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Symposium Report

Posttransplantation Management Strategies for Patients with Lymphoma

Adapted from a continuing medical education symposium presented at the 2015 BMT Tandem Meetings on February 12, 2015, in San Diego, California.

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Statement of Need

Non-Hodgkin lymphoma (NHL) is the 8th most common cancer in men and the 11th most frequent cancer in women worldwide. In the United States, NHL is the most common hematopoietic neoplasm. The National Cancer Institute (NCI) estimates that in 2014 there were 70,800 new cases of NHL in the US and some 18,990 deaths. NHLs are a group of lymphoproliferative malignancies with differing patterns of presentation and responses to treatment. These tumors characteristically originate in the lymphoid tissues and may result from genetic alterations or damage to the cells related to infection, immunosuppression, or chronic inflammation. Hodgkin lymphoma (HL) is less common than NHL. The NCI estimates that in 2014 there were 9,190 new cases of HL in the US and some 1,180 deaths.

Treatment for lymphoma depends on the histologic type, stage, and grade. In asymptomatic patients with indolent forms of advanced NHL, treatment may be deferred until the patient becomes symptomatic. Frequent and careful observation is required in these patients to monitor possible disease progression. To assist practitioners, standardized guidelines for treatment and response assessment have been suggested.

Traditional therapies for lymphoma may include radiation therapy; rituximab standalone therapy; combination therapy of rituximab, cyclophosphamide, hydoxydaunorubicin, vincristine, and prednisone (R-CHOP) with or without radiotherapy (IF-XRT); lenalidomide; ibritumomab tiuxetan; and tositumomab. In addition, several new therapies are being investigated as standalone options and in combination with existing treatment regimens. These include: alisertib, bendamustine hydrochloride, brentuximab vedotin, and lenalidomide.

The National Cancer Institute recommends bone marrow transplantation (BMT) as the treatment of choice for patients whose lymphoma has relapsed. Data suggest that approximately 20% to 40% of

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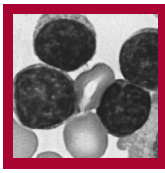

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patients will have a long-term disease-free status following BMT. The NCI notes that in general, re-treatment with standard agents rarely produces a cure in patients with relapsed/refractory lymphoma, though several salvage chemotherapy regimens are available and trials are underway on emerging therapeutic options.

This activity is based on a live symposium where leading experts discussed the role of BMT; current and emerging treatment strategies for patients with relapsed/refractory lymphoma following transplantation; and the post transplantation management strategies for patients with lymphoma.

Learning Objectives

Upon completion of the program, participants should be able to:

1. Discuss the established role and controversies in bone marrow transplantation and post transplantation management of patients with lymphoma
2. Review the current treatment strategies and expected outcomes for patients with relapsed/refractory lymphoma following transplantation
3. Evaluate recent safety and efficacy data from clinical trials of new post-transplant treatment strategies for lymphoma

Target Audience

This activity has been developed and is intended for transplant specialists, oncologists, hematologists, and other healthcare professionals involved in the treatment of patients with lymphoma.

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Jack W. Hsu, MD, has no relevant financial relationships to disclose.

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A Cornucopia of Options for Improving Outcomes for High Risk Lymphomas

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Hematopoietic cell transplantation has become a cornerstone in the management of patients with lymphoma. The use of autologous transplant in Hodgkin's and non-Hodgkin's lymphoma has significantly improved the survivals of patients with relapsed disease. In patients with high risk disease, allogeneic transplant can improve both progression free and overall survivals by harnessing the graft-versus-tumor effect. Unfortunately, relapse is still a major problem post-transplant, and remains the most frequent reason for failure. In particular, patients who relapse after transplantation have received a significant number of lines of chemotherapy and have limited hematopoietic reserve. They may also have significant comorbidities, which limit their tolerance to traditional chemotherapeutic agents. Despite these obstacles, new strategies have been devised to treat these difficult populations of patients. Some options include maintenance regimens, immune manipulation, and novel agents.

Maintenance therapies are low toxicity regimens designed to prevent relapse after completion of intensive chemotherapy. Previously, the benefit of maintenance regimens is minimal because of patient intolerance (interferon) or toxicity (chemotherapy). Novel agents, such as ibrutinib, and biologic agents, such as rituximab and brentuximab, are generally associated with lower toxicity and improved patient tolerance compared to traditional chemotherapy. This has allowed us to re-address the question of benefit of maintenance regimens. Encouraging results have been seen using these drugs in certain lymphoma subtypes.

For patients who relapse after transplant, options for treatment were limited due to comorbidities and patient intolerance. The higher therapeutic index of novel and biologic agents have been used with success to improve survivals in this difficult to treat population. In those patients who have received an allogeneic transplant, cellular immunotherapy and vaccination therapies are additional strategies for long term control of relapsed lymphoma.

It is an exciting time for patients with lymphoma. Since the development of rituximab and its approval in 2006, we have seen an explosion in the number of new agents for the treatment of lymphoma. In combination with transplantation, these novel agents hold the promise of improving the survival of patients with relapsed lymphoma. This issue of Blood and Marrow Transplantation Reviews provides a concise review of rapidly changing perspectives on prognostic considerations, pre- and post-transplant options to extend disease control, and transplant considerations. Dr. Gopal provides an insightful review of transplant options and outcomes. Dr. Soiffer next considers maintenance treatment options after transplant. Finally, Dr. O'Conner examines the shift in emphasis in treatment options for post-transplant relapse away from cytotoxic chemotherapy regimens to less toxic and more tolerable therapies.

Introduction

Although chemoimmunotherapy in the rituximab era is curative for many of the diverse subtypes of lymphoma, a substantial proportion of patients will relapse after first-line therapy. The current standard of care for select patients with chemosensitive relapsed or refractory disease involves second-line salvage chemotherapy followed by high-dose therapy (HDT) and autologous stem cell transplantation (ASCT). For patients with high-risk disease factors, allogeneic SCT (allo-SCT) may be the preferred approach with curative potential. The therapeutic benefit of allo-SCT is driven by the graft-versus-lymphoma effect (GVL), wherein the donor immune system recognizes and eradicates residual lymphoma. Conversely, the donor immune system can also attack normal host tissues, resulting in graft versus host disease (GVHD). Thus, the curative potential of allo-SCT must be balanced against multiple limitations.

For patients with relapsed or refractory lymphoma following transplantation, current treatment options are limited. Emerging post-transplant treatment strategies, such as the use of novel biologic and small-molecule therapies, may improve prognosis in the relapsed/refractory post-transplant setting.

Review the Current Use of Bone Marrow Transplantation for Patients with Lymphoma

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Non-Hodgkin's lymphoma (NHL) describes a heterogeneous and diverse family of approximately 40 distinct malignancies. Diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL) are the most common subtypes, accounting for 30% and 25% of NHL cases, respectively [1]. The next most common subtypes include the T cell and natural killer (NK) cell neoplasms (12%), mucosa-associated lymphoid tissue (MALT)-type marginal-zone B cell lymphoma (7.5%), small lymphocytic lymphoma (SLL) (7%), and mantle cell lymphoma (6%). The least common subtypes of NHL are Burkitt lymphoma (2.5%), nodal-type marginal B-cell lymphoma (<2%) and lymphoplasmacytic lymphoma (<2%) [1].

Diffuse Large B-Cell Lymphoma

Salvage chemoimmunotherapy followed by HDT-ASCT is the standard of care for patients with chemosensitive relapsed or refractory DLBCL. Multiple factors can influence the results of transplant, however, including chemotherapy sensitivity prior to ASCT, time from diagnosis to relapse, and the presence of prognostic factors at the time of relapse [2-4].

Early Rituximab Failure

The Collaborative Trial in Relapsed Aggressive Lymphoma (CORAL) study examined various parameters affecting treatment outcomes in patients with refractory or relapsed DLBCL undergoing rituximab-based salvage chemotherapy followed by high-dose conditioning and ASCT with or without rituximab maintenance therapy [2]. In the multicenter phase III CORAL trial, 396 patients with CD20-positive refractory or relapsed DLBCL were randomly assigned to treatment with 1 of 2 standard rituximab-based salvage chemotherapy regimens: rituximab, ifosfamide, carboplatin, and etoposide (R-ICE; n = 202) or rituximab, dexamethasone, high-dose cytarabine, and cisplatin (R-DHAP; n = 194). In responding patients, peripheral progenitor cells were harvested after salvage chemotherapy and reinfused following the high-dose conditioning regimen.

The overall response rates after salvage chemotherapy were similar in the R-ICE and R-DHAP treatment arms (63.5% versus 62.8%, respectively) [2]. In addition, similar mobilization failure rates of approximately 10% were observed after both treatment regimens. Indeed, all efficacy outcomes including overall survival (OS), event-free survival (EFS), and progression-free survival (PFS) were similar in both salvage arms, suggesting that it may be difficult to improve salvage regimens without the development of new therapies. After induction chemotherapy, 206 patients (52%) were able to proceed to ASCT.

One of the major findings from the CORAL study involved the identification of early rituximab failure (ERF) as a poor prognostic factor in patients with relapsed DLBCL [2]. Prior rituximab treatment in the first-line setting and early relapse (< 12 months after diagnosis) defined a high-risk subgroup with a poor response rate to salvage therapy (n = 187). Within this subgroup, the 3-year PFS was 39% for responding patients who underwent ASCT (n = 68), compared with 14% for patients who did not receive transplantation (n = 119; P < .001).

