than in MF with or without transformation [59].

Other groups have shown no difference in CTCL patient outcomes with or without large cell transformation [60]. Overall, the theme of all reported retrospective studies of allo-BMT in CTCL supports a GVL effect that works better in patients who have a low disease burden and fewer lines of therapy. The advanced stage cutaneous T cell lymphomas pose a unique challenge for allo-BMT given the infection risk in patients with skin disease along with skin GVHD after BMT. The best time to get these high-risk patients to allo-BMT is when the disease is in remission, especially in the skin compartment. Our practice is to consider it early, especially in patients with erythrodermic SS, who are in a good remission.

Hodgkin Lymphoma (HL)

The antibody-drug conjugate Brentuximab vedotin (BV) produces an overall response rate of 75% in patients with relapsed/refractory cHL after failed auto-BMT, but only a small fraction of those who have a complete response (CR) are durable without further consolidation. In the pivotal trial, of the 34 patients who achieved a CR after BV, 6 underwent a consolidative allo-BMT with estimated 5-year PFS and OS rates of 67% and 83%. The other 28 patients in CR who did not undergo consolidative allo-BMT had estimated 5-year PFS and OS rates of 48% and 60% respectively [39]. Overall, only 9% of all enrolled patients remained in sustained CR without receiving any further anticancer therapy after treatment with BV.

The benefit of allo-BMT in relapsed/refractory HL was not realized until recently; the lack of donors and high NRM drastically limited the long-term benefit that patients could derive from the GVL effect in early studies. A meta-analysis of allo-HSCT of 1850 patients treated for HL showed 3-year relapse-free survival of 31% and OS of 50%. Accrual initiation year in 2000 or later was associated with 5–10% lower non-relapse mortality and relapse rates, and 15–20% higher relapse-free and overall survival [61].

Genetic alterations causing overexpression of programmed death-1 (PD-1) ligands are near universal in Hodgkin lymphoma and thereby make these tumors exquisitely sensitive to PD-1 blockade with the checkpoint inhibitors Nivolumab or Pembrolizumab. In patients with relapsed /refractory HL, Pembrolizumab monotherapy showed an overall response rate of 71.9% with a median duration of response of 16.5 months and 2 year PFS rate of 31.3% [62]. Similarly, in patients with relapsed/refractory HL, Nivolumab had a 69% response rate with a median duration of response of 16.6 months and median progression-free survival of 14.7 months [63]. Despite these impressive results, the PFS curves with checkpoint inhibitors show a continuous decline over time. The most durable responses were observed in patients who attained initial complete response to Nivolumab (16% of the entire cohort); approximately two-thirds of these patients were free of progression and alive at the 21-month mark.

The GVL effect, which is responsible for durable remission is not dependent on the intensity of the preparative regimen. Multiple studies have now shown improved NRM and OS with RIC regimens [64, 65]. Alternate donor sources using umbilical cord blood and HLA haploidentical donors have overcome most problems related to donor availability for allo-BMT [66, 67]. A multicenter retrospective review of RIC allo-BMT in 90 patients with relapsed or refractory HL compared outcomes with using matched related ($n = 38$), unrelated ($n = 24$), or haplo with PTCy ($n = 28$) donors. Two-year OS and PFS were 53% and 23% (matched related), 58% and 29% (unrelated), and 58% and 51% (haplo), respectively. The risks of relapse were lower in the HLA-haploidentical recipients compared with the other two groups and neither acute nor chronic GVHD rates were increased [67]. Although limited by small numbers and short follow-up, there does not seem to be an adverse safety signal in patients undergoing allo-BMT after PD-1 inhibition. Forty-four patients underwent consolidative allo-BMT after treatment with Nivolumab; the rates of transplant-related mortality and acute grade 3–4 GVHD were not higher than expected despite prior exposure to checkpoint blockade. Median PFS and OS after allo-BMT were not reached in this group, with a 6-month PFS estimate of 82% and a 6-month OS estimate of 87% [63]. Thus, in eligible patients with relapsed HL who have failed auto-HSCT or had an incomplete response to salvage therapy (such as BV), our practice is to consolidate with non-myeloablative allo-BMT using related, including haplo, donors.

Summary

Despite advances in drug therapy for lymphoma, there remains a large unmet need for novel approaches that harness the immune system for a durable response. Allo-BMT related toxicities have declined dramatically in the last decade using non-myeloablative conditioning, and modern-day immunosuppression with PTCy has minimized long-term risks such as GHVD. The availability of a suitable related donor (including haplo) makes the procedure available for nearly all patients in need. The GVL effect ultimately can serve as a relatively inexpensive alternative to novel targeted or immunotherapy of indefinite duration. A year (1 month before to 12 months after) all-inclusive cost of mini allo-BMT at our institution is USD 150,000–200, 000, significantly less than approved CD19 CAR T cell therapies (approximately USD 400,000 for manufacture alone, excluding the cost of toxicity management) and cumulative cost of most novel drugs that need to be given for years to maintain remission. Post-transplant maintenance therapy such as rituximab [[23, 24]]

and other targeted agents may be particularly effective in improving outcomes in the setting of low tumor burden and a new, non-tolerant immune system. More trials and tools are needed to fine-tune the right patient and timing for allo-BMT in patients with different subtypes, but allo-BMT remains alive and kicking in the world of lymphoma therapeutics.

Compliance with Ethical Standards

Conflict of Interest Satish Shanbhag has received institutional research support from America Regent/Daiichi-Sankyo and participated on an advisory board for Takeda.

Nina Wagner-Johnston has participated on advisory boards for Bayer and Gilead.

Richard F. Ambinder declares that he has no conflict of interest.

Richard J. Jones declares that he has 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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