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Chronic Graft-versus-Host Disease

Stephanie J. Lee,[1] Georgia Vogelsang,[2] Mary E.D. Flowers[3]

[1]Department of Adult Oncology, Dana-Farber Cancer Institute, and Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts; [2]Department of Oncology, Johns Hopkins University School of Medicine, Baltimore, Maryland; [3]Division of Clinical Research, Fred Hutchinson Cancer Research Center and Department of Medicine, University of Washington, Seattle, Washington

Correspondence and reprint requests: Stephanie Lee, MD, MPH, Dana-Farber Cancer Institute, Boston, MA 02115 (e-mail: stephanie_lee@dfci.harvard.edu).

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ABSTRACT

Chronic graft-versus-host disease (GVHD) remains a vexing and dangerous complication of allogeneic stem cell transplantation. Mild forms of chronic GVHD are often manageable with local or low-dose systemic immunosuppression and do not affect long-term survival. In contrast, more severe forms of chronic GVHD require intensive medical management and adversely affect survival. This report reviews current concepts of the pathogenesis, clinical risk factors, classification systems, organ manifestations, and available treatments for chronic GVHD. It also provides a comprehensive listing of the published clinical trials aimed at prevention and primary treatment of chronic GVHD.

KEY WORDS

Chronic graft-versus-host disease • Allogeneic stem cell transplantation

BACKGROUND

Chronic graft-versus-host disease (GVHD) is one of the most common and clinically significant problems affecting long-term survivors of allogeneic hematopoietic cell transplantation (HCT). Up to 60% of patients receiving HLA-identical sibling marrow grafts and 70% of patients receiving alternative donor marrow grafts who survive beyond day 100 develop chronic GVHD [1-3]. Chronic GVHD is the leading cause of nonrelapse mortality more than 2 years after allogeneic transplantation [4]. In addition, chronic GVHD is associated with decreased quality of life, impaired functional status, and ongoing need for immunosuppressive medications [4-7]. The incidence of chronic GVHD is increasing (Figure 1) because of several factors: expansion of the donor population beyond HLA-identical siblings, older recipient age, use of peripheral blood cells as the graft source, and infusion of donor lymphocytes for treatment of recurrent malignancy after HCT. Although prevention and treatment of acute GVHD have improved during the past 3 decades, similar progress in chronic GVHD has remained elusive.

PATHOGENESIS

Compared with the advances in our understanding of acute GVHD, the pathophysiology of chronic GVHD remains poorly defined. Clinical studies of chronic GVHD in humans have been difficult, in part because of the delayed onset relative to other transplant complications of interest. Several animal models of chronic GVHD have been reported [8-15]. In one murine model (parent into F1 hybrid) that more closely resembles lupus (due to renal involvement) than chronic GVHD, extensive antibody-mediated damage appears to be associated solely with a Th2 response [16]. In contrast, both Th1 and Th2 cells have been implicated in humans [17-20]. In another murine model of sclerodermatous chronic GVHD, chemokines and donor mononuclear cells appear to play important roles, and administration of neutralizing antibody against transforming growth factor (TGF)-β prevented the development of chronic GVHD [15]. In this model, T cells and donor-derived monocyte/macrophages expressing markers of antigen presentation are the predominant cells infiltrating the skin early in the disease. Up-regulation of TGF-β expression and several chemokines are temporally re-

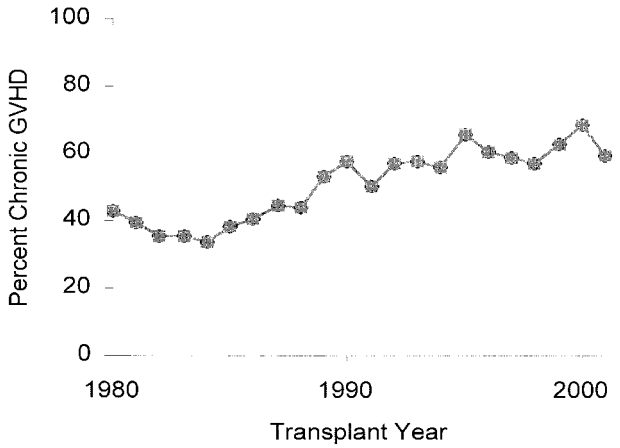

Figure 1. Percentage of patients surviving at least 100 days who were diagnosed with chronic GVHD at the Fred Hutchinson Cancer Research Center during the past 2 decades.

lated to increased collagen messenger RNA synthesis, skin thickening, and pulmonary fibrosis.

In humans, T-lymphocyte imbalances, from overexpansion of pathological subsets and/or loss of appropriate regulation, have long been suspected of causing chronic GVHD. The etiologic contribution of alloreactive T cells to the development of chronic GVHD is supported by the observation that T-cell depletion is associated with less chronic GVHD in HLA-matched sibling marrow transplantation [21], whereas peripheral blood stem cell (PBSC) transplantation [22-29] and donor lymphocyte infusions (DLI) are associated with higher rates of chronic GVHD [30,31]. Autoreactive T cells have been implicated in the pathogenesis of cyclosporine-induced autologous GVHD, which clinically resembles allogeneic chronic GVHD but is mediated by autoreactive T cells that recognize the CLIP region of major histocompatibility complex class II molecules [32]. Cyclosporine (CSA) inhibits thymic-dependent clonal deletion of autoreactive T cells, thereby paradoxically disrupting self-tolerance. The effector cells have broad-based recognition of tissues, and the clinical manifestations, when fully evolved, are identical to chronic GVHD. It is speculated that autoreactive T cells may arise in the allogeneic setting because of thymic injury from acute GVHD (or from other causes) that allows the survival of autoreactive clones rather than their deletion [33,34]. These autoreactive T lymphocytes can act with interferon (IFN) to produce the increased collagen deposition seen histopathologically in chronic GVHD [35].

Given the similarities between chronic GVHD and autoantibody-associated diseases, several studies have attempted to link B cells and humoral immunity with chronic GVHD. However, a study of 53 long-term survivors failed to find an association between classic autoantibodies and chronic GVHD [36]. Some antigens, such as promyelocytic leukemia (PML) gene product, are expressed aberrantly in chronic GVHD lesional tissue but not in uninvolved skin or normal controls, although circulating antibodies to PML have not been detected [37]. Some reports link cytomegalovirus (CMV) infection with chronic GVHD. CD13 is aberrantly expressed in CMV-infected individuals, and antibodies to CD13 have been associated with chronic GVHD [38,39].

Cytokine dysregulation also has been implicated through observations that high levels of interleukin (IL)-1β, IL-6, IFNγ, and tumor necrosis factor (TNF)-α are associated with more severe chronic GVHD [40]. High serum TGF-β also was associated with chronic GVHD independent of platelet and white blood cell counts [41], and antibodies to TGF-β prevented the development of sclerodermatous GVHD in a murine model [15]. Patients with chronic GVHD have low levels of IL-10, an anti-inflammatory cytokine thought to suppress IFN-γ and immunoglobulin (Ig) production, compared with patients without chronic GVHD [42].

