LETTER TO THE EDITOR

Target Populations in Allogeneic Hematopoietic Cell Transplantation for Autoimmune Diseases—A Workshop Accompanying: Cellular Therapy for Treatment of Autoimmune Diseases, Basic Science and Clinical Studies, Including New Developments in Hematopoietic and Mesenchymal Stem Cell Therapy

After our recent discussion of feasibility of allogeneic hematopoietic stem cell transplantation for autoimmune disease [1], important questions remained as to the patient populations that are most appropriate for such clinical trials. To consider the problem of patient selection further, many of the same international group of autoimmune disease experts and hematopoietic cell transplantation (HCT) physicians met as a workshop in Newport Beach, CA, in October 2005.

The group reached agreement on the following points.

1. Allogeneic HCT offers the potential to effect remission and/or cure of refractory autoimmune diseases including multiple sclerosis, systemic sclerosis, and systemic lupus erythematosus, as suggested by case reports and follow-up of patients with autoimmune disease who received this therapy for another primary indication. In addition, for acquired aplastic anemia, considered by many to have an autoimmune etiology [2], allogeneic HCT is the treatment of choice for many patients who have an HLA-matched sibling donor [3,4]. A significant number of patients with severe autoimmune disease failed to respond to conventional therapies and none of these are curative. Studies of high-dose immunosuppressive/immune ablative therapy with autologous HCT are currently underway in the United States and Europe, but several years will be required for follow-up to evaluate long-term efficacy.

2. To obtain experience in allogeneic HCT for autoimmune disease that is scientifically well founded and maximally informative, it would be desirable to enroll patients in studies at a time during their disease course when the disorder is most likely to respond to HCT and who are optimal transplantation candidates. Status of the autoimmune disease (HCT early in the disease might provide a chance for cure of the disease and prevention of organ damage caused by the disease), comorbidities (major organ dysfunction would constitute a risk for HCT), motivation, and type of donor (an HLA-matched sibling would be preferred) should be considered. Patient age theoretically could also be important due to better preserved thymic tolerance acquisition pathways [5], but this notion needs to be proven in HCT clinical trials. Classically, experimental therapies such as HCT, with measurable risk of morbidity and mortality, have been provided initially to patients who had late disease and no other options for therapy. However, transplantation may not improve the clinical course for patients with autoimmune disease that is already very advanced. Such patients might be “cured” of autoimmune disease by HCT but achieve no therapeutic benefit due to failure to prevent irreversible organ damage and end-stage organ failure caused by the autoimmune disease. Further, such patients may have multiple comorbidities and thus be at high risk for complications of HCT.

3. Current autologous HCT protocols in multiple sclerosis target those patients who have early relapsing remitting disease with features indicating high risk for evolution to secondary progressive disease. A more accessible and practical population for pilot studies of allogeneic HCT for multiple sclerosis might include those patients who are in the process of developing or have just developed secondary progressive disease. For

---

1Sponsored by the Bernie Marcus Foundation and the City of Hope National Medical Center, in Collaboration with NIAID, NCI, EULAR, and EBMT; Newport Beach, California; October 7, 2005.
systemic sclerosis, the ideal group would have aggressive cardiac/pulmonary and/or renal disease predictive of 50% survival at 5 years. Among patients with lupus, the target group for HCT should have progressive disease and/or involvement of a vital organ that is resistant to ≥1 major line of therapy. While autologous protocols continue to enroll, it would be desirable to specify noncompeting entry criteria for pilot studies of allogeneic HCT. A reasonable option in patient selection for phase I/II pilot studies of allogeneic transplantation for autoimmune diseases would be those with aggressive disease and poor prognosis who are unable to tolerate the high-dose preparative regimens commonly used for autologous HCT. Many of these patients would be suitable candidates for the reduced intensity or nonmyeloablative regimens of allogeneic HCT, which also have the advantage of reduced treatment-related morbidity and mortality compared with conventional regimens [6]. In future phase II studies, it may be informative to prospectively randomize subjects to either autologous or allogeneic HCT.

4. When developing end points for clinical trials of allogeneic HCT for autoimmune disease, the concept of “extended remission” off immunosuppression and “cure” of disease should be considered because the definition of benefit may vary depending on the disease and type of patients who are enrolled. Toxicity should be monitored as a stopping rule.

