New Strategies for Prevention and Treatment of Graft-versus-Host Disease and for Induction of Graft-versus-Leukemia Effects

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Abstract

Graft-versus-host disease (GVHD) continues to be a problem in allogeneic hemopoietic stem cell transplantation; however, our understanding of the basic pathophysiology of GVHD has improved. Although not all data obtained from murine or other animal models can be extrapolated to the clinic, there are leads that deserve to be pursued. The skin, intestinal tract, and liver are the 3 major target organs of GVHD and share the feature of presenting a barrier to the “environment” of the host. There is evidence that the damage inflicted to these organs, the epithelial and endothelial cells in particular, by the conditioning regimen causes a release of various cytokines and a penetration of endotoxin into the systemic circulation. According to these observations, the nonimmunologic aspects of GVHD have been likened to an inflammatory process. If this characterization is valid, blocking these nonspecific inflammatory changes would ameliorate GVHD without interfering with the graft-versus-leukemia (GVL) reaction. In fact, one study has shown a substantial amelioration of GVHD with a molecule that directly blocks endotoxin. Clinical data also suggest that patients with organ dysfunction early after transplantation that is presumed to be treatment related may benefit from preemptive interventions aimed at controlling GVHD. Furthermore, there is growing evidence that the mechanisms involved in GVHD may differ from organ to organ (for example, Fas/Fas-ligand interactions in the liver versus tumor necrosis factor α/receptor interactions in the intestinal tract), and from a therapeutic point of view, the time of onset of clinical GVHD may be important in choosing the appropriate therapy. Thus, combinations of interventions chosen and timed appropriately may be more effective in preventing and managing GVHD than are the standard across-the-board approaches that have been used so far. Such a strategy may also be successful in maintaining a GVL effect and possibly in incorporating direct antileukemic therapy, such as the use of cytotoxic T-cells directed at minor histocompatibility antigens, without increasing the risk of GVHD. The development of nonmyeloablative conditioning regimens and the observations on GVHD kinetics and the progression or eradication of leukemia with that strategy are likely to add new insights into how one can optimally combine various modalities to achieve engraftment, prevent GVHD, and at the same time maintain a GVL effect. Int J Hematol. 2003;77:15-21.

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1. Introduction

Graft-versus-host disease (GVHD) is one of the most studied iatrogenic complications in medicine. Although termed a disease, GVHD actually is the clinical manifestation of the attempts of 2 immune systems, donor and recipient, to defend their identities. The physician undermines the recipient’s defense by a barrage of immunosuppression that opens the gates to invading donor cells but also activates the chemical weaponry of cytokines and chemokines. The ensuing battle progressively decimates the defending troops but in the process may also severely damage and inflict scars on the civilian bystanders unless a truce in the form of tolerance is reached quickly.

2. Graft-versus-Host Disease

2.1. Pathophysiological Considerations

In recent years there has been substantial improvement in our understanding of the pathophysiology of GVHD, at least
in its acute form, largely because of the work by Ferrara, Blazar, and others [1-11]. For discussion purposes we can consider 3 phases in GVHD: an initial phase that is largely related to tissue damage induced by the preparative regimen, a second phase of donor cell activation and expansion, and, third, an effector phase that leads to the destruction of target cells and tissues [6,10]. In the following discussion I examine the donor and host components involved in these processes.

2.1.1. Conditioning

All transplantation strategies currently in clinical use employ some form of “conditioning” to prepare the transplant recipient for sustained engraftment of donor hemopoietic stem cells. The type and intensity of the conditioning regimen have been correlated with the incidence and severity of GVHD [12-14]. Although cytotoxic components such as irradiation or chemotherapeutic agents may induce tissue damage directly, the release of cytokines and possibly chemokines from damaged cells and tissues appears to create the milieu that leads to the expansion of donor cells and the amplification of the attack of donor cells against the recipient [15]. High-intensity conditioning regimens have generally been associated with increased nonrelapse morbidity and mortality, particularly in older patients. Experience with more recently developed reduced-intensity conditioning (RIC) or nonmyeloablative (NMA) conditioning regimens has shown that early posttransplantation nonrelapse morbidity and mortality can be reduced [16-19]. The incidence of acute GVHD, however, has remained approximately 50%, although, notably, the severity of GVHD may be lessened [16,20]. This observation provides additional evidence that factors other than direct tissue damage are pivotal for the development of GVHD. Trials with RIC furthermore suggest that a graft-versus-leukemia (GVL) (or graft-versus-tumor) effect is achievable with such an approach.

2.1.2. Donor Cells

The requirements for GVHD to develop were classically formulated approximately 35 years ago by Billingham [21] that indicated that immunocompetent donor cells are essential. Subsequent studies showed these donor cells to be T-lymphocytes, and experiments with murine models found that, depending on the type of histoincompatibility between donor and recipient, both CD8+ and CD4+ cells induced GVHD [9]. In fact, T-cell depletion of the donor cell inoculum prevented GVHD completely in these models. More recent work suggests that a more potent GVHD effect may be conveyed by CD4+ T-cells expressing interferon (IFN)-γ, particularly in older recipients [22]. Functionally defined T-helper 2 (Th2) and T-cytotoxic 2 cell populations contribute to the regulation of GVHD and to a GVL effect [23]. Natural killer (NK) cells have also been shown in murine models to be involved in GVHD [24]. Recent trials with patients who received transplants from HLA-nonidentical donors suggest that CD56+ donor cells play an important role in engraftment and that these cells can mediate a GVL effect without inducing GVHD [25]. Tanaka et al [26] have shown that the numbers of NK cells expressing killer cell inhibitory receptors (CD158b, CD94) were lower in patients with chronic GVHD than in those patients without GVHD. CD94+ cells notably were induced by interleukin 15 (IL-15), a cytokine derived from monocytes and macrophages [27] (reviewed in [15]) and thought to be involved in GVHD. Conceivably, these observations are reconciled by the fact that IL-15 levels were elevated early after transplantation in all patients but later only in patients who developed GVHD. Additional studies have provided evidence for a role of a newly recognized subset of CD25+CD4+ regulatory T-cells that is functionally reminiscent of classic “suppressor” cells [1].

Another cellular function that has recently attracted renewed interest is veto activity. Gur et al have shown that CD34+ precursors (in addition to CD8+ and Fas-ligand+ T-cells) possess veto activity and that in vitro cultures in the presence of Flt-3 ligand, c-kit ligand, and thrombopoietin permit the expansion into CD34+ CD33+ or CD34+ CD33- cells with a 4-fold increase in veto activity. The authors suggest that these cells can induce immunologic tolerance and prevent GVHD [28].

2.1.3. Host Cells

The objective of clinical hemopoietic cell transplantation is generally the correction or eradication of an underlying disease, ie, the destruction of some host targets. Thus, an allogeneic effect against abnormal or malignant cells, for example a GVL effect, is welcome. Any damage to normal recipient tissues, however, is undesirable. Nevertheless, it is known that marrow-derived host cells serve as targets and as antigen-presenting cells for donor lymphocytes. Work first presented by Shlomchik and colleagues [29] indeed provided evidence that host dendritic cells (DC) play a central role in the pathophysiology of GVHD development. Another factor that is positively correlated with GVHD is recipient age, and recent murine studies have shown that serum levels of lipopolysaccharide (LPS) and tumor necrosis factor α (TNF-α) were higher in older recipients with GVHD than in younger recipients [22]. These investigators then showed that DC from older mice had stronger allostimulating capacity than did DC from younger mice and expressed higher levels of TNF-α and IL-12 than did DC from younger mice [4,22]. Consistent with those data were observations that manifestations of GVHD were more severe in young mice first reconstituted with hemopoietic cells (including DC) from old donors than in young mice reconstituted with cells from young mice, and that GVHD manifestations were less severe in old mice reconstituted with cells from young mice than in old mice reconstituted with cells from old donors. The same investigators also showed that the expression of major histocompatibility complex molecules on DC was sufficient to induce GVHD in target organs such as skin, liver, and gut; major histocompatibility complex expression on epithelial cells was not required [30,31]. These data support the notion that manifestations of GVHD in target organs are antigen independent and presumably cytokine mediated. These cytokines in turn contribute to aberrant antigen expression on potential target tissues, which then are perceived as foreign by the immune system.