

Chronic graft-versus-host disease after allogeneic stem cell transplantation

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ABSTRACT

Chronic Graft-versus-Host disease (chronic GVHD) is a clinicopathological syndrome which is the major determinant of long-term outcome and quality of life after allogeneic bone marrow or peripheral stem cell transplantation. Chronic GVHD may develop within 3 to 18 months after allografting and occurs in approximately 33% of HLA-identical sibling recipients and 50-70% of recipients of unrelated or mismatched-related marrow grafts. Individuals with the limited chronic GVHD have a favorable course and patients with extensive chronic GVHD have an unfavorable natural history. Chronic GVHD is a pleiotropic disease with clinical and pathological signs and symptoms similar to several naturally occurring autoimmune disorders. Organ involvement in extensive chronic GVHD affects the skin, mouth, eyes, sinuses, gastrointestinal tract, lungs, muscles, tendons, serous surfaces and nerves. Owing to the prolonged time to immunological recovery sinopulmonary infections may be common in patients with chronic GVHD. In standard-risk chronic GVHD patients early treatment with prednisone and cyclosporine has better results in high-risk patients. New treatment approaches include the use of FK506, thalidomide, mycophenolate mofetil, rapamycin and extracorporeal photopheresis. Supportive care includes correction of hypogammaglobulinemia and administration of antibiotics to reduce the risk of infection. [Turk J Cancer 2003;33(1):9-22]

KEY WORDS:

Chronic Graft-versus-Host disease, late effects of stem cell transplantation, bone marrow transplantation, late complications

INTRODUCTION

Hematopoietic stem cell transplantation has evolved into an accepted treatment for a variety of hematological, neoplastic and immunological diseases. Long-term follow-up monitoring of all transplant recipients are essential for observing interrelationships and times of onset of potential late complications (Figure 1).

Chronic GVHD is a distinct clinicopathological syndrome which is the major determinant of long-term outcome (mortality) and quality of life (morbidity) after allogeneic bone marrow transplantation and may develop within 3 to 18 months after allografting and occurs in approximately 33% of HLA-identical sibling recipients and 50-70% of recipients of unrelated or mismatched-related marrow grafts (1-3). Chronic GVHD is an immunologic disorder presumed to be initiated by immunocompetent and viable donor lymphocytes recognizing and reacting against recipient (patient=host) tissue antigens of variety of tissues. Chronic GVHD usually develops after Day +80 of allogeneic stem cell transplantation and it involves several organs. Chronic GVHD is a well-defined clinical and pathological entity which have features quite similar to autoimmune disorders such as

