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Guideline

Role of Cytotoxic Therapy with Hematopoietic Cell Transplantation in the Treatment of Hodgkin Lymphoma: Guidelines from the American Society for Blood and Marrow Transplantation

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A B S T R A C T

The role of hematopoietic cell transplantation (HCT) in the therapy of Hodgkin lymphoma (HL) in pediatric and adult patients is reviewed and critically evaluated in this systematic evidence-based review. Specific criteria were used for searching the published literature and for grading the quality and strength of the evidence and the strength of the treatment recommendations. Treatment recommendations based on the evidence are included and were reached unanimously by a panel of HL experts. Both autologous and allogeneic HCT offer a survival benefit in selected patients with advanced or relapsed HL and are currently part of standard clinical care. Relapse remains a significant cause of failure after both transplant approaches, and strategies to decrease the risk of relapse remain an important area of investigation.

INTRODUCTION

In 1999 the American Society for Blood and Marrow Transplantation (ASBMT) began an initiative to sponsor evidence-based reviews of the scientific and medical literature for the use of blood and marrow transplantation in the therapy of selected diseases. Eight previous reviews and 3 updates have been published in *Biology of Blood and Marrow Transplantation for these diseases*: diffuse large B cell non-Hodgkin lymphoma [1,2], multiple myeloma [3], pediatric acute lymphocytic leukemia [4,5], adult acute lymphocytic leukemia [6,7], pediatric acute myeloid leukemia [8], adult acute myeloid leukemia [9], myelodysplastic syndrome [10], and follicular lymphoma [11]. The goals of this review are to assemble and critically evaluate all evidence regarding the role of hematopoietic cell transplantation

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(HCT) in the therapy of patients with Hodgkin lymphoma (HL), make treatment recommendations based on the available evidence, and identify areas of needed research.

EXPERT PANEL AND GRADING SYSTEM

Experts in the treatment of HL were invited to join the independent expert panel that examined the literature and provided subsequent treatment recommendations based on the available evidence. Members of the expert panel first reviewed and agreed on a list of topics to be included in the review. Articles were then organized into subtopics by 2 authors (M.-A.P. and I.C.), and reviewers were provided with a list of studies specific to the subtopic they were reviewing as well as a master list of all studies.

A standardized grading system that includes grading the levels of evidence was used to grade the studies included in this review and the treatment recommendations [12], as recommended by the ASBMT Steering Committee for evidence-based reviews [13] (Supplemental Tables 1 and 2). Studies were also evaluated based on study design, sample size, patient selection criteria, duration of follow-up, and treatment plan. Articles in each subtopic were reviewed and graded by 2 to 3 experts, who then submitted treatment recommendations. When differences were noted in the grading system, the lead author (M.-A.P.) discussed these with the reviewers for that specific topic and consensus was reached for the final grading and recommendation. This iterative process concluded when final versions of the treatment recommendation tables were approved by all panelists.

After the final draft of the review was approved by the disease-specific expert panel, it underwent peer review, first by the ASBMT Committee on Practice Guidelines and then by the ASBMT Executive Committee before submission to the journal. Any changes requested during the peer-review process were reviewed and approved by all disease-specific expert panelists.

LITERATURE SEARCH METHODOLOGY

The literature search methodology was adapted from the search methodology used for the diffuse large B cell non-HL evidence-based review update published in 2011 [2], with the following modification: articles that included fewer than 20 HL (rather than 25 as for diffuse large B cell non-HL) cases were excluded because of the lower incidence of the disease. PubMed was searched in July 2012, using the search terms "Hodgkin Lymphoma" AND "transplant" limited to "human trials," "English language," and a publication date of January 1, 2001 or later. The search terms were ("Hodgkin disease"[MeSH Terms] OR ("Hodgkin"[All Fields] AND "disease"[All Fields]) OR "Hodgkin disease"[All Fields] OR ("Hodgkin"[All Fields] AND "lymphoma"[All Fields]) OR "Hodgkin lymphoma"[All Fields]) AND ("transplants"[MeSH Terms] OR "transplants"[All Fields] OR "transplant"[All Fields] OR "transplantation"[MeSH Terms] OR "transplantation"[All Fields]) AND (("2001/01/01"[PDAT]: "3000/12/31"[PDAT]) AND "humans"[MeSH Terms] AND English[lang]). Articles published before January 2001, included fewer than 20 HL patients, or were not peer reviewed were excluded. Also excluded were editorials, letters to the editor, phase I (dose escalation or dose finding) studies, reviews, consensus conference papers, practice guidelines, and laboratory studies with no clinical correlates.

The initial search resulted in the identification of 2004 papers. Of these, 166 were selected for the evidence-based review. Two updated searches were performed in April 2013 to include articles published in 2012 (172 articles identified, 14 articles previously not identified selected) and in September 2014 to include articles published in 2014 (187 articles identified, 20 articles previously not identified selected). A total of 200 articles were included in the review. All articles were briefly reviewed and classified by 2 authors (M.-A.P. and I.C.), who also retrieved basic information on the studies, including study design and number of patients. Finally, additional important studies presented in 2014 have been included.

SUMMARY RECOMMENDATIONS

This section highlights summary recommendations for both autologous stem cell transplant (ASCT, Table 1) and allogeneic HCT (allo-HCT, Table 2) for patients with HL that are based on higher level evidence.

