



**STANDARD AND EMERGING THERAPIES FOR  
ACUTE  
GRAFT-VERSUS-HOST DISEASE**

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## Introduction

Graft vs. host disease (GVHD) is the principal cause of severe morbidity and mortality after allogeneic hematopoietic cell transplantation (HCT). The pathobiology of GVHD is complex and involves the interaction of multiple effector cell populations, and proinflammatory cytokines, many of which have been targets of therapy for GVHD (1). Acute GVHD (aGVHD) has historically been defined by its time of onset (prior to 100 days post HCT) as opposed to chronic GVHD which occurs at day 100 or later. An earlier onset of the typical clinical manifestations of chronic GVHD is well recognized, however, and late onset GVHD is also being increasingly diagnosed. The apparent increase in late onset aGVHD is likely a result of peripheral blood stem cells rather than bone marrow for HCT, and the use of reduced intensity conditioning (RIC) therapies (with the frequent use of post HCT DLI). Multiple risk factors for aGVHD have been elucidated (2). Histoincompatibility is uniformly recognized as an important risk factor for GVHD, thus the incidence of aGVHD is higher after alternative donor (unrelated donor, haploidentical related donor or umbilical cord blood donor) compared with HLA matched sibling donor HCT. Other risk factors for aGVHD include increasing patient and donor age, sex mismatched donor (particularly parous female donor and male recipient), cytomegalovirus seropositivity, stem cell source, and method of GVHD prophylaxis. Ex vivo T cell depletion of the graft leads to a substantially lower incidence of aGVHD but is associated with increased probabilities of relapse (particularly for myeloid malignancies) and of graft rejection (3). RIC transplants may be associated with less aGVHD than myeloablative transplants (4). This comparison is difficult, however, given the lack of data from randomized controlled trials and the significantly different patient populations that are the basis of retrospective comparisons (i.e. older, sicker patients in RIC trials).

## Clinical manifestations of acute GVHD

The target organs of acute GVHD are primarily the skin, GI tract and liver. Skin is most commonly affected, although an apparent increase, particularly in the late onset form of aGVHD, of isolated gut or liver GVHD has been recognized. Typical skin findings of GVHD include a maculopapular rash with the earliest rash often apparent on the face, scalp, neck and/or palms or soles. GI GVHD can involve the upper GI tract

(nausea/vomiting and/or pain), lower GI tract (predominantly pain and diarrhea) or both. Hepatic GVHD has historically been described as a predominantly cholestatic process. Recently described, particularly in RIC transplant recipients (and post DLI) has been a predominantly hepatocellular form of hepatic GVHD (characterized by significant elevation of transaminase levels) (5).

The diagnosis of GVHD is a clinicopathologic one and corroborating histologic evidence of GVHD is important whenever possible. While no absolutely pathognomonic histologic features of GVHD have been determined, certain features which connote epithelial cell injury by immune effector cells are generally believed to be the most relevant histopathologic findings. For example, typical skin findings include epidermal keratinocytic dyskeratosis with mononuclear cell satellitosis; GI tract findings may include prominent apoptosis and glandular damage, while hepatic GVHD is characterized by an inflammatory bile duct injury. Because of the frequent occurrence of confounding illnesses that may affect the same organs and tissues (e.g. infection such as cytomegalovirus causing enteritis or hepatitis, and drugs causing GI tract symptoms or hepatic injury), each of the target organs should be addressed individually, with as much supporting histopathologic evidence of GVHD as possible. Distinction of engraftment syndrome (which is characterized by fever, rash and often elevation of liver function tests) from GVHD can be difficult (6). Given that early manifestations of aGVHD, (often referred to as hyperacute GVHD if the clinical manifestations occur before engraftment) may be indistinguishable from engraftment syndrome (and may in fact be one in the same in many cases), the distinction may not be clinically relevant in some cases. Some patients with engraftment syndrome have resolution of the clinical manifestations of the syndrome with a short course of corticosteroids (and do not develop GVHD later), appropriate diagnostic evaluations at the onset of clinical presentation are warranted. Acute GVHD should be staged according to one of two accepted staging classifications. Each of these takes into account the degree of skin involvement, height of the bilirubin level, and volume of diarrhea for skin, hepatic and G.I. GVHD, respectively. These classifications, however, miss the predominantly hepatocellular injury variant of hepatic GVHD.

## **Prevention of GVHD**

The introduction of calcineurin inhibitors (CNI) (cyclosporine and tacrolimus) has added substantially to protection from GVHD, and has allowed for the transplantation of higher risk (by age, disease status, co-morbidity, etc.) patients. A CNI plus methotrexate is the most widely used pharmacologic GVHD prophylaxis strategy. Tacrolimus with methotrexate is associated with less GVHD than transplants employing cyclosporine and methotrexate for GVHD prophylaxis, in both the matched related and unrelated donor settings. No overall survival benefit of the tacrolimus combinations has been realized, however (7, 8). A novel GVHD prophylaxis strategy combines tacrolimus with the mTOR inhibitor sirolimus with or without low dose methotrexate (9). Very low incidences of

acute GVHD have been seen in both the related and unrelated donor settings. A CNI with mycophenolic mofetil (MMF) is also being evaluated as GVHD prophylaxis with early results suggesting similar or possibly inferior GVHD protection, but with less toxicity compared to methotrexate and CNI combinations (particularly less mucositis). Ex vivo T cell depletion is highly effective in preventing acute GVHD but is associated with an increased probability of graft rejection and relapse, particularly for myeloid malignancies. In a prospective randomized trial evaluating its efficacy in the setting of unrelated donor transplantation, no survival benefit of ex vivo T-cell depletion was realized (10). Ex vivo T cell depletion may be, however, the most effective strategy in overcoming the otherwise prohibitively high GVHD risk following haploidentical stem cell transplantation.

### **Treatment of Graft Vs. Host Disease**

The cornerstone of therapy of GVHD has been high dose corticosteroids. Sustained response rates of greater than 60% have been demonstrated for the treatment of cutaneous GVHD, but only 20-40% of patients have achieved sustained responses for hepatic and gastrointestinal GVHD (11, 12). The long term morbidity of corticosteroids, moreover, complicates the management of an already immunocompromised host, particularly with regards to the high risk of infectious complications in this patient population. Multiple other immunosuppressive therapies have been used for the treatment of a GVHD. Anti-thymocyte globulin (either of equine or rabbit source) may lead to transient responses, but a survival advantage was not shown when equine ATG was combined with corticosteroids compared to corticosteroids alone for patients with moderately severe aGVHD (13). More targeted immunosuppressive approaches with agents such as daclizumab (an anti-IL-2 receptor monoclonal antibody), denileukin diftitox (an IL-2 diphtheria toxin hybrid molecule) and infliximab (an anti-tumor necrosis factor alpha monoclonal antibody) have been used in steroid refractory GVHD with impressive response rates but disappointingly low long term survival probabilities. An inferior survival was, however, reported in a trial combining daclizumab with corticosteroids compared with corticosteroids alone for the initial treatment of GVHD (14). Oral non-absorbable corticosteroids (budesonide or beclomethasone) may be effective for GI GVHD. In a randomized, placebo-controlled evaluation of beclomethasone dipropionate for GI GVHD, a 1 year survival advantage was demonstrated for the beclomethasone treated patients (15). In a recently completed Clinical Trials Network multicenter trial, the combination of corticosteroids with etanercept, MMF, deoxycoformycin or denileukin diftitox for newly diagnosed aGVHD were compared. A higher day 28 complete response rate and a survival advantage were observed in the MMF group (16). Anti CD 52 monoclonal antibody therapy (alemtuzumab) has activity in corticosteroid refractory GVHD but because of its profound immunosuppressive effects is associated with a high risk of opportunistic infections (17).

## Emerging Therapies for Acute GVHD

In an effort to circumvent the global immunosuppressive properties of many pharmacologic agents, efforts are underway to manipulate the cellular environment post-transplant, not only to prevent or treat GVHD, but to enhance a graft versus tumor effect. Extracorporeal photopheresis has some activity in the treatment of aGVHD but has been most effective for patients with the cutaneous variants of chronic GVHD (18). Human mesenchymal stem cells (MSCs), based on potent MHC non-restricted immunomodulatory properties, have been shown in early clinical trials to reverse severe aGVHD in selected instances, and are currently being evaluated in prospective randomized controlled trials (19). Selective T-cell depletion (e.g. CD8+ T-cell depletion) of the graft (or DLI) may prevent GVHD while preserving a GVT effect (20) and strategies to augment CD4+ CD25+ T regulatory cells in the graft or via adoptive cellular immunotherapy post-transplant are being explored (21). Ex vivo selective allodepletion showed promise in the prevention of aGVHD following haploidentical HCT (22).

## Conclusions

Acute graft versus host disease is the chief cause of morbidity and mortality following allogeneic stem cell transplantation. Multiple pharmacologic and non-pharmacologic strategies exist for the prevention of aGVHD:

1. Standard pharmacoprophylaxis consists of a CNI and either methotrexate or MMF (early results with CNI and sirolimus are promising as well).
2. Ex vivo T-cell depletion is largely reserved for experimental clinical trials, particularly those involving haploidentical stem cell transplantation.

For patients who develop aGVHD a commonly employed strategy is to:

1. Begin corticosteroids with methylprednisolone 1-2 mg/kg/day (or equivalent), depending on the severity and number of organs involved, along with continuation of CNI therapy.
2. Add another immunosuppressive agent early, if the patient is corticosteroid refractory, or efforts to taper the steroids are unsuccessful. MMF may be an appropriate drug in this situation given early data suggesting potent anti-GVHD activity when combined with corticosteroids for newly diagnosed aGVHD.
3. Other agents that can be used for steroid refractory GVHD include polyclonal anti-thymocyte globulin, denileukin diftitox and inhibitors of tumor necrosis factor alpha (e.g. infliximab or etanercept).
4. Enrollment in a clinical trial whenever possible, exploring new immunomodulatory cellular therapies (such as MsC) is encouraged.

5. As survival is ultimately dependent on the prevention and control of opportunistic infections, an aggressive anti-infective strategy is crucial. This should include vigorous monitoring (particularly for herpesvirus infections and invasive mold infections), and prophylaxis (with, for example, extended spectrum azole therapy and antiviral prophylaxis) and early therapy of infectious complications (CMV, and possibly EBV, for example).

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