The Yin and Yang of Alloreactivity: Chronic Graft-versus-Host Disease and Leukemia Relapse

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Chronic graft-versus-host disease is a frequent complication of allogeneic hematopoietic cell transplantation and plays an important role in posttransplant morbidity and mortality, yet is correlated with the graft-versus-tumor effect in some studies. New approaches to separate the graft-versus-tumor from the graft-versus-host effect are urgently needed. Clinical Cancer Research; 21(9); 1–3. ©2015 AACR.

see related article by Boyiadzis et al., p. 2020

In this issue of Clinical Cancer Research, Boyiadzis and colleagues (1) examine the impact of chronic graft-versus-host disease (cGVHD) on the incidence of late leukemia relapse after myeloblastic allogeneic hematopoietic cell transplantation (HCT). The rationale for this work was to find the setting in which the benefit from leukemia control (graft-versus-leukemia effect, GVL) outweighs the risk of transplant-related mortality (TRM) that results in part from GVHD. If found, this could then potentially pave the way for GVHD therapy tailored to the patient’s risk of malignancy relapse.

This rationale rests upon a long-held understanding that the same mechanism is operant in GVL and GVHD. Indeed, both GVL and GVHD are manifestations of donor-versus-recipient alloreactivity, in the former case directed against hematopoietic tissues and in the latter against epithelial tissues. Several studies have already shown that patients experiencing GVHD are less likely to relapse (2). This has been shown in the setting of myeloablative or reduced intensity HCT, sibling or unrelated donors, and in the setting of acute or chronic GVHD. However, the fresh perspective of the current study is in performing a strict landmark analysis at 1 year after HCT, analyzing only patients who were still disease-free and still at risk for relapse. The landmark analysis at 1 year had the additional effect of minimizing the impact of acute GVHD on relapse rates. The effect of acute GVHD was not totally excluded, however, as prior acute GVHD is a significant risk factor for subsequent chronic GVHD.

In this very large retrospective registry study, Boyiadzis and colleagues found that the presence of cGVHD was associated with a diminished risk of late relapse only in patients with chronic myelogenous leukemia (CML). Patients with acute myelogenous leukemia, acute lymphoblastic leukemia, or myelodysplastic syndrome (MDS) did not experience lower relapse in the context of GVHD. Indeed, all groups (including CML) experienced worse disease-free survival and increased TRM in the setting of cGVHD. It is notable that most patients with acute leukemia relapse early after HCT. In contrast, most patients with CML relapse with slower kinetics. This observation likely explains the absence of a salutary effect of alloreactivity on late relapses of acute leukemia as by 1 year after transplant approximately two thirds of patients with acute leukemia destined to relapse will have already relapsed, whereas one third or less of patients with CML destined to relapse will have done so (3).

These findings do not significantly challenge the notion that some alloreactivity is beneficial for leukemia control; the benefit derived from GVHD is outweighed by toxicity in those patients who have not yet relapsed by 1 year (Fig. 1). Their most useful interpretation for the practicing clinician is in the strict setting of a patient with leukemia who is still disease free 1 year after HCT and is developing cGVHD. Is there any benefit to the patient? Clearly not, except perhaps in the vanishingly few patients who undergo HCT for CML. The observation, made recurrently in several studies, that cGVHD is associated with worse outcome raises these questions: What causes cGVHD and how do we predict, prevent, and treat it?

Allogeneic HCT has been around for four decades, and approximately 7,500 patients undergo this procedure each year. Registry-based studies, such as the one by Boyiadzis and colleagues, indicate that approximately 50% of patients develop chronic GVHD. In this context, it is remarkable that the pathogenesis and optimal management strategies of cGVHD still remain opaque.

Mouse models of GVHD imperfectly recapitulate the human disease, but bear enough similarities to be informative. In mice, cGVHD appears to be predominantly mediated by CD4+ T cells, secreting Th2- or Th17-type cytokines. There is a role for impaired thymic negative selection, leading to persistence of autoreactive T cells. This is one potential explanation for the tight association of prior aGVHD and cGVHD. In some models, there is activation of B cells with production of autoantibodies that in turn lead to some of the fibroblastic manifestations of the disease (4). A recent article implicates donor-derived CSF1-dependent macrophage infiltration in the pathophysiology of sclerodermatosus murine GVHD (5). In contrast, human cGVHD is very difficult to study mechanistically.

Clinical parameters predictive of the development of cGVHD include prior aGVHD, female to male HCT, mismatched HCT, and use of peripheral blood grafts compared with bone marrow (BM) grafts (6). Recently, a plasma proteomic approach to diagnose acute GVHD at a presymptomatic stage has been advanced.

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and offers the tantalizing possibility that one day we might be able to treat aGVHD pre-emptively. However, similar data are not currently available for chronic GVHD. Until such time, it appears that the best way to prevent chronic GVHD is with T-cell depletion (usually using antibodies such as alemtuzumab or anti-thymocyte globulin; ref. 7). Unfortunately, T-cell depletion also increases the probability of disease relapse.

So where are we in early 2015? We know some of the risk factors for development of cGVHD yet have no way to predict who will develop this complication. Effective means to prevent GVHD result in abrogation of the T-cell–mediated GVL effect for which the patient underwent HCT in the first place and hence defeat the purpose of the considerable investments incurred by the patient and the health system. Steroids are still the cornerstone of cGVHD therapy yet are beset by well-known complications and disappointing response rates.

Successful deployment of approaches that target one or more of the non–T-cell pathways implicated in the pathogenesis of cGVHD would therefore represent a vertical advance in the field. Extra-corporeal photophoresis has been used in the treatment of skin GVHD and appears to be nonimmunosuppressive, though its mechanism of action remains obscure (8). Inhibition of the fibrosis-inducing platelet-derived growth factor receptor pathway using drugs such as imatinib may play a limited role in some patients (9). B-cell activation has been targeted using rituximab and more recently in mice using ibrutinib (10). The latter approach is currently being studied in a clinical trial (NCT02195869). The recent description of donor-derived activated M2-like macrophages infiltrating skin and lung and demonstration that CSF1 receptor inhibition can prevent the development of cGVHD are particularly exciting new avenues of investigation, although it is notable that these preclinical results were obtained in a preventive/prophylactic setting rather than therapeutic intervention after the development of cGVHD. However, as CSF1R-inhibiting antibodies are currently being used to target tumor-associated macrophages, this may be attractive way to combine reduction of GVHD with enhancement of the antitumor effect. The role of regulatory T cells (Treg) in acute GVHD is well established, and it appears that strategies to enhance Treg in the relapse rate (11). Finally, although immune checkpoint inhibition is a promising modality for enhancing T-cell–based immunity, this approach would have to be trialed very cautiously in alloHCT patients due to the risk of precipitating GVHD (12).

Chronic GVHD is an undesirable complication of allogeneic HCT as it is associated with significant morbidity and with increased rates of TRM. The goal of alloHCT still remains the reliable separation of GVL from GVHD. This could potentially be achieved by targeting immune pathways that are unique to cGVHD and that are dispensable to GVL. Inhibition of B-cell function, recruitment of Treg, or inhibition of activated macrophage infiltration may be particularly promising strategies.

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References


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