Building on findings from the CORAL trial, Hamadani and colleagues analyzed data from the Center for International Blood and Marrow Transplant Research (CIBMTR) registry to better understand the role of ASCT in patients with DLBCL experiencing ERF (Table 1) [3]. In the CIBMTR analysis, patients with ERF (n = 300) were defined as those who were treated with rituximab-based first-line chemoimmunotherapy regimens and either had primary refractory disease or relapsed within 1 year of initial diagnosis. By comparison, patients with late rituximab failure (LRF; n = 216) were defined as those who received first-line rituximab-based therapies and relapsed >12 months after initial diagnosis.

In the CIBMTR study, the cumulative 3-year risk of progression or relapse was 47% in the ERF group and 39% in the LRF cohort (P = .10). In a multivariate analysis, ERF was associated with a nearly 3-fold increase in the risk of lymphoma progression or relapse during the first 6 months following ASCT (RR, 2.86; P < 0.001). Beyond 6 months following ASCT, however, there was no

Table 1. Phase III CORAL Trial: Outcomes of Patients Experiencing Early Versus Late Rituximab Failure Following ASCT in Relapsed DLBCL [3]

Outcome at 3 Years	Early Rituximab Failure	Late Rituximab Failure
Nonrelapse mortality	9%	9%
Progression/relapse	47%	39%
Progression-free survival	44%	52%
Overall survival	50%	67%

ASCT = autologous stem cell transplant; DLBCL = diffuse large B-cell lymphoma.

difference between the ERF and LRF groups in risk of progression or relapse (RR, 0.68; P = .054). The estimated 3-year OS in the ERF and LRF groups was 50% and 67%, respectively (P < .001). The multivariate analysis showed that ERF significantly increased the risk of mortality within the first 9 months after ASCT (RR, 3.75; P < .001), but had no effect on mortality beyond 9 months after ASCT (RR, 0.86; P = .43). Thus, patients with ERF faced a significantly increased risk of progression/relapse and mortality in the initial 6 to 9 months period following ASCT relative to patients with LRF, but showed similar prognosis beyond this timeframe.

Findings from the CIBMTR analysis indicate that patients with DLBCL experiencing LRF can achieve excellent outcomes with HDT-ASCT. Moreover, despite ERF, treatment with ASCT can provide durable disease control for half of chemosensitive patients.

IPI Risk Score and ASCT in DLBCL

The International Prognostic Index (IPI) score has emerged as a potential tool for identifying which patients with DLBCL are most likely to benefit from consolidation with ASCT at the time of first remission (CR1) [4].

The Southwest Oncology Group (SWOG) trial 9704 examined the efficacy of ASCT during CR1 in patients with aggressive NHL classified as high-intermediate risk or high risk as defined by the IPI score (N = 397) [4]. The majority of patients (67%) had DLBCL. Following treatment with 5 cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or CHOP plus rituximab (R-CHOP), responding patients were randomly assigned to receive 3 additional cycles of induction chemotherapy (n = 128) or 1 additional cycle of induction chemotherapy followed by ASCT (n = 125).

According to an unplanned subgroup analysis by IPI risk category, the treatment effect of ASCT differed between the high-intermediate and high-risk groups. Among patients with high-intermediate risk, the 2-year OS was similar between ASCT and control groups (70% versus 75%, respectively; P = .48). Among high-risk patients, however, ASCT significantly improved 2-year OS relative to control treatment (82% versus 64%, respectively; P = .01). Similarly, in the subgroup of high-intermediate risk patients, there was no difference in 2-year PFS rates between ASCT and control (66% versus 63%, respectively; P = .32). In contrast, in high-risk patients, ASCT increased 2-year PFS compared with control (75% versus 41%, respectively; P = .001).

Several features of the SWOG 9704 study design limit the interpretation of the unplanned IPI subgroup analysis [4]. Approximately 40% of patients did not receive rituximab-based induction chemotherapy, which limits the generalizability of these results in the rituximab era. In addition, in the absence of information on molecular abnormalities, it is unclear whether the treatment effects observed in the high-risk IPI group are attributable to a higher prevalence of high-risk molecular subtypes such as "double-hit" lymphoma (DHL), which harbor both MYC and BCL2 translocations. Moreover, the enrollment criteria did not include response by 18F-fluorodeoxyglucose with positron-emission tomography (FDG-PET), leaving room for the possibility that some patients were not truly in CR1. Despite these limitations, however, the SWOG 9704 study supports the role of early transplantation for patients presenting with high-risk DLBCL.

Molecular Prognostic Markers

Advances in understanding the biology of DLBCL include the identification of multiple molecular subtypes of disease. In many cases, these subtypes serve as prognostic and predictive markers that can influence the selection of optimal treatment. Key molecular subtypes and markers in DLBCL include:

- Activated B-cell-like (ABC) subtype
- MYC translocation or overexpression
- DHL, which describes the presence of gene-activating MYC and BCL-2 translocations detected by fluorescence in situ hybridization (FISH)
- Double-hit score (DHS) positive, which describes MYC and BCL-2 overexpression by immunohistochemistry (IHC); also known as dual overexpresser lymphoma
- Triple-hit lymphoma, which describes MYC, BCL-2, and BCL6 translocations
- Investigational markers such as stromal signature and DNA methylation

Patients with DHL face a poor prognosis across multiple stages of disease, from CR1 to relapse. In a recent retrospective study, Petrich and colleagues examined treatment patterns and outcomes in patients with DHL (N = 311) treated across 23 North American academic medical centers [5]. The most frequently used induction regimen was R-CHOP (32%), followed by dose-adjusted, fractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone, and rituximab (R-HyperCVAD) and dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab (DA-EPOCH-R) in 21% of patients each. Among patients who achieved a first complete remission following induction, there was no difference in OS between those managed with observation (n = 112) and those who proceeded to treatment with autologous (n = 28) or allogeneic (n = 11) transplantation (P = .14). It is important to note, however, that the retrospective study was not powered to demonstrate a statistically significant difference in OS between treatment approaches. Moreover, the survival curves suggest a trend in favor of consolidative SCT in first remission. Additional prospective evidence is needed to clarify the potential role of transplantation in patients with DHL in CR1.

At the 2014 ASH annual meeting, Cassaday and colleagues presented findings from an institutional analysis of patients with relapsed/refractory NHL treated at the Fred Hutchinson Cancer Research Center in Seattle, Washington [6]. The study included 43 patients with NHL and a MYC gene abnormality, including 18 patients with DHL and 2 patients with THL. The most common initial chemotherapy regimen was CHOP (n = 24), following by more intensive regimens such as hyperCVAD (n = 7), and dose-adjusted EPOCH (n = 7). A similar proportion of patients who initially received CHOP (50%) or intensified therapy (60%) underwent ASCT.

The survival outcomes suggested that a durable remission is possible for patients who achieve a response to salvage therapy and proceed to ASCT [6]. The 1-year OS measured from the time of initial treatment failure was 38% in patients who underwent ASCT compared with 7% among patients who were unable to undergo ASCT (P = .02). However, salvage therapy remained challenging after failed induction treatment, particularly for patients who relapsed after the intensive induction regimens. The 1-year OS rate after initial treatment failure was 34% among patients who initially received CHOP, compared with 0% for patients who received intensified upfront therapy (P = .01).

Allogeneic SCT for DLBCL

Some centers perform allogenic HSCT as a third-line treatment approach for patients with

DLBCL who have failed second-line treatment with ASCT. To date, few prospective studies have evaluated outcomes associated with allo-SCT in this treatment setting.

In 2012, Bacher and colleagues examined factors influencing treatment outcomes after conditioning regimens of different intensity in patients with DLBCL undergoing allotransplants (N = 396) [7]. Myeloablative conditioning (MAC) regimens were used most commonly (n = 165), followed by reduced-intensity conditioning (RIC; n = 143) and nonmyeloablative conditioning (NMAC; n = 88). Compared with MAC, allotransplantation with RIC or NMAC was associated with a lower risk of NRM (P = .007) but a higher risk of progression or relapse (P = .031). However, these differences were likely attributable to disease factors and other baseline characteristics, which were unbalanced across treatment groups. Patients treated with MAC regimens tended to have higher disease risk and features associated with poor prognosis (eg, chemorefractory disease). By comparison, patients treated with RIC and NMAC tended to be older and have a higher prevalence of comorbidities. Regardless of the intensity of the conditioning regimen, relapse was the major cause of treatment failure. Furthermore, disease status prior to allo-SCT was the strongest predictor of treatment failure.

Overall, there was no difference between the 3 conditioning regimens in survival at 1 year (range, 38% to 46%), 3 years (range, 21% to 29%), and 5 years (range, 18% to 26%) [7]. These findings suggest that allo-SCT may be curative for select patients with relapsed DLBLC. For younger patients and those with a low comorbidity burden, MAC regimens may provide additional reduction in the risk of relapse. For elderly patients and those with severe comorbidities, RIC regimens may reduce the risk of NRM.

