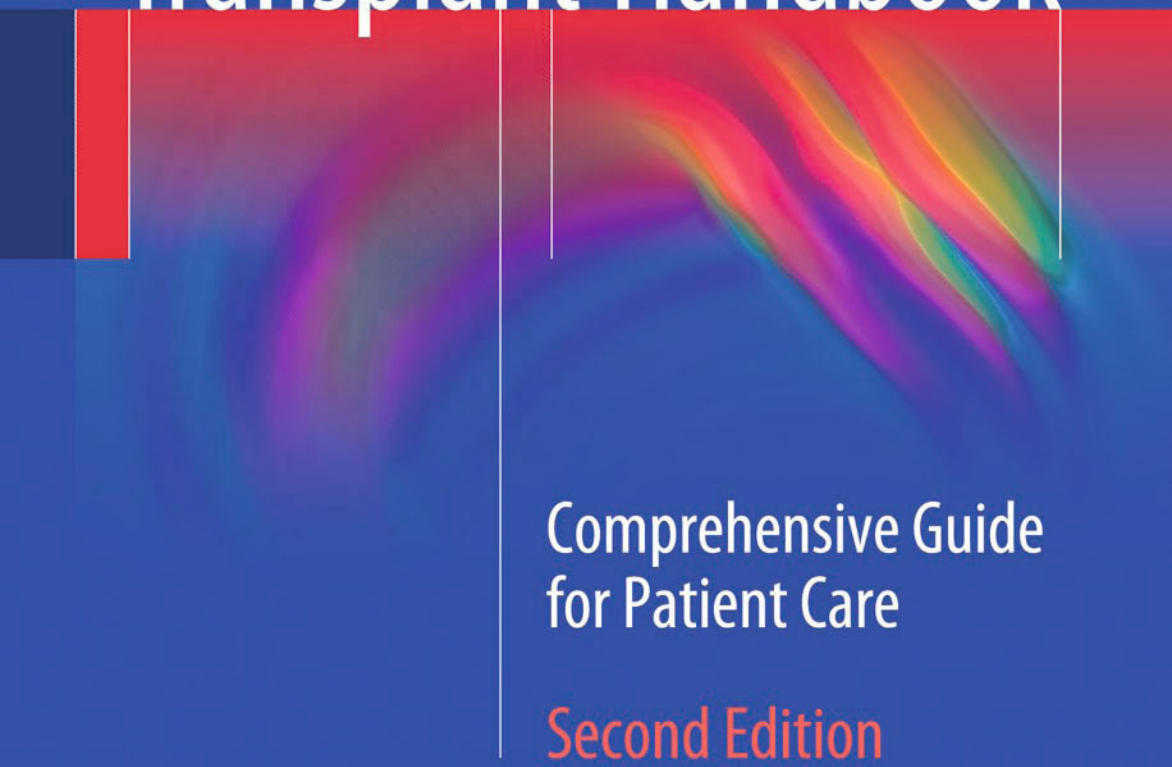
Richard T. Maziarz
Susan Slater *Editors*

Blood and Marrow Transplant Handbook



Comprehensive Guide for Patient Care

Second Edition

Springer

Blood and Marrow Transplant Handbook

Richard T. Maziarz • Susan Schubach Slater
Editors

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Editors
Richard T. Maziarz
Center for Hematologic Malignancies
Adult Blood and Marrow Stem Cell
Transplant Program
Knight Cancer Institute
Oregon Health & Science University
Portland, OR, USA

Susan Schubach Slater
Center for Hematologic Malignancies
Adult Blood and Marrow Stem Cell
Transplant Program
Knight Cancer Institute
Oregon Health & Science University
Portland, OR, USA

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Introduction and Acknowledgments

Hematopoietic stem cell transplantation has experienced a dramatic increase of activity over the past decade with a continued marked escalation of procedures projected over the next 10–15 years. This expansion is not only a reflection of an ever-changing field with increasing demand but also the pursuit of innovation that contributes to continued improved outcomes with less risk of adverse events or deleterious long-term consequences for the transplant patient population. Cellular therapy is a dynamic field. It requires multispecialty input for the management of these complex patients. In the past, transplantation was the sole responsibility of a few academic centers and information resided within the hands of a few individuals. However, with the dissemination of technology and the ongoing proliferation of these procedures, there has been an obligatory need for the development of tools to provide standard guidelines and algorithms for the management of patients.

Most institutions have established their own set of guidelines and recommendations designed for consensus management as patients are in constant need of shared care. As new workforce demands have emerged, there have been changes in the workplace with ongoing predictions of a marked shortage of transplant-trained physicians, advanced practice providers, nurses, and pharmacists. Efforts to recruit health care providers to this field are paramount to continue to provide day-to-day care of the transplant patient. In light of these changes, it becomes imperative to provide detailed and shared consensus guidelines to achieve the best outcomes for our patients.

This guide to patient management is the product of 20 years of evolution of patient care at our institution. Wherever possible, the information herein has been altered to reflect the multiple options that exist for treatment of various conditions. However, *it is not meant to define the exact care pathway for all patients*. Rather, we have provided a practical set of guidelines that can be shared across institutions. This effort is our contribution to the workforce shortage for transplant providers. By providing an easy-to-use manual that covers the basics of care of the stem cell transplant patient which can be utilized to educate junior faculty, physician assistants, nurse practitioners, residents, fellows, and other providers that may be recruited to the day-to-day care of the patient, we have achieved our goal. As this second edition demonstrates, this pocket guide remains a work in progress, and we anticipate that

as time passes, even potentially quite quickly, a new set of guidelines will need to be generated.

We recognize that this manual is incomplete. We do not discuss graft engineering or stem cell expansion approaches to any great degree. We are not addressing the nuances of haploidentical transplantation or other therapies that remain in clinical trial development and are only now emerging into the clinical arena. Nor are we talking about regeneration medicine, its futures, and its overlap with hematopoietic stem cell transplantation. Rather, we provide information about standards of care and assimilate knowledge gained from others.

