
Graft-Versus-Host Disease (GVHD)

An Evidence-Based Management Guidelines

Görgün AKPEK

Attending Physician in Blood and Marrow Transplantation Program at University of Maryland Greenebaum Cancer Center, Maryland, USA

Turk J Haematol 2003;20(3): 123-142

INTRODUCTION

Hematopoietic stem cell transplantation (SCT) provides effective therapy for patients with lymphohematopoietic, immunologic, metabolic and other disorders. Current estimates of annual numbers of allogeneic SCT are 12.000 to 15.000 worldwide, with continuing growth rate of 10 to 20% per year. Transplant-related mortality at one year after HLA-identical sibling transplants is about 30%. A major impediment to successful allogeneic-SCT or donor lymphocyte infusion (DLI) is the graft-versus-host disease (GVHD) mediated by immunologically competent cells, mainly T-lymphocytes, in the grafted blood or marrow. The resultant GVHD is a complex clinical syndrome, which involves the graft-versus-host reaction, as well as the infectious complications related to the compromised host immunity secondary to treatment of GVHD and/or GVHD per se. Altho-

ugh improvements have been made in the prevention of GVHD, these advances have not resulted in a concomittant improvement in the treatment of this condition, particularly of the severe form of GVHD that accounts for as much as 50% of the cases. Allo-SCT is used in increasingly older patients, in whom the risk for GVHD is greater. The use of unrelated donors and related but nonhuman leukocyte antigen (HLA)-identical donors is expanding. Acute and chronic GVHD are larger problems, both in incidence and in severity, in recipients of alternative-donor SCT. The use of DLI to treat relapsed disease or to achieve full donor chimerism after nonmyeloablative transplantation has resulted in the development of GVHD in a substantial number of these patients. Finally, many studies including a recent meta-analysis have clearly shown that patients receiving allogeneic peripheral blood stem cell transplants have a much higher incidence of chronic GVHD than comparable patients receiving marrow grafts.

GVHD is usually divided into an early (acute GVHD) and a late (chronic GVHD)

Graft-Versus-Host Hastalığı (GVHD)

Anahtar Kelimeler: Graft-versus-host hastalığı.

Key Words: Graft-versus-host disease.

form of the disease. Acute GVHD occurs in approximately 60% of unmanipulated HLA-matched sibling transplants and 80% of unrelated donor transplants. It is characterized in its mildest forms of skin rash. As the disease worsens, however, the confluent rash may progress to blistering of the skin similar to severe burn, profound diarrhea with abdominal pain, and hepatic dysfunction with marked hyperbilirubinemia. The overall fatality rate is about 20% but exceeds 80% in the severe form of the disease. High dose corticosteroids are the mainstay of therapy. However, therapy of corticosteroid resistant acute GVHD continues to be disappointing; most patients with stage IV disease do not survive. Prophylaxis of GVHD has been more successful than treatment. Pharmacologic agents can inhibit GVHD, and one useful combination is cyclosporine plus methotrexate; another is a triple regimen of cyclosporine, methotrexate, and corticosteroids. T-cell depletion in donor graft results in a significant reduction in aGVHD at the expense of disease relapse.

Chronic GVHD is the single major determinant of long-term outcome and quality of life following BMT. In early 1990's chronic graft-versus-host disease (GVHD) was the most common late complication of allogeneic SCT, with reported incidences ranging from 30% to 80%. Currently, as many as 50-60% of patients may develop chronic GVHD usually within 2 years of allo-SCT depending on the risk factors present. The greatest risk factor for the development of chronic GVHD is the prior occurrence of acute GVHD. Patients with chronic GVHD usually present with a lichenoid skin eruption. Dryness of eyes and mouth is also common. Many patients also have lichenoid involvement of the mouth, with food sensitivities and oral pain. The diagnosis of chronic GVHD is generally made on clinical parameters. A biopsy of the affected area is recommended to confirm the diagnosis. Histologically, lymphocytes are seen at the dermal epidermal junction. As the disease progresses, skin becomes more scler-

odermatous in appearance with thickening, limitation of mobility as a result of fascial involvement, and loss of hair and sweat glands as a result of the thick fibrosis. The treatment principles of chronic GVHD are based on immunosuppression until disease become stable and regress; topical measures to prevent skin breakdown; and antibiotic prophylaxis of infection.

Although prevention and treatment of acute GVHD have improved over the past two decades, similar progress in chronic GVHD has remained elusive as it continues to be the leading cause of late nonrelapse mortality following allogeneic SCT. Not surprisingly, large observational studies identified chronic GVHD as the most common cause of nonrelapse deaths occurring more than two years posttransplant and increasing severity of chronic GVHD is associated with higher mortality rates. 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 over the past 30 years. It has been recently reported that the high rate of chronic GVHD after allogeneic peripheral blood stem cell transplantation (PBSCT), an expanding area of research and clinical application, that some of the clinical factors altered the risk of chronic GVHD, and that high-risk chronic GVHD adversely affected the survival outcome. Chronic GVHD is also associated with decreased quality of life, impaired functional performance status, and continued need for immunosuppressive medications. Although social and emotional functioning and satisfaction with transplantation are relatively preserved, chronic GVHD may cause abnormalities of growth and development in children, decrease general health status, sexual inactivity, and loss of employment in long-term survivors.

While severe GVHD is associated with increased mortality, it also provides the beneficial graft-versus-leukemia effect. The risk

of relapse after allo-SCT is remarkably lower in patients with GVHD than in patients who do not develop GVHD. We need new methods in addition to clinical parameters to predict the occurrence and monitor the activity of GVHD. This paper is intended to provide clinical guidelines for diagnosis, staging/grading, prevention and treatment of GVHD.

ACUTE GRAFT-VERSUS-HOST DISEASE

Acute GVHD is a clinicopathological syndrome mainly involving the skin, liver, and gut. Biopsy of the affected organ is essential for the diagnosis. Histologic findings are not specific for GVHD and sometimes may be difficult to distinguish from the effects of chemoradiotherapy preparative regimen, especially during the first three weeks after BMT (level of evidence IIa)^[1]. Diagnosis of GVHD often requires both clinical and histopathological criteria.

Histopathologic Diagnosis of Acute GVHD (Level of Evidence IIa)^[2].

a. Skin biopsy: Histologic grading (level of evidence IIa)^[3].

Grade I: Epidermal basal cell vacuolization.

Grade II: Epidermal basal cell death or apoptosis + lymphocyte infiltration + satellitosis.

Grade III: Bulla formation.

Grade IV: Ulceration of the skin.

In clinical practice, both lymphocytes and basal cell apoptosis are the required histopathologic criteria for diagnosis of acute GVHD. The central histologic features of acute GVHD have to be interpreted in the context of the time after chemoradiotherapy, the status of engraftment, the degree of HLA match, and the drugs used to prevent or to treat GVHD. The effects of chemoradiotherapy usually wear off in three to four weeks. If histologic findings are equivocal for the diagnosis of acute GVHD, a subsequent biopsy may be needed to confirm the diagnosis be-

fore initiating high-dose systemic corticosteroid therapy.

b. Gastrointestinal GVHD: Diarrhea is the most common clinical symptom associated with acute GVHD. However, acute GVHD of gastrointestinal (GI) tract may present with only nausea and vomiting (level of evidence IIa)^[4]. In clinical practice biopsy from upper GI tract (stomach and duodenum) is preferred because of higher sensitivity and safety as compared to rectal or colonic biopsy. It also provides additional information about upper GI GVHD (level of evidence IIa)^[2]. As skin biopsy, GI biopsy is usually not useful before day 21.

Histologic grading of acute GI GVHD (level of evidence IIa)^[2]:

Grade I: Individual cell necrosis or apoptosis in basal and lateral crypts, with sparse lymphocytic infiltrate.

Grade II: Crypt abscess, in which polymorphonuclear leukocytes and eosinophils may participate.

Grade III: Crypt loss.

Grade IV: Mucosal denudation.

c. Liver GVHD (level of evidence IIa)^[2]: The principle histologic findings in acute liver GVHD vary according to the stage of liver GVHD.

Early phase:

- Destructive bile duct lesions, which may result in degenerative cytoplasmic masses with a few hyperchromatic nuclei.

- Variable inflammation (mostly lymphocytes) of the portal space.

- Liver transaminases are usually elevated in the early stage of acute GVHD.