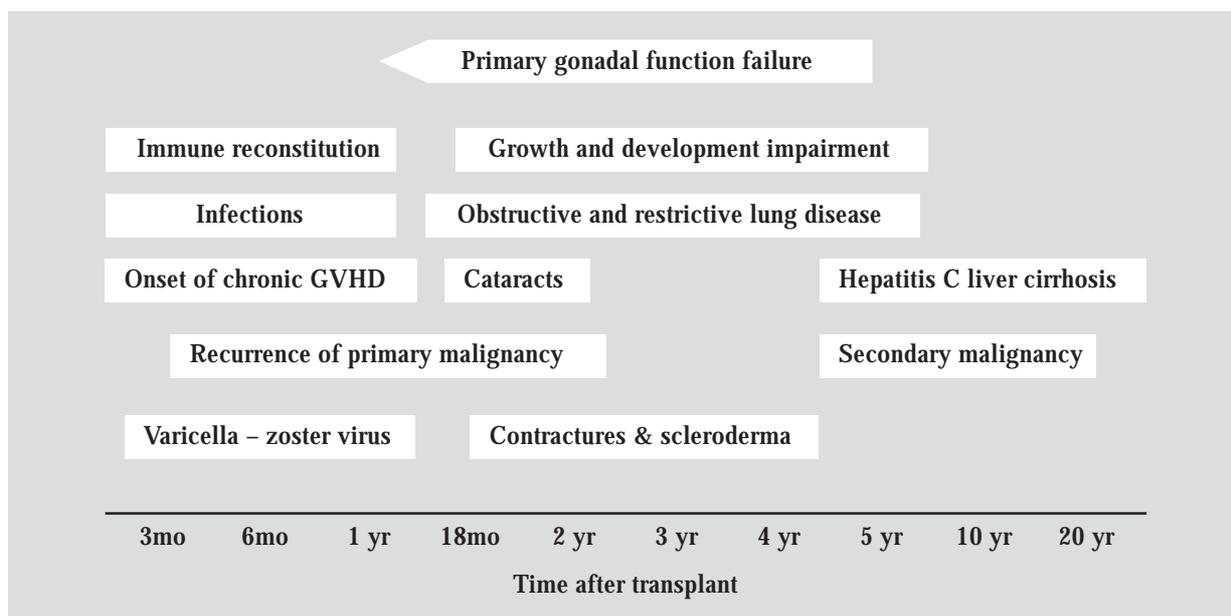


Fig1. Late complications of hematopoietic stem cell transplantation (3)

scleroderma, systemic lupus erythematosus, Sjogren's syndrome, rheumatoid arthritis and primary biliary cirrhosis (4). Approximately 50% of patients will develop this complication within 6 months after the transplants despite continued treatment with immunosuppressive medications. Close monitoring is recommended during the first two years after allogeneic stem cell transplantation so that appropriate treatment is instituted promptly in patients who develop chronic GVHD. Debilitation, joint contractures and profound immunosuppression resulting in recurrent bacterial infections are prominent characteristics of untreated chronic GVHD (4,5).

During the early phase of the disease especially dermal and gastro-intestinal manifestations may appear similar to acute GVHD. HLA-disparity, positive history for acute GVHD and older patient age have been reported to be associated with an increased risk of developing chronic GVHD appears to be a marker for severe chronic GVHD and is often associated with progressive type onset. Chronic GVHD is observed in 33% of HLA-identical sibling transplantations and in 50 to 70% of the recipients of unrelated or mismatched-related marrow grafts (4,6).

Chronic GVHD may present in two clinical forms; "Limited Disease" and "Extensive Disease". "Limited

Disease" is defined as signs and symptoms of chronic GVHD involving one organ system (skin and/or liver) with at least one biopsy showing characteristics histopathological GVHD findings (Table 1). "Extensive Disease" is defined as the presence of signs and symptoms involving more than one organ system, at least one biopsy showing characteristic of either generalized skin involvement, or localized skin involvement and/or hepatic dysfunction due to chronic GVHD plus liver histology with chronic aggressive hepatitis, eye involvement with decreased abnormal Schirmer's test (less than 5 mm wetting), or involvement of minor salivary glands with Sjogren's syndrome and involvement of any other target organ (Table 1). Chronic GVHD is classified into three patterns according to the onset. *Progressive chronic GVHD* is defined as direct continuation of signs and symptoms of acute GVHD and it is associated with a higher mortality rate. *Quiescent onset of chronic GVHD* is observed following the complete resolution of prior acute GVHD. Third category includes *De novo onset of chronic GVHD* during which chronic GVHD may appear without prior history of acute GVHD. All these categories are briefly summarized in table 2. Among these three different chronic GVHD presentations, *De novo onset of chronic GVHD* has been reported to have the best prognosis (4-7).

Table 1	
Clinical forms of chronic graft-versus-host disease	
LIMITED	
Signs or symptoms of chronic GVHD involving one organ system with at least one biopsy showing characteristic pathological GVHD findings (may be the same or a different organ system)	
<i>Either or both</i>	
<ul style="list-style-type: none"> ● Localized skin involvement ● Hepatic dysfunction due to chronic GVHD 	
EXTENSIVE	
Signs or symptoms with chronic GVHD involving more than one organ system at least one biopsy showing characteristic	
<i>Either</i>	
<ul style="list-style-type: none"> ● Generalized skin involvement, or ● Localized skin involvement and/or hepatic dysfunction due to chronic GVHD 	
<i>Plus</i>	
<ul style="list-style-type: none"> ● Liver histology showing chronic aggressive hepatitis, bridging necrosis or cirrhosis, or ● Involvement of eye (Schirmer’s test with less than 5 mm wetting), or ● Involvement of any other target organ 	
<i>NOTE: Karnofsky Clinical Performance: Patients with 60% scores secondary to clinical GVHD with at least one organ involvement and documented by biopsy are classified as clinical extensive chronic GVHD</i>	

Table 2	
Classification of clinical chronic graft-versus-host disease according to onset	
<i>Progressive</i>	Direct continuation of acute GVHD (i.e. persistent signs and symptoms of acute GVHD)
<i>Quiescent</i>	Onset of chronic GVHD after complete resolution of acute GVHD (i.e. no clinical signs or symptoms of acute GVHD; off steroids)
<i>De novo</i>	Onset of chronic GVHD with no prior history of acute GVHD

Manifestations of chronic GVHD

Karnofsky or Lansky Clinical Performance scores <60%, 15% weight loss, and recurrent infections are usually signs of clinical extensive chronic GVHD. Abnormalities that could indicate chronic GVHD are categorized by organ system as listed below in figure 2.