The work presented within this volume represents not the work of a few but the work of many. A number of our authors were members of the team that helped to create our institution-specific consensus guidelines. We have also recruited new members to assist in generating these ever changing set of standards. We wish to thank the many contributors, as well as our mentors and colleagues who have inspired us to pursue this field and who have provided us with the energy to make this contribution. Their contributions to our program cannot be underestimated. In addition, we thank our team of dedicated nurses, social workers, CMAs, CNAs, physical therapists, nutrition specialists and all providers that are present at the patients' bedside. We also thank our collaborating community partners: referring physicians, advanced practice providers and nurse coordinators. Finally, we acknowledge the national and international efforts focused on improving patient outcomes through organizations such as ASBMT, EBMT, NMDP, BMT CTN, FACT, JACIE, ISCT, AABB, CBMTG, APBMT, WBMT, SBTMO, and others. Through collaboration and shared information, we hope to assure the best outcome of our patients as they return to their communities across the country.

Richard T. Maziarz
Susan Schubach Slater

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Contributors

Peggy Appel, MHA Northwest Marrow Transplant Program, Oregon Health & Science University, Portland, OR, USA

Alan F. Barker, MD Pulmonary and Critical Care Medicine, Oregon Health & Science University, Portland, OR, USA

Jonathan Brammer, MD Division of Cancer Medicine, Dept. of Stem Cell Transplantation and Cellular Therapy, MD Anderson Cancer Center, Houston TX

Joseph S. Bubalo Pharmacy Services, Oregon Health & Science University, Portland, OR, USA

Andy Chen, MD, PhD Center for Hematologic Malignancies, Knight Cancer Institute, Oregon Health & Science University, Portland, OR, USA

Stanley Chou, MD Cedars-Sinai Heart Institute, Cedars-Sinai Medical Center, Los Angeles, CA, USA

Erin Corella, PharmD, BCPS, BCOP Pharmacy Services, Oregon Health & Science University, Portland, OR, USA

Thomas DeLoughery, MD Divisions of Hematology/Oncology and Laboratory Medicine, Oregon Health & Science University, Portland, OR, USA

Tonja Dirkx, MD Portland Veterans Administration Medical Center, Oregon Health & Science University, Portland, OR, USA

Stacey Evert, RD, CSO, LD Food & Nutrition Services, Oregon Health & Science University, Portland, OR, USA

James Gajewski, MD Center for Hematologic Malignancies, Adult Blood and Marrow Stem Cell Transplant Program, Knight Cancer Institute, Oregon Health & Science University, Portland, OR, USA

Marc Gosselin, MD Diagnostic Radiology, Oregon Health & Science University, Portland, OR, USA

Amy Guthrie , MSN, CNS, ACHPN Taussig Cancer Institute-Cleveland Clinic, Cleveland, OH, USA

Lisa Hansen, RN, MS, ONS, AOCN Autologous Stem Cell Transplantation, Legacy Good Samaritan Hospital, Portland, OR, USA

Brandon Hayes-Lattin, MD Center for Hematologic Malignancies, Adult Blood and Marrow Stem Cell Transplant Program, Knight Cancer Institute, Oregon Health & Science University, Portland, OR, USA

Stephen B. Heitner Knight Cardiovascular Institute, Oregon Health & Science University, Portland, OR, USA

Shernan Holtan, MD Division of Hematology, Oncology, and Transplantation, University of Minnesota, Minneapolis, MN, USA

Carol Jacoby, MSN, ACNP-AC Center for Hematologic Malignancies, Adult Blood and Marrow Stem Cell Transplant Program, Knight Cancer Institute, Oregon Health & Science University, Portland, OR, USA

Keren McCord, MSW, LCSW, OSW-C Center for Hematologic Malignancies, Adult Blood and Marrow Stem Cell Transplant Program, Knight Cancer Institute, Oregon Health & Science University, Portland, OR, USA

Jose F. Leis, MD, PhD Adult Blood and Marrow Transplant Program, Mayo Clinic, Phoenix, AZ, USA

Marlise R. Luskin, MD Division of Hematology/Oncology and the Abramson Cancer Center, Perelman School of Medicine at the University of Pennsylvania Medical Center, Philadelphia, PA, USA

Ashley Manning, PA-C Center for Hematologic Malignancies, Adult Blood and Marrow Stem Cell Transplant Program, Knight Cancer Institute, Oregon Health & Science University, Portland, OR, USA

Richard T. Maziarz, MD Center for Hematologic Malignancies, Adult Blood and Marrow Stem Cell Transplant Program, Knight Cancer Institute, Oregon Health & Science University, Portland, OR, USA

Gabrielle Meyers, MD Center for Hematologic Malignancies, Adult Blood and Marrow Stem Cell Transplant Program, Knight Cancer Institute, Oregon Health & Science University, Portland, OR, USA

Lyudmila Morozova, MD Radiology Specialists of the Northwest, Providence Health Services, Portland, OR, USA

Bart Moulton Pulmonary and Critical Care Medicine, Oregon Health & Science University, Portland, OR, USA

Sara Murray, BS, DAS Center for Hematologic Malignancies, Hematopoietic Cell Processing Laboratory & Unrelated Donor Program, Knight Cancer Institute, Oregon Health & Science University, Portland, OR, USA

Nancy Boyle, MSW, LCSW, OSW-C Center for Hematologic Malignancies, Adult Blood and Marrow Stem Cell Transplant Program, Knight Cancer Institute, Oregon Health & Science University, Portland, OR, USA

Eneida R. Nemecek, MD Pediatric Blood and Marrow Transplantation, Doernbecher Children's Hospital, Portland, OR, USA

Jennifer Pidkowicz, BSKine, MSOT, OTR/L Department of Rehabilitation, Oregon Health & Science University, Portland, OR, USA

David L. Porter, MD Division of Hematology/Oncology and the Abramson Cancer Center, Perelman School of Medicine at the University of Pennsylvania Medical Center, Philadelphia, PA, USA

David Schiff, MD Department of Neurology, Neurological Surgery, and Medicine (Hematology/Oncology), Neuro-Oncology Center, University of Virginia Health System, Charlottesville, VA, USA

Susan Schubach Slater Center for Hematologic Malignancies, Adult Blood and Marrow Stem Cell Transplant Program, Knight Cancer Institute, Oregon Health & Science University, Portland, OR, USA

Mary Denise Smith, MSN, ONS, ACHPN Palliative Medicine/Comfort Care Team, Oregon Health & Science University, Portland, OR, USA

Leon Speroff, MD Department of Obstetrics and Gynecology, Oregon Health & Science University, Portland, OR, USA

Lynne Strasfeld, MD Division of Infectious Diseases, Oregon Health & Science University, Portland, OR, USA

