GVHD—The Nuts and Bolts

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Acute graft-versus-host disease (GVHD) is the most frequent, morbid complication following allogeneic hematopoietic stem cell transplantation (HSCT). Its clinical toxicity, requirement for intensive immunosuppressive management, and associated infections lead to the greatest risks of nonrelapse mortality in HSCT recipients. In acute GVHD, donor-derived T lymphocyte–mediated alloreactivity is complicated by inflammatory responses, cytokine release, direct tissue injury through target cell apoptosis, and secondary tissue injury. The therapeutic management includes effective GVHD prophylaxis to limit the incidence and severity of acute GVHD, prompt and effective therapy if it develops—modified if possible to protect against chronic GVHD—and intensive supportive care relevant to its association with delayed immune reconstitution. As the major ongoing morbid complication following allografting, chronic GVHD is another barrier to patients' recovery and long-term survival. Recognition of the critical elements in the pathogenesis of GVHD has prompted new approaches to its management and its role in controlling the risks of malignant relapse after allotransplantation. Important elements in the practical management of GVHD will be reviewed.

Introduction

New approaches to graft-versus-host disease (GVHD) prophylaxis have involved novel combinations (most prominently tacrolimus plus sirolimus), depletion of host antigen-presenting cells (APCs) that may present host alloantigens to incoming donor T-cells, or strategies to augment T-regulatory (Treg) cell function in order to blunt host antigen-specific T-cell activation and expansion during the initial phases of donor-host interaction and thereby limit GVHD. Blunting T-cell expansion with Treg activity, if transient, can blunt GVHD and donor antihost responses while not preventing donor anti-infection or antitumor responses necessary for immunocompetence and long-term survival.

Following allogeneic hematopoietic stem cell transplantation (HSCT), conditioning toxicity, infections, and malignant disease recurrence may occur, but the major, immunologically important complication following allografting is GVHD. The pathogenesis of GVHD is multifactorial, including conditioning regimen toxicity that exposes neoantigens, enhances cytokine release, augments APC presentation of alloantigen to incoming donor T cells and initiates the immunologic storm.[1] Infused donor T cells recognize alloantigenic peptides and are activated, expand, and migrate to lymphoid organs allowing further peripheral expansion. This triggers the cytokine and cytolytic apoptotic injury manifest as GVHD. Targeting the skin, gut, liver, and probably the lung, acute GVHD occurs in 30% to 50% of sibling donor recipients and a higher fraction of unrelated donor (URD) recipients due to the greater histoincompatibility and augmented T-cell activation seen in these pairs. Acute GVHD yields four specific consequences: direct organ injury requiring immunosuppressive therapy, secondary risks of infection, heightened risks of the distinct but related chronic GVHD syndrome, and, for some malignancies, an enhanced antitumor effect accompanying this alloreactive response. Each of these events will be briefly reviewed with management strategies and areas requiring further study highlighted.

Acute GVHD Organ Injury

The original experimental animal manifestations of GVHD were called secondary or runting disease and manifest as diarrhea, skin sloughing, weight loss, and death accompanied by lymphoid hypoplasia and hepatic necrosis. Cytotoxic T cells as well as inflammatory cytokines produce this injury to the GVHD target organs through direct cytolytic effect and induction of apoptosis. Both major and minor histocompatibility antigens, viral antigens, and epithelial target–associated antigens trigger T-cell activation and proliferation. Recent evidence suggests that antibody-mediated B-cell responses may be involved in GVHD as well.

Acute GVHD induces an erythematous skin rash progressing to bullae in its most severe form.[2-5] It has predilection for dorsal surfaces of the extremities, malar regions, tops of the ears, back of the neck, and involvement of the palms and soles, sites that are rarely involved with other skin rashes. A rash may be pathognomonic of acute GVHD if palmar involvement is present. Gastrointestinal (GI) involvement can manifest in the upper tract as persistent nausea, anorexia, and vomiting,[6] but most characteristically involves a watery, protein-rich, secretory diarrhea that can progress to bloody diarrhea and/or ileus in its most severe form. Hepatic involvement typically targets the biliary epithelium with cholestasis and alkaline phosphatase elevation though a hepatitic form, particularly of chronic GVHD, has been reported. While the vast majority of patients present with skin involvement, a minority (20% or less) have GI involvement without cutaneous manifestations, and the smallest group (less than 10%) have liver involvement without a rash.[7-9]

Interstitial pneumonitis, lymphocytic bronchiolitis, or alveolar hemorrhage, either alone or compounded by infection, occur more often in allogeneic HSCT recipients than following autografts. Along with extensive preclinical data, this suggests that these syndromes may be, at least in part, manifestations of an allogeneic epithelial injury and part of the broad GVHD spectrum. It is not fully accepted, however, that these pulmonary syndromes represent acute lung GVHD. In contrast, bronchiolitis obilterans is one of the most severe and distinctive manifestations of chronic GVHD. The distinctions in pathogenesis of these differing syndromes and their relationship to the other components of the GVHD syndrome is incompletely understood.

