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Review

How to Approach a Hodgkin Lymphoma Patient With Relapse After Autologous SCT: Allogeneic SCT

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Abstract

Hodgkin lymphoma (HL) is a highly curable B-cell lymphoma, and ~90% of patients who present with early-stage (stage I-II) disease and 70% of patients who present with late-stage disease will be cured with standard frontline treatment. For patients with relapsed or refractory (r/r) disease after initial therapy, the standard of care is salvage chemotherapy, followed by autologous transplantation (autoSCT). Although this approach will cure a significant proportion of patients, upto 50% of patients will experience disease progression after autoSCT, and this population has historically had a very poor prognosis. In the past, further salvage chemotherapy, followed by allogeneic transplantation (alloSCT), has been the only option associated with a significant probability of long-term survival, owing to a graft-versus-lymphoma effect. However, this approach has been complicated by high rates of treatment-related morbidity and mortality and a high risk of disease relapse. Furthermore, many patients have been unable to proceed to alloSCT because of disease refractoriness, poor performance status, or the lack of a donor. However, significant therapeutic advances in recent years have greatly expanded the options for patients with post-autoSCT r/r HL. These include the anti-CD30 antibody–drug conjugate brentuximab vedotin and the checkpoint inhibitors nivolumab and pembrolizumab, as well as increasing experience with alternative donor alloSCT, especially from haploidentical donors. In the present review, we discuss the current role of alloSCT in the treatment of HL after autoSCT relapse.

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Introduction

Although Hodgkin lymphoma (HL) is often thought of as a disease that is easy to cure, upto 10% of patients with early-stage disease and 30% of patients who present with advanced-stage disease will experience disease progression at some point after receiving standard frontline therapy with ABVD (Adriamycin, bleomycin, vinblastine, doxorubicin).[1,2] For patients who are not cured with first-line treatment, ~50% can be cured with salvage chemotherapy, followed by autologous stem cell transplantation (autoSCT).[3] However, patients who experience disease recurrence after autoSCT have a far worse prognosis, with a median survival of only 29 months.[4] In this population, further chemotherapy, followed by allogeneic SCT (alloSCT) has been the traditional approach, given its superiority compared with chemotherapy alone.[5] However, many patients are unable to proceed to alloSCT at all owing to a lack of disease control with salvage therapy, declining performance status or organ function from the cumulative treatment, or lack of a suitable matched donor.[6] For patients who do proceed to allogeneic transplantation, the outcomes have been suboptimal. A recent meta-analysis showed that although transplantation outcomes have improved significantly over time, even in the more recent studies, only 40% of patients will be alive without disease relapse 3 years after alloSCT, with a 15% to 20% nonrelapse mortality (NRM) rate and cumulative incidence of relapse (CIR) of > 40%.[7]

Despite these sobering statistics, reason exists for optimism. Novel agents such as brentuximab vedotin (BV) and the checkpoint inhibitors (CPIs) nivolumab and pembrolizumab have resulted in much greater response rates as single agents compared with traditional cytotoxic chemotherapy when given as third-line treatment or beyond. Moreover, the responses realized with these agents can be quite durable and, as discussed in the present review, might potentially obviate the need for immediate alloSCT in select cases. Simultaneously, significant improvements in the field of alloSCT have also been made, including advances in supportive care, donor

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selection, and increasing familiarity and expertise in alternative donor transplantation, in particular, haploidentical alloSCT (haploSCT). In the present report, we review briefly the historical context of alloSCT for HL, followed by a discussion of the emerging role of haploidentical alloSCT. We then discuss the role of BV and CPIs for r/r HL, focusing on their role for patients who might potentially proceed to alloSCT. We also briefly address the difficult situation of post-alloSCT relapse. Finally, we conclude with a summary of our recommendations for the treatment of HL patients experiencing disease relapse after autoSCT.

AlloSCT for HL

Although alloSCT has been performed for r/r HL for > 30 years,[8] its applicability has always been limited by many factors. The high cure rate in the frontline setting and the reasonable cure rate and low morbidity afforded by autoSCT has meant that virtually all patients proceeding to alloSCT have been very heavily pretreated, with a large majority developing progression after previous autoSCT. In this population, a declining performance status, an inability to control the disease, and a lack of donor availability have been common barriers precluding consideration of alloSCT. Also, for patients who are able to undergo alloSCT, the morbidity and mortality of this procedure have been high. Despite these issues, alloSCT has continued to be a part of the treatment paradigm for r/r HL, because it offers curative potential for patients with progression after autoSCT, likely as a result of the graft-versus-lymphoma effect exerted by the donor immune cells and leading to a state of ongoing immune surveillance.[9] Furthermore, advances in transplantation medicine, especially with the ongoing development and refinement of haploSCT, have made alloSCT much more accessible. Finally, expansion of the therapeutic arsenal for HL to include BV and CPIs has also had a large effect on the management of r/r HL, because they confer relatively little toxicity, yet offer excellent disease control with or without subsequent alloSCT.