What Are the Indications for ASCT in HL?

Table 3 outlines the recommendations for the use of ASCT versus nontransplantation therapy.

Role of up-front ASCT

Results from randomized studies support that ASCT should not be performed as consolidation even in patients with high-risk or advanced disease [14-16]. Long-term follow-up of a randomized study of 163 patients with unfavorable HL showed similar 10-year overall survival (OS) of 85% (95% confidence interval [CI], 78% to 90%) and 84% (95% CI, 77% to 89%) for patients who underwent high-dose therapy and ASCT or conventional chemotherapy, respectively [14,16]. Similar results were noted in a randomized study comparing early versus late intensification [15].

ASCT for relapse or primary induction failure

HL is one of the most common indications for ASCT [117]. The expert panel recommends that persistent or relapsed disease be confirmed by biopsy. In contrast to up-front ASCT, outcomes in patients who have relapsed have shown a benefit of ASCT over conventional therapy [17-21,24-26,29-32]. Schmitz et al. [17] randomized 161 patients with relapsed HL to ASCT versus chemotherapy, with 144 patients with chemosensitive disease proceeding with the planned treatment. Although no significant difference in OS was found between the 2 groups, freedom from treatment failure at 3 years was significantly improved among patients who underwent ASCT (55%) compared with those treated with chemotherapy (34%; $P = .019$). Several retrospective studies that reported favorable outcomes with ASCT have combined patients with relapsed disease or primary induction failure in the analysis. In general, progression-free survival (PFS) ranged from 50% to 60% and OS from 50% to 80% for patients who had relapsed [18-21,24-26,29-32,39,69,117]. Patients with primary induction failure also appear to benefit from ASCT, with reported PFS rates of 40% to 45% and OS rates of 30% to 70% [17-28,69]. This area, however, remains controversial because it is supported only by retrospective data.

A recent Cochrane review on the role of ASCT in HL concluded that although ASCT as salvage therapy improves event-free survival (EFS) and PFS compared with nontransplant approaches, the benefit for OS showed a positive trend in favor of ASCT but did not reach statistical significance [33]. Although ASCT is the most commonly recommended salvage therapy, exceptions can be made for patients with localized late relapses who may benefit from salvage chemotherapy or involved field radiation therapy (IFRT) only when the lesion is amenable to this approach [30,31,34]. A review of existing pediatric data similarly concluded that salvage chemotherapy and radiation may provide similar outcomes to ASCT for subsets of pediatric HL patients [118].

Additional Considerations for the Use of ASCT in HL: Salvage, Conditioning, IFRT, and Special Populations

Additional considerations for ASCT use are displayed in Table 4.

Table 1
Summary of Treatment Recommendations for ASCT for HL

Recommendation	Grade of Recommendation	Highest Level of Evidence	References
ASCT should not be offered as first-line therapy for advanced disease	A	1+	[14-16]
ASCT should be offered as first-line therapy for patients who fail to achieve CR	B	2++	[17-28]
ASCT should be offered as salvage therapy over nontransplantation (except localized disease, where IFRT may be considered, or patients with low-stage disease and late relapse, where chemotherapy may be considered)	A	1+	[17-21,24-26,29-33]
ASCT should be offered to pediatric patients with primary refractory disease or high-risk relapse who respond to salvage therapy	B	2++	[30,34-39]
Several salvage chemotherapy regimens may be considered before ASCT in adult patients	B	2++	[40-51]
Several salvage chemotherapy regimens may be considered before ASCT in pediatric patients	B	2++	[52-56]
BEAM or CBV are the most common conditioning regimens for ASCT in standard-risk patients	B	2++	[20,21,39,51,57-71]
IFRT should be considered in patients with bulky disease not previously irradiated	C	2+	[51,65,72-74]
Tandem ASCT is not routinely recommended in standard-risk patients	C	2+	[75-79]
Maintenance therapy with brentuximab vedotin post-ASCT is recommended in high-risk patients*	A	1+	[80]
Chemosensitive disease and negative functional imaging are associated with improved outcome	B	2++	[51,69,81-88]

* High-risk patients were defined in the AETHERA trial as having 1 of the following: refractory to frontline therapy, relapse $<$ 12 months after frontline therapy, or relapse $\geq$ 12 months after frontline therapy with extranodal disease [80].

