Management of Chronic Graft-Versus-Host Disease

Melissa Baker, RN, MSN, APN-C, and Phyllis McKiernan, RN, MSN, APN-C

Chronic graft-versus-host disease (GVHD) is an immune-mediated disorder that adversely affects quality of life and clinical outcomes in patients following hematopoietic stem cell transplantation. Conventional treatment of GVHD includes prolonged and high-dose corticosteroids; however, those drugs are associated with multiple side effects. This article describes the ability of extracorporeal photopheresis therapy to exhibit a steroid-sparing effect, which can reduce long-term complications as a consequence of steroid treatment.

Graft-Versus-Host Disease

GVHD, a complex complication following allogeneic HSCT, adversely affects the quality of life and clinical outcomes for HSCT survivors (Barton-Burke et al., 2008). The incidence of acute and chronic GVHD is about 30%–60% and carries a mortality rate of 50% (Anders & Barton-Burke, 2007). Acute GVHD occurs within the first 100 days after transplantation in response to activation of donor-derived T cells that mediate a cytotoxic response against specific target host cells, leading to cellular damage and subsequent clinical manifestations (Ferrara & Antin, 2009). The target organs of acute GVHD are the skin, liver, and gastrointestinal tract (Pavletic et al., 2005). In contrast to acute GVHD, the pathophysiology of chronic GVHD is not well defined. Chronic GVHD is believed to involve both alloreactive donor-derived T cells as well as recipient T cells that have been educated by the thymus and become autoreactive (Woltz, Castro, & Park, 2006).

The variable clinical manifestations of chronic GVHD resemble an autoimmune syndrome and are most commonly seen in the skin and mouth, although ocular, gastrointestinal, hepatic, pulmonary, vascular, musculoskeletal, and hematopoietic involvement may be evident (Horwitz & Sullivan, 2006; Mattson, 2007; Pavletic et al., 2005). In human leukocyte antigen-matched marrow grafting, the incidence of chronic GVHD with liver involvement is estimated as 40%–73%, skin involvement as 65%–80%, eye involvement as 18%–47%, and oral involvement as 48%–72% (Higman & Vogelsang, 2004).

Glucksberg et al. (1974) proposed the first grading system for acute GVHD using time of onset to distinguish between acute and chronic disease (less or more than 100 days after transplantation) based on the degree of skin, liver, and gut involvement. Criteria to establish a chronic GVHD diagnosis include the presence of at least one diagnostic clinical manifestation or at least one distinct manifestation confirmed by biopsy and exclusion of other possible etiologies (Joseph, Couriel, & Komanduri, 2008; Lee & Flowers, 2008). Histologic confirmation may be used to corroborate a clinical diagnosis. Specific to liver GVHD, a biopsy is necessary to confirm GVHD, along with distinctive manifestations of the complication in at least one other organ system (Joseph et al., 2008; Lee & Flowers, 2008).

Treatment

Corticosteroids are the mainstay of treatment in acute and chronic GVHD (Mattson, 2007). In chronic GVHD, prolonged immunosuppressive therapy is required, averaging two to three years, with 10% of patients continuing treatment longer than five years (Lee & Flowers, 2008). Potential adverse effects of prolonged steroid treatment include hypertension, body habitus changes, osteoporosis, insomnia, emotional lability, cataracts, diabetes mellitus, and life-threatening infections (Knobler et al., 2009) (see Figure 1). Complications of steroid treatment have led to the development of steroid-sparing regimens and use of alternative immunosuppressive agents (Greinix & Antin, 2009; Knobler et al., 2009). Treatment

Melissa Baker, RN, MSN, APN-C, and Phyllis McKiernan, RN, MSN, APN-C, both are nurse practitioners in the Adult Blood and Marrow Stem Cell Transplantation Program in the John Theurer Cancer Center at Hackensack University Medical Center in New Jersey. The authors take full responsibility for the content of the article. The authors did not receive honoraria for this work. No financial relationships relevant to the content of this article have been disclosed by the authors or editorial staff. Digital Object Identifier: 10.1188/11.CJON.429-432
• Avascular necrosis
• Cataract formation
• Changes in body or face shape
• Glucose intolerance
• Hypertension
• Insomnia
• Mood swings
• Osteoporosis
• Weight gain