Matched Sibling Donor and Matched Unrelated Donor Transplantation

The earliest studies of alloSCT for HL demonstrated poor outcomes, primarily owing to the prohibitive rates of NRM.[10,11] Refinements in transplant medicine such as the development of reduced-intensity conditioning (RIC), with disease control provided by the graft-versus-lymphoma effect, resulted in a significant improvements in NRM. An analysis from 2008 by the European Society for Blood and Marrow Transplantation (EBMT) of patients who had undergone transplantation from 1997 to 2001 showed improved survival without an increase in relapse for patients who had undergone RIC alloSCT compared with myeloablative (MAC) alloSCT.[12] However, more recent data from the EBMT have suggested that MAC alloSCT might not be more toxic than RIC alloSCT, possibly owing to better patient and donor selection and improvements in supportive care.[13] A meta-analysis from 2016 of alloSCT for r/r HL found that patients who had undergone transplantation after 2000 had a 3-year overall survival (OS) and relapse-free survival (RFS) of ~60% and ~40%, respectively, and fared significantly better than patients treated before 2000. Regarding other prognostic factors, chemosensitivity and previous autoSCT both were associated with improved OS and RFS, and previous autoSCT was also associated with decreased NRM.[7]

The EBMT conducted a large retrospective registry analysis of 312 patients who had undergone alloSCT for r/r HL from 2006 to 2010 with the goal of comparing the outcomes between patients treated with MAC (n = 63) versus RIC (n = 249). The primary outcomes were OS and event-free survival (EFS). OS was not significantly different between the 2 cohorts and was 73%, 64%, and 45% at 1, 2, and 5 years, respectively. EFS was nonsignificantly improved in the MAC cohort, with a hazard ratio of 0.7 ($P = .07$). In addition, NRM was not different between the 2 groups, with a 1-year NRM rate of 5% and 10%, respectively, in the MAC and RIC cohorts. The 2 groups were significantly different with respect to a number of clinical parameters, especially previous autoSCT (62% in the RIC cohort and 27% in the MAC cohort) and the interval from diagnosis to alloSCT (35.6 months in the RIC cohort and 21 months in the MAC cohort). Chemosensitivity, or disease status, was the only factor significantly predictive of relapse, OS, and EFS.[13] However, although chemosensitivity has been consistently associated with improved post-alloSCT outcomes in multiple series, achievement of a metabolic complete response (CR) before transplantation, a crucial prognostic factor with autoSCT,[14,15] might not be crucial. Reyal et al[16] analyzed 116 patients with r/r HL who had undergone T-cell–depleted alloSCT, none of whom had had progressive disease before alloSCT. The final pretreatment positron emission tomography/computed tomography scan findings, stratified by the Deauville score, did not correlate significantly with either OS or progression-free survival (PFS).[16] Similarly, in a report from Giaccone et al[17] of 69 patients with r/r HL who had undergone alloSCT, with a median follow-up of 7.2 years, the 5-year OS and RFS was 51% and 39%, respectively. Also, chemosensitivity was associated with improved RFS; no difference was found in RFS between patients with a CR versus a partial response (PR).[17]

An analysis from the MD Anderson Cancer Center by Anderlini et al[18] examined the results for 58 patients undergoing RIC alloSCT for r/r HL (matched sibling donor [MSD], n = 25; mismatched unrelated donor [MUD], n = 33) conditioned with fludarabine and melphalan. Graft-versus-host disease (GVHD) prophylaxis consisted of a calcineurin inhibitor with methotrexate (MTX). Some of the MUD recipients received antithymocyte globulin (ATG; n = 14). The 2-year OS, PFS, and CIR was 64%, 32%, and 55%, respectively, with no differences seen between the MUD and MSD groups. However, chronic GVHD (cGVHD) developed more often in the MUD recipients (85% vs. 57%). A trend toward improved PFS was seen in patients with a CR or unconfirmed CR compared with all other disease states. However, no difference in OS was seen.[18] Kako et al[19] performed a retrospective analysis of data from the Japanese Society for Hematopoietic Cell Transplantation. Of 122 patients with r/r HL who had undergone alloSCT from 2002 to 2009, the 3-year PFS, OS, and NRM was 31%, 42%, and 32%, respectively. Female recipient gender and performance status were significantly associated with improved OS, and a mismatched donor and umbilical cord blood (UCB) predicted for worse OS. In their series, disease status before alloSCT was only associated with a trend toward improved OS and PFS.[19] Peggs et al[20] reported on 67 patients from Spain and the United Kingdom who had undergone MSD RIC alloSCT from 1997 to 2004. The 36 patients from Spain received cyclosporine (CsA) and alemtuzumab for GVHD prophylaxis. The 31 patients from the United Kingdom received CsA

