Biol Blood Marrow Transplant 23 (2017) 870–881

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

ASBMT American Society for Blood and Marrow Transplantation

Report

National Institutes of Health Hematopoietic Cell Transplantation Late Effects Initiative: The Immune Dysregulation and Pathobiology Working Group Report

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Article history:
Received 5 October 2016
Accepted 5 October 2016

Key Words:
Immune reconstitution
Late infections
Immunization
Intravenous immunoglobulin

A B S T R A C T

Immune reconstitution after hematopoietic stem cell transplantation (HCT) beyond 1 year is not completely understood. Many transplant recipients who are free of graft-versus-host disease (GVHD) and not receiving any immunosuppression more than 1 year after transplantation seem to be able to mount appropriate immune responses to common pathogens and respond adequately to immunizations. However, 2 large registry studies over the last 2 decades seem to indicate that infection is a significant cause of late mortality in some patients, even in the absence of concomitant GVHD. Research on this topic is particularly challenging for several reasons. First, there are not enough long-term follow-up clinics able to measure even basic immune parameters late after HCT. Second, the correlation between laboratory measurements of immune function and infections is not well known. Third, accurate documentation of infectious episodes is notoriously difficult. Finally, it is unclear what measures can be implemented to improve the immune response in a clinically relevant way. A combination of long-term multicenter prospective studies that collect detailed infectious data and store samples as well as a national or multinational registry of clinically significant infections (eg, vaccine-preventable severe infections, opportunistic infections) could begin to address our knowledge gaps. Obtaining samples for laboratory evaluation of the immune system should be both calendar and eventdriven. Attention to detail and standardization of practices regarding prophylaxis, diagnosis, and definitions of infections would be of paramount importance to obtain clean reliable data. Laboratory studies should specifically address the neogenesis, maturation, and exhaustion of the adaptive immune system and, in particular, how these are influenced by persistent alloreactivity, inflammation, and viral infection. Ideally, some of these long-term prospective studies would collect information on long-term changes in the gut microbiome and their influence on immunity. Regarding enhancement of immune function, prospective measurement of the response to vaccines late after HCT in a variety of clinical settings should be undertaken to better understand the benefits as well as the limitations of immunizations. The role of intravenous immunoglobulin is still not well defined, and studies to address it should be encouraged.

Published by Elsevier Inc. on behalf of the American Society for Blood and Marrow Transplantation.

Financial disclosure: See Acknowledgments on page 878.

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http://dx.doi.org/10.1016/j.bbmt.2016.10.001
1083-8791/Published by Elsevier Inc. on behalf of the American Society for Blood and Marrow Transplantation.

INTRODUCTION

The National Institutes of Health Blood and Marrow Transplantation Late Effects Initiative, comprising pediatric and adult hematopoietic stem cell transplantation (HCT) health care providers, administrators, researchers, advocates, and survivors across federal and non-federal groups and sponsored by the National Cancer Institute and National Heart, Lung and Blood Institute aims to identify knowledge gaps, develop practice recommendations, and formulate important research questions to improve transplantation survivor monitoring and management [1]. The Immune Dysfunction and Pathobiology Working Group, established as 1 of 6 working groups within this initiative, convened in September 2015 with the goal of providing recommendations for immune function and infection control in the field of HCT survivorship. The working group focused on identifying trends in late infections, describing immune reconstitution in the lab and reviewing interventions to improve immune function in HCT survivorship studies. These findings and recommendations for research were presented at a public meeting in June 2016, including over 150 participants with expertise across HCT survivorship. The findings were revised based on audience comments and are presented here.

A major goal after allogeneic HCT is to achieve *optimal immune reconstitution*, which we define operationally (in the case of allogeneic HCT) as the restoration of functional pathogen-specific immunity and establishment of anticancer immunity in the absence of immune dysregulation (eg, GVHD and/or HCT-associated autoimmunity). Late after transplantation (ie, > 1 year), variable degrees of immune recovery are observed in different patients, and the data are limited.

