Cytotherapy, 2017; ■■: ■■–■■

International Society for Cellular Therapy ISCT®

Cellular therapy for multiple pathogen infections after hematopoietic stem cell transplant

GAURAV SUTRAVE[1,2], EMILY BLYTH[1,2] & DAVID J. GOTTLIEB[1,2]

[1]*Department of Haematology, Westmead Hospital, Sydney, Australia,* [2]*The Westmead Institute for Medical Research, The University of Sydney, Sydney, Australia*

Abstract

Hematopoietic stem cell transplantation (HSCT) represents the only crative treatment option for many hematological conditions but results in a profound T-cell deficiency in the post-HSCT period. Infections account for a significant proportion of non-relapse morbidity and mortality, and infections with multiple organisms either simultaneously or at different times after transplant are common. Adoptive cellular therapy (ACT) with prophylactic or therapeutic infusion of donor derived or third-party, pathogen-specific T-cells represents a novel methodology to rapidly reconstitute T-cell mediated immunity in this context. For cytomegalovirus (CMV) and Epstein-Barr virus (EBV) infection, clear evidence of efficacy with limited toxicity has been observed, with response rates up to 90%. Infusion of third-party, partially human leukocyte antigen–matched pathogen-specific T-cells have also demonstrated remarkable efficacy with responses seen in up to 70% of patients with resistant CMV, EBV and adenoviral infection. This review addresses the nature of post-HSCT immune deficiency, the common infections that occur in the post-HSCT period and how advances in ACT manufacturing methodologies is allowing for wider implementation of T-cell therapies targeting multiple pathogens in HSCT recipients.

Key Words: *cell- and tissue-based therapy, hematopoietic stem cell transplantation, immune reconstitution, immune system, immunity, lymphocytes*

Introduction

Allogeneic hematopoietic stem cell transplant (HSCT) remains the only curative option for most relapsed/refractory hematological malignancies and for bone marrow failure syndromes. The use of conditioning chemotherapy before transplant results in a complex immunocompromised state, consisting of an initial profound innate immune deficiency followed by B- and T-lymphopenia that can persist for several years. Consequently, infections are a significant clinical problem and are among the leading causes of non-relapse mortality, accounting for up to 48% of cases in some series [1]. Infection with more than one pathogen either simultaneously or at different times occurs with moderate frequency and increases the non-relapse mortality risk associated with HSCT [2].

Current treatments for opportunistic pathogens occurring post-HSCT are far from perfect. For cytomegalovirus (CMV), preemptive pharmacologic therapy is effective in reducing early onset end organ disease but has no effect on the incidence or mortality associated with late onset infections [3]. If used long-term, antimicrobials can result in the emergence of resistant organisms and cause drug toxicity. Furthermore, there are several pathogens for which no effective pharmacological therapy exists. Above all, pharmacological control of infection fails to repair the immune deficits that predispose to infection in the first instance, increasing the chance of recurrence with the original or another pathogen [4].

Adoptive cell therapy (ACT) through the transfer of T-cells from donor to recipient has been explored as a strategy to restore the underlying immunological defects occurring post-HSCT. ACT offers potential benefits over pharmacotherapy. These include pathogen specificity and the establishment of long-term immunological memory. Nonspecific ACT in the form of donor lymphocyte infusion (DLI) is effective in restoring pathogen-specific immunity but carries the risk of graft versus host disease (GVHD) [5]. Advances in isolation and/or expansion of antigen-specific T-cells have facilitated the development of pathogen-specific allogeneic therapies. The clinical efficacy of these therapies in small phase I and II trials has led to expansion of research into the generation of specific T-cell therapies against a number of opportunistic pathogens to more rapidly reconstitute a broad spectrum T-cell

Correspondence: **David J. Gottlieb**, MBBS, FRACP, FRCPA, MD, Department of Medicine, Westmead Hospital, Hawkesbury Road, Westmead, Sydney, NSW 2145, Australia. E-mail: david.gottlieb@sydney.edu.au

(Received 26 June 2017; accepted 27 July 2017)

ISSN 1465-3249
http://dx.doi.org/10.1016/j.jcyt.2017.07.012

immune response following HSCT. The perceived requirement for a rapidly available, "off-the-shelf" product has also resulted in the development of immediately available third-party donor-derived banks of cryopreserved pathogen-specific T-cells that do not require full human leukocyte antigen (HLA) matching between product and recipient for antiviral efficacy.

