

Statement of the Steering Committee for Evidence-Based Reviews of the American Society for Blood and Marrow Transplantation (ASBMT)

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Evidence based medicine is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients. The practice of evidence based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research¹.

Evidence-based medicine is a style of practice and teaching which may also help plan future research².

There are few fields of medicine that have been subjected to as much scrutiny or have generated as much controversy as high-dose cytotoxic therapy with stem cell transplantation (SCT). Although transplantation has been widely accepted by the medical community, many ongoing clinical trials continue to investigate accepted indications and others that are not firmly established.

The American Society for Blood and Marrow Transplantation (ASBMT) initiated a project to conduct systematic, evidence-based reviews of the scientific literature for the use of blood and marrow transplantation for specific diseases. These reviews will use evidence-based medicine (EBM) guidelines to define therapy as effective or ineffective, indicate treatment that has been inadequately studied, and suggest areas requiring well-designed clinical trials. Problematic study design issues also will be identified in these reviews, and recommendations about the conduct of future trials will be made.

In today's health care environment, EBM is sometimes viewed as synonymous with "cost cutting" medicine and may be used to refuse reimbursement for expensive tests and treatments, thus limiting the clinical freedom of physicians and other providers. Often, however, reimbursement decisions are made not on the basis of evidence, but on a lack of convincing evidence. Of course, many existing "standards of care" were originally established on the basis of anecdotal or other untested evidence. They are nonetheless difficult to replace with new options that have not met the rigorous standards of modern, evidence-based medicine.

Unfortunately, patients continue to be denied SCT because of its relatively high cost even when it is widely accepted by clinicians as the most efficacious therapy. In some cases, blood and marrow transplantation continues to be viewed as investigational or experimental. Some managed care organizations are reluctant to reimburse medical procedures that they perceive to be novel, investigational, or more expensive than conventional therapies. These reviews will therefore also address the issue of inadequate reimbursement for transplantation in cases where efficacy is widely recognized, and document its role in treating a variety of diseases.

SCT as Therapy for Diffuse Large Cell B-Cell Non-Hodgkin's Lymphoma

The first in the series of reviews, published in this issue of the Journal, focuses on the use of high-dose cytotoxic therapy and SCT for the treatment of diffuse large cell B-cell non-Hodgkin's lymphoma (DLCL). The review was

conducted with the guidance of an independent expert panel that included clinicians with expertise in the entire spectrum of treatment options for non-Hodgkin's lymphoma, a representative of a patient advocacy group, and a physician representative of a third-party payer organization.

The panel reviewed nearly 350 published articles and recent abstract presentations on DLCL, applying criteria established for the project in the “ASBMT Policy Statement Regarding the Methodology of Evidence-Based Reviews in Evaluating the Role of Blood and Marrow Transplantation in the Treatment of Selected Diseases”³. The relative strength of treatment recommendations was graded based on accepted standards for evaluating the strength and quality of the available evidence, and made with the consensus of the panel members.

The systematic review of the medical literature that was conducted by the expert panel documents the evidence for SCT in the treatment of DLCL and the relative efficacy of various transplantation techniques. The review also identifies important questions that cannot be answered with confidence due to insufficient evidence and suggests areas where future research is needed. Many study design and reporting practices increase our awareness of inconsistencies in data presentation and other factors that may compromise the strength of the evidence, even in well-designed clinical trials.

Making Treatment Recommendations

In the DLCL review, the expert panel presents unanimous consensus in its treatment recommendations and grades the strength of the recommendations. Of the total of 18 recommendations, however, only 8 are definitive: 6 indications are graded as “effective treatment,” 2 as “not an effective treatment” and 10 as “inadequately evaluated treatment and recommended for comparative study.”

Limitations of Current Research and Future Research Needs

An important goal of the ASBMT evidence-based review process is to identify areas where additional research is most needed. Based on the evidence available to them, the DLCL expert panel identified 5 major disease-related questions and 5 treatment-related questions that remain to be answered. It is our hope that the review will help advance knowledge in the field of SCT by providing an objective assessment of areas where investigators might best focus their future research efforts.

An especially important lesson learned from the review process is that it is imperative to adhere to certain standards in conducting studies related to SCT. Among the criteria established at the outset of the review by the expert panel was that studies would be included only if the study population comprised a minimum of 70% DLCL patients, unless the results were stratified by histology subtype. Many studies, including well-designed randomized trials and registry reports addressing issues such as comparisons between autologous and allogeneic transplantation and between PBSCT and BMT, were excluded because of this and other methodologic issues. It also became apparent that there is a wide variance in the way DLCL is defined. Some clinicians, for example, include anaplastic large cell lymphoma in the definition of DLCL, whereas others do not.

Recommendations to Strengthen the Evidence

We strongly support the recommendation of the expert panel that all clinical studies specify the lymphoma classification schema and percentage of histologic subtype. Without this information, it is difficult to judge whether a study's results are applicable to a specific histology, or to compare the conclusions of various studies.

The availability of the International Prognostic Index⁴ was not among the inclusion criteria for the DLCL review because most of the phase III trials were accruing patients or had been analyzed before the IPI project was published. Nonetheless, significant differences in prognoses and outcomes based on IPI scores have been identified, and the applicability of study results may be problematic if the study does not state patients' IPI risk categories. It is recommended that patients be identified by IPI score in all future publications.

Any evidence-based review of the medical literature must be viewed as a work in progress, and revisited at regular intervals to assess new evidence. It is also important to remember that, while such reviews are valuable aids to physicians and other decision makers, they have limitations. High-quality evidence does not exist in many areas of

clinical practice and may never be available due to the practical limitations of conducting large-scale randomized trials, ethical issues, and other factors. Support of government and the insurance industry for well-designed prospective trials necessary to develop quality evidence is an essential component of this process. Despite their drawbacks, systematic reviews of available evidence play an increasingly important role in health care, improve confidence in treatment and reimbursement decisions, and help assure that good research findings are applied more quickly to clinical practice.

References

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