Graft-Versus-Host Disease: Review and Nursing Implications

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Hematopoietic stem cell transplantation (HSCT) has become a standard treatment option in the management of a variety of hematologic malignancies and also is indicated in a number of other malignant and nonmalignant disease states (Saria & Gosselin-Acomb, 2007). Advances in this treatment modality have produced therapies designed to control, or even cure, specific hematologic diseases. The goal of allogeneic HSCT is to rescue and restore function of the hematopoietic system after high-dose chemotherapy with or without total body irradiation. Despite decades of improvement in care and recipient quality of life, allogeneic stem cell transplantation continues to produce significant, long-term complications. Specifically, the process of allogeneic HSCT can initiate a cascade of autoimmune events known as graft-versus-host disease (GVHD). In GVHD, the new donor immune system recognizes antigen-presenting cells (APCs) in the host (i.e., patient) as foreign, thus producing an inflammatory response (Neumann, 2004). GVHD can be divided into two types, acute and chronic. Collectively, acute and chronic GVHD (cGVHD) continue to cause significant morbidity and mortality in patients undergoing HSCT.

Acute Graft-Versus-Host Disease

Acute GVHD (aGVHD) is characterized by the time of onset postallogeneic transplantation. It occurs after stem cell engraftment and from 7–100 days after transplant. The most important predisposing factor for aGVHD development is the degree of major histocompatibility complex mismatch between the donor and recipient (Beatty et al., 1985). Other risk factors for aGVHD development include patient and donor age (Kollman et al., 2001; Weisdorf et al., 1991), source and dose of hematopoietic stem cells (Cutler et al., 2001; Przepiorka et al., 1999), and intensity of the preparative regimen (Couriel, Saliba, et al., 2004). An estimated 30%–40% of human leukocyte antigen- (HLA-) identical transplant recipients develop aGVHD. Stem cell recipients with one antigen mismatch have a 60%–80% risk of developing aGVHD (Flowers, Kansu, & Sullivan, 1999).

Pathophysiology

The pathophysiology of aGVHD involves a complex inflammatory response, regulated by the release of various cytokines. An initial development of an inflammatory environment results from host tissue damage from the preparative chemotherapy and radiotherapy regimen. The damaged tissues secrete inflammatory cytokines, interleukin-1, and tumor necrosis factor alpha. Donor and recipient APCs and additional inflammatory cytokines trigger the activation of donor-derived T cells. The activated donor T cells mediate the cytotoxic response against target host cells, which leads to the clinical manifestations of aGVHD (Ferrara, Cooke, & Teshima, 2003; Hill et al., 1997; Hill & Ferrara, 2000). Mortality associated with aGVHD is directly related to the severity and extent of organ involvement (Flowers et al., 1999).

Manifestations

Manifestations of aGVHD are observed most often in the target organs of the skin, gastrointestinal tract, and liver. The most frequently involved site of aGVHD is the skin, where observed symptoms include a sometimes painful, pruritic, and maculopapular rash. The rash initially affects the palms of the hands and soles of the feet, with progression to the trunk, chest, and upper back. Gastrointestinal symptoms of aGVHD include diarrhea with or without anorexia, nausea, and emesis. Progression of these symptoms can lead to gastrointestinal bleeding and ileus formation. In addition, aGVHD of the liver manifests as hyperbilirubinemia.

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and an increase in alkaline phosphatase. Elevated transaminase levels also may be observed. Progressive aGVHD of the liver can lead to hepatic failure (Couriel, Caldera, Champlin, & Komanduri, 2004; Przepiorka et al., 1995).

**Diagnosis and Staging**

A diagnosis of aGVHD is established after biopsy and histopathologic confirmation of the affected organ. To determine the area of body surface affected by aGVHD, the Rule of Nines or a burn chart commonly is used (see Figure 1). The Rule of Nines Chart provides a quick approximation of the percentage of the body that is involved and generally is used only for adult body surface area estimation.

**Chronic Graft-Versus-Host Disease**

Similar to aGVHD, cGVHD also is characterized by time of onset. Generally, symptoms of cGVHD occur 100 days after allogeneic transplant. In addition, cGVHD is characterized by chronic immunodeficiency; therefore, it often is described as an autoimmune disorder. Symptom onset 100 days after transplant can create diagnostic difficulties. Patients may no longer be at a transplant center, often having returned to a community-based physician practice where familiarity with cGVHD may be limited. Frequent follow-up and diligent communication between practice environments are necessary to promote the best possible outcomes. As a multiorgan syndrome, cGVHD is the most frequent cause of poor long-term outcomes after allogeneic HSCT (Bhushan & Collins, 2003).