and MTX. The 4-year OS and PFS for patients receiving alemtuzumab was 62% and 39%, respectively. The 4-year OS and PFS for the patients receiving MTX was 39% and 25%, respectively. Neither the OS nor the PFS difference achieved statistical significance.[20] The administration of alemtuzumab was associated with significantly reduced rates of both acute GVHD (aGVHD) and cGVHD and did not appreciably affect the CIR. However, patients receiving alemtuzumab were more likely to have chemosensitive disease.[20] An interesting finding was that the responses to donor lymphocyte infusion (DLI) in the setting of post-alloSCT relapse were much more durable in the patients who had received alemtuzumab.[20] Armand et al[21] reviewed the results from 36 patients with r/r HL who had undergone RIC alloSCT from 2000 to 2006. All 36 patients had undergone conditioning with fludarabine and busulfan. The 3-year OS, PFS, CIR, and NRM was 56%, 22%, 63%, and 15%, respectively.[21] Also, the development of cGVHD appeared to be associated with improved PFS but not OS.[21] Although cGVHD was also associated with a decreased relapse risk in the EBMT retrospective analysis from 2008,[12] a larger Center for International Blood and Marrow Transplant Research analysis specifically examining the effect of cGVHD on the relapse rate did not find a positive correlation in the HL subset (n = 466).[22] Some of the larger trials of alloSCT for HL with accrual primarily after 2000 are listed in Table 1.

Alternative Donors

As stated, one of the many obstacles that exist for patients to proceed to alloSCT has been donor availability because not all patients will have a MSD or a matched or suitably MUD. However, the advances in transplant medicine have made possible alternative donor transplants such as UCB and haploSCT; thus, as a result, a donor can be located for the large majority of patients. Although few trials have compared UCB and haploSCT directly for HL and none in a prospective manner, the available evidence strongly favors the latter. Also, increasing data have suggested that the haploSCT outcomes are comparable to those of MSD and MUD transplants from the standpoint of relapse and survival with decreased cGVHD.

UCB AlloSCT

Although somewhat limited, the data regarding UCB alloSCT for r/r HL have shown that it is feasible, albeit associated with a high rate of relapse. One of the larger data sets is from the EBMT analysis of UCB transplantation for patients with lymphoma, of whom 29 had HL.[25] The follow-up duration was only 1 year, and the OS, PFS, NRM, and CIR were 41%, 30%, 35%, and 37%, respectively. The chemosensitivity, the incorporation of low-dose total body irradiation into the conditioning regimen, and a total nucleated cell count of $\geq 2 \times 10^7$/kg were associated with improved PFS in the entire cohort.[25] However, specific prognostic factors for the HL subset were not specified.[25] Thompson et al[26] summarized the results for 27 poor-risk patients who had undergone UCB alloSCT at the MD Anderson Cancer Center and The Royal Melbourne Hospital with both RIC and myeloablative regimens. The 5-year PFS was 31%, and the 5-year OS was not reported. The median OS was 27 months, and the CIR was 38% at 5 years. The 100-day NRM was 26%, primarily owing to infection with 5 early deaths, all of whom had received rabbit ATG for in vivo T-cell depletion (22 of the 27 patients had received ATG).[26] The regimen intensity was not associated with either PFS or OS, and disease status was not specifically stated either, although the investigators noted that 3 of 7 patients with progressive disease at transplantation achieved a durable remission.[26] The University of Minnesota reviewed the results for 23 patients receiving UCB alloSCT, all of whom were conditioned with fludarabine, cyclophosphamide, and low-dose TBI and had received CsA and mycophenolate mofetil as GVHD prophylaxis. The 3-year OS and PFS were 43% and 33%, respectively, and the NRM was 13%.[27] Also, grade 2-4 aGVHD, grade 3/4 aGVHD, and cGVHD at 2 years had developed in 57%, 25%, and 19% of