Classical Hodgkin Lymphoma

In 2002, a randomized trial from the German Hodgkin's Lymphoma Study Group (GHSG) established high-dose chemotherapy with ASCT as the standard of care for patients with relapsed chemosensitive classical Hodgkin lymphoma (cHL) [8]. After initial treatment with 2 cycles of dexamethasone and carmustine, etoposide, cytarabine, and melphalan (Dexa-BEAM), 161 patients with relapsed cHL were randomly assigned to 2 additional cycles of Dexa-BEAM or high-dose BEAM and ASCT. Only patients with chemosensitive disease, defined as complete or partial remission after 2 cycles of Dexa-BEAM, continued through randomization to further treatment. At 3 years, 55% of patients treated with BEAM-HSCT achieved freedom from treatment failure, compared with 34% of patients treated with Dexa-BEAM (P = .019). Importantly, there was no difference in OS between the treatment groups.

Emerging Prognostic Factor: Functional Imaging Status

In 2010, Moskowitz and colleagues described the role of pretransplantation functional imaging (FI) in predicting outcomes following ASCT in patients with relapsed or refractory cHL [9]. The observational study included 153 patients with cHL undergoing treatment at Memorial Sloan-Kettering Cancer Center in New York, NY. All patients had chemosensitive disease after treatment with ifosfamide, carboplatin, and etoposide (ICE)-based salvage regimens and proceeded to ASCT. Prior to salvage therapy and again prior to transplant, patients were evaluated with computed tomography (CT) and FI (gallium or FDG-PET). In a multivariate analysis, FI status before ASCT was the only factor that significantly predicted EFS and OS. The 5-year EFS for patients with positive and negative pre-ASCT FI findings were 31% and 75%, respectively (P < .0001).

In a follow-up phase II trial of patients with relapsed or refractory cHL, Moskowitz and colleagues examined a risk-adapted treatment protocol that used FDG-PET response following salvage chemotherapy to determine whether additional therapy was warranted before proceeding to HDT and ASCT [10]. After 2 cycles of ICE, patients with a negative FDG-PET scan received transplant. Patients with a positive FDG-PET scan received 4 additional biweekly doses of gemcitabine, vinorelbine, and liposomal doxorubicin (GVD) before proceeding to ASCT.

After a median follow-up of 51 months, the EFS was >80% for patients transplanted with a negative FDG-PET scan after salvage therapy with ICE or GVD, compared with 28.6% for patients with a positive FDG-PET scan or disease progression after GVD (P < .001). Outcomes for patients achieving FDG-PET-negative status after GVD were indistinguishable from those who achieved FDG-PET-negative status after ICE-based therapy.

These findings confirm a role for HDT and ASCT in patients with FDG-PET-negative findings following salvage chemotherapy. However, the optimal treatment for patients with chemosensitive FDG-PET-positive disease remains controversial.

Posttransplant Relapse

Relapse after ASCT is associated with a poor prognosis in patients with cHL. In a study of 756 patients with cHL relapsing after ASCT, there was a nonsignificant trend toward improved survival among patients with late relapse (> 12 months from ASCT) compared with those who experienced early relapse (≤ 12 months from ASCT) [11]. Regardless of the timing of relapse, however, survival outcomes for all patients were poor, with a median post-progression survival of 1.3 years.

There is a clear need for better treatment strategies in patients with post-transplant relapse. Current options include sequential palliation or induced remission followed by consolidation with allo-SCT.

Allo-SCT: Role of the Donor

Donor source does not appear to influence posttransplant outcomes in patients with cHL undergoing allo-SCT. In a study of 90 patients with HL treated with NMC followed by allo-SCT, there were no significant differences in OS, PFS, or cumulative incidence of relapsed/progressive disease 2 years after allo-SCT with HLA-matched related, unrelated, or HLA-haploidentical related donors (Table 2) [12]. Given

Table 2. Outcomes Following Allo-SCT By Donor Type in Relapsed/Refractory Hodgkin Lymphoma [12]

Outcome	Allo-SCT Donor Source		
	HLA-Matched Related (n = 38)	Unrelated (n = 24)	HLA-Haploidentical Related (n = 28)
2-year OS	53%	58%	58%
2-year PFS	23%	29%	51%
2-year incidence of relapsed/progressive disease	56%	63%	40%

HLA = human leukocyte antigen; HSCT = hematopoietic stem cell transplantation; OS = overall survival; PFS = progression-free survival.

the apparent lack of interaction between donor type and outcome, alternative donor stem cell sources may be viable in this patient population.

Another retrospective study examined the role of donor availability as a predictor of outcomes in patients with HL who relapsed following ASCT [13]. In the study of 185 patients with HL, 55% found a matched sibling donor, 32% had a matched unrelated donor, and 13% found a haploidentical donor. In addition, 63 patients did not find a donor. Compared with patients without a donor, patients in the donor group had a significantly 2-year PFS rate (14.2% versus 39.3%, respectively; P < .001) and 2-year OS rate (42% versus 66%, respectively; P < .001). Patients who underwent allo-SCT in complete remission also had better PFS and OS than those who were not in complete remission at the time of transplant.

Of note, these studies were conducted in the pre-rituximab and pre-anti-PD1 era. The availability of rituximab and anti-PD1 agents may influence the choice of optimal therapy for patients with HL at multiple stages of disease.

Mantle Cell Lymphoma

Advanced MCL is associated with an aggressive clinical course, with a median survival of 3 to 4 years. Several studies support the use of ASCT to prolong PFS in MCL patients in first remission. Most randomized clinical trials to date have used total body irradiation (TBI)-based conditioning regimens in this setting, although similar results have been observed with non-TBI regimens.

In 2005, the European MCL Network reported findings from a landmark trial evaluating early consolidation with radiochemotherapy followed by ASCT compared with interferon (IFN) maintenance therapy in patients aged 65 years or younger with advanced MCL in first remission after CHOP induction therapy [14]. The median PFS was 39 months in patients treated with ASCT compared with 17 months for patients treated with IFN maintenance (P = .0108). Despite the improvement in PFS, however, there was no difference between the ASCT and IFN arms in OS at 3 years (83% versus 77%, respectively; P = .18).

Prognostic and Predictive Markers

Many patients with MCL can achieve prolonged remissions of 5 to 10 years or longer. Until recently, however, few tools were available to identify patients who are most likely to benefit from posttransplant strategies to improve remission duration and survival. Emerging tools include the MCL International Prognostic Index (MIPI) and minimal residual disease (MRD) status [15, 16].

Baseline risk categories defined by the MIPI have been shown to predict posttransplant outcomes in patients with MCL [15]. In one study of patients with MCL undergoing ASCT, the 5-year OS rates for patients with low, intermediate, and high-risk MCL were 83%, 63%, and 34%, respectively. In addition, the median OS was not reached in the low- and intermediate-risk groups, compared with 3.8 years in the high-risk group (P < .001).

Evidence of pretransplant MRD also correlates with outcomes in patients with MCL undergoing ASCT in complete remission [16]. At the 2015 BMT Tandem Meetings, Cowan and colleagues presented findings from a study of 75 transplanted patients with MCL who underwent MRD assessment by PCR or flow cytometry of blood or bone marrow samples. Prior to ASCT, 11% of patients had evidence of MRD. The median OS for MRD-positive patients was 3 years and not reached for MRD-negative patients (HR, 4.04; P = .009). The median PFS for MRD-positive and MRD-negative patients was 2.38 years and not reached, respectively (HR, 3.69; P = .002). Thus, despite achieving clinical remission, MRD positivity prior to ASCT independently predicts worse OS and PFS following transplantation in patients with MCL.

ASCT for Relapsed Disease

For patients with relapsed and/or refractory MCL, outcomes following ASCT are typically poor. Therefore, it is important to identify which patients are most likely to benefit from this treatment strategy. Cassaday and colleagues recently identified 3 factors associated with improved PFS in this treatment setting [17]. These include:

- Pre-transplant MIPI score (HR, 2.9; P = .002)
- Presence of B symptoms at diagnosis (HR, 2.7; P = .005)
- Remission quotient, which reflects the time (in months) from diagnosis to ASCT divided by the number of prior treatments (HR, 1.4; P = .02)

The estimated 5-year PFS estimates for patients with favorable risk factors (n = 23) and unfavorable risk factors (n =44) were 58% and 15%, respectively. The 5-year OS estimates for the favorable and unfavorable risk groups were 76% and 32%, respectively.

Posttransplant Relapse

As observed with other NHL subtypes, patients with MCL who relapse within 12 months of ASCT have a poor prognosis. In a retrospective study from the EMBT registry, Dietrich and colleagues described treatment trends and outcomes among patients with MCL relapsing after ASCT (N = 1054) [18]. In a multivariate analysis, a long interval (> 12 months) between ASCT and relapse was associated with a 38% reduction in the risk of death compared with early relapse (HR, 0.62; P < .001).

In total, 22% of patients in the EMBT registry study underwent additional treatment with rescue allo-SCT [18]. Most patients (91%) achieved a complete or partial response to salvage therapy before proceeding to allografting. A better response to the first salvage regimen correlated with better OS (P < .0001). Among all patients who underwent allo-SCT, the 2-year OS was 46%. These finding support the use of salvage allo-SCT in select patients who experience an MCL recurrence after ASCT. In the future, the use of novel agents may as part of the salvage regimens may improve posttransplant survival.

