Blood and Marrow Transplant Handbook

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Comprehensive Guide for Patient Care

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Springer

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ISBN 978-1-4419-7505-8 e-ISBN 978-1-4419-7506-5
DOI 10.1007/978-1-4419-7506-5
Springer New York Dordrecht Heidelberg London

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

Preface 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 ten to fifteen 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. Cell therapy is a dynamic field. It requires multi-specialty 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 recent predictions of a marked shortage of transplant physicians. As an alternative, more non-physician providers are being recruited to this field 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 ensure the best and most predictable outcomes of our patients can be achieved.

This guide to patient management is the product of fifteen 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 physicians. 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 physician assistants, nurse practitioners,

residents, post-doctoral fellows, and other hospitalists that may be recruited to the day-to-day care of the patient, we have achieved our goal. We recognize that this pocket guide is 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 to any great degree. We are not addressing the nuances of cord blood transplantation. We are not considering haplo-identical transplantation or other therapies that remain in clinical trial development and may emerge soon 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 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. We would like to thank Thomas Thomas for his assistance in the preparation of this manual. We specifically acknowledge the work of Florence Seelig, Peter Curtin, Mark Brunvand, Kamar Godder, Gerald Segal, and the late Keith Hansen among many of our former team members. 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, mid-level providers, and nurse coordinators. Through collaboration and shared information, we hope to assure the best outcome of our patients as they return to their communities across the country.

Editors, 2011

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PART I

The Nuts and Bolts of Stem Cell Transplant

CHAPTER 1
Overview of Hematopoietic Stem Cell Transplantation

Richard T. Maziarz

Hematopoietic stem cell transplantation (HSCT) has evolved over the past 50–60 years to become the standard of care procedure for many disorders. Advances in immunogenetics and immunobiology, conditioning regimens, disease characterization and risk stratification, immune suppression, antimicrobials, and other types of supportive care have made this expansion possible. Some of the earliest work contributed to the first successful bone marrow transplant, performed in a young child with immune deficiency syndrome in 1968. Approximately 15 years later, the graft-versus-leukemia response was recognized as overlapping with the development of graft-versus-host disease (GvHD). In the early 1980s, bone marrow transplantation was no longer considered experimental, but as the standard of care for a variety of disorders including acute leukemia and aplastic anemia. With this recognition, the incidence 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 THE LANGUAGE OF TRANSPLANTATION

HSCT can often appear daunting to newcomers to the field as a consequence of the intensity of treatments administered to patients, the breadth of medical knowledge required by the clinical transplantation specialist, and the specialized language used by the HSCT expert. A partial list of definitions is provided to assist the newcomer.

R.T. Maziarz, S. Slater (eds.), *Blood and Marrow Transplant Handbook*, DOI 10.1007/978-1-4419-7506-5_1,

1. *Hematopoietic stem cell*: A bone marrow-derived stem cell with the capacity for self-renewal and the ability to generate downstream mature products of red cells, white blood cells, and platelets. By definition, a transplantable product
2. *Autologous*: Cells derived or obtained from the afflicted individual
3. *Allogeneic*: Cells derived or obtained from another individual
4. *Syngeneic*: Cells derived or obtained from an identical twin
5. *HLA*: Histocompatibility locus antigen
   a. HLA Class I: Gene products of HLA A, B, C, universally expressed on the surface of all cells of an individual (with some specific exceptions, e.g., trophoblast tissue); the class of histocompatibility molecules that present cellular peptides to CD8 T-cell effectors
   b. HLA Class II: Gene products of HLA DR, DP, DQ, cell surface expression normally limited to lymphohematopoietic tissues but can be induced on many tissues after inflammatory cytokine exposure; the class of histocompatibility molecules that present cellular peptides to CD4 T-cell effectors
   c. Antigen: Any molecule that is recognized and bound by immunoglobulin or T-cell receptors; in immunogenetics, this term is often interchangeably used to describe a particular HLA molecule
   d. Allele: Molecular variants of a single gene
   e. Antigenic determinant/epitope: The specific part of an antigen bound by immunoglobulin or T-cell receptor
6. *MHC*: Major histocompatibility complex. The collection of genes located on human chromosome 6 that encode the polymorphic proteins involved in antigen presentation to T cells; the regulators of the cellular immune response
7. *Haplotype*: The location of a linked set of polymorphic HLA genes on a single chromosome; all cells, other than the germ cells of an individual, express two haplotypes, each inherited from a single parent
8. *Haploidentical*: The circumstance in transplantation in which there is a partial or complete mismatch at a single HLA locus between two individuals
9. *CD34*: A surface marker of the earliest progenitors and stem cell pools. Clinical exploitation has been achieved using this molecule in determining if adequate numbers of transplantable stem cells are obtained prior to a procedure