Jennie W. Taylor, MD Division of Hematology/Oncology, Department of Neurology, Stephen E. and Catherine Pappas Center for Neuro-Oncology, Massachusetts General Hospital Cancer Center, Boston, MA, USA

Kimberly Brennan Tyler, MSN, ANP-BC Center for Hematologic Malignancies, Adult Blood and Marrow Stem Cell Transplant Program, Knight Cancer Institute, Oregon Health & Science University, Portland, OR, USA

Kevin C. J. Yuen, MBChB, MD, FRCP (UK) Swedish Pituitary Center, Swedish Neuroscience Institute, Seattle, WA, USA

Part I
The Nuts and Bolts of Stem Cell Transplantation

Chapter 1
Overview of Hematopoietic Stem Cell Transplantation

Richard T. Maziarz

Hematopoietic stem cell transplantation (HSCT) is currently a standard-of-care procedure for many disorders. Frequently, HSCT procedures are curative in situations where no other curative treatment options exist. Specifically, the key element in HSCT as a therapy is the replacement of the host (recipient) marrow function by another source of hematopoietic stem cells (HSC). These sources could include HSC collected from the patient (autologous) or from another individual (allogeneic). Allogeneic sources include family-related or unrelated products, collected either directly from healthy donors or cryopreserved stem cell products, including umbilical cord blood. A few rare patients have a syngeneic (identical twin) donor. In the setting of allogeneic HSCT, products are preferentially matched at major histocompatibility complex (MHC) human leukocyte antigen (HLA) class I and II molecules located on chromosome 6, which guide immunologic recognition as self or nonself. Advances in immunogenetics and immunobiology, conditioning regimens, disease characterization and risk stratification, immune suppression, antimicrobials, and other types of supportive care have all contributed to improvements in disease control and overall survival. These outcomes have resulted in a marked increase in the number of procedures performed annually worldwide. However, it is critical to always recognize that HSCT requires substantial resources. Thus delivering this therapy requires large multidisciplinary teams of nursing, pharmacists, physicians, social workers, nurse practitioners, physician assistants, nutrition experts, and occupational and physical therapists, in addition to specialized facility and technical resources.

HSCT has been developed over the past 50–60 years since the first human clinical experimental transplants were performed in the 1950s. One of the earliest curative allogeneic bone marrow HSCT procedures transplant was performed in a young child with immune deficiency syndrome in 1968. By the early 1980s,

R. T. Maziarz (✉)
Center for Hematologic Malignancies, Adult Blood and Marrow Stem Cell Transplant Program, Knight Cancer Institute, Oregon Health & Science University, 3181 SW Sam Jackson Park Road, UHN 73C, Portland, OR 97239, USA
e-mail: maziarzr@ohsu.edu

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bone marrow transplantation was no longer considered experimental but as the standard of care for a variety of disorders including acute and chronic leukemia, aplastic anemia, lymphoma, multiple myeloma, and a number of inherited disorders including severe combined immune deficiency, thalassemia, and other inborn errors of metabolism. With this recognition, the utilization of this procedure rapidly increased to the current state where over 50,000 procedures are performed worldwide each year as estimated by the Center for International Blood and Marrow Transplant Research (CIBMTR).

1.1 Key Principles

1. Bone marrow stem cells are capable of repopulating all hematopoietic and lymphocytic populations while maintaining capacity for self-regeneration, assuring long-term immunologic and hematopoietic viability.
2. Allogeneic HSCT achieves two goals: replacement of host HSC pools after conditioning and establishment of the donor immune system, either by expansion of naïve immune progenitors or by adoptive transfer of mature donor immune cells.
3. Treatment of nonmalignant disorders is directed at stem cell or immune system replacement while the treatment of malignant disorders requires both replacement of an underlying stem cell or immune system and eradication of malignancy.
4. The decision to use high-dose myeloablative chemoradiotherapy is based upon the identification of malignancies that (a) have a therapy sensitivity threshold that can be overcome and/or (b) have a short enough doubling time to allow the greatest number of malignant cells to be impacted by the conditioning regimen.
5. Conditioning agents whose dose-limiting toxicity is hematologic in nature are primarily selected for myeloablative chemotherapy.
6. Organ-specific toxicities can be experienced and represent “collateral damage” of myeloablative chemoradiotherapy, thus necessitating the need for evaluation of organ function reserve prior to HSCT.
7. The benefits of autologous HSCT are dependent upon dose escalation of conditioning regimens.
8. Graft-versus-host disease (GVHD) after allogeneic HSCT may be a consequence of the transfer of a competent donor immune system that recognizes host target antigens.
9. Prophylaxis for GVHD with immune suppressive medications is warranted in nearly all standard allogeneic HSCT settings.
10. GVHD can be eliminated by depletion of mature T cells from the donor allograft.
11. Depletion of mature T cells from an allograft is associated with an increased risk of relapse of the underlying malignancy.

12. In T cell replete allografts, the occurrence of GVHD has been associated with immunologic-based graft versus leukemia (GVL) therapeutic benefit and can be directly linked to improved survival. As populations of T cells are selectively separated, the relationship may become less linked.
13. The emergence of reduced intensity and nonmyeloablative allogeneic HSCT is the direct result of an effort to maximize the immunologic GVL effect while minimizing risk of regimen-related morbidity and mortality.
14. Patient selection influences outcomes; patients with better overall functional performance status, limited comorbidities and underlying organ damage, and stronger support systems have superior outcomes.

The material included within the following chapters of this patient management handbook provides details that substantiate these principles.

1.2 Research Efforts in HSCT

The success of HSCT has its origins in the research laboratories and clinical research units of many worldwide institutions. The HSCT community has also had the foresight to track outcomes of recipients in center-specific databases and in registry databases, which have been instrumental in providing opportunities for ongoing research. However, it is also recognized that HSCT patients still face significant morbidity and mortality substantiating the continued need for ongoing research. There have been measurable improvements in survival despite the growing number procedures performed in older patients and patients with preexisting comorbidities. However, there remains room for improvement.

Much of the material within this handbook reflects established standards of care of management in the HSCT patient. However, the field demands more. There are many areas of active research including new conditioning regimens, new immune suppressive approaches, vaccines (both prior to and after HSCT) focused at infectious pathogens as well as the primary malignancy, T regulatory cells, new indications for HSCT such as autoimmune disease or sickle cell disease, applications of natural killer cells, novel stem cell mobilization agents, and continued improvement in supportive care. Recently, the American Society for Blood and Marrow Transplant (ASBMT) published a set of research priorities to assist in the focus of attention to those fields that are most likely to lead to continued development of hematopoietic cellular therapy.

