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Guideline

Clinical Practice Recommendations for Use of Allogeneic Hematopoietic Cell Transplantation in Chronic Lymphocytic Leukemia on Behalf of the Guidelines Committee of the American Society for Blood and Marrow Transplantation

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A B S T R A C T

We sought to establish clinical practice recommendations to redefine the role of allogeneic hematopoietic cell transplantation (allo-HCT) for patients with chronic lymphocytic leukemia (CLL) in an era of highly active targeted therapies. We performed a systematic review to identify prospective randomized controlled trials comparing allo-HCT against novel therapies for treatment of CLL at various disease stages. In the absence of such data, we invited physicians with expertise in allo-HCT and/or CLL to participate in developing these recommendations. We followed the Grading of Recommendations Assessment, Development and Evaluation methodology. For standard-risk CLL we recommend allo-HCT in the absence of response or if there is evidence of disease progression after B cell receptor (BCR) inhibitors. For high-risk CLL an allo-HCT is recommended after failing 2 lines of therapy and showing an objective response to BCR inhibitors or to a clinical trial. It is also recommended for patients who fail to show an objective response or progress after BCR inhibitors and receive BCL-2 inhibitors, regardless of whether an objective response is achieved. For Richter transformation, we recommend allo-HCT upon demonstration of an objective response to anthracycline-based chemotherapy. A reduced-intensity conditioning regimen is recommended whenever indicated. These recommendations highlight the rapidly changing treatment landscape of CLL. Newer therapies have disrupted prior paradigms, and allo-HCT is now relegated to later stages of relapsed or refractory CLL.

INTRODUCTION

Chronic lymphocytic leukemia (CLL) represents the most common leukemia in the Western hemisphere. In 2016, it is anticipated that 18,960 cases of CLL will be diagnosed in the United States [1]. A better understanding of the biologic, molecular, and genetic aspects of CLL have resulted in better prognostic risk stratification of this disease [2-7] and have brought novel and highly active therapies targeting various kinases downstream of the B cell receptor (BCR) pathway along with a new generation of monoclonal antibodies, among others [8-13]. Although emergence of these therapies has certainly altered the therapeutic landscape of CLL, mostly because of improved efficacy and better tolerability, the disease remains incurable unless patients are offered allogeneic hematopoietic cell transplantation (allo-HCT), especially those with high-risk disease [14-17].

In 2007 Dreger et al. [18] published on behalf of the European Society for Blood and Marrow Transplantation (EBMT) a consensus paper with indications for allo-HCT in patients with CLL. Allo-HCT candidates were considered those with previously treated poor-risk CLL defined by the following: not achieving response, relapsing after 3 scenarios (ie, within 12 months after purine analogue–containing therapy, or within 24 months after purine analogue combination therapy, or autologous HCT), or presence of *TP53* mutation or 17p deletion (del17p13) [18]. Emergence of ibrutinib, a BCR inhibitor, and other targeted therapies that have proved to be effective treatment options for CLL even in high-risk disease has undoubtedly challenged the appropriateness of the 2007 EBMT consensus recommendations [19,20]. Several randomized controlled trials (RCT) and a meta-analysis have shown that high-dose chemotherapy and autologous HCT do not offer an overall survival (OS) advantage compared with conventional chemotherapy or chemoimmunotherapy; accordingly, relapsed CLL after an autologous HCT is not considered, today, as a prerequisite for an allo-HCT [21-25]. Moreover, autologous HCT has been abandoned from current treatment algorithms for CLL [21-25]. Recognizing the pressing need to incorporate the new realities of treating CLL in this modern treatment era [19], the American Society for Blood and Marrow Transplantation convened a group of experts to develop clinical practice recommendations related to the role of allo-HCT for CLL.

METHODS

Twenty-six physicians recognized for their expertise in allo-HCT and/or treatment of CLL were invited to contribute to the development of these recommendations. The composition of the panel was both national and international and purposely designed to include both transplant and nontransplant physicians to embrace diversity of opinion with the goal of enhancing applicability of the final recommendations.

Search and Study Selection

We searched the literature using Medline via PubMed from inception until May 28, 2015 using a MeSH and broadly general text terms ("Leukemia, Lymphocytic, Chronic, B-Cell"[Mesh]) AND "Transplantation, Homologous"[Mesh]). In addition, references of relevant nonsystematic review articles were scanned to identify additional relevant studies. No search limits were applied, but we excluded studies that were only presented in abstract form but had not yet been published as a peer-reviewed article.

Panel of Experts

A transplant physician was an individual who spent > 75% of his or her time in the care and management of patients undergoing HCT, whereas a nontransplant physician spent > 75% of his or her time in the care and management of patients outside the transplant setting. A mixed practice was defined as spending approximately 50% of the physician's time in each of the aforementioned modalities of therapy (ie, HCT and nontransplant-related CLL clinical care). We also included a methodologist (A.K.) with expertise in systematic reviews/meta-analysis and Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology who did not vote in the question prioritization or recommendations process.

Survey Methodology and Survey Questions

GRADE methodology was used to assist in moving from evidence to decision-making and generating recommendations. To generate evidence before making recommendations, we performed the aforementioned systematic review (not meta-analysis) because data were very scarce. Our approach intentionally included a diverse group of panel participants (transplant and nontransplant physicians) because of the rapidly changing therapeutic landscape where new and more effective drugs to treat CLL, even for those with high-risk disease, are becoming available. Toward this goal, we aimed at developing recommendations by a majority vote (defined as >50% of voting participants).

Panelists were surveyed using www.Qualtrics.com (Qualtrics LLC, Provo, UT). Questions included panelists' demographics (age, gender, years of experience, practice focus), volume of CLL patients seen in a routine week, information relevant to their respective transplant program (number of allo-HCT performed per year, preferred preparative regimen(s), cell source and donor source, criteria for selection of patients and donors), and questions pertaining to risk definition, timeliness, and appropriateness of allo-HCT for CLL.

After the identification of key clinical questions, a second survey was conducted wherein panelists were asked to vote on the direction of recommendations (in favor of versus against) for each key question along with strength (strong versus weak) of rendered recommendations. As previously noted, recommendations were issued based on the majority vote. Questions that were specifically related to the procedural aspects of allo-HCT (eg, donor selection, preferred cell source, and choice of the intensity of the preparative regimen, among others) were addressed to all panel members, but for the purpose of issuance of final recommendations, responses from the panelists who identified themselves as predominantly transplant physicians and those in the mix practice category were taken into