The extent of this inflammation varies with the duration of, being less in acute than chronic GVHD. Immunosuppressive treatment may also decrease the extent of inflammation and make the assessment of bile duct changes easier.

Late phase:

- Hepatocellular-cholangiolar cholestasis.
- Portal-portal bridging, collapse and proliferation of cholangioles along limiting plates.
- Alkaline phosphatase and bilirubin are elevated.

The distinction between acute and chronic GVHD of liver may be difficult because flares of chronic GVHD resemble early acute GVHD. Dense portal fibrosis and loss of bile ducts are more consistent with chronic GVHD (level of evidence IIa)^[5].

The typical GVHD-damaged bile ducts/ductules with anucleated, focally vacuolated eosinophilic cytoplasm are sometimes best appreciated by other stains such as cytokeratins, trichrome, and periodic acid-Schiff (level of evidence IIa)^[2].

Acute GVHD Grading (Modified Keystone Grading)

Grade I: No need for treatment.

Grade II-IV: Need for treatment.

See Table 1 (level of evidence IV).

GVHD Prophylaxis

Six months of cyclosporin-A (CsA) and short-course methotrexate (MTX) is considered gold standard in GVHD prophylaxis for patients undergoing unmanipulated (T-cell replete) allogeneic stem cell transplantation (level of evidence Ib) (recommendation grade A)^[6-8].

Cyclosporine is given at 3-5 mg/kg IV starting the day before stem cell infusion. All IV doses are given in one dose over six hours. Inpatients will receive this dose from 8:AM-2PM, or hung after AM bloods have been drawn. Some centers administer IV CsA over 24-hour continuous infusion. Patients on 5 mg/kg/day of CSA should receive 5 cc/kg/hour of hydration (1/2 normal saline) during the CSA infusion. IV cyclosporine is continued until the patient tolerates oral

dosing (10 mg/kg in two divided doses). Trough CSA levels should be checked three days after any dose reduction for renal toxicity or after patient is changed to PO CSA. Steady state blood levels of CSA will not be achieved for at least 48-72 hours after any change in dosing (assuming normal hepatic function—even longer if abnormal), so blood CSA levels before this time are not helpful unless acute toxicity is suspected (e.g. seizures). The goal is to maintain a level greater than 200. This is especially important in patients receiving unmanipulated or unrelated grafts, those being treated for GVHD, and those with aplastic anemia. While some drugs (rifampin, phenobarbital, dilantin, carbamazepine) may decrease the level of CSA, others (voriconazole) may increase. Dose reduction is only necessary to maintain a level between 200-500 in patients with CSA toxicity such as seizures or renal toxicity (doubling creatinine or creatinine is > 2 mg), or patients enrolled in the high-risk trial. Routine levels are not necessary unless there is toxicity, questions about absorption, new onset GVHD, questions of compliance, or the patient enrolled in the high-risk clinical trial (level of evidence IIa, IV) (recommendation grade B)^[9].

Methotrexate can be given in two doses on day 1, 3, 6, and 11. Standard dose is 15 mg/m² on day 1, 10 mg/m² on days 3, 6 and 11 (level of evidence Ib) (recommendation grade A)^[6-8]. Mini MTX regimen is 5 or 10 mg/m² on day 1 and 5 mg/m² on days 3, 6, and 11 (level of evidence IIb) (recommendation grade B).

Tacrolimus (FK506) may be used instead of CsA. Two phase-III trials have shown a significant decrease in grade II-IV acute GVHD when comparing FK506/MTX to CsA/MTX. In that particular randomized trial, there was no difference in the incidence of chronic GVHD. Disease-free survival and overall survival were also not different. Regimen-related toxicities, especially nephrotoxicity was higher in the FK506 group (level of evidence Ib) (recommendation grade A)^[10].

Table 1. Acute GVHD grading

Acute graft versus host disease staging		GVHD grading (modified Keystone criteria)		
Stage	Skin	Liver	Gut (adults)	Gut (children)
0	No evidence of GVHD	Bili < 2.0 mg/dL	< 500 mL diarrhea per day	< 10 mL/kg/day
1	< 25%	2.0-3.0 mg/dL	≥ 500 mL/day, or persistent nausea with histologic evidence	10-15 mL/kg
2	25-50%	3.1-6.0 mg/dL	≥ 1.000 mL diarrhea per day	16-20 mL/kg
3	> 50%	6.1-15.0 mg/dL	≥ 1.500 mL diarrhea per day	21-25 mL/kg
4	W/bullous formation	> 15.0 mg/dL	Severe abdominal pain w-w/o ileus	> 26 mL/kg
Overall grade				
Grade	Skin	Liver	Gut	
0	None	None	None	
1	Stage 1-2	None	None	
2	Stage 3, original	Stage 1, original	Stage 1	
3	-----	Stage 2-3, original	Stage 2-4	
4	Stage 4, original		Stage 4-----	

Note:

Use 'Rules of Nines' or burn chart to determine extent of rash.

Range given as total bilirubin.

Volume of diarrhea applies to adults. For pediatric patients, the volume of diarrhea should be based on body surface area. Gut staging criteria for pediatric patients was not discussed at the Consensus Conference.

Persistent nausea with histologic evidence of GVHD in the stomach or the duodenum.

Criteria for grading as a minimum degree of organ involvement required conferring that grade.

Grade IV may also include lesser organ involvement but with extreme decrease performance status.

New onset or flare of GVHD, check cyclosporine or tacrolimus levels.

Cyclosporine levels should be maintained greater than 200.

Tacrolimus levels should be maintained between 5-15.

Mycophenolate mofetil (MMF) is mainly used for GVHD prophylaxis after nonmyeloablative transplants. Twenty-four patients with malignancies received busulfan, fludarabine, and 200 cGy TBI followed by HLA-identical PBSC. GVHD prophylaxis-CsA and MMF (1000 mg PO BID days 1-40) 25% of patients-grade II-IV acute GVHD; too early to determine incidence of chronic GVHD (level of evidence III) (recommendation grade C)^[11].

Treatment of Acute GVHD

Patients with stage I skin GVHD (rash < 25% of body surface area-BSA by rule of 9's) are often observed. Alternatively, stage I and II skin GVHD (< 50% BSA involvement) may be treated with topical steroids, (usually with 1% triamcinolone ointment). Selected patients such as those with HLA-mismatched or unrelated donors can be treated with systemic steroid if GVHD is stage II (between 25-50% BSA involvement) because of the perceived high-risk of rapid development of more extensive GVHD (level of evidence IIa) (recommendation grade B)^[12].

Treatment of acute GVHD should not be solely based on the stage and overall grade of acute GVHD. While some patients need an intensive immunosuppression and more aggressive treatment of GVHD such as patients with aplastic anemia in which the GVL effect is not needed, others may be treated with less intensive approach since the GVHD and GVL is the only hope for controlling or curing the aggressive malignancy.

Primary Treatment

High-dose corticosteroids are well established first line treatment of acute GVHD. Treatment more than 2 mg/kg/day does not improve response rates but may increase infectious complications (level of evidence Ib) (recommendation grade A)^[13,14].

Patients with moderate to severe acute GVHD (overall grade 2 or greater) are initially treated with intravenous. Methylprednisolone at 2 or 2.5 mg/kg in two divided doses

with tapering dose every four days (level of evidence IIa) (recommendation grade B)^[15-17]. Oral corticosteroid treatment at dose of 1 mg/kg can be used without parenteral treatment for patients with mild to moderate acute GVHD involving skin only (level of evidence Ib) (recommendation grade A)^[12]. Patients with GI and liver involvement are recommended to receive parenteral corticosteroids as their initial treatment (level of evidence Ib) (recommendation grade A)^[12]. Treatment consists of continuing the original immunosuppressive prophylaxis (CSA or FK-506) and adding methylprednisolone (level of evidence Ib) (recommendation grade A).

Tapering the steroid dose depends on the response to initial dose of steroid. Once response is achieved, tapering every four days by 25% is usually recommended. Once the dose of methylprednisolone is equal to 1 mg/kg, then taper should be slowed (25% per week). During steroid tapering, oral prednisone can be substituted for intravenous methylprednisolone (4 mg methylprednisolone equals to 5 mg of prednisone) (level of evidence IIa, IV) (recommendation grade B)^[9]. Tapering more slowly has not resulted in a significant decrease in GVHD flares, incidence of chronic GVHD, or early mortality (level of evidence IIa) (recommendation grade B)^[18]. If the taper of corticosteroid treatment is delayed (greater than six-eight weeks), ACTH stimulation test needs to be performed before complete discontinuation of corticosteroids to prevent adrenal insufficiency (level of evidence III) (recommendation grade B).