These include:

1. Stem cell biology
    a. Cell manipulation
    b. Stem cell sources
    c. Inducible pluripotent stem cells
    d. Cancer stem cells

2. Tumor relapse
    a. Prevention of and therapy for post-HSCT relapse
    b. Immunotherapy with T cells and dendritic cells
3. GVHD
    a. Separation of GVHD and graft-versus-tumor effects
    b. Immune reconstitution and GVHD
    c. Biomarkers predicting GVHD
    d. Role of regulatory T cells
4. Applying new technology to HSCT
    a. Genomics
    b. Proteomics
    c. Imaging
    d. Markers of immunologic recovery
    e. Phamacogenomics
5. Expanded indications for HSCT
    a. Solid tumors
    b. Regenerative medicine
    c. Autoimmune disease
    d. Response to bioterrorism in radiation accidents
6. Survivorship
    a. Long-term complications
    b. Longevity
    c. Quality of life
7. Transplants in older patients
    a. Biology of aging
    b. Indications for transplant
    c. Outcomes and quality of life
8. Improving current use of HSCT
    a. Graft sources
    b. Conditioning intensity
    c. Cost effectiveness

1.3 Horizons/Challenges

HSCT remains an ever-changing field. As described briefly above, these technologies have been applied to thousands of people within dozens of countries. The success of the varied research initiatives will extend these applications to a greater

degree. Currently, the National Marrow Donor Program (NMDP) projects the number of unrelated HSCT procedures to double over the next five years, from current levels of nearly 6000 annually to over 10,000 by 2020. This growth has been multifactorial and is impacted by broader indications, improved supportive care, changing age demographics with increased incidence of cancers reported, and improved survivorship of patients with cardiovascular disease.

With these predictions, one must also be aware that the development of molecular therapeutics may lead to an alternate future. Much of cancer therapy research today is focused on the "personalized" medicine approach in which small molecules that target the multiple signaling pathways might convert life-threatening malignancies to truly chronic diseases. The impact of imatinib mesylate (Gleevec®) on HSCT for chronic myeloid leukemia (CML) is a prime example. Recognizing that the vast majority of patients with CML do not proceed to early HSCT and the prevalence of CML in the general population has increased, patients who now undergo HSCT are those with advanced or resistant disease. Despite this observation, HSCT outcomes for patients with CML remain excellent. Additionally, data are emerging that aggressive pretreatment of Philadelphia chromosome-positive acute lymphoblastic leukemia (ALL) with tyrosine kinase inhibitors (TKI) has actually led to improved outcomes after allogeneic HSCT. Similar observations with autologous HSCT for multiple myeloma have been made. The use of imides and proteasome inhibitors pre-HSCT and as maintenance therapy post-HSCT has led to marked improvements in progression-free survival and, in some studies, observations of improved overall survival. Active studies addressing the role of TKI oral therapy as adjuncts to HSCT for treatment of FLT3-ITD+ acute myeloid leukemia (AML) and chronic lymphocytic leukemia (CLL) are planned and/or underway. As a result, comparative effectiveness and outcomes research will remain essential as we compare HSCT therapies to these new options. The availability of registry databases has been vital for these analyses and will remain critical for the future.

It is not just small molecule therapy that has driven the personalized medicine efforts. One cannot underestimate the potential impact that will emerge from graft engineering efforts in immune mediated therapies. Both humoral and cellular immune systems are being exploited. Bi-specific antibodies and genetically modified T cells are actively being studied, either as a bridge to HSCT or for relapse after HSCT. The resounding success of small institutional investigator-initiated studies of chimeric antigen receptor-modified T cells (CAR-T) used for relapsed/refractory ALL and CLL have launched large multicenter, industry sponsored, as well as National Institutes of Health (NIH)-sponsored clinical trials to further explore these treatments in hematologic malignancies and multiple other disease settings.

However, we must be aware that the increased numbers of patients undergoing HSCT, as well as the observed improvement in survival, will lead to a greater demand for specialists in the field of HSCT. Not only are the patients who undergo HSCT in need of specialized providers, the rapidly expanding population of survivors, particularly those with chronic GVHD, have difficulty finding a medical home with their primary care providers or referring medical oncologists. One potential future is that the comprehensive care delivery systems developed for HSCT patients that resemble a medical home may become a model for other specialties. These

care delivery systems have evolved from capitated-risk contracts for HSCT patients and reflect the need for the mixed team of providers including HSCT physicians, advanced practice providers, nurses, social workers, and cell-processing laboratory technologists along with medical specialty assistance from infectious diseases, critical care, gastroenterology, etc. This evolution of care may become the model for survivor management.

A recent analysis suggested that within the very near future, that there will be a significant shortfall in physicians trained and focused on the care of HSCT patients. Thus, new paradigms must be developed for the delivery of care to the HSCT survivor, including expansion of the advanced practice provider workforce of physician assistants and nurse practitioners, as well as active recruitment of new trainees in the field of hematology and medical oncology. Most importantly, training programs and generation of training tools must be established for a new specialty of primary care providers focused on delivery of chronic care to the cancer survivor. Such a training curriculum for HSCT providers has been developed by the American Society of Blood and Marrow Transplantation (ASBMT) and is available through the ASBMT website (ASBMT.org).

This handbook of blood and marrow HSCT provides the background for medical providers to manage the HSCT recipient. Guidelines are provided for evaluating and selecting the appropriate transplant candidate, recognizing that medical but also socioeconomic factors influence outcomes. Detailed descriptions of appropriate pre-HSCT conditioning as well as identification of key prophylaxis strategies to avoid complications are provided. Supportive care efforts are critical, including appropriate selection of blood products, maintaining nutritional and functional abilities, as well as identifying the appropriate follow-up care for the recipient to minimize complications. However, consequences of the immunologic and chemoradiotherapeutic interventions are expected, and we have provided immediate hands-on, what to do, treatment recommendations for the provider. Finally, information on management of the long-term survivor as well as those that experienced post-HSCT relapse is included.

