The Role of Cytotoxic Therapy with Hematopoietic Stem Cell Transplantation in the Treatment of Diffuse Large B Cell Lymphoma: Update of the 2001 Evidence-Based Review

Among the primary objectives of the American Society for Blood and Marrow Transplantation (ASBMT) are to:

- Define commonly accepted medical and evidence-based practice
- Develop standards of medical care for autologous and allogeneic transplants
- Provide recommendations for physicians, patients, and third-party payers on the role of transplantation as a therapeutic approach.

Toward this end, in 1999, the Society began sponsoring evidence-based reviews (EBRs) of the scientific and medical literature to document when blood and marrow transplantation is indicated in the treatment of selected diseases.

In 2009, the ASBMT EBR Steering Committee determined that previously published reviews should be updated regularly, at approximately 5-year intervals. The diffuse large B cell lymphoma (DLBCL) EBR is the first in the series to be updated.

GOALS

The goals of the EBRs are to:

- Determine which disease will be the subject of each review, establish the focus for each review, and develop a list of questions to be addressed
- Assemble and critically evaluate all valid, peer-reviewed evidence regarding the role of cytotoxic therapy with hematopoietic stem cell transplantation (SCT) related to the disease
- Provide treatment recommendations based on the available evidence
- Identify discrepancies in study design or methodology among published studies that may impact the quality of the evidence
- Identify areas of needed research.

The goals of the DLBCL EBR update are to:

- Provide a summary of recent clinical evidence
- Provide timely treatment recommendations
- Determine if new evidence strengthens or changes treatment recommendations provided in the original DLBCL EBR published in 2001.

UPDATED TREATMENT RECOMMENDATIONS FOR DLBCL

The following updated treatment recommendations are offered for the role of SCT as treatment for DLBCL, and are based on consensus reached by an expert panel following a systematic review of the literature published since the 2001 original EBR.

Autologous SCT versus Nontransplantation Therapy

1. Autologous SCT provides a significant survival benefit and is recommended as part of salvage therapy for patients with chemosensitive relapsed DLBCL. This original recommendation is unchanged, with no new data published since the original EBR.

2. Autologous SCT is not recommended for patients who achieve only a partial response to an abbreviated (3 cycles) induction regimen. This original recommendation is unchanged, with no new data published since the original EBR.

3. Based on new data published since the original EBR, autologous SCT as first-line therapy is not recommended for any International Prognostic Index group at this time; however, none of the published studies included rituximab in their treatment protocols. Ongoing studies that include rituximab may change this recommendation.

Autologous SCT: Timing and Protocol

1. Based on new data published since the original EBR, older age (>60 years), in and of itself, is not a contraindication for autologous SCT as long as
other SCT eligibility criteria are met. No upper age limit has been defined. However, SCT outcomes (transplant-related mortality, relapse, survival) in older adults are not as good as in younger adults.

2. Based on new data published since the original EBR, autologous SCT using peripheral blood, compared to bone marrow, provides no survival benefit or improved tumor control. However, autologous SCT using peripheral blood is safer and easier to use with faster engraftment and lower rate of death because of infection; hence, peripheral blood is the standard autologous stem cell source.

3. Based on new data published since the original EBR, planned tandem, or multiple sequential autologous SCTs are not recommended.

4. The new data published since the original EBR are insufficient to recommend routine post-autologous SCT maintenance with rituximab outside of a clinical trial.

5. The new data published since the original EBR are insufficient to make a treatment recommendation regarding fewer versus more cycles of induction therapy prior to first-line autologous SCT.

**Autologous versus Allogeneic SCT**

Based on new data published since the original EBR, there are equivalent survival outcomes after autologous and allogeneic SCT. Neither donor option is recommended over the other because they have competing risks with regard to relapse and transplant-related mortality. Comparison of these two techniques is biased by different patient selection criteria.

**Allogeneic SCT: Conditioning**

The new data published since the original EBR are insufficient to recommend reduced intensity versus myeloablative conditioning for allogeneic SCT. Based on one study and expert opinion, reduced intensity conditioning (RIC) appears to be an acceptable alternative approach for selected patients who cannot tolerate a myeloablative allogeneic SCT. Longer follow-up is needed to clarify the competing risks of relapse and chronic graft-versus-host disease (cGVHD) and their impact on overall survival (OS) and quality of life. Comparison of these regimen intensities is biased by patient selection criteria which have changed over time.

**AREAS OF NEEDED RESEARCH**

After reviewing the updated evidence, the expert panel identified the following important areas of needed research in DLBCL:

1. Identify more effective induction regimens to optimize disease response and reduce the need for autologous SCT.

2. Identify and examine the efficacy of predictive tests (ie, positron emission tomography scans) to classify patients who are at high risk for early treatment failure (those who are primary refractory to initial therapies and those who respond but quickly relapse) and candidates for autologous SCT.

3. Update the International Prognostic Index to include molecular markers and/or gene expression profiling to better discriminate prognostic groups that would benefit from SCT.

4. Determine the potential benefit of first-line autologous SCT for patients with central nervous system involvement.

5. Identify effective salvage regimens to optimize disease response prior to autologous SCT.

6. Identify effective high-dose therapy regimens to optimize complete response, improve hematopoietic recovery, and reduce transplant-related mortality and incidence of secondary malignancies.

7. Identify effective maintenance regimens to optimize disease control post-autologous SCT.

8. Examine the efficacy of reduced intensity allogeneic SCT as rescue after a failed autologous SCT.

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