Finally, the clinical manifestations of chronic GVHD closely resemble those of several well-recognized autoimmune syndromes, suggesting similar pathophysiology. Scleroderma, which has cutaneous manifestations similar to late fibrosing chronic GVHD, occurs predominantly in women and has been associated with an increased incidence of circulating fetal male cells, suggesting that persistent microchimerism may play a role [43,44].

CLINICAL RISK FACTORS

Table 1 presents the patient, donor/graft, and procedural factors that have been associated with the development of chronic GVHD. Consistently identified clinical risk factors include older patient age, female donors and male patients, certain diagnoses (chronic myeloid leukemia and aplastic anemia), use of mismatched or unrelated donors, infusion of donor lymphocytes, use of PBSCs instead of bone marrow, lack of T-cell depletion, and grade II to IV acute GVHD [21,45-50]. Although acute GVHD is the most powerful predictor of subsequent chronic GVHD, de novo chronic GVHD (no prior acute GVHD) is associated with similar patient and donor risk factors [47,51]. More controversial risk factors for chronic GVHD include CMV seropositivity, CMV reactivation, splenectomy, steroid prophylaxis for acute GVHD, ethnic difference between donor and patient, high CD34+ cell count in the graft, and absence of methotrexate in PBSC transplantation [21,46,50,52-54]. Early reports of umbilical blood stem cell grafting suggest lower rates of chronic GVHD [55].

Table 1. *Reported Risk Factors for Chronic GVHD According to the Patient and Donor Characteristics, Hematopoietic Stem Cell Source, and Posttransplantation Events*

	Patient	Donor and Graft Characteristics	Transplant Events
Consistently observed	**Older age** **Chronic myeloid leukemia or aplastic anemia**	**Female donor (especially parous) if male patient** **Mismatched or unrelated** **PBSC** **DLIs** **T-cell replete graft**	**Acute GVHD**
Controversial or limited evaluation	**CMV seropositive** **CMV reactivation** **Splenectomy**	**Ethnic difference between donor and patient** **Lower incidence with umbilical cord blood**	**Corticosteroids in the acute GVHD prophylaxis regimen** **High CD34+ count (PBSC)** **Lack of methotrexate in acute GVHD prophylaxis (PBSC)**

Peripheral blood progenitor cells have been associated with an increased incidence of chronic GVHD (50%-90%) in most studies of HLA-matched sibling transplantation [22-27,29]. Cutler et al. performed a meta-analysis using data from 16 studies and reported a pooled relative risk (RR) for extensive chronic GVHD (RR 1.66; 95% confidence interval, 1.35-2.05; $P < .001$) compared with bone marrow [28]. Recent data suggest that high CD34+ counts may be the most important factor driving this observation, because chronic GVHD did not correlate with CD3+ and CD14+ counts [54]. The use of granulocyte colony-stimulating factor (G-CSF) during stem cell collection also has been suspected of increasing chronic GVHD after PBSC transplantations because G-CSF is known to preferentially shift T-helper cells to a Th2 phenotype [56]. However, a trial performed by Morton et al. suggests that donor treatment per se with G-CSF is not the cause of the higher chronic GVHD incidence. They randomized HLA-matched sibling donors to marrow or PBSC collection after both groups received G-CSF stimulation (N = 57). Rates of chronic GVHD were higher in the PBSC arm (80% versus 22%; $P < .02$), although overall survival was the same [29]. In the unrelated donor marrow setting, patients have a higher risk for chronic GVHD than HLA-matched siblings [3], but it is not clear whether PBSCs further elevate this risk [57,58].

Finally, several factors have been studied and not found to be associated with chronic GVHD. These include type of myeloablative conditioning regimen, type of calcineurin inhibitor used for acute GVHD prophylaxis, and whether 3 or 4 doses of methotrexate are administered. The reported incidence of chronic GVHD is similar for busulfan/cyclophosphamide and total body irradiation/cyclosphosphamide preparative regimens [59]. Use of either tacrolimus or CSA prophylaxis resulted in similar rates of chronic GVHD, although there was less extensive chronic GVHD in the tacrolimus group [60]. Failure to give day 11 methotrexate was not shown to influence rates of chronic GVHD, although only a small number of patients was studied [61,62].

CLASSIFICATION OF CHRONIC GVHD

Chronic GVHD can be classified according to the type of onset, need for systemic immunosuppressive therapy, or mortality risk. The majority of patients with chronic GVHD have had prior acute GVHD. Their disease may evolve directly from acute GVHD (*progressive*), which has a grim prognosis, or may follow a period of resolution (*quiescent*, or *interrupted*) GVHD, with an intermediate prognosis. Patients may develop chronic GVHD with no history of prior acute GVHD ("de novo"), and these patients have a relatively good prognosis. Based on data from the International Bone Marrow Transplant Registry (IBMTR), the distribution of chronic GVHD onset for HLA-matched siblings is 20% to 30% progressive, 30% to 40% interrupted, and 35% de novo. Data from the National Marrow Donor Program for unrelated donor recipients, where the incidence of acute GVHD is higher, shows the spectrum of onset as 19% progressive, 69% interrupted, and 12% de novo onset [3].

The most commonly used staging system is the "limited/extensive" classification proposed by the Seattle Group in 1980 based on a retrospective clinical and pathological review of 20 patients with chronic GVHD. In this group, mortality correlated best with Karnofsky performance status [63]. Localized skin involvement with or without hepatic dysfunction (limited disease) was associated with less severe disease and fewer infections. Generalized skin involvement or limited disease plus eye involvement, oral involvement, hepatic dysfunction with abnormal liver histology, or involvement of any other target organ was classified as extensive disease and was associated with more frequent infections. However, review of data

Table 2. *Original and Revised Seattle Classification for Limited and Extensive Chronic GVHD*