Management of the HSCT patient has never been accomplished as the effort of a sole individual. There is a saying that “It takes a village to raise a child,” allegedly attributed to an old African proverb. Similarly, a very large and extensive professional community has developed to care for the individual patients. The ASBMT and the European Group for Blood and Marrow Transplantation (EBMT) are two large societies focused at providing the research and educational forums to further the field and have sponsored the two principal professional journals of our field, *Biology of Blood and Marrow Transplantation* and *Bone Marrow Transplantation,* respectively. However, they are not alone. The American Society of Hematology, the NMDP (“Be the Match”), and the Foundation for Accreditation of Cell Therapy (FACT) all have instructional websites and literature that support the efforts. The National Heart, Lung and Blood Institute (NHLBI) and National Cancer Institute-funded Blood and Marrow Transplant Clinical Trial Network (BMT CTN) was created to facilitate the generation of multicenter, transplant-focused trials for the advancement of the field. These professional societies and groups represent our village.

Bibliography

Burns LJ, Gajewski JL, Majhail NS, Navarro W, Perales MA, et al. Challenges and potential solutions for recruitment and retention of hematopoietic cell transplantation physicians: the National Marrow Donor Program's System Capacity Initiative Physician Workforce Group Report. Biol Blood Marrow Transplant. 2014;20:617–21.

Copelan E. Hematopoietic stem-cell transplantation. N Engl J Med. 2006;354:1813–26.

Deeg J, DiPersio J, Young J, Maziarz R, Perreault C, Margolis D, et al. ASBMT policy statement 2009 research priorities. Biol Blood Marrow Transplant. 2009;15:1489–91.

Gajewski J, LeMaistre F, Silver S, Lill M, Selby G, Horowitz M, et al. Impending challenges in the hematopoietic stem cell transplantation physician workforce. Biol Blood Marrow Transplant. 2009;15:1493–501.

Giralt S, Arora M, Goldman J, Lee S, Maziarz R, McCarthy P, et al. Impact of imatinib therapy on the use of allogeneic haematopoietic progenitor cell transplantation for the treatment of chronic myeloid leukaemia. Br J Haematol. 2007;135:461–7.

Horowitz M. The role of registries in facilitating clinical research in BMT: examples from the Center for International Blood and Marrow Transplant Research. Bone Marrow Transplant. 2008;42:S1–2.

Majhail NS, Murphy EA, Denzen EM, Ferguson SS, Anasetti C, Bracey A, et al. The National Marrow Donor Program's Symposium on Hematopoietic Cell Transplantation in 2020: a health-care resource and infrastructure assessment. Biol Blood Marrow Transplant. 2012;18:172–82.

Maus MV, Grupp SA, Porter DL, June CH. Antibody-modified T cells: CARs take the front seat for hematologic malignancies. Blood. 2014;123:2625–535.

Weisdorf D, Carter S, Confer D, Ferrara J, Horowitz M. Blood and marrow transplant clinical trials network (BMT CTN): addressing unanswered questions. Biol Blood Marrow Transplant. 2007;13:257–62.

Chapter 2
The Business of Cellular Therapy and Hematopoietic Stem Cell Transplantation

Peggy Appel and Richard T. Maziarz

Hematopoietic stem cell transplantation (HSCT) is extremely complex and expensive, requiring significant personnel, pharmaceutical, supportive, and patient/family resources. Classically, after achieving primary disease control, the first step in HSCT involves high doses of chemotherapy and/or radiation in an attempt to eradicate residual disease. The subsequent infusion of the stem cell product leads to hematopoietic and immunologic recovery, of which the latter may often require months to years to achieve.

The first transplant procedures were successfully performed more than 40 years ago. As indications multiplied and transplant-related mortality declined, HSCT utilization expanded with a dramatic increase in the number of both autologous and allogeneic procedures performed over the past decade (see Fig. 2.1).

HSCT has demonstrated efficacy for the treatment of selected malignancies (e.g., multiple myeloma, acute and chronic leukemia, lymphoma), as well as for immunodeficiency, bone marrow failure, and infiltrative disorders such as amyloidosis. The development of reduced intensity-conditioning regimens has allowed successful treatment of older patients and those with comorbidities that would deem them ineligible for myeloablative therapy (see Fig. 2.2).

Finally, the expansion beyond human leukocyte antigen (HLA)-identical sibling allogeneic HSCT to unrelated donor transplants as well as alternative donors, including unrelated cord blood transplants and related haploidentical donors, has resulted in donor availability for nearly all patients in need.

P. Appel (✉)
Northwest Marrow Transplant Program, Oregon Health & Science University, 3181 SW Sam Jackson Park Road, UHN73C, Portland, OR 97239, USA
e-mail: appelp@ohsu.edu

R. T. Maziarz
Center for Hematologic Malignancies, Adult Blood and Marrow Stem Cell Transplant Program, Knight Cancer Institute, Oregon Health & Science University, 3181 SW Sam Jackson Park Road, UHN 73C, Portland, OR 97239, USA

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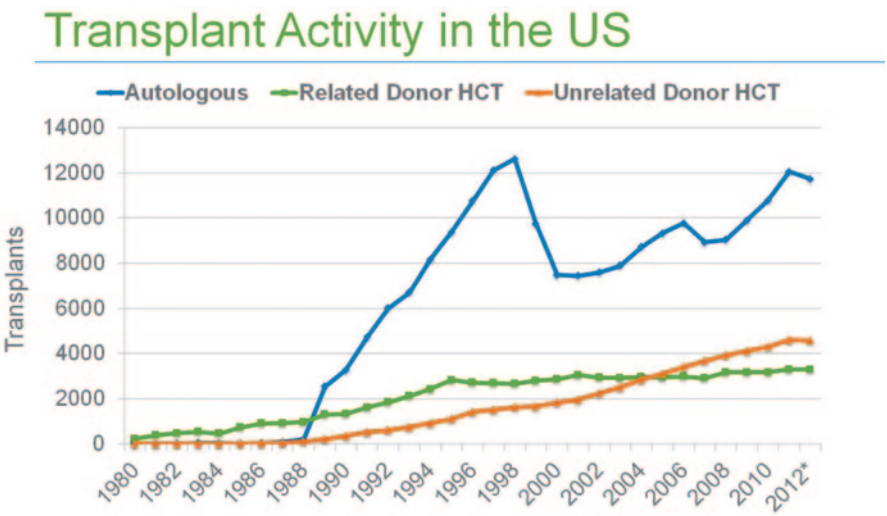