10. *Bone marrow harvest*: The procedure through which donor stem cells are collected directly from the bone marrow cavity
11. *Peripheral blood stem cell collection (apheresis)*: The procedure by which stem cells are mobilized directly into the blood of the donor for harvesting by leukapheresis
    a. Mobilization: The act of enhancing the movement of stem cells from their microenvironment niche into circulation; usually performed with growth factor or growth factor plus chemotherapy exposure
12. *Conditioning*: The euphemistic term for the chemotherapy- or radiation-based preparation of the host prior to the transplant, the goals of which include immune suppression and myelosuppression
13. *Myeloablative*: Conditioning regimens designed to eliminate all host stem cells
14. *Non-myeloablative*: Conditioning focused on immune suppression and establishment of donor chimerism without dose intensity enough to destroy all residual host stem cells
    a. Chimerism: the establishment of donor cells within another recipient; can be partial or complete
15. *Reduced intensity transplantation*: A blanket term for any degree of conditioning that is less intense than traditionally defined maximal myeloablative conditioning
16. *CIBMTR*: Center for International Blood and Marrow Transplant Registry, the registry of >400 transplant centers worldwide that contribute outcomes data to a central data repository for analysis
17. *NMDP*: National Marrow Donor Program. An American organization focused on facilitating unrelated donor and cord blood transplant procedures
18. *ASBMT*: American Society for Blood and Marrow Transplantation. An international professional association that promotes the blood and marrow transplantation field
19. *BMT CTN*: Blood and Marrow Transplant Clinical Trials Network. National Heart, Lung, and Blood Institute (NHLBI) and National Cancer Institute (NCI)-sponsored intergroup focused on the development of clinical trials in the hematopoietic stem cell transplantation arena
20. *NCI CTC*: National Cancer Institute Common Toxicity Criteria. A widely accepted criteria for assessing severity of adverse events. Its utilization allows for overcoming institutional variation in reporting and for comparative outcomes research to be performed

21. *EBMT*: The European Group for Blood and Marrow Transplantation. An organization based in Europe that promotes cooperative studies and collects transplant outcome data from multiple European and Eurasian countries
22. *WMDA*: The World Marrow Donor Foundation. An international organization focused on donor safety, stem cell accessibility, and generation of standard practices for the exchange of hematopoietic stem cells for clinical transplantation worldwide

1.2 RESEARCH EFFORTS IN HSCT

The success of HSCT has had its origins in the research laboratories and clinical research units at many institutions. However, it is also recognized that there is a continued need for ongoing research. Much of the material within this guidebook reflects established standards of care of management in the HSCT patient. However, the field demands constant efforts for improvement. There are many areas of active research including new conditioning regimens, new immunesuppressive approaches, vaccines (both prior to and after transplantation) focused at infectious pathogens as well as the primary malignancy, T regulatory cells, new indications such as autoimmune disease or sickle cell disease, applications of natural killer cells, novel stem cell mobilization ages, and continued improvement in supportive care. Recently, the 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-transplant relapse
   b. Immunotherapy with T-cell and dendritic cells
3. Graft-versus-host disease
   a. Separation of GvHD and graft-versus-tumor effects
   b. Immune reconstitution in GvHD
   c. Markers 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. Pharmacogenomics
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 expanding 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 NMDP projects facilitation of double the number of unrelated transplant procedures over the next 5 years, from current levels of nearly 5,000 annually to over 10,000 by 2015. 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 transplantation for chronic myeloid leukemia is a prime example.

However, we must be aware that the increased numbers of patients undergoing transplantation, 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 transplantation in need of specialized providers but also the rapidly expanding population of survivors, particularly those with chronic graft-versus-host disease, has difficulty finding a medical home with their primary care providers or referring medical oncologists.

A recent analysis suggests that within the very near future 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 non-physician 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 tools must be established for a new specialty of primary care providers focused on delivery of chronic care to the cancer survivor.

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

Peggy Appel and Richard T. Maziarz

Hematopoietic stem cell transplant (HSCT) is a complex process that is associated with a heavy demand for resources and need for multispecialty teams. The first transplant procedures were performed over 40 years ago. There has been a dramatic increase in the number of procedures performed over the past 10 years (Fig. 2.1).

National Marrow Donor Program (NMDP) projections for growth in unrelated donor transplants are significant with an expected doubling of facilitated transplants projected at 10,000 by the year 2015. These projections can be frightening, but recent analysis of US hospitalization utilization indicates that in the past 5 years, there has already been a doubling of activity. Bone marrow transplant ranked highest among the commonly performed procedures with the most rapidly increasing hospital inpatient costs from 2004 to 2007, with a percentage change in total costs of 84.9% and a percentage change in total hospital stays of 51.3%. In the breakdown, it was observed that specifically inpatient costs for Medicare covered stays increased 90.4% and costs for private payer insured stays increased 100.6% during this period (Table 2.1).

In the settings of increasing demand and increasing cost of technologies, it is critical for providers and hospital systems to assure that contractual arrangements with payers have sufficient complexity to support the provision of the best care while protecting from excessive financial risk, resulting in financial stability of the transplant program.

R.T. Maziarz, S. Slater (eds.), *Blood and Marrow Transplant Handbook*, DOI 10.1007/978-1-4419-7506-5_2,

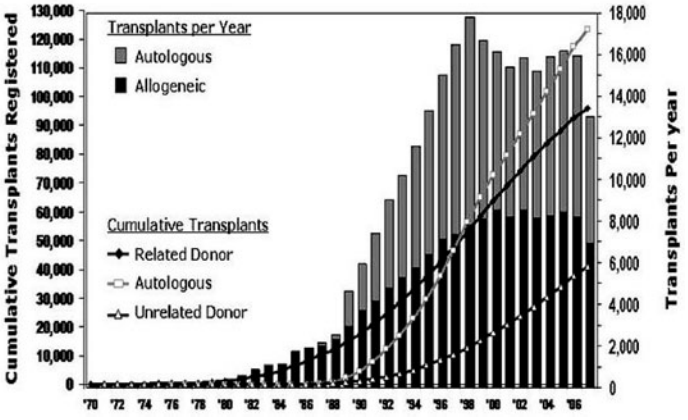

FIG. 2.1. Annual and cumulative transplant procedures reported to the CIBMTR

2.1 COMPLEXITY OF CARE

Hospitals and payers alike typically wish to "carve out" HSCT services from general medical services contracts. Due to the complexity of care delivered, variability in patient care requirements, and potential risk of need for catastrophic care, HSCT services are often divided into phases for the purposes of authorization and reimbursement methodologies. These phases may encompass consultation, evaluation, transplant, and post-transplant.

2.2 PHASES

1. Transplant evaluation
   a. Begins when a new patient is referred for transplant evaluation
   b. Ends when patient is approved as a transplant candidate
   c. Inclusions
      i. Physician and clinic charges for consultation and physical exam
      ii. Lab tests
      iii. Radiology studies
      iv. Psychiatric evaluation
      v. Dental evaluation
      vi. Patient and donor HLA typing
      vii. Donor infectious disease testing

TABLE 2.1. Commonly performed procedures with the most rapidly increasing hospital inpatient costs, 2004–2007

Principal procedure category	Total costs (2007)	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

Source: AHRQ, Center for Delivery, Organization, and Markets, Healthcare Cost and Utilization Project, Nationwide Inpatient Sample, 2004 and 2007

[a]2004 costs were adjusted to 2007 dollars using the overall Consumer Price Index

   d. Exclusions
      i. Non-transplant-related services
2. Pre-transplant
   a. Begins when a patient is identified as a transplant candidate
   b. Ends the day prior to the transplant admission
   c. Inclusions
      i. All inpatient and outpatient facility, professional, ancillary, and laboratory services related to routine surveillance of patient to assure maintenance of transplant-ready status
   d. Exclusions
      i. Disease-related services
3. Harvest/acquisition (typically included in pre-transplant phase or transplant phase)
   a. Inclusions
      i. Mobilization
      ii. Bone marrow or peripheral blood stem cell harvest
      iii. Acquisition charges for unrelated donor product procurement
      iv. Cell processing
4. Transplant stay
   a. Begins on the day of admission; or for outpatient transplants, with the initiation of preparative regimen
   b. Ends on the day of discharge; or for outpatient transplants, *x* number of days following stem cell infusion
   c. Inclusions
      i. All facility, professional, and ancillary charges
5. Post-transplant
   a. Begins on the day of discharge; or for outpatient transplants, *x* number of days following stem cell infusion
   b. Ends *x* number of days post-infusion or post-discharge
   c. Inclusions
      i. All transplant-related outpatient and inpatient facility and professional charges
      ii. Inpatient readmissions
   d. Exclusions
      i. Non-transplant-related services
6. Special circumstances

   There are some HSCT-associated activities that require special arrangements or should be addressed separately from case rate provisions in contracts due to their unpredictability and/or variation in occurrence.
   a. Sequential transplants (pre-planned)

b. Donor leukocyte infusions
c. Re-transplants
d. Reduced intensity transplants
e. High-cost pharmacy items (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.

1. Reimbursement methodologies
   a. Discount off charges – a flat percent discounting of billed charges
   b. Case rate – fixed fee that covers all transplant-related services for a specified period of time
   c. Global case rate – fixed fee that includes hospital and physician charges for a specified period of time; typically includes post-transplant care
2. Case rate and global case rate methodologies typically include provisions that protect the transplant center from financial risk. These provisions vary in the amount of financial protection they provide.
   a. Outlier days – per diem for each inpatient day in a defined post-infusion time period
   b. Outlier threshold – percentage of billed charges once a specified threshold beyond the case rate is reached
   c. Floor provision – at no time shall hospital be reimbursed less than *x%* of billed charges. This provision is usually used in tandem with the outlier day provision to provide added financial risk protection
3. Given the variation in patients' clinical circumstances that may impact evaluation and work-up, patients' geographic locations and the willingness and expertise of the referring physician to be involved in pre-transplant testing, consideration should be given to structuring the reimbursement rate for the evaluation, pre-transplant period, and post-transplant time periods on a percentage discount off billed charges basis.
4. The case rate time period typically includes related donor or autologous harvest, the transplant stay, and a specified number of post-infusion days.

5. Reimbursement for unrelated donor testing and stem cell acquisition may be based on invoice or invoice plus mark-up to cover costs related to administration of the unrelated donor search.
6. The setting in which the HSCT procedure is performed, inpatient or outpatient, can 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 significant complexity of contracting for HSCT services can be demonstrated 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. HSCT 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 PRIVATE PAYERS

There is significant variability among commercial insurers in all aspects of coverage for HSCT. Private payers often follow

Medicare guidelines for coverage determinations for indications for transplant. Reimbursement structures, benefit packages, donor search and acquisition, financial caps, and clinical trial coverage are examples of areas in which this variation is evident.

1. Centers of Excellence and National Transplant Networks
   a. Many of the large insurance and reinsurance companies have Center of Excellence (COE) or National Transplant Network programs. These programs vary in size depending on the types of transplants, the number of insured lives, and the geographic region covered by those insured lives.
   b. Participation in COE programs and national transplant networks allows a transplant center to have access to a greater number of patients. Patients may be directed to the transplant center because they are a participant in the COE. Participation is based on meeting selection criteria typically based on volumes and outcomes. The selection process typically includes submission of program-specific information and disease-specific outcomes information, as well as an onsite inspection of facilities and review of program standards.
   c. Selection criteria vary among payer networks. In return for a potential increase in patient volumes, transplant centers may agree to package their transplant procedures at rates which cause them to assume some financial risk for above-average costs.

2.6 GOVERNMENTAL PAYERS

1. Medicare DRG Reimbursement
   a. Medicare coverage is limited to items and services that are within the scope of a Medicare benefit category. HSCT is a procedure for which Medicare has developed a National Coverage Determination (NCD). Local Coverage Determinations (LCD) may also apply. These local determinations are developed in the absence of regulation or a national coverage policy. Familiarity with coverage information is of obvious importance and is a critical responsibility of the managed care specialists. The national coverage information is available online from the Medicare Coverage Database (MCD). The NCD for HSCT is in Section 110.81 of this database.

b. Under the Medicare Hospital Acquired Conditions (HAC) initiative, hospitals will be penalized with decreased or no reimbursement for services to Medicare patients if the patient has what is considered a preventable event (e.g., hospital-acquired infection, central line infection, falls resulting in harm). This can be problematic for the HSCT program, given the HSCT patient's proclivity to infection due to immune system compromise. Number of readmissions and time between discharge and readmission are also critically examined.

2. Medicaid

There is wide state-to-state variation in Medicaid coverage for HSCT. There may be limitations based on indication for transplant, maximum allowable inpatient days, and inpatient vs. outpatient service provision. Familiarity with coverage information is of obvious importance and is a critical responsibility of the managed care specialists.

2.7 REGULATORY

1. FACT
   a. The Foundation for the Accreditation of Cellular Therapies (FACT) accreditation is voluntary, but has become an almost necessary qualification for a program to be accepted and competitive. Many insurers, Centers of Excellence programs, and National Transplant Networks include FACT accreditation as a requirement for selection/inclusion.
   b. FACT accreditation addresses clinical care, donor management, cell collection, cell processing, and cell administration.
   c. Accreditation is awarded after successful documentation of compliance with FACT standards. Compliance is judged by evaluation of written documentation and through on-site inspections.
2. CIBMTR

The Center for International Blood and Marrow Transplant Research (CIBMTR), chosen by Health Resources and Services Administration (HRSA), is the contractor for implementation and ongoing management of the Stem Cell Therapeutic Outcomes Database (SCTOD). As one of four components of the C.W. Bill Young Cell Transplantation Program, the SCTOD provides information about allogeneic

blood and marrow transplant outcomes. Submission of patient data to the CIBMTR for the SCTOD is a requirement of all transplant centers that perform allogeneic transplants.

3. FDA
   a. The Food and Drug Administration's (FDA) mission is to protect the public health. In May 2005, the FDA created a registration system for establishments that collect, manipulate, and manufacture cellular therapy products. The registration system was created to establish procedures to prevent the introduction, transmission, and spread of communicable disease by cellular therapy products. HSCT programs are required to register and submit a list of all types of cellular therapy products collected or infused in their institution. The registration must be updated annually.
   b. The FDA requires documentation of complaints that involve distributed cellular therapy products which allegedly involve transmission of a communicable disease to the recipient of the product.
   c. Enforcement of the registration and reporting requirements is accomplished by FDA inspections.

2.8 QUALITY

Assessment of a transplant center's quality is performed internally to evaluate all systems and elements that influence the quality of the HSCT product and service, and performed by external agencies to assess conformance with pre-established specifications or standards.

1. Typical measures of quality – overall mortality and non-relapse mortality – can be difficult to compare between transplant centers due to the potentially significant variability between patient populations managed by individual centers.
   a. Independent bodies such as the University Health Care Consortium attempt to bridge the center-to-center variation by creating assessment tools that normalize the data across centers.
   b. Algorithms for risk assessment based on patient characteristics (co-morbidities) prior to transplant and categorization of disease-related characteristics are used to provide enhanced assurance of valid comparison of outcomes across transplant programs.

c. Standardized determinations of severity of illness (SOI) for the transplant stay are derived from the discharge diagnostic codes. Tools have been generated which use this information to make predictions of expected percentage mortality that can be compared to the observed percentage mortality, with the observed:expected ratio used to comparatively standardize outcomes between centers.

2.9 DATA MANAGEMENT

A transplant program's data management enterprise supports compliance with regulatory standards, internal assessment of quality and quality improvement initiatives, and research development. HSCT programs are expected to contribute data regarding transplant procedures to the NMDP, CIBMTR, or similar data repositories. These data are then available for research purposes on outcomes.

2.10 SUMMARY

The ability to maintain and expand an HSCT program requires the efforts of a specialized business team to develop, implement, and manage contracts; personnel knowledgeable of the most current regulatory standards and data reporting requirements; and a clinical team dedicated to the critical ongoing communication with the referring physician. The partnership between referring physicians and the transplant program is supported by communication related to the pre-transplant workup, the transplant stay, and the requirements of ongoing care post-transplant. This partnership is critical to the promotion of long-term survivorship for the HSCT patient.

2.11 RESOURCES

2.11.1 Websites

Foundation for the Accreditation of Cellular Therapies www.thefactwebsite.org

National Marrow Donor Program www.bethematch.com

Center for International Blood and Marrow Transplant Research www.cibmtr.org

American Society for Blood and Marrow Transplantation www.asbmt.org

European Group for Blood and Marrow Transplantation www.ebmt.org

Stem Cell Therapeutic Outcomes Database http://bloodcell.transplant.hrsa.gov

Blood and Marrow Transplant Clinical Trials Network www.bmtctn.net

Medicare http://www.cms.gov/mcd

Reference

Stranges, E. (Thomson Reuters), Russo, C.A. (Thomson Reuters), Frideman, B. (AHRQ). *Procedures with the Most Rapidly Increasing Hospital Costs, 2004–2007*. HCUP Statistical Brief #82. December 2009. Agency for Healthcare Research and Quality, Rockville, MD. http://www.hcup-us.ahrq.gov/reports/statbriefs/sb82.pdf

CHAPTER 3
Stem Cell Sources

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There are various sources of hematopoietic stem cells (HSC) in use today, including bone marrow, peripheral blood, and umbilical cord blood. HSCs may be obtained from autologous (marrow or PBSC) or allogeneic (HLA-matched related [MRD], HLA-matched unrelated [MUD], mismatched related or unrelated donors, and umbilical cord blood [UCB]) sources. An international inventory of the majority of available adult unrelated donors and cord blood units is maintained by Bone Marrow Donors Worldwide (www.bmdw.org). In 2010, there were an estimated 13–14 million adult donors and 400,000–500,000 cord units available for use in HSCT.

3.1 DONOR SELECTION

1. HLA considerations – critical impact on allogeneic HSCT
   a. Single most important factor in outcome
   b. Low-resolution (antigen equivalent) or high-resolution (allele equivalent) typing done at HLA-A, B, C, DRB1, DQ. (DRB3, 4, 5 and DP typing is also performed, but of uncertain importance)
   c. For marrow, 9/10 match associated with worse overall survival (OS), disease-free survival (DFS), treatment-related mortality (TRM), and acute GVHD
   d. No difference if mismatch in marrow at antigen or allele level except for HLA-C (antigen worse than allele)
   e. 10% lower overall survival with each additional mismatch
   f. For PBSCs, antigen mismatch worse than allele mismatch with increased mortality

R.T. Maziarz, S. Slater (eds.), *Blood and Marrow Transplant Handbook*, DOI 10.1007/978-1-4419-7506-5_3,

   g. For PBSCs, a C-antigen mismatch confers increased risk for OS, DFS, TRM, and acute GVHD (grades III–IV)
   h. Other donor factors such as age, sex, parity, CMV-status, ABO-matching may have weak effects on outcome
2. Donor Screening
   a. To ensure safety for the donor and that administration of the HSC product is safe for the recipient
   b. Medical history questionnaire should target risk factors for transmission of genetic or infectious diseases
   c. Infectious disease testing includes: HIV 1 and 2, HTLV 1 and 2, hepatitis B and C, CMV, West Nile virus, syphilis, HSV 1 and 2, VZV, and Chagas disease
   d. Physical examination, urinalysis, ECG, chest X-ray
   e. Baseline laboratory testing: CBC, comprehensive metabolic panel, LDH

3.2 BONE MARROW

1. Gold standard of allogeneic HSCT for three decades
2. Advantages
   a. Less T-cells in graft compared with peripheral blood source
   b. Decreased risk of chronic GVHD
   c. Decreased mortality in children and adolescents
3. Disadvantages
   a. Requires operating room, spinal or general anesthesia
   b. Increased morbidity to donors
      i. Potential risks include pain, infection, blood loss, nerve and musculoskeletal damage
      ii. May require blood transfusions for young pediatric donors
   c. Slower neutrophil and platelet engraftment
   d. Increased risk relapse in some studies
4. Target cell dose
   a. Minimum 1×10^8 total mononuclear cells (TMNC)/kg body weight of recipient
   b. Target dose 2×10^8 TMNC/kg body weight of recipient

3.3 PERIPHERAL BLOOD (PBSC)

1. Has largely replaced marrow as primary sources of HSCs
   a. Principal and preferred source of all autologous HSCT products