Original Seattle Classification	Revised Seattle Classification*
Limited	**Clinical limited**
One or both of:	1. Oral abnormalities consistent with chronic GVHD, a positive skin or lip biopsy, and no other manifestations of chronic GVHD
Localized skin involvement	2. Mild liver test abnormalities (alkaline phosphatase ≤2 × upper limit of normal, AST or ALT ≤3 × upper limit of normal, and total bilirubin ≤1.6) with positive skin or lip biopsy, and no other manifestations of chronic GVHD
Hepatic dysfunction due to chronic GVHD	3. Less than 6 papulosquamous plaques, macular-papular or lichenoid rash involving <20% of BSA, dyspigmentation involving <20% BSA, or erythema involving <50% BSA, positive skin biopsy, and no other manifestations of chronic GVHD
	4. Ocular sicca (Schirmer's test ≤5 mm with no more than minimal ocular symptoms), positive skin or lip biopsy, and no other manifestations of chronic GVHD
	5. Vaginal or vulvar abnormalities with positive biopsy, and no other manifestations of chronic GVHD
Extensive	**Clinical extensive**
One of:	1. Involvement of 2 or more organs with symptoms or signs of chronic GVHD, with biopsy documentation of chronic GVHD in any organ
Generalized skin involvement	2. Karnofsky or Lansky Clinical Performance scores <60%, ≥15% weight loss, and recurrent infections not due to other causes, with biopsy documentation of chronic GVHD in any organ
Localized skin involvement and/or hepatic dysfunction due to chronic GVHD, plus:	3. Skin involvement more extensive than defined for clinical limited chronic GVHD, confirmed by biopsy
Liver histology showing chronic aggressive hepatitis, bridging necrosis, or cirrhosis, or:	4. Scleroderma or morphea
	5. Onycholysis or onychodystrophy thought to represent chronic GVHD, with documentation of chronic GVHD in any organ
Involvement of eye (Schirmer's test with <5 mm wetting), or:	6. Decreased range of motion in wrist or ankle extension due to fasciitis caused by chronic GVHD
	7. Contractures thought to represent chronic GVHD
Involvement of minor salivary glands or oral mucosa demonstrated on labial biopsy, or:	8. Bronchiolitis obliterans not due to other causes
	9. Positive liver biopsy; or abnormal liver function tests not due to other causes with alkaline phosphatase >2 × upper limit of normal, AST or ALT >3 × upper limit of normal, or total bilirubin >1.6, and documentation of chronic GVHD in any organ
Involvement of any other target organ	10. Positive upper or lower GI biopsy
	11. Fasciitis or serositis thought to represent chronic GVHD and not due to other causes

*Provided by Mary E.D. Flowers and Paul J. Martin, Fred Hutchinson Cancer Research Center.
AST indicates aspartate aminotransferase; ALT, alanine aminotransferase; BSA, body surface area.

from HLA-matched sibling recipients reported to the IBMTR suggests that transplantation centers are not applying the formal definitions accurately, perhaps in part because many patients are unclassifiable by the strict organ criteria [3]. The Seattle Group has developed revised clinical criteria for limited and extensive chronic GVHD to clarify ambiguities of the original definition (Table 2). In the revised classification, prolonged treatment with systemic immunosuppression is indicated for patients with clinically extensive chronic GVHD or anyone with high-risk features (ie, platelets count $<100 \times 10^9$/L, progressive onset, or receipt of treatment with corticosteroids at the time of the diagnosis of chronic GVHD).

Several investigators have tried to develop improved prognostic grading scales based on larger numbers of observed patients and with survival as the primary endpoint. Table 3 lists the scales that have been proposed thus far [3,63-67]. In aggregate these studies show that thrombocytopenia (platelet count $<100 \times 10^9$/L), progressive onset, skin involvement, poor performance status, and gastrointestinal (GI) involvement portend a poorer prognosis. The Hopkins model stratifies patients into risk categories according to whether or not extensive skin involvement, thrombocytopenia, and progressive-type onset is present [66]. This model was validated using data from 1108 patients from the IBMTR (n = 711), Fred Hutchinson Cancer Center (n = 188), University of Nebraska (n = 60), and University of Minnesota (n = 149). Despite significant heterogeneity of the data, for each data set the proposed grading system was able to separate patients into 3 groups with different survival outcomes (personal communication, G. Akpek, December 2002).

The IBMTR also has reported a grading system predictive for survival developed by using data from 1827 HLA-matched sibling marrow recipients reported to the registry [3]. Karnofsky performance score, diarrhea, weight loss, and cutaneous and oral involvement were found to be independent prognostic variables, from which a grading scheme was generated. This scheme, the limited/extensive classification system, and a classification based on clinical impres-

Table 3. *Risk Factors for Survival at the Time of Diagnosis of Chronic GVHD*

Reference	N	Platelets	Onset	Skin	Liver	Other Poor Prognostic Factors
Shulman et al. [63]	20	—	—	Generalized involvement	Cirrhosis	"Extensive," poor Karnofsky performance status, recurrent infections, active chronic GVHD after 2 mo of therapy
Wingard et al. [64]	85	—	Progressive	Lichenoid involvement	Bilirubin >1.2 mg/dL	
Morton et al. [65]	102	$<100 \times 10^9$/L	—	—	Bilirubin >2.0 mg/dL	On steroids at onset, IFN-α >6 mo duration before transplantation (CML)
Akpek et al. [66]	151	$<100 \times 10^9$/L	Progressive	>50% BSA	—	Karnofsky score when primary therapy fails
Lee et al. [3]	727	—	—	Involved	—	Karnofsky score, diarrhea, weight loss, lack of oral involvement
Arora et al. [67]	159	$<100 \times 10^9$/L	Progressive	—	—	GI involvement, no response at 6 months

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sion of overall chronic GVHD severity (mild, moderate, or severe) was assessed in a parallel analyses of 1092 HLA-matched sibling transplant recipients from the IBMTR and 553 recipients of unrelated donor marrow from the National Marrow Donor Program. Presence of chronic GVHD was associated with fewer relapses (RR, 0.5-0.6) but more treatment-related mortality (RR, 1.8-2.8) in the 3 analyses. No grading scheme correlated chronic GVHD severity with relapse rates, but all schemes predicted treatment-related mortality. Survival and disease-free survival of the most favorable chronic GVHD group in each scheme were similar, or better, than those of patients without chronic GVHD. Notably, an overall clinical summary scale of mild, moderate, or severe chronic GVHD was the best predictor of survival based on Akaike's information criterion, a qualitative biostatistical method of comparing prognostic schemes [3]. However, formal definitions for the mild, moderate, and severe categories have not been established [68] (Figure 2).

Comparison of the Hopkins and IBMTR reports illustrates the advantages and disadvantages of single-institution versus registry studies. The Hopkins model has a smaller sample size (N = 151) and was based on the consistent diagnostic criteria of a single group of