![Figure 1. Side Effects of Long-Term Prednisone Use](image)


Strategies in the management of steroid-refractory chronic GVHD vary by provider preference in the absence of consensus guidelines (Horwitz & Sullivan, 2006). Salvage therapies including extracorporeal photopheresis (ECP), monoclonal antibodies, mycophenolate mofetil, calcineurin inhibitors, antithymocyte globulin, and topical preparations have been used with varied success (Barton-Burke et al., 2008; Higman & Vogelsang, 2004). As a result of the profound immunosuppressive effects of the disease and its treatment, infection is the primary cause of mortality in patients with chronic GVHD (Couriel, Carpenter, et al., 2006). In the search for therapeutic options for steroid-refractory GVHD, ECP has emerged as a suitable, well-tolerated treatment agent that has an immunomodulatory benefit without an immunosuppressive effect. Unlike corticosteroids, ECP lacks cumulative toxicity (Marshall, 2006). Studies indicated that ECP allows for accelerated tapering of corticosteroids, thus decreasing the effects seen with prolonged steroid use (Knobl er et al., 2009).

Extracorporeal Photopheresis

ECP is an immunomodulatory therapy developed in 1987 by Richard Edelson, MD, for use in cutaneous T-cell lymphoma (Klassen, 2010). Since then, ECP has been used effectively in the treatment of systemic sclerosis, rheumatoid arthritis, Crohn disease, and GVHD (Klassen, 2010). The ECP procedure involves collection of peripheral blood via apheresis, followed by separation of blood cells (see Figure 2). The red blood cells are immediately returned to the patient and the white blood cells are treated with a photosensitizing agent (methoxsalen) and ultraviolet radiation, and then infused (Joseph et al., 2008). Treated lymphocytes initiate apoptosis of the pathogenic T cells. Although only 2%–10% of patients’ lymphocytes are treated during ECP, untreated lymphocytes undergo apoptosis within 48 hours of the procedure (Greinix & Antin, 2009; Woltz et al., 2006). Stimulation of the cytokine cascade increases production of anti-inflammatory cytokines (e.g., interleukin-10) and inhibition of proinflammatory cytokines (Greinix & Antin, 2009). Unlike calcineurin inhibitors that decrease the number of regulatory T cells, ECP stimulates dendritic cells to increase the generation of regulatory T cells, (Klassen, 2010). The proposed mechanism of action in ECP is (a) inhibition of proinflammatory cytokines, (b) anti-inflammatory cytokine production, (c) decreased stimulation of effector T cells, (d) deletion of effector T cells, and (e) stimulation of regulatory T cells (Peritt, 2006). Clinical studies indicated that patients with active, chronic GVHD have decreased levels of regulatory T cells; therefore, strategies to increase the frequency of regulatory T cells may be a reasonable adjunct therapy for chronic GVHD (Zorn et al., 2005).

Couriel, Hosing, et al. (2006) conducted a large retrospective evaluation of 71 patients with chronic GVHD who were treated with ECP. The overall response rate was 61%, with 20% showing a complete response. The highest responses were seen in patients with chronic GVHD involving the skin (n = 33; 59%), liver (n = 15; 71%), oral mucosa (n = 7; 77%), and eye (n = 4; 67%). A significant response was reported among patients with bronchiolitis obliterans (n = 6; 54%) (Couriel, Hosing, et al., 2006; Knobl er et al., 2009). ECP may be a beneficial steroid-sparing treatment option in patients with steroid-refractory chronic GVHD; Bisaccia et al. (2003), Greinix et al. (2006), and Rubegni et al. (2005) showed a complete or partial response in 3 of 3, 21 of 25, and 18 of 23 patients with hepatic chronic GVHD who received ECP, respectively.