Treatment of Steroid- Refractory Acute GVHD

Prognosis is poor if steroid fails to control acute GVHD. There is no proven second line treatment for steroid-refractory acute GVHD. Antithymocyte globulin has been traditionally used in these patients. However, no reproducible benefit has been shown. Newer therapies are aimed at abrogating the ongoing inflammatory response (anticytokine) and inhibiting T-cell proliferation and reacti-

vity (lympholytic) (level of evidence IIb) (recommendation grade B)^[12]. These include;

1. Inhibitors of antigen processing and presentation (thalidomide, hydroxychloroquin).
2. Inhibitors of early T-cell activation (tacrolimus).
3. Antimetabolites (mycophenolite mofetil).
4. Anti-lymphocyte antibodies (ATG, Campath-1H).
5. Anti-T-cell receptor antibodies (OKT3, Anti-CD3).
6. Antibodies against T-cell activation antigens (anti-IL-2 receptor antibody).
7. Antibodies against T-cell costimulatory and adhesion molecules (anti-CD4, anti-LFA-1, anti-CD5 immunotoxin, anti-CD2).
8. Cytokine antagonist (anti-TNF- α , recombinant IL-1 receptor antagonist, soluble rhIL-1 receptor).
9. Phototherapy (extracorporeal photopheresis).

None of the above treatment modalities reduced GVHD related mortality, and prolonged survival. Therefore, additional studies to improve the response in patients with steroid-refractory acute GVHD are needed. The study must be well designed to answer one or two important questions and generate new ideas for future trials. Along with GVHD response, survival and transplant-related mortality should always be described when reporting the effects of regimens on GVHD prevention and treatment.

Supportive Care

Supportive care can greatly improve the quality of life for patients with acute GVHD.

Skin care: Optimum skin improve the survival in patients with stage IV skin GVHD. The skin care given to GVHD patients is similar to burn management. Bullae and vesicles must be kept intact (no perforation or peeling off). Open areas are cleaned with li-

beral normal saline and topical antibiotics such as silver sulfadiazine is applied. Such patients should be placed in an air-filled-bed to facilitate the healing.

The abdominal pain/cramps secondary to intestinal GVHD may require systemic narcotics with laxatives. Patients with severe gut GVHD is fed by TPN. Octreotide can be used for patients with severe secretory diarrhea (level of evidence IIb) (randomization grade B)^[19].

Infection prophylaxis is indicated in all patients on intensive immunosuppressive treatment. The following infection prophylaxis is strongly recommended until patients are off all steroids (level of evidence IIa, IV) (recommendation grade B)^[9]. Once steroid dose down to 1 mg/kg, antibiotic prophylaxis and lab work-up can be adjusted by the medical team.

1. Gram positive and negative bacterial infection prophylaxis (IV if patient has diarrhea). Bactrim single strength 1 tablet once a day, continuous or penicillin VK 250 mg PO BID. Levofloxacin is another alternative.

2. Viral infection prophylaxis (acyclovir or valacyclovir) for patients on high-dose (greater than 0.5-1 mg/kg/day) corticosteroids and other immunosuppressives.

3. PCP prophylaxis (Bactrim SS once a day or DS twice a week BID dapsone if allergic).

4. Fungal prophylaxis (fluconazole 200-400 mg/d) until high-dose corticosteroids is tapered down to 0.5-1 mg/kg.

5. CMV prophylaxis: Either weekly or bi-weekly CMV antigenemia monitoring. Prophylactic ganciclovir until day 60 or day 90 can also be considered for those at high-risk for CMV reactivation (CMV seropositive recipient and/or donor).

6. Immunoglobulin replacement: Controversial. If IgG level is below 500, consider replacement every three to four weeks until day 90 post transplant.

7. Stress ulcer prophylaxis (omeprazole or ranitidine).

8. Lab monitoring for blood chemistries (daily), CBC (daily), CMV antigenemia (weekly or bi-weekly), blood cultures (weekly), surveillance cultures (weekly).

CHRONIC GRAFT-VERSUS-HOST DISEASE

Diagnosis: The diagnosis of chronic GVHD is generally made on clinical and laboratory parameters. Because the therapies for chronic GVHD are highly immunosuppressive and must be continued for a prolonged time, it is important to confirm the diagnosis by biopsy and rule out other etiologies such as drug eruption and infection before initiating therapy. Histopathologic findings in lichenoid form of chronic GVHD resemble those in idiopathic lichen planus. These include hyperkeratosis, acanthosis, dyskeratosis, and vacuolar alterations in the basal cell layer, together with monocytic and lymphocytic infiltrates in the papillary dermis (level of evidence IIa) (recommendation grade B)^[20]. The lesions heal without dermal fibrosis or loss of elastic tissue. In contrast, the sclerodermatous form of chronic GVHD is associated with sclerosis and thickening of the reticular dermis, loss of distinction between the papillary and reticular dermis plus loss of rete pegs due to increased collagen deposition, and a mild perivascular lymphocytic infiltrate. Characteristically, the sweat glands are infiltrated with lymphocytes and melanophages.

The diagnosis of chronic GVHD is traditionally made after day 100 posttransplant although there is no biologic reason for this distinction since chronic GVHD can occur before day 100. Recent IBMTR/NMDP data showed that the median time of diagnosis of chronic GVHD is 4.5 months after HLA-identical sibling transplant and four months after unrelated donor transplant, with only 5% of cases diagnosed after one year (level of evidence III) (recommendation grade B)^[21].

Clinical manifestations 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 gastrointestinal tract/weight loss (16-26%), lung (10-15%), esophagus (6-8%), and joints (2-12%) (level of evidence III) (recommendation grade B)^[21,22]. Neuromuscular, genitourinary, and serosal involvements are even more rare. Chronic GVHD causes profound immune dysfunction, (level of evidence III) (recommendation grade B) and most chronic GVHD deaths are secondary to infection^[23,24]. Increased susceptibility to infection is attributable to both features of the disease and its treatment. The basis for impaired immunity is multifactorial and includes disrupted mucosal barriers, thymic injury, hypogammaglobulinemia, and qualitative T-cell and B-cell abnormalities (level of evidence IIa) (recommendation grade B)^[25,26]. Functional asplenia with an increased susceptibility to encapsulated bacteria is common, and circulating Howell-Jolly bodies may be seen on peripheral blood smear. All patients should be carefully monitored for bacterial, viral and fungal infections. Patients are particularly at risk for invasive fungal infections and *Pneumocystis carinii* pneumonia (PCP). Therefore antimicrobial prophylaxis is indicated until patients off of immunosuppressive regimens.

Clinical grading/classification of chronic GVHD: The most commonly employed clinical grading system is the "limited/extensive" classification proposed by Seattle in 1980 based on a retrospective clinical and pathological review of 20 patients with chronic GVHD (level of evidence III) (recommendation grade B)^[27]. Although this classification is highly reproducible (level of evidence III) (recommendation grade B), it provides little information about prognosis and is of limited clinical utility (level of evidence IIb) (recommendation grade B)^[28,29]. Beyond separating patients needing treatment (extensive GVHD) from those

who do not (limited GVHD) (level of evidence III) (recommendation grade B)^[21]. Furthermore, review of data from HLA-matched sibling recipients reported to the IBMTR suggests that transplant centers are not applying the formal definitions accurately, perhaps in part because many patients are unclassifiable by the strict organ criteria (level of evidence III) (recommendation grade B)^[21]. Therefore, the current system of grading chronic GVHD as limited or extensive has severe limitations. The significant proportion of patients falls into the extensive chronic GVHD category and there is great heterogeneity in manifestations of chronic GVHD and patient outcomes within this group.

The Seattle group has developed revised clinical criteria for limited and extensive chronic GVHD in order to clarify ambiguities of the original definition. In the revised classification, prolonged treatment with systemic immunosuppression is indicated for patients with clinically extensive chronic GVHD or anyone with high-risk features (i.e., platelets count $< 100 \times 10^9/L$, progressive onset, or receiving treatment with corticosteroids at the time of the diagnosis of chronic GVHD (level of evidence IV) (recommendation grade C).

