Immune reconstitution post allogeneic transplant and the impact of immune recovery on the risk of infection

Rohtesh S. Mehta and Katayoun Rezvani

Division of Hematology, Oncology and Transplantation, University of Minnesota, Minneapolis, MN, USA; Department of Stem Cell Transplantation and Cellular Therapy, MD Anderson Cancer Center, Houston, TX, USA

ABSTRACT

Infection is the leading cause of non-relapse mortality after allogeneic haematopoietic cell transplantation (HCT). This occurs as a result of dysfunction to the host immune system from the preparative regimen used prior to HCT, combined with a delay in reconstitution of the donor-derived immune system after HCT. In this article, we elaborate on the process of immune reconstitution post-HCT that begins with the innate system and is followed by recovery of adaptive immunity. Simultaneously, we describe how the tempo of immune reconstitution influences the risk of various infections. We explain some of the key differences in immune reconstitution and the consequent risk of infections in recipients of peripheral blood stem cell, bone marrow or umbilical cord blood grafts. Other factors that impact on immune recovery are also highlighted. Finally, we allude to various strategies that are being tested to enhance immune reconstitution post-HCT.

KEYWORDS

adaptive immunity; allogeneic haematopoietic stem cell transplant; immune reconstitution; infection; innate immunity

Introduction

Allogeneic haematopoietic cell transplantation (HCT) is a potentially curative treatment option for a variety of malignancies. A large part of this benefit is derived from the transfer of the donor’s immune system to the host, which can elicit a potent graft-vs.-tumor effect. However, the recovery of a broad, functional T- and B cell immunity is delayed following HCT. The reason for this is manifold. High dose chemotherapy and/or radiation therapy used as conditioning regimen for allogeneic HCT results in severe mucosal, humoral and cellular immune dysfunction. Moreover, the host’s thymopoiesis may be blunted, even prior to transplantation, as a result of thymic toxicity induced by cytotoxic therapy or radiation, which can further delay functional immune recovery. These factors collectively predispose the host to a variety of infections. In fact, despite the routine use of prophylactic antimicrobials in the peri-transplant period, infections occur in about 80–85% of HCT recipients and are one of the leading causes of non-relapse mortality after allogeneic HCT, even in long-term survivors.

Epidemiology of infections post transplantation

The spectrum of infections after HCT appears to correlate with the kinetics of immune recovery. [Fig. 1]. In the very early period post-HCT (up to day 30), conditioning regimen-related mucosal injury and severe aplasia predisposes patients to a variety of bacterial (mostly coagulase-negative Staphylococcus, Enterococcus, gram negative gastrointestinal bacteria and Clostridium difficile), fungal (mostly related to Candida species), and viral infections (mostly secondary to herpes simplex virus (HSV) reactivation). Reactivation of cytomegalovirus (CMV), Epstein-Barr virus (EBV) and infections from Pneumocystis jirovecii and Aspergillus species generally occur from engraftment until around day 100 or later, in the presence of graft-versus-host disease (GVHD) or prolonged immunosuppression. Varicella-zoster virus (VZV) reactivation usually occurs after day 100 – reflecting functional immaturity of T lymphocytes. During the same time period, infections secondary to encapsulated bacteria (such as Streptococcus pneumoniae, Neisseria meningitides and Haemophilus influenzae) are also common due to deficient humoral immunity and impaired opsonization. Risks of invasive fungal infections, community respiratory viruses and parasitic infections are evenly spread for up to 2 y post-transplantation. Depending upon the graft source, infections account for 15–30% of deaths in the first 100 d post-transplant, and about 10–40% of deaths beyond day 100. Fungal organisms are responsible for most of the infection-related mortality (50–80%), followed by bacterial causes (15–50%).

CONTACT Katayoun Rezvani krezvani@mdanderson.org MD Anderson Cancer Center, Stem Cell Transplantation, 1515 Holcombe, Houston, TX 77030, USA.