Frequency and duration of ECP varies by institution, but patients often are initiated on photopheresis twice weekly on consecutive days, then tapered to two treatments every other week once a clinical benefit is seen. Symptom response in patients undergoing treatment with ECP enables tapering of immunosuppressive medications (Marshall, 2006). Response to therapy varies by disease type and up to one year may be needed to see full effects in some types of chronic GVHD, such as sclerodermatous chronic GVHD.

Case Study

C.D., a 24-year-old man, received a myeloablative allogeneic sibling HSCT in the...
treatment of Philadelphia chromosome-positive chronic myelogenous leukemia. He achieved prompt hematologic recovery with filgrastim support, reaching an absolute neutrophil count (ANC) greater than 500 cells/mcL 12 days after transplantation. C.D. did not experience acute GVHD, and day-100 bone marrow regrowth did not show evidence of disease.

Four months after HSCT, C.D. presented with hyperbilirubinemia, elevated liver function tests, sudden onset jaundice, and sclera with severe pruritis. Laboratory values revealed a white blood cell count of 5.7 cells/mm$^3$ (normal = 4–10.8 cells/mm$^3$), hemoglobin of 11.3 g/dL (normal = 14–18 g/dL), platelet count of 30,000 mcL (normal = 150,000–400,000 mcL), total bilirubin of 16.8 mg/dL (normal lower than 1.9 mg/dL), aspartate aminotransferase of 557 units/L (normal less than 40 units/L), alanine aminotransferase of 582 units/L (normal lower than 56 units/L), and alkaline phosphatase of 546 units/L (normal lower than 147 units/L). The onset of symptoms coincided with tapering of immunosuppressants given as prophylaxis therapy for GVHD. Differential diagnoses include iron overload, hepatitis or viral infection, drug-induced liver injury, and cholestasis (Higman & Vogelsang, 2004). To exclude those diagnoses, a multitude of testing was performed. An ultrasound of the abdomen revealed mild splenomegaly, but no abnormalities of the gallbladder, bile ducts, or pancreas. C.D. was afebrile, with no right upper quadrant abdominal pain or tenderness and no significant weight gain, hepatomegaly, or ascites. Serologic tests for infection with hepatitis A, B, and C viruses, varicella-zoster virus, and herpes simplex virus all were negative; a cytomegalovirus antigenscreen was also negative. Medications with potential hepatotoxicity were withdrawn to decrease the possibility of drug-induced liver injury, but withdrawal did not improve liver function. A liver biopsy was deferred because of the risk of procedure-related morbidity in the setting of thrombocytopenia.

After differential diagnoses were excluded, a clinical diagnosis of hepatic GVHD was established in the presence of cholestatic jaundice with asymptomatic elevations in serum bilirubin, aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase. Laboratory values associated with liver GVHD include asymptomatic elevation in serum bilirubin, alanine aminotransferase, alkaline phosphatase, and gamma-glutamyltransferase, slowly progressive cholestatic jaundice, and acute hepatocellular injury (Higman & Vogelsang, 2004). Treatment was initiated with methylprednisolone 2 mg/kg per day and ursodeoxycholic acid 15 mg/kg per day. Tacrolimus was restarted at 1 mg twice daily and then adjusted to maintain therapeutic levels from 5–15 mcg/L. C.D.’s bilirubin level steadily decreased to 7.7 mg/dL after two weeks of therapy. ECP was started two weeks after steroids in an effort to accelerate the corticosteroid taper. ECP was initiated at four procedures per week for the first month and then decreased to two procedures per week. ECP schedules are empirically based and often relate to those used in the treatment of cutaneous T-cell lymphoma. Optimum schedules are not defined and, therefore, are physician determined (Marshall, 2006). As a result, liver function tests and bilirubin normalized, and prednisone dose subsequently was tapered to 1 mg/kg every other day. After six months of treatment, ECP was reduced to two procedures every other week. Eight months after diagnosis of GVHD, prednisone was discontinued without compromising liver function. C.D. experienced complete resolution of GVHD, as evidenced by normalization of serum bilirubin and alkaline phosphatase levels.