Salvage regimens for adult patients

A number of studies have looked at different salvage and conditioning regimens. Platinum-based regimens with non–cross-resistant drugs are the preferred regimens for salvage and stem cell mobilization in the United States (Supplemental Table 3a). One of the most commonly used regimens is ICE (ifosfamide, carboplatin, and etoposide) [40,51], although alternative salvage regimens such as ESHAP (etoposide, methylprednisolone, high-dose cytarabine, and cisplatin) or gemcitabine-containing regimens such as GDP (gemcitabine, dexamethasone, cisplatin) or IGEV (ifosfamide, gemcitabine, etoposide, vinorelbine) are considered acceptable alternatives [41-50,65,119]. In the study by Moskowitz et al. [40], the response rate to 2 cycles of ICE was 88% in 65 patients with HL (22 with primary refractory and 43 with relapsed HL). The OS and EFS rates for patients who underwent transplantation were 83% and 68%, respectively. Similar results have been reported with the other regimens, with overall response rates (ORRs) ranging from 62% to 88%, OS rates from 52% to 90%, and EFS rates from 36% to 70%. One study that randomized patients to further intensification of salvage therapy before ASCT did not show a survival benefit and higher toxicity [121]. In a more recent study, the use of sequential non–cross-resistant regimens, based on restaging with 2-deoxy-2-[fluorine-18]fluoro-D-glucose (^{18}F-FDG) positron emission tomography (PET) scan after 2 cycles of ICE, was examined [51]. Patients with a negative scan proceeded to transplantation, whereas those who still had a positive scan received 4 biweekly doses of GVD (gemcitabine, vinorelbine, and liposomal doxorubicin) and were subsequently transplanted if they had a negative scan. The EFS rates was >80% in patient transplanted with negative FDG-PET after 1 or 2 salvage programs versus 28.6% for patients with a positive scan ($P < .001$).

With the approval of the antibody drug conjugate targeting CD30 brentuximab vedotin in patients who relapse after an ASCT or fail to achieve a remission after second-line therapy [122], its use is being investigated in the salvage setting before ASCT, either as a single agent (NCT01508312, NCT01393717) or in combination with bendamustine (NCT01874054). In a study by Moskowitz et al. [123], 45 patients with relapsed/refractory HL who failed 1 prior regimen received weekly brentuximab vedotin for 2 cycles followed by a PET scan. Twenty-seven percent achieved a PET complete remission (CR) and proceeded directly to high-dose therapy/ASCT; 32 remaining patients with persistent abnormalities on PET received 2 cycles of augmented ICE, 22 of whom normalized their PET. After a median follow-up of 23 months, 80% of patients were event-free. Similarly, in a study by Chen et al. [124], 37 patients with relapsed/refractory HL who failed induction chemotherapy received brentuximab vedotin once every 3 weeks for a maximum of 4 cycles. Thirty-six percent achieved a PET CR, with an ORR of 69%. Patients not in CR were allowed to receive additional salvage chemotherapy before transplantation. Finally, the combination of bendamustine and brentuximab vedotin is also being studied in relapsed patients [125]. Preliminary results have shown a CR rate of 82% and ORR of 94% in 45 patients treated with this combination.

It should be noted that the latter 2 studies have only been presented in abstract form, and the reader is referred to the final publications when they are available. For

Table 2
Summary of Treatment Recommendations for Allo-HCT for HL

Recommendation	Grade of Recommendation	Highest Level of Evidence	References
Allo-HCT should be used instead of conventional therapy for relapse after ASCT	B	2++	[89-94]
RIC is the recommended regimen intensity	B	2++	[91,95-110]
All donor sources can be considered	A	1+	[96,100-102,104,105,111-113]
DLI can be given for relapse or progressive disease (limited data for mixed donor chimerism)	B	2++	[89,91,95-98,102,104,105,109,114,115]
There are limited data for tandem ASCT/Allo-HCT	D	4	[91]
Allo-HCT is preferred over ASCT as second HCT (except in late relapse)	C	2+	[90,116]

Table 3
ASCT versus Nontransplantation Therapy

	Recommendation	Grade of Recommendation	Highest Level of Evidence	References
Should ASCT be offered as first-line therapy for advanced disease?	No	A	1+	[14-16]
Should ASCT be offered as first-line therapy for patients who fail to achieve a CR?	Yes	B	2++	[17-28,69]
Should ASCT or nontransplantation be offered as salvage therapy?	ASCT	A	1+	[17-21,24-26,29-33,39]

recommendations on stem cell mobilization, readers are referred to recent guidelines on this topic published by ASBMT [126,127].

Salvage regimens for pediatric and young adult patients

A broad array of salvage regimens have been tested in clinical trials for pediatric and young adult patients (Supplemental Table 3b). Although these regimens differ significantly in intensity, the observed ORRs overlap. For this reason, salvage therapy for pediatric patients with relapsed or refractory HL not enrolled on a clinical trial may be selected by considering risk for acute and chronic toxicity. The combination of gemcitabine with vinorelbine is an example of a salvage regimen that avoids additional alkylating agents or etoposide yet produces high response rates and successful stem cell collection among pediatric and young adult patients with relapsed or refractory HL [50,54]. More intensive regimens (eg, ifosfamide with vinorelbine, ICE, or high-dose methotrexate, ifosfamide, etoposide, dexamethasone) can be reserved for those patients who do not have a negative FDG-PET scan after the initial salvage regimen [55]. Collection of stem cells after priming with an etoposide-containing regimen may increase the risk of secondary malignancies post-transplantation [128], for example, and should be approached with caution. Once achieving a CR defined by negative functional imaging (FDG-PET), all pediatric and young adult patients with primary refractory disease and most with relapsed HL should proceed to high-dose chemotherapy with ASCT. Conventional chemotherapy with or without radiation therapy can be considered for those with low-risk relapse, defined by initial stage other than IIIB or IVB, time to relapse greater than 12 months, and absence of extranodal disease or B symptoms at relapse.

