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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.