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Several donor, host and transplant-related factors determine the risk of infections after HCT. For instance, higher infection risk is associated with older age or advanced disease at the time of transplant, use of myeloablative regimens compared with reduced-intensity conditioning (RIC) regimens, use of ex vivo or in vivo T-cell depletion (TCD), delayed engraftment of neutrophils, development of GVHD, HCT with human leucocyte antigen (HLA)-mismatched grafts, use of umbilical cord blood (UCB) or bone marrow (BM) grafts compared with granulocyte-colony stimulating factor (G-CSF)-mobilized peripheral blood stem cells (PBSC), to name a few.

**Immune reconstitution post transplantation**

Recovery of the immune system after HCT is a highly dynamic process. It begins with resurgence of innate immunity within the first few weeks of HCT, followed by that of the adaptive immune system. The latter may take 2 y or longer to recover fully, as depicted in Figure 2.

**The innate immune system**

**Recovery of mucosal injury**

The conditioning regimen often results in a breach of epithelial surfaces and mucous membranes, which are the first line of defense against infections. This damage is expected to be worse with myeloablative than with RIC regimens, worse with BM compared to PBSC grafts, and is observed more frequently with matched unrelated donor (MUD) than with matched sibling donor (MSD) HCT. Due to the diversity of the normal microbial flora that flourishes on mucous membranes, regimen-related mucosal damage can lead to an array of infections as a result of the organisms entering the blood stream. Patients with oral mucositis are especially at risk of infections by \( \alpha \)-hemolytic streptococcal bacteria, Candida species and HSV. Patients with gastrointestinal tract mucositis are prone to enterocolitis and systemic infections caused by colonic and opportunistic organisms, including pseudomonas and fungal organisms.

The recovery of damage to the intestinal epithelial barrier is mediated by the secretion of antimicrobial peptides, such as Reg3\( \alpha \) by the Paneth cells, which regulates the normal gut microbiome and protects against GVHD. Absence of this protective mechanism leads to bacterial overgrowth, low microbial diversity, uncontrolled GVHD and high risk of non-relapse mortality after HSCT. This may be partly explained by the important role of gut bacteria in the induction of colonic regulatory T cells (T\( _{reg} \)).

A recent elegantly designed murine study reported that the reduction in the micro-biota-derived short-chain fatty acids, specifically the histone deacetylase inhibitor (HDACi) butyrate, in
intestinal epithelial cells was associated with GVHD. In this study, restoration of butyrate improved intestinal epithelial junctional integrity, decreased apoptosis, decreased clinical GVHD scores and improved survival. This effect was independent of intestinal Tregs or macrophages, but associated with reduced intestinal infiltration by CD4+ and CD8+ activated T cells.

It is conceivable that protection of the mucous membranes from conditioning-regimen related damage may reduce the risk of infections. A recombinant keratinocyte growth factor - Palifermin is approved by the US. Food and Drug Administration for prophylaxis and treatment of severe oral mucositis. Interestingly, it also has the potential to preserve normal thymopoiesis and enhance thymic cellularity. However, the impact of palifermin on the recovery of specific immune subsets has not been studied extensively. An exploratory analysis from a double-blind placebo controlled study of palifermin in patients undergoing autologous HCT showed at lower incidence of febrile neutropenia (75% vs. 92%, P < 0.001) and a trend toward a lower incidence of blood-borne infections (15% vs. Twenty-five%) in the palifermin group. Another retrospective study reported that in patients undergoing BEAM (carmustine, etoposide, cytarabine and melphalan) or busulfan-thiotepa conditioned autologous HCT, treatment with palifermin is associated with a lower risk of febrile neutropenia and severe infections not related to gram-positive organisms. Similarly, oral or intravenous glutamine can reduce the severity of mucositis, but clinical evidence for its efficacy in preventing infections is lacking.

Without any specific interventions, mucosal damage starts to heal just before, or with the recovery of granulocytes in peripheral blood (PB), as neutrophil recruitment to the site of mucosal injury may occur up to a week before recovery of neutrophils in PB.