Fig. 2.1 Estimated annual numbers of transplants in the USA were compiled according to the number registered with CIBMTR. Estimates of how closely the numbers reported are representative of actual transplant activity vary according to the type of transplant and number of centers reporting data per year. Prior to 2007, all except unrelated donor allogeneic transplant facilitated by the NMDP were reported voluntarily. It was estimated that the CIBMTR captured 90 % of all unrelated donor transplants performed in the USA, 60–90 % of related donor allogeneic transplants and 65–75 % of autologous transplants. These estimates were extrapolated from other databases that capture transplant center activity, accreditation, or hospital discharges. After 2007, the Stem Cell Transplant Outcomes Database (SCTOD) was initiated which changed reporting requirements and data capture to an electronic format. The SCTOD requires that all allogeneic transplants performed in the USA be registered with CIBMTR. Data reporting of autologous transplants remains voluntary and the numbers in the CIBMTR database are estimated to be 80 %. US numbers of allogeneic transplants in the CIBMTR are representative of the actual transplant activity. The number of autologous transplants in the USA has steadily increased since 2000, mainly for treatment of plasma cell and lymphoproliferative disorders. The ongoing increase of autologous transplants is likely related to a higher number of patients older than 60 years being performed nationwide. Allogeneic transplants from unrelated donors surpassed the number of allogeneic transplants from related donors after 2006 and the gap between these two types of approaches continues to widen annually. The major contributing factors to this trend are the growth of unrelated donor databases, improvements in unrelated donor transplant, and increase in numbers of allogeneic transplants for patient older than 60 years with reduced intensity conditioning. (Pasquini MC, Wang Z. Current use and outcome of hematopoietic stem cell transplantation: CIBMTR Summary Slides, 2013. Available at: http://www.cibmtr.org)

2.1 Increase in Utilization and Impact of HSCT on National Health-Care Costs

The amplification in numbers of HSCT procedures has been associated with a dramatic increase in overall costs. Utilization of unrelated cord blood products has further impacted expenditure, as those patients generally experience slower hematopoietic and immunologic recovery, requiring increased resource utilization.

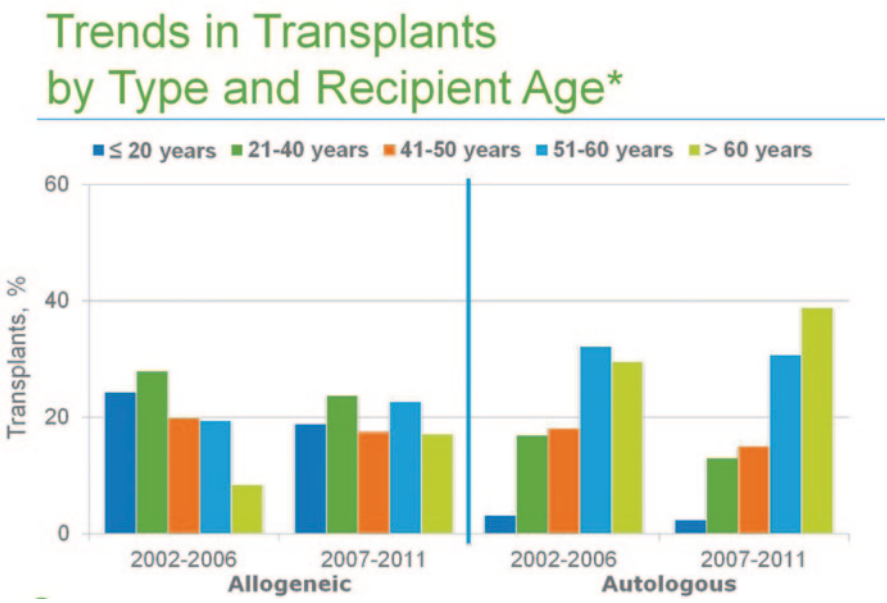

Fig. 2.2 The number of autologous and allogeneic transplants for treatment of malignant diseases in older patients continue to increase. Thirty-nine percent of autologous transplant recipients and 17% of allogeneic transplant recipients in 2007–2011 were older than 60. The majority of autologous transplant recipients (70%) and 40% of allogeneic transplant recipient were older than 50 in this later period. Among allogeneic transplant recipients, the proportion of patients older than 60 years doubled from 8% to 17% during the decade analyzed. (Pasquini MC, Wang Z. Current use and outcome of hematopoietic stem cell transplantation: CIBMTR Summary Slides, 2013. Available at: http://www.cibmtr.org)

The improved survivorship of cancer patients has been confirmed as recently reported by the National Cancer Institute (NCI). Annual expenditures on cancer have also increased in the USA with cancer-care costs estimated at US $ 124.6 billion in 2010, of which, the transplantable malignancy of lymphoma was #3 and leukemia was #6 in expenditure by disease sites. Costs are estimated to exceed US $ 160 billion by 2020. The increase in HSCT utilization was substantiated in a recent report from the Agency for Healthcare Research and Quality (AHRQ) of an analysis performed by the Healthcare Cost and Utilization Project (HCUP) of the Nationwide Inpatient Sample, a database of hospitalization and inpatient stays, representative of all short-term, nonfederal hospitals. For activity between January 2004 and December 2007, it was shown that the HSCT procedure was ranked highest in percentage increase for commonly performed inpatient procedures for hospital costs (84.9%) and for total hospital stays (51.3%) with approximate costs of US $ 1.28 billion in 2007 (Table 2.1). Recognizing that the HSCT procedure represented approximately 1% of total hospital stays, 4.4% of the total costs were encumbered for HSCT.

