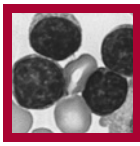
Blood and Marrow TRANSPLANTATION

REVIEWS

A Publication of the American Society for Blood and Marrow Transplantation

Issues in Hematology, Oncology, and Immunology VOLUME 16 NO 1 2006

IN THIS ISSUE



ASBMT™
American Society for Blood and Marrow Transplantation

What We Have Learned and What We Need to Know

John R. Wingard, MD, Editor

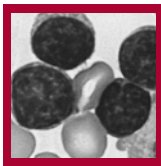
"Evidence-based medicine is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients. The practice of evidence-based medicine means integrating individual clinical experience with the best available external clinical evidence from systematic research" [1].

The American Society for Blood and Marrow Transplantation (ASBMT) has supported the conduct of a series of evidence-based reviews exploring the role of hematopoietic cell transplantation (HCT) in various hematologic disorders over the past several years. Earlier reviews can be viewed at the Society's Web site at www.asbmt.org. The enclosed abridged report summarizes the major findings of two recent reviews addressing the role of HCT in the management of acute lymphoblastic leukemia, one review in children, the other in adults.

A number of lessons have been learned during the course of this effort and the Society's Steering Committee describes some of these lessons in the companion editorial in this issue. Aside from offering both patients and clinical decision-makers important information about the application of this therapy to this disease, each review also identifies gaps in knowledge and research opportunities. Indeed, this latter lesson is perhaps as important as the former.

This has been and continues to be a valuable effort. These reviews represent the Society's commitment to the ultimate goal of every clinician: to make the best decision that will optimize each patient's prospect for disease control and quality of life.

1. Sackett DL, Rosenberg WM, Gray JA, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. *Br Med J.* 1996;312:71-72.



ASBMT™

American Society for Blood and Marrow Transplantation

Executive Office
American Society for Blood and Marrow Transplantation
85 West Algonquin Road, Suite 550
Arlington Heights, IL 60005-4425
(847) 427-0224; fax (847) 427-9656
e-mail: mail@asbmt.org

Publishing and Production Services
CJP Medical Communications, a division of Carden Jennings Publishing Co., Ltd.

Blood and Marrow Transplantation Reviews is published quarterly by CJP Medical Communications.
375 Greenbrier Dr., Suite 100, Charlottesville, VA 22901
phone (434) 817-2000; fax (434) 817-2020

PRELIMINARY APPLICATION

Be a part of a national organization established to promote education, research, and medical development in the field of blood and marrow transplantation.

Full Membership is open to individuals holding an MD or PhD degree with demonstrated expertise in blood and marrow transplantation as evidenced by either the publication of two papers on hematopoietic stem cell transplantation–related research as recorded by curriculum vitae, or documentation of two years of experience in clinical transplantation as recorded by curriculum vitae or letter from the director of a transplant center attesting to the experience of the candidate.

Associate Membership is open to individuals with an MD or PhD degree who otherwise do not meet the criteria for full membership.

Affiliate Membership is available to allied non-MD or non-PhD professionals who have an interest in blood and marrow transplantation. This category is especially appropriate for nursing and administrative staff of bone marrow transplant centers, collection centers, and processing laboratories, and for professional staff of corporations that provide products and services to the field of blood and marrow transplantation.

In-Training Membership is open to fellows-in-training in bone marrow transplantation programs. A letter from the transplant center director attesting to the applicant's training status is required.

Included in the membership fee is a one-year subscription to ***Biology of Blood and Marrow Transplantation.***

To become a member of ASBMT

copy and return this page with the required documentation and annual dues to:

ASBMT
85 West Algonquin Road, Suite 550
Arlington Heights, IL 60005

name _____ position _____

institution _____

address _____

city _____ state _____ zip/postal code _____ country _____

telephone number _____ fax number _____

email address _____

Membership:
☐ full $175 ☐ associate $175 ☐ affiliate $125 ☐ in-training $75

NMDP Provides Funding for Evidence-Based Reviews

The National Marrow Donor program (NMDP) has awarded a $600,000 grant to ASBMT to support the development and dissemination of evidence-based reviews. The funds will be disbursed over a three-year period as work on the reviews progresses. The next in the series of reviews will address acute myelogenous leukemia, and an expert panel is being assembled.

ASBMT Membership Free for Fellows in Training

Post-doctoral fellows and physicians-in-training for blood and marrow transplantation are eligible for free ASBMT membership.

The annual dues of $75 is waived for new fellows-in-training in North America who join the Society. The program to recruit and waive the dues of in-training members is supported by an educational grant from PDL BioPharma, Inc.

Included in ASBMT membership is a subscription to *Biology of Blood and Marrow Transplantation*, and the bulletin, *Blood and Marrow Transplantation Reviews*. Among other membership benefits are reduced member-rate registration at the BMT Tandem Meetings and access to new investigator awards and travel grants.

Membership applications are available from the ASBMT Executive Office or by download from the ASBMT Web Site at *www.asbmt.org*. Click "Membership Application" on the home page.

Membership Jumps 17.5% to record 1,370

ASBMT membership climbed 17.5% during 2005, well exceeding the 10% goal that was set for the year by the Society's leaders. Part of the strategy for membership growth was a $50 across-the-board reduction in dues for most membership categories. The largest increase was among In-Training members, climbing from 114 to 209. Health professionals outside of the United States and Canada comprise 12% of ASBMT members.

BBMT Adds New Associate Editor and Two New Editorial Board Members

The ASBMT Board of Directors has appointed Ronald Gress, MD, of the National Cancer Institute as an associate editor for *Biology of Blood and Marrow Transplantation.*

Also appointed are two new members for the journal's Editorial Board:

H. Joachim Deeg, MD
Fred Hutchinson Cancer Research Center
Seattle, Washington

Steven Pavletic, MD
National Cancer Institute
Bethesda, Maryland

Announcing the new appointments was Editor-in-Chief Robert Korngold, PhD.