Allo-SCT in MCL

The EMBT registry study described above demonstrated the potential role of allo-SCT in patients with MCL who relapsed following ASCT [18]. Data from the CIBMTR registry provide further support for early allo-SCT in patients with chemosensitive MCL [19, 20].

In the CIBMTR study, early transplant was defined as transplant in patients in first partial or complete remission with no more than 2 prior lines of chemotherapy. In a multivariate analysis, early RIC allo-SCT was associated with a significant reduction in the risk of death beyond the first 2 years since diagnosis compared with late transplant (RR, 0.31; P = .017). In contrast, however, early RIC allogenic HSCT also increased the risk of death within the first 24 months of transplant, primarily due to NRM (RR, 2.34; P = .017). Therefore, although RIC allo-SCT is potentially curative for some patients with MCL, these findings illustrate the persistent challenge of NRM within the first 2 years of transplant.

Another study from the CIBMTR registry examined allogenic HSCT in patients with

chemorefractory MCL (N = 202) [20]. The analysis included patients who underwent allo-SCT using MA (n = 74) or RIC/NMA (n = 128) conditioning regimens. After 3 years, there were no differences between the MA and RIC/NMA groups in terms of PFS (20% versus 25%, respectively; P = .53) or OS (25% versus 30%, respectively; P = .45). Other outcomes, including NRM, relapse, and progression, were also similar. Therefore, regardless of conditioning intensity, approximately 25% of patients with chemorefractory MCL are able to achieve durable remissions with allo-SCT.

Follicular Lymphoma

In the pre-rituximab era, randomized clinical trials examining the effects of HDT/ASCT for patients with chemosensitive FL showed mixed results. Several trials failed to show a survival benefit associated with ASCT for patients in CR1 or PR1. In contrast, 2 randomized trials showed a clear survival benefit with HDT/ASCT in this patient population [21, 22].

In 2003, the European CUP trial showed that treatment with HDT followed by ASCT, with or without in vivo B-cell purging, significantly improved survival compared with standard CHOP chemotherapy in patients with chemosensitive relapsed FL [21]. At the 2014 ASH annual meeting, Ubieto and colleagues presented findings from a long-term analysis of data from the GELTAMO Spanish Group Registry [22]. In this large cohort of patients with FL (N = 666), treatment with HDT/ASCT was associated with a median PFS of 9.4 years and a median OS of 21.3 years. After a median follow-up of 12.25 years patients transplanted in CR1 achieved significantly better PFS (68%) and OS (73%) than patients transplanted in CR2 (P < .0005) or PR1 (P < .0005). Moreover, survival appears to plateau beyond 15.9 years in patients transplanted in first remission, suggesting that HDT/ASCT is potentially curative in these patients.

Prognostic Markers

In the rituximab era, prognostic tools such as the Follicular Lymphoma International Prognostic Index (FLIPI) have proven helpful for identifying which patients with FL are most likely to benefit from treatment with HDT/ASCT. In a retrospective study of patients with FL undergoing HDT/ASCT (n = 207), the baseline FILIPI score significantly predicted OS when examined as a categorical (P = .01) or continuous (P = .002) variable [23].

Rituximab sensitivity is also strongly correlated with outcomes following HDT-ASCT in FL. In 2015, Phipps and colleagues examined the impact of rituximab sensitivity on outcomes in patients with chemosensitive relapsed FL (n = 194) [24]. Patients were categorized as rituximab-sensitive (n = 35), rituximab-refractory (n = 65), or no rituximab (n = 94) if they were transplanted prior to the availability of rituximab. The estimated 3-year PFS was 85% among rituximab-sensitive patients, compared with 35% for those who were rituximab-refractory (P = .0004). In a multivariate analysis, rituximab sensitivity was the only factor that significantly correlated with improved OS (HR, 0.24; P = .01) and improved PFS (HR, 0.35; P = .006). Despite the strong link between rituximab sensitivity for favorable outcomes, approximately one-third of patients with rituximab-refractory disease achieved a PFS of > 3 years with HDT-ASCT.

Allo-SCT in FL

For patients with relapsed or refractory indolent NHL, RIC allo-SCT represents a potentially curative treatment option. One study examined outcomes in 62 patients with indolent or transformed NHL who were treated with allo-SCT from related (n = 34) or unrelated (n = 28) donors following conditioning with TBI with or without fludarabine [25]. The estimated 3-year OS and PFS rates were 43% and 38%, respectively. Compared with related donor grafts, the use of unrelated grafts mismatched at ≥1 HLA antigen level significantly increased the risk of mortality (HR, 2.73; P = .03).

The Blood and Marrow Transplant Clinical Trials Network (BMT CTN) launched a prospective multicenter trial comparing ASCT and RIC allo-SCT in patients with chemosensitive FL beyond CR1 or PR1 [26]. Although the trial closed early due to poor accrual, preliminary findings suggest that both transplant strategies provide durable disease control in patients with relapsed FL. At 3 years, the estimated OS in the ASCT and allo-SCT groups were 73% and 100%, respectively, and the estimated PFS was 63% and 85%, respectively. No patients developed grade ≥2 acute GVHD, although 2 patients developed extensive chronic GVHD.

In summary, RIC allo-SCT can be curative in patients with relapsed FL. Strategies to reduce the risk of NRM and GVHD may further improve prognosis for these patients.

Peripheral T-cell Lymphoma

Peripheral T-cell lymphoma (PTCL) is associated with poor prognosis following treatment with conventional chemotherapy. With contradictory results from multiple clinical trials, no clear standard of care for patients with PTCL has emerged. In 2009, Reimer and colleagues demonstrated the benefits of frontline ASCT in a prospective trial of patients with PTCL (N = 83) [27]. Following induction chemotherapy, 66% of patients achieved complete remission (CR) or partial remission (PR) and underwent myeloablative chemoradiotherapy and ASCT. After a median follow-up of 33 months, the estimated 3-year OS rate was 71% for patients who proceeded to ASCT, compared with only 11% for patients who did not undergo transplantation (P < .001).

Upfront allo-SCT is also a promising strategy in patients with PTCL. In 2015, Loirat and colleagues described findings in a single-center study of patients with newly diagnosed PTCL scheduled to undergo treatment with upfront allo-SCT (N = 49) [28]. After induction chemotherapy, 60% of patients proceeded to transplant. The 2-year PFS rate for patients who did not proceed to transplant was <20%. Among transplanted patients, the 1-year and 2-year OS rates were 76% and 72.5% respectively. The 1-year TRM rate was 8.2%. Thus, upfront allo-SCT appears to be feasible in patients with PTCL, with a low risk of TRM and long-term disease control.

Summary

Based on current evidence, ASCT in CR1/PR1 can be considered for patients with MCL, double-hit DLBCL, high-risk DLBCL, and some T-cell lymphomas. In addition, ASCT may be appropriate for patients with chemosensitive relapsed/refractory DLBCL, classic HL, and select patients with MCL and T-cell lymphomas. Although allo-SCT is more controversial, some patients can be cured with allografting. Evidence supporting the GVL effect is strongest in indolent lymphoma, followed by MCL, DLBCL, and classic HL. Even with advances in this patient population, relapse remains the major cause of treatment failure across lymphoma subtypes. Novel options for induction, pre-transplant conditioning, and post-transplant management are needed to improve outcomes for patients with lymphoma.

Impact of Maintenance Therapy After Hematopoietic Cell Transplantation for Lymphoproliferative Disease

Robert J. Soiffer, MD

Maintenance Therapy after Autologous Transplantation

The promise of maintenance therapy to improve the results of autologous transplantation was first definitively realized with the publication of two landmark trials in patients with multiple myeloma [29, 30]. Large prospective randomized trials conducted in France and the U.S. established the role of lenalidomide maintenance in patients who had undergone autologous transplantation of myeloma with superior progression free and overall survival for patients receiving lenalidomide compared to placebo. In contrast, for patients with lymphoma, benefits of maintenance therapy have until now been difficult to demonstrate.

Is there a role for maintenance therapy after ASCT in lymphoma? To date, investigators have examined the benefits and limitations of standard rituximab maintenance therapy in multiple lymphoma subtypes, DLBCL, FL, and MCL [31-33].

Maintenance Therapy in DLBCL

As described in the previous section, the CORAL study evaluated rituximab maintenance therapy following HDT and ASCT in patients with first relapse or primary refractory DLBCL (N = 477) [31]. Following rituximab-based salvage chemotherapy, 242 responding patients underwent ASCT and were randomly assigned to maintenance therapy rituximab every 2 months (n = 122) or observation (n = 120) for 1 year. After a median follow-up of 44 months, maintenance therapy with rituximab did not improve outcomes compared with observation alone. The 4-year EFS rate in the maintenance therapy and observation arms was 52% and 53%, respectively (P = .74). Based on these findings, post-ASCT maintenance therapy with rituximab has not been recommended for patients with relapsed DLBCL [31].