This rapid increase in HSCT procedures took place in a 48-month interval within the past decade. However, these numbers are a small fraction of what is currently projected for the near future. Based on population demographics and surveillance,

Table 2.1 AHRQ analysis of medical and surgical procedures with increased utilization in the USA. Commonly performed procedures with the most rapidly increasing hospital inpatient costs, 2004–2007. (AHRQ, Center for Delivery, Organization, and Markets, Healthcare Cost and Utilization Project, Nationwide Inpatient Sample, 2004 and 2007)

Principal procedure category	Total costs (2007) (US $)	Total hospital stays (2007)	Percentage change	
			Total costs (2004–2007) (%)	Total hospital stays (2004–2007) (%)
Bone marrow transplant	1,282,645,000	15,100	84.9	51.3
Open prostatectomy	1,032,016,000	88,500	68.6	40.8
Aortic resection; replacement or anastomosis	1,872,908,000	61,600	38.5	31.9
Cancer chemotherapy	2,616,504,000	187,400	33.2	14.2
Spinal fusion	8,863,922,000	350,700	29.5	15.6
Lobectomy or pneumonectomy	1,757,748,000	81,400	29.2	24.9
Incision and drainage, skin and subcutaneous tissue	1,108,187,000	158,600	28.6	31.5
Arthroplasty knee	9,217,740,000	605,200	27.5	25.7
Nephrotomy and nephrostomy	682,609,000	38,600	25.3	11.7
Mastectomy	660,173,000	70,100	23.8	3.6
Total for top 10 procedures[a]	*29,094,452,000*	*1,657,100*	*32.3*	*22.2*

[a] 2004 costs were adjusted to 2007 dollars using the overall consumer price index

epidemiology, and end results (SEER) data for the incidence and prevalence of malignancies, the National Marrow Donor Program (NMDP) anticipates a doubling of the current number of unrelated transplants performed (~5500 in 2011) as early as 2015 (estimated as high as 12,500 procedures). They also predict a concomitant 30% increase in autologous HSCT.

These reports from the HCUP and the NMDP are supported by the Milliman 2011 US Organ and Tissue Transplant Cost Estimates and Discussion report. The analysis suggests that there was a 110% increase in billed charges for allogeneic HSCT between 2003 and 2008. The estimates were based on billed charges (recognizing that charges do not equate to cost of procedures nor do charges indicate what percent of charges are paid by the governmental or private payer). Autologous transplant charges increased from approximately US $ 205,000 to US $ 370,000, and allogeneic transplant charges increased from approximately US $ 380,000 to US $ 805,000 in this short period of time. Also, recognizing that approximately 20,000 procedures were performed, these individual numbers suggest that transplantation may become a US $ 10 billion industry.

2.2 Complexity of Care Increases Costs

In the setting of increasing demand for HSCT and increasing cost of health care and novel technologies, it remains critical for providers and health systems to assure that adequate reimbursement is obtained to cover the costs of the individual procedures, costs associated with the defined incident of care, and the potential associated with medical complications and sequelae.

Reimbursement based on a fee-for-service indemnity approach no longer exists for the vast majority of patients. Insurance carriers have developed case rate contacts for HSCT with negotiated payments for pretransplant evaluation, HLA typing, transplant product acquisition, and patient care. In contrast, government payers (Medicaid and Medicare) have set reimbursement schedules:

1. Medicare coverage provides funding for a period of time surrounding the actual transplant procedure, typically in a diagnosis-related group (DRG)-based reimbursement structure.
2. It is important to recognize that DRG payments are provided with the presumption of a predictable resource consumption encountered by the recipient.
3. In some instances, the payer does not differentiate between autologous, allogeneic-related, and allogeneic-unrelated transplant in their rate-setting process:
    a. This approach ignores the greater complexity of workup, cell source selection, and post-treatment risk of complications for the allogeneic recipient.
4. Preexisting comorbidities as well as the disease state and donor type drive resource consumption. These variables, seen across the spectrum of patients for whom transplant services are provided, are not accounted for by the limited DRG codes.

Contractual arrangements with private/commercial payers will often carve out HSCT services from general medical services contracts:

1. Services related to HSCT will often have a bundled payment for all services performed within a boundary of time around the transplant, usually covering the first 30 days for an autologous and 100 days for an allogeneic HCST procedure.
2. These contracts should be designed to cover:
    a. Recipient evaluation and assessment of transplant eligibility
    b. Donor search benefits
    c. Harvest and acquisition of stem cell product
    d. The immediate peri-transplant period and the post-transplant phase
    e. Special circumstances (preplanned second transplant procedure, donor leukocyte infusion, retransplants, high-cost pharmaceuticals (e.g., plerixafor)

2.3 Contracts and Reimbursement Strategies

If structured appropriately, contracts should reflect mutual exposure to financial risk. Reimbursement methodologies vary in the degree to which financial risk is shared.

One of the confounding issues that those involved in the care of the transplant patient face is that the actual transplant procedure is generally an infusion that occurs at a precise moment in the midst of a complicated medical treatment course. The infusion defines the actual transplant. However, reimbursement usually is focused on providing coverage for that event and for a series of surrounding days, which defines an episode of care. Various reimbursement methodologies have been undertaken, including reimbursement of:

1. All charges generated by providers and health systems in care of an HSCT patient
2. A discount of charges which actually represents a fixed rate percent, discounting total billed charges
3. A case rate, which incorporates a fixed fee that covers all transplant-related hospital or clinic services for a specified period of time, predating and following the actual infusion event
4. A global case rate which represents a fixed fee that covers all hospital and physician charges for a specified period of time, typically involving post-transplant care

Recognizing the unique needs of individual patients, many of the case rate and global case rate methodologies will include provisions that protect the transplant center as well as the payer from financial risk. These provisions vary in the degree of financial protection they provide. Examples include:

1. *Outlier days*, which provide a per diem reimbursement for each inpatient day beyond a well-defined post-infusion time period
2. An *outlier threshold* which reimburses the provider and institutions a defined percentage of billed charges after a specified threshold beyond the case rate has been reached
3. A *floor provision* which assures that at no time will a hospital be reimbursed less than a specific percent of billed charges

The setting in which the HSCT procedure is performed, i.e., inpatient or outpatient, may influence reimbursement. Pharmaceuticals may be reimbursed at a higher level per dollar of charge in the outpatient setting. The differences in reimbursement based on setting can have a significant impact on the financial performance of the HSCT program.

2.4 Integrated Structure for Contract Management

The complexity of contracting for HSCT services is reinforced by the implementation of separate transplant specialty contracting personnel by hospitals and payers. Development of rate structures that support the center's strategic initiatives, monitoring of the center's performance on each contract, and providing assistance to patients in understanding their benefits as they relate to the contract require an integrated team approach:

1. A typical team for contract management would include:
    a. Managed care contracting
    b. HCST program medical director
    c. HSCT program administrator
    d. Patient billing services
    e. Financial counseling personnel
    f. Program's managed care clinical liaison/coordinator:
        i. Review of patient referral insurance information
        ii. Review of patients' benefits:
            - Lifetime maximum
            - Transplant maximum
            - Prescription coverage
        iii. Communication with patient regarding benefits
        iv. Liaison with insurance company in communication of patients' status in the process
    g. Medical social worker

2.5 Payer Types

Understanding reimbursement variability between governmental and private payers is a necessity. Traditionally, since HSCT was performed in younger patients, private payers dominated the health coverage. However, over the last half decade, there has been a significant change in the payer mix with an increase in patients with governmental insurance support (Medicare or Medicaid).