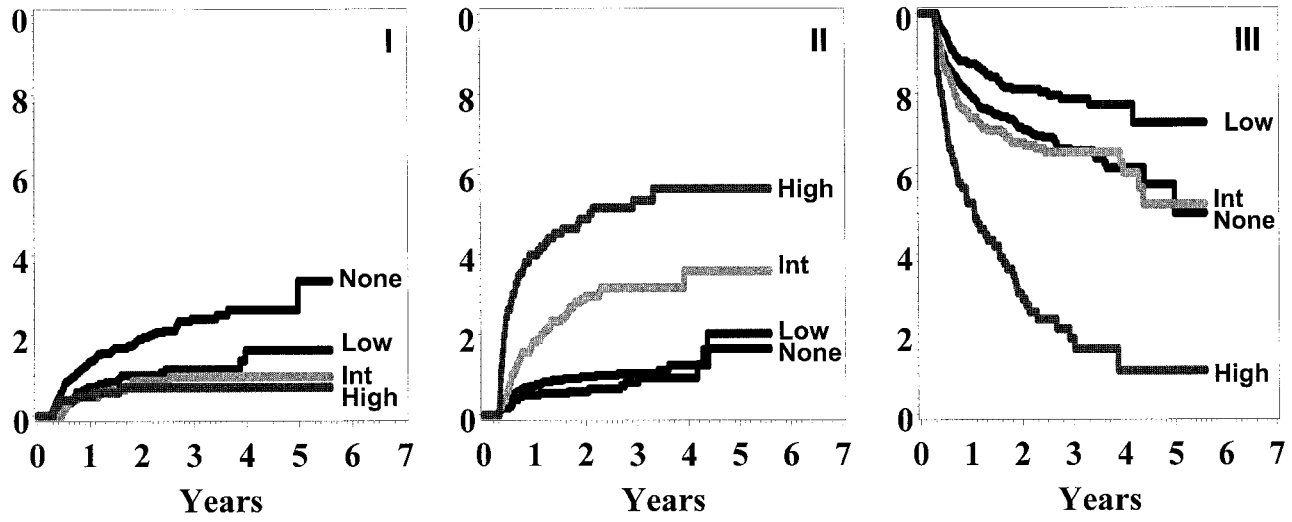

Figure 2. Association of severity of chronic GVHD with relapse (I), treatment-related mortality (II), and disease-free survival (III) for patients with none, low, intermediate, or high-risk chronic GVHD. From: Lee SJ, Klein JP, Barnett AJ, et al. Severity of chronic graft-versus-host disease: association with treatment-related mortality and relapse. Blood 2002;100:406-414. Copyright American Society of Hematology, used by permission.

clinicians, but may suffer from referral bias. In contrast, the IBMTR model is based on reports from many centers but is limited by the expertise of those evaluating the patients and the amount of detail that can be captured on specific chronic GVHD manifestations.

CLINICAL MANIFESTATIONS

Manifestations of "acute" GVHD without pathognomonic features of chronic GVHD can begin after day 100 posttransplantation, whereas classic "chronic" GVHD can be present before day 100. For this reason, the distinction between acute and chronic GVHD cannot be made solely according to the time interval from transplantation. The median time of diagnosis of chronic GVHD is 4.5 months after HLA-identical sibling transplantation and 4 months after unrelated donor transplantation [3], with only 5% of cases diagnosed after 1 year. The diagnosis of chronic GVHD requires at least 1 manifestation that is distinctive for chronic GVHD (eg, lichenoid-oral or vaginal findings, ocular sicca, skin dyspigmentation, scleroderma, bronchiolitis obliterans, and esophageal web formation). Whenever possible, biopsies and other diagnostic tests should be pursued to rule out alternative etiologies, such as infections, and to confirm the diagnosis of chronic GVHD. In HLA-matched marrow grafting with primarily methotrexate-based prophylaxis, skin (65%-80%), mouth (48%-72%), liver (40%-73%), and eye (18%-47%) involvement are most commonly reported. Other less frequently involved organs include GI tract/weight loss (16%-26%), lung (10%-15%), esophagus (6%-8%), and joints (2%-12%) [3,21,69]. Flowers et al. have reported that PBSC recipients have a similar time to onset and spectrum of organ involvement [70]. Table 4 outlines the signs, symptoms, and histopathologic findings associated with chronic GVHD.

Skin and Dermal Appendages

Chronic GVHD often presents with a lichenoid eruption, an erythematous, papular rash that resembles lichen planus and has no typical distribution pattern. Sclerodermatous GVHD may involve the dermis and/or the muscular fascia and it clinically resembles systemic sclerosis. The skin is thickened, tight, and fragile with very poor wound-healing capacity. Alteration in pigmentation, either hypopigmentation or hyperpigmentation, may occur. In severe cases, the skin may blister from poor lymphatic drainage or ulcerate from minor trauma. Because the sclerosis histologically affects the dermis, hair loss and destruction of the sweat glands are common. In cases of severe ulceration, skin grafts from the donor have been successful, and the tissue remains healthy and uninvolved with chronic GVHD [71,72]. Serial assessments should document the extent, type, and distribution of skin involvement.

Fingernails and toenails may be affected by chronic GVHD. Nails develop vertical ridges and cracking and are very fragile. Nail problems may persist even after skin changes have resolved. Hair loss in areas of affected skin also may persist after treatment, although recovery of hair is frequently a sign of recovery. Brittle hair often precedes alopecia. Premature graying of hair, eyebrows, and eyelashes may occur with chronic GVHD, even in children.

Eyes

Ocular GVHD often presents with irritation, burning, dry eyes, or photophobia from irreversible destruction of the lacrimal glands. Excessive tearing can be a sign of ocular sicca. Conjunctival GVHD is a rare manifestation of severe chronic GVHD and can be quite refractory to treatment. Protective eyeglasses and sunglasses, frequent lubrication, application of ophthalmic ointment at night, and punctal plugs or cauterization can help symptomatically and prevent further damage. Moisture chamber eyeglasses (a prosthetic device coupled to the eyeglasses) can significantly relieve the symptoms of dry eyes [73]. Schirmer's tests can be performed in clinic and are useful to follow chronic GVHD.

Mouth

Oral GVHD usually starts with xerostomia and/or food sensitivity. More advanced disease may cause odynophagia due to extension of damage, although a rare patient will have esophageal involvement without oral disease. Physical examination in mild disease shows erythema with white plaques that may be confused with thrush or herpetic infections, whereas extensive lichenoid or hyperkeratotic changes are found in advanced disease [74]. Pseudomembranes, large, nonhealing ulcers, may be found anywhere in the mouth including tongue and palate but are often along the bite lines. Both major and minor salivary dysfunction occurs [75]. Local infections may cause changes in symptoms without changes in physical findings. Secondary infections with viruses (especially herpes simplex and human papilloma virus) and yeasts are almost universal and patients usually require treatment as long as their oral disease persists and/or immunosuppression is prescribed. Fibrosis causing decreased oral range of motion is a very late manifestation. Patients with chronic GVHD undergoing dental work should receive antibiotic prophylaxis.