Upcoming Conference Calendar

32nd Annual Meeting of the European Group for Blood and Marrow Transplantation (EBMT)
March 19-22, 2006
Hamburg, Germany
General Information:
http://www.akm.ch/ebmt2006/

American Association for Cancer Research (AACR) 97th Annual Meeting
April 1-5, 2006
Washington, DC, USA
General Information:
http://www.aacr.org

American Society of Pediatric Hematology/Oncology (ASPH/O) 19th Annual Meeting
April 28-May 1, 2006
San Francisco, CA, USA
General Information:
http://www.aspho.org

International Society for Cellular Therapy (ISCT) 12th Annual Meeting
May 4-7, 2006
Berlin, Germany
General Information:
http://www.celltherapy.org/

The 4th Annual International Umbilical Cord Blood Transplantation Symposium
May 19-20, 2006
Los Angeles, CA, USA
General Information:
http://www.cordbloodsymposium.org/

World Marrow Donor Association 6th International Donor Registry Conference and Working Group Meetings
May 24-27, 2006
Cape Town, South Africa
General Information:
http://www.worldmarrow.org

American Society for Apheresis (ASFA) 27th Annual Meeting
May 23-26, 2006
Las Vegas, NV, USA
General Information:
http://www.apheresis.org

Federation of Clinical Immunology Societies (FOCIS) 6th Annual Conference
June 1-5, 2006
San Francisco, CA, USA
General Information:
http://www.focisnet.org

American Society of Clinical Oncology (ASCO) 2006 Annual Meeting
June 2-6, 2006
Atlanta, GA, USA
General Information:
http://www.asco.org/

11th Congress of the European Hematology Association
June 15-18, 2006
Amsterdam, Netherlands
General Information:
http://www.eurocongres.com/eha

International Society for Stem Cell Research (ISSCR) 4th Annual Meetings
June 29-July 1, 2006
Toronto, ON, Canada
General Information:
http://www.isscr.org

World Transplant Congress 2006
Joint meeting of the American Society of Transplant Surgeons (ASTS) and the American Society of Transplantation (AST)
July 22-27, 2006
Boston, MA, USA
General Information:
http://www.wtc2006.org

29th International Congress of the International Society of Blood Transfusion
September 2-7, 2006
CapeTown, South Africa
General Information:
http://isbt-web.org/capetown/

American Society for Hematology 48th Annual Meeting
December 9-12, 2006
Orlando, FL, USA
General Information:
http://www.hematology.org

BMT Tandem Meetings ASBMT and CIBMTR Annual Meetings
February 8-12, 2007
Keystone, CO, USA
General Information:
http://www.asbmt.org

ASBMT REVIEW

Blood and Marrow TRANSPLANTATION REVIEWS

This abridgment is presented as a summary of two reports that appeared in recent issues of *Biology of Blood and Marrow Transplantation*. The complete papers can be found in Volume 11, Issue 5 (pages 823-861), and Volume 12, Issue 1 (pages 1-30).

ASBMT Evidence-Based Reviews for Pediatric and Adult Acute Lymphoblastic Leukemia

Theresa Hahn,[1] Roy Jones,[2] Donna Wall[3]

[1]Roswell Park Cancer Institute, Buffalo, New York; [2]M.D. Anderson Cancer Center, Houston, Texas; [3]Texas Transplant Institute, San Antonio, Texas

The Role of Cytotoxic Therapy with Hematopoietic Stem Cell Transplantation in the Treatment of Acute Lymphoblastic Leukemia in Children [1], the third in a series of evidence-based reviews sponsored by the American Society for Blood and Marrow Transplantation (ASBMT), was published in the November 2005 issue of the journal **Biology of Blood and Marrow Transplantation.** It was followed in January 2006 by the Society's second acute lymphoblastic leukemia (ALL) review: *The Role of Cytotoxic Therapy with Hematopoietic Stem Cell Transplantation in the Treatment of Acute Lymphoblastic Leukemia in Adults* [2].

Following are excerpts from the pediatric and adult ALL reviews with top line results of their findings and treatment recommendations. Also included is an overview of the ASBMT evidence-based review initiative, including a summary of the methodology and rationale behind the review process.

(The unabridged ALL manuscripts and the Society's earlier reviews, *The Role of Cytotoxic Therapy with Hematopoietic Stem Cell Transplantation in the Therapy of Diffuse Large Cell, B Cell Non-Hodgkin's Lymphoma,* and *The Role of Cytotoxic Therapy with Hematopoietic Stem Cell Transplantation in the Therapy of Multiple Myeloma*, are available on the ASBMT Web site at www.asbmt.org. Click on "Guidelines, Policy Statements and Reviews." ASBMT Position Statements based on these reviews also can be found on the site.)

The Role of SCT in the Treatment of Pediatric and Adult ALL

The Society's evidence-based reviews on the use of stem cell transplantation (SCT) in the treatment of pediatric and adult acute lymphoblastic leukemia (ALL) were conducted by a panel of independent experts [3] comprising transplantation specialists, ALL specialists, a third-party payer representative, and a patient advocate.

Review Methodologies: Literature Search and Grading the Evidence

The first step in conducting the ALL evidence-based reviews was a systematic search of the peer-reviewed scientific literature. PubMed and Medline, the Web sites of the National Center of Biotechnology Information at the National Library of Medicine of the National Institutes of Health, were searched for publications related to transplantation as therapy for ALL. The search was limited to data from human trials published in the English language. The Medline subject heading terms encompassed publications about acute lymphoblastic leukemia, acute lymphoid leukemia, and acute lymphocytic leukemia, regardless of which term was used in the published articles. The original search, which included publications from January 1980 through August 2002, was updated in February 2003, and underwent a final update in January 2005. Manuscripts were excluded if they were:

- not peer-reviewed reports;
- editorials;
- letters to the editor;
- case reports of 10 or fewer patients;
- phase I (dose escalation or dose finding) studies;
- reviews;
- consensus conference reports;
- practice guidelines;

Table 1. Grading the Quality of Design and Strength of Evidence

Levels of Evidence	
1++	High-quality meta analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias
1+	Well conducted meta analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1–	Meta analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2++	High-quality systematic reviews of case-control or cohort studies High-quality case-control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal
2+	Well conducted case control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal
2–	Case control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal
3	Non-analytic studies; eg, case reports, case series
4	Expert opinion

From: Harbour and Miller. *Brit Med J*. 2001;323:334-6.