Recently, we reported a new prognostic grading system for chronic GVHD that stratifies patients into risk categories according to whether or not extensive skin involvement (ESI), thrombocytopenia (TP), and progressive-type onset (PTO) is present at diagnosis (level of evidence IIa) (recommendation grade B)^[30]. In the recent update, a simple three-factor clinical grading system that predicted ten-year rates of survival without recurring malignancy ranging from 9% to 90% (level of evidence IIa) (recommendation grade B)^[31]. The difference in survival at 10 years was 30% between favorable-and intermediate-risk groups and 50% between intermediate-and high-risk groups. This data set included many patients transplanted before 1990 and median follow-up was over eight years. A new prognostic score (PS) was calculated for each

patient using the weighted averages of these three risk factors. The hazard ratio (HR) for mortality of the patients with $0 < PS < 2$ (TP and PTO or only 1 RF, intermediate-risk group) compared to those with $PS = 0$ (no RF, favorable-risk group) was 3.7; the HR for patients with $PFS \geq 2$ (more than 1 RF, high-risk group) compared to those with $0 < PFS < 2$ was 6.9. The probability of survival at 3 years for 54 patients with PS of 0 was 92%, 47 patients with $PS < 2$ had 71% and 50 patients with $PS \geq 2$ had 9% probability of survival at 3 years (level of evidence IIa) (recommendation grade B)^[31]. The validity of this new prognostic grading was recently tested using multiple data sets that included a total of 1105 patients from three different transplant center and the IBMTR (Table 2). For each data set, the proposed grading system identified three prognostic groups, each with different survival outcomes (level of evidence IIa) (recommendation grade B)^[32]. While the HR for mortality of the patients with $0 < PS < 2$ vs. those with $PS = 0$ ranged from 2.3 to 8.9 across the centers; it was between 1.6 to 6.9 for patients with $PS \geq 2$ vs. $0 < PS < 2$ (level of evidence IIa) (recommendation grade B)^[32]. The model was predictive of chronic GVHD-specific survival but the mortality hazard associated with ESI was lower in each of these test samples compared to the Hopkins sample possibly because of the variability and inconsistency in the skin extent data collected by the centers. The new clinical grading based on the model appears promising because of its utility across multiple independent data sets.

Prevention of chronic GVHD: Therapies that prevent the development of chronic GVHD have been largely unsuccessful except for T-cell depletion from the graft (level of evidence IIa) (recommendation grade B) and use of umbilical cord blood as a stem cell source since lower rates of both acute and chronic GVHD are observed with these approaches (level of evidence IIa) (recommendation grade B)^[33-35]. Various immunosuppressive drugs or regimens were studied to reduce the inci-

dence of chronic GVHD without success. Extended cyclosporine administration has initially been reported to reduce the incidence of chronic GVHD (level of evidence III) (recommendation grade B)^[36]. Seattle group recently reported the incidence of clinical extensive chronic GVHD and other transplant outcomes among recipients randomly assigned to receive a 24-month or a six-month course of cyclosporine prophylaxis after transplantation of allogeneic marrow from an HLA-identical sibling or alternative donor. Clinical extensive chronic GVHD developed in 35 of the 89 patients (39%) in the 24-month group and 37 of the 73 patients (51%) in the 6-month group. The hazard of developing chronic GVHD was not significantly different in the two groups. In addition, there were no significant differences between the two groups in transplantation-related mortality, survival, or disease-free survival (level of evidence Ib) (recommendation grade A)^[37].

A phase II trial in matched unrelated marrow recipients who were given FK506 (tacrolimus) and methotrexate prophylaxis yielded a cumulative incidence of chronic GVHD of 48% (level of evidence IIa) (recommendation grade B) less than the 64% incidence observed in the past with cyclosporine/methotrexate combination (level of evidence III) (recommendation grade B)^[22,38]. In a consecutive series of 116 evaluable HLA-identical blood stem cell transplant recipients, GVHD prophylaxis with tacrolimus and methotrexate was significantly associated with a three-fold reduced risk of chronic GVHD by multivariate analysis (level of evidence IIa) (recommendation grade B)^[39]. A phase III trial comparing FK-506 and methotrexate and cyclosporine plus methotrexate was recently completed. There was no difference in the incidence of chronic GVHD between the tacrolimus and the cyclosporine group (55.9% and 49.4%, respectively). However, there were a significantly higher proportion of patients in the cyclosporine group who had clinical extensive chronic GVHD (level of evidence Ib) (recommendation grade

A)^[10]. A recent trial using a triple drug combination including tacrolimus, methotrexate, and methylprednisolone failed to reduce the occurrence of chronic GVHD (level of evidence III) (recommendation grade B)^[40].

Patient evaluation: Once the diagnosis of chronic GVHD has been suspected clinically and confirmed histologically, the extent of involvement must be ascertained. A comprehensive initial evaluation can then be used as a baseline to assess progression of the disease or response to therapy. Elements of the initial and subsequent evaluations are shown in Table 3 (level of evidence IIa, IV) (recommendation grade B)^[41,42].

Treatment of chronic GVHD: The most successful treatment of patients with chronic GVHD results when a systematic approach to diagnosis, evaluation, and co-ordinated management is undertaken by a multidisciplinary team whose members share an interest in this complex disorder. In addition to bone marrow transplant physicians and nurses, team members should include dermatologists, ophthalmologists, dentists, dieticians, physical and occupational therapists, and social workers. Pathologists with expertise in the histologic features of GVHD are crucial. Because chronic GVHD can affect virtually any organ system, consultants in subspecialty areas such as rehabilitation medicine, gastroenterology, pulmonary medicine, neurology, and infectious diseases that are experienced in seeing patients with chronic GVHD can be invaluable resources to the team. Even if the patient is unable to return to the transplant center, this team should be able to help in management issues (level of evidence IIa, IV) (recommendation grade B)^[42].

Primary Immunosuppressive Treatment

1. Gold standard: Patients are initially treated with daily prednisone at 1 mg/kg per day and daily CsA at 10 mg/kg per day, divided into 2 doses based on ideal or actual weight, whichever is lower. If chronic GVHD is

stable or improving after two weeks, prednisone is tapered by 25% per week to a target dose of 1 mg/kg every other day. Once the steroid taper has been completed without a flare in GVHD, CsA is reduced by 25% per week to alternate day dosing such that the patient takes CsA (10 mg/kg in 2 divided doses) one day and alternates with prednisone (1 mg/kg) the next day (level of evidence IIa, IV) (recommendation grade B)^[42].

Patients are evaluated at 3 months after alternate day dosing is achieved. The 3-month time frame for evaluation of response to a given therapy is based on our own observation that 90% of patients who are ultimately going to respond to therapy will show signs of response at that point (level of evidence IIa, IV) (recommendation grade B)^[43].

If the disease has completely resolved, patients are gradually weaned from medication, with dose reductions made approximately every two weeks. Patients who continue to respond (incomplete response) are kept on the same therapy and are re-evaluated in another three months. Once patients reach their maximal response, therapy is continued for another three months (total of 9 months) and then weaned from both medications, with dose reductions approximately every two weeks. For those who have not responded by the initial 3-month time point or

who progress while on therapy, alternative salvage regimens should be instituted (level of evidence IIa, IV) (recommendation grade B)^[42].

2. Cyclosporine prednisone vs. prednisone alone: Although this regimen of alternating CSA and prednisone is widely employed for the treatment of high-risk (platelet count < 100,000/ μ L) extensive GVHD, until recently, there was no data on its effectiveness in standard risk patients. Flowers recently reviewed the success of initial combination therapy for patients treated in the 1980's. She reported a non-relapse mortality of 21% in standard risk patients (N= 126) and 39% in high-risk (N= 111) patients, 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 (level of evidence IIa) (recommendation grade B)^[44]. Seattle group has recently reported the results on a study comparing prednisone alone to prednisone plus CSA in patients without thrombocytopenia in 287 evaluate patients with extensive GVHD (level of evidence Ib) (recommendation grade A)^[45].