Table 4. *Signs, Symptoms, and Clinicopathologic Findings of Chronic GVHD*

System	Signs/Laboratory Findings	Symptoms	Histopathology
Skin (common)	Hyper- and hypopigmentation, lichen planus (violaceous flat-topped papules), poikiloderma (atrophy, telangectasias, dyspigmentation), cutaneous ulcers, scleroderma (thickening due to collagen deposition, may cause decreased range of motion and contractures), ichthyosis	Pruritis, lack of flexibility	Lichenoid: Hyperkeratosis, focal hypergranulosis, acanthosis, dyskeratotic keratinocytes, vacuolar degeneration, colloid bodies, perivascular and periadnexal lymphoplasmacellular infiltrate Poikiloderma: epidermal atrophy, loss of rete ridges Scleroderma: epidermal atrophy, dermal fibrosis, less inflammation than lichenoid lesion, adnexal structures destroyed Differential diagnosis: drug reaction, eczema
Cutaneous structures	Onchodystrophy, alopecia, loss of sweat glands	Heat sensitivity	Destruction and fibrosis of cutaneous appendages
Liver (common)	Elevated alkaline phosphatase, transaminases, bilirubin	Pruritis	Small bile duct atypia and damage with subsequent necrosis and drop-out, moderate lymphocytic infiltrate, cholestasis and ballooning Differential diagnosis: drug toxicity (cholestasis, inflammation), veno-occlusive disease, viral infections, gallstones, and infiltrative processes
Mouth (common)	Lichen planus, erythema, ulcers, xerostomia, dental caries, fibrosis, decreased salivary flow	Food sensitivity, pain, dry mouth, decreased oral range of motion from fibrosis	Mucosal atrophy, lymphoplasmacytic inflammation, increased mucopolysaccharides, fibrosis and destruction of minor salivary glands Differential diagnosis: Herpes virus infection, Sjogren's syndrome
Eyes (common)	Keratoconjunctivitis sicca, corneal ulcerations, Schirmer's test with <5 mm wetting at 5 min	Dry eyes, photophobia, pain	Differential diagnosis: postradiation xerophthalmia, Sjogren's syndrome
Esophagus	Esophageal web, desquamation, ulcerations, strictures, submucosal fibrosis, abnormal motility	Odynophagia, dysphagia, heartburn, retrosternal pain	Differential diagnosis: reflux esophagitis, infection
Intestines	Fibrosis, malabsorption	Diarrhea, nausea, anorexia, abdominal pain, weight loss	Differential diagnosis: irritable or inflammatory bowel syndrome, infection
Lung	Obstructive more than restrictive abnormalities on pulmonary function testing, BO, pneumothoraces, bronchiectasis, pseudomonal colonization, pulmonary infiltrates; air trapping on high resolution CAT scan of chest	Dyspnea, nonproductive cough, wheezing	BO with granulation tissue plugs and fibrosis obliterating small airways, interstitial pneumonitis
Musculoskeletal	Polymyositis, arthritis, fasciitis	Arthralgias, myalgias, weakness	
Serous	Pericardial, peritoneal, and pleural effusions	Clinical syndromes of cardiac tamponade, ascites, dyspnea	Usually transudative
Nervous	Entrapment of nerves, peripheral neuropathy, myasthenia gravis	Pain, paresthesias	
Urologic	Cystitis, phimosis	Pain, hematuria	
Vagina	Erythema, lichen-planus like, sicca, strictures, stenosis, ulcers	Pain, dyspareunia, difficulty voiding	
Hematopoietic	Thrombocytopenia, neutropenia, eosinophilia, hemolytic anemia		
Immune system	Lymphoid hypocellularity, hyper- or hypogammaglobulinemia	Frequent infections, especially sinus, upper respiratory tract	

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Gastrointestinal Tract

Esophageal symptoms of dysphagia and odynophagia result from desquamation, web and stricture formation, and reflux esophagitis. Periodic endoscopic dilations and antacid medications may help symptomatically. Stomach and small intestinal pathology are relatively rare. However, many patients have anorexia, nausea, lower abdominal pain, cramping, and diarrhea. Pancreatic insufficiency without characteristic laboratory and radiographic studies may occur, and this syndrome responds to enzyme supplementation [76]. Weight loss is common and is probably multifactorial from decreased oral intake, poor absorption, increased resting energy expenditures [77], and increased TNF levels. Degree of weight loss should be followed up closely so appropriate interventions can be instituted. Hopkins reviewed 93 patients with chronic GVHD and reported malnutrition in 43% of patients and severe malnutrition with body mass index <18.5 in 14% of patients[78]. Symptoms often improve with successful treatment of GVHD.

Many patients with chronic GVHD have GI symptoms that are not necessarily related to their chronic GVHD. When the Hopkins group reviewed 40 patients with chronic GVHD who underwent endoscopy for GI symptoms, more than half (59%) were found to have ongoing acute GVHD and an additional 27% had both acute and chronic GVHD when biopsy specimens were obtained. Chronic GVHD alone was found in only 14% of cases. Other causes of GI symptoms included infection, drug side effects, motility disorders, and malabsorption. Patients with ongoing acute GI GVHD had poor survival.

Liver

Hepatic disease typically presents as cholestasis, with laboratory evaluation showing increased alkaline phosphatase levels and/or increased serum bilirubin levels. Occasionally, chronic GVHD of the liver presents as a picture of acute hepatitis [79]. Liver biopsy is required to confirm the diagnosis and is especially important in patients with no other symptoms of chronic GVHD because viral infection and drug toxicity may mimic GVHD. Isolated hepatic chronic GVHD may be increasing with the use of DLI [80]. Liver transplantation has been successfully performed for end-stage hepatic chronic GVHD [81].

Respiratory Tract

Bronchiolitis obliterans (BO) is a late manifestation of chronic GVHD. Patients typically present with a cough, wheezing, dyspnea on exertion, or history of recurrent bronchitis or sinusitis [82]. Pulmonary function testing shows new obstructive lung defects defined by an FEV_1 <80% of predicted or a decrease of FEV_1/FVC by <10% within a period of less than 1 year, not explained by infection, asthma, or recurrent aspiration from the sinuses or from gastroesophageal reflux. In the absence of chronic GVHD in any other organ, the diagnosis of BO requires negative microbiological tests from bronchoalveolar lavage, evidence of air trapping by high-resolution end-expiratory and end-inspiratory computer-assisted tomography scan of the lungs, or confirmation using lung biopsy showing granulation tissue and obliteration of the small airways. Although low Ig levels and chronic GVHD are associated with BO, a randomized trial of prophylactic Ig replacement did not decrease the incidence of BO [83]. Patients with BO have minimal response to therapy and a very poor prognosis; serial pulmonary function tests can quantify the degree of respiratory compromise. Bronchiolitis obliterans organizing pneumonia not caused by infections also may represent a manifestation of chronic GVHD. Patients with bronchiolitis obliterans organizing pneumonia should be carefully evaluated for the presence of chronic GVHD manifestation in other organs. Successful lung transplantation has been performed in a small number of patients with end-stage pulmonary chronic GVHD [84]. Outside of HCT, an underlying autoimmune process is implicated by the association of BO with lung transplantation, collagen-vascular diseases, and viral infections [85,86].

Even without BO, pulmonary sicca and bronchiectasis lead to frequent infections and bacterial colonization, often with *Pseudomonas* species. Patients with chronic GVHD are also at risk for chronic sinopulmonary disease, which may be relatively asymptomatic given the extent of involvement. The sinuses should be considered as a potential fever source in any patient with chronic GVHD.

Musculoskeletal System

Muscle cramps are a common symptom, although the pathophysiology is not understood. Myositis, with tender muscles and increased muscle enzymes, may start as a proximal myopathy, but is rare and does not explain the frequent occurrence of severe cramps. Fascial involvement in sclerodermatous GVHD is usually associated with skin changes, but may develop with normal, but fixed overlying skin [87]. Fasciitis often affects forearms and legs causing significant limitations in range of motion and joint contractures. Patients with restricted range of motion benefit from a regular program of physical therapy and deep muscle fascial massage. Serial assessments of joints should document range of motion.

