Blood and Marrow Transplant Handbook

Comprehensive Guide for Patient Care

Richard T. Maziarz
Susan Schubach Slater
Editors

Third Edition

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Preface

Hematopoietic cell transplantation has experienced a dramatic increase in activity over the past two decades with a continued marked escalation of procedures projected over the next 10 to 15 years. This expansion is not only a reflection of an ever-changing field with increasing demand but also the ongoing development of innovations that contribute to continued improved outcomes with less risk of adverse events or deleterious long-term consequences for the transplant patient population. The use of non-myeloablative, reduced-intensity conditioning regimens has allowed transplantation for patients who were previously deemed too old or frail to endure ablative conditioning regimens. Additionally, the expanded use of alternative donors, including both umbilical cord blood and haplo-identical family donors, has made the therapeutic option of transplantation available to patients who previously could not find a suitable donor.

Currently, we are in the midst of a seismic shift in the care of cancer patients, including those with hematologic malignancies who are the focus of this handbook. Precision medicine and immunotherapy have emerged as critical new tools that are providing new diagnostic and therapeutic options and contributing to improvements in disease control, overall survival, and quality of life of our patients. Antibody therapies (humoral immunity arm) have long been part of the care for hematologic malignancy patients, but multiple novel humoral immune options have recently emerged with the regulatory agencies' approval of bispecific antibodies, immune conjugates, and checkpoint inhibitors. In addition, we are now seeing the emergence of cellular therapies. Heralded a decade ago by the development and FDA approval of sipuleucel-T, a cellular vaccine therapy for prostate cancer, we are now witnessing the rapid emergence of multiple cellular therapeutics as options for our patients. With the FDA approvals of the chimeric antigen receptor T cell gene therapies, tisagenlecleucel and axicabtagene ciloleucel, multiple new cell therapies are anticipated to enter our armamentarium, including T cell, dendritic cell, natural killer cell, and mesenchymal stromal cell products. Of course, as anticipated, new challenges arise in parallel with the introduction of these new therapies. We must now address new logistical issues of maintaining and monitoring supply chain for these manufactured and transported drugs and, of course, be ready to address new complications linked to these treatments. Thus, "cytokine release syndrome" and "immune effector cell

associated neurotoxicity syndrome" are new language that is routinely used in the day-to-day discussions that take place on hematologic malignancy services.

Practicing in the field of cellular therapy 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 to all practitioners, as well as a set of 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 healthcare providers to this field are paramount for uninterrupted day-to-day care of transplant patients as well as those who will benefit from the increasingly available novel cellular and humoral immune therapeutics. 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 began as a product of years of evolution of patient care at our institution. For this third edition, we have incorporated the expertise of providers from across the USA for a broader perspective on the day-to-day care of our patients. However, *this guide is not meant to define the sole, exact care pathway for all patients*. We all know far too well that this field is constantly evolving, primarily through rigorous, controlled, well-designed, statistically valid clinical trials. Rather, we have provided a practical set of guidelines that can be shared across institutions. This effort is our contribution to the workforce shortage of transplant and cell therapy providers. By providing an easy-to-use manual that covers the basics of care for hematologic malignancies and particularly cell therapy patients, which can be utilized to educate junior faculty, physician assistants, nurse practitioners, residents, fellows, and other providers that may be recruited for the day-to-day care of patients, we have achieved our goal. We have also seen that previous editions of this handbook have been used by those primary hematology and medical oncology practitioners who accept their patients back from our programs. It is a source of management information that allows community providers to care more confidently for their patients across time. As this third edition demonstrates, this guide remains an evolving work in progress, and we anticipate that as time passes, even potentially quite quickly, a new set of guidelines will need to be generated for you to care for your patient's daily needs.

We recognize that this manual is incomplete. We do not discuss the laboratory aspects of graft engineering or stem cell expansion approaches to any great degree. We do not address the nuances of many therapies that remain in clinical trial development nor do we discuss regeneration medicine, its futures, and its overlap with cell therapy and hematopoietic cell transplantation. Rather, we provide information about standards of care needed to handle the day-to-day issues that may arise, and to accomplish this goal, we have assimilated knowledge gained from many others in the field.

Acknowledgments

The work presented within this volume represents not the work of a few but the work of many. Many of the current authors were members of the team that helped create our original 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 individual growth and ultimately to the creation and advancement of our program cannot be underestimated. For RTM, this group is broad but is highlighted by (a) his original cellular and molecular immunology mentors—Drs. Steven J. Burakoff and Jack L. Strominger and members of their laboratories; (b) his earliest mentors and colleagues in the clinical transplantation world—Drs. Hillard Lazarus, Joseph Antin, and Philip McCarthy; and (c) Dr. Grover Bagby who provided the opportunity to build the OHSU transplant and cellular therapy programs from its fledgling origins. For SSS, this includes (a) her first mentors—her parents Margaret and Ted, who stressed the value of education and a job well done; (b) her OHSU mentors—Drs. Richard T. Maziarz, Jose Leis, and Rachel Cook, who have provided an environment for continued growth and learning; and (c) her husband Greg who, has firmly supported this effort from the idea of first edition to the submission of this last edition.

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. We acknowledge the national and international efforts focused on improving patient outcomes through organizations such as ASTCT, 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.

Finally, we wish to thank the thousands of patients and their families who have walked through our door over the past 30+ years, putting their trust in us to guide them through the most challenging time in their lives. Many of them did not walk back out of our doors, while others have gone on to experience personal and family events that, were it not for these transplantation and cellular therapeutic procedures, would have occurred without them. We have learned from them all.

Portland, OR, USA

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Chapter 1
Overview of Hematopoietic Cell Transplantation and Cellular Therapy

Richard T. Maziarz

Introduction

Hematopoietic cell transplantation (HCT) is currently a standard-of-care procedure for many disorders. Frequently HCT procedures are curative in situations where no other potentially curative treatment options exist. Specifically, the key element in HCT as a therapy is the replacement of the host (recipient) marrow function by another source of hematopoietic stem cells (HSCs). These sources could include HSC collected from the patient (autologous) or from another individual (allogeneic). Allogeneic sources include family-related or unrelated products, either collected 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 HCT, products are preferentially matched at the major histocompatibility complex (MHC) 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 HCT 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.

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HCT has been developed over the past 60 to 70 years since the first human clinical experimental transplants were performed in the 1950s. The first curative allogeneic bone marrow transplant was performed in a young child with immune deficiency syndrome in 1968. By the early 1980s, bone marrow transplantation was no longer considered experimental but emerged 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).

As these HCT procedures evolved and were refined, in parallel, but emerging at a slower pace has been the clinical development of cellular immune therapies, which has required a far more detailed analysis of the molecular immunology of the immune response to infectious organisms and malignant targets. Long after transplantation was established as a clinical tool, the dissection of the immune response occurred with identification of the crystal structure of HLA, the characterization of the complex effector:target cell adhesion interactions, and the appreciation of the need for costimulatory pathways for activation and inactivation of the T cell response. All these single cell understandings were coupled with the identification of multiple cellular subsets including dendritic cells, natural killer cells, T regulatory cells, activating and suppressing macrophages, and mesenchymal stromal cells, as well as discerning the role of naïve, effector, and memory cell populations. The seminal studies of Dr. Steven Rosenberg at the National Institutes of Health (NIH) in the generation and application of various cellular therapeutics, lymphocyte active killer (LAK) cells, and tumor infiltrating lymphocytes (TILs), and the training of a generation of immune therapists cannot be overlooked. The sequencing of the human genome in the 1990s and the development of successful gene transfer and expression, as well as the exploding field of gene editing, has further opened curative opportunities for patients. All these advances merge in an intricate dance of cellular biologic cross talk and the immune response, with an evolution that dates back to invertebrate coral and sponge species and their ability to perform the most critical role of immunity: the identification of self from nonself. These parallel investigations have now led to the application and commercialization of multiple cellular pharmaceuticals recently culminating in the worldwide approvals for chimeric antigen receptor T (CAR-T) cells as well as exciting gene replacement and editing studies that are tackling worldwide disorders such as sickle cell anemia and thalassemia major.

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 HCT achieves two goals: (a) replacement of host HSC pools after conditioning and (b) 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 with hematologic dose limiting toxicities 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 HCT.
7. The benefits of autologous HCT are dependent upon dose escalation of conditioning regimens.
8. Graft-versus-host disease (GvHD) after allogeneic HCT may be a consequence of the adoptive 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 HCT 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 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 HCT 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 will provide details that substantiate these principles.

Research Efforts in HCT

The success of HCT has its origins in the research laboratories and clinical research units of many worldwide institutions. The HCT 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 HCT 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 pre-existing comorbidities. But there remains room for improvement.

Much of the material within this handbook reflects established standards of care of management in the HCT 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 HCT) focused at infectious pathogens as well as the primary malignancy, T regulatory cells, new indications for HCT such as autoimmune disease or sickle cell disease, applications of natural killer cells, novel stem cell mobilization agents, and continued improvement in supportive care. In 2011, the American Society for Transplantation and Cellular Therapy (ASTCT) published a set of amended 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 [1, 2]. These priorities remain central in our focus and remain visible on the ASTCT website, available to all to review and serve as a guiding light to our field.

These include the following:

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-HCT relapse
    b. Immunotherapy with T cells and dendritic cells
3. Graft-versus-host disease
    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 HCT
    a. Genomics
    b. Proteomics
    c. Imaging
    d. Markers of immunologic recovery
    e. Phamacogenomics

5. Expanded indications for HCT
    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 HCT
    a. Graft sources
    b. Conditioning intensity
    c. Cost effectiveness

However, what is a glaring omission and likely will be the subject of the next ASTCT priority focus is the optimization of the cellular therapies that are rapidly emerging. The US Food and Drug Administration (FDA), European Medicines Agency (EMA), Canadian and Australian approvals of tisagenlecleucel (Kymriah®) and axicabtagene ciloleucil (Yescarta®) demonstrate the rapid acceptance of these novel T-cell therapeutics, with the expectation that multiple new drugs will follow in the very near future. We are only at the forefront of understanding the use of these agents. Additional questions remain as follows: When will they optimally be used? Will they remain as single agent therapies or will they best be served in combination with other classes of therapeutics? How can we avoid the unique associated CAR-T toxicities of cytokine release syndrome and neurotoxicity? Perhaps most importantly, how can all patients in need access these agents with their current high costs regardless of their home country?

Horizons/Challenges

As HCT remains an ever-changing field, so will be the field of cellular immunooncology. 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. The National Marrow Donor Program (NMDP) reported 6200 unrelated donor transplants in the United States in 2018 with an approximate total of 23,000 autologous and allogeneic transplants performed in the same timeframe [3]. Worldwide, there are now approximately 37 million available donors as reported by the World Marrow Donor Association (WMDA) and over 50,000 total transplants performed annually [4]. 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 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 HCT for chronic myeloid leukemia (CML) is a prime example [5]. Recognizing that the vast majority of patients with CML do not proceed to early HCT and the prevalence of CML in the general population has increased, patients who now undergo HCT are those with advanced or resistant disease. Despite this observation, HCT 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 HCT. Similar observations with autologous HCT for multiple myeloma have been made. The use of imides and proteosome inhibitors pre-HCT and as maintenance therapy post-HCT has led to marked improvements in progression-free survival and improved overall survival in myeloma patients. Active studies addressing the role of TKI oral therapy as adjuncts to HCT for treatment of FLT3-ITD+ acute myeloid leukemia (AML) are underway. Phase II studies have demonstrated that the use of post-HCT midostaurin (Rydapt®) or sorafanib (Nexavar®) has enhanced the likelihood of survival; an international multicenter, placebo-controlled randomized trial assessing gilteritinib vs placebo is ongoing and will provide definitive answers.

Another critical advancement is in the development of highly sensitive tools and devices to detect disease-specific molecular fingerprints and residual molecular signals after transplantation. These tools are defining new levels of molecular detection and guiding therapeutic interventions. These assays often can detect residual disease to a level of less than one in a million cells or lower (see also Chap. 57).

As a result, comparative effectiveness and outcomes research will remain essential as we compare HCT therapies to these new options. The availability of registry databases has been vital for these analyses and will remain critical for the future [6].

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 as a bridge to HCT, for relapse after HCT, and as standalone therapeutics. The resounding success of small institutional investigator-initiated

studies of chimeric antigen receptor-modified T cells (CAR-T) used for relapsed/refractory ALL and chronic lymphocytic leukemia (CLL) has launched large multicenter, industry-sponsored, and NIH-sponsored clinical trials to further explore these treatments in hematologic malignancies and multiple other disease settings, and as stated above has led to the regulatory approval of the first generation agents.

However, we must be aware that the increased numbers of patients undergoing HCT, as well as the observed improvement in survival, will lead to a greater demand for specialists in the field of HCT and cellular immuno-oncology [7–9]. Not only are the patients who undergo HCT or receive cellular therapeutics in need of specialized providers, the rapidly expanding population of survivors, particularly those with chronic GvHD, have difficulty in finding a medical home with their primary care providers or referring medical oncologists [10]. One potential future is that the comprehensive care delivery systems developed for HCT patients that resemble a medical home may become a model for other specialties. These care delivery systems have evolved from capitated-risk contracts for HCT patients and reflect the need for a mixed team of providers including HCT 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 previous analysis suggested that within the very near future, there will be a significant shortfall in physicians trained and focused on the care of HCT patients and the potential large number of patients that may receive T cell, natural killer cell, or other cellular therapies [8]. Thus, new paradigms must be developed for the delivery of care to the HCT 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 HCT providers has been developed by The American Society of Transplantation & Cellular Therapy (ASTCT) and is available through the ASTCT website (ASTCT.org). Similar training programs have been developed by the ASTCT Pharmacology Interest Group for pharmacists in the field as well as multiple training programs developed by the European Group for Blood and Marrow Transplantation (EBMT).

This handbook will provide the background for all medical professionals involved in the management of the HCT recipient, including physicians, advanced practice providers, pharmacists, nurses, etc.; however, its main focus will be those providers who provide daily bedside care. Guidelines are provided for evaluating and selecting the appropriate transplant candidate, recognizing that not only medical but also socioeconomic factors influence outcomes. Detailed descriptions of appropriate pre-HCT conditioning and 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. Information on management of the long-term survivor as well as those that experienced post-HCT relapse is included. Finally, multiple contributions regarding the application of and consequences associated with varying immune effector cell therapies are provided.

Management of the HCT 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, there is a very large and extensive professional community that has developed to care for the individual patients. The ASTCT and the 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. But they are not alone. The American Society of Hematology (ASH), 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 & Marrow Transplant Clinical Trial Network (BMT CTN) [11] were created to facilitate the generation of multicenter, transplant-focused trials for the advancement of the field. As our field rapidly expands to incorporate the advances of cellular therapy, the International Society of Cell Therapy (ISCT), the American Society of Gene & Cell Therapy (ASGCT), and the rapidly growing Society of the Immunotherapy in Cancer (SITC) are welcome new partners. These professional societies and groups represent our village.

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Chapter 2
The Business of Cellular Therapy and Hematopoietic Cell Transplantation

Peggy L. Appel and Gary Goldstein

Introduction

Hematopoietic cell transplantation (HCT) and immune effector cell (IEC) therapy are extremely complex and expensive procedures, requiring significant personnel, pharmaceutical, supportive, and patient/family resources.

Classically, after achieving primary disease control, the first step in HCT 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 over 50 years ago. As indications multiplied and transplant-related mortality declined, HCT utilization expanded with a dramatic increase in the number of both autologous and allogeneic procedures performed over the past decade (Fig. 2.1).

HCT has demonstrated efficacy for treatment of selected malignancies (e.g., multiple myeloma, acute and chronic leukemia, and lymphoma), as well as for immunodeficiency, bone marrow failure, and infiltrative disorders such as amyloidosis. 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 (Figs. 2.2 and 2.3).

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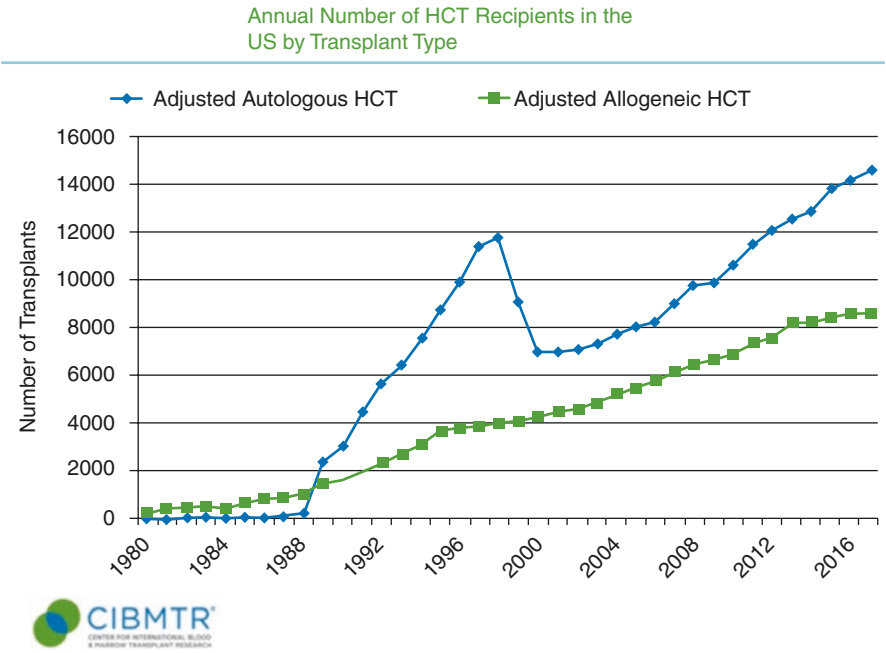

Fig. 2.1 Annual number of HCT recipients in the US by transplant type

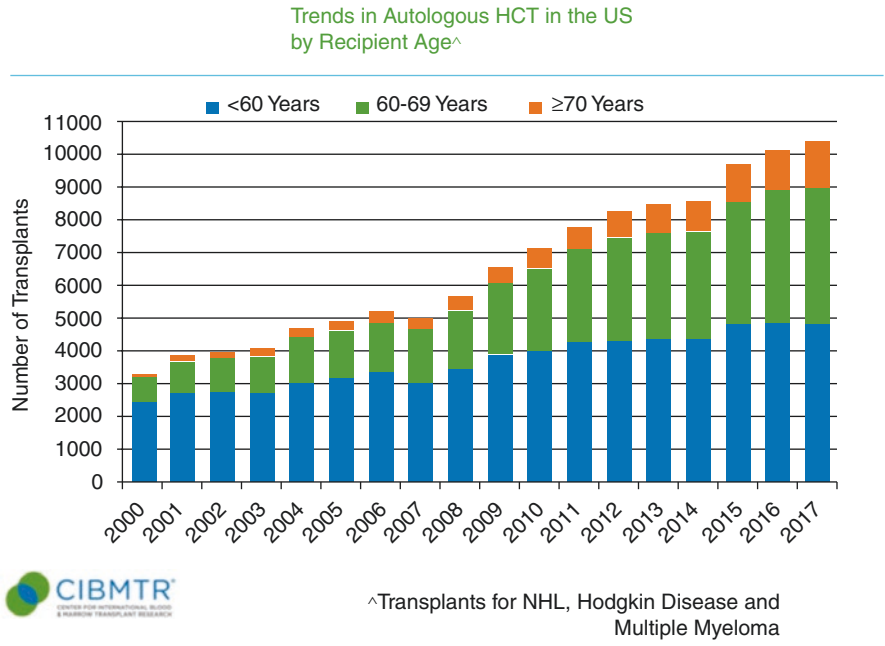

Fig. 2.2 Trends in autologuous HCT in the US by recipient age (Transplants for NHL, Hodgkin Disease and Multiple Myeloma)