Table 1 AlloSCT Trials of HL With Patient Accrual After 2000

Investigator	Patients (n)	Conditioning	GVHD Prophylaxis	NRM (%)	OS (%)	PFS/EFS (%)	aGVHD (%)	cGVHD (%)
Anderlini et al[18]	58	Flu/Mel	Tac/MTX ± ATG	2-y, 15	2-y, 64	2-y, 32	28	73
Armand et al[21]	36	Flu/Bu	CNI/Sir ± MTX	3-y, 15	3-y, 56	3-y, 22	G2-4, 22; G3/4, 11	2-y, 67
Chen et al[23]	24	Flu/Mel	Tac/Sir ± MTX (n = 16), CsA/MMF ± MTX ± ATG (n = 8)	2-y, 13	2-y, 60	2-y, 27	G2-4, 46; G3/4, 8	58
Genadieva-Stavrik et al[13]	312	MAC (n = 63), RIC (n = 249)	NA	5-y, 13	5-y, 45	5-y, 30	NA	NA
Giaccone et al[17]	69	MAC (n = 5), RIC (n = 64)	CNI/MTX (n = 53), CNI/MMF (n = 12), CNI/CY/MMF (n = 2), CNI/alemtuzumab (n = 2)	5-y, 18	5-y, 51	5-y, 39	G2-4, 37	46
Kako et al[19]	122	NS; 62% RIC, 47% TBI-based	NS	3-y, 32	3-y, 42	3-y, 31	G2-4, 53	47
Peggs et al[20,a]	31	Flu/Mel	CsA, ATG	2-y, 7	4-y, 62	4-y, 39	G2-4, 3	2-y, 33
Peggs et al[20]	36	Flu/Mel	CsA, MTX	2-y, 29	4-y, 39	4-y, 25	G2-4, 31; G3/4, 6	2-y, 58
Sureda et al[24]	78	Flu/Mel	CsA, MTX ± ATG	2-y, 17	4-y, 41	4-y, 18	32	2-y, 44

Abbreviations: aGVHD = acute graft-versus-host disease; alloSCT = allogeneic transplantation; ATG = antithymocyte globulin; Bu = busulfan; cGVHD = chronic graft-versus-host disease; CNI = calcineurin inhibitor (either tacrolimus or cyclosporine); CsA = cyclosporine; CY = cyclophosphamide; EFS = event-free survival; Flu = fludarabine; G = grade; GVHD = graft-versus-host disease; HL = Hodgkin lymphoma; Mel = melphalan; MMF = mycophenolate mofetil; MTX = methotrexate; NA = not available; NRM = nonrelapse mortality; NS = not specified; OS = overall survival; PFS = progression-free survival; RIC = reduced-intensity conditioning; Sir = sirolimus; Tac = tacrolimus; TBI = total body irradiation.
[a]The 2 cohorts from Peggs et al[20] are listed separately because they used different GVHD prophylaxis regimens and were compared with each other in the study.

patients, respectively.[27] Piñana et al[28] reported the results for 30 patients who had undergone UCB alloSCT after conditioning with thiotepa, busulfan, and either fludarabine or cyclophosphamide. GVHD prophylaxis consisted of rabbit ATG (for all but 1 patient), CsA, and prednisone or mycophenolate mofetil. One patient experienced primary graft failure, and the 4-year EFS and OS were 28% and 30%, respectively.[28] Nine patients developed Epstein-Barr virus-related complications, with 6 cases of Epstein-Barr virus–related post-transplant lymphoproliferative disorder.[28]

A few reported studies have included comparisons of UCB alloSCT with SCT with other donor sources. Marcais et al[29] reported on 191 patients who had undergone alloSCT for r/r HL with RIC conditioning. Most of the 191 patients had undergone MSD or MUD alloSCT; however, 17 had undergone UCB alloSCT. The risk of death appeared to be increased with UCB alloSCT, despite the more favorable disease status at transplantation. The 3-year OS, PFS, NRM, and CIR were 44%, 26%, 18%, and 56%, respectively. In the entire cohort, the only 2 factors associated with worse OS were the lack of chemosensitivity and UCB as the stem cell source.[29] Gauthier et al[30] performed a retrospective analysis of alternative donor alloSCT (UCB, n = 37; haploSCT, n = 34; MUD, n = 27). In the UCB arm, the 3-year OS, EFS, NRM, and CIR were 80%, 53%, 11%, and 36%, respectively.[30] The endpoint of GVHD-free, RFS (GRFS) was also analyzed. The 3-year GRFS was 31%. Disease status at transplantation was the only significant prognostic risk factor for OS on multivariate analysis, and the GRFS was lower in the haploSCT arm.[30] Taken together, although some patients will achieve long-term remission with UCB alloSCT, the toxicity and relapse rates both appear to be high compared with those with other donor sources. The larger data sets of UCB alloSCT for HL are summarized in Table 2.