Reconstitution of the innate cellular immune system

The appearance of granulocytes, monocytes, dendritic cells and natural killer (NK) cells in PB hallmarks the commencement of cellular recovery. With the routine use of recombinant human granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF), neutrophil engraftment occurs within 2 weeks after myeloablative HCT using PBSC, and 2–3 weeks after unmanipulated BM or UCB grafts. The use of growth factors not only hastens engraftment of granulocytes and monocytes but also enhances their function to some extent. As compared with G-CSF, which primarily aids in the proliferation of neutrophils, GM-CSF also increases the number or monocytes and macrophages. A prospective randomized trial reported that the use of GM-CSF or a combination of GM-CSF and G-CSF post-HSCT is associated with a significantly lower incidence of IFI-related mortality (1.5%) compared with G-CSF alone (12%), P = 0.034. However, despite the routine use of growth
factors, neutrophils can remain dysfunctional for up to 2 months post-HCT, and for up to a year in those who develop GVHD. The ability of neutrophils to kill invasive fungi is regained in most patients by about 3 months post-HSCT; however, in patients who develop invasive fungal infection (IFI), neutrophil function may take 6–12 months to recover.

Polymorphisms in genes involved in the innate recognition of fungi also appear to play a critical role in determining infection outcomes. Fungal pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) are recognized by pattern recognition receptors (PRRs) on various innate immune cells. Among several major PRRs are the toll-like receptors, C-type lectin receptors (such as galectin 3). Several single nucleotide polymorphisms (SNPs) in these innate immune genes have been reported to be associated with susceptibility to fungi such as Candida, Aspergillus, and other fungal infections. The review of significance of these SNPs in fungal infections is outside the scope of this paper and interested readers are directed to review by Romani.

**Natural killer cell immune reconstitution**

NK cells influence both innate and adaptive immune responses and are the first lymphocyte subset to appear in PB after HCT. They have a protective role against many viral infections commonly encountered after HCT including, but not limited to, HSV, VZV, CMV and influenza virus as well as some bacterial infections. The role of NK cells in antifungal immunity is controversial. In patients who develop IFI, NK cell recovery of is delayed for up to 6 months, while in those with well controlled IFI, NK cell numbers are significantly increased. Moreover, in patients with IFI, higher number of NK cells is correlated with fewer fungal lesions. These correlative data and some in vitro studies suggest that NK cells may have a role in the prevention of fungal infections although the exact mechanism for this protection is not yet clear. Interestingly, whereas, patients with an isolated absolute, classical or functional NK cell deficiency are prone to severe viral infections, fungal infections are much less common, suggesting that in the absence of neutropenia NK cells may have a less important role in fungal protection.

Reconstitution of NK cells varies by graft source. NK cell recovery in the first few months post-HCT is more robust in BM and UCB graft recipients compared to PBSC recipients, despite the fact that PBSC grafts contain 10-fold higher absolute number of NK cells than other grafts. This may be related to the relative delay in T- and B-lymphocyte recovery in BM and UCB graft recipients, as elaborated in the following sections.

NK cell recovery differs from the recovery of other lymphocytes in several aspects. Not only do NK cells appear early, they also acquire functional competence much earlier than other lymphocytes. Specifically, while B- and T-cells may take months to years to become fully functional, NK cells can mature in about 2–4 weeks. Another unique feature of NK cells is that their activity after HCT remains normal even in the presence of severe GVHD, which usually suppresses the activity of other immune subsets such as T and B lymphocytes. CMV reactivation or infection, which occurs commonly after HCT, can further augment NK cell activity. The cytolytic mechanism of NK cells is also unique. In contrast to B- and T-cells, NK cells do not possess antigen specific receptors. Instead, they recognize their targets not by detection of foreign antigens, but by a failure to detect self HLA class I expression, a common antigen present on all healthy cells. This forms the basis for the ‘missing-self hypothesis’. Viruses often downregulate HLA class I molecules on the surface of cells they invade in order to avoid T cell recognition and thus, can be targeted by NK cells. CMV reactivation or infection, which occurs commonly after HCT, can further augment NK cell activity. However, viruses have also evolved mechanisms to escape NK cell recognition via upregulation of ligands that bind inhibitory NK cell receptors, and downregulation of ligands for the activating NK cell receptors. When the innate immune system fails to eradicate an infection, the adaptive immune system is activated, which is also critical for long-term memory and protection against re-infection.

