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 concepts

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.

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performed using alternative donor stem cell sources, such as volunteer unrelated donors or cord blood, than have been performed using related donors [9]. RIC haploidentical-related donor or cord blood transplantations have emerged as alternatives to fill the gap for those patients who do not have a matched related donor or unrelated donor, and the outcomes of these types of transplantations are expected to be better than chemotherapy alone or even better than auto-HCT for selected indications. The result of this is a steadily increasing number of long-term survivors after allo-HCT, creating an enlarging pool of children and young and mature adults who are at risk of long-term complications of allo-HCT.

**Late effects after hematopoietic cell transplantation**

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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 alloHCT. 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 preventative 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