Haploidentical AlloSCT

Accumulating evidence supports the efficacy of haploSCT in r/r HL, with an incidence of cGVHD comparable to, if not lower than, that with MSD and MUD alloSCT. One of the earlier reported data sets of haploSCT for HL was a multicenter retrospective analysis from Burroughs et al[31] compared MSD, MUD, and haploSCT for r/r HL. All 28 patients who underwent haploSCT received unmanipulated bone marrow stem cells (BMSCs). The 2-year OS, PFS, and NRM were 58%, 51%, and 9%, respectively, which compared favorably with the MSD and MUD cohorts.[31] Raiola et al[32] described the results of 26 patients who had undergone haploSCT with a 3-year PFS and OS of 63% and 77%, respectively. However, the cumulative NRM was only 4%, and the cumulative incidence (CI) of cGVHD at 3 years was 9%. Again, all patients had received BMSCs.[32] Castagna et al[33] reported the results from 62 haploSCT patients; 11 had been included in the report by Raiola et al.[32] The 1-year NRM, 3-year PFS, 3-year OS, and CIR were 20%, 59%, 63%, and 21%, respectively, and the CI of cGVHD was 16%. Of the 62 patients, 39 received BMSCs and 23 patients received peripheral blood stem cells (PBSCs). Increased OS and PFS were seen in the latter group, along with a trend toward a lower incidence of relapse.[33] Pitombeira de Lacerda et al[34] reported the results of 24 patients who had undergone haploSCT for r/r HL across 6 centers in Brazil. The 2-year PFS, 2-year OS, 2-year CI of cGVHD, and NRM were 54%, 66%, 24%, and 26%, respectively.[34] The patients were divided fairly evenly with respect to graft source (13 patients received BMSCs and 11 received PBSCs); however, this was not included in the outcomes analysis.[34]

With respect to registry trials, the Center for International Blood and Marrow Transplant Research performed 2 separate retrospective analyses of haploSCT for lymphoma compared with MUD and MSD

Table 2 Umbilical Cord Blood AlloSCT in HL

Investigator	Patients (n)	Conditioning	GVHD Prophylaxis	NRM (%)	OS (%)	PFS/EFS (%)	aGVHD (%)	cGVHD (%)
EBMT[25]	29	Reported in aggregate but not for HL subset	Reported in aggregate but not for HL subset	1-y, 35	1-y, 41	1-y, 30	1-y, 12	NA
Thompson et al[26]	27	Flu/CY/TBI (n = 5), Flu/Mel (n = 2), Mel/T/Flu (n = 12), Flu/Clo/Bu/TBI (n = 3)	NR but 22/27 patients received ATG	100 d, 26; 5-y, 38	NR	5-y, 31	G2-4, 33.5; G3/4, 0	40.5; extensive
Gauthier et al[30]	27	Flu/CY/TBI (1 patient received Flu/CY/Mel)	CsA, MMF	3-y, 11	3-y, 75	3-y, 53	G2-4, 45; G3/4, 21	2-y, 3
Brunstein et al[27]	23	Flu/CY/TBI	CsA + MMF (7 patients also received horse ATG)	3-y, 13	3-y, 43	3-y, 33	G2-4, 57; G3-4, 25[a]	2-y, 19[a]
Piñana et al[28]	30	TT/Flu/Bu (n = 28), TT/Flu/CY (n = 2)	CsA + prednisone (n = 19), CsA + MMF (n = 11); all but 1 patient received rabbit ATG	4-y, 47	4-y, 30	4-y, 28	G2-4, 34	4-y, 43

Abbreviations: aGVHD = acute graft-versus-host disease; alloSCT = allogeneic transplantation; ATG = antithymocyte globulin; Bu = busulfan; cGVHD = chronic graft-versus-host disease; Clo = clofarabine; CsA = cyclosporine; CY = cyclophosphamide; EFS = event-free survival; Flu = fludarabine; G = grade; GVHD = graft-versus-host disease; HL = Hodgkin lymphoma; Mel = melphalan; MMF = mycophenolate mofetil; NA = not available; NR = not reported; NRM = nonrelapse mortality; OS = overall survival; PFS = progression-free survival; RIC = reduced-intensity conditioning; TBI = total body irradiation; TT = thiotepa.
[a]Reported only for the entire cohort, including patients with non-HL.