Maintenance Therapy in FL

In 2013, the EBMT examined the role of pretransplant rituximab when used as an in vivo purging agent before the collection of peripheral blood progenitor cells (PBPCs) and/or as post-transplantation maintenance to consolidate remission in patients with relapsed FL [32]. The trial included 280 patients with relapsed FL who achieved either CR or very good partial remission (VGPR) with salvage chemotherapy. Using a 2 x 2 factorial design, patients were randomly assigned to rituximab purging (n = 141) or observation (n = 139) before HDT-ASCT, and to maintenance rituximab (n = 138) or observation (n = 142) following transplant. Patients assigned to in vivo purging underwent treatment with rituximab 375 mg/m2 once weekly for 4 infusions prior to PBPC collection. Those assigned to maintenance therapy received 375 mg/m2 once every 2 months for a total of 4 infusions. The primary endpoint was PFS.

After a median follow-up of 8.3 years, the study found no benefit associated with pretransplant rituximab purging. The 10-year PFS with and without purging was 48% and 42%, respectively (HR, 0.80; P = .18). In contrast, rituximab maintenance following HDT-ASCT significantly prolonged PFS. The 10-year PFS following maintenance therapy or observation was 54% and 37%, respectively (HR, 0.66; P = .012). When PFS was evaluated across the 4 treatment arms, there was a trend toward improved PFS in patients who received rituximab (test for trend: HR, 0.98; P = .028). The 10-year PFS rates were:

- Rituximab purging and rituximab maintenance: 52.1%
- Rituximab maintenance only: 48.8%
- Rituximab purging only: 37.7%
- No rituximab: 35.8%

In a multivariate analysis, rituximab maintenance therapy was the only factor that independently predicted improved PFS (HR, 0.66; 95% CI, 0.47-0.91). However, in the analysis of OS, neither rituximab purging nor rituximab maintenance prolonged survival in this patient population.

Maintenance Therapy in MCL

Two studies presented at the 2014 ASH annual meeting described the impact of rituximab maintenance therapy in patients with MCL [33, 34] In the first study, Graf and colleagues retrospectively compared outcomes among 167 consecutive patients with MCL who did (n = 60) or did not (n = 107) receive rituximab maintenance therapy following ASCT [33]. The median follow-up was 4.75 years. According to a multivariate analysis, rituximab maintenance reduced the risk of progression by 67% (HR, 0.33; P = .0005) and reduced the risk of death by 60% (HR, 0.40; P = .01). Rituximab maintenance significantly improved PFS and OS in the subgroup of patients who were alive and free from progression at day 100 following ASCT (n = 147) (Table 3).

Also at the 2014 ASH annual meeting, Le Gouill and colleagues presented the first interim analysis of the prospective, randomized, phase III LyMa trial [34]. The trial included 299 patients aged ≤65 years with previously untreated MCL. All patients received 4 courses of R-DHAP followed by ASCT, and those who did not achieve a PR or better were eligible to receive 4 additional courses of R-CHOP. Patients then underwent conditioning with rituximab (500 mg/m2) plus BEAM. Patients who achieve a CR or PR after ASCT were randomly assigned to maintenance therapy with rituximab (375 mg/m2 every 2 months) or observation for 3 years. The primary endpoint was EFS at 4 years.

Table 3. Effects of Rituximab Maintenance in Patients Alive and Without Progression at Day 100 After ASCT (n = 147) [33]

	Rituximab Maintenance	No Rituximab Maintenance	P Value
3-year PFS	78%	59%	.004
3-year OS	86%	71%	.01

ASCT = allogeneic stem cell transplantation; PFS = progress-free survival; OS = overall survival.

The median patient age at study entry was 57 years (range, 27 to 65 years). The baseline MIPI score indicated low-risk disease in 53.2% of patients, intermediate-risk disease in 27.4%, and high-risk disease in 19.4%. Following induction chemotherapy, 86% of patients proceeded to ASCT. The rates of CR and unconfirmed CR (uCR) were 81.4% and 92% before and after ASCT, respectively. A total of 238 patients underwent randomization to rituximab maintenance therapy (n = 119) or observation (n = 119).

At the time of the preliminary analysis of the LyMa trial, the median follow-up was 29.7 months from randomization. The estimated 2-year EFS was 93.2% in the rituximab arm compared with 81.5% in the observation arm (HR, 2.1; P = .015). The estimated 2-year OS

was similar in the maintenance and observation groups (93.4% versus 93.9%, respectively). Thus, despite the significant improvement in PFS, the interim findings from the LyMa trial do not yet establish a clear role for rituximab maintenance after ASCT in younger patients with previously untreated MCL.

Novel Approaches to Maintenance in Lymphoma

Brentuximab vedotin in Hodgkin Lymphoma

Brentuximab vedotin is a CD30-targeted antibody that is currently FDA-approved for the treatment of patients with HL after failure of ASCT, or after failure of 2 or more combination chemotherapy regimens in patients who are not candidates for transplant. At the 2014 ASH annual meeting, Moskowitz and colleagues presented findings from the AETHERA trial, which examined early consolidation with brentuximab vedotin following ASCT in patients with recurrent HL [35]. The AETHERA trial included 329 patients with HL who were at high risk for post-transplant disease progression based on 1 of 3 eligibility criteria: refractory to frontline therapy, relapsed within 12 months of frontline therapy, or relapsed 12 months or longer after frontline therapy with extranodal disease. All patients received salvage therapy and those who achieved CR, PR, or stable, non-progressing disease proceeded to ASCT. Following transplant, patients were randomly assigned to treatment with best supportive care plus up to 16 cycles of brentuximab vedotin 1.8 mg/kg every 3 weeks (n = 165) or placebo (n = 164) for up to 1 year. Patients who progressed on placebo were eligible to leave the trial and receive brentuximab vedotin as part of another study. The primary study endpoint was PFS by independent review.

The median follow-up was 24.4 months. The 2-year PFS was significantly better in the brentuximab vedotin group than in the placebo group, as determined by investigator review (65% versus 45%, respectively; HR, 0.50; 95% CI, 0.36-0.70) (Table 4). An independent review of PFS also showed an improvement with brentuximab vedotin compared with placebo (63% versus 51%, respectively; HR, 0.57, 95% CI: 0.40-0.81, P = 0.001).

A subgroup analysis of PFS favored treatment with brentuximab vedotin across all patient groups defined by baseline age, gender, or ECOG performance status; disease status or presence of B symptoms after frontline therapy; and number of systemic treatments, FDG status, extranodal involvement, or response to salvage therapy pre-ASCT.

Table 4. Phase III AETHERA Trial of Brentuximab Vedotin Maintenance Therapy Versus Placebo After ASCT in High-Risk Hodgkin Lymphoma [35]

	Brentuximab Vedotin (n = 165)	Placebo (n = 164)	HR (95% CI)	P Value
Independent Review				
Median PFS	43 months	24 months	0.57 (0.40-0.81)	.001
2-year PFS	63%	51%		
Investigator Review				
Median PFS	Not reached	16 months	0.50 (0.36-0.70)	NR
2-year PFS	65%	45%		

ASCT = allogeneic stem cell transplantation; HR = hazard ratio; NR = not reported; PFS = progress-free survival.

However, there was no difference in OS between the brentuximab vedotin maintenance therapy and placebo groups (P = 0.62). Of note, the assessment of OS was confounded by the fact that 85% of patients in the placebo group crossed over to brentuximab vedotin. In addition, other patients initially assigned to placebo underwent allo-SCT and/or received subsequent salvage therapy at the time of progression. Among all patients in the study, the 2-year estimated OS was 88%.

Based on findings from AETHERA, maintenance therapy with brentuximab vedotin may become an accepted standard of care for patients with HL who undergo ASCT.

PD-1 Blockade

Programmed death 1 (PD-1) is an immune-checkpoint receptor that mediates signals to block T cell activation and attenuate the host antitumor response. Nivolumab is anti-PD-1 monoclonal antibody that blocks anti-PD-1 signaling, potentiates T cell activity, and restores antitumor immunity. Nivolumab is currently approved for the treatment of patients with unresectable or metastatic refractory melanoma and squamous non-small cell lung cancer.

At the 2014 ASH annual meeting, Armand and colleagues presented preliminary findings from an ongoing study of nivolumab in patients with relapsed/refractory cHL, which were published simultaneously in the New England Journal of Medicine [36]. The ongoing study has enrolled 23 patients with cHL who failed aggressive first-line therapy, including treatment with brentuximab vedotin and/or ASCT. Patients received nivolumab (3 mg/kg) by IV infusion every 2 weeks until disease progression or excessive toxicity. The study objectives were to measure the safety and efficacy of PD-1 blockade in HL.

All patients achieved a reduction in tumor burden in response to nivolumab (Figure 1). The overall response rate (ORR) was 87% and included a CR in 4 patients (17%) and a PR in 16 patients (70%). Three additional patients (13%) achieved stable disease. No patient experienced disease progression during treatment with nivolumab.

At the time of the analysis, 11 patients (48%) had ongoing responses. Among responding patients, 60% of responses occurred in the first 8 weeks of treatment with nivolumab. The 24-week PFS was 86%. In summary, nivolumab demonstrated substantial anti-lymphoma activity in patients with relapsed or refractory HL, including a reduction in tumor burden in 100% of patients. Based on these preliminary phase I findings, the FDA has granted nivolumab breakthrough therapy designation in HL. A phase II trial is currently evaluating nivolumab in patients with HL who relapse after ASCT.

