



REVIEW ARTICLE

Conference Synopsis: Hematopoietic Stem Cell Therapy in Autoimmune Diseases, October 2001

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ABSTRACT

Since 1996, patients with autoimmune diseases have been treated on single-arm investigational protocols with high-dose immunosuppressive therapy and autologous peripheral blood stem cell transplantation (HSCT). In a conference held in October 2001 at the City of Hope National Medical Center, participants discussed current laboratory studies in autoimmunity, the rationale of HSCT in autoimmune diseases, results of phase I-II studies, and the prospects for controlled trials. This conference synopsis summarizes major discussion points in clinical sessions and in sessions devoted to ethical and regulatory aspects of this investigational treatment. Protocols for controlled studies in multiple sclerosis (MS) and systemic sclerosis (SSc), originating in Europe and in the United States, have been designed or are in the final stages of design. The only controlled trial presently underway is for SSc in Europe (Autologous Stem Cell Transplantation International Scleroderma Trial [ASTIS]). There are current plans for a controlled trial for rheumatoid arthritis (RA) in Europe (ASTIRA) but not in the United States. Eventual cross-study analysis of the European and United States trials may give valuable comparative information on the different mobilization and immunosuppressive regimens used. Recognition of the importance of axonal degeneration in secondary progressive MS and the use of mitoxantrone as a rescue medication are two relatively recent developments now being considered in the design of controlled HSCT protocols in MS. The importance of informed consent and study accessibility was discussed as well as the continuing role of the US Food and Drug Administration in regulating these protocols in the United States.

KEY WORDS

Juvenile idiopathic arthritis • Multiple sclerosis • Rheumatoid arthritis • Systemic lupus erythematosus • Systemic sclerosis

INTRODUCTION

Since 1996, international conferences on hematopoietic stem cell transplantation (HSCT) in autoimmune diseases have been held every 2 years in Basel, Switzerland, under sponsorship of the European Group for Blood and Marrow Transplantation (EBMT) and the European League against Rheumatism (EULAR). As phase I-II studies matured with longer follow-up, the advantage of a meeting in 2001 became apparent, and the EBMT along with the American Society for Blood and Marrow Transplantation (ASBMT) and the Autologous Blood and Marrow Transplant Registry (ABMTR) agreed to cosponsor a meeting in the United States. This conference, Hematopoietic Stem Cell Therapy in Autoimmune Diseases, was held October 4-5, 2001, at the City of Hope National Medical Center in Duarte, California.

The morning sessions were devoted to the topics of immunological tolerance, experimental autoimmunity, and stem cell biology. Speakers included John DiPersio (St. Louis), Garrison Fathman (Palo Alto), Robert Korngold

(Philadelphia), Nora Sarvetnick (La Jolla), Judith Shizuru (Palo Alto), and Kenneth Weinberg (Los Angeles). Richard Burt (Chicago) gave a general talk on future directions of HSCT in autoimmune diseases, and Peter McSweeney (Denver) discussed the potential of nonmyeloablative allogeneic transplantation for autoimmune diseases. Most of the afternoon clinical presentations at the meeting concerned phase I-II feasibility studies of autologous HSCT in autoimmune diseases. Recent reviews have presented the rationale and current results of this treatment [1,2]. Rather than presenting detailed results, this synopsis summarizes major points of discussion of the clinical sessions. Also summarized here are the sessions on ethical and regulatory aspects of HSCT in autoimmune diseases.