Tissue biopsies may be valuable for confirmation of the clinical diagnosis, though their specificity has been debated, especially in the first weeks following myeloablative conditioning therapy. The mild histologic signs of GVHD in the rectum and the skin may overlap with conditioning toxicity. However, after reduced-intensity conditioning or beyond 3 weeks following transplantation, this histologic confusion is unlikely. Histopathologic confirmation of the diagnosis should be used to confirm the clinical diagnosis and, importantly, to exclude opportunistic enteric infections, cutaneous drug eruptions, or other cholestatic syndromes (veno-occlusive disease, total parenteral nutrition effects, drug-associated cholestasis), which mimic the signs and symptoms of GVHD.

Variant Presentations of GVHD

Acute GVHD may differ when it develops in a context other than following a conventional, myeloablative (MA) marrow or peripheral blood stem cell (PBSC) graft. GVHD following umbilical cord blood (UCB) transplantation may be less frequent or less severe, but definitive data in comparable patient populations are lacking. Following reduced-intensity or nonmyeloablative (NMA) HSCT, acute GVHD could manifest later and be slower in its evolution following the more gradual engraftment of donor lymphoid cells. Early data from Seattle suggested this slower onset (nearly 20% of sibling, but not URD recipients developing acute GVHD beyond day 60), but the onset of chronic GVHD was similar in recipients of either conditioning intensity. In preliminary data from the Center for International Blood and Marrow Transplant Research (CIBMTR) on patients alive at 60 days or longer with no GVHD, only 5% to 8% will subsequently develop any signs of acute GVHD (M. Pasquini, personal communication, 2007). In a series from the University of Minnesota comparing 39 UCB recipients of MA UCB grafts with 33 somewhat older patients receiving NMA UCB transplants, both the incidence (MA: 34% [95% CI 24-44]; NMA: 45% [95% CI 31-54] $P = .14$), timing of onset (MA median day 35 [12-137]; NMA 30 [15-96], $P = .4$), and severity were similar (M. Arora, personal communication, 2007). Finally, GVHD developing after donor lymphocyte infusions (DLI) may differ in its manifestations and severity. DLI, particularly when infused for treatment of persisting or recurrent cancer, is most often given without pharmacologic immunosuppression, and may be deliberately undertreated in hopes of maximizing the antitumor effects. GVHD after DLI occurs in 40% to 70% of recipients and can be severe. In all these situations, clear data on the incidence and best management of GVHD are inadequately studied.

Infectious Complications of GVHD

GVHD itself as well as needed immunosuppressive therapy can exaggerate and confound the risks of opportunistic infection. Infections, particularly in the gut, may mimic acute GVHD and may, of course, co-exist, thus compounding the GI symptoms. Enteric infections are additional, rather than alternate, differential diagnoses for nausea, vomiting, or diarrhea. Since GI involvement without a rash is uncommon, signs and symptoms suggestive of enteric GVHD and confirmed as infection in the gut may be GI infection with or without GVHD in the absence of a rash. Thus, histologic confirmation can be of critical importance in establishing the presence of one or both diagnoses.

GVHD is, in itself, immunosuppressive. As residual host defenses are depleted, immunosuppressive therapy produces lymphopenia. Cutaneous and GI epithelial barriers are disrupted by GVHD and, in addition, the dysregulated immune attack on host tissues blunts and confounds successful host defense against opportunistic pathogens. GVHD that develops following neutrophil recovery is accompanied by higher risks of cytomegalovirus (CMV) reactivation, invasive fungal infections, pneumocystis pneumonia, varicella zoster reactivation, and, importantly, sepsis with encapsulated organisms, including pneumococcus and *Haemophilus influenza*. Appropriate management of these infectious hazards in patients with acute GVHD requires pharmacologic prophylaxis. Prevention of yeasts is most often with fluconazole or, if suspicions are heightened, with more broadly active azoles (voriconazole, posaconazole) or even parenteral amphotericin or echinocandins. Surveillance against CMV reactivation with antigenemia assays or DNA PCR facilitates prompt, empiric therapy of asymptomatic CMV reactivation. In some centers, acyclovir (10 mg/kg/day intravenously) or valacyclovir prophylaxis has been used. Antipneumococcal prophylaxis with penicillin or, in the case of penicillin resistance, extended spectrum quinolones (e.g., levofloxacin) may be indicated. Antipneumocystis prophylaxis (trimethoprim-sulfamethoxazole, dapsone, atovaquone, or inhaled pentamidine) is also essential. These measures should continue for the duration of immunosuppressive therapy and likely for 3 to 6 months following as well. Since hypogammaglobulinemia often accompanies acute GVHD, patients with recurrent enteric or sinonasal infections may benefit from intravenous IgG (IVIG) supplementation. However, broadly applied IVIG prophylaxis for all with GVHD is neither cost-effective nor clinically effective, as it may delay B-cell reconstitution.