- laboratory studies with no clinical correlates;
- studies that did not focus on an aspect of therapy with SCT for the treatment of ALL;
- abstracts or presentations at professional meetings.

Evidence for the Pediatric ALL review included data from studies in which greater than 50 percent of the study population was under 16 years of age; articles in which fewer than 50 percent of patients were age 16 or younger were included in the Adult ALL review.

Qualitative and Quantitative Grading of the Evidence

The most recent guidelines for establishing the hierarchy of evidence, including a grading scheme for the quality and strength of the evidence, and strength of each treatment recommendation, were published as an editorial policy statement of the ASBMT Steering Committee for Evidence-Based Reviews in **Biology of Blood and Marrow Transplantation** in 2005 [4] and reprinted in this issue of **Blood and Marrow Transplantation Reviews** (page 10).

In Tables 1 and 2, criteria used to grade the evidence included in the reviews and to grade the treatment recommendations are defined. Study design, including sample size, patient selection criteria, duration of follow-up and treatment plan, also were considered in evaluating the studies.

Abstracts and Treatment Recommendations

Abstract: Stem Cell Transplantation in the Therapy of ALL in Children [1]

Evidence supporting the role of hematopoietic stem cell transplantation (SCT) in the therapy of acute

Table 2. Grading the Strength of the Treatment Recommendation

Grades of Recommendation	
A	At least one meta analysis, systematic review, or randomized controlled trial (RCT) rated as 1++, and directly applicable to the target population; or A systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+

From: Harbour and Miller. *Brit Med J*. 2001;323:334-6.

Table 3. Summary of Treatment Recommendations Made by the Expert Panel for Acute Lymphoblastic Leukemia in Children*

Indication for SCT	Treatment Recommendation†	Highest Level of Evidence‡	Comments
SCT versus chemotherapy in first complete remission	B	2++	Demonstrated benefit only for matched related allogeneic SCT in very high-risk (Ph+ only) ALL. Not recommended for standard or other high-risk (ie, induction failure, hypodiploidy, etc) patients except in the context of a clinical trial.
SCT versus chemotherapy in second complete remission	B	2++	Recommended only for matched related allogeneic transplant versus chemotherapy; however the recommendation is tempered because of 1 prospective trial that did not demonstrate a benefit for transplantation when analyzed by the presence versus absence of a related donor in an intent-to-treat analysis. Evidence is insufficient to support a recommendation for an unrelated allogeneic transplant versus chemotherapy.
Autologous, purged SCT	C	2+	Although a majority of patients with late relapses achieve extended leukemia-free survival (LFS) with an autologous purged SCT, the evidence is insufficient to determine that this is better than chemotherapy alone. For those with an early relapse, the outcomes with autologous purged SCT are even less promising.
Autologous, unpurged SCT	N/A	N/A	Data are unavailable on outcomes of unpurged autologous SCT.
Related allogeneic SCT	C	2+	A substantial proportion of patients achieve extended LFS.
Unrelated allogeneic SCT	C	2++	A substantial proportion of patients achieve extended LFS.
Related versus unrelated allogeneic SCT	None	2+	Outcomes of related versus unrelated donor allogeneic SCT have not been adequately studied, especially in patients who have had high-resolution typing. No recommendation can be made at this time.
Comparison of conditioning regimens	B	1+	TBI-containing regimens have better outcomes than non–TBI-containing regimens.
Autologous versus allogeneic SCT	None	2+	The outcomes of autologous versus allogeneic SCT have not been adequately studied. No recommendation can be made at this time.

*The references listed represent the highest level of evidence used to make the treatment recommendation and are not inclusive of all evidence described in the review. For references of the publications from which evidence and recommendations were derived, see Table 3 in the unabridged manuscript at www.asbmt.org.
†For definitions, see Table 2.
‡For definitions, see Table 1.

lymphoblastic leukemia (ALL) in children is presented 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 presented in Table 3 of this review and were reached unanimously by a panel of ALL experts. The priority areas of needed future research in pediatric ALL are: unrelated marrow or blood donor vs. unrelated cord blood donor allogeneic SCT; alternative, non-family allogeneic donor vs. autologous SCT; better methods for identifying high relapse risk patients; assessments of the impact of current chemotherapy regimens on early relapse; and use of pre-SCT detection of minimal residual disease to predict post-SCT outcomes.

Treatment Recommendations

Table 3 summarizes the treatment recommendations for the use of hematopoietic stem cell transplantation in the therapy of acute lymphoblastic leukemia in children.

Abstract: Stem Cell Transplantation in the Therapy of ALL in Adults [2]

Evidence supporting the role of hematopoietic stem cell transplantation (SCT) in the therapy of acute lymphoblastic leukemia (ALL) in adults (≥15 years) is presented and critically evaluated in this systematic evidence-based review. Specific criteria were used for searching the published medical 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 presented in Table 4 of this review and were reached unanimously by a panel of ALL experts. The priority areas of needed future research for adult ALL are: definition of high-risk patients in CR1, beyond Ph+; outcomes of SCT in older (>50 years) adults; determination if reduced intensity vs. myeloablative conditioning regimens yield an equivalent graft-versus-leukemia effect with reduced toxicity; monitoring of minimal residual disease to achieve

Table 4. Summary of Treatment Recommendations Made by the Expert Panel for Acute Lymphoblastic Leukemia in Adults*