Approximately 40% of HLA identical-sibling transplants and 70% of matched-unrelated donor transplants will develop cGVHD (Vogelsang, 2001). The incidence of cGVHD is widespread with risk factors similar to aGVHD. The degree of HLA histoincompatibility, patient and donor age, source, and dose of hematopoietic stem cells (i.e., peripheral versus bone marrow) all are established cGVHD risk factors. However, a history of prior aGVHD is the most important predictor of cGVHD incidence (Atkinson et al., 1990).

**Pathophysiology**

The pathophysiology of cGVHD largely is unclear and much less understood than aGVHD. Donor-derived alloreactive T cells and thymic CD4+ T cells are believed to be involved in cGVHD at the cellular level (Vogelsang, 2001). Thymus injury by previous history of aGVHD, pretransplant conditioning regimen, or age-related atrophy impairs the normal ability of the thymus to delete autoreactive T cells (Ferrara & Antin, 1999). Most experts agree that cGVHD is a combination of autoimmune and alloreactive processes (Vogelsang).

**Manifestations**

Clinical manifestations of cGVHD can be restricted to a single organ or may be expressed on an extensive scale. Classic symptoms of cGVHD are skin changes resembling scleroderma and the presence of sicca syndrome (i.e., extreme dryness of the skin, eyes, and mouth). Most organ systems can be affected by cGVHD. See Table 1 for common sites and associated signs and symptoms.

**Diagnosis and Staging**

The development of cGVHD may evolve from aGVHD (progressive), follow a period of recovery (quiescent), or develop without prior history of aGVHD (de novo). Current cGVHD staging is described as limited (one organ site) or extensive (more than one site). This staging has posed problems capturing the depth and degree of affected systems in the past. An updated staging system has been introduced that arranges patients in categories based on their clinical characteristics at the time of diagnosis (Akpek et al., 2003). The additional factors for cGVHD staging include the following.

- Extensive skin involvement (> 50% of body surface)
- Thrombocytopenia (< 100,00 platelets/mcL)
- Progressive onset of cGVHD
- Karnofsky performance status of less than 50% at primary treatment failure
A consortium of cGVHD experts known as the Working Group presented another potential advancement in the diagnosis and staging of cGVHD. Published recommendations of the Working Group stated that clinical manifestations should determine whether GVHD is considered acute or chronic rather than the time of onset. The Working Group differentiated between diagnostic and distinctive signs and symptoms of cGVHD and outlined a revised clinical scoring system for cGVHD assessment. The proposed scoring system is based on the number of organs involved, as well as the degree of affected organ involvement (i.e., mild, moderate, or severe) (Filipovich et al., 2005). Despite the recommendations, current clinical practice continues to support the use of limited versus extensive cGVHD staging categories.

### Treatment

Immunosuppression is the primary treatment for aGVHD and cGVHD. Prevention of GVHD occurrence is the rationale for prophylactic immunosuppressive medications prior to stem cell infusion (Couriel, Caldera, et al., 2004; Neumann, 2004). Cyclosporine and tacrolimus commonly are used for GVHD prophylaxis. Despite the attempt at prevention, GVHD still may occur. At the first signs and symptoms of GVHD, additional treatment is initiated. First-line therapy for both types of GVHD is the addition of high-dose steroids to the prophylactic GVHD regimen. Desired outcomes include reduction in GVHD symptoms and an eventual steroid taper.

Second-line therapy is indicated if patients are refractory to the prescribed dose of steroids. Therapy may include antithymocyte globulin, sirolimus, infliximab, pentostatin, mycophenolate mofetil, and thalidomide (Blushan & Collins, 2003; Vogelsang, 2001). In cGVHD, nonpharmacologic interventions, including psoralen, ultraviolet A, and extracorporeal photopheresis, may be indicated. In addition to immunosuppression, symptom management related to the specific organ system involved is essential. Common complications in GVHD