Prednisone was administered initially at a dose of 1.0 mg/kg per day orally for two weeks, followed by a prolonged taper (1 mg/kg

Table 2. Proposed new prognostic grading system for chronic GVHD at initial diagnosis^[32]

Grade	Risk factors	Hazard Ratio (95% CIs)	Survival 10-year	p
I	None	1.00	84%	-
II	Presence of one risk factor (extensive (> 50% BSA) skin GVHD or thrombocytopenia or progressive-type of onset) or Combination of thrombocytopenia and progressive-type onset	3.7 (1.4-9.3)	59%	0.007
III	Presence of at least two risk factors including extensive skin GVHD	25 (10.3-60.1)	9%	< 0.001

qod to week 20-22, 0.5 mg/kg qod to week 40, then STOP if no cGVHD) and cyclosporine was administered at 6 mg/kg orally twice daily every other day until week 40. PRED/CSA appeared equivalent in efficacy and survival to PRED alone. Adding CSA decreased overall use of steroids (as evidenced by decreased rates of glucocorticoid morbidities). In high-risk, progressive onset cGVHD patients, CSA did not improve survival (level of evidence Ib) (recommendation grade A)^[45].

The hazards of transplant-related mortality, overall mortality, recurrent malignancy, secondary therapy and discontinuation of all immunosuppressive therapy were not significantly different between the two arms, but survival without recurrent malignancy was better in prednisone-only arm ($p=0.03$) although the incidence of avascular necrosis was also higher. Eighteen (13%) of the 142 patients in the CSP plus prednisone arm and 32 (22%) of the 145 patients in the prednisone arm developed avascular necrosis ($p=0.04$). Thus, there is no evidence that initial combination therapy improved control of chronic GVHD in patients with platelet counts greater than $100 \times 10^9/L$. These results contradict our knowledge that administration of CSP reduces transplant-related mortality among patients with chronic GVHD. The uncertainty regarding the choice of front-line 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.

Salvage immunosuppressive therapies:

Approximately one-third of patients do not respond to initial steroid based therapy. Steroid-refractory chronic GVHD is formally defined as either failure to improve after at least two months, or progression after one month of standard immunosuppressive therapy including corticosteroids and cyclosporine (level of evidence IIb) (recommendation grade B)^[46,47]. There is no standard approach for patients who are refractory to initial

therapy. Again, the best choice is a clinical trial. A number of phase II trials of secondary or salvage regimens have been published, and most report a success rate of 25-50%. However, most trials contain 40 or fewer patients. Reported response rates are usually based on four 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) (level of evidence IIa) (recommendation grade B)^[46,48]. For patients receiving steroids alone or an investigational therapy, combination CsA and steroids, as outlined above, is the first choice. For patients who have not responded or who have had recurrences after CsA plus prednisone, there are several potential therapies. The survival rate is approximately 75% in patients who were treated with alternating cyclosporine/steroid or thalidomide after failure to initial steroid therapy (level of evidence IIa, III) (recommendation grade B)^[48,49].

The status of patients' responsiveness to further immunosuppressive therapy can be predicted by a short course high dose (pulse) corticosteroid therapy. Methylprednisolone at 10 mg/kg/day was given for 4 days in our recent pulse therapy regimen (level of evidence III) (recommendation grade B)^[50]. If disease progression is not controlled (no major response) after pulse steroid, novel treatment modalities should be investigated under clinical protocols.

3. Tacrolimus (FK506): The pharmacology of this drug, with highest concentrations achieved in the liver, make it particularly appealing for patients with hepatic disease, though this initial report did not demonstrate such an effect in the liver. A retrospective review of 26 patients with refractory chronic GVHD treated with this steroid-sparing combination showed that it was well tolerated, and nearly half the patients showed an objective response (level of evidence III) (recommendation grade B)^[51]. A recent phase II

study from Seattle reported a modest response to tacrolimus (level of evidence IIa, IV) (recommendation grade B)^[52].

A total of 39 evaluable patients with chronic GVHD who failed previous immunosuppressive therapy with cyclosporine and prednisone were treated with tacrolimus. A total of 31 patients (79%) experienced treatment failure. Infections were the most frequent adverse event. Nephrotoxicity occurred in 16 patients (41%); tacrolimus was discontinued in only two patients because of progressive deterioration in renal function. Seven patients had discontinued all immunosuppression at last contact, leading to an estimated 29% probability of stopping all immunosuppression by 3 years posttransplantation.

4. Thalidomide: In a second phase II study Parker et al from City of Hope treated 80 patients with steroid-refractory chronic GVHD with thalidomide. Sixteen patients (20%) had a sustained response, nine with a complete remission and seven with a partial response. Twenty-nine patients (36%) had thalidomide discontinued because of side effects, which included sedation, constipation, neuritis, skin rash, and neutropenia. Side effects were reversible with drug discontinuation except for mild residual neuritis in one case (level of evidence IIa) (recommendation grade B)^[46]. Other investigators also witnessed the high side effect profile with thalidomide. In a recent randomized, placebo-controlled, double-blinded trial, thalidomide or placebo together with glucocorticoids and either cyclosporine or tacrolimus was administered as initial therapy for clinical extensive chronic GVHD. All patients had thrombocytopenia or progressive-type of onset (high-risk). Thalidomide was administered initially at a dose of 200 mg orally per day, followed by a gradual increase to 800 mg/d if side effects were tolerable. Treatment with the study drug was discontinued before resolution of chronic GVHD in 23 (92%) of the 25 patients because of neutropenia and neurologic symptoms (level of evidence Ib) (recom-

mendation grade A)^[53]. Thalidomide should not be considered for patients with preexisting neuropathies, and the sedation and constipation seen with thalidomide may be intolerable to some patients.

5. PUVA: Patients with refractory lichenoid GVHD may also benefit from the addition of nonpharmacologic approaches, such as PUVA (8-methoxypsoralen plus ultraviolet A irradiation). In a review of 40 patients treated with PUVA at Johns Hopkins dermal responses were observed in 31 of 40 patients including 16 complete responses (level of evidence IIa) (recommendation grade B)^[54]. Minimal improvement was noted at extracutaneous sites. PUVA was well tolerated except for three patients who had therapy discontinued after phototoxicity (burn). PUVA is very difficult to administer to sclerodermatous GVHD and does not have significant effect on disease resolution.

6. Photopheresis: Extracorporeal photopheresis (EP), extracorporeal exposure of peripheral blood mononuclear cells to a photosensitizing compound and UV-A light to selectively eliminate lymphocytes, is another therapeutic intervention which has demonstrated efficacy in patients with refractory acute and chronic GVHD (level of evidence IIa) (recommendation grade B)^[55-57]. Clinical responses have been reported in skin and visceral GVHD. EP has also been reported by other investigators to be useful in chronic GVHD with improvement in oral manifestations, sclerodermatous involvement, and joint contractures (level of evidence III) (recommendation grade B)^[58,59]. A group of investigator from Boston treated 10 patients who had refractory chronic GVHD with ECP. Seven patients had a response and three had no change in clinical manifestations of chronic GVHD. One patient died from catheter-related sepsis (level of evidence IIb) (recommendation grade B)^[60]. However, the mechanics of this therapy, including the need for a long-term pheresis catheter and the location of the machine to deliver the therapy, have made it difficult to do trials with this appro-

ach. 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.

7. Total lymphoid irradiation: Low dose total lymphoid irradiation was also reported to lead to improvement. In a very recent study, 40 patients with refractory chronic GVHD were given a total dose of 1 Gy to the abdomen midline with a median dose rate of 0.5 Gy/min. A clinical response was observed in 90% of patients at a median of two months after low dose throacoabdominal irradiation. Overall complete resolution of chronic GVHD was observed in 21% of patients at one year. Majority of patients however continued to take immunosuppressive medications (level of evidence III) (recommendation grade B)^[61].

New Immunomodulatory Approaches

Various new immunomodulatory methods are actively explored in the treatment of chronic GVHD. These include IL-2 receptor antagonists, anti-TNF approaches, pentostatin, sirolimus (level of evidence III) (recommendation grade B). However, all of these treatments are in their experimental stage and they should only be used under protocol or in select cases.

Adjunctive Therapies in Chronic GVHD

Adjunctive therapies have been developed to improve the effects of immunosuppressive treatments and patients' functional status. Particularly challenging are those patients with refractory sclerodermatous chronic GVHD.

1. Topical therapy: Although virtually all patients with extensive disease require systemic therapy, patients with symptomatic disease limited to the oral cavity may benefit from topical steroids, thus, sparing them the effects of systemic immunosuppression. Decadron elixir (0.5 mg/5 mL) can be effective local therapy when the patient rinses the

mouth with 10 mL for 2 to 3 minutes at least 4 times a day (level of evidence IIa, IV) (recommendation grade B)^[42].