Indication for SCT	Treatment Recommendation†	Highest Level of Evidence‡	Comments
SCT versus chemotherapy in first complete remission	B	1+	In first complete remission, SCT yields outcomes similar to chemotherapy and is not recommended as first choice therapy in standard-risk patients. For high-risk patients, there are no direct comparisons, but some data suggest an advantage for SCT.
SCT versus chemotherapy in second complete remission	D	3	In second complete remission, SCT is recommended over chemotherapy as a sizable fraction of patients achieve extended leukemia-free survival (LFS) compared to chemotherapy alone, however there are no direct comparative data.
Autologous, purged SCT	D	2–	LFS is in the same range seen with chemotherapy.
Autologous, unpurged SCT	D	2+	LFS is in the same range seen with chemotherapy.
Related allogeneic SCT	C	2++	Effective at producing extended LFS in some patients. High-risk Ph+ ALL patients have very poor LFS (<10%) with chemotherapy; although there are no direct comparisons, there appears to be a survival advantage for related allogeneic SCT in Ph+ ALL patients in first or subsequent remissions.
Unrelated Allogeneic SCT	C	2++	Produces extended LFS in some patients. There is a possible benefit of unrelated allogeneic SCT over chemotherapy in Ph+ ALL patients, although there are no direct comparisons. Higher treatment related mortality (TRM) may compromise the potential anti-tumor advantage of unrelated allogeneic SCT.
Related versus Unrelated Allogeneic SCT	D	2+	Equivalent outcomes between related and unrelated allogeneic SCT in 1 study.
Comparison of Conditioning Regimens	N/A	N/A	There are not enough data to make a recommendation of the superiority of 1 conditioning regimen. There appears to be a benefit to TBI-containing regimens compared to non-TBI containing regimens. There are not enough data evaluating non-myeloablative conditioning regimens to determine the effect on TRM and LFS.
Autologous versus Allogeneic SCT	B	1+	Preponderance of evidence favoring allogeneic over autologous SCT. There are insufficient data to determine if this effect is more apparent in risk subgroups, including Ph+ ALL.

*The references listed represent the highest level of evidence used to make the treatment recommendation and are not inclusive of all evidence described in the review. For references of the publications from which evidence and recommendations were derived, see Table 3 in the unabridged manuscript at www.asbmt.org.
†For definitions, see Table 2.
‡For definitions, see Table 1.

disease control before SCT and the use of cord blood and other alternative sources of stem cells for use in adult SCT recipients.

Treatment Recommendations

Table 4 summarizes the treatment recommendations for the use of hematopoietic stem cell transplantation in the therapy of acute lymphoblastic leukemia in adults.

Discussion and Limitations of the Reviews

The expert panel strongly recommended that future investigators standardize methodology, including study design, endpoint definitions, and reporting of study results. The authors noted that multi-center randomized phase III comparative trials with large enrollments and high statistical power are required to advance the field more constructively than single-institution phase II trials with one treatment arm or retrospective multi-center or registry studies. In addition, publication of preliminary analyses should be reserved for studies in which the trial was terminated early due to excessive toxicity or to significantly inferior or superior results. For most studies, 3 years of follow-up in surviving patients is needed to detect significant differences between treatment arms. The authors advocated prompt reporting of mature data in full-length manuscript format.

Much of today's therapies for cancer result from the clinical trial process. It is currently estimated that less than 60 percent of pediatric cancer patients and less than 5 percent of adults eligible to participate in cancer clinical trials actually enroll in a trial. The authors acknowledge the importance of removing barriers to participation in clinical trials, which may include patients' reluc-

tance to be randomized; lack of patient access to clinical trials, such as geographic, transportation and cultural barriers; financial constraints, such as no or incomplete insurance coverage for trial expenses; stringent trial eligibility criteria; and reluctance of community physicians to refer patients for clinical trial participation.

An additional factor contributing to the low rate of participation in clinical trials by adult cancer patients is the relatively low incidence of adult ALL. According to the Surveillance, Epidemiology and End Results (SEER) Cancer Statistics Review [5], it is estimated that there will be approximately 1,700 to 1,800 new cases of adults age 20 and older diagnosed with ALL in the United States in 2005. Thus, there is a small number of adult ALL patients who may be eligible for enrollment in a clinical trial examining any one of numerous therapeutic options.

There are limitations to any evidence-based review of the published literature. The criteria for the ALL reviews included reliance on published data, specifically peer-reviewed articles published since 1980. Unpublished data, which did not meet the inclusion criteria, often represent "negative" findings and do not undergo peer review. The panel also excluded data published in abstract form because data are usually not peer reviewed, are presented in an abbreviated format, and usually represent preliminary, not final, data analyses. In addition, published literature may not address the management of all disease-specific clinical situations.

Limitations specific to the review of ALL include the variability in reporting patient characteristics pre-SCT, changing treatment modalities over time and the paucity of randomized controlled trial data. The success of SCT is affected by prior sites of relapse, presence of extramedullary disease and duration of first complete remission (CR). Many studies did not report this information, making it difficult to compare SCT outcomes across studies. Chemotherapy regimens, particularly those used for salvage, pre-SCT conditioning regimens and post-SCT supportive care have changed over the more than 20 years during which the trials included in this review were conducted. The effectiveness of salvage regimens impacts attainment of second or greater CR, which in turn impacts the effectiveness of SCT. Finally, randomized controlled trial data were lacking in many areas; the result was that several treatment recommendations were necessarily based on small prospective studies and/or large retrospective registry reports. For example, the expert panel determined that there were insufficient data available to make recommendations for or against the use of SCT for patients not in CR.

Future Initiatives

The comprehensive systematic reviews of the available evidence for the role of cytotoxic therapy with hematopoietic SCT in the therapy of pediatric and adult ALL are the third and fourth, respectively, in a series of sequential articles sponsored by ASBMT.

In 2006-2007, the Society will complete 2 additional reviews: *The Role of Cytotoxic Therapy with Hematopoietic Stem Cell Transplantation in the Treatment of Acute Myeloid Leukemia in Children* and *The Role of Cytotoxic Therapy with Hematopoietic Stem Cell Transplantation in the Treatment of Acute Myeloid Leukemia in Adults.*

The ASBMT Evidence-Based Reviews

The Society began the development of evidence-based reviews of the scientific and medical literature in 1999 in an effort to provide objective documentation of when blood and marrow transplantation is—and when it is not—indicated in the treatment of selected diseases.

Goals and Objectives

The Society's goals and objectives in initiating the evidence-based review process 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 the evidence regarding the role of cytotoxic therapy with hematopoietic stem cell transplantation related to the disease and the questions to be addressed in each review.
- Make 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 needed areas of additional study.
- Define commonly accepted medical practice.
- Develop standards of medical care for autologous and allogeneic transplants.
- Provide recommendations and guidelines about the role of transplanta-

tion as a therapeutic approach for reimbursement by third-party payers.