Conditioning regimens

A number of conditioning regimens are routinely used for HL (Supplemental Table 4), including BEAM (BCNU, etoposide, cytarabine, melphalan), CBV (cyclophosphamide, carmustine [BCNU], etoposide), Bu/Cy (busulfan, cyclophosphamide) ± etoposide, Bu/Mel (busulfan, melphalan), or total lymphoid irradiation/chemotherapy [20,21,39,51,57-63,65-67,69-71]. For primary refractory HL, some authors consider radiation-based therapy (eg, total lymphoid irradiation) a preferred approach, although there are no randomized data in this regard. Although BEAM is one of the most commonly used regimens, there are a number of different dosing variations. In general, the following intravenous dosing is suggested: BCNU 300 mg/m^2, etoposide 800 to 1200 mg/m^2, cytarabine 1600 mg/m^2, melphalan 140 mg/m^2. Some studies have suggested that more intense regimens incorporating busulfan, melphalan, and either gemcitabine or thiotepa may provide an advantage in EFS and OS over BEAM, despite increased toxicity [69,70]. This may be particularly the case in poor-risk patients, and further studies are warranted to address this question. It should be noted, however, that neither study included patients above the age of 65, and caution is recommended in using more intense regimens in older patients in the absence of data.

Finally, a recent analysis by the Center for International Blood and Marrow Transplant Research (CIBMTR) that included 1012 patients with HL reported that CBV (with median BCNU dose of 450 mg/m^2; hazard ratio [HR]1.54), CBV (with median BCNU dose of 300 mg/m^2; HR1.53), BuCy (HR1.77), and total body irradiation (HR 3.39) were associated with higher mortality compared with BEAM ($P < .001$) [71]. Overall, reported treatment-related mortality (TRM) for ASCT ranges from 0 to 19% in some older series. OS and EFS

Table 4
Additional Considerations for ASCT

	Recommendation	Grade of Recommendation	Highest Level of Evidence	References
What are common regimens of salvage therapy before ASCT in adult patients?	ICE, ESHAP, or GDP*	B	2++	[40-51,119]
What are common regimens of salvage therapy before ASCT in pediatric patients?	GV, IV	B	2++	[52-56]
What is the recommended conditioning regimen for ASCT?	BEAM, CBV, Bu/Cy (±Et), Bu/Mel, or TLI/chemotherapy	B	2++	[20,21,39,51,57-71]
Is there a role for tandem ASCT?	Not in standard-risk patients	C	2+	[75-79]
What is the role of IFRT and when should it be performed?	Recommended in bulky disease previously not irradiated, post-ASCT in most centers	C	2+	[51,65,72-74]
Should maintenance therapy be given after ASCT?	Yes†	A	1+	[80]
What is the role of comorbidities in outcomes?	Paucity of data	—	—	[120]
Should ASCT be offered to pediatric patients?	Yes	B	2++	[30,34-39]

GV indicates gemcitabine, vinorelbine; IV, ifosfamide, vinorelbine; Et, etoposide; TLI, total lymphoid irradiation.

* More recent studies have incorporated brentuximab vedotin in the salvage setting (see text for details).

† Maintenance with brentuximab vedotin is recommended in high-risk patients, defined in the AETHERA trial as having 1 of the following: refractory to frontline therapy, relapse < 12 months after frontline therapy, or relapse ≥ 12 months after frontline therapy with extranodal disease [80].

rates range from 45% to 88% and 42% to 79%, respectively. There is a risk of secondary malignancies, particularly myelodysplastic syndrome and treatment-related acute myeloid leukemia, which has been observed in up to 5% of patients.

Tandem ASCT

Tandem ASCT for HL has been evaluated in a small number of studies [75-78]. The Groupe d'Étude des Lymphomes de l'Adulte/Société Française de Greffe de Moelle study group performed a prospective multicenter trial to evaluate risk-adapted salvage therapy with single or tandem ASCT in 245 HL patients [78]. Ninety-two intermediate-risk patients (97%) received single ASCT, whereas 105 poor-risk patients (70%) received tandem ASCT. The 5-year OS estimates were 85% and 57% for the intermediate-risk and poor-risk group, respectively. In the study by Fung et al. [76], 46 patients with primary progressive or recurrent HL with poor prognostic factors underwent tandem ASCT. Conditioning consisted of high-dose melphalan for the first transplant and total body irradiation or BCNU in combination with etoposide and cyclophosphamide for the second transplant. Five-year estimates of OS and PFS were 54% and 49%, respectively. The Southwest Oncology Group recently presented results of a follow-up phase II study of tandem ASCT in patients with HL using the same approach (NCT00233987) [79]. Of 92 eligible patients, 89 were treated and 82 completed both cycles of ASCT, without any TRM. With a median follow-up of 5.4 years (range, 2 to 7.6 years), the 2-year PFS rate was 63% (95% CI, 52% to 72%) and 2-year OS rate was 91% (95% CI, 83% to 95%). The high OS is likely due to salvage options for patients who progress after ASCT, including brentuximab vedotin and allo-HCT. This study also was only presented in abstract form at the time of publication. Given the current data, the panel does not recommend routine use of tandem ASCT for patients with HL, although further studies may be warranted in high-risk patients.