2. Retinoids: Etretinate is a synthetic retinoid that has been used to treat patients with systemic scleroderma. Based on reports of response in this patient population, it has been used to treat patients with sclerodermatous and fascial chronic GVHD (level of evidence IIa) (recommendation grade B)^[62]. Etretinate is not currently commercially available and acitretin, a more rapidly cleared derivative, has been used in its place. In patients responding to treatment, we usually add acitretin to the main immunosuppressive therapy to increase the cutaneous response. In addition, in patients without evidence of sclerodermatous disease worsening after immunosuppression, acitretin can be used to try to decrease sclerosis.

3. Hydroxychloroquine: Plaquenil (hydroxychloroquine) is an antimalarial drug used in the treatment of autoimmune diseases. It interferes with antigen presentation and cytokine production, and is synergistic with CSA and tacrolimus in vitro. This drug appears to be effective and relatively nontoxic adjunctive treatment of chronic GVHD. In patients who do not tolerate acitretin because of skin drying, flaking, or ulceration, plaquenil (Sanofi Winthrop) is an alternative drug to add to the immunosuppressive regimen (level of evidence III) (recommendation grade B)^[63].

Supportive Therapy in Chronic GVHD

1. Infection Prophylaxis

Infection is the primary cause of death in patients with chronic GVHD. All patients should receive antimicrobial prophylaxis. It should include *Pneumocystis carinii* prophylaxis (such as TMP-SMX) and prophylaxis against encapsulated organisms including pneumococcus (such as penicillin). Patients receiving topical steroid therapy for oral GVHD should be treated with clotrimazole troches or nystatin swishes. If thrush occurs despite this, systemic antifungal therapy is

indicated (level of evidence IIa, IV) (recommendation grade B)^[42].

Patients should receive prophylactic acyclovir for prevention of VZV infection during the first year after the transplant and later if systemic immunosuppression is still needed to control chronic GVHD. Patients who are not on antiviral prophylaxis should be followed closely for herpetic infections, especially those with oral GVHD. Chronic GVHD patients who are at risk for late cytomegalovirus (CMV) disease (receiving systemic corticosteroids) should also have CMV activity monitored closely, and treatment initiated at reactivation. A positive antigenemia test should be treated preemptively with ganciclovir, and immunoglobulin infusions should be added to the treatment for those with evidence of pulmonary disease CMV disease, detected by imaging studies. Additional protection is afforded patients by supplemental intravenous IgG therapy if they have very low serum IgG levels and recurrent infections (level of evidence IIa, IV) (recommendation grade B)^[42].

Vaccination series should be delayed until one year after the completion of GVHD therapy because most patients will not mount an immune response with active disease or while receiving immunosuppressive medications. Vaccinations used in transplant recipients should be delayed until one year after GVHD therapy has been completed and then only given when there is no evidence of active disease. Antibody titers can be used to check responses to vaccines that are typically given to patients after SCT, such as inactivated polio, diphtheria, and tetanus toxoid. Patients can also be immunized against polyvalent influenza, pneumococcus, and *Haemophilus influenzae* B at that time. Live virus vaccines such as measles, mumps, rubella (MMR); oral poliovirus; oral typhoid; and bacillus Calmette Guerin (BCG) should not be given to immunocompromised host. Clinical studies suggest that MMR can be given two years after transplantation in individuals who are free of chronic GVHD. Posttransplant vaccination guidelines are available on the Centers for Disease Control and Prevention web site

(www.cdc.gov/mmwr/mmwr_rr.html) (level of evidence IIa, IV) (recommendation grade B)^[64].

2. Symptom management in chronic GVHD (level of evidence IIa, IV) (recommendation grade B) see Table 3^[42]

a. Skin care: Dry skin should be aggressively lubricated. Agents that are free of perfume and preservatives are best. Petroleum jelly offers excellent lubrication, but patients often complain about its messiness. Patients should avoid sunburn and should wear sunscreen with a skin protection factor of at least 15. For those whose sweat glands are affected, precautions must be taken to avoid overheating.

b. Management of sicca symptoms: For patients with ocular sicca syndrome, the use of preservative-free artificial tears at least every 4 hours during the day and preservative-free ointment at night is important. Protective eye- and sunglasses, frequent lubrication, can help symptomatically and prevent further damage. Placement of punctual plugs or cauterization may be of benefit to conserve corneal wetting in severely dry eye. Artificial saliva may be used for dry mouth. Pilocarpin has been reported to be helpful in alleviating dry mouth symptoms in chronic GVHD. Authors suggested a minimum of six to eight week of treatment before it is considered to have failed.

c. Muscle cramps: Electrolyte imbalances should be corrected. If the cramps persist, quinine may be added. If the cramps are disabling, dantrolene may be tried, but it must be used cautiously and monitored carefully because of the side effects muscle weakness, drowsiness, diarrhea, abnormal liver function findings, and sun sensitivity. It should not be used in patients treated with PUVA. Clonazepam treatment has been reported to improve muscle cramping, aches, and carpal spasm.

d. Cholestasis: Cholestasis secondary to hepatic chronic GVHD has been improved in

Table 3. Clinical manifestations and management of chronic GVHD

Organ	Clinical manifestation	Evaluation	Intervention
Skin	Erythematous papular rash (lichenoid) or thickened, tight, fragile skin (sclerodermatous)	Clinical and biopsy to confirm the diagnosis of GVHD	Moisturize (petroleum jelly), treat local infections, protect from further trauma
Nails	Vertical ridging, fragile	Clinical	Nail polish may help to decrease further damage Avoid excessive heat
Sweat glands	Destruction leading to risk of hyperthermia	Clinical	
Hair	Scalp and body hair is thin and fragile, can be partially or completely lost		
Eyes	Dryness, photophobia, and burning. Progression to corneal abrasion	Regular ophthalmologic evaluation including Schirmer's test	Preservative free tears during the day and preservative free ointment at night
Mouth	Dry, sensitivity to mint, spicy food, tomato. Whitish lace like plaques in the cheeks and tongue identical to lichen planus. Erythema and painful ulcerations, mucosal sclerosis with decreased sensitivity to temperature can also happen	Regular dental evaluation (with appropriate endocarditis prophylaxis). Viral and fungal cultures at diagnosis and at any worsening	Avoid foods, which are not tolerated. Regular dental care preceded by appropriate endocarditis prophylaxis
Respiratory tract	Bronchiolitis obliterans can manifest as dyspnea, wheezing, cough with normal CT scan and marked obstruction at pulmonary function tests. Chronic sinopulmonary symptoms and/or infections are also common	Pulmonary function tests including FEV ₁ , FVC, DLCO, and helium lung volumes. CT scan in symptomatic patients. With abnormal chest CT must rule out infections. Lung biopsy if clinically indicated	Investigational therapy
Gastrointestinal	Abnormal motility and strictures. Weight loss	Swallowing studies, endoscopy if clinically indicated. Nutritional evaluation	Systemic treatment of GVHD; endoscopic/surgical treatment of strictures. Nutritional intervention
Liver	Cholestasis (increased bilirubin, alkaline phosphatase). Isolated liver involvement needs histologic confirmation	Liver function tests. Liver biopsy if clinically indicated	No specific therapy is proven superior. FK506 may concentrate in the liver
Musculoskeletal	Fasciitis. Myositis is rare. Osteoporosis may occur secondary to hormonal deficits, use of steroids, decreased activity	Periodical physical therapy evaluation to document the range of motion. Bone density evaluation especially in patients using steroids	Aggressive physical therapy program
Immune system	Profound immunodeficiency. Functional asplenia. High risk of pneumococcal sepsis, PCP, and invasive fungal infections. Variable IgG levels	Assume all patients as severely immunocompromised and asplenic	PCP prophylaxis (until 6 months after no GVHD) and pneumococcal prophylaxis (lifetime). Delay vaccinations to 6 months after GVHD has resolved.
Hematopoietic system	Cytopenias. Occasional eosinophilia	Counts. Bone marrow aspirate and biopsy, antineutrophil and antiplatelet antibodies when indicated	Systemic treatment of GVHD
Others	Virtually all autoimmune disease manifestations have been described in association with chronic GVHD	As clinically indicated	

30% of patients treated with ursodeoxycholic acid (UDCA) therapy.

e. Wasting: Wasting is common in these patients, and malnutrition may result. Nutritional assessment and monitoring is important to maintain the patient's well being. Patients who are unable to maintain adequate caloric intake by mouth may need parenteral nutrition or enteral feeds through surgically placed tubes.

f. Osteoporosis: For patients who are receiving long-term corticosteroid therapy, estrogen replacement in young women, calcium supplements and biphosphonates should be considered for individuals at risk for osteopenia and bone fracture.

g. Joint contractures: A thorough physical therapy evaluation and an individually designed program of activities can be invaluable for maintaining and increasing strength, range of motion, and mobility. For patients with sclerodermatous chronic GVHD, range-of-motion exercises may preserve joint mobility and decrease the pain associated with joint contractures. Although detailed literature on its efficacy is lacking, it is our practice to have all patients evaluated by a physical therapist familiar with the disease.