MULTIPLE SCLEROSIS

The multiple sclerosis (MS) session began with an introduction to the rationale of high-dose immunosup-

pression with HSCT, presented by Jerry Wolinsky (Houston). This presentation was followed by four reports of clinical results: Athanasios Fassas (Thessaloniki) on the first 85 patients reported to the European (EBMT) registry, Bruce Cohen (Chicago) on 27 patients treated on the Northwestern/ Medical College of Wisconsin protocol, Richard Nash (Seattle) on 26 patients treated by the Seattle group on the protocol originating at Fred Hutchinson Cancer Research Center, and Gianluigi Mancardi (Genoa) on 16 Italian patients followed closely by monthly magnetic resonance imaging (MRI) scans. A detailed report on the first 85 MS patients reported to the EBMT registry is in press [3], and abstracts by the Northwestern, Seattle, and Italian groups have been published subsequent to the meeting [4-6]. Following the clinical presentations, there was a panel discussion that included the presenters along with Donald Paty (Vancouver) and Leslie Weiner (Los Angeles).

Controlled trials are planned both in Europe and in the United States. Drs. Mancardi and Nash presented some details on these planned studies (with the caveat that the protocols for both studies were still in draft form and agreement of all principal investigators involved in protocol designs had not yet been obtained). The studies will probably be similar in terms of criteria for patient eligibility, including Expanded Disability Status Scale (EDSS) scores of 3.5 to 6.0 or 6.5 and probable requirement of documented recent gadolinium enhancement; use of mitoxantrone in the control arm; and population size requirement of 200 or more subjects. Differences in the studies include mobilization and preparatory regimens: granulocyte colony-stimulating factor (G-CSF) plus cyclophosphamide and BEAM (BCNU, etoposide, cytosine arabinoside, and melphalan) with antithymocyte globulin (ATG) in the European study versus G-CSF plus prednisone and total body irradiation (TBI) plus cyclophosphamide and ATG in the United States study. The United States study will use autologous grafts T-cell depleted by CD34 cell selection. The potential for cross-study comparisons, particularly of the preparatory regimens, was briefly discussed. Comparisons could reasonably be done if the entrance requirements and methods of evaluation were sufficiently similar in the final design of these studies. Mark Freedman (Ottawa) presented a brief report on the recently initiated Canadian phase II study of 24 patients (EDSS score, 3.0-6.0) receiving busulfan and cyclophosphamide conditioning and a doubly T-cell-depleted graft. Patients followed in this study will undergo tests with a panel of immunological assays, including assays with specific myelin antigens.

During Dr. Wolinsky's introduction and the concluding panel discussion, there was discussion of newer developments in understanding MS that have changed the way many neurologists view HSCT now compared to 4 to 5 years ago when the first feasibility studies were initiated. Although there has been evidence for many years of an axonal degenerative process in MS, the importance of this process in terms of progression at the higher EDSS levels has only recently been fully appreciated. Dr. Wolinsky showed an example of progressive destruction of myelin matrix, visible on MRI scans in the absence of gadolinium enhancement, as evidence supporting the likelihood of clinical

progression in the absence of an ongoing systemically initiated inflammatory process. Of course, HSCT may not address this late-evolving noninflammatory aspect of MS. The most appropriate patients for HSCT may be those at lower EDSS levels, at which the inflammatory component of the disease is most active. Unfortunately, of the patients previously treated in feasibility studies, relatively few were at the lower EDSS levels. Also, the view was expressed that the lower the patient score on the EDSS scale, the lower the transplantation-related morbidity and mortality would have to be for an acceptable protocol. Another recent change in MS therapy is the concept of rescue medication (ie, for those patients worsening on the immunomodulators β -interferon or glatiramer acetate) and the availability of a US Food and Drug Administration (FDA)-approved rescue medication, mitoxantrone (generally given at 12 mg/m² every 3 months for 2 years). As presently used, HSCT itself would be considered a rescue treatment, and thus comparison of its effectiveness with that of mitoxantrone, as intended in the planned controlled trials, is appropriate. However, it was pointed out that patients who had undergone prior mitoxantrone treatment would have to be excluded from HSCT studies because mitoxantrone would be the control arm and there is a limitation on the total dose of mitoxantrone because of cardiac toxicity. This exclusion will make recruitment to the HSCT control trials more difficult, especially with the number of investigational studies now adding mitoxantrone to immunomodulators. Finally, the study that led to FDA approval of mitoxantrone for MS (as yet unpublished but available on the FDA Web site) reported a very good response in patient participants during 2 years of treatment and 1 year of follow-up. There are no plans for a repeat study of mitoxantrone; the planned controlled HSCT trials in Europe and the United States may provide the best data to replicate the mitoxantrone results on the FDA Web site.