**Humoral immunity**

**Normal development of B cells**

The earliest B cells formed in BM are immature transitional cells (CD10+CD38hiCD24hiCD44lo). These cells emigrate to secondary lymphoid organs, where they differentiate into mature naïve cells. After antigen-mediated activation with the help of T helper (Th) cells, naïve cells undergo clonal expansion and either differentiate into plasma cells that secrete antibodies or form memory B cells [reviewed by Kurosaki and Battista]. The presence or absence of IgD and CD27 delineates naïve B cells (IgD+CD27-), non-class-switched/ IgM+ memory B cells (IgD+CD27+) and class-switched memory B cells (IgD-CD27+). In healthy adult PB, transitional B cells constitute only about 2% of total B cells, naïve B cells comprise about 50%, and IgM+ memory B cells and IgM- class-switched memory B cells each comprise about 10–15%.
**B cell reconstitution post-HCT**

After HCT, the *proportion* of total B cells in most patients reach normal levels by 3 months, but the *absolute numbers* may take up to 6–12 months to normalize, which is further delayed in patients with GVHD.19,107,106 Moreover, although the number of total B cells may reach levels comparable to adult controls, most of the reconstituting B cells in the first year after HCT are comprised primarily of transitional and naïve subsets, while the recovery of memory B cells occurs much later.108,109 One exception is EBV reactivation, which leads to preferential expansion of IgG+ or IgA+ class-switched memory B cells.108

Different graft sources have differential impacts on the tempo of B cell reconstitution. For instance, the number of total B cells, naïve and memory B cells are 10–20-fold higher in PBSC grafts compared to BM.96 Consequently, these mature B cell subsets are passively transferred in the PBSC graft and can be found at higher numbers in PBSC recipients for up to 3 months post-transplantation.96,110 On the other hand, the pace of B cell recovery is steeper in BMT compared to PBSC recipients, likely due to higher numbers of progenitor B cells being infused in the BM graft.96 By 3 months post-transplant, the total immunoglobulin (Ig) levels are comparable in PBSC and BM graft recipients; however, for the first year post HCT, Ig levels remain significantly lower than that seen in normal controls.96 Recipients of UCB grafts achieve very rapid recovery of B cells, and have higher numbers of total B cells compared to PBSC recipients for up to 2 y post-HCT.74 Recovery of immunoglobulins is also faster after UCBT compared with PBSC HCT.74

**Functional reconstitution of B cells**

Functional recovery of B lymphocytes takes several months to years, and follows that of normal ontogeny.106,107,117-119 In the first few months of transplant, regenerating B cells lack proliferative and differentiative responses to antigen-specific factors, indicating their functional incompetence.120 Coincident with the recovery of B cell counts after HCT, IgM production normalizes after about 3 months.19,107 Isotype-switched memory B cells that produce IgG can be detected between 3 and 6 months and their ability to secrete specific IgG (in response to pokeweed antigen or *Staphylococcus aureus* antigen) is gradually acquired between 1–2 y post-transplantation.107 However, although the levels of IgG1 and IgG3 normalize during the first year after HCT, the deficiencies of IgG2 and IgG4 persist for more than 18 months.19,20,106,107,114,121-123 As IgG2 responses are protective against capsular carbohydrate antigens from gram-positive bacteria,124 prolonged deficiency of IgG2 can explain the undue susceptibility of HCT recipients to late bacterial infections. The last immunoglobulin to recover is IgA, which may be undetectable for several years.119 The prominent role of IgA in mucosal humoral immunity partly explains why patients remain at risk of recurrent sino-pulmonary and gastrointestinal tract infections, even years after transplantation. The deficiencies of immunoglobulins is much more pronounced and prolonged in those who develop GVHD or those who receive antithymocyte globulin (ATG).19,107,121,125 However, interestingly, the functional recovery of B cells is similar after T-replete or T-deplete HCT, and after B- and T-deplete PB graft (CD34+ selected) vs. unmanipulated grafts.126

The functional immaturity of donor-derived lymphocytes, combined with a decrease in the recipient plasma cells and Ig levels over time, result in the loss of immunity against viral and bacterial pathogens attained through childhood vaccination or infection.127-129 Therefore, patients need to be re-vaccinated - the precise timing of which can be challenging due to remarkable differences in functional recovery of B cells in individual patients [reviewed Pirofski and Casadevall 130 and Avigan et al 131]. In general, vaccinations are avoided in the first 3–6 months after HCT, after administration of rituximab or intravenous immunoglobulins, in the presence of GVHD, or while patients are on immunosuppressive drugs. Due to a lack of clear evidence, the recommended vaccination schedule is similar for autologous and allogeneic HCT recipients, regardless of the type of conditioning regimen or the graft source.5,132,133