The Evolution of the Evidence-Based Review

The Levels of Evidence and Grades of Recommendation (see Tables 1 and 2) for the ALL evidence-based reviews are based on guidelines developed by the Scottish Intercollegiate Guidelines Network (SIGN) of the Royal College of Physicians of Edinburgh, and were adopted by the ASBMT Steering Committee for Evidence-Based Reviews in an editorial [4] published in 2005. The committee wrote, "In little more than a decade, evidence-based medicine has evolved from a theoretical—and often controversial—concept into a widely practiced methodology that can enhance the critical processes of medical decision-making. Fears that evidence-based medicine would elevate the science at the expense of the art of medicine, and handcuff physicians to rigid, "one size fits all" practice guidelines have diminished. A thorough, systematic evidence-based review is a powerful tool to assist physicians and patients who otherwise must make choices based on conventional wisdom, hearsay and piecemeal empirical data.

"We have learned much since 1999, when ASBMT launched its initiative to conduct evidence-based reviews of the use of blood and marrow transplant in the treatment of selected diseases. Often, the process has been as valuable for what it cannot tell us as for what it can. A systematic review may reveal a preponderance of conflicting studies or conclude that there simply is not enough empirical evidence to support one recommendation over another. By taking a hard look at the quality and quantity of the science, evidence-based medicine often highlights the gaps in our science and validates the "art" that every good physician brings to clinical practice—an art based on a synergistic blend of empirical knowledge, clinical experience, and human intuition...

"It is our belief that the … [SIGN] system will enhance the Society's evidence-based review process by addressing:

- The many areas of medical science where randomized trials may not be practical or ethical.
- Concerns that the controlled, randomized trial, although widely accepted as the most robust study design with the least risk of bias to answer questions of effectiveness, may not always be the best evidence to answer other questions, or may have methodological flaws that undermine its strength.
- Interpretations of studies that overgeneralize results, contributing to misleading expectations about efficacy.
- The limitations of guidelines that grade the *strength* but not the *importance* of the evidence, which may potentially result in user confusion and discourage consideration of some low-grade yet significant recommendations [6].

References

1. Hahn T, Wall D, Camitta B, Davies S, Dillon H, Gaynon P, Larson R, Parsons S, Seidenfeld J, Weisdorf D, McCarthy P. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the therapy of acute lymphoblastic leukemia in children: an evidence-based review. *Biol Blood Marrow Transplant*. 2005;11:823-861.
2. Hahn T, Wall D, Camitta B, Davies S, Dillon H, Gaynon P, Larson R, Parsons S, Seidenfeld J, Weisdorf D, McCarthy P. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the therapy of acute lymphoblastic leukemia in adults: an evidence-based review. *Biol Blood Marrow Transplant*. 2006;12:1-30.
3. Expert panel members and authors of the review are: Theresa Hahn, PhD, Roswell Park Cancer Institute, Buffalo, NY; Donna Wall, MD, Texas Transplant Institute, San Antonio, TX; Bruce Camitta, MD, Midwest Children's Center, Medical College of Wisconsin and Children's Hospital of Wisconsin, Milwaukee, WI; Stella Davies, MD, PhD, Cincinnati Children's Hospital and Medical Center, Cincinnati, OH; Hildy Dillon, MPH, The Leukemia and Lymphoma Society, White Plains, NY; Paul Gaynon, MD, Children's Hospital of Los Angeles, Los Angeles, CA; Richard A. Larson, MD, University of Chicago, Chicago, IL; Susan Parsons, MD, Dana-Farber Cancer Institute/Harvard Medical School, and Tufts New England Medical Center/Tufts University School of Medicine, Boston, MA; Jerome Seidenfeld, Blue Cross and Blue Shield Association Technology Evaluation Center, Chicago, IL; Daniel Weisdorf, MD, University of Minnesota, Minneapolis, MN; Philip L. McCarthy, Jr, MD, Roswell Park Cancer Institute, Buffalo, NY.
4. Jones R, Nieto Y, Rizzo JD, et al. The evolution of the evidence-based review: evaluating the science enhances the art of medicine. *Biol Blood Marrow Transplant*. 2005;11:819-822.
5. National Cancer Policy Board (2003). Childhood Cancer Survivorship: Improving care and quality of life. Washington, DC: National Academies Press.
6. Harbour R, Miller J. A new system for grading recommendations in evidence based guidelines. *BMJ*. 2001;323:334-336.

ASBMT

EDITORIAL

Blood and Marrow TRANSPLANTATION REVIEWS

The following editorial initially appeared in *Biology of Blood and Marrow Transplantation*, 2005;11:819-822.
The editorial has been reprinted with permission.

The Evolution of the Evidence-Based Review: Evaluating the Science Enhances the Art of Medicine—Statement of the Steering Committee for Evidence-Based Reviews of the American Society for Blood and Marrow Transplantation

Roy Jones,[1] Yago Nieto,[2] J. Douglas Rizzo,[3] Donna Wall,[4] John R. Wingard,[5] Philip McCarthy, Jr,[6] Theresa Hahn[6]

[1]M.D. Anderson Cancer Center, Houston, Texas; [2]Clinica Universitaria de Navarra, Pamplona, Spain; [3]Medical College of Wisconsin, Milwaukee, Wisconsin; [4]Texas Transplant Institute, San Antonio, Texas; [5]University of Florida Health Science Center, Gainesville, Florida; [6]Roswell Park Cancer Institute, Buffalo, New York

Correspondence and reprint requests: Theresa Hahn, PhD, Roswell Park Cancer Institute, Elm and Carlton Streets, Buffalo, NY 14263 (e-mail: Theresa.hahn@roswellpark.org).
Received June 27, 2005; accepted June 28, 2005

KEY WORDS

Hematopoietic stem cell transplantation • Evidence-based medicine • Methodology

In little more than a decade, evidence-based medicine has evolved from a theoretical—and often controversial—concept into a widely practiced methodology that can enhance the critical processes of medical decision making. Fears that evidence-based medicine would elevate the science at the expense of the art of medicine and handcuff physicians to rigid "one size fits all" practice guidelines have diminished. A thorough, systematic evidence-based review is a powerful tool to assist physicians and patients who otherwise must make choices on the basis of conventional wisdom, hearsay, and piecemeal empirical data.

We have learned much since 1999, when the American Society for Blood and Marrow Transplantation (ASBMT) launched its initiative to conduct evidence-based reviews of blood and marrow transplantation in the treatment of selected diseases. Often, the process has been as valuable for what it cannot tell us as for what it can. A systematic review may reveal a preponderance of conflicting studies or conclude that there simply is not enough empirical evidence to support one recommendation over another. By taking a hard look at the quality and quantity of the science, evidence-based medicine often highlights the gaps in our science and validates the art that every good physician brings to clinical practice—an art based on a synergistic blend of empirical knowledge, clinical experience, and human intuition.

We also have learned that the art of medicine has a role in the review process itself. In practice, reviewers often must grapple with numerous variables that are difficult to quantify objectively yet affect the quality and strength of the evidence. In response, the standards of evidence-based medicine have evolved beyond grading schema that rank evidence on strictly objective criteria. Although these objective measurements remain important, the Society's first evi-

dence-based reviews for diffuse large-cell B-cell lymphoma (DLCL) [1] and multiple myeloma (MM) [2] taught us not to rely on study design alone to define the best evidence. To do so can undermine optimal patient care, such as when a study is compromised by poor methodology or inappropriate interpretation of results. There were some instances, for example, when the independent experts who served on the DLCL and MM panels unanimously agreed to discount some of the randomized controlled trials (RCTs) because, in the end, they did not sufficiently answer the questions posed.

Changing Criteria for ASBMT Reviews

The original methodology called for a periodic assessment of the process of conducting the reviews [3]. In response to an evaluation of the first 2 reviews, the ASBMT Steering Committee for Evidence-Based Reviews in 2004 adopted the following changes in criteria for conducting future reviews.

Focus of Reviews

The evidence-based reviews conducted by the ASBMT thus far (DLCL, MM, and acute lymphoblastic leukemia [ALL]) have considered all relevant aspects of transplantation for each disease state within a single review article. For future topics, the Steering Committee will establish the initial focus for each review and develop a list of questions to be addressed. This approach not only shortens the review process, but also, more importantly, allows us to focus on the questions that are most relevant to today's clinicians and scientists.

Inclusion Criteria

In past reviews, inclusion criteria for evidence were largely determined by each expert panel. For future reviews, the Steering Committee has established 4 standard criteria:

1. *Meeting abstracts and data from non–peer-reviewed journals will be excluded.*
2. *Only evidence from studies published in 1990 or later will be included.*
3. *A minimum of 70% of study subjects must be patients with the disease under review, or study results must be stratified by the disease to be included.*
4. *Studies with fewer than 25 patients will be excluded, unless they will affect treatment recommendations (eg, where no large studies exist or where they are flawed by problems in design, methodology, or reporting of results).*

Methodology

The methodology for the ASBMT-sponsored reviews was established in 1999 according to well-accepted standards for evidence-based medicine. In April 2001, the US Agency for Healthcare Research and Quality sponsored a study of the methods used for systematic reviews. The agency published a critical evaluation of the established schemas for grading the quality and strength of the evidence and reviewed the 20 it determined to be of the highest quality. After reviewing the systems recommended by the Agency for Healthcare Research and Quality, the Steering Committee selected a grading schema for future reviews based on guidelines developed by the Scottish Intercollegiate Guidelines Network (SIGN) of the Royal College of Physicians of Edinburgh [4]. The SIGN criteria most closely resemble the original grading criteria for the ASBMT reviews yet also address a deficiency of our prior grading schema: the lack of an assessment of quality for individual studies within each category of study design. To evaluate methodologic quality, SIGN uses standardized checklists of criteria to rate studies as follows:

++ All or most criteria from the checklist are fulfilled or, when not fulfilled or adequately described, are judged to be highly unlikely to alter the study's conclusions.

\+ Some of the criteria from the checklist are fulfilled; where not fulfilled or adequately described, they are unlikely to alter conclusions.

– Few or no criteria are fulfilled, and those not fulfilled or adequately described are very likely or likely to alter conclusions.

More information about SIGN, including the criteria checklists for rating methodologic quality, can be found at http://www.sign.ac.uk/guidelines/fulltext/50/.

Validating the System

An unanswered question about SIGN was whether the methodology for quality assessment was sufficiently objective to facilitate consistent, unbiased application of the grading criteria by multiple raters. Before formally adopting the new system for the ASBMT reviews, the Steering Committee undertook an interrater reliability study to validate the SIGN methodology.

Of the approximately 180 scientific articles initially selected for inclusion in the ALL review, approximately 10% (n = 18) were randomly chosen by a

third party. Four members of the ASBMT Steering Committee acted as raters of these studies and were asked to rank each article according to the SIGN checklist and rating system. The consensus rating among the 4 raters was significantly consistent: 44% of the time, the raters had perfect agreement; 33% of the time, 1 rater differed; 17% of the time, the raters were split evenly; and only 6% of the time, there was no consensus between raters ($P < .0001$; Pearson exact χ^2). The κ statistic can be used only to compare interrater agreement between 2 raters; therefore, the Pearson exact χ^2 was used to compare the consistency of grading among the 4 raters.

How SIGN Enhances the ASBMT Review Process

The SIGN criteria are comparable to those that governed the ASBMT's first 2 reviews, and their application, in the Committee's opinion, will not change or invalidate the consensus recommendations reached by the expert panels that conducted the DLCL and MM evidence-based reviews. At the same time, the new schema advances the process by:

- Giving due weight to methodologic variables within a study's design that can significantly affect the quality of evidence or affect the study's applicability to a given patient population.
- Presenting a more thorough overall picture of the entire body of available evidence and avoiding the pitfall of overreliance on the conclusions of single studies or types of studies.

The SIGN system also preserves the strengths of our earlier review criteria. The hierarchy of study types recommended by the Agency for Healthcare Research and Quality and widely accepted by experts remains the first step in grading the quality of design and strength of the evidence.