At the onset of this session, Dr. Wolinsky set out what hurdles, in his opinion, are to be cleared in order for HSCT to be an acceptable therapy for MS. These include a reduction in morbidity and mortality from the initial open-label trials, elimination of central nervous system inflammation, and elimination of the matrix destructive phase of the disease. In addition, for its equivalency to mitoxantrone to be established, HSCT would have to decrease attack frequency at least 70% and decrease sustained EDSS score progression of 1.0 point to 8% of patients at 2 years and 17% at 3 years after HSCT. Few investigators expect mitoxantrone to sustain effectiveness for more than a few years after it is discontinued. Therefore, it will be important for HSCT to have a durable response that stretches well beyond 3 years. The consensus among specialists is that little will be achieved with additional single-arm studies. Controlled trials against mitoxantrone are needed with evaluators blinded to the subjects' treatment group. It will be important for these studies to incorporate early stopping rules for excessive toxicity and differences in early progression. Studies as long as 5 years (ie, 3 years after subjects on the nontransplantation arm complete mitoxantrone) will probably be necessary because the advantage of HSCT over mitoxantrone may be in the durability of the response.

RHEUMATOLOGICAL DISEASES

Ken Kalunian (Los Angeles) reviewed eligibility criteria and results on systemic lupus erythematosus (SLE) patients reported by Traynor [7]. Robert Brodsky (Baltimore) sent an abstract updating results of high-dose cyclophosphamide without autografts in autoimmune diseases [8].

Rheumatologist Walter Barr (Chicago) presented an overview of systemic sclerosis (SSc). This overview was followed by a presentation by J. M. van Laar (Leiden, The Netherlands) of the recently opened (March 2001) European SSc trial (Autologous Stem Cell Transplantation International Scleroderma Trial [ASTIS]) and a review by Keith Sullivan (Durham) of patients treated in the United States on the Seattle consortium protocol [9]. An abstract provided for the meeting by Alan Tyndall (Basel) noted 72 SSc patients have been reported to the EBMT registry. A report on the first 45 SSc registry patients has been published [10]. Data now available on 65 registry patients indicate that these patients have a transplantation-related mortality of 12.5%, decreased from 17% in the first 45 registry patients.

Treatments used in the ASTIS trial included cyclophosphamide and G-CSF for stem cell mobilization and cyclophosphamide (200 mg/kg) plus rabbit ATG (7.5 mg/kg) for conditioning. In contrast, the Seattle consortium uses G-CSF without cyclophosphamide for mobilization and 8 Gy TBI (2 Gy to the lungs), cyclophosphamide (120 mg/kg), and equine ATG (90 mg/kg) for conditioning [10]. The primary end point of the ASTIS trial is time to death or development of persistent heart, lung, or kidney failure within the intended 2-year follow-up period. Treatment for the ASTIS control group is monthly pulsed cyclophosphamide (750 mg/m²) for 12 months. The control study in the United States (which will be sponsored by the National Institutes of Health [NIH]) is still under design, but the expectation is that it will use the Seattle consortium protocol and the same control group treatment of monthly pulsed cyclophosphamide. Both studies will enroll SSc patients with poor prognosis indicators with an anticipated 5-year natural history mortality of 50%. To be eligible, patients must have a disease duration of <3 years (Seattle consortium) or <4 years (ASTIS).