Role of IFRT

Patients with HL undergoing ASCT remain at risk for relapse, particularly in areas of bulky disease. As a result, investigators have studied the potential role of IFRT to decrease the risk of relapse [39,51,65,72-74]. In a study by Kahn et al. [74], 46 HL patients treated with IFRT within 2 months of ASCT were matched to 46 HL patients who did not receive IFRT. The use of IFRT significantly improved disease-free survival ($P = .032$), but not OS, when stratified by disease bulk. Most centers have adopted the use of peritransplant IFRT in patients with bulky disease who have not previously been irradiated. There are no specific data regarding the timing of IFRT, either before or after ASCT. In general, most centers perform IFRT after ASCT. The potential benefits of IFRT need to be weighed against the risk of pulmonary toxicity [129].

Post-ASCT maintenance

The use of brentuximab vedotin for post-transplant maintenance was investigated in a randomized phase III study that included 327 patients [80]. Patients were enrolled on the study if they met criteria for high-risk disease, defined as having one of the following: refractory to frontline therapy, relapse $<$ 12 months after frontline therapy, or relapse $\geq$ 12 months after frontline therapy with extranodal disease. Patients were required to have obtained a CR, partial remission (PR), or stable disease to salvage therapy before ASCT. Thirty to 45 days after transplant, patients were randomized to receive either brentuximab vedotin or placebo for up to 1 year. With a median follow-up of 2 years, PFS was 65% in the treatment arm versus 45% in the placebo group (hazard ratio, .50; 95% CI, .36 to .70]. Two-year OS was the same in both arms at 88%, but crossover was allowed in the placebo arm. Based on the phase III data, we recommend the use of post-ASCT maintenance with brentuximab vedotin in high-risk patients. The histone deacetylase inhibitor panobinostat was also under evaluation for post-ASCT maintenance therapy in a phase III trial (NCT01034163), based on encouraging phase II data [130], but the study closed due to slow accrual.

Pediatric ASCT studies

Although there are fewer studies in pediatric patients (reviewed in [118]), the panel recommends that pediatric patients also be considered for ASCT based on the data available and by extrapolation of the adult data [35-39]. These results should be balanced with other studies suggesting similar outcomes with salvage chemotherapy compared with ASCT in pediatric patients, particularly those with late relapse ($>$12 months) [30,34]. The CIBMTR Lymphoma Working Committee has approved a study looking at outcomes of ASCT in children and young adults with HL.

ASCT in older patients and patients with comorbidities

Finally, there are a paucity of data on older patients and patients with comorbidities, and the panel recommends this as an area that warrants ongoing research [120,131]. For recommendations on chemotherapy dosing in obese patients or patients with renal insufficiency, readers are referred to recent reviews or ASBMT guidelines on these topics [132,133].

Prognostic Factors for ASCT

Prognostic factors may provide a useful tool to better stratify patients and use risk-adapted therapy to improve outcomes (Table 5). Studies have examined prognostic factors both at time of relapse and before ASCT. It is important to note that none of the presumed prognostic factors has been studied in a prospective manner. In the studies reported, we have included risk factors that were associated with inferior outcome in at least 2 studies. The following adverse factors were identified as useful at time of relapse: anemia (hemoglobin $<$ 10 g/dL), stage (III/IV), remission duration $<$ 12 months, B symptoms, extranodal sites of disease, and bulky disease at diagnosis [20-22,24,25,31,40,41,59,61,62,64,81,134-142]. Short remission duration is the factor most consistent across different series. The CIBMTR proposed a prognostic model for PFS after ASCT in patients with HL [88]. Four adverse factors at the time of ASCT were identified in a multivariate analysis: Karnofsky performance scale score $<$ 90, chemoresistant disease at ASCT, $\geq$3 chemotherapy regimens, and extranodal sites of disease at ASCT. The first 2 factors were assigned 1 point and the latter 2 factors assigned 2 points. The 4-year PFS in low (score = 0, n = 176), intermediate (score = 1 to 3, n = 261), and high (score = 4 to 6, n = 283) groups was 71% (95% CI, 63% to 78%), 60% (95% CI, 53% to 66%), and 41% (95% CI, 36% to 49%), respectively.

Role of chemosensitive disease

A number of retrospective series have demonstrated that chemosensitive disease at the time of ASCT, defined as having achieved at least PR, is a significant prognostic factor for

Table 5
Prognostic Factors for ASCT

	Recommendation	Grade of Recommendation	Highest Level of Evidence	References
Which factors at relapse predict poor outcomes?	Anemia (hemoglobin < 10 g/dL) Stage (III/IV) Early relapse (<12 mo) Systemic symptoms (B Sx) Extranodal sites Bulky disease at diagnosis	B	2++	[20-22,24,25,31,40,41,59,61,62,64,81,88,134-142]
Which pre-ASCT factors predict better outcomes?	Chemosensitivity CR or PR before transplant Number of salvage regimens ≤2	C	2+	[20,22,24,29,32,57,64,66,138,141,143-149]
What is the role of FDG-PET imaging?	Negative PET before transplant is associated with improved outcome	B	2++	[51,69,81-87]

both improved OS and PFS/disease-free survival [20,22,24,29,32,57,64,66,137,138,141,143-149]. For example, in a study of 141 patients, the presence of chemoresistant disease was independently associated with poor PFS (relative risk, 2.9; 95% CI, 1.7 to 5.0) [141]. With a few exceptions [20,22,23], similar findings have been observed in other series, including registry data [57,145].