Levels of Evidence

1++ High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias.
1+ Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias.
1– Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias.
2++ High-quality systematic reviews of case-control or cohort studies; high-quality case-control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal.
2+ Well-conducted case-control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal.
2– Case-control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal.
3 Nonanalytic studies, eg, case reports or case series.
4 Expert opinion.

Synthesis of the Evidence

After the evidence has been assembled and rated according to the hierarchy of the study design and the quality of the methodology, relevant data are abstracted from studies that meet the inclusion criteria for the review. Relevant data from the individual studies are summarized in text format, and tables summarizing information about study quality (eg, sample size and duration of follow-up) also are created to facilitate expert assessment of the overall direction and weight of the evidence.

Considered Judgment

Once the evidence has been synthesized according to rigorous objective standards, the art of medicine comes into play as members of the expert panels begin the process of making and grading the strength of their recommendations. Here, the experts' individual knowledge and clinical experience are drawn upon as they consider the evidence—or lack of evidence—to answer the questions posed by the review. To reduce the risk of introducing personal bias into the review, this step relies on the consensus of many individuals who are experts in myriad aspects of the disease under investigation. The expert panel convened to conduct the evidence-based review of ALL, for example, comprises nationally recognized authorities in both pediatric and adult ALL, including those who specialize in transplantation and those whose expertise is in other treatment modalities for the disease.

Grades of Recommendation

The treatment recommendations of the expert panel also are subject to a standardized grading system.

A At least 1 meta-analysis, systematic review, or RCT rated as 1++ and directly applicable to the target population or a system-

atic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results.

B A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results or extrapolated evidence from studies rated as 1++ or 1+.

C A body of evidence including studies rated as 2+, directly applicable to the target population, and demonstrating overall consistency of results or extrapolated evidence from studies rated as 2++.

D Evidence level 3 or 4 or extrapolated evidence from studies rated as 2+.

Implications for Past and Future Reviews

The SIGN system was adopted for the Society's evidence-based reviews of ALL in children and adults, which respectively appear in this issue and the January 2006 issue of this journal, and will be the standard for subsequent ASBMT reviews. The new system also will be applied to the completed reviews on DLCL and MM when they are updated as new evidence becomes available.

It is our belief that the new system will enhance the Society's evidence-based review process by addressing the following:

- The many areas of medical science in which randomized trials may not be practical or ethical.
- Concerns that the controlled, randomized trial, although widely accepted as the most robust study design with the least risk of bias to answer questions of effectiveness, may not always be the best evidence to answer other questions or that it may have methodologic flaws that undermine its strength.
- Interpretations of studies that overgeneralize results, thus contributing to misleading expectations about efficacy.
- The limitations of guidelines that grade the strength but not the importance of the evidence; this may result in user confusion and discourage consideration of some low-grade yet significant recommendations [4].

With this modification in the system for conducting the reviews, the Society signals its commitment to the highest current standards of evidence-based medicine. The more thorough and unbiased the review, the more it meets our objective to support patients and providers in the complicated process of choosing treatment options.

At its best, evidence-based medicine advances its field of inquiry and points toward research that will lead to better diagnostic and treatment options. Panelists for the ASBMT evidence-based reviews identify areas where there is insufficient evidence to support treatment recommendations and prioritize the questions that, in their expert opinion, are most important to answer through future research.

As the science of evidence-based medicine evolves, the ASBMT review process also will evolve to keep pace with advances. The ultimate goal, however, remains unchanged: to give every patient access to the treatment option that offers the best chance for survival and a high quality of life.

References

1. Hahn T, Wolff SN, Czuczman M, et al. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the therapy of diffuse large cell B-cell non-Hodgkin's lymphoma: an evidence-based review. *Biol Blood Marrow Transplant.* 2001;7:308-331.

2. Hahn T, Wingard JR, Anderson KC, et al. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the therapy of multiple myeloma: an evidence-based review. *Biol Blood Marrow Transplant.* 2003;9:4-37.

3. Jones R, Horowitz M, Wall D, et al. Policy statement regarding the methodology of evidence-based reviews in evaluating the role of blood and marrow transplantation in the therapy of selected diseases. *Biol Blood Marrow Transplant.* 2000;6:524-525.

4. Harbour R, Miller J. A new system for grading recommendations in evidence based guidelines. *BMJ.* 2001;323:334-336.

Journal Watch

A scan of recent medical literature identified these articles of special importance in the science and clinical application of blood and marrow transplantation.

Görgün G, Holderried TAW, Zahrieh D, et al: Chronic lymphocytic leukemia cells induce changes in gene expression of CD4 and CD8 T cells. J Clin Invest. 2005; 115:1797-1805.

Cancer is associated with immune suppression, which might contribute to the immune system's failure to reject the cancer cells. The mechanisms of the observed T-cell defects are unknown—production of immune-suppressive factors by cancer cells, interactions between T cells and cancer cells, and induction of regulatory T-cell subsets are all possible explanations. The mechanisms of cancer-related immune defects were examined using T cells from patients with chronic lymphocytic leukemia (CLL).

The investigators obtained CD4 and CD8 T cells from the peripheral blood of 29 patients with previously untreated B-cell CLL; and from age-matched healthy donors. Gene expression profiling techniques were used to compare the two groups of highly purified CD4 and CD8 cells. Genes with differential expression were analyzed in detail. Coculture experiments were performed to examine the effects of direct contact between healthy T cells and cancer cells.

There were significant differences in gene expression between CD4 and CD8 T cells from CLL patients and healthy subjects, even though T cells from the CLL subjects were not part of the malignant clone. In CD4 cells, most of the differentially expressed genes were involved in cell differentiation. The gene expression differences in CD8 cells were related to cytoskeleton formation, vesicle trafficking, and cytotoxicity.

Soluble factors derived from B cells from CLL patients led to changes in chemokine and chemokine-receptor expression by healthy T cells, but had no effect on cytoskeletal proteins. In coculture experiments, donor CD4 cells developed changes in protein expression, similar to those observed in CLL CD4 cells, within 48 hours of contact with cancer cells. Cell-cell contact also induced changes in CD8 cell expression, consistent with the patterns observed on gene expression profiling.