Steven Pavletic (Omaha) presented an update on 6 rheumatoid arthritis (RA) patients treated at Northwestern and Omaha. These patients were initially described in 1999 [11], and now are at 24- to 42-month follow-up. Most patients achieved a major response, according to American College of Rheumatology (ACR) criteria, of 70% to 80% for 6 to 22 months, and after relapse there was a greater tendency to respond to disease-modifying antirheumatoid drugs than before HSCT [12]. Dr. Paul Emery's abstract (Leeds, UK) introduced the planned ASTIRA (Autologous Stemcell Transplantation International Rheumatoid Arthritis) study. This will be a randomized study, under the auspices of EBMT/EULAR, enrolling patients with severe active disease who have had documented failure of methotrexate and/or leflunomide as well as failure of anti-TNF α treatment. The HSCT arm will use unmanipulated grafts, cyclophosphamide, G-CSF mobilization, cyclophosphamide conditioning (200 mg/kg), and posttransplantation maintenance therapy of methotrexate or leflunomide, whereas the non-HSCT arm will use conventional therapy of methotrexate or leflunomide alone. All subjects enrolled will undergo stem

cell collection prior to randomization. The primary end point will be disease activity at 6 months postrandomization, and patients in the nontransplantation arm may proceed to HSCT at this point if the response is inadequate.

Nico Wulfraat (Utrecht) presented an update on the European transplantation results for juvenile idiopathic arthritis (JIA). Twenty-three patients from 4 centers in the Netherlands, Germany, and Belgium have been registered to the EBMT database. For JIA treatment most patients received low-dose TBI (4 Gy) and cyclophosphamide (50 mg/kg per day for 4 days) along with ATG in the preparatory regimen. However, 7 patients undergoing transplantation in Belgium and Germany had cyclophosphamide and ATG without TBI, and all 7 achieved drug-free remission for more than a year. There are concerns of growth inhibition by TBI, but children who achieved remissions with TBI conditioning in Utrecht had impressive growth spurts of 1 to 4 standard deviations. Future studies should assess the need for TBI in the preparatory regimen and the necessity of T-cell depletion of the graft. The regimen used for 18 patients in Utrecht induced a severe CD4 lymphopenia lasting 6 to 12 months and resulted in multiple infectious complications: 10 varicella-zoster virus infections, 2 septicemias, 1 atypical mycobacterial infection, and 1 Epstein-Barr virus reactivation.

ETHICAL AND REGULATORY ASPECTS

HSCT treatment for autoimmune diseases raises several ethical and regulatory issues. David Snyder (Duarte), chair of the ethics committee at the City of Hope National Medical Center, discussed the importance of patient autonomy in making informed decisions. He stressed that an understanding of the potential risks and benefits of this novel therapy is particularly important in illnesses that are non-life-threatening although potentially associated with significant morbidity. With this concept as the central theme, Dr. Snyder reviewed other specific issues in designing clinical trials in autoimmune disease. The acute leukemia historical model of first treating patients at a very late disease stage is likely not to be helpful in treating autoimmune disease, Dr. Snyder noted, because patients with late-stage autoimmune disease, particularly MS, may not benefit; patients with reversible but high-risk disease should be identified. He also emphasized the importance of phase III trials as well as the difficulty in performing them because of the difficulty in guarding against patients' preconceptions, which generally favor the new therapy. The last issue on this topic was that of "justice," ie, balancing interests in new therapies with the appropriate use of limited resources. How should these trials be funded? Do third-party payers have an obligation to underwrite these trials? Such a position is arguable because insurance companies are potential benefactors of decreased long-term health care costs if these therapies are demonstrated efficacious in preventing disability.

In a second session, Mary Horowitz (Milwaukee) interviewed Jeffrey Siegel (Rockville) on the role of the FDA in regulating trials of HSCT for autoimmune disease in the United States. Dr. Siegel is a clinical reviewer in the Division of Clinical Trials at the Center for Biologics at the FDA and is the principal rheumatologist reviewing development of biological therapeutics. He is chair of the FDA Rheumatology

Focus Group and serves as clinical reviewer for many of the Investigational New Drug applications (INDs) for HSCT.