**Cellular adaptive immunity**

**Normal development of T cells**

The name “T” lymphocyte denotes the essential role of the thymus in the maturation of T-cells. Double negative (CD4-CD8-) precursor T cells produced from pluripotent haematopoietic stem cells in the BM migrate to the thymus, where they undergo positive and negative selection to become naïve CD4+ or CD8+ T cells. Naïve T-cells encounter foreign antigens in secondary lymphoid tissues. After a prolonged period of stimulation (about 20 hours), T-cells either proliferate to form activated effector cells, or they become memory cells of central memory (T~CM~) or effector memory (T~EM~) phenotype. T~CM~ cells express homing receptors (CCR7 and CD62L), reside in secondary lymphoid tissues, possess little effector function but can undergo terminal differentiation upon re-stimulation with an
antigen. TEM cells, on the other hand, are terminally differentiated and respond immediately to antigenic stimulation. In contrast to naive T cells, effector T cells require a short period of stimulation (about 30 min or shorter) to trigger proliferation and immediate effector functions.  

**T cell reconstitution post-HCT**

After HCT, T cell reconstitution occurs in 2 distinct phases. The initial phase is thymus-independent, antigen-driven peripheral expansion of T cells infused with the graft that possess a limited and skewed T cell receptor (TCR) repertoire. The later phase is thymus-dependent expansion of naïve T cells derived from the donor stem cells that possess a diverse TCR repertoire. Because thymopoiesis after HCT is extremely slow, the thymus-dependent T cell recovery can remain incomplete for years. This is further delayed in older patients due to thymic involution and those who develop GVHD as the thymic epithelial cells are damaged by alloreactive T-cells. There are 2 important consequences of impaired thymopoiesis post HCT. First, thymic-independent pathway can rapidly generate CD8+, but not CD4+ T cells, resulting in an inversion in the CD4:CD8 ratio. Second, it leads to peripheral expansion of memory (CD45+RO+ / CD45RO+CD27+) T cells, as the generation of naïve T cells (CD45+RA+ / CD45RO-CD27+) from prethymic progenitors is largely dependent on a functional thymus.

The inversion of CD4:CD8 ratio is one of the earliest features of T cell reconstitution after autologous or allogeneic transplantation from any graft source and can persist for up to several years after HCT. Different graft sources, however, can impact on other aspects of T cell reconstitution. The majority of these differences are a consequence of substantially higher absolute numbers of CD4+ and CD8+ T cells infused with a PBSC (10-20-fold higher) than with a BM graft. As a result, PBSC transplant is associated with faster T cell reconstitution compared to other graft sources. However, even after PBSC transplant, the absolute number of CD4+ T cells, including both CD4+ regulatory T cells (Treg) and conventional CD4+ cells (CD4Tcon), remain low for up to 2 y post-HCT, while normalization of CD8+ T cells and their subsets can take anywhere from 1 month to a year, depending upon the conditioning regimen and GVHD prophylaxis regimen. Compared with other grafts, UCB contains the lowest numbers of total nucleated cells and T cells, most of which are antigen-naïve. Additionally, in contrast to other graft sources, UCBT is associated with delayed thymopoiesis; as a result, T cell recovery after UCBT occurs primarily due to thymus-independent peripheral expansion of mature donor T cells for long time. Moreover, many of the UCBT regimens incorporate in vivo T cell depletion with antithymocyte globulin (ATG), which leads to a prolonged period of lymphopenia. Therefore, reconstitution of all T cell subtypes is delayed for at least 6 months after UCBT but becomes comparable to that of PBSC graft by one year and reaches normal level by 2 y.