<table>
<thead>
<tr>
<th>ORGAN SYSTEM</th>
<th>RATE (%)</th>
<th>SIGNS AND SYMPTOMS</th>
<th>MANAGEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermal</td>
<td>70</td>
<td>Alopecia, nail ridging, premature graying Dyspigmentation erythema; desquamation; patch hyperpigmentation; erythematous popular rash; thickened, tight, fragile skin Joint contracture, gutate lesions (i.e., stretch marks) Weeping, ulcerated skin; secondary infection</td>
<td>Immunosuppressive medications for prevention and treatment PUVA therapy Extracorporeal photopheresis</td>
</tr>
<tr>
<td>Oral</td>
<td>70</td>
<td>Tissue atrophy, erythema, whitish lace-like plaques in cheeks and tongue, ulcerations, mucosal scleroderma Pain, burning, xerostomia, dryness, irritation, taste loss, sensitivity to spicy and acidic foods</td>
<td>Immunosuppressive agents for cGVHD Topical steroids Dexamethasone or azathioprine Topical steroids Oral rinse with saline, water, artificial saliva</td>
</tr>
<tr>
<td>Liver</td>
<td>30</td>
<td>Jaundice Bile duct damage</td>
<td>Rule out cholestasis, viral infection, and hepatotoxic drug reactions. Ursodeoxycholic acid</td>
</tr>
<tr>
<td>Ocular</td>
<td>80</td>
<td>Photophobia, cataracts secondary to steroid treatment, dryness, burning</td>
<td>cGVHD immunosuppressive medications Ophthalmologist referral Prednisolone eye drops, preservative-free artificial tears</td>
</tr>
<tr>
<td>Respiratory</td>
<td>10</td>
<td>Bronchiolitis obliterans can manifest as dyspnea, wheezing, and cough. Chronic sinopulmonary symptoms and recurrent respiratory tract infections</td>
<td>cGVHD immunosuppressive medications Pulmonary function tests ABG CT imaging</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>43</td>
<td>Anorexia, nausea, vomiting, diarrhea, weight loss Abnormal motility</td>
<td>Swallowing studies, GI x-ray series Endoscopy Stool cultures to rule out infection Dietary supplements Total parenteral nutrition</td>
</tr>
<tr>
<td>Infection and immune system</td>
<td>100</td>
<td>Pancytopenia, profound immunodeficiency Functional asplenia, risk for bacterial, viral, fungal, and CMV infections</td>
<td>PCP prophylaxis with trimethoprim and sulfamethoxazole Post-transplant vaccinations per CDC guidelines CMV surveillance if history of CMV infection</td>
</tr>
</tbody>
</table>

ABG—arterial blood gas; cGVHD—chronic graft-versus-host disease; CDC—Centers for Disease Control and Prevention; CMV—cytomegalovirus; CT—computed tomography; GI—gastrointestinal; PCP—Pneumocystis carinii pneumonia; PUVA—psoralen and ultraviolet light.
are electrolyte disturbances, alterations in skin integrity, and an increased risk of infection.

Vogelsang (2001) recommended that patients with GVHD continue Pneumocystis carinii pneumonia prophylaxis for six months after the completion of immunosuppression and subscribe to the Centers for Disease Control and Prevention’s post-transplant vaccination guidelines.

Nursing Implications

A diagnosis of GVHD has numerous implications for oncology nurses. Timely and accurate assessment of presenting symptoms is crucial to GVHD treatment. Nursing management should focus on educating patients and family members or significant others about the signs and symptoms of GVHD. Close monitoring at an appropriate transplant center also is required.

The treatment of GVHD can be stressful and extremely debilitating. The psychological impact of GVHD treatment and quality of life currently is under investigation. Patients may be deconditioned physically or debilitated, as well as psychologically overwhelmed with their diagnosis and treatment. Strategies for managing fatigue, infection risk, and other survivorship issues (e.g., fertility, quality of life) are necessary. Patient and family education is essential for successful outcomes in allogeneic HSCT recipients.

Conclusion

GVHD is a major obstacle to successful HSCT. Treatment modalities have improved, but aGVHD and cGVHD remain difficult to treat. The possibility of long-term complications after HSCT is ever present; therefore, patient care requires astute clinical assessment skills. Nurses play an important role in the early recognition of signs and symptoms of GVHD. Detailed patient monitoring also is required to care for patients. Nurses are essential to patient and family education regarding the many complications associated with GVHD. Research is needed to better understand the long-term psychosocial and quality-of-life issues that patients face when dealing with the complications of HSCT.

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References