As in any immunocompromised host, even if not neutropenic, patients with acute GVHD need prompt intervention for any syndrome suggestive of infection. In the winter season, community-acquired respiratory infections (respiratory syncytial virus or influenza) need prompt recognition and antiviral therapy, as lower respiratory tract involvement with severe pneumonitis may develop. Parainfluenza can yield an identical syndrome, though without the fall and winter predominance. Yearly influenza immunization of patients and, most importantly, their household contacts is important.

Treatment of GVHD

Therapy of acute GVHD involves pharmacologic suppression of T-cell activation, cytokine release, and re-establishment of donor-host immunotolerance. Therapeutic strategies aim to blunt T-cell activation while facilitating Treg cell expansion. However, the optimal strategy to induce this immunoregulatory balance is not well defined. Sirolimus without calcineurin inhibitors might facilitate regulatory T-cell expansion, but conventional management with corticosteroids and calcineurin inhibitors (cyclosporine or tacrolimus) produces broad immunosuppression and lymphopenia, and shows neither preference nor specificity for suppression of cytolytic versus Treg cells.

While 30% to 50% of patients respond to corticosteroids (1-2 mg/kg/day prednisone) as initial therapy for acute GVHD, new agents have been tried to improve the response rate and limit steroid exposure.[10-26] Limited-severity, upper-GI–only GVHD may respond to oral budesonide or beclomethasone along with lower-dose prednisone, though formal studies comparing this approach to conventional higher-dose corticosteroids are not conclusive. Numerous other agents (mycophenolate mofetil [MMF], etanercept, denileukin diftitox [Ontak], or pentostatin) have shown promise[27-33] and are currently under study in a prospective randomized trial assessing their value when added to corticosteroids for initial therapy of acute GVHD (Blood and Marrow Transplant Clinical Trials Network [BMT CTN] Study 0302). Additional agents directed towards activated T-cells (daclizumab) or blunting other components of tumor necrosis factor activation (infliximab) have been formally tested but have not shown higher response rates or improved survival compared with prednisone alone. ATGs (either horse or rabbit) are potent lympholytic agents with long histories of use in treating acute GVHD, mostly resistant to primary corticosteroid therapy. While varying response rates have been reported, no studies have consistently shown improved survival using ATG either initially or as a secondary therapy. Its use is complicated by higher risks of opportunistic infection, particularly by severe risks of Epstein-Barr virus reactivation and occasional post-transplantation lymphoproliferative disorders.

The optimal drug combination for acute GVHD therapy is undefined. Newer approaches, including sirolimus, alemtuzumab, or infusion of mesenchymal stem cell,s also show suggested activity, but their comparative value, safety, and likelihood of improving survival in patients with steroid-resistant acute GVHD is unproven and requires formal, well-designed studies to establish their utility.

Chronic GHVD

Another major consequence of acute GVHD is a high likelihood of developing chronic GVHD, a related but distinct syndrome with similar and yet overlapping features.[34,35] Shared acute and chronic signs and symptoms include erythematous skin rash, nausea, vomiting, diarrhea, and cholestatic liver disease, and has been recognized as an overlap syndrome. However, chronic GVHD also has distinctive signs and symptoms. These include sicca syndrome (dry eyes and dry mouth), obstructive bronchiolitis, and lichenoid or sclerotic skin changes. Less common chronic GVHD features include esophageal dysmotility, fasciitis, arthropathy, and autoimmune manifestations. The chronic inflammatory and fibrotic processes accompanying chronic GVHD may induce articular stiffness, limited mobility, oral stomatitis limiting jaw opening and chewing, and vaginal stenosis interfering with sexual function. The major risk factor for chronic GVHD is preceding acute GVHD, though a small fraction of patients develop this latter syndrome without earlier acute GVHD (*de novo* chronic GVHD). A recent National Cancer Institute–sponsored series of consensus papers[36-41] defined the diagnostic criteria for chronic GVHD, described its pathology, outlined techniques for measuring its manifestations, and documented its response to therapy as well as identifying critical elements of supportive care, plus highlighting limitations of pathophysiologic and clinical knowledge about how best to study its prophylaxis and treatment. These are expert opinion pieces, but they need further study, objective testing, and validation in prospective trials. They also may need modification and refinement to improve their precision and their utility.

Therapy of Chronic GVHD

Treatment of chronic GHVD is usually less aggressive than that of acute GVHD. It requires extended duration immunosuppressive therapy, specific infection prophylaxis, and important supportive care, including nutritional management, physical therapy, and aggressive management of the polypharmacy accompanying its treatment.[42] Similar to acute GVHD, corticosteroids (sometimes alternate day) plus calcineurin inhibitors are the most common agents used for treatment.[43,44] Newer agents are under formal study, including MMF, sirolimus, pentostatin and, intriguingly, extracorporeal photopheresis.[45] Previously used therapies including ATG and thalidomide have failed to sustain their initial promise in formal prospective trials, though occasional patients have apparent clinical responses. Recent evidence suggesting anti-HY antibodies and partial efficacy of rituximab in managing at least the acute inflammatory erythematous and lichenoid skin changes of chronic

GVHD suggest a potential role for B-cell activation and antibody-associated tissue injury in components of the syndrome.

Even more than acute GVHD, the varying and protean manifestations of chronic GHVD, its slowly progressive and protracted course and, most importantly, its pathophysiology are all less well understood.[46-48] As the major long-term morbid complication of allotransplantation, the syndrome demands important attention and research to improve the precision of its diagnosis and its management.

Chronic GVHD also represents the most important cause of nonrelapse mortality beyond 2 to 3 months after transplantation and the major syndrome limiting quality of life and function in allogeneic transplantation survivors. High-risk features (extensive skin involvement, progressive onset of chronic following acute GVHD, thrombocytopenia at diagnosis, and multiorgan involvement, particularly including the lung) have a major impact on survival and result in double the risks of nonrelapse mortality compared with patients with limited, single organ, non-progressive onset of chronic GVHD, particularly with preserved platelet production.

GVHD is Not Always Graft versus Leukemia

Acute and chronic GVHD are both associated with protection against malignant relapse, particularly in chronic myeloid leukemia (CML), chronic lymphocytic leukemia (CLL), follicular non-Hodgkin lymphoma, and possibly in acute myeloid leukemia (AML) and myeloma. Less certain graft-versus-tumor effects accompany GVHD in patients with acute lymphocytic leukemia (ALL), high-grade non-Hodgkin lymphoma, and some other tumors. Importantly, the extent and severity of acute and chronic GVHD do not directly correlate with protection against malignant relapse. Some manifestations of GVHD and its allogeneic attack do accompany the antineoplastic potency of the syndrome and can possibly be exploited. The potency of the antineoplastic effect, however, is not directly tied to the morbidity of acute and chronic GVHD. The development of limited GVHD symptoms, managed with the least toxic therapy, may offer the best benefits including the ideal balance of limited morbidity, protection against opportunistic infection, and most importantly limited risks of relapse. This harnesses the therapeutic potency of the GVHD reaction to improve patient survival.

Therefore, the most important elements of GVHD management are the following:

- Be certain of diagnosis and clinical manifestations. Don't confuse GVHD with infections, drug reactions, or other peritransplantation complications.
- Critically address risks of infection providing pharmacologic prophylaxis, extended infection surveillance, and prompt and aggressive intervention for any infection syndromes to limit their severity.
- Pay aggressive attention to nutritional support, physical therapy, polypharmacy and drug interactions.
- Ensure that close communication takes place between the transplant center, the patient, and the local managing physician if patients have returned home to improve patient safety and recognize treatment-associated complications early.
- Limit the intensity of immunosuppression to that required for GVHD control.

Future Research

Directed, planned, protocol-driven management of GVHD should be developed and implemented, as patient-specific tailoring of therapy is unwise. Established protocols for initial GVHD therapy, duration of taper, and second-line treatments can improve patient education and compliance, highlight the expected response, and enhance recognition of both treatment failures and therapy-associated toxicities. Individualized therapy has little place in the manifestation of these inadequately understood syndromes. Carefully designed diagnostic, supportive, and treatment protocols can improve the care of patients with GVHD and most importantly, improve the quality and duration of their life.

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