In the setting of haploidentical HSCT with post-transplantation high dose cyclophosphamide, which selectively depletes transferred memory T cells and rapidly proliferating alloreactive T cells in vivo, the early stages of T cell development are dominated by large numbers of memory T cells with stem-like properties (TSCM). These TSCM are derived from naïve T cells in the donor graft and are responsible for the reconstitution of a T cell compartment with a diverse TCR repertoire post-HCT.

**Assessment of T cell receptor repertoire**

The TCR is a heterodimer composed of α and β chains. Both α and β chains consist of variable (V), joining (J) and constant (C) regions, while the β chains also have an additional diversity (D) region. T cells undergo somatic V(D)J recombination during their developmental phase, producing an extensive TCR repertoire. During this rearrangement, nucleotides are added or removed at a specific region denoted as CDR3, which imparts clonality and specificity to individual T cells. This rearrangement phenomenon can be exploited to assess reconstitution of the TCR repertoire after HCT. Traditional methods employed southern blot analysis, reverse transcriptase-polymerase chain reaction (RT-PCR) or flow cytometric techniques to study the Vβ repertoire. Another method assesses the heterogenity in the size of the CDR3 region within Vβ gene families using V family-specific PCR, a technique called CDR3 size spectratyping. These techniques are, however, limited to measuring only the known exons and none of them is able to determine the frequency of individual TCRs. More recently, novel deep sequencing techniques have been employed to assess TCR diversity with very high resolution. One such technique combines the use of 5’ rapid amplification of cDNA ends (RACE)-PCR to amplify all the possible combinations of TCR α and β chains followed by next-generation sequencing of TCR. Using this method, a study showed that recipients of double unit UCBT without ATG had the highest diversity of CD4+ and CD8+ TCR repertoire, a greater proportion of which were naïve T cells, as compared with recipients of conventional or TCD PBPC grafts at 6- and 12-months post-transplantation.
With the deep sequencing methods, the correlation of TCR diversity with GVHD and relapse is also recognized. A study including haploidentical-UCB donors and matched related or unrelated donors using in vivo TCD showed that patients who remained in remission displayed a significantly higher TCR diversity compared with patients with relapsed disease. It is therefore conceivable that acquisition of higher TCR diversity may be protective against disease relapse. The study also found that the diversity of TCR α and β was significantly lower in patients with GVHD (presumably related to preferential expansion of certain T cell clones) than in patients who do not develop this complication. Similar results were seen in prior studies using CDR3 spectratyping. In contrast, another study utilizing deep sequencing methods reported that grade 2–3 acute GVHD is actually associated with a higher TCR diversity than those who developed grade 0–1 acute GVHD, suggesting that GVHD did not restrict recovery of TCR repertoire. The differences noted in these studies are a reflection of different graft and donor sources, conditioning regimens and the use of T cell depletion.

Functional reconstitution of T cells

Despite differences in the number of T cells in BM and PB grafts and the different pace of immune reconstitution after HCT, differences in the functional recovery of T cells are rather subtle. For instance, the in vitro responsiveness of T cells to HSV and VZV antigens or to non-specific mitogens such as phorbol myristate acetate (PMA) is similar in PB samples collected from PBSC or BM graft recipients at all time points after transplantation. After BM transplantation, T cell proliferative responses to specific antigens, such as candidin, tetanus toxoid, tuberculin or toxoplasma, are absent in about 20–50% of patients, even up to a year after transplantation. Primary T cell immunity against fungi is provided by CD4+ Th1 and Th17 cells as well as memory CD8+ T-cell cells. Consequently, at 3 months or later after HCT, fewer than a quarter of patients will have detectable functional T cell responses against the most common invasive fungal infection. In a study by Einsele’s group, T-cell response against Aspergillus fumigatus antigen was detected at higher levels in patients with invasive aspergillosis and disease regression on antifungal therapy compared to those with stable or progressive disease. This may partly explain the bimodal incidence of invasive aspergillosis seen after allogeneic H SCT. The first peak occurs within the first 2 weeks with neutropenia, after which the incidence declines with reconstitution of the innate immunity. A second peak occurs at around 3 months, coinciding with the deficient T cell immunity. In contrast to antifungal immunity, CMV-specific CD4+ and CD8+ T cells can be detected within 2–3 months after HCT.