In closing, we note that when developing patient selection criteria and evaluating risk/benefit for allogeneic transplantation for nonmalignant indications including autoimmune diseases, despite advances in transplantation in recent years, many of the basic considerations remain the same [7]. If successful, these studies of allogeneic HCT for autoimmune disease will provide an alternative for care of patients with otherwise very limited or no options.

APPENDIX: WORKSHOP PARTICIPANTS

Cochairs

Linda M. Griffith, Division of Allergy, Immunology and Transplantation, National Institute of Allergy and Infectious Diseases, National Institutes of Health (NIH), Bethesda, MD; Daniel E. Furst, Division of Rheumatology, Department of Medicine, University of California Los Angeles School of Medicine, Los Angeles, CA; and Richard A. Nash, Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA.

Rheumatology

Philip J. Clements, Division of Rheumatology, Department of Medicine, University of California Los Angeles School of Medicine, Los Angeles, Calif; Ga-bor G. Illei, National Institute of Dental and Craniofacial Research, NIH, Bethesda, MD; Jacob M. van Laar, Department of Rheumatology, Leiden University Medical Center, Leiden, The Netherlands; Maureen D. Mayes, Division of Rheumatology, Department of Medicine, University of Texas—Houston Health Science Center, Houston, TX; Samuel Strober, Departments of Immunology and Rheumatology, Stanford University School of Medicine, Stanford, CA; and Alan Tyndall, Department of Rheumatology, Felix-Platter Spital, Basel, Switzerland.

Neurology and Neurologic Imaging

Jacqueline Chen, Magnetic Resonance Spectroscopy Unit, Montreal Neurological Institute and Hospital, McGill University, Montreal, Canada; Samia J. Khoury, Department of Neurology, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA; Paolo A. Muraro, Neuroimmunology Branch, National Institute of Neurological Disorders and Stroke, NIH, Bethesda, MD; and Harry Openshaw, Department of Neurology, City of Hope National Medical Center, Duarte, CA (who was unable to attend this workshop but whose symposium discussion was contributory).

Hematopoietic Cell Transplantation

Harold L. Atkins, Blood and Marrow Transplant Programme, Department of Medicine, University of Ottawa, Ottawa, Canada; Stephen J. Forman, Division of Hematology and Hematopoietic Cell Transplantation, City of Hope National Medical Center, Duarte, CA; Alois Gratwohl, Department of Hematology, University Hospital Basel, Basel, Switzerland; Edwin M. Horwitz, Division of Stem Cell Transplantation, Division of Experimental Hematology, Department of Hematology-Oncology, St. Jude Children’s Research Hospital, Memphis, TN; Steven Z. Pavletic, Experimental Transplantation and Immunology Branch, National Cancer Institute, NIH, Bethesda, MD; Ricardo Saccardi, Bone Marrow Transplant Unit, UO Ematologia, Policlinico Careggi, Florence, Italy; Judith A. Shizuru, Bone Marrow Transplantation, Stanford University Medical Center, Stanford, CA; and Keith M. Sullivan, Division of Cellular Therapy, Department of Internal Medicine, Duke University Medical Center, Durham, NC (who was unable to attend this workshop but whose symposium discussion was contributory).

REFERENCES


Linda M. Griffith, MD, PhD
Division of Allergy, Immunology and Transplantation, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD

Steven Z. Pavletic, MD
Experimental Transplantation and Immunology Branch, National Cancer Institute, WG Magnuson Clinical Center, National Institutes of Health, Bethesda, MD

Alan Tyndall, MD
Department of Rheumatology, Felix Platter-Spital, Basel, Switzerland

Alois Gratwohl, MD
Department of Hematology, University Hospital Basel, Basel, Switzerland

Daniel E. Furst, MD
Rheumatology Division, Department of Medicine, University of California Los Angeles School of Medicine, Los Angeles, CA

Stephen J. Forman, MD
Divisions of Hematology and Hematopoietic Cell Transplantation, and Medical Oncology and Therapeutics Research, City of Hope National Medical Center, Duarte, CA

Richard A. Nash, MD
Clinical Research Division, Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA