Foreword

The rationale for pursuing hematopoietic stem cell transplantation (HSCT) in patients with rheumatoid arthritis (RA) evolved from evidence of a poor prognosis in selected RA patients and from the increased safety of transplants. By analogy with lymphoma patients, where a "bad lymphocyte" perpetuates the disease, it was hoped that high dose chemotherapy and autologous HSCT would be sufficiently powerful to eliminate the disease process and establish or prolong cures. The newly reconstituted hematopoietic stem cell derived immune system would undergo tolerance induction and not attack the host.

In spite of more persuasive evidence from hematological malignancies showing higher curative potential with transplantation of allogeneic bone marrow cells, the concerns of higher toxicity of allogeneic transplantation persuaded investigators in the late 1990s to adhere to the much safer autologous stem cell transplantation techniques. In March 2000, barely three years after the first successfully transplanted case of RA was published in *Lancet*[1], a group of clinical investigators interested in this field met in Anaheim, California. At that time evidence of safety and promising early efficacy of high dose cyclophosphamide based regimens was already becoming evident, and more than 70 patients with RA had received autologous HSCT worldwide. Several centers were in the final phases of completing their pilot trials, and etanercept and infliximab were both approved in the USA. It was time to summarize the field and answer questions: (1) What did trials of autologous HSCT in RA show? (2) Which patients should be transplanted? and (3) How should future transplantation studies for RA be designed?

Several conclusions emerged from the meeting. First, autologous transplants for RA are feasible, with no transplant related deaths described using the 200 mg/kg cyclophosphamide based preparative regimens. Second, the majority of transplanted patients who failed numerous prior disease modifying antirheumatic drug (DMARD) regimens achieved major responses at three months post-transplantation, typically in the range of 50–70% by American College of Rheumatology criteria. Third, many patients developed further synovitis within the first year post-transplant. Some of them improved spontaneously and many after successful reintroduction of DMARD to which they had previously been nonresponsive. Nevertheless, rapid and frequent recurrence of RA remains the major barrier for wider implementation of autologous HSCT in RA: few patients continue to enjoy the benefit beyond 2 years post-transplant. HSCT procedure engages major financial and human resources. Although some patients perceive short-time post-transplant improvements as very important, only more prolonged benefits from transplantation would justify such investments.

Several strategies that have been advocated to capitalize on the current safety and early efficacy observed in pilot studies of HSCT for RA are discussed in this supplement: (1) Engineering of the stem cell grafts; (2) introduction of early DMARD maintenance immediately after transplant; (3) intensification of preparative regimens to achieve more myeloablation or selective lymphoablation; and (4) nonmyeloablative allogeneic stem cell transplantation.

These are challenging times; there is lots of work to be done. Autologous HSCT techniques are safe but may not be ultimately effective. A better understanding of RA pathophysiology is necessary to define desirable immunological goals after autologous HSCT. The transplant procedure itself may represent an opportunity to study the immunological forces that drive the RA process. Nonmyeloablative allogeneic stem cell transplant (NST) techniques have been evolving over the last 3 years and have unequivocally pushed allogeneic transplantation related mortality in hematological malignancies down to only 10%. The predefined transplantation related mortality threshold to allow these procedures in RA should not be higher than 5%. With further improvements in NST techniques this goal will be achievable in the near future.

Needless to say, RA is a common disease, and about 10% of RA patients continue to have a desperate need for better and more definitive therapies. The advent of tumor necrosis factor blockers and future biologicals is unlikely to fundamentally change this fact[2]. Today's science of hematopoietic stem cell transplantation in concert with the emerging technologies may offer promising answers for selected patients with severe RA.

This supplement summarizes meeting presentations updated by the authors to reflect the situation as of March 2001. To tie the current status of the field to the future we added reviews on preparative regimens (Kashyap, *et al*) and on future trends (Burt, *et al*).

So what is next? Following this supplement we await the EBMT guided international project and the Australian randomized trial, which are on the same mission of propagating the message of safety and early efficacy of HSCT for RA. This is an interdisciplinary area of collaboration and the success will depend on the ability to identify groups of dedicated hematologists and rheumatologists willing to work together.

The rheumatology community is correctly cautious concerning the current achievements in the field of transplantation for RA. However, there is probably an information gap and some prejudice about the safety and aggressiveness of the transplantation techniques. This can be overcome only by intensifying the communication between experts. Next steps in the use of HSCT for RA include prospective randomized phase III studies as proposed in Europe (ASTIRA Trial) and

several innovative pilot studies proposed by US investigators. Internationally designed data collection forms exist and data must be reported to EBMT (outside North and South America) or IBMTR registries. We propose that any future meeting on RA and transplantation should focus only on planning specific studies based on the collective experience obtained so far.

ACKNOWLEDGMENT

The editors would like to thank all contributors for their enthusiasm and for making this publication possible.

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Special IBMTR/ABMTR Workshop on the Role of Hematopoietic Stem Cell Transplantation for Rheumatoid Arthritis

Anaheim, California, USA
March 26, 2000

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Supported through unrestricted educational grants from SuperGen,
Amgen, and Aventis Pharmaceuticals

ACKNOWLEDGMENT

The Co-Chairmen of the Special IBMTR/ABMTR Workshop on the Role of Hematopoietic Stem Cell Transplantation for Rheumatoid Arthritis would like to thank the following companies for their generous support.

Amgen

Aventis Pharmaceuticals

Nexell Therapeutics, Inc.

Pharmacia & Upjohn

Sangstat Medical Corporation

Supergen

For inspiring and supporting this workshop special thanks to:

The International Bone Marrow Transplant Registry

The Autologous Blood & Marrow Transplant Registry, and

Mary Horowitz, MD, MS,

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