This paper will review what is currently known about immune function late after HCT, identify knowledge gaps, and propose research priorities to fill those gaps, with an emphasis on what is arguably the most important function of the immune system: protection against infection.

SECTION 1. LATE INFECTIONS AFTER HCT

Historically, infection is 1 of the 3 leading causes of death after HCT (along with relapse and GVHD) [2]. Most infections occur during the first year and different types of infectious syndromes predominate at various times [3,4]. Multiple factors influence the pace of immune recovery and the risk for and type of infectious complications. These factors include patient age, underlying disease, antecedent immunosuppressive state, prior infections, conditioning regimen, type of donor, degree of match, stem cell source, immunosuppressive regimen used to prevent GVHD, anti-infective practice, occurrence of post-transplantation GVHD and viral infections, and use of certain post-transplantation therapies to prevent disease relapse that alter immune recovery (Table 1) [5-9].

By 1 year, immune reconstitution is well underway for many HCT recipients [16]. However, some immunologic deficits are detectable in many patients using sensitive immunologic assays at 1 to 2 years and even beyond 10 years [17,18]. Patients with GVHD or cytomegalovirus (CMV) infection or recipients of HLA-mismatched donors frequently have delayed, incomplete, or dysregulated immune reconstitution. Chronic GVHD (cGHVD) is associated with multiple deficits in different arms of immunity and many types of protective responses are dysregulated [19-22]. Late infections are common complications and causes of death in patients with persistently active GVHD [23]. Functional asplenia has been reported to predispose to rapidly developing sepsis from *S. pneumoniae*, which can lead to mortality among GVHD patients [21]. Older studies suggested the use of unrelated donors (with or without GVHD) was also associated with an increase in late infections [23,24], although many of those patients were likely mismatched as low-resolution typing methods were in use then. In the absence of active GVHD, persistently low CD4 counts and persistently low immunoglobulin levels have been associated with the risk for late infectious morbidity [3,25].

Thus, the risk of late infection for patients with ongoing GVHD and prolonged immunosuppressive therapy remains substantial. In contrast, in most patients without GVHD, the incidence of life-threatening infection is much lower and continues to decline with passing time after transplantation.

Two large retrospective Center for International Blood and Marrow Transplant Research (CIBMTR) studies have investigated late deaths (defined as beyond 2 years) of allogeneic HCT survivors. The first study, with more than 6000 2-year survivors and a median follow-up of 6.6 years, estimated a risk of death from infection in the absence of GVHD of approximately 6% [26]. One-half of the infections were bacterial. A similar study 10 years later of more than 10,000 2-year survivors with a median follow-up of 9 years estimated that 10% to 20% of all deaths were caused by infection in the absence of active GVHD [27]. Proportions of deaths due to infection were similar in all major categories of diseases for which the transplantation was performed. Generally, the risk of infectious death decreased over time after transplantation, with less risk after 10 years compared with after 2 to 4 years. Unfortunately, this kind of large retrospective registry study lacks the capability to capture and analyze fine details regarding specific infections and risk factors.

Table 1
Selected Factors that Influence Late Infections After HCT

Factor		References
Age	Higher incidence of late fungal infections in older patients	[10]
Preparative regimen	Fewer early infections with NMA versus MAC Higher infection rate with total body irradiation	[6,11]
T cell depletion	More CMV and Aspergillus seen with T cell depletion in MUD	[8]
PB versus BM	Higher incidence of infection over 2 years with BM	[9]
Alternative donors	High incidence of infection in recipients of mismatched unrelated donor and umbilical cord blood (UCB)	[12]
cGVHD	In many studies cGVHD turns out to be the only independent risk factor for severe infection	[8,11]
CMV infection	CMV seropositivity and reactivation has been associated with delayed immune reconstitution and increased infectious mortality	[11,13,14]
Post-HCT rituximab	Patients treated with pre-emptive rituximab for EBV reactivation had increased late infections	[15]

NMA indicates nonmyeloablative; MAC, myeloablative conditioning; MUD, matched unrelated donor; PB, peripheral blood; BM, bone marrow; UCB, umbilical cord blood.