The BMT Data Book

Including Cellular Therapy

Third edition

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Contents

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Foreword

It is over 50 years since the basic concepts underpinning bone marrow transplantation were revealed in radiation protection experiments in mice. It seems curious now that in the 1950s the idea that marrow cells could grow and reconstitute hematopoiesis in an irradiated recipient was so revolutionary that it took a series of critical experiments to prove the "cellular theory" and disprove the "humoral theory" of radiation protection. Equally remarkable is the fact that within a few years (and at a time when our knowledge of lymphocytes was sketchy) the unique allotransplant-associated phenomena of graft-versus-host disease, graft rejection, and graft-versus-leukemia effects were teased out, paving the way for human transplant studies in the 1960s.

Fast forward to today, bone marrow transplantation has become stem cell transplantation (SCT), incorporating the use of umbilical cord and peripheral blood as stem cell sources. The complexity of the field has increased exponentially as transplant biology is defined increasingly at the molecular level. SCT or HCT (hematopoietic cell transplantation) is continually being extended to new malignant and nonmalignant diseases and is increasingly used because more unrelated donors and cord blood donations are available, and mismatched transplants can be performed more safely. Currently, over 25 000 SCTs are performed annually in over 70 countries. As confidence to deliver transplants with low mortality has grown, SCTs are being applied increasingly to older patients. Luckily, expertise in the clinical transplant community has kept pace with this expansion. There has been an overall increase in transplant "know how" and many procedures and approaches are standardized worldwide. To maintain our standards of care at the cutting edge, clinicians need a reference volume for the many algorithms of treatment we now handle in treating our patients. The editors of *The BMT Data Book*, Drs Munker, Hildebrandt, Lazarus, and Atkinson, have striven to produce a book that fulfills the stem cell transplanter's need for a practical guide and data source. Particularly, attention has been given to the practical issues of who should have a transplant and what type of transplant approach should be chosen.

However, no medical discipline can afford to stand still and textbooks must also move with advances or perish. SCT is no exception–in fact, there is a sense that the pace of development, both in new concepts and new clinical practice, has quickened in the last decade. In particular, improvements in transplant and nontransplant approaches, which are never in step with each other, have altered the indications for transplant. There has been ever-increasing use and success of umbilical cord blood transplantation and the emergence of safer regimens for haploidentical transplants. Progress has also been made in cell therapy with the use of mesenchymal stromal cells and regulatory T-cells to treat graft-versus-host disease and antigen-specific T-cell lines to treat viral infections. The third edition of this volume, therefore, is both timely and necessary. The editors have excelled in updating the indications for transplantation and incorporating the newest developments into this completely updated book.

So let us welcome this new edition of *The BMT Data Book Including Cellular Therapy*. It will continue to serve the stem cell transplantation community well and will play its part in the constant honing of our clinical practice so as to deliver the best and most advanced care to our patients.

John Barrett
Bethesda, MD

Preface

The last 15 years have seen a major change, expansion, and improvement in the discipline of clinical bone marrow and blood stem cell transplantation. Unifying bone marrow and peripheral blood stem cell transplants, the term hematopoietic cell transplantation has been proposed. New data have become available to support the decision for or against transplantation. The future has started already. Basic science has made progress: new genes and microRNAs have been characterized as risk factors in the outcomes of hematologic malignancies. The involvement of natural killer cells in the graft-versus-tumor reactions has been recognized. New cell populations like dendritic cells and mesenchymal stem cells have been characterized. Clinical science has made progress. New indications for transplants have been developed and evaluated. Examples are renal cell cancer, autoimmune disorders, and amyloidosis. New stem cell sources (e.g., from cord blood) were implemented. Owing to sophisticated typing methods, unrelated transplants have become safer. Because of increased donor numbers, matched unrelated transplants can now be offered to more than 70% of patients who do not have a family match. Old indications (breast cancer) have become obsolete or are being reevaluated (chronic myelogenous leukemia) because of advances in the nontransplant arena. In the first edition of this book, transplant for multiple myeloma was put into context against "conventional" treatments. Now, autologous transplant has become the standard of care for multiple myeloma, which has to compete and will join forces with antiangiogenic agents or proteasome inhibitors. New treatment protocols for older patients or those who have significant comorbidities were introduced (reduced-intensity conditioning).

Overall, in the United States more than 17 000, in Europe more than 30 000, and in Australia 1200 hematopoietic stem cell transplants are being performed each year. In addition to Europe and North America, South America, Mexico, China, and India have all started active transplant programs. The registry data evaluating the outcomes of autologous and allogeneic transplants now are based on thousands of patients instead of hundreds of patients. Therefore, in many instances, the promise of cure is being replaced or is supported by realistic long-term survival data.

Reacting to these many new developments, we decided to publish a third edition of *The BMT Data Book*. The basic structure is conserved. In the first section, the global trends in hematopoietic cell transplantation, the biology of stem cells, and the science underlying transplantation are discussed. Next, the indications for transplant in different diseases (malignant and non-malignant) are given. Pediatric aspects are noted when indicated. In a new chapter, pediatric neurologic and metabolic disorders treated with transplant are discussed. We review in detail the established and novel cellular therapies. Coauthors specialized in different areas have made contributions. All chapters are concise. The nontransplant options are mentioned briefly. Registry data are given when available. As in the first two editions, major articles from respected journals were chosen for each topic and with the permission of the authors, some figures were reproduced. These articles not only support our recommendations but also illustrate current controversies. In the other two major sections, the practical aspects and the complications of allogeneic and autologous transplantation are discussed. The "BMT pharmacopoeia" is updated with many new drugs, whereas standard-dose protocols (available in other textbooks) were removed. Finally,

current transplant protocols and certain aspects of laboratory medicine are included. As in the second edition, *The BMT Data Book* has a guide to the internet and printed databases. This book is a work in progress. Owing to the enormous amount of literature and information available, it cannot be 100% complete or free from errors. However, we hope, by providing recent and solid data, to help the physicians and patients to make informed decisions and choose the best individual treatment.

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Preface to the first edition

The use of hemopoietic stem cell transplantation to support high-dose chemotherapy or chemoradiotherapy is rapidly developing and fast changing. During the 1980s and 1990s, many marrow transplantation physicians had to start treating diseases they may not have treated for many years. Examples would be the use of autologous transplantation for breast, testicular, and ovarian cancer. Likewise, medical oncologists had to start becoming familiar with marrow and blood stem cell transplantation medicine.

In addition, effective new nontransplant treatments were introduced and made therapeutic decision making for an individual patient even more difficult. Examples included α-interferon for chronic myeloid leukemia and fludarabine for chronic lymphatic leukemia and low-grade non-Hodgkin lymphoma.

All this change occurred against a background of shrinking hospital budgets and an increasing concern for cost constraint.

These elements spurred the production of this book. Many long but useful hours were spent arguing such issues for individual patients in the weekly meeting of the marrow transplant program at St. Vincent's Hospital. It became clear that "change" was becoming the norm and marrow transplant physicians, like everyone else, had to adapt quickly. It thus seemed important to provide data-driven outcome analyses to help therapeutic decision making for individual patients.

Kerry Atkinson

Disclaimer: As in the first two editions, the authors have attempted to provide the most accurate data and guidance possible. We recognize, however, that there may be unforeseen errors in drug dosage and modification recommendations. We always encourage treating physicians and their staff to consult the original source documents when developing specific treatment plans.

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