

## The Role of Cytotoxic Therapy with Hematopoietic Stem Cell Transplantation in the Treatment of Follicular Lymphoma

Among the primary objectives of the American Society for Blood and Marrow Transplantation 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 of the scientific and medical literature to document when blood and marrow transplantation is indicated in the treatment of selected diseases.

### GOALS

The goals of the evidence-based reviews 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.

### TREATMENT RECOMMENDATIONS

The following treatment recommendations are offered for the role of SCT as treatment for follicular lymphoma (FL), and are based on consensus reached by an expert panel<sup>1</sup> following a systematic review of the literature.<sup>2</sup>

### Autologous SCT versus Nontransplantation Therapy

1. Based on prerituximab data, there is a statistically significant improvement in overall survival (OS) and progression-free survival (PFS) using autologous SCT as salvage therapy.
2. With only one retrospective study, there are insufficient data to make a recommendation on the use of autologous SCT versus nontransplantation therapy as salvage treatment for patients who have had rituximab as part of their salvage therapy.
3. Autologous SCT is recommended for transformed FL based on expert opinion and accepted clinical practice.
4. Although there is consistent improvement in PFS and event-free survival (EFS) with autologous SCT, it is not recommended as first-line treatment for most patients because of no significant improvement in OS, a higher incidence of secondary myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML), and a lack of comparative data with rituximab-containing regimens. Longer follow-up may be needed to identify differences in OS.

### Autologous SCT: Timing and Protocol

1. There are insufficient data to make a recommendation on the efficacy of autologous SCT as first-line versus salvage therapy.
2. Because of conflicting data, a recommendation cannot be made on the use of rituximab as part of first-line or salvage regimens prior to autologous SCT.
3. There are insufficient data to make a recommendation regarding purging of autologous SCT.
4. There are insufficient data to recommend one high-dose regimen over another. Total-body irradiation (TBI)-containing regimens are usually avoided because of a concern for the risk of secondary MDS or AML.

### Autologous versus Allogeneic SCT

1. There are insufficient data comparing autologous SCT and myeloablative allogeneic SCT to

recommend one option over the other; both appear to have a survival benefit, but have competing risks. Comparison of these two techniques is biased by different patient selection criteria.

2. There are currently no data available to make a recommendation regarding the use of reduced intensity/nonmyeloablative allogeneic SCT versus autologous SCT. Comparison of these two techniques is biased by different patient selection criteria.

### **Allogeneic SCT: Conditioning and Donor Source**

1. Reduced intensity conditioning (RIC) appears to be an acceptable alternative approach in allogeneic SCT based on one study and expert opinion.
2. There are insufficient data to recommend one conditioning regimen over another for allogeneic SCT.
3. In allogeneic SCT, an HLA-matched unrelated donor appears to be as effective as an HLA-matched related donor using RIC based on expert opinion.

### **AREAS OF NEEDED RESEARCH**

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

1. Rituximab-based therapy followed by autologous SCT versus rituximab-based therapy without SCT.
2. Post-autologous SCT rituximab maintenance therapy versus no post-autologous SCT maintenance rituximab.
3. *Ex vivo*-purged autologous SCT.
4. T cell-depleted allogeneic SCT.

5. Comparison of matched-related versus matched-unrelated or other alternative donor for allogeneic SCT.
6. The efficacy and toxicity of reduced-intensity regimens before autologous and allogeneic SCT.
7. Reduced intensity allogeneic SCT as salvage therapy after failed autologous SCT.
8. Radioimmunotherapy as part of the preparatory regimen for autologous SCT or reduced intensity allogeneic SCT.
9. The impact of radioimmunotherapy and newer agents (ie, bendamustine, rituximab, alemtuzumab, fludarabine, etc.) on stem cell quality.
10. Identification of surrogate molecular markers pre-SCT that are predictive of long-term survival in FL patients.
11. The association of FLIPI score at diagnosis and at SCT with prognosis in FL patients.

<sup>1</sup>Expert panel members and authors of the review are: Denise M. Oliansky, Roswell Park Cancer Institute (RPCI), Buffalo, NY; Leo I. Gordon, Northwestern University Feinberg School of Medicine and the Robert H. Lurie Comprehensive Cancer Center, Chicago, IL; Jerry King, Blue Cross and Blue Shield of Illinois, Chicago, IL; Ginna Laport, Stanford University Medical Center, Stanford, CA; John P. Leonard, Cornell University, Weill Medical College, New York, NY; Peter McLaughlin, MD Anderson Cancer Center, Houston, TX; Robert J. Soiffer, Dana Farber Cancer Institute, Boston, MA; Koen W. van Besien, University of Chicago, Department of Medicine, Chicago, IL; Michael Werner, Lymphoma Research Foundation, Chicago, IL; Roy B. Jones, MD Anderson Cancer Center, Houston, TX; Philip L. McCarthy, Jr., RPCI, Theresa Hahn, RPCI.

<sup>2</sup>Reference: Oliansky D, Gordon L, King J, et al. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the therapy of follicular lymphoma: an evidence-based review. *Biol Blood Marrow Transplant*. 2010;16:443-468.

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