Hematopoietic System

Cytopenias are common in patients with chronic GVHD. They may be a result of stromal damage or caused by autoimmune processes. Thrombocytopenia

at the time of chronic GVHD diagnosis has been associated with a poor prognosis [66,88,89]. Eosinophilia may be seen and may be an indicator of chronic GVHD activity.

Other Organ Systems

Pericardial and pleural effusions can cause compressive loss of function and may require drainage and sclerosis. Peripheral edema may be severe. Myasthenia gravis and peripheral neuropathy also have been attributed to chronic GVHD. Women may develop vaginal or vulvar lichenoid changes, ulcers, web formation, and strictures, and should have a biopsy to confirm the diagnosis if no other organs are involved. Topical corticosteroids can be effective treatment for vaginal chronic GVHD, and mechanical or surgical dilation may be necessary for relief of symptoms.

In pediatrics, chronic GVHD or its treatment can inhibit growth, although most children do catch up once chronic GVHD is controlled and immunosuppression is tapered. Chronic GVHD involvement of heart, kidney, and central nervous system is questionable despite occasional rare reports.

Immunodeficiency

Chronic GVHD causes profound immune dysfunction [90-93], and most chronic GVHD deaths are attributable to infection. Defects in mucosal integrity, immunosuppressive medications, and reduced number and function of mature T and B cells contribute to the high fatality rate from bacterial, fungal, and viral pathogens [90-93]. Functional asplenia with an increased susceptibility to encapsulated bacteria, particularly pneumococcus, is common, and circulating Howell-Jolly bodies may be seen on peripheral blood smear. Patients are also at high risk for invasive fungal infections and *Pneumocystis carinii* pneumonia [94].

EVALUATION OF SUSPECTED CHRONIC GVHD

Many patients will have returned to the care of their primary hematologist-oncologist when chronic GVHD develops. Although not every rash or GI symptom represents GVHD, the accurate and timely diagnosis of chronic GVHD is an important first step in its successful treatment. Because therapy for chronic GVHD is highly immunosuppressive and must be continued for a prolonged time, it is important to confirm the diagnosis before initiating therapy. Conversely, subtle manifestations of chronic GVHD may go undiagnosed for months, and this delay may make successful treatment and rehabilitation difficult. For example, the diagnosis of fasciitis without skin changes may be difficult to recognize, but systematic assessment of range of motion of wrists and ankles may detect early signs before permanent disability. In addition, pulmonary function testing at 3 months and at 1 year after transplantation may detect early signs of BO before symptoms become apparent.

Once chronic GVHD is diagnosed, intermittent evaluation at an experienced center can help guide management. In a series of 123 patients referred to Johns Hopkins for the management of refractory chronic GVHD, 9 patients were judged to never have had chronic GVHD and 26 patients had inactive disease [95]. Restaging with the use of the Schirmer's test, pulmonary function tests, gynecological evaluation, liver function, complete blood cell counts, and medical photographs if skin involvement is present is helpful to assess the extent of the disease. A morbidity scale can be used to record the severity of manifestation of the chronic GVHD at the time of diagnosis, whenever therapy is changed, and at yearly intervals if treatment continues or if manifestations of chronic GVHD persist.

PREVENTION

Although acute GVHD is a predictor for development of chronic GVHD, successful efforts to decrease acute GVHD have not resulted in decreased rates of chronic GVHD. The two notable exceptions are T-cell depletion and use of umbilical cord blood as a stem cell source because lower rates of both acute and chronic GVHD are observed with these approaches [96,97]. Specific attempts to decrease chronic GVHD rates through prolongation of CSA administration, addition of Ig or thalidomide, and preemptive treatment on the basis of subclinical chronic GVHD found in skin and lip biopsy specimens [52,98,99] have proven unsuccessful (Table 5).

TREATMENT OF CHRONIC GVHD

Because the main manifestation of this disease is immunodeficiency, patient education and infection prophylaxis are very important components of chronic GVHD management. Infection is the leading cause of death in patients with chronic GVHD. Prophylaxis against *P carinii* should be administered to all patients undergoing treatment of chronic GVHD for 6 months after discontinuation of immunosuppressive medications. Lifelong splenic dysfunction occurs with chronic GVHD, and prophylaxis against encapsulated bacteria is recommended. The guidelines published by the American Heart Association for endocarditis prophylaxis should be followed when patients are undergoing dental or other invasive procedures. Patients treated with topical steroids for oral GVHD should be treated with clotrimazole troches or nystatin swishes to prevent oral candidiasis. Patients at risk for late CMV disease (receiving systemic corticosteroids)

Table 5. *Prevention Trials (All Patients Received Bone Marrow)*

Intervention	Population	Comment	Chronic GVHD Conclusions	Reference
Randomized trials of acute GVHD prophylaxis				
Cyclosporine/steroids vs. cyclosporine alone	HLA-matched sibling recipients at high risk of relapse posttransplantation, N = 60	Decreased incidence of acute GVHD with combination prophylaxis but similar survival	Higher incidence of chronic GVHD (44% vs. 21%, *P* = .02) with combination prophylaxis	125
Cyclosporine/methotrexate vs. methotrexate alone	HLA-matched sibling recipients with aplastic anemia, N = 46	Decreased incidence of acute GVHD with combination prophylaxis and better survival	Trend toward higher chronic GVHD in combination prophylaxis (58% vs. 36%, *P* = .18)	126
CSA/methotrexate vs. CSA alone	HLA-matched sibling recipients with AML in CR1 or CML, N = 93	Decreased incidence of acute GVHD with combination prophylaxis and improved survival	No difference	127
CSA/methotrexate +/− steroids	HLA-matched (N = 122) or 1 antigen mismatched (N = 25) recipients, heterogeneous diseases		Higher incidence of chronic GVHD (62% vs. 40%, *P* = .01) in group receiving steroids independent of acute GVHD	128
CSA/steroids +/− methotrexate	HLA-matched sibling recipients with acute leukemia in CR1 or CML, N = 149		No difference	129
Randomized trials aimed directly at chronic GVHD prevention				
Dose of CSA (high vs. low dose)	HLA-matched sibling recipients with acute leukemia, N = 81	Low-dose CSA associated with lower relapse rate	No difference	130
Duration of CSA administration (24 mo vs. 6 mo)	Prior acute GVHD or skin biopsy positive for subclinical chronic GVHD, N = 162	Incidence of chronic GVHD in 6-mo CSA arm lower than historical controls	No difference	124
Duration of CSA administration (6 mo vs. 60 d)	No active acute GVHD, N = 103	Onset of chronic GVHD more rapid in short CSA arm, higher treatment-related mortality in short CSA arm if prior acute GVHD	No difference in incidence	131
CSA/methotrexate +/− thalidomide	90% matched sibling recipients, N = 54	Double-blinded, study closed early due to lower survival and more chronic GVHD in the group receiving thalidomide	Thalidomide associated with more chronic GVHD and worse survival	123
Ig vs. no Ig	Heterogeneous population, N = 250	Ig arm had more total infections in year 2 than control patients	No difference	83
Different doses of Ig	Heterogeneous population, N = 627	Double-blinded, 3 dose levels of IgG, similar rates of infection and interstitial pneumonitis	No difference	132

AML indicates acute myelogenous leukemia; CR1, first complete remission; CML, chronic myelogenous leukemia.