Role of Functional Imaging

The use of pre-ASCT functional imaging has become routine in patients with HL. Although historical data also include gallium scans, FDG-PET is now considered the standard [51,69,81-87]. As noted above, in the study by Moskowitz et al. [51] that used sequential non–cross-resistant regimens, a negative PET after salvage chemotherapy was associated with an EFS rate > 80% compared with 26% in patients with a positive PET pre-ASCT, highlighting the significance of a pre-ASCT negative PET scan. We recommend the use of the Deauville scoring system when reporting PET/computed tomography results [150]. The system uses a 5-point scale, with scans scored according to uptake in sites initially involved by lymphoma as (1) no uptake, (2) uptake equal to the mediastinum blood pool, (3) uptake equal to the liver, (4) moderately increased uptake greater than the liver, or (5) markedly increased uptake greater than the liver and/or new lesions. A score of 1 to 3 is regarded as negative and 4 or 5 as positive.

Indications for Allo-HCT

Table 6 displays the indications for allo-HCT.

Role of Allo-HCT

Although relatively limited data assess the best approach for patients who relapse after an ASCT, the available data support the benefit of allo-HCT versus standard therapy [89,91,92,94,151]. In a multivariate analysis of 185 patients who relapsed after ASCT performed by the Gruppo Italiano Trapianto di Midollo Osseo, the 2 factors associated with significantly improved OS and PFS were having a donor and relapse beyond 12 months after ASCT [92]. Patients from this analysis were combined with European Society for Blood and Marrow Transplantation (EBMT) data to analyze prognostic factors in 511 patients who relapsed after ASCT [151]. Twenty-nine percent of patients underwent allo-HCT. In this larger dataset, the factors that predicted OS were early relapse (<6 months), stage IV, bulky disease, poor performance status, and age ≥ 50 years at relapse. The 5-year OS rate was 62% in patients with no risk factors compared with 37% and 12% for those having 1 and ≥2 factors, respectively. Some patients with limited disease not previously irradiated may benefit from IFRT [90,93,94]. Although there are currently limited data on the long-term benefit of brentuximab vedotin salvage in the absence of allo-HCT [153], its use before allo-HCT appears to be associated with improved PFS compared with historical data [154].

Regimen intensity for allo-HCT

Early studies of allo-HCT in patients with HL reported in the 1990s to 2000s demonstrated low OS due to high TRM, likely resulting from the use of myeloablative conditioning (MAC) in heavily pretreated patients (Supplemental Table 5) [99,144,155]. In a retrospective comparison of MAC and reduced-intensity conditioning (RIC) performed by the EBMT, recipients of RIC had significantly decreased nonrelapse mortality (hazard ratio, 2.85; 95% CI, 1.62 to 5.02; $P < .001$) and improved OS (hazard ratio, 2.05; 95% CI, 1.27 to 3.29; $P = .04$) compared with those who received MAC. The improved OS in RIC was seen despite an increased risk of relapse or progression. Furthermore, this study supported the role of a graft-versus-lymphoma effect, with a significantly decreased incidence of relapse and a trend for a better PFS associated with the development of chronic graft-

Table 6
Allo-HCT in Patients with HL

	Recommendation	Grade of Recommendation	Highest Level of Evidence	References
Should allo-HCT be used instead of conventional therapy for patients who relapse after ASCT?	Yes	B	2++	[89-94,151]
What is the recommended regimen intensity?	RIC	B	2++	[91,95-110,112]
Is there a preferred donor source?	No	A	1+	[96,100-102,104,105,111-113]
When should DLI be given?	Progressive disease/relapsed	B	2++	[89,91,95-98,102,104,105,109,114,152]
	Incomplete donor chimerism	D	3	[104,115]
What is the role of comorbidities in outcomes?	Paucity of data	—	—	[104,105]

versus-host disease. Registry data from the CIBMTR reported PFS and OS rates of 30% and 56% at 1 year and 20% and 37% at 2 years, respectively, in HL patients after RIC HCT from unrelated donors [103]. These results are consistent with those of other prospective and retrospective studies in which patients with HL were transplanted with RIC or nonablative cytoreduction, with slightly better outcomes reported in single-institution or multicenter studies [89,95-97,100-102,104,107-110,114]. As a result, the preferred conditioning intensity in adult patients with relapsed/refractory HL is RIC, which results in acceptable TRM including in patients who have had a prior ASCT. One of the commonly used regimens in patients with HL is fludarabine and melphalan [96,97,102,107]. This regimen is also combined with alemtuzumab in some centers [95,115].

Pediatric studies of allo-HCT

In an EBMT study of pediatric patients, the TRM was similar for RIC and MAC regimens [105]. However, RIC was associated with higher risk of relapse compared with MAC, most apparent beginning 9 months post-HCT ($P = .01$). Although PFS was lower in patients after RIC from 9 months onward ($P = .02$), no difference was observed in OS. Despite a potential higher risk of relapse, RIC has also become the most commonly used regimen in pediatric patients.

Selection of donor source

Regarding preferred donor source, with the exception of a study that showed worse outcomes in cord blood recipients [112], no differences have been observed in analyses incorporating donor source [102,104]. It should be noted that only 9% of patients received cord blood in that study, and a recent systematic review concluded that all donor sources, including related, unrelated, and haploidentical donors and cord blood, were a reasonable consideration for allo-HCT in patients with HL [113]. Therefore, standard recommendations for donor selection for allo-HCT should be followed.