Dr. Horowitz first asked why the FDA has become involved in regulating devices and drugs that are regularly used (without IND) in HSCT for malignancies. Dr. Siegel explained that in many instances these devices and drugs are approved, but not for treating autoimmune disease. Although the FDA does not in general regulate the practice of medicine, ie, off-label use of many approved drugs, it does have an important role in regulating use of products for new indications when there are significant safety concerns. Because HSCT carries substantial risk of early treatment-related mortality, its use in autoimmune diseases, in which early mortality is unusual, warrants careful scrutiny and regulation, ie, procedures to obtain proof of safety and efficacy. Dr. Siegel also commented that there is FDA regulation of HSCT just as there is FDA regulation of blood banking and blood products. The level of regulation depends on the level of concern regarding transmission of communicable disease, processing, and clinical safety and efficacy. Detailed FDA regulations regarding use of other than manipulated hematopoietic stem cells for nonhomologous uses are in final stages of preparation.

Dr. Horowitz asked about the perceived pressure from the FDA for randomized study designs (phase III studies) in evaluating the use of HSCT in treating autoimmune diseases, despite limited phase II data in this setting. Dr. Siegel commented that the push for randomized studies comes out of concerns that HSCT can be highly toxic and its benefits are not yet proven to outweigh its risks. Faced with a rapidly increasing number of uncontrolled studies, the FDA felt that data to address this risk versus benefit question would not be forthcoming in a timely manner. However, Dr. Siegel agreed that in some (but not all) diseases, the data are not sufficient to adequately plan large phase III trials and that there is a role for moderately sized randomized phase II trials to estimate effect sizes and learn more about the appropriate HSCT regimens to take to phase III trials. Dr. Siegel pointed out that many pharmaceutical trials randomize even at the phase I level so that risk/benefit ratio can be more accurately and efficiently estimated.

In response to a question as to what would constitute adequate control groups and control therapies, Dr. Siegel said that for many studies the control group would not have to receive a single strictly controlled non-HSCT regimen but, rather, could be randomized to “standard of care” or some other non-HSCT experimental treatment. If a primary end point for the study could be chosen that demonstrated success or failure in a reasonable time frame, patients failing to respond to therapy in the control group could be offered HSCT. On the other hand, if it is possible to identify a patient population that has a uniformly poor outcome (high mortality) with standard therapy, a nonrandomized design might be acceptable. Getting agreement on patient characteristics that define such a group is often difficult in the diseases under consideration—and these patients may not be the ones most likely to benefit from HSCT. In the absence of defined groups with uniformly poor prognosis, success or failure of the treatment may be determined to a large extent by patient selection practices. Control groups determined by lack of insurance or refusal of the therapy

may be biased. Use of disease-based databases with detailed patient data may be acceptable in some instances for evaluation of phases I or II level data.

FDA-regulated studies carry a high burden of reporting requirements for adverse events. Dr. Horowitz commented that HSCT is an aggressive therapy for which certain adverse events are expected, eg, febrile neutropenia, platelet transfusion requirement, intravenous catheter infections. Dr. Siegel stated that adverse events must indeed be recorded and reported, although expedited reporting, which is the most burdensome, is required only for unexpected serious or life-threatening events. If an event is listed as expected in the investigators’ brochure, it does not need expedited reporting, and the level of reporting detail required is less. Dr. Horowitz pointed out that recording events for reporting, whether immediate or delayed, is time-consuming and costly even if the events are expected. She noted that modified requirements for HSCT studies have been discussed in several forums.

Dr. Horowitz asked about the respective roles of the NIH and the FDA in reviewing and approving studies. Dr. Siegel noted that the NIH funds studies, and the studies for which it provides funding must have NIH approval for the study design. The FDA makes sure that studies meet regulatory standards. The FDA approves studies when patient safety is adequately protected and the trial is adequately designed to meet its goals of proving safety and efficacy. Dr. Siegel suggested that investigators involve the FDA early in designing studies so that designs unlikely to be approved on regulatory grounds are not pursued.

CLINICAL PARTICIPANTS

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