**Patient Management and Nursing Care**

Use of a multidisciplinary model to address dietary needs, social and financial implications, and psychosocial facets is recommended to ensure comprehensive patient care. ECP is an expensive treatment that requires strict adherence to the prescribed regimen. A single ECP session lasts three to four hours, and the treatment course may endure months of therapy; therefore, availability of a support system should be assessed prior to starting ECP. Patients receiving treatment with ECP require trained nurses to provide skilled care and ongoing education (Woltz et al., 2006). Teaching points may include infection precaution, care of catheter site, use of sun block and sun-protective measures, potential complications, and necessary dietary modifications. Dietary habits should be discussed with a trained nutritionist, explaining to patients that elevated triglyceride levels interfere with ultraviolet light and impede treatment results (Higman & Vogelsang, 2004; Woltz et al., 2006).

Access to care remains a limiting factor in patients otherwise suitable for ECP (see Figure 3). Therakos, Inc., the only provider, has an estimated 120 photopheresis centers in the United States (Therakos, Inc., 2009), thus posing a challenge when ECP availability is beyond driving distance. To locate a treatment center, visit http://www.therakos.com/t-home/find-a-treatment-center.

Few side effects are associated with ECP. However, risks such as infection or thrombosis exist because many patients require a central venous access device. During treatment, patients may feel dizzy or become hypotensive as a result of the fluid shift. After treatment, some patients report feeling tired or having a low-grade fever, but most are able to resume normal activity (Couriel, Hosing, et al., 2006; Mattson, 2007; Woltz et al., 2006). The procedure requires anticoagulation with acid citrate or heparin, so monitoring platelet level is essential; the dose of anticoagulant is adjusted based on the patients’ platelet counts. Patients may require transfusion support to maintain hematocrit higher than 28 g/dL (Klassen, 2010; Marshall, 2006; Woltz et al., 2006). Although only a small amount of blood loss occurs with each treatment, some patients require iron supplementation to maintain adequate iron stores.

**Advantages**

- Immunomodulatory treatment not immunosuppressive
- Few side effects
- Steroid sparing
- Treats graft-versus-host disease but preserves graft-versus-tumor effect
- No cumulative toxicity

**Disadvantages**

- Cost
- Requires IV access
- Risk of infection if central access used
- Timeliness of each session; prolonged treatment course
- Limited access to treatment

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**Figure 3. Extracorporeal Photopheresis Pros and Cons**

Note. Based on information from Knobler et al., 2009; Marshall, 2006.
Conclusion

C.D.’s case study illustrates a patient with chronic GVHD without extrahepatic involvement who responded to a regimen using ECP and corticosteroids. In this study, early intervention with ECP permitted an accelerated steroid taper, thus decreasing effects associated with prolonged steroid use.

Several studies have documented the efficacy of ECP in patients with steroid-refractory chronic GVHD; however, the studies were small with varied measurement of treatment response, making comparison difficult (Bisaccia et al., 2003; Couriel, Hosing, et al., 2006). Additional studies are needed to better understand the role of ECP in chronic GVHD. The response of hepatic GVHD is assessed using serial laboratory investigations; however, limited data are available comparing treatment response of hepatic GVHD using ECP and corticosteroids versus corticosteroids alone. ECP is considered a relatively safe, effective treatment option that optimizes immunomodulation without the adverse effects of immunosuppressant medications. Data that quantify the absolute reduction of steroid doses as a result of concomitant ECP are lacking; therefore, additional studies are needed.

Author Contact: Melissa Baker, RN, MSN, APN-C, can be reached at mbaker@humed.com, with copy to editor at CJONEditor@ons.org.

References