Role of donor lymphocyte infusions

A main benefit of an allo-HCT is the graft-versus-lymphoma effect [99]. The graft-versus-lymphoma effect after donor lymphocyte infusion (DLI) has been documented in a number of studies [89,91,95-98,102,104,105,109,115,152]. Peggs et al. [95] reported an ORR to DLI of 56% (CR = 8, PR = 1) for persistent disease or progression in 16 patients after allo-HCT. These findings were confirmed in the UK Cooperative Group study that reported an ORR of 79% (CR = 14, PR = 5) for DLI in 24 patients who relapsed [115]. Both studies incorporated alemtuzumab in the conditioning regimen with resultant in vivo T cell depletion and increased host chimerism, for which patients also received DLIs. The data on DLI for incomplete donor chimerism is primarily derived from these studies that include alemtuzumab, and its extension to other conditioning regimens remains to be determined. Similar to other indications in allo-HCT, the best responses to DLI were often associated with additional cytotoxic therapy before DLI [102,104,109,152].

Salvage before allo-HCT

As noted above, brentuximab vedotin is indicated in patients who relapse after an ASCT or who fail to achieve a remission after second-line therapy [122]. Also as noted above, the use of brentuximab vedotin before allo-HCT appears to be associated with improved PFS compared with historical data [154]. Beyond brentuximab vedotin, there is no standard salvage regimen recommended before allo-HCT for HL, and treatment selection depends on the patient's prior therapy and comorbidities. For further details on this topic, readers are referred to a recent review of salvage regimens in patients with HL relapsing after ASCT [156]. This is a patient population for whom it is also reasonable to consider investigational therapies.

Patients with comorbidities

Similar to ASCT, there are little data on comorbidities in outcomes after allo-HCT in both pediatric and adult populations. In the pediatric study by Claviez et al. [105], poor performance status at HCT was associated with significantly increased risk of disease recurrence in univariate and multivariate analyses. Poor performance status was also identified as a risk factor for nonrelapse mortality in the EBMT study [104].

Are There Indications for Allo-HCT Selection over ASCT?

ASCT versus allo-HCT as first-line transplant

The studies that compare ASCT with allo-HCT as first-line transplant are older series that include MAC and do not reflect current practice, which favors ASCT because the additional risks of graft-versus-host disease in the allogeneic setting are not generally considered to be warranted [144,155,157] (Table 7). Up-front RIC allo-HCT has been reported in subsets of patients as part of larger studies and typically has been reserved for patients with poor prognostic features [102,109]. Currently, insufficient data support the role of allo-HCT as first-line transplant in patients with HL, with the exception of patients who have another indication for allo-HCT, such as concomitant diagnosis of myelodysplastic syndrome, for example. This is an area that requires further investigation in patients with poor prognostic factors indicating that ASCT is unlikely to be of benefit.

Second ASCT versus allo-HCT

Similarly, limited data compare the benefit of a second ASCT versus an allo-HCT in patients who relapse after ASCT [116,158]. For patients who relapse within the first year after ASCT, outcomes with a second ASCT have been very poor [92,116]. Based on the available data, the current practice is to offer most patients an allo-HCT over a second ASCT. Because

Table 7
Autologous Stem Cell Transplant versus Allo-HCT

	Recommendation	Grade of Recommendation	Highest Level of Evidence	References
Should allo-HCT be performed instead of ASCT as first SCT?	No	C	2+	[144,155,157]
Should allo-HCT be performed instead of ASCT as second SCT in most patients?	Yes	C	2+	[90,116]
Should second ASCT be considered for patients who relapse after ASCT?	Not within 1 year	C	2+	[92,116,158]
Is there a role for tandem ASCT-allo-HCT?	No	D	4	[91]

Table 8
Prognostic Factors for Allo-HCT

	Recommendation	Grade of Recommendation	Highest Level of Evidence	References
Are there useful prognostic factors before allo-HCT?	Yes	B	2++	[92,103,105,112,159,160]
Is there a role for PET imaging?	To be determined	C	2+	[161]

donor options have expanded with the use of alternate donors, this option should be available to most patients who otherwise meet criteria for allo-HCT.

Tandem autologous-allogeneic HCT

Tandem autologous-allogeneic HCT has been proposed for patients with poor-risk HL at high risk for relapse after ASCT [91]. Similar to other diseases, currently very limited data support this approach.

Prognostic Factors for Allo-HCT

Although there are less data regarding prognostic factors before allo-HCT, the data are consistent with factors that are predictive of outcomes for ASCT (Table 8). The data are derived either from studies that have evaluated relapse after ASCT or studies of allo-HCT [92,103,105,112,159]. In the Gruppo Italiano Trapianto di Midollo Osseo study described above, status at HCT (PR versus CR and PD/stable disease versus CR) was associated with significantly worse OS and PFS [92]. This finding was confirmed in the EBMT study and a recent Societe Francaise de Greffe de Moelle study [104,112]. PFS and OS were both associated with performance status and disease status at transplant in the EBMT study [104]. Patients with neither risk factor had a 3-year PFS and OS rates of 42% and 56%, respectively, compared with 8% and 25% for patients with one or more risk factors. In contrast, in the CIBMTR study, the presence of extranodal disease and a Karnofsky performance scale score < 90 were significant risk factors for TRM, PFS, and OS, whereas chemosensitivity at transplantation was not [103]. In another study that included 40 patients with HL who had active or progressive disease at the time of HCT, the 3-year OS and PFS rates after allo-HCT were 49% $\pm$ 8% and 17% $\pm$ 6%, respectively [160].