Levels of evidence

Level	Type of evidence
Ia	Evidence obtained from meta-analysis of randomised controlled trials
Ib	Evidence obtained from at least one randomised controlled trial
IIa	Evidence obtained from at least one well-designed controlled study without randomisation
IIb	Evidence obtained from at least one other type of well-designed quasi-experimental study
III	Evidence obtained from well-designed nonexperimental descriptive studies, such as comparative studies, correlation studies and case control studies
IV	Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities

Grades of recommendation

Grade	Evidence level	Recommendation
A	Ia, Ib	Required—at least one randomised controlled trial as part of the body of literature of overall good quality and consistency addressing specific recommendation
B	IIa, IIb, III	Required—availability of well-conducted clinical studies but no randomised clinical trials on the topic of recommendation
C	IV	Required—evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities Indicates absence of directly applicable clinical studies of good quality

REFERENCES

1. Sale GE, Lerner KG, Barker EA, Shulman HM, Thomas ED. The skin biopsy in the diagnosis of acute GVHD in man. *Am J Pathology* 1977;89:621-35.
2. Sale GE, Shulman HM, Hackman RC. Pathology of hematopoietic cell transplantation. In: Thomas ED, Blume KG, Forman SJ (eds). *Hematopoietic Cell Transplantation*. Massachusetts: Blackwell Science, 1999:248-63.
3. Lerner KG, Kao GF, Storb R, et al. Histopathology of graft-versus-host reaction (GVHR) in human recipients of marrow from HLA-matched sibling donors. *Transplant Proc* 1974;6:389-93.
4. Spencer GD, Hackman RC, McDonald GB, et al. A prospective study of unexplained nausea and vomiting after marrow transplantation. *Transplantation* 1986;42:602-7.
5. Shulman HM, Sharma P, Amos D, Fenster LF, McDonald GB. A coded histological study of hepatic graft-versus-host disease after human transplantation. *Hepatology* 1988;8:463-70.
6. Storb R, Deeg HJ, Whitehead J, et al. Methotrexate and cyclosporine compared with cyclosporine alone for prophylaxis of acute graft-versus-host disease after marrow transplantation for leukemia. *N Engl J Med* 1986;314:729-35.
7. Storb R, Deeg HJ, Pepe M, et al. Methotrexate and cyclosporine versus cyclosporine alone for prophylaxis of acute graft-versus-host disease in patients given HLA-identical marrow grafts for leukemia: Long-term follow-up of a controlled trial. *Blood* 1989;73:1729-34.
8. Nash RA, Pepe MS, Storb R, et al. Acute graft-versus-host disease: Analysis of risk factors after allogeneic marrow transplantation and prophylaxis with cyclosporine and methotrexate. *Blood* 1992;80:1838-45.
9. Vogelsang GB. Cyclosporine administration guidelines. *Johns Hopkins University BMT Clinical Practice and Procedures Manual* 2001.
10. Ratanatharathorn V, Nash RA, Przepiorka D, Devine SM, Klein JL, Weisdorf D, Fay JW, Nademanee A, Antin JH, Christiansen NP, van der Jagt R, Herzog RH, Litzow MR, Wolff SN, Longo WL, Petersen FB, Karanes C, Avalos B, Storb R, Buell DN, Maher RM, Fitzsimmons WE, Wingard JR. Phase III study comparing methotrexate and tacrolimus (prograf, FK506) with methotrexate and cyclosporine for graft-versus-host disease prophylaxis after HLA-identical sibling bone marrow transplantation. *Blood* 1998;92:2303-14.
11. Bornhauser M, Thiede C, Schuler U, Platzbecker U, Freiberg-Richter J, Helwig A, Plettig R, Rollig C, Naumann R, Kroschinsky F, Neubauer A, Ehninger G. Dose-reduced conditioning for allogeneic blood stem cell transplantation: Durable engraftment without antithymocyte globulin. *Bone Marrow Transplant* 2000;26:119-25.
12. Przepiorka D, Cleary K. Therapy of acute graft-versus-host disease. In: Ball ED, Lister J, Law P (eds). *Hematopoietic Stem Cell Therapy*, Philadelphia PA: Churchill Livingstone, 2000:531-40.
13. Tutchka PJ, Farmer E, Beschorner WE, et al. Therapy of acute graft-versus-host disease (GVHD)- Baltimore experience. *Exp Hematol* 1981;9:26.
14. Van Lint MT, Uderzo C, Locasciulli A, et al. Early treatment of acute graft-versus-host disease with high or low-dose 6-methylprednisolone: A multicenter randomized trial from the Italian group for bone marrow transplantation. *Blood* 1998;92:2288-93.
15. Kendra J, Barret AJ, Lucas C, et al. Response of graft-versus-host disease to high doses of methylprednisolone. *Clin Lab Haematol* 1981;3:19-26.
16. Kanojia MD, Anagnostou AA, Zander AR, et al. High-dose methylprednisolone treatment of acute graft-versus-host disease after bone marrow transplantation in adults. *Transplantation* 1984;37:246-9.
17. Deeg HJ, Hanslee-Downee PJ. Management of acute GVHD. *Bone Marrow Transplant* 1990;6:1-8.
18. Hings IM, Severson R, Filipovich AH, et al. Treatment of moderate and severe acute GVHD after allogeneic bone marrow transplantation. *Transplantation* 1994;58:437-42.
19. Ely P, Dunitz J, Rogosheke J, et al. Use of a somatostatin analogue, octreotideacetate, in the management of acute gastrointestinal graft-versus-host disease. *Am J Med* 1991;90:707-10.
20. ER Farmer. The histopathology of graft-versus-host disease. *Adv Dermatol* 1986;1:173-88.
21. Lee SJ, Klein JP, Barrett AJ, et al. Severity of chronic graft-versus-host disease: Association with treatment-related mortality and relapse. *Blood* 2002;100:406-14.
22. Sullivan KM, Agura E, Anasetti C, et al. Chronic graft-versus-host disease and other late complications of bone marrow transplantation. *Semin Hematol* 1991;28:250-9.
23. Storek J, Witherspoon RP, Webb D, Storb R. Lack of B cells precursors in marrow transplant recipients with chronic graft-versus-host disease. *Am J Hematol* 1996;52:82-9.
24. Maury S, Mary JY, Rabian C, et al. Prolonged immune deficiency following allogeneic stem cell transplantation: Risk factors and complications in adult patients. *Br J Haematol* 2001;115:630-41.
25. Atkinson K, Farewell V, Storb R, et al. Analysis of the infections after human bone marrow transplantation: Role of genotypic nonidentity between marrow donor and recipient and of nonspecific suppressor cells in patients with chronic graft-versus-host disease. *Blood* 1982;60:714-20.

