Immune Reconstitution: The Major Barrier to Successful Stem Cell Transplantation

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The numerous advances in our understanding of transplantation biology combined with enhancements in supportive care have substantially improved the health of our patients. Transplant-related morbidity has progressively declined over the last 30 years, and this can be at least in part measured by our ability to provide stem cell transplantation to an aging population and by our fledgling ability to cross histocompatibility barriers. However, a persistently frustrating limitation in transplantation medicine is delayed, inadequate, or incomplete reconstitution of the immune system. Patients die of opportunistic infections despite well-controlled graft-versus-host disease (GVHD) and eradication of the underlying disease. Although GVHD control, improvements in antibiotic spectra, and circumspection in the use of immunosuppressants have helped, too many patients still die of infections because of insufficient immunologic recovery.

Immunologic recovery and GVHD are intrinsically linked. It is helpful to think of acute GVHD as an inflammatory disorder in which T-cells from the donor behave appropriately in the context in which they find themselves. In other words, the donor’s T cells recognize minor histocompatibility antigens in the setting of upregulated adhesion molecules, inflammatory cytokines, and damaged epithelia. Thus, the T cell’s view of the world is that the host is seriously infected, and its job is to respond to this infection by initiating and sustaining an effective immune response. Of course, the problem is that the effective immune response is directed against minor histocompatibility differences rather than microbial proteins. This response is maladaptive from the perspective of a transplant clinician. We want the T cells to identify viral, bacterial, and fungal products in the context of major histocompatibility complex but not minor histocompatibility antigens per se. The T cell may not be quite so obliging; therefore, we are obligated to limit T-cell numbers and paralyze T-cell function. The consequences of this strategy are self-evident. One cannot control GVHD without increasing susceptibility to infection—the 2 entities go hand in hand. This is why we often have patients who die of severe opportunistic infections after we have induced a “remission” with our therapy for acute GVHD. We cannot selectively control T-cell function—at least, not yet.

Clinically, we approach transplantation-related immune incompetence in stages [1,2] (Table 1). Initially the patient is myelosuppressed, and the principal risks are gram-positive and gram-negative bacteria, herpes simplex virus, and candida infection (to name a few). This reflects a failure of innate immunity. Poor granulocyte and monocyte function occurs in the setting of mucosal injury from the conditioning regimen. Myeloid reconstitution is relatively straightforward and has been facilitated by hematopoietic growth factors and stimulated peripheral blood stem cell products. After myeloid recovery, there is a transition period in which there is a small amount of passively transferred T-cell function from the graft. It was hoped that the larger T-cell numbers transferred with a peripheral blood stem cell product would provide better initial T-cell function, but such a benefit has yet to be convincingly demonstrated [3,4]. There is a modicum of additional protection from pre-formed immunoglobulin, but it is safe to say that there is minimal immunologic capacity at this stage of transplantation. This failure of the adaptive immune system translates into susceptibility to virus reactivation (eg, cytomegalovirus and varicella-zoster virus), continued susceptibility to fungal disease, and inability to respond to less obvious risks such as respiratory syncytial virus, parainfluenza, and other respiratory pathogens. Vaccination studies have clearly demonstrated incompetence of both cellular and humoral immunity [5,6].
the absence of GVHD and in association with the tapering of immunosuppressants, we expect slow re-
constitution of NK cells, T cells, and eventually B-cell function [7]. Much of this component of the problem 
may be attributable to poor thymic function in adults, as well as limitations in the homeostatic recovery of 
T- and B-cell numbers. Recovery is slow, but in fortunate patients there is a restoration of CD4 T-cell 
numbers, responsiveness to vaccinations, and reduced susceptibility to pneumocystis infections and so on in 
the months surrounding a year from the transplantation. Insight into this process can be gleaned from 
the analysis of both T-cell receptor reconstitution and immunoglobulin recovery [8,9]. Both systems recon-
stitute with oligoclonal expansion of the respective elements. This phenomenon can be clearly observed 
by analyzing T-cell receptor Vβ spectrotyping. Clearly, active acute or chronic GVHD, prolonged 
use of immunosuppressants, mismatched transplantation, unrelated donor transplantation, and relapse de-
press the already slow pace of immune reconstitution [10-12]. Furthermore, some data suggest that the use 
of filgrastim after transplantation may increase the risk of infection by altering the recovery of T-helper cells 
[12]. It is interesting to note that chronic GVHD may result in a specific inability to synthesize IgG2 and 
IgG4, which results in prolonged susceptibility to encapsulated bacteria [13]. How T-regulatory cells in-
fluence immunologic recovery is just now being analyzed [14].

We are increasingly recognizing that the prior framework of immunohematologic recovery was too di-
chotomized. Granulocyte and monocyte reconstitution 
is critical, but it now seems that the recovery of the innate immune system is closely tied to the recovery of 
the adaptive immune system. Toll-like receptors are involved in many steps in the generation of inflammation 
and help to coordinate both innate and adaptive immunity. Monocytes have a central role in the reticuloendo-
thelial system but produce cytokines such as interleukin (IL)-12 and IL-10 that have profound effects on T-cell 
function. Natural killer cells have intrinsic activity as part of innate immunity, but they also interact with dendritic 
cells; they can depress or enhance dendritic cell function and thus influence T-cell function. Ultimately, elucida-
tion of these relationships may provide the insights that will allow us to influence the process. It is unrealistic to 
think that we will be able to intervene in a functionally complex system in a way that will be entirely effective. As much as we hope that cytokine infusions (eg, IL-7) will influence some component of this process, it is likely that 
such agents will affect only a limited component of a complex repertoire [15]. It is more likely that combina-
tions of cytokines, cellular therapies, and vaccine strategies will be required to see any effects on immunologic 
recovery. Ultimately, we may need to rethink the entire approach to allogeneic transplantation.

REFERENCES