UCB graft recipients experience remarkably delayed T cell functional recovery compared with BM or PBSC graft recipients. Specifically, T cell activity against staphylococcal enterotoxin B, CMV, EBV, and adenovirus is delayed for at least 8–9 months post CBT, while activity against BK virus, influenza and respiratory syncytial virus is delayed even further. Consequently, more than 50% of UCB recipients develop virai reactivation or infection in the first 6-months, and over 90% within a year of transplantation. On the other hand, graft source does not appear to independently contribute to the risk of CMV infection; the risk of CMV reactivation, CMV disease and the probability of response to antiviral therapy is similar in UCB, PBSC and BM graft recipients. Depletion of T cells from PBSC or BM grafts also leads to significant delay in the recovery and functional maturity of T cells. As a result, around 50–70% of patients who receive TCD grafts have evidence of CMV reactivation within the first year post HCT, with a median time to reactivation of less than a month.

Strategies to enhance immune reconstitution

Various strategies have been attempted to augment immune recovery after HCT. The majority of these approaches are directed at the thymus, and include strategies to protect the thymic epithelium, stimulate thymopoiesis, or increase the number of T-lymphoid precursors. Approaches under investigation include administration of cytokines such as interleukin (IL)-2, IL-7 or IL-15, growth factors including insulin-like growth factor-1, recombinant human growth hormone, parathyroid hormone, sex steroid ablation using luteinizing hormone-releasing hormone agonist (goserelin), or small molecules such as kertinocyte growth factor (palifermin), the tyrosine kinase inhibitor sunitinib, and anti-CD25 antibody, to name a few. Another approach is the use of biological or cellular therapies such as the use of Notch-based culture systems to obtain T-cell lineage committed precursor cells, ex vivo expansion and infusion of T cell precursors, or transplantation of thymic tissue. Most of these methods are either still in pre-clinical development or have failed to demonstrate a significant improvement in in immune recovery or infection risk to date. Review of these methods is beyond the scope of this paper and interested readers are referred to articles by Bernstein and Seggewiss. Infusion of ex vivo expanded virus-specific cytotoxic T cells, on the other hand, have
resulted in impressive responses in early phase clinical trials for the treatment of specific infections [reviewed Barrett & Bollard 177].

**Conclusion**

Over the past several years, substantial knowledge has been gained on the complexity of immune reconstitution after HCT; however, the translation of these findings to the clinic has been rather disappointing. Moreover, despite the recognition that the pace of immune recovery varies considerably depending on recipient age, underlying disease, graft source, type of conditioning regimen, GVHD prophylaxis and other factors, our current approach to antimicrobial prophylaxis and vaccination post HCT is essentially non-specific. Moreover, although several techniques are being tested to enhance the recovery and speed of immune reconstitution, none has resulted in a conclusive reduction in the risk of infections. Two major factors contribute to delayed immune reconstitution after HCT—(i) preparative regimen-related damage to the host microenvironment, and (ii) the inevitable lag in the natural maturity of donor-derived immune cells. Thus, combination strategies that aim at protecting the host immune microenvironment, while facilitating recovery of donor-derived immune subsets, may be more beneficial than using either of these approaches alone.

**Abbreviations**

- **ATG** antithymocyte globulin
- **BM** bone marrow
- **CD** cluster differentiation
- **CMV** cytomegalovirus
- **EBV** Epstein–Barr virus
- **G-CSF** granulocyte colony-stimulating factor
- **GM-CSF** granulocyte-macrophage colony-stimulating factor
- **GVHD** graft-versus-host disease
- **HCT** haematopoietic cell transplantation
- **HLA** human leucocyte antigen
- **HSV** herpes simplex virus
- **IFI** Invasive fungal infection
- **Ig** immunoglobulin
- **MSD** matched sibling donor
- **MUD** matched unrelated donor
- **NK** natural killer
- **PBSC** peripheral blood stem cells
- **PHA** phorbol myristate acetate
- **RIC** reduced intensity conditioning
- **TCD** T cell deplete
- **TCM** central memory
- **TEM** effector memory
- **TCR** T cell receptor
- **Th cell** helper T cells
- **UCB** umbilical cord blood
- **UCBT** umbilical cord blood transplantation
- **VZV** Varicella-zoster virus (VZV)

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