26. Lapp WS, Ghayur T, Mendes M, et al. The functional and histological basis for graft-versus-host-induced immunosuppression. *Immunol Rev* 1985;88: 107-33.
27. Shulman HM, Sullivan KM, Weiden PL, McDonald GB, Striker GE, Sale GE, Hackman R, Tsoi MS, Storb R, Thomas ED. Chronic graft-versus-host syndrome in man. A long-term clinicopathologic study of 20 Seattle patients. *Am J Med* 1980;69: 204-17.
28. Atkinson K, Horowitz MM, Gale RP, et al. For the Advisory Committee of the International Bone Marrow Transplant Registry. Consensus among bone marrow transplanters for diagnosis, grading and treatment of chronic graft-versus-host disease. *Bone Marrow Transplant* 1989;4:247-54.
29. Lee SJ, Vogelsang G, Gilman A, et al. A survey of diagnosis, management, and grading of chronic GVHD. *Biol Blood Marrow Transplant* 2002;8:32-9.
30. Akpek G, Zahurak ML, Piantadosi S, Margolis J, Doherty J, Davidson R, Vogelsang GB. Development of a prognostic model for grading chronic graft-versus-host disease. *Blood* 2001;97:1219-26.
31. Akpek G. Clinical grading in chronic graft-versus-host disease: Is it time for change? *Leuk Lymphoma* 2002;43:1211-20.
32. Akpek G, Lee SJ, Flowers ME, Pavletic SZ, Arora M, Lee S, Piantadosi S, Guthrie KA, Lynch JC, Takatu A, Horowitz MM, Antin JH, Weisdorf DJ, Martin PJ, Vogelsang GB. Performance of a new clinical grading system for chronic graft-versus-host disease: A Multi-Center Study. *Blood* 2003, in press.
33. Horowitz MM, Gale RP, Sondel PM, et al. Graft-versus-leukemia reactions after bone marrow transplantation. *Blood* 1990;75:555-62.
34. Kurtzberg J, Laughlin M, Graham ML, et al. Placental blood as a source of hematopoietic stem cells for transplantation into unrelated recipients. *N Engl J Med* 1996;335:157-66.
35. Gluckman E, Rocha V, Boyer-Chammard A, et al. Outcome of cord-blood transplantation from related and unrelated donors. Eurocord Transplant Group and the European Blood and Marrow Transplantation Group. *N Engl J Med* 1997;337:373-81.
36. Lonnqvist B, Aschan J, Ljungman P, Ringden O. Long term cyclosporine therapy may decrease then risk of chronic graft-versus-host disease. *Br J Haematol* 1990;74:547-8.
37. Kansu E, Gooley T, Flowers ME, Anasetti C, Deeg HJ, Nash RA, Sanders JE, Witherspoon RP, Appelbaum FR, Storb R, Martin PJ. Administration of cyclosporine for 24 months compared with 6 months for prevention of chronic graft-versus-host disease: A prospective randomized clinical trial. *Blood* 2001;98:3868-70.
38. Nash RA, Pineiro LA, Storb R, et al. FK506 in combination with methotrexate for the prevention of graft-versus-host disease after marrow transplantation from matched unrelated donors. *Blood* 1996;88: 3634-41.
39. Przepiorka D, Anderlini P, Saliba R, Cleary K, Mehra R, Khouri I, Huh YO, Giralt S, Braunschweig I, van Besien K, Champlin R. Chronic graft-versus-host disease after allogeneic blood stem cell transplantation. *Blood* 2001;98:1695-700.
40. Ogawa H, Soma T, Hosen N, Tatekawa T, et al. Combination of tacrolimus, methotrexate, and methylprednisolone prevents acute but not chronic graft-versus-host disease in unrelated bone marrow transplantation. *Transplantation* 2002;74:236-43.
41. Wingard J, Vogelsang GB, Deeg HJ. *ASH Hematology Education Book*, 2002.
42. Vogelsang GB. How I treat chronic graft-versus-host disease. *Blood* 2001;97:1196-201.
43. Wingard JR, Piantadosi S, Vogelsang GB, et al. Predictors of death from chronic graft-versus-host disease after bone marrow transplantation. *Blood* 1989;74:1428-35.
44. Flowers MED. Traditional treatment of chronic graft-versus-host disease. *Blood and Marrow Transplantation Reviews* 2002;12:5-8.
45. Koc S, Leisenring W, Flowers ME, Anasetti C, Deeg HJ, Nash RA, Sanders JE, Witherspoon RP, Storb R, Appelbaum FR, Martin PJ. Therapy for chronic graft-versus-host disease: A randomized trial comparing cyclosporine plus prednisone versus prednisone alone. *Blood* 2002;100:48-51.
46. Parker PM, Chao N, Nademanee A, et al. Thalidomide as salvage therapy for chronic graft-versus-host disease. *Blood* 1995;86:3604-9.
47. Browne PV, Weisdorf DJ, DeFor T, Miller WJ, Davies SM, Filipovich A, McGlave PB, Ramsay NK, Wagner J, Enright H. Response to thalidomide therapy in refractory chronic graft-versus-host disease. *Bone Marrow Transplant* 2000;26:865-9.
48. Vogelsang GB, Farmer ER, Hess AD, et al. Thalidomide for the treatment of chronic graft-versus-host disease. *N Engl J Med* 1992;326:1055-8.
49. Sullivan KM, Mori M, Sanders J, et al. Late complications of allogeneic and autologous marrow transplantation. *Bone Marrow Transplant* 1992;10:127-34.
50. Akpek G, Lee SM, Anders V, Vogelsang GB. A high-dose pulse steroid regimen for controlling active chronic graft-versus-host disease. *Biol Blood Marrow Transplant* 2001;7:495-502.
51. Mookerjee B, Altomonte V, Vogelsang G. Salvage therapy for refractory chronic graft-versus-host disease with mycophenolate mofetil and tacrolimus. *Bone Marrow Transplant* 1999;24:517-20.
52. Carnevale-Schianca F, Martin P, Sullivan K, Flowers M, Gooley T, Anasetti C, Deeg HJ, Furlong T, McSweeney P, Storb R, Nash RA. Changing from

- cyclosporine to tacrolimus as salvage therapy for chronic graft-versus-host disease. *Biol Blood Marrow Transplant* 2000;6:613-20.
53. Koc S, Leisenring W, Flowers ME, Anasetti C, Deeg HJ, Nash RA, Sanders JE, Witherspoon RP, Appelbaum FR, Storb R, Martin PJ. Thalidomide for treatment of patients with chronic graft-versus-host disease. *Blood* 2000;96:3995-6.
 54. Vogelsang GB, Wolf D, Altomonte V, et al. Treatment of chronic graft-versus-host disease with ultraviolet radiation and psoralen (PUVA). *Bone Marrow Transplant* 1996;17:1061-7.
 55. Greinix HT, Volc-Platzer B, Rabitsch W, Gmeinhart B, Guevara-Pineda C, Kalhs P, Krutmann J, Honigsmann H, Ciovica M, Knobler RM. Successful use of extracorporeal photochemotherapy in the treatment of severe acute and chronic GVHD. *Blood* 1998;92:3098-104.
 56. Child FJ, Ratnavel R, Watkins P, Samson D, Apperley J, Ball J, Taylor P, Russell-Jones R. Extracorporeal photopheresis (ECP) in the treatment of chronic graft-versus-host disease (GVHD). *Bone Marrow Transplant* 1999;23:881-7.
 57. Foss FM, Görgün G, Miller KB. Extracorporeal photopheresis in chronic graft-versus-host disease. *Bone Marrow Transplant* 2002;29:719-25.
 58. Owsianowski M, Gollinck H, Siegert W, et al. Successful treatment of chronic graft-versus-host disease with extracorporeal photopheresis. *Bone Marrow Transplant* 1994;14:845-8.
 59. Rosetti F, Zulian F, Dall'Amico R, et al. Extracorporeal photochemotherapy as single therapy for extensive, cutaneous, chronic graft-versus-host disease. *Transplantation* 1995;59:149-51.
 60. Alcindor T, Görgün G, Miller KB, Roberts TF, Sprague K, Schenkein DP, Foss FM. Immunomodulatory effects of extracorporeal photochemotherapy in patients with extensive chronic graft-versus-host disease. *Blood* 2001;98:1622-5.
 61. Guardiola P, Fernandez G, Girinski T, Socie G, Ribaud P, Esperou H, Gluckman E, Devergie A. Low-dose Thoracoabdominal irradiation for the treatment of refractory chronic GVHD (abstract). *Blood* 2002;100(Suppl 1):3341a.
 62. Marcellus DC, Altomonte VL, Farmer ER, Horn TD, Freemer CS, Grant J, Vogelsang GB. Etreinate therapy for refractory sclerodermatous chronic graft-versus-host disease. *Blood* 1999;93:66-70.
 63. Gilman AL, Chan KW, Mogul A, Morris C, Goldman FD, Boyer M, Cirenza E, Mazumder A, Gehan E, Cahill R, Frankel S, Schultz K. Hydroxychloroquine for the treatment of chronic graft-versus-host disease. *Biol Blood Marrow Transplant* 2000;6:327-34.
 64. Guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. *Biol Blood Marrow Transplant* 2000;6:659-713, 715,717-27.

Address for Correspondence:

Görgün AKPEK, MD

Attending Physician in Blood and Marrow Transplantation Program at University of Maryland Greenebaum Cancer Center, Maryland, USA