PD-1 blockade has also shown promising activity after ASCT in patients with other lymphoma subtypes, including DLBCL [37]. In an international phase II study, Armand and colleagues examined the safety and efficacy of post-ASCT treatment with pidilizumab, an investigational anti-PD-1 monoclonal antibody. The trial included 66 patients with DLBCL who received 3 doses of pidilizumab beginning 1 to 3 months following ASCT. At 16 months, the PFS was 72% and the OS was 85%. In the subgroup of patients who remained PET-positive at the end of salvage therapy (n = 24), the 16-month PFS was 70%. These findings support the antitumor activity of immune checkpoint blockade in patients with lymphoma.

Tandem Autologous/Allogeneic Transplant

Tandem ASCT and RIC allo-SCT is an emerging strategy designed to combine the benefits of both transplant strategies, including enhanced cytotoxicity from high-dose chemotherapy during ASCT, the GVL effect of allo-SCT, and a reduced toxicity profile relative to myeloablative allo-SCT. Multiple studies have examined tandem autologous-allo-SCT

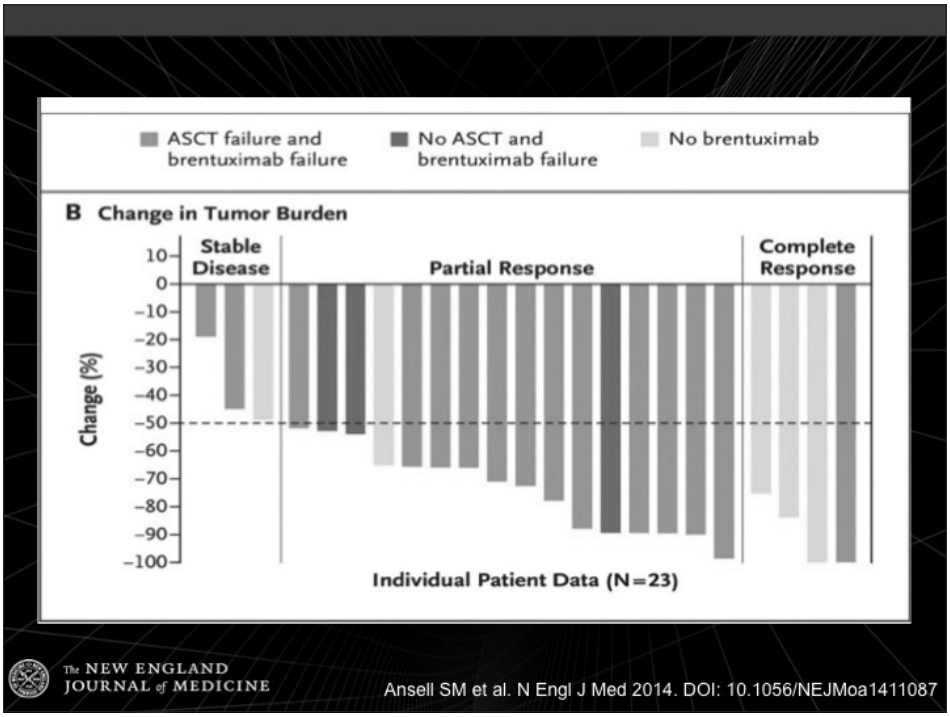

Figure 1. Change in Tumor Burden in Response to Nivolumab in Patients with Hodgkin Lymphoma [36]

in patients with mixed lymphoma [38-41], FL [42], and high-risk NHL [43, 44].

At the 2014 BMT Tandem Meetings, Chen and colleagues described findings from a phase II trial of busulfan-based HDT-ASCT followed by RIC allo-SCT in patients with high-risk lymphoma (N = 42) [40]. The high-dose chemotherapy regimen consisted of busulfan (11.2 mg/kg IV total), cyclophosphamide (120 mg/kg IV total), and etoposide (30 mg/kg IV total) (BuCyE). Patients with non-progressive disease any time between 40 days to 6 months following BuCyE ASCT (n = 29) proceeded to RIC allogenic HSCT. Following RIC with busulfan (3.2 mg/kg IV total) and fludarabine (120 mg/kg IV total) (BuFlu), 16 patients received a matched related donor allograft and 13 received allografting from a matched unrelated donor. Standard GVHD prophylaxis included tacrolimus, sirolimus, and methotrexate.

The median time from ASCT to RIC allo-SCT was 96 days (range, 48 days to 169 days). Among 29 patients who underwent both transplant procedures, 1 patient had died and 5 had relapsed at the time of the analysis. The median follow-up was 11.8 months for the 28 patients who survived following RIC allogenic HSCT. In this group, the 1-year PFS and OS was 87% and 95%, respectively. Disease status prior to ASCT and RIC allo-SCT appeared to be prognostic for relapse, with no cases of relapse in patients in CR prior to both transplant procedures (Table 5). Overall, busulfan-based tandem ASCT followed by RIC allogenic HSCT may be a safe and effective strategy in patients with high-risk lymphoma. (This has just been published in BBMT

Ibrutinib Maintenance

ibrutinib is a potent, oral inhibitor of Bruton's tyrosine kinase (Btk) that interferes with B-cell receptor signaling. Single-agent ibrutinib is currently approved as a treatment for patients with MCL and chronic lymphocytic leukemia (CLL). Ibrutinib also shows activity against other B-cell malignancies, including ABC-type DLBCL. In a recent phase II study of patients with heavily pretreated DLBCL, ibrutinib showed a 40% ORR in patients with the ABC subtype, compared with only 5% in patients with germinal center B cell-like (GCB) DLBCL [45]. Ibrutinib was well tolerated, with 13% of patients experiencing grade ≥3 adverse events.

Several cooperative groups are planning to evaluate the safety and efficacy of ibrutinib therapy during and after ASCT in patients with ABC-type DLBCL in a randomized, placebo-controlled, phase III study [46]. In the trial, patients with relapsed/refractory ABC-type DLBCL who are chemosensitive to salvage therapy will be randomly assigned to ibrutinib and placebo groups. Treatment with ibrutinib (560 mg/day) will start during the pretransplant period and continue through 12 months following ASCT with standard CBV or BEAM. Patients who progress on placebo will be eligible to cross over to the ibrutinib arm. The primary endpoint is 2-year PFS. Secondary efficacy and safety endpoints will include tolerability, OS, EFS, DFS, response rate at day 100, engraftment, RTM, hematologic toxicity, and secondary malignancies.

Table 5. Relapse Patterns Following Busulfan-Based Tandem ASCT and RIC Allogenic HSCT in Patients with High-Risk Lymphoma [40]

Disease Status Prior to ASCT	Disease Status Prior to RIC Allo-SCT	Patients (n)	Cases of Relapse (n)
CR	CR	14	0
PR	CR	9	1
PR	PR	6	4

BuCYE = busulfan, cyclophosphamide, etoposide; BuFlu = busulfan, fludarabine; CR = complete response; HSCT = hematopoietic stem cell transplantation; PR = partial response; RIC = reduced-intensity conditioning.

Summary

Maintenance therapy following ASCT is emerging as a feasible treatment strategy for improving PFS in select patients with DLBCL, FL, MCL, and other lymphoma subtypes. Several novel therapies also show promise in improving patient outcomes in this setting. In the AETHERA trial, maintenance therapy with brentuximab vedotin significantly improved 2-year PFS compared with placebo following ASCT in patients with high-risk HL. Treatment with nivolumab induced a tumor response in 100% of patients with relapsed/refractory HL, while treatment with another anti-PD-1 antibody, pidilizumab, demonstrated antitumor activity following ASCT in patients with DLBCL. Busulfan-based tandem HDT-ASCT and RIC allo-SCT is also emerging as an effective treatment strategy for patients with high-risk lymphoma. After showing promising activity in patients with heavily pretreated ABC-type DLBCL, ibrutinib maintenance therapy is currently under evaluation in a phase III trial of patients with relapsed/refractory ABC-type DLBCL undergoing ASCT.

Emerging Treatment Options and Strategies for Patients Relapsing After Transplantation

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Transplantation is an intensive curative treatment option for patients with high-risk malignancies. When transplant fails to prevent disease relapse, few options for successful salvage treatment remain. Indeed, relapse is the most common cause of treatment failure after allo-SCT, as well as one of the leading causes of treatment failure after ASCT for hematologic malignancies. Following allo-SCT, the leading causes of death for those with an HLA-identical sibling donor are relapse (44%), infection (16%), GVHD (12%), and organ toxicity (9%) [47]. For unrelated donor allograft recipients, the leading causes of death show a similar distribution: relapse (33%), infection (19%), GVHD (13%), and organ toxicity (10%) [47].

Within the heterogenous lymphoma population, multiple prognostic factors appear to be consistent across patient groups. Prognosis tends to depend on factors such as time elapsed from transplant to relapse; disease burden; conditions of the initial transplant; and age [47]. Lymphoma subtype also influences prognosis, with some subtypes more vulnerable to high-dose chemotherapy or the GVL effect [47]. Therefore, reflecting the diversity of lymphoproliferative malignancies, treatment approaches vary widely. One promising strategy involves reducing immunosuppression in patients undergoing allo-SCT, with the goal of augmenting the GLV effect. Modified second transplant procedures and salvage therapies have also been studied to improve long-term disease control. Due to a paucity of randomized clinical trial evidence to date, however, no standards of care have been established.