alloSCT.[35,36] In both studies, cGVHD was lower in the haploSCT cohort as a whole, and survival, relapse, and NRM were comparable. Slightly more patients were included in the haploSCT versus MUD than in the haploSCT versus MSD study. Of the 46 patients with r/r HL, the 3-year PFS and OS were 45% and 68%, respectively. The large majority of patients received a bone marrow graft; thus, the effect of the graft source could not be assessed. Finally, the largest reported data set is a retrospective EBMT registry analysis comparing the results for patients undergoing MSD (n = 338), MUD (n = 273), and haploSCT (n = 98).[37] In the haploSCT cohort, the 2-year OS and PFS were 67% and 43%, respectively, with a 1-year NRM of 17% and 2-year cGVHD incidence of 26%. Although survival was comparable among all 3 types of alloSCT, cGVHD was less common in the haploSCT than in the MUD alloSCT group, and cGVHD was similar between patients receiving BMSCs (n = 60) and those receiving PBSCs (n = 38). Absent a prospective clinical trial, the available data are not sufficient to recommend haploSCT over traditional MSD or MUD alloSCT. However, the data do suggest that haploSCT is a very viable option for HL with a low rate of cGVHD and survival and relapse comparable to those with MSD and MUD transplantation.[37] Just as is the case with other types of alloSCT, disease status at transplantation and chemorefractory disease appear to be the most important prognostic factors seen in all the cited trials. Some of the large trials examining haploidentical alloSCT in HL are summarized in Table 3.

BV and AlloSCT

BV is an antibody–drug conjugate consisting of an anti-CD30 monoclonal antibody connected to the antitubulin agent monomethyl auristatin E via a dipeptide linker.[38] In HL, it was initially approved by the Food and Drug Administration in 2011 for the treatment of patients with disease progression after autoSCT or in whom ≥ 2 previous regimens had failed but were not candidates for autoSCT. The approval was based on the results from a phase II trial showing an overall response rate (ORR) of 75%, with a CR rate of 34%.[39] Subsequently, it was also approved for maintenance after autoSCT for HL patients deemed at high risk of relapse or progression on the basis of the phase III AETHERA clinical trial [a phase 3 study of brentuximab vedotin (SGN-35) in patients at high risk of residual Hodgkin Lymphoma following stem cell transplant].[40] Given the excellent tolerability and efficacy of BV, from a practical standpoint, nearly all patients currently considered for alloSCT will have been exposed to it at some point.

The role of BV as a bridge to alloSCT has been examined in multiple small studies. Chen et al[41] analyzed the results of 19 patients from the City of Hope and University of Washington who had received BV for r/r HL before reduced-intensity alloSCT. The 1-year OS and PFS after alloSCT was 100% and 92.3%, respectively,[41] and the 2-year PFS was 59.3%. These results compared highly favorably with those of historical controls.[42] Similarly impressive results were also seen in a small study by Garciaz et al,[43] with no NRM identified by 100 days and 100% OS at a median of 20 months for 12 patients with HL who had undergone alloSCT after BV salvage. Although most patients who receive BV for HL will eventually develop progression, a key finding that has emerged is that a CR (but not PR) realized with BV might be durable.[44] In the original phase II study of BV with autoSCT, 34 of 102 patients achieved a CR. Of these 34 patients, 13 remained in CR at 5 years, 9 of whom had received no further therapy after BV.[45] Therefore, BV appears to function as a highly effective bridge to alloSCT for patients with relapse after autoSCT. However, for the patients who achieve a CR with this agent, it might be reasonable to defer alloSCT, because some of them might enjoy prolonged remission without further therapy.

Checkpoint Inhibitors

One of the genetic hallmarks of HL is overexpression of the programmed cell death-1 (PD-1) ligands PD-L1 and PD-L2 on the

Table 3 Haploidentical AlloSCT in HL

Investigator	Patients (n)	Conditioning	GVHD Prophylaxis	NRM (%)	OS (%)	PFS/EFS (%)	aGVHD (%)	cGVHD
Pitombeira de Lacerda et al[34]	24	Flu/CY/TBI	PTCY, CNI, MMF	2-y, 26	2-y 66	2-y, 54	G2-4, 17	24% (all mild)
Castagna et al[33]	62	Flu/CY/TBI ± TT	PTCY, CNI, MMF	1-y, 20	3-y, 63	3-y, 59	G2-4, 23; G3-4, 4	16%
Gauthier et al[30]	34	Flu/CY/TBI, 1 patient each received Flu/Bu/TT, Flu/Bu, and Flu/CY/Bu	PTCY, CNI, MMF, 1 patient received PTCY, ATG, CNI, MMF	3-y, 9	3-y, 75	3-y, 66	G2-4, 28; G3-4, 3	15%, 9% extensive
Raiola et al[32]	26	Flu/CY/TBI	PTCY, CNI, MMF	3-y, 4	3-y, 77	3-y, 63	G2-4, 24	3-y, 9%
CIBMTR[36,a]	46	Flu/CY/TBI	PTCY, CNI, MMF (95%)[a]	3-y, 17	3-y, 68	3-y, 45	G2-4, 27; G3-4, 8	2-y, 15%
EBMT[37]	98	Flu/CY/TBI, Flu/CY/Bu (80%), other (20%)	PTCY, CNI, MMF (94%)	1-y, 17	2-y, 67	2-y, 43	G2-4, 33; G3-4, 9	2-y, 26%