Direct contact with cancer cells can produce significant changes in gene expression by previously healthy T cells, the new results demonstrate. This could help to explain the host immune suppression observed in cancer patients, and possibly the inadequate immune response to tumor cells. The authors plan further studies to clarify the impact of tumor development on T cell function and expression profiles, as well as the implications for allogeneic stem cell transplantation.

Schneider A, Krüger C, Stiegleder T, et al: The hematopoietic factor G-CSF is a neuronal ligand that counteracts programmed cell death and drives neurogenesis. J Clin Invest. 2005; 115:2083-2098.

Techniques to encourage neuronal generation from progenitor cells would offer a valuable new option for the treatment of stroke. The hematopoietic factor granulocyte colony stimulating factor (G-CSF), commonly used for the treatment of neutropenia, acts by stimulating the growth of neutrophil granulocyte precursors. Recent studies in an acute stroke model have suggested a neuroprotective effect of G-CSF. Further experiments were performed to assess the mechanisms of this effect.

Experiments were performed in two rodent models of ischemic stroke: an occlusive model and a prothrombotic model. In both models, treatment with C-CSF resulted in significant and stable reductions of infarct size. Survival and functional recovery were significantly improved in G-CSF-treated animals. Experiments confirmed that G-CSF passed through the intact blood-brain barrier.

The G-CSF receptor and ligand were widely expressed throughout the brain, particularly in the large principal neurons. Ischemia induced G-CSF expression, consistent with an autocrine activation mechanism. Studies in cultured neurons suggested that G-CSF induced activation of antiapoptotic pathways. Adult neuronal stem cells also expressed the G-CSF receptor, indicating a functional role in neural stem cell differentiation. In vivo experiments suggested that G-CSF treatment enhanced hippocampal neurogenesis in animals with and without cerebral ischemia.

Granulocyte colony stimulating factor demonstrates significant neuroprotective effects in models of acute stroke. This hematopoietic factor is widely expressed in the central nervous system, is upregulated in the presence of ischemia, passes through the intact blood-brain barrier, and is well-tolerated therapeutically. With further research, G-CSF may provide a useful new treatment option for stroke and other psychiatric and neurologic disorders associated with neuronal death or disturbance of neurogenesis.

Wagner JE, Thompson JS, Carter SL, et al: Effect of graft-versus-host disease prophylaxis on 3-year disease-free survival in recipients of unrelated donor bone marrow (T-cell Depletion Trial): a multi-centre, randomised phase II–III trial. Lancet. 2005;366:733-741.

Graft-versus-host disease (GVHD) is a major limiting factor on the successful use of unrelated-donor bone marrow transplantation in patients with lymphohematopoietic malignancies. T-cell depletion reduces GVHD risks in recipients of sibling bone marrow transplants. Physical and immunologic techniques of T-cell depletion were compared for efficacy in patients receiving unrelated-donor bone marrow transplantation.

The randomized, multicenter trial included 405 patients, all less than 56 years old, receiving unrelated-donor bone marrow for leukemia or other lymphohematopoietic malignancies. One group of patients was transplanted with T-cell-depleted marrow plus cyclosporine A (TCD group). The other group received non-T-cell-depleted marrow, followed by treatment with methotrexate and cyclosporine A (M/C group). The main outcome of interest was 3-year disease-free survival.

There were 5 pretransplant deaths; non-T-cell-depleted marrow was used in 7 patients assigned to the TCD group. On intention-to-treat analysis, 3-year disease-free survival was 27% in the TCD group and 34% in the M/C group—the difference was not significant. Patients in the TCD group achieved neutrophil recovery in a median of 15 days, compared with 20 days for the M/C group.

The TCD strategy was also associated with a lower risk of grade III to IV acute GVHD, 18% vs 37%; and a reduced risk of grade III to IV toxic effects, 19% vs 29%, respectively. Length of initial hospital stay was shorter in the TCD group, 32 vs 38 days. However, the rate of relapsed chronic myelogenous leukemia was 20% with TCD vs 7% with M/C. The TCD regimen was also associated with a higher risk of cytomegalovirus infection, 28% vs 17%.

Unrelated-donor bone marrow transplant recipients show no significant survival advantage with partial marrow TCD, as performed in this multicenter trial. T-cell depletion is associated with a lower risk of acute GVHD and early toxic effects. Regardless of which approach to GVHD prophylaxis is used, unrelated-donor marrow recipients remain at high risk of disease relapse and opportunistic infections.

Zinselmeyer BH, Dempster J, Gurney AM, et al: In situ characterization of CD4$^+$ T cell behavior in mucosal and systemic lymphoid tissues during the induction of oral priming and tolerance. J Exp Med. 2005;201:1815-1823.

Immune tolerance and immunity both seem to result from activation and clonal expansion of antigen-specific T cells after interaction between a naïve T cell and an antigen-presenting cell (APC). The outcome of priming vs tolerance may depend on the duration or frequency of interaction between APCs and T cells. However, no previous study has directly examined the behavior of CD4$^+$ T cells during initial exposure to antigen.

This issue was addressed in a previously described mouse model of peripheral priming and tolerance. Two-photon excitation microscopy was used to track the behavior of antigen-specific CD4$^+$ T cells in local and systemic lymphoid tissues in situ, after antigen feeding. This allowed real-time comparison of cell behavior during oral priming vs oral tolerance.

The results showed several significant differences in cell movement and clustering between naïve T cells and those exposed to immunogenic and tolerogenic antigen. However, the main difference was that tolerized T cells formed larger and more persistent cell clusters, compared with primed T cells. Clusters of primed T cells were observed simultaneously in mucosal and peripheral lymph nodes. Despite major differences in immunologic outcomes, the differences on the cellular level were relatively subtle.

The study provides new insights into T-cell behavior during the induction of priming and tolerance. Seemingly small differences in the size and persistence of T-cell clusters in local and peripheral lymphoid organs lead to major differences in immunologic outcome. With further study, these observations may have important implications for vaccines and immunotherapeutic interventions, especially those delivered via the mucosa.

ASBMT™
American Society for Blood and Marrow Transplantation

Non-Profit Organization
U.S. Postage
PAID
Charlottesville, Virginia
Permit No. 232