Emerging Themes in Post-Transplant Management

Treatment options for patients relapsing after transplantation represent an area of unmet medical need. Patients with post-transplant relapse face multiple challenges, including exclusion from clinical trial eligibility, compromised performance status, poor hematopoietic reserve, and chemotherapy resistance (Table 6). For each of these challenges, however, corresponding opportunities are also emerging. New opportunities include cellular immunotherapy, immunosuppression, hematopoietic expansion, and vaccination strategies.

Table 6. Challenges and Opportunities for Managing Post-Transplant Relapses

Therapeutic Constraints	Opportunities Post Transplant
Transplants often an exclusion for clinical trail access to investigational agents	Established donor immune system (platform for cellular immunotherapy)
Compromised performance status	Induction of GVL effect with immunosuppression
Poor hematopoietic reserve often limits use of cytotoxic drug	Hematopoietic expansion of immune cells: DLI, ex vivo expanded cytotoxic T-cell and NK cells
Enriched acquired and intrinsic chemotherapy resistance	Vaccination strategies

DLI = donor lymphocyte infusion; GVL = graft versus lymphoma.

In general, recent themes in post-relapse treatment include de-emphasizing the use of cytotoxic combination chemotherapy regimens and emphasizing the use of agents with more favorable tolerability profiles that facilitate prolonged use. Although clinical trial evidence in the post-transplant setting is limited, there is an opportunity for guidance within existing data sets that have included transplant recipients. Moreover, new findings on the pharmacologic manipulation of the GVHD and GVL responses may provide valuable insight into optimal post-transplant management. These approaches are discussed in greater detail below.

Peripheral T-Cell Lymphomas

Most patients with relapsed or refractory PTCL have poor prognosis and short survival. In an observational study of 204 patients with the 3 most common subtypes of PTCL in North America, the median OS following relapse or progression after primary therapy was 7.1 months [48]. The median PFS following relapse/progression in this cohort was 4.7 months [48]. These findings underscore the need for novel therapies that are specifically active in PTCL.

Pralatrexate

In 2009, pralatrexate became the first drug to gain FDA approval for the treatment of patients with relapsed or refractory PTCL. The approval of pralatrexate was based on data from the PROPEL trial, an international, multicenter, single-arm, open-label, phase II trial [49]. The PROPEL trial enrolled 115 patients with patients with relapsed or refractory PTCL. Of these 111 patients were treated in 7-week cycles with pralatrexate (30 mg/m2 over 3 to 5 minutes) once weekly for 6 weeks followed by 1 week of rest until progressive disease or unacceptable toxicity.

Among 109 patients evaluable for response in PROPEL, the ORR was 29% as determined by central review [49]. This included a CR in 10% of patients, a CRu in 1%, and a PR in 18%. Among patients who responded, 70% achieved a response within the first cycle of treatment. In a subgroup analysis, the ORR was 33% for patients who underwent prior ASCT and 20% for those without a prior transplant, suggesting that prior ASCT did not adversely affect the likelihood of response to pralatrexate. In the overall cohort, the median PFS and OS were 3.5 months and 14.5 months, respectively.

Based on clinical experience with pralatrexate, some important considerations for post-transplant management have emerged. The goal of treatment is safe, longer-term administration of pralatrexate. Patients with longest durations of response, lasting for 7 to 9 years or longer, received treatment for 12 months or longer. Thus, to facilitate long-term administration:

- Assure patients are treated with continuous folic acid and B12 for as long as possible prior to receiving the first dose of pralatrexate
- Escalate dose gradually; 10 mg/m2 to 20 mg/m2 to 30 mg/m2
- Hold the dose escalation of pralatrexate for any mucositis; use oral leucovorin 15 mg to mitigate mucositis (hold leucovorin the day before through 1 to 2 days after pralatrexate administration)
- Modify treatment schedule to 3 of 4 weeks or 6 of 7 weeks, as needed

HDAC Inhibitors

Histone deacetylase (HDAC) inhibitors induce the acetylation of histones and other proteins, resulting in antitumor activity through growth inhibition, increased tumor suppressor gene transcription, cell-cycle regulation, and apoptosis [50]. In 2009, romidepsin was approved by the FDA based on evidence of durable disease control in cutaneous T-cell lymphoma (CTCL) [51, 52]. Additional evidence from the National Cancer Institute also demonstrated the benefit of romidepsin in patients with PTCL [53].

In 2011, the FDA expanded romidepsin's indication to include the treatment of patients with PTCL following at least 1 prior therapy based on data from a phase II trial of 130 patients with relapsed or refractory PTCL (N = 130) [50]. In the phase II trial, the ORR was 26%, including 10 patients (8%) with CR and 7 patients (5%) with CRu. The median duration of response was 12 months for all patients, and not reached for those with CR/CRu following treatment with romidepsin. Of note, the ORR in this trial (26%) was consistent with response

rates observed in the earlier romidepsin trials in patients with prior SCT (24% to 33%). Together, these findings suggest no loss of treatment benefit with romidepsin in patients with heavily pretreated disease and/or prior transplant.

Belinostat, a pan-HDAC inhibitor, was approved in 2014 for the treatment of relapsed or refractory PTCL based on data from the BELIEF study [54]. The single-arm BELIEF trial evaluated treatment with belinostat (1000 mg/m2 administered over 30 minutes on days 1-5 of each 3-week cycle) in patients with relapsed or refractory PTCL after failure of 1 or more prior systemic therapies (N = 129). The median number of prior lines of therapy was 2 (range, 1 to 8). For 29 patients (23%), prior therapy included previous autologous (n = 27) or allogeneic (n = 2) stem cell transplant. Although the numbers in the analysis were small, a history of transplant did not appear to affect probability of response. Patients received a median of 2 cycles of belinostat treatment (range, 1 to 33). The ORR was 26% for the entire study cohort, including a CR in 10% and a PR in 16%.

As a class, the HDAC inhibitors appear to be very well tolerated event in patients who are heavily pretreated [50, 54]. In the BELIEF study, belinostat was associated with a low incidence of grade ≥3 hematologic abnormalities, including anemia (12%), leukopenia (13%), neutropenia (13%), and thrombocytopenia (15%) [54]. Patients with platelet counts <100,000/μL (n = 24) were able to tolerate belinostat, with grade ≥3 hematologic toxicities in 25% to 54%. For all patients, the incidence of grade ≥3 non-hematologic treatment-emergent adverse events was also low. These included dyspnea (6%), pneumonia (6%), febrile neutropenia (5%), fatigue (5%), and hypokalemia (4%).

Hodgkin Lymphoma

Brentuximab is an antibody-drug conjugate directed against the cell-surface protein CD30, which is expressed in hematologic malignancies including HL. In a multicenter case series, Gopal and colleagues described outcomes among 25 patients with relapsed CD30-positive HL who received brentuximab vedotin following allo-SCT [55]. The patients were originally enrolled in 1 of 3 open-label, non-randomized, phase I or II multicenter studies of brentuximab. The median number of prior regimens was 5 (range, 2 to 12), and included prior ASCT in 76% of patients. Five patients (20%) also received at least 1 donor lymphocyte infusion (DLI). All patients received brentuximab vedotin 1.2 mg/kg or 1.8 mg/kg over 30 minutes every 21 days on an outpatient basis. The median interval between allo-SCT and brentuximab vedotin was 42 months (range, 6 months to 116 months). The median treatment duration was 27.4 weeks and included a median of 8 treatment cycles.

The response results demonstrate substantial antitumor activity with brentuximab vedotin following allo-SCT (Figure 2) [55]. The ORR was 50%, including CR in 38% and PR in 13% of patients. The median time to CR/PR was 8.1 weeks, and the minimum duration of objective response was 21 weeks. In addition, 42% of patients achieved stable disease.

In the safety analysis, the most common grade ≥3 adverse events included neutropenia (36%), lymphocytopenia (36%), hypophosphatemia (24%), leukopenia (20%), and thrombocytopenia (20%). No cases of febrile neutropenia or GVHD were reported after the initiation of brentuximab vedotin therapy.

Given concerns that targeting an antigen on activated T cells with brentuximab vedotin could impair cell-mediated immunity in this high-risk population, patients also underwent testing for potentially clinically significant infections. Serial post-baseline cytomegalovirus (CMV) surveillance using PCR in 20 patients revealed low-level CMV reactivation in 5 patients. Two patients had positive PCR results at the initial test. Of these, 1 remained asymptomatic and 1 died with Streptococcus pneumoniae sepsis, pneumonia, and multisystem organ failure in the setting of CMV reactivation. Among patients with a negative initial test (n = 18), 2 patients tested positive for CMV during the study but remained asymptomatic, and 1 patient had CMV viremia that cleared within 1 week of antiviral treatment. These findings suggest a potential role for CMV monitoring, particularly for patients with a positive or unknown history of CMV infection or viremia.