Abbreviations: aGVHD = acute graft-versus-host disease; alloSCT = allogeneic transplantation; ATG = antithymocyte globulin; Bu = busulfan; cGVHD = chronic graft-versus-host disease; CIBMTR = Center for International Blood and Marrow Transplant Research; CNI = calcineurin inhibitor (either tacrolimus or cyclosporine); CY = cyclophosphamide; EFS = event-free survival; Flu = fludarabine; G = grade; GVHD = graft-versus-host disease; HL = Hodgkin lymphoma; MMF = mycophenolate mofetil; NRM = nonrelapse mortality; OS = overall survival; PFS = progression-free survival; PTCY = post-transplant cyclophosphamide; RIC = reduced-intensity conditioning; TBI = total body irradiation; TT = thiotepa.
[a]The CIBMTR analysis included many histologic types; the data listed are in the aggregate, except for PFS and OS, which were specifically reported in HL patients.

surface of the Reed-Sternberg cell due to copy number alterations involving 9p24.1 This results in both a direct increase in surface PD-L1 expression and an amplification of JAK2, which further increases downstream PD-L1 gene transcription.[46] Therapeutic agents aimed at disrupting this pathway are included in the broader class of medications known as CPIs, and 2 monoclonal antibodies directed against PD-1 have been approved in the United States for treatment of r/r HL. The first agent is nivolumab, which in the CHECKMATE 205 trial [study of nivolumab in patients with classical Hodgkin's lymphoma (Registrational)] demonstrated an impressive response rate of 66% in a heavily pretreated population,[47] and was approved in 2016 for patients with progression after autoSCT and BV. Subsequently, pembrolizumab was approved by the Food and Drug Administration in 2017 for patients with refractory HL or relapse after ≥ 3 previous lines of therapy on the basis of the KEYNOTE-087 trial [study of pembrolizumab (MK-3475) in participants with relapsed or refractory classical Hodgkin lymphoma]. In the KEYNOTE-087 trial, pembrolizumab had a single-agent response rate of 69% in heavily pretreated patients, most of whom had previously undergone autoSCT and had received BV.[48]

Given the high response rates and relatively low toxicity seen with these agents, one potential application of these drugs is as a bridge to alloSCT. The clinical experience with CPIs before alloSCT at present remains small; however, the current evidence suggests that this approach is feasible, albeit potentially associated with increased toxicity. A retrospective study of 39 patients who had undergone reduced intensity alloSCT for lymphoma after CPI, 31 of whom had HL, was recently reported.[49] The 1-year OS and PFS were favorable at 90% and 74%, respectively, and the 1-year CI of grade 2-4 and grade 3/4 aGVHD were 44% and 23%, respectively, in the entire cohort. Of interest, 7 patients developed a noninfectious febrile syndrome without clear GVHD, and 3 patients died of aGVHD, more than would be normally expected.[49]

Just as is the case with BV, the responses to these agents appear to be far more durable than those seen with cytotoxic chemotherapy. However, the short follow-up duration has been a major limitation. For instance, the extended 12-month follow-up period of the CHECKMATE 205 trial found the median PFS and mean duration of response with nivolumab to be 14.8 months and 13.1 months, respectively.[50] However, the PFS curve did not demonstrate an obvious plateau.[50] The follow-up length has been even shorter with pembrolizumab, with a median follow-up duration of only 10.1 months, with the median duration of response not yet reached and a 9-month PFS of 63.4%.[48] At present, the question of whether a patient who is responding well to PD-1 blockade should proceed to alloSCT before disease progression remains, and a decision for alloSCT should consider the immune-mediated toxicities that have been reported.

Post-alloSCT Relapse

The probability of disease relapse after alloSCT is substantial, and the prognosis is poor for these patients. Aside from rapidly minimizing systemic immunosuppression, no standard strategy is available. Depending on the clinical context, the options include DLI, salvage systemic therapy, and, potentially, even second alloSCT. The data for all of these are limited, however, and mostly consist of small single-institution retrospective studies. From a practical standpoint, usually > 1 strategy is used; for instance, many, but not all, patients undergoing DLI are first given cytoreductive therapy.