In this review, we summarize the common pathogens and co-infections currently recognized as important in the period following HSCT, the primary manufacturing methods used to generate pathogen-specific T-cells against them including those recognizing multiple pathogens and we review the results of clinical trials assessing their safety and efficacy.

Immune deficiency after HSCT

Allogeneic HSCT requires pre-transplantation chemotherapy to assist in providing disease control and facilitate donor stem cell engraftment. This results in profound immunosuppression affecting both the innate and adaptive immune systems. The kinetics of immune recovery are influenced by multiple clinical variables with cord blood donor stem cell source, older recipient age, use of *in vivo* or *ex vivo* T-cell depletion and development of GVHD all associated with a delay in immune recovery [6].

Figure 1 illustrates immune recovery over the first year post-HSCT. The recovery of the innate immune system involves establishing normal numbers of neutrophils (usually 2–3 weeks after stem cell infusion), whereas natural killer (NK) cells, monocytes and basophils normalize by 1 month [7]. Quantitative recovery in circulating dendritic cells (both myeloid and plasmacytoid) is achieved by 1 month with the majority being of donor origin, but tissue dendritic cells are still 70% recipient by day 14, and a proportion can remain recipient for up to 1 year [8].

The adaptive immune system takes much longer to recover on both quantitative and qualitative levels. B-cells recover to normal numbers by 1–2 years after HSCT, whereas maturation of antibody responses to generate a diverse immunoglobulin subtype reservoir takes longer. Initial Ig M recovery occurs at 2–6 months, with class switching to IgG occurring at 3–18 months with a final delayed IgA recovery at the 3-year mark [8]. This is most likely because class switching requires concurrent $CD4^+$ T-cell support, hence B-cell functional recovery is inherently linked to T-cell recovery [9].

Recovery of T-cell immunity after transplant can be mediated by two processes. The first is expansion of mature T-cells that are infused within the donor product. Their expansion is aided by high endogenous interleukin-7 levels in the recipient following conditioning chemotherapy [8,10] resulting in an increase in memory T-cells (usually $CD8^+$) with a limited T-cell receptor (TCR) repertoire, the breadth of which is determined by the exposure of the donor immune system to different antigens. The second T-cell recovery process occurs through generation of naive T-cells from donor stem cells transferred in the graft and their subsequent education in the thymus. This results in the development of a wider TCR repertoire [11], increased numbers of $CD4^+$ T-cells, removal of potentially alloreactive T-cells and development of a functional

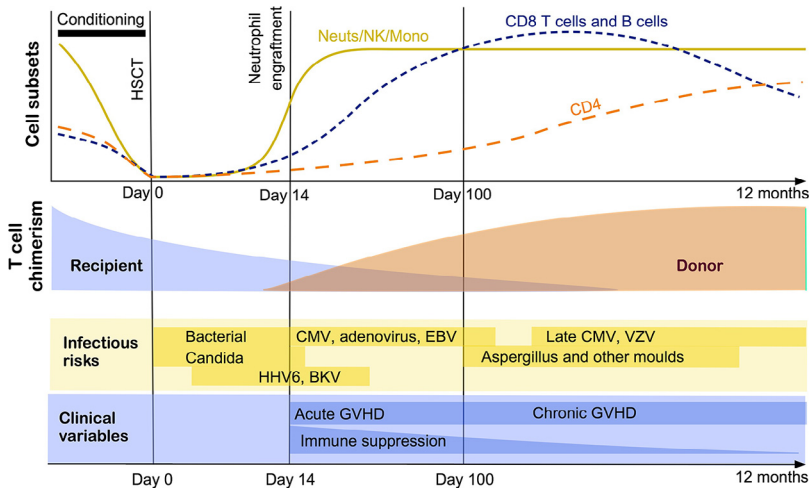

Figure 1. Immune reconstitution post-HSCT and the associated risks of opportunistic infection. The risk of opportunistic infection post-transplant is closely linked to the phases of immunological reconstitution. Bacterial and *Candida* infections are common before recovery of innate immune function (neutrophils, monocytes and NK cells) in the first few weeks after stem cell infusion. Adaptive immune function recovers over months or years, and viral and non-candidal mold infections occur in this period. Clinical factors such as conditioning, donor source and post-transplant events such as GVHD and immune suppression affect the immune recovery process and therefore modulate infectious risks.