Manipulating the Graft Versus Leukemia Effect

Preventing the development of GVHD while sustaining the GVL effect is an important therapeutic goal for patients undergoing allo-SCT. The pleiotropic effects of HDAC inhibition may be instrumental in achieving these goals. HDAC inhibition is associated with apoptosis, cell-cycle arrest, immunomodulatory effects, and inhibition of lipopolysaccharide (LPS)-induced inflammatory responses. In preclinical models, the HDAC inhibitor vorinostat has been shown to delay the development of GVHD through significant inhibition of the systemic inflammatory response that occurs shortly after myeloablative conditioning and HSCT [56]. Importantly, treatment with vorinostat appears to modulate systemic and local inflammation through the downregulation of cytokines active along the JAK-STAT signaling pathway, but without inhibiting T-cell expansion or activation [56].

In a recent phase I/II trial, Choi and colleagues examined the use of vorinostat in combination with standard GVHD prophylaxis in patients undergoing RIC allo-SCT [57]. The trial included adults with high-risk malignancies (N = 50) who

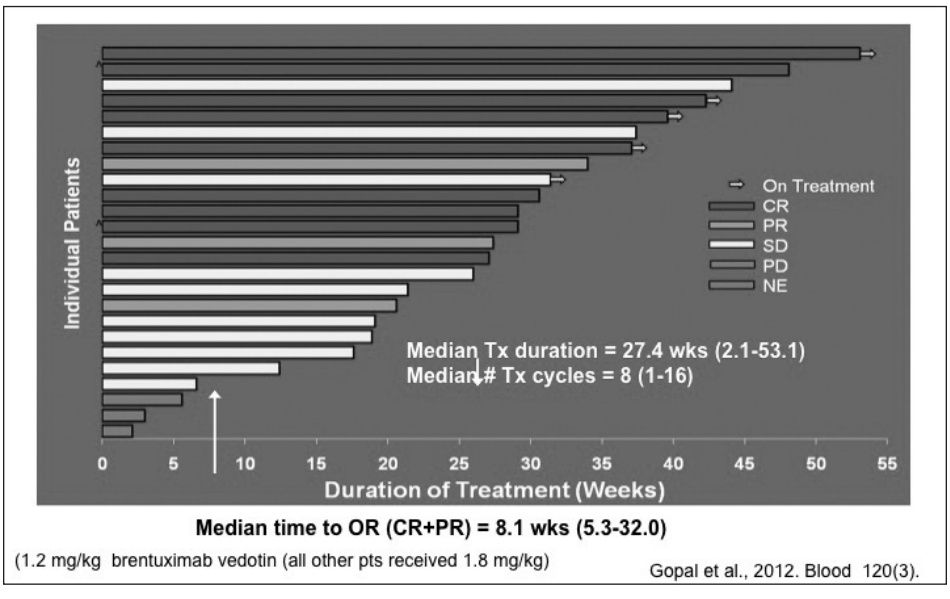

Figure 2. Treatment Duration and Best Clinical Response to Brentuximab Vedotin Following Allo-SCT in Patients with Hodgkin Lymphoma [55]

were candidates for RIC allo-SCT and had an available 8/8 or 7/8 HLA-matched related donor. All patients received conditioning with fludarabine (40 mg/m2 daily for 4 days) and busulfan (3.2 mg/kg daily for 2 days), as well as GVHD prophylaxis with mycophenolate mofetil (1 g, 3 times daily, days 0 to 28) and tacrolimus (0.03 mg/kg/day, titrated to a goal of 8-12 ng/mL, on days -3 to 180). In addition, treatment with vorinostat (either 100 mg or 200 mg twice daily) was initiated 10 days prior to transplant and continued until day 100. The primary endpoint was cumulative incidence of grade 2-4 acute GVHD by post-transplant day 100.

Based on historical data, the expected incidence of severe acute GVHD in this patient population was approximately 45%. By comparison, the cumulative incidence of grade 2-4 acute GVHD by day 100 among patients treated with vorinostat was 22%. The cumulative incidence of relapse was 16% at 1 and 2 years, with a median time to relapse of 98 days. The cumulative risk of all-cause NRM and GVHD-related mortality were 10% and 6%, respectively, at 1 and 2 years. There was no increase in the risk of infection or delayed engraftment associated with vorinostat.

In pharmacodynamic studies, samples obtained on day 30 post-transplant were compared between study patients and similar patients who were not treated with vorinostat. Treatment with vorinostat was associated with a significant increase in acetylation, demonstrating HDAC inhibition, as well as a reduction in proinflammatory cytokine expression. Vorinostat-treated patients showed an upregulation of the immunomodulatory enzyme indoleamine 2,3-dioxygenase (IDO), as well as increased expression of IDO-activated FOXP3+ T-regulatory (Treg) cells and other Treg subtypes. In contrast, vorinostat-treated patients demonstrated no change in the number of peripheral CD4+CD8+ T cells or absolute lymphocyte counts. The pharmacodynamic findings are consistent with preclinical models and correlated with a significant reduction in acute GVD.

Overall, findings from this phase I/II study support the use of vorinostat combined with standard GVHD prophylaxis in patients with high-risk malignancies undergoing RIC allo-SCT [57]. Additional studies are warranted to confirm these findings and to evaluate this strategy in broader transplant settings. A phase II study of vorinostat combined with tacrolimus and methotrexate for GVHD prevention is currently underway in the setting of unrelated donor transplant following myeloablative conditioning [58].

Post-Transplant Safety Considerations

Lenalidomide maintenance following allo-SCT appears to trigger acute GVHD in patients with some hematologic malignancies [59, 60]. In the phase II LENAMAINT study of patients with high-risk MDS or AML treated with allo-SCT, 6 of 10 patients (60%) developed grade 3-4 acute GVHD within the first 2 cycles of maintenance therapy [59]. The trial was stopped early due to suspicion that lenalidomide was the cause of the GVHD. The acute GVHD resolved in 4 of 6 patients after stopping lenalidomide and initiating steroids. However, restarting lenalidomide led to the reappearance of acute GVHD and the permanent discontinuation of treatment in 4 of 6 patients.

In the phase II HOVON 76 study of lenalidomide maintenance following nonmyeloablative allo-SCT in patients with multiple myeloma, 14 of 35 patients (47%) had to stop treatment due to the development of acute GVHD [60]. Together, findings from the LENAMAINT and HOVON 76 studies indicate that early lenalidomide maintenance therapy to prevent relapse following allo-SCT is not feasible in these patient populations [59, 60]. In addition, these findings underscore the importance of frequent monitoring for any emergence of acute GVHD following allo-SCT.

Summary

In summary, de-emphasizing cytotoxic combination chemotherapy has emerged as a leading strategy for managing post-transplant relapse risk in patients with high-risk hematologic malignancies. Single-agent targeted therapies with minimal hematologic toxicity allow for protracted dosing with the possibility of prolonged disease control. Furthermore, HDAC inhibition may mitigate the risk of acute GVHD without compromising the GVL effect. Lenalidomide should be used with caution following allo-SCT due to an increased risk of severe acute GVHD. Additional studies are needed to understand the biology underlying acute GVHD and to identify new opportunities for risk management. To facilitate a greater understanding of treatment options in this high-risk setting, clinical trials should consider expanding patient eligibility criteria to include patients who have been treated with ASCT or allo-SCT.

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1. **In the CORAL trial, which of the following was associated with poor outcomes following ASCT in patients with relapsed DLBCL?**
   A. Lower cumulative rituximab dose
   B. Higher cumulative rituximab dose
   C. Early rituximab failure
   D. Late rituximab failure

2. **In the AETHERA trial, maintenance therapy with brentuximab vedotin following ASCT was associated with which of the following compared with placebo in Hodgkin lymphoma?**
   A. Increased progression-free survival
   B. Increased overall survival
   C. Increased treatment-related mortality
   D. Increased discontinuation due to adverse events

3. **Which of the following maintenance strategies is associated with an increased risk of severe acute GVHD?**
   A. Lenalidomide maintenance following ASCT
   B. Rituximab maintenance following ASCT
   C. Lenalidomide maintenance following allo-SCT
   D. Rituximab maintenance following allo-SCT

4. **What was the effect of treatment with nivolumab, an anti-PD-1 antibody, in patients with relapsed/refractory Hodgkin lymphoma?**
   A. Overall response rate of 100%
   B. 24-week PFS rate of 100%
   C. Reduction in tumor burden in 100% of patients
   D. Grade 1-2 hematologic toxicity in 100% of patients

5. **Which of the following best describes outcomes from a phase II study of patients with high-risk lymphoma treated with busulfan-based tandem HDT-ASCT and RIC allo-SCT?**
   A. Only 19% of patients were able to undergo both transplant procedures
   B. Patients with CR prior to both transplant procedures had the lowest risk of relapse
   C. Among patients who underwent both transplants, the median PFS was 96 days
   D. Patients using matched unrelated donor allografts had a high risk of relapse

6. **In the BELIEF trial of patients with relapsed/refractory PTCL, which of the following best describes the safety profile of belinostat?**
   A. Low risk of grade ≥3 hematologic adverse events
   B. High rate of treatment discontinuation due to adverse events
   C. Dose-limiting toxicity of febrile neutropenia
   D. Unacceptable toxicity for patients with platelet counts <100,000/μL

7. **Which of the following agents appears to reduce the risk of GVHD without diminishing the GVL effect in patients with high-risk malignancies?**
   A. Pidilizumab
   B. Pralatrexate
   C. Romidepsin
   D. Vorinostat