The response rates to cytotoxic chemotherapy have been low and tend to be short-lived,[51] and the more recent studies have either focused on the incorporation of novel agents (BV or CPIs) and/or have incorporated DLI. A cohort study of 25 patients who received single-agent BV for post-alloSCT relapse demonstrated an ORR of 50% and median PFS of 7.8 months.[51] Although these patients had not received previous BV, retreatment with BV has been shown to be safe and effective in other settings.[44] BV, followed by DLI, has also been studied and shown to be effective, albeit in a limited number of patients.[52,53]

The largest data set for DLI included 27 patients from the MD Anderson Cancer Center and found an ORR of 37% and median response duration of 7.5 months. All the patients with a treatment response developed GVHD, and the OS for the entire cohort was 20% at 4 years.[54] Peggs et al[55] found an ORR of 79% for relapsed disease with a fairly durable responses and a 4-year PFS of 59%. However, all the patients in that study had undergone in vivo T-cell depletion with alemtuzumab, which might be associated with greater rates of response to DLI.[20] Alvarez et al[56] reported a response rate of 54% (6 of 11 patients), although the response duration was not specified.

Finally, the administration of CPIs has also been tested for post-alloSCT relapse, and, although response rates have been high, the toxicity has also been substantial. One multicenter retrospective trial of 31 lymphoma patients, 29 of whom had HL, who had received either nivolumab or pembrolizumab after alloSCT relapse, found a high ORR of 77%.[57] However, treatment-related GVHD developed in 55% of patients and tended to be highly refractory to conventional GVHD management, with 26% of the patients dying of GVHD.[57] Another retrospective trial examining 20 HL patients receiving nivolumab after alloSCT found an ORR of 95% with a 30% incidence of GVHD, and 10% of the patients died of GVHD.[58] Because PD-1 inhibitors interrupt both PD-1/PD-L1 and PD-1/PD-L2 interactions, whether these toxicities can be attenuated with dedicated PD-L1 inhibition is an open question. A recent phase 1b study of the anti—PD-L1 monoclonal antibody avelumab included 8 patients with previous allogeneic transplantation.[59] Of these 8 patients, 2 developed grade 3 acute GVHD. Complete resolution of the GVHD in both patients was achieved with reinstitution of immunosuppressive therapy and withdrawal of avelumab, and no deaths from GVHD occurred.[59] Overall, in light of these results, significant caution should be exercised if a CPI is given after alloSCT and should preferably be administered in the context of a clinical trial.

Recommendations

Given the rapidly changing treatment landscape of HL with novel agents such as BV and CPIs, no consensus guidelines are available for the management of relapsed disease after autoSCT. As such, the usual admonition of a well-designed clinical trial being the best therapy also holds in this situation. All patients eligible for alloSCT should undergo human leukocyte antigen typing, including identification of potential haploidentical donors, although not all patients will need to proceed directly to alloSCT. Also, the administration of salvage therapy after autoSCT does not need to be done solely with the intent of bridging patients to alloSCT.

For patients who have not received BV, we would recommend BV administration. Also, for the approximately one third of patients who will achieve a CR (but not PR) with BV, we would recommend administering the full 16 doses without immediate alloSCT, because up to one third of these patients could remain in remission without further treatment.[45] In contrast, a PR realized with BV will not be durable, and all such patients will require further therapy. Waiting until disease progression to administer a CPI is reasonable, just as is proceeding directly to alloSCT. No data are yet available to compare the 2 approaches, and the decision is at the discretion of the treating physician. Our institutional practice at the City of Hope for such patients in the absence of a clinical trial is to attempt to administer a CPI first at disease progression.

The decision to proceed to alloSCT must be carefully made, and chemorefractory disease before alloSCT is the main prognostic factor associated with poor outcomes, although achievement of a metabolic CR before alloSCT does not seem to be important. In the context of post-autoSCT relapse, we recommend using a RIC regimen because the improvement in NRM with MAC alloSCT has been primarily seen in patients who had not undergone previous autoSCT. Data have shown strong support for haploSCT as a reasonable alternative to MSD or MUD alloSCT, given the decreased rates of cGVHD with comparable survival outcomes. Thus, if no matched sibling or fully matched unrelated donor is available, we would recommend haploSCT over UCB or MUD alloSCT. If no MSD, MUD, or haploidentical donor can be identified, UCB transplantation can be considered. Although alloSCT can be performed after previous CPI administration, caution should be exercised, given the possibly increased rates of toxicity.

For patients with relapse after alloSCT, the limited available evidence points to a reasonable rate of response when cytoreductive therapy is given, followed by DLI, although GVHD is a significant concern. Treatment with CPI has been associated with significant toxicity in this setting and should only be performed with great care.

Disclosure

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