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should have CMV activity monitored closely and treatment initiated or reactivated. Patients should receive prophylatic acyclovir for prevention of varicella zoster virus reactivation during the first year after the transplantation and later if systemic immunosuppression is still needed to control chronic GVHD. Some centers administer intravenous IgG to patients with hypogammaglobulinemia if levels are <400 mg/dL) to maintain serum IgG levels >500 mg/dL. Posttransplantation vaccination guidelines are available on the Centers for Disease Control and Prevention web site (www. cdc.gov/mmwr/mmwr_rr.html) [100]. Patients

Table 6. *Primary Therapy for Chronic GVHD*

Treatment	N	Comments	Conclusions
Group I: untreated, group II: corticosteroids and/or anti-thymocyte globulin, group III: corticosteroids and cyclophosphamide, procarbazine, or azathioprine	52	Sequential study, alive and free of disability: untreated 15%, corticosteroids and/or anti-thymocyte globulin 23%, combination therapy 71%	Most effective regimen was corticosteroids and azathioprine [133]
Corticosteroids +/− azathioprine	179	Standard-risk patients were randomized, high-risk patients given single-agent prednisone, 40% of patients in each group had subclinical disease only	Higher mortality from infection if azathioprine part of initial treatment regimen. In high-risk patients (platelets < 100000), prednisone alone resulted in 26% survival [98]
Alternating-day corticosteroids and CSA	61	Phase 2 design, high-risk extensive chronic GVHD, 40 given primary therapy, 21 given salvage, long-term survival >50% compared with historical control of 26%	Alternating-day, combination therapy better [88]
Cyclosporine, steroids +/− thalidomide	54	Randomized, unblinded trial, patients with extensive chronic GVHD.	Closed early (target enrollment N = 134) after interim analysis showed slow accrual and higher response rates in both arms than projected [134]
Steroids, CSA or tacrolimus, +/− thalidomide	51	Randomized, placebo-controlled trial of thalidomide added to standard upfront therapy in higher-risk patients with thrombocytopenia or progressive presentation.	Closed early (target enrollment N = 132) after interim analysis showed slow accrual and only 42% probability of reaching statistical significance by enrolling remainder of patients [135]
Steroids +/− CSA	287	Randomized, unblinded trial, enrolled 1985-1992	Disease-free survival was lower in the combination arm (hazard ratio 1.51; 95% CI, 1.03-2.21; $P = .03$) in multivariate analysis. Transplant-related mortality, relapse, secondary chronic GVHD therapy, rates and discontinuation of all immunosuppressive therapy were not different [103]

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with chronic GVHD should not receive live virus vaccinations such as measles, mumps, and rubella.

The most widely used first-line therapy for treatment of chronic GVHD is CSA and prednisone, administered on alternating days. Sullivan et al reported that prednisone alone is superior to prednisone plus azathioprine for primary treatment of patients with standard-risk extensive chronic GVHD [98]. However, in patients classified as high risk on the basis of platelet counts $< 100 \times 10^9$/L, treatment with prednisone alone resulted in only a 26% 5-year survival rate. When a similar group of patients was treated with alternating day CSA and prednisone, the 5-year survival rate exceeded 50% [88]. After this encouraging report, most centers adopted this regimen for initial treatment of all patients, not just those deemed at high risk. Patients start treatment with daily prednisone at 1 mg/kg/d and daily CSA at 10 mg/kg/d divided twice a day. If chronic GVHD is stable or improving after 2 weeks, prednisone is tapered by 25% per week to a target dosage of 1 mg/kg every other day. After successful completion of this steroid taper, CSA is reduced by 25% per week to alternate-day dosing of 10 mg/kg/d divided twice a day, every other day. If the disease has completely resolved, patients are slowly weaned from both medications after 9 months, with dose reductions approximately every 2 weeks. Patients with incomplete responses are kept on therapy for 3 more months and then re-evaluated. If patients fail to respond by 3 months or show progressive disease, salvage regimens are warranted [101].

Until recently, there was no data on the effectiveness of this regimen in standard-risk patients. Flowers recently reviewed the success of initial combination therapy for patients treated in the 1980s. She reported a nonrelapse mortality rate of 21% in standard-risk patients (N = 126) and 39% in high-risk patients (N = 111), defined by progressive onset or thrombocytopenia. Successful discontinuation of all immunosuppressive medications eventually occurred for 60% of standard-risk patients and 40% of high-risk patients [102]. Koc et al recently reported the long-awaited results of a study comparing prednisone alone to prednisone plus CSA in patients with extensive chronic

Table 7. *Secondary Therapy for Chronic GVHD*

Agent	Published Success Rate	Hypothesized Mechanism of Action	Side Effects	Reference
High-dose corticosteroids	48% major response rate (N = 56)	Lympholytic at these doses	Infection, glucose intolerance, osteoporosis, avascular necrosis, cataracts, psychological effects including psychosis, insomnia	136
Tacrolimus	35% response rate (N = 39)	Binds to FKBP-12 (FK binding protein) and inhibits T-lymphocyte activation, concentrates in liver	Renal dysfunction, neurotoxicity, hypertension	137, 138
Mycophenolate mofetil	46% objective response (N = 26)	Prodrug of mycophenolic acid that is a noncompetitive reversible inhibitor of inosine monophosphate dehydrogenase. Cytostatic for T and B lymphocytes because they lack salvage pathways	Nausea, vomiting, diarrhea, neutropenia	139, 140
Rapamycin	Not available	Binds to FKBP-12 and mammalian target of rapamycin to inhibit cytokine-driven T-cell proliferation	Hyperlipidemia, hypertension, rash	
Extracorporeal photopheresis	33%-80% N = (11-18)	Induces apoptosis in alloreactive T cells, normalization of CD4/CD8 ratios by decreasing CD8 cells, increases natural killer cells, decreases dendritic cells	GI upset, potential need for central IV access	141-144
Psoralen and UVA	40% CR, 38% PR (N = 11-40)	Interferes with antigen presentation and inflammatory cytokine production by Langerhan's cells, increases IL-10 production by keratinocytes	Increase in skin cancer, phototoxicity, nausea, hepatoxicity	145-149
UV-B radiation	Case series	Treats epidermis only, induces IL-10 in human epidermal cells	Increase in skin cancer, phototoxicity	150
Thalidomide	9%-42% CR rate (N = 14-80)	Anti-inflammatory and immunosuppressive properties	Neuropathy, somnolence, constipation, neutropenia	104-106, 151
Etretinate (no longer available), acitretin	74% improvement (N = 27)	Synthetic vitamin A derivative, may affect production of cytokines	Skin scaling, breakdown, nail cracking, xerosis, cheilitis, pruritis, rare pseudotumor cerebri	152
Azathioprine	Not available	Cleaved to mercaptopurine	GI symptoms, neutropenia, thrombocytopenia	
Hydroxychloroquine	9% CR and 44% PR (N = 40)	Interferes with antigen processing and presentation, proliferation, TNFα production, and cytotoxicity, synergistic with CSA and tacrolimus in vitro	GI symptoms, rare retinal toxicity	153
Ursodeoxycholic acid	33% decreased in bilirubin levels, but not sustained off therapy (N = 12)	Replaces native human bile acids, reduces class I HLA expression on hepatocytes	Diarrhea, abdominal pain, headache	154
Clofazimine	55% PR (N = 22)	Atypical immunomodulatory effects	Abdominal cramping, hyperpigmentation	155
Anti-thymocyte globulin	Not available	In vivo T-cell depletion	Anaphylaxis, serum sickness	
Daclizumab	Not available	Humanized anti–IL-2 receptor antibody	None	
Infliximab	Reported in abstracts	Chimeric IgG monoclonal antibody, binds to TNFα and prevents binding with receptors	Hypersensitivity reactions, infections	
2-deoxycoformycin	Reported in abstracts	Inhibits adenosine deaminase	Nausea, vomiting, myelosuppression, rash, headache	