According to transplant center estimates, as many as 25–30 % of their patients were supported by governmental payers in 2012, an increase from previous estimates of approximately 15 % in 2007. This shift in payer mix can have a dramatic impact on transplant program financial viability, given the low average rates of reimbursement by Medicare and state Medicaid programs.

1. Affordable Care Act:
    a. The Patient Protection and Affordable Care Act (ACA) was signed into law on March 23, 2010 and could add more than 30 million Americans to the insured ranks by 2019.
    b. The intent of the law is to increase access while reducing the overall cost of health care.
    c. Patients who have had or who will need an HSCT should benefit from expanded access to affordable insurance options and the removal of long-standing benefit and coverage restrictions as provided under the ACA.
    d. Prior to the enactment and implementation of the ACA, HSCT patients seeking new insurance coverage faced the potential of a lack of insurers willing to insure them, limited benefit insurance plans with high premiums, and/or preexisting condition exclusions of HSCT-related costs.
    e. The ACA assures access to health insurance for HSCT patients in the following ways:
        i. A requirement that anyone eligible for insurance cannot be denied coverage.
        ii. Prevents insurers from rescinding coverage when diagnosed with an illness or condition.
        iii. Elimination of lifetime dollar limits on total paid benefits.
        iv. Annual dollar limits are allowed only in a more restricted manner, specifically for services not covered by the definition of the essential health benefits (EHB). While there is not a specific mention of HSCT as an EHB at the federal level, the components of the HSCT process all fall into covered categories.
        v. Removal of preexisting condition exclusions.
    f. In addition to access, the other significant principle of the ACA is an overall reduction in health-care spending, particularly in the Medicare program:
        i. The expected impact on transplant centers is uncertain but will likely be significant, given that Medicare eligible patients are the fastest growing segment of allogeneic HSCTs.
        ii. The elimination of lifetime, annual, and procedural financial caps and removal of preexisting condition exclusions could influence third-party reimbursement strategies.
    g. In conjunction with the ACA, the delivery of patient care by coordinated care organizations (CCOs) and accountable care organizations (ACOs) is focused on managing populations and efficient delivery of primary care. Hematology and oncology patients could be viewed differently by hospital systems as the resource consumption by these patients would be significant, based on current pricing of many cancer therapeutics and procedures.

h. Transplant centers should consider how to prepare for new models of payment bundling, pay-for-quality programs, and an increased focus on cost-effectiveness and value from all payer types.

    i. Transplant centers will be under pressure to document quality of care to avoid penalties and/or earn incentives.

2. Medicare services

a. Federal governmental payers are predominantly guided by Medicare coverage decisions.
b. Medicare coverage will be limited to items and services that are determined to be covered and within the scope of a Medicare benefit category.
c. HSCT is a procedure for which Medicare has developed a national coverage determination, and the coverage information is available to all online within the Medicare coverage database.
d. Medicare's two-midnight rule for inpatient admissions:

    i. As of October 1, 2013, Centers for Medicare & Medicaid Services (CMS) finalized a new way to identify/determine appropriate inpatient admissions: A patient admission is presumed to be an appropriate inpatient admission for purposes of a Medicare severity-diagnosis-related group (MS-DRG) payment when there is the expectation that the patient will require a stay for more than two midnights.
    ii. If the stay is expected to last fewer than two midnights, it generally would not be appropriate for an inpatient hospital admission.
    iii. An inpatient admission may be justified based on patient's medical history, comorbidities, severity of signs and symptoms, current medical needs, and the risk/probability of an adverse event occurring during the hospitalization period.
    iv. With reduced intensity regimens, transplant programs are able to treat certain Medicare patients mostly in the outpatient setting and admit them only for the cell infusion.
    v. Since patients can react differently, some may stay more than two midnights, while others may not, and it is often not known at the time of admission what the patients' clinical course will be. *Should a program change how care is provided*?
    vi. Page 50,945 of the final rule states: "…when it is difficult to make a reasonable prediction, the physician should not admit the beneficiary but should place the beneficiary in observation as an outpatient. As new information becomes available, the physician must then reassess the beneficiary to determine if discharge is possible or if it is evident that an inpatient stay is required."
    vii. This ruling has implications for reimbursement of donor search and product acquisition charges:

- Donor search and product acquisition fees are tied to the inpatient DRG payment for the transplant procedure and are not included in the daily incident of care ambulatory payment classification (APC) reimbursement used for outpatient services.

viii. In addition, reimbursement for Medicare day patients is considerably less than the average inpatient DRG rate for this procedure.
ix. Patient out-of-pocket expenses are also affected by a day-patient stay.

3. Medicaid services:

a. At the state level, there is wide variation in Medicaid reimbursement and coverage for HSCT:

i. There may be limitations based on indications for HSCT, maximal allowable inpatient stays, and medication support, as well as variation in inpatient or outpatient service provision.
ii. Clinical trial coverage variability also can be dramatically different:

- HSCT is not a mandatory covered benefit for adults, and all states have the discretion to choose whether to provide coverage or to determine the extent of coverage.
- In austere times, states may identify control of Medicaid costs as a means to reduce their deficits and balance their budgets.
- Recent data released by HCUP demonstrated that Medicaid coverage was provided to 3064 HSCT hospitalizations or 16 % of all discharges for HSCT in the USA in 2010.
  A recent analysis of the Medicaid programs in 47 states by the NMDP, assessing the degree of recommended benefit support which included transplant procedure and disease indications, donor search, medications, clinical trial support, and transportation and lodging, was unable to identify any state that provided minimal coverage benefits in all five categories and identified only three states that met minimum supports level in four of the five categories. Eight states had perceived adequate Medicaid support coverage in only one of the five categories.

b. The ACA mandated that all states must expand coverage under Medicaid to individuals up to 133 % of the federal poverty level (FPL) and provided federal funding to cover the cost of increased coverage:

i. The US Supreme Court declared that this requirement was unconstitutional and that each state had the right to decide whether or not to implement this provision. As a result, the extent of Medicaid coverage is to be determined on a state-by-state basis.

c. Expanded Medicaid will have both positive and negative repercussions for patients and HSCT programs: