Blood and Marrow Transplantation Long-Term Management
Prevention and Complications

Edited by
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WILEY Blackwell
Blood and Marrow Transplantation
Long-Term Management
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The science and clinical application of stem cell transplantation began soon after the Second World War, prompted by intensive research to find ways to treat radiation sickness. But substantial numbers of allogeneic stem cell transplants only began to be performed in the 1970s. Decade by decade the number of transplant centers has increased, and the number of successful transplants has increased. Long-term survivors from transplant thus represent a new field of medicine born out of the success of a procedure that is every year becoming both increasingly applied and more successful in its outcome.

No reliable data exist as to how many long-term survivors are now living, but we can make some estimates: The World Blood and Marrow Transplantation Organization (WBMT) has assembled data from over 1400 stem cell transplant teams from 72 countries in 5 continents. In recent years the combined reported world output for stem cell transplants is in the order of 50,000 transplants a year. As a rough estimate, this represents about half a million transplants per decade, but this figure is conservative given a steady increase in the number of transplants being performed in all parts of the world every year. Assuming a conservative global 30% long-term survival for the 1 million transplants performed in the last 20 years, we can expect around 300,000 long-term transplant survivors. Allowing for underreporting and adding in survivors from all transplants since 1970, it is likely that there are substantially more than half a million long-term survivors from transplant worldwide.

This book is therefore timely and at the same time unique: the first textbook on long-term survivorship after stem cell transplantation. It will be an invaluable source for all practitioners and caregivers responsible for the lifelong management of this burgeoning group of individuals. Bipin Savani, the editor, has assembled what must be the definitive text on this subject and has called upon 74 co-authors to put together this authoritative book. Section 1 sets the stage, with contributions from acknowledged experts in the field from Europe and the USA, covering the organizational aspects of long-term care of transplant patients. Section 2 is devoted to management of the major issues facing our survivors: second malignancies, graft-versus-host disease, infections, organ-specific complications, and the long-term screening systems needed to manage transplant recipients over the years. As risks of serious complications diminish, the quality of life of the survivors becomes a paramount and not-to-be forgotten consideration. It is appropriate that Section 3, in its entirety, deals with the supportive care and management of our survivors who have been changed in many ways by the transplant procedure. Finally, the list of appendices is a source of practical “go-to” information that caregivers of all types will find extremely helpful in the management of our population of valiant survivors.

In clinical medicine, which is often subject to vogues and trends with short-lived impact, the care of stem cell transplant recipients stands out as a critical area of medicine which will inevitably grow in importance and remain with us over the years ahead. Blood and Marrow Transplantation Long Term Management: Prevention and Complications, is a book well shaped to introduce the field and is likely to run into multiple editions in the decades to come. My congratulations go to Dr Savani and the world-class panel of authors for this timely and essential contribution to the practice of stem cell transplantation!

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Survivors of hematopoietic cell transplantation have already faced myriad challenges to their health. The majority received treatment for their diseases before transplantation. Almost all have received supportive care and frequent monitoring. The transplant process itself may have been physically painful and debilitating, and the emotional journey can be exhausting. Afterwards, patients and their families face recovery, reintegration, and the rest of their lives.

This book is about that last concept: “the rest of their lives.” Transplant survivors have higher rates of cancers, heart and kidney disease, diabetes, infections, and premature death than people who have not had the transplant experience. It is tragic that in the course of trying to cure one life-threatening disease we may be sowing the seeds of collateral suffering and deaths from other diseases. Some treating physicians may view late effects as the inevitable price to pay for cure. The premise of this book is that the goal of transplantation should not just be eradication of the underlying disease, but also the return to as much of a normal and healthy life as possible. We care providers have a responsibility to transplant survivors to improve our ability to address the physical and emotional sequelae of transplantation. I use the term “providers” because many survivors no longer receive care from oncologists or hematologists, but instead are treated by general pediatricians or internists. Increasingly, mid-level providers, pharmacists, and other health professionals will help care for transplant survivors and need this information too.

This book presents the most current knowledge about how to prevent, detect, and treat problems that arise after hematopoietic cell transplantation. In some cases, extensive epidemiologic studies and case series have defined the increased risks; for other complications, rare occurrences are known to happen but the true incidence is less certain. Our understanding of late effects prevention is still largely at the stage of identifying clinical risk factors. Genetic and environmental factors either are not examined or are poorly understood. Treatment approaches are primarily based on knowledge gained from other patient populations. High-quality studies designed to develop and test prevention and treatment strategies in transplant survivors are logistically daunting and rarely performed because of decentralized patient care, patient heterogeneity, lack of funding, or lack of effective interventions. Thus, another purpose of this book is to highlight gaps in our clinical knowledge and treatment armamentarium so that additional studies can be performed. It is my fervent hope that this book will soon be out of date and in need of another edition, since that would mean that much more information about late effects is accumulating and treatments have advanced.

Some say the true meaning of cure is being able to forget that you had a transplant. But your body and organs do not forget. Late effects of transplantation, the unintended adverse consequences of our aggressive attempts to eradicate hematologic cancers and other diseases, cause significant morbidity and mortality. We can decrease their impact by making sure that providers are prepared to diagnose them and provide the best treatments available. The message of this book is one of optimism: better information and proactive care can help people stay healthier “for the rest of their lives” despite having had a transplant.

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Though, sadly, there was been little progress in recent years in some areas of medicine, the clinical use of hematopoietic stem cell transplantation is not one of them. If 50 years ago one had suggested to an experienced hematologist that one could collect nucleated cells from the marrow or indeed from the blood of normal persons and infuse them in relatively small numbers into a suitably “prepared” patient with leukemia or another hematologic or immunologic disorder and thereby cure the disease, the suggestion would have been greeted with incredulity. In reality, the pioneering preclinical work of many laboratory scientists, the increased understanding of histocompatibility antigen, and the dedicated commitment of clinicians such as Georges Mathé, Robert Good, and Don Thomas laid the foundations for the first successful bone marrow transplants in the 1970s. It is difficult today to appreciate the scepticism or, indeed, formal opposition with which the initial work of these enthusiasts was met.

In the beginning of the 21st century, stem cell transplantation in some form or another is practised in 60 to 70 countries of the world and there is no aspiring hematologist who does not learn early that there are certain diseases for which allogeneic or autologous stem cell transplantation offers a real chance of cure or at worst just useful palliation. This means that the number of persons surviving and in many cases cured of a serious and usually life-threatening disease has increased enormously in recent years. This collection of papers written by experts in the field of stem cell transplantation could not have been contemplated by earlier researchers in the field for the simple reason that the number of patients who had survived long term would have been very few. Today, clinical data on transplant recipients are carefully collected and analysed by two very valuable organizations: on a global scale by the International Center for Blood and Marrow Transplant Research and by the European Group for Blood and Marrow Transplantation, which focuses mainly on Europe. Data collated by these two agencies and the multiplicity of individual publications covering many aspects of health in patients alive at 5, 10, or more years after a transplant procedure show clearly that some long-term survivors do still have specific problems associated with their original transplant procedures, but most of these are relatively minor and eminently treatable. The fact that there are so many “ex-patients” alive today is a truly impressive testament to the progress that has been made in this field since the 1960s.

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SECTION 1
Late effects concepts
CHAPTER 1
Introduction
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Background

Allogeneic hematopoietic cell transplantation (allo-HCT) provides curative therapy for a variety of diseases. Over the past several decades, significant advances have been made in the field of allo-HCT and now allo-HCT has become an integral part of treatment modality for a variety of hematological malignancies and nonmalignant diseases. Advances in transplantation technology and supportive care measures have resulted in significant decrease in early mortality, resulting in continued growth in the number of long-term HCT survivors.

These patients have increased risks for a variety of late complications (Figure 1.1), which can cause morbidity and mortality [1].

As HCT survivorship increases, the focus of care has shifted to the identification and treatment of long-term complications that may affect long-term survival and quality of life [2–7]. Preventive care and early detection and treatments are important aspects to reducing morbidity and mortality in long-term survivors after HCT. This book focuses on the essential knowledge about diagnosis, screening, treatment, and long-term surveillance of long-term survivors after HCT.

Long-term survivorship after hematopoietic cell transplantation

Since the first three cases of successful allo-HCT in 1968, the number of allo-HCTs performed annually has increased steadily over the past three decades [8–11]. It is estimated that by 2015 more than 100,000 patients will receive HCT (combined allogeneic and autologous) annually throughout the world, and numbers are increasing rapidly. Long-term survival after HCT has improved significantly since its inception over 40 years ago owing to improved supportive care and early recognition of long-term complications. With broadening indications, more options for HCT, and improvement in survival, there may be up to a million long-term survivors after HCT by 2020 worldwide [12].

The rapidly growing population of HCT survivors creates an obligation to educate patients and physicians about the late complications observed in patients after this therapy. Historically, limitation of allo-HCT has been transplant-related mortality (TRM). In order to offer the curative allo-HCT treatment option in most patients, safer regimens with acceptable graft-versus-host disease (GVHD)-associated morbidity and TRM are preferred. A recently published M.D. Anderson Cancer Center study showed an excellent overall survival and progression-free survival (85% and 83%, respectively, after median follow-up of 60 months) for relapsed follicular lymphoma after fludarabine, cyclophosphamide, and rituximab reduced-intensity conditioning (RIC) allo-HCT [13]. Similarly, many disease-specific transplant regimens are in development to improve transplant outcome after HCT.

In this era, a stem cell source can be found for virtually all patients who have an indication to receive allo-HCT. Since 2007, more allo-HCT procedures have been
Late effects after hematopoietic cell transplantation

Several studies have investigated the late effects of allo-HCT recipients, and the cumulative incidence of a late effect among long-term survivors has been reported to be 32–93.2% [7, 14–17]. Bresters et al. [15] reported that the cumulative incidence of late effects was 93.2% after a median follow-up time of 7.2 years after HCT, and Sun et al. [16] reported that survivors were twice as likely as their siblings to develop a chronic condition and 3.5 times as likely to develop severe conditions.

Among long-term survivors after allo-HCT, mortality rates are four- to nine-fold higher than observed in an
age-adjusted general population for at least 30 years after HCT, yielding an estimated 30% lower life expectancy than someone who has not been transplanted [17]. Among long-term survivors, the most common causes of excess deaths other than recurrent malignancy are chronic GVHD, infections, second malignancies, respiratory diseases, and cardiovascular disease [10, 18–20]. Higher than average rates of second malignancies and cardiopulmonary, infectious, endocrine, and renal diseases, bone loss or avascular necrosis, and many other late complications after HCT suggest that this population requires more frequent screening and earlier interventions than the general population [21–24].

Chronic GVHD is a multisystem chronic alloimmune and autoimmune disorder that occurs later after allo-HCT. It is characterized by immunosuppression, immune dysregulation, decreased organ function, significant morbidity, and impaired survival. Approximately 10–30% of patients require continued immunosuppressive treatment beyond 5 years from the initial diagnosis of chronic GVHD. Therefore, it is not surprising that corticosteroid and other immunosuppressive therapies are major contributors of late complications after allo-HCT. Several factors impact on recovery from and late effects of allo-HCT, including prior therapy for the underlying disease, pre-transplant comorbidities and psychosocial status, intensity of the transplant conditioning regimen, and, most importantly, duration of chronic GVHD and immunosuppressive therapy [12, 25, 26].

**Developing resources and a guide for long-term survivors**

Transplant society guidelines for screening and preventive practices for pediatric and adult survivors of auto- and allo-HCT were updated and published in 2012 [27]. Ongoing research is focused on better understanding of late-effect issues and prediction of posttransplant long-term complications, which allows transplant-eligible patients to incorporate this knowledge into more informative decision making. Therefore, significant resources should be focused on the better implementation of how patients and physicians use extensive data regarding post-transplant late complications in clinical care.

We also recommend early referral or discussion with a transplant center for enrollment of patient in available late-effect studies and for management guidelines. A better understanding of the pathogenesis of late effects will allow for more effective screening to identify patients at risk prior to the HCT procedure, and allow more effective monitoring to detect early evolution of the late effects after HCT. This may, in turn, allow for improved therapeutic decision making while evaluating patients for HCT, and early institution of treatments directed at preventing and treating late effects in patients at risk after HCT.

With survivorship, a shift in survivorship care occurs from large transplant centers to community health care providers. As a result, many hematologists/oncologists and primary care physicians are assuming the post-HCT late-effects care of long-term survivors. Long-term survivors should be assessed lifelong after HCT; all health care providers involved in the follow-up of these patients should be aware of the premature health threats of long-term complications after transplantation. This book offers practical advice and outlines late-effect experts’ personal approaches in managing long-term complications after HCT.

**Declaration of commercial interest**

None.

**References**


Hematopoietic stem cell transplantation (HSCT) has evolved to become a standard of care for many patients with congenital or acquired disorders of the hematopoietic system and for a wide variety of chemo-sensitive, hematologic malignancies [1–3]. Fifty years have passed since the first reports of successful bone marrow transplants from human leukocyte antigen (HLA)-identical siblings for patients with immune deficiency disorders. After an initially slow evolution, HSCT has seen rapid expansion over the last two decades and major changes in technology use [4–7].

HSCT is a high-cost, highly specialized procedure. It requires significant infrastructure and a network of specialists from multiple fields of medicine. It is not available without preparative work by setting up a transplant center and organizing all the auxiliary services required to perform this procedure. Information on indication and trends is essential for healthcare agencies in order to prepare the necessary infrastructure. Given costs for HSCT, use of this technology is predominantly limited to high- and middle-income countries where the expansion in procedures performed has occurred [3]. In such a complex field, standardization is necessary and scientific societies have classified indications for HSCT by the degree by which they are supported by scientific evidence [8]. Furthermore, quality management systems have been created in order to support transplant centers to achieve the best possible outcomes [9].

The European Group for Blood and Marrow Transplantation (EBMT) introduced an annual activity survey in 1990 that provides data on HSCT use by indication, type of transplant, donor type, and stem cell source [10]. Using data from that survey, we will highlight in this chapter the current trends in technology use and in changes occurring. As this book is on long-term complications of HSCT, we will try to estimate the number of patients at risk for such long-term complications in Europe based on transplant numbers as provided by the EBMT activity survey and based on survival estimates as provided by the EBMT database. Through the Worldwide Bone Marrow Transplant Group (WBMT), data from Europe have been combined with reports from North, Middle and South America, the eastern Mediterranean and Africa, and from Asia–Pacific registries in order to provide a world view of transplant activity [3]. In 2006, 50,417 transplants were reported to the WBMT from these global registries.

The European experience can be largely extrapolated to areas with similarly highly developed medical systems. We will limit the data presented here to the European experience as we do have a long-term view over more than 20 years of annual surveys [4].

Teams participating in the annual survey are requested to report annually by indication, stem cell source, and donor type. Quality control measures include several independent systems: confirmation of validity of the
entered data by the reporting team, selective comparison of the survey data with data sets in the EBMT registry database, crosschecking with the national registries and onsite visits of selected teams. A total of 654 centers were contacted for the 2010 survey, of which 634 teams reported their numbers. This corresponds to a 97% return rate. In all, 22 active teams failed to report in 2010. By tradition, some centers outside of Europe are EBMT members and report data. These comprise 7% of the total data set and are included in all analyses.

According to the EBMT 2010 annual survey 33362 transplants were performed in 30012 patients. Of these 33362 transplants, 13345 were allogeneic and 20017 autologous (Table 2.1). The indications for autologous and allogeneic HSCT are shown in Table 2.1. Only first transplants are shown, corresponding to number of patients rather than number of transplants. It is well known that indications for allogeneic and autologous HSCT differ and that more leukemia patients receive allogeneic HSCT and more patients with lymphoid neoplasia and plasma cell neoplasia receive autologous HSCT. The number of transplants for bone marrow failure, autoimmune disorders, and congenital diseases is smaller than those for malignancy. Figure 2.1 shows the evolution of transplant numbers for autologous and allogeneic HSCT, with a continuous increase between 1990 and 2010. Two changes in clinical practice are mirrored in the curves displayed. The first is the introduction of imatinib (in 1999) for the treatment of chronic myeloid leukemia, resulting in a transient slowing of allogeneic transplant numbers in the early 2000s. The second is the discontinuation of autologous HSCT for breast cancer after the publication of negative data, resulting in a hump in the curve depicting numbers of autologous transplant numbers in the early 2000s. The second is the discontinuation of autologous HSCT for breast cancer after the publication of negative data, resulting in a hump in the curve depicting numbers of autologous transplant numbers in the early 2000s. The current increase in transplant numbers are due to higher rates of allogeneic HSCT for leukemia and more recently in myelodysplastic syndrome and chronic lymphocytic leukemia. Autologous HSCT increases are mainly due to transplants for lymphoid neoplasias and plasma cell disorders.

If the total of transplanted patients from 1990 to 2010 is cumulated, there is a total of 375948 patients that have been reported to the survey, of which 135179 had an allogeneic HSCT (36%) and 240769 an autologous

<table>
<thead>
<tr>
<th>Indication</th>
<th>Allogeneic 1st HSCT</th>
<th>Autologous 1st HSCT</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukaemia</td>
<td>8685</td>
<td>670</td>
<td>9355</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>1411</td>
<td>7550</td>
<td>8961</td>
</tr>
<tr>
<td>Plasma cell disorder</td>
<td>566</td>
<td>7835</td>
<td>8401</td>
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<tr>
<td>Solid tumor</td>
<td>81</td>
<td>1504</td>
<td>1585</td>
</tr>
<tr>
<td>Bone marrow failure</td>
<td>676</td>
<td>1</td>
<td>677</td>
</tr>
<tr>
<td>Non-malignant disorder</td>
<td>773</td>
<td>159</td>
<td>932</td>
</tr>
<tr>
<td>Other</td>
<td>84</td>
<td>17</td>
<td>101</td>
</tr>
<tr>
<td>Total</td>
<td>12276</td>
<td>17736</td>
<td>30012</td>
</tr>
</tbody>
</table>

Figure 2.1 Development of autologous and allogeneic HSCT in Europe from 1990–2010 [4].
HSCT (64%). The main indications were leukemias with 125,139 patients (33% – 98,108 allogeneic (78%) and 27,031 autologous (22%)), lymphoid neoplasias with 189,299 patients (50% – 17,625 allogeneic (9%) and 171,674 autologous (91%)), solid tumors with 41,070 patients (11% – 13,540 allogeneic (3%) and 39,716 autologous (97%)), and nonmalignant disorders with 17,953 patients (5% – 16,457 allogeneic (92%) and 14,962 autologous). An additional 2,487 patients (0.7% – 1,635 allogeneic and 852 autologous), were listed as “other indications.”

Trends over the last 20 years have included the shift from marrow as a stem cell source to using peripheral blood, first in autologous HSCT and later in allogeneic HSCT. The association of peripheral blood use for allogeneic HSCT with higher risks of chronic graft versus host disease has been recognized, and in nonmalignant disorders the trend towards increasing use of peripheral blood over marrow as a stem cell source has been halted. New sources of stem cells have been developed, such as cord blood, which is used in 7–8% of all allogeneic HSCT. A major shift in donor use for allogeneic HSCT is shown in Figure 2.2. Around the beginning of the last decade, the introduction of HLA high-resolution typing has resulted in better typed volunteer unrelated donors, resulting in better outcomes. As a consequence of this, and of the availability of high-resolution typing technology at a reasonable price, the unrelated donor registries have expanded and now include more than 20 million volunteer donors. Figure 2.2 shows that since 2007 and 2008 the number of unrelated donor transplants done in Europe has exceeded the number of transplants from sibling donors. The use of unrelated donors is in large part responsible for increasing transplant numbers, in addition to changes in transplant technology for allogeneic HSCT, in particular reduced-intensity conditioning transplants amounting to 30–60% of all allogeneic HSCT with variation between countries. Reduced-intensity conditioning HSCT has opened up the option of allogeneic HSCT in older patients, who are the majority of patients with hematologic malignancies, with median age of onset for most diseases being between 60 and 70 years of age.

Long-term survival after HSCT has increasingly become the center of attention in recent years [11–16]. It has been recognized that many of these patients suffer from late complications that need to be recognized, diagnosed, and treated appropriately. Furthermore, all patients, and in particular those treated many years ago as children having reached adult life, require medical care adapted to their prior medical experience, even though many of them lead an active life [15]. In addition, in the early years of HSCT, every patient treated was considered as a single medical achievement and patients were followed long term at their transplant center. With increasing numbers of transplants performed and with

Figure 2.2 Allogeneic HSCT in Europe from 1990 to 2010 by donor type [4].
increasing numbers of long-term survivors, as shown above, organizing this care becomes increasingly difficult and some of this care may be delegated to referring physicians. Tools and guidelines have been developed to help with this care, and much of this will be discussed in the upcoming chapters.

A quantitative assessment of the magnitude of the issue of the number of patients requiring long-term care is difficult to provide, and modeling may be complex as transplant rates are increasing rapidly, as is the age of patients undergoing allogeneic and autologous HSCT. To estimate this number for Europe, we took the total cumulative number of patients transplanted in Europe during 1990–2010 that were reported to the EBMT activity survey and multiplied this number by survival estimates from the EBMT data registry, which indicate that, for 1990–2010, the overall survival at 5 years is approximately 53% and at 10 years this is 44%, including all diseases and all types of transplant. Extrapolating from this information, approximately 200,000 patients are expected to be alive in Europe having had an HSCT in the past. This estimate may be criticized as being imprecise, as there are patients included that are from non-European centers; all the patients transplanted before 1990 are not counted, and appropriate adjustments for patient age and from the recent increase in transplant activity are not made. Nonetheless, this number, however imprecise, provides a stimulus for the tasks ahead. These patients are at risk of late effects and are the focus of our attention.

References

CHAPTER 3
Long-term transplant clinic setup

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Introduction

With the increasing number of hematopoietic stem cell transplants (HSCTs) performed yearly worldwide, and the improvement of survival after transplantation, the number of patients surviving 2 years and longer after transplantation is continuously increasing. Between 1980 and 2010, the European Group for Blood and Marrow Transplantation (EBMT) registry included 339,402 patients who underwent either first autologous (211,543) or allogeneic (127,859) HSCT. From these 339,402 patients, 150,235 (44.3%) patients survived 2 years or longer since first HSCT: 97,531 autologous and 52,704 allogeneic HSCT (unpublished data from the EBMT registry). By 2020, there may be worldwide up to half a million long-term survivors after allogeneic HSCT [1]. Long-term recipients who have overcome the acute toxicity phase of HSCT and are in remission of their primary disease have completed their treatment and will no longer be considered as patients. Nevertheless, long-term HSCT recipients, similar to cancer patients, do not return to prediagnosis status [2] and, therefore, cannot be considered as healthy persons. Indeed, about two-thirds of the transplanted patients will experience at least one late effect that is not related to the primary disease, but the direct or indirect consequence of the cancer treatment or the transplant procedure [3]. Malignant and nonmalignant late complications after HSCT will interfere with the general health condition, the quality of life, family life, and the reinsertion in social life at school or at employment of the patient. During the transplantation period the focus of care has extended from the cure of the primary disease to the screening and management of late effects and improvement of quality of life. The transition from the acute phase of HSCT to post-treatment care is critical to maintain long-term health. At this phase, recipients of transplantation need specialized follow-up care. This involves not only the patient themselves and their family, but also the transplantation center and its organization.

In cancer medicine, the need of special attention to long-term cancer patients has been recognized for more than 50 years. The definition of long-term survivor and the concept of cancer survivorship were introduced by the Institute of Medicine by engaging a committee to examine medical and psychological issues of cancer survivors and to make recommendations to improve their health care and quality of life. According to the Institute of Medicine, cancer survivorship is the phase of care that follows primary treatment. However, this definition allows a wide range of interpretation, depending on the time of diagnosis, the completion of treatment, and the time interval between the diagnosis and the end of treatment of the cancer. A Cancer Survivorship Program is intended to provide a specialized follow-up care to long-term survivors who are in remission after having completed their cancer treatment, usually for at least 2 years or longer. Some of the controversial issues of a survivorship program concern the type and frequency of optimal follow-up care, the increased expenses caused, as well as the extra time and the physical space needed to run such a program. In many countries the costs of the follow-up care are no longer covered by the insurances that covered expenses of the cancer treatment. Cancer survivors are
usually seen once a year in a follow-up program. However, this cancer survivorship program does not replace the regular primary health care of long-term survivors. Both, regular primary health care and long-term follow-up are complementary.

Compared with cancer survivorship care, posttransplant long-term follow-up programs emerged with some delay. The reason for this delay is obvious, since efficient cancer therapies have been available now for more than 60 years, whereas the first transplantation centers started about 30–35 years ago. The transplant survivorship programs have adopted much from the experience of the cancer survivorship programs and, therefore, they are roughly based on the models of cancer survivorship care. In analogy to cancer survivorship, the long-term survivors after HSCT are usually defined as patients currently in remission of their primary disease and surviving 2 years or longer since completion of transplantation. However, survivorship after HSCT has its own particularities owing to the type and intensity of the conditioning regimen, the prolonged immune incompetence, and, in patients treated with allogeneic HSCT, the late effects due to graft-versus-host disease (GVHD) and its treatment. Survivorship programs and long-term transplant clinics will therefore share many characteristics with cancer survivorship programs, but also present some features of their own.

Setting up a long-term transplant clinic is a challenging but rewarding experience for a transplantation center. When a center starts with a transplantation program, the whole team is initially confronted with the immediate survival and disease control. The major focus is placed on problems related to acute toxicity, relapse, GVHD, and infectious complications. Usually, there is not much time left for patients without acute medical issues. With advancing time, the number of long-term survivors of the new transplant center is increasing. Their needs and expectations become different. In general, they require less acute medical interventions and immediate care, but have increasing expectations of good physical and mental health and quality of life. For the long-term survivorship care, the focus is on careful screening, prevention, and early treatment of possible late effects that interfere with good health condition. Transition from acute care to long-term follow-up is a process rather than an event. Some particular aspects have to be considered when choosing a model of a long-term transplant clinic. A common outpatient HSCT clinic, where acute care and long-term follow-up are mixed, allows continuity in the care, but faces the risk that the particular needs of long-term survivors are left behind the daily care of the new posttransplant patients. In contrast, dedicated long-term follow-up clinics run into the danger of losing continuity of care from the acute phase to the follow-up care. Community-based models, where long-term survivors are followed by community healthcare providers, discharge the transplant centers from the ever-increasing of burden of long-term survivors. However, these primary care doctors are not necessarily experts in chemotherapy agents, specific transplantation problems, and in long-term effects after HSCT. Furthermore, they are not surrounded by a complete network of specialists needed for the care of long-term survivors.

In this chapter, the setup of a long-term transplant clinic and the essential functions and components of a survivorship care program will be outlined. Different models of survivorship programs and clinics will be considered, and the minimal requirements discussed. This chapter consists of two parts. In the first part we will present the lessons learned from the experience of cancer survivorship programs. In the second part we will concentrate on the particular aspects of transplant survivorship clinic programs.

**What we have learned from cancer survivorship models**

The concept of survivorship in cancer patients was created by the National Coalition for Cancer Survivorship (NCCS) in 1986. Accordingly, a cancer survivor is a person with a cancer diagnosis who has completed treatment. The Institute of Medicine and leaders in cancer survivorship have recommended cancer centers to examine and evaluate the setup of services for survivors. In a first step, general recommendations and the development of guidelines have been assessed for pediatric and adult cancer survivors [4, 5]. Today, the Institute of Medicine provides a template for the four essential elements of the survivorship care: prevention and detection of late effects, surveillance, interventions to manage side effects, and coordination of care and information [6]. Cancer survivors’ needs vary depending on the type of disease and the treatments received. Long-term events may be