Table 7. *(Continued)*

Agent	Published Success Rate	Hypothesized Mechanism of Action	Side Effects	References
Rituximab	Case report	Chimeric anti-CD20 monoclonal antibody	Allergic reactions	156
Total lymphoid radiation	Case series		Leukopenia	157, 158
Topical azathioprine	Case report	Purine analog metabolized to 6 mercaptopurine	Rash, fever, pancreatitis, arthralgias, malaise, nausea, diarrhea, pancytopenia, hepatitis, infections, malignancy	159
Topical tacrolimus	Case series	0.1% ointment	Localized skin burning, pruritis, irritation	160
Opthalmic cyclosporine	Case series	1% solution	None	161
IV lidocaine	Case report	Vascular and anti-inflammatory properties	Seizures, drowsiness, tremors, hypotension	162

IV indicates intravenous; CR, complete response; PR, partial response.

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GVHD without thrombocytopenia [103]. In this trial (N = 287 evaluable patients), the cumulative incidence of transplant-related mortality, survival, relapse, need for secondary chronic GVHD therapy, and discontinuation of immunosuppressive medications were not significantly different between the 2 arms. Intriguingly, survival without recurrent malignancy was better in the prednisone-only arm ($P = .03$) although the incidence of avascular necrosis was also higher. Thus, there is no evidence that initial combination therapy improved control of chronic GVHD in patients with platelet counts $> 100 \times 10^9$/L. The uncertainty regarding the choice of frontline therapy emphasizes the importance of enrolling patients on clinical trials so that fundamental questions about the pathogenesis and treatment of chronic GVHD may be answered. Currently 2 large randomized trials are planned or underway for frontline therapy. One trial through the Children's Oncology Group is looking at the addition of hydroxycholoroquine to CSA plus prednisone. The other multi-centered trial organized by the Fred Hutchinson Cancer Research Center is examining the addition of mycophenolate mofetil to prednisone plus calcineurin inhibitor in patients with extensive chronic GVHD or high-risk features. Table 6 reviews published trials of initial treatment for chronic GVHD.

SECONDARY THERAPIES

If patients fail to respond or progress through steroid-based therapy then secondary therapy is indicated. Steroid-refractory chronic GVHD is formally defined as either failure to improve after at least 2 months, or progression after 1 month of standard immunosuppressive therapy, including corticosteroids and CSA [104,105]. A number of phase 2 trials of secondary or salvage regimens have been published, and most report a success rate of 25% to 50%. However, most trials contain 40 or fewer patients. Reported response rates are usually based on 4 categories: complete (resolution of all chronic GVHD manifestations), partial (≥50% but less than complete organ responses), no response (<50% response), and progression (worsening while on therapy) [104,106]. Table 7 provides information about salvage therapies in chronic GVHD. A multicenter, randomized trial with extracorporeal photopheresis is currently being conducted in the United States and Europe for patients with corticosteroid-dependent or refractory chronic GVHD with skin involvement.

IMPACT OF CHRONIC GVHD ON MAJOR TRANSPLANTATION OUTCOMES

Nonrelapse Mortality

Chronic GVHD is the major cause of nonrelapse mortality in patients surviving more than 2 years after allogeneic transplantation, and increasing severity of chronic GVHD is associated with higher nonrelapse mortality rates [4,82] (Figure 2). Infection from a broad array of pathogens is the major cause of death, followed by progressive organ failure from chronic GVHD involvement. De novo chronic GVHD occurs later than the other forms of chronic GVHD and does not seem to adversely affect survival [107]. In aplastic anemia and refractory anemias where the risk of relapse and death from the primary disease is low, chronic GVHD has a substantial adverse impact on survival that has not improved significantly during the past 30 years [2,108].

Graft-versus-Malignancy Effect

Chronic GVHD is associated with lower relapse rates in both early- and advanced-stage leukemia [3,107,109-113]. However, the nature of this graft-versus-malignancy effect is poorly understood, and it is not known whether the protective effect relies on development of overt chronic GVHD or is durable once chronic GVHD resolves [110]. Recent observational data suggest that increased severity of chronic GVHD is not associated with a decreased relapse risk (Figure 2). Nevertheless, studies examining preventive and treatment strategies should carefully follow up relapse rates, especially in situations where disease is advanced or cure is thought to be heavily reliant on an intact graft-versus-malignancy effect. For example, eradication of Philadelphia chromosome– positive cells in patients with chronic myeloid leukemia was correlated with development of chronic GVHD in one study [114].

Impact on Functional Status and Quality of Life

Chronic GVHD is associated with substantial quality of life deficits, particularly in the areas of physical and functional status [5,115-117]. In addition, patients with chronic GVHD report more specific symptoms, such as rashes, mouth sores, and frequent infections than unaffected individuals [7,118]. Social and emotional functioning and satisfaction with transplantation are relatively preserved, although chronic GVHD is associated with decreased general health status, sexual inactivity, and loss of employment in long-term survivors [69,117,119-122]. In addition, long-term treatment with corticosteroids for chronic GVHD may result in compromised quality of life due to the significant morbidity associated with this treatment. A 30-item survey allowing patient self-report of chronic GVHD symptoms has been validated [113].

FUTURE DIRECTIONS

Efforts to prevent the development of chronic GVHD, including the use of Ig and thalidomide, have been unsuccessful [83,123]. Likewise, trials of prolonged administration of CSA found no difference in chronic GVHD or mortality when CSA was given for 24 months rather then 6 months [124]. Current transplantation practices, including the use of DLIs and PBSCs, older patient age, and increasing use of unrelated and mismatched stem cell donors make it likely that chronic GVHD is going to be a progressively more common problem. Ongoing research to further characterize the pathogenesis of this disease is crucial to the development of new therapeutic approaches, whereas well-organized, multicenter trials are needed to test clinical questions.

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