In a study of FDG-PET performed before allo-HCT in patients with HL (n = 46) and non-HL (n = 34), patients with positive FDG-PET scans had a 3-year risk of relapse of 59% (95% CI, 41% to 86%) compared with 27% (95% CI, 13% to 55%; $P < .066$) in those with a negative scan [161]. Of note, the crude cumulative incidence of disease recurrence in patients with HL was 59% (95% CI, 41% to 86%) in those with a positive FDG-PET scan and 27% (95% CI, 13% to 55%; $P = .066$) in those with a negative scan. A recent study also identified serum thymus and activation-regulated chemokine, which is produced by Reed-Sternberg cells, as a potential biomarker for poor prognosis [162]. In patients who relapsed after allo-SCT, thymus and activation-regulated chemokine level increased progressively and preceded evidence of PET-positive disease. Further research is warranted on the prognostic significance of PET imaging before allo-HCT in HL.

Survivorship in HL Patients after ASCT and Allo-HCT

The main complications observed after ASCT in patients with HL are similar to those seen in other hematologic malignancies (Table 9) and include secondary malignancy, organ impairment, and reduced quality of life [25,29,82,145,146,163-170]. Similarly, the complications seen in recipients of allografts are consistent with complications of allo-HCT in general. In the report from the Bone Marrow Transplantation Survivor Study, the morbidity burden was assessed in 324 (HL = 26) 10+ year survivors of autologous and allogeneic HCT [170]. The 15-year cumulative incidence of severe, life-threatening, or fatal conditions was 41%, and HCT survivors were 5.7 times as likely to develop severe or life-threatening conditions and 2.7 times as likely to report somatic distress compared with siblings. ASCT recipients had a similar incidence of chronic health conditions compared with allo-HCT recipients. These are significant limitations considering the young median age of patients undergoing HCT for HL. Readers are referred to published recommended guidelines for the follow-up of patients after autologous and allogeneic HCT [171,172].

AREAS OF NEEDED RESEARCH AND ONGOING RESEARCH

Although there are established data supporting the role of HCT in patients with advanced HL, several areas would benefit from further study. In particular, there is a paucity of data regarding the outcomes after both autologous and allogeneic HCT in older patients or patients with comorbidities. In addition, prospective studies investigating the role of prognostic factors would also be helpful in improving patient selection for HCT as well as the use of risk-adapted therapy to reduce the risk of relapse while minimizing toxicity. These studies may also identify patients who would benefit from allo-HCT over ASCT. Patients who undergo either autologous or allogeneic HCT still carry a significant risk of relapse, and further work is required to develop strategies to reduce this risk.

Table 9
Survivorship after ASCT or allo-HCT

	Complication	Grade of Recommendation	Highest Level of Evidence	References
What is the long-term toxicity of ASCT?	Second malignancy	B	2++	[25,29,82,145,163-166]
	Organ impairment	B	2++	[25,146,167,168]
	Reduced quality of life	B	2++	[25,146,165-167,169,170]
What is the long-term toxicity of allo-HCT?	Chronic graft-versus-host disease, organ impairment, reduced quality of life	B	2++	[170]
Are there guidelines for follow-up?	Yes	N/A	N/A	[171,172]

An important consideration for these recommendations is that most data on which these recommendations are based precedes the approval of newer agents that are being routinely incorporated into treatment algorithms for patients with HL. In particular, recent or ongoing studies have examined the role of brentuximab vedotin in several settings, including up-front treatment (NCT01712490), salvage treatment (NCT01508312, NCT01393717, NCT01874054) [123-125], and post-transplant maintenance [80]. Results of these studies should further inform the role of this active agent in the management of patients with HL. In addition to brentuximab vedotin, other drugs shown to have activity after ASCT relapse or being investigated in that setting include bendamustine [173,174], the mTOR inhibitor everolimus [175], and, more recently, immune checkpoint blockade drugs such as the anti-PD-1 antibody nivolumab [176].

CONCLUSIONS

Both ASCT and allo-HCT offer a survival benefit in selected patients with advanced or relapsed HL and are currently part of standard clinical care. Patients who relapse after frontline therapy are offered salvage second-line chemotherapy regimens followed by high-dose therapy and ASCT. In randomized studies, ASCT offered as salvage therapy improved EFS and PFS compared with nontransplant approaches, although these studies were not powered to show a benefit in OS. In patients who relapse after ASCT, allo-HCT is considered the standard approach for patients with a donor. The main adverse prognostic factors identified in both transplant settings include short remission duration, either to frontline therapy or ASCT. The main favorable prognostic factors are presence of chemosensitive disease and negative pre-HCT FDG-PET imaging results. Relapse remains a significant cause of failure after both transplant approaches, and strategies to decrease the risk of relapse through the use of post-transplant maintenance and/or DLI in the case of allo-HCT warrant further investigation.

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SUPPLEMENTARY DATA

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