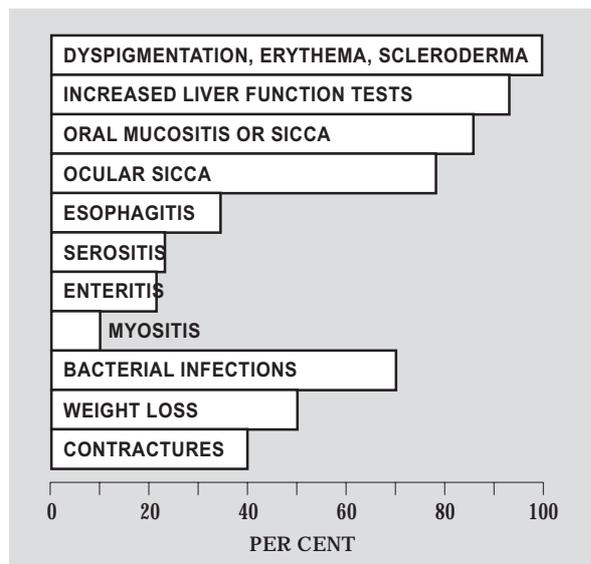


Fig 2. Frequency of clinical manifestations in extensive chronic GVHD (2,3)

Dermal

Skin involvement is the most frequent clinical feature of chronic GVHD. Erythema, dryness, pruritis, pigmentary changes (i.e., hyperpigmentation, vitiligo), mottling, papulosquamous plaques, nodules, exfoliation, macular-papular or urticarial rash, scleroderma, morphea (one or several circumscribed, indurated and shiny lesions) may be observed. In some patients clinical features may resemble morphea and occasional nodules can be seen (8). Skin grids, medical photos, and skin thickening scores are useful for assessing the extent of skin involvement and response to treatment. (Figure 3a, 3b)

Nails

Ridging, onychodystrophy and onycholysis can be observed (Figure 4).

Hair

Premature graying (scalp hair, eyelashes, eyebrows), thinning scalp hair, alopecia or decreased body hair can be seen.

Oral

By day 100 post-transplant, chemoradiotherapy induced oral mucositis and dryness are resolved or should be improving. The development of new oral pain or dryness after day 100 should alert the physician to the development of chronic GVHD. Signs and symptoms include dryness, burning pain, gingivitis, mucositis, striae, atrophy, erythema, lichenoid changes and ulcers (9). Atrophy and pigmentary changes on the lip and tooth decay may be present. Lip biopsy shows characteristic pathologic findings (Figure 5a and Figure 5b).

Ocular

Ocular symptoms are characteristics of "ocular sicca" including dryness, burning, blurring, gritty eyes, photophobia and pain. Schirmer's test showing a mean value of both eyes <5 mm at 5 minutes, or <10 mm with signs of keratitis (slit light exam) (3,4).

Vagina/Vulva

Vaginal dryness, dyspareunia, stricture formation and stenosis, erythema, atrophy and/or lichenoid changes not induced by ovarian failure can be seen (4,10). Biopsy and cultures are required to rule out infection and to confirm chronic GVHD.

Hepatic

Liver function tests mainly show cholestatic features. Elevated liver function test not due to other causes with alkaline phosphatase > 3 x upper normal limits with or without elevation of SGOT >4 x upper normal values and/or elevated total serum bilirubin >2.5 in absence of chronic GVHD involving other organs (11). Liver biopsy is required to confirm the diagnosis.

Pulmonary

Chronic GVHD may be associated with recurrent sinopulmonary infections and progressive obstructive lung defects (figure 6). Obstructive lung defect with FEV1/FVC <70% or an FEV1 <80% predicted or a decrease of FEV1/FVC by 15% from previous pulmonary tests are thought to represent bronchiolitis obliterans (4,12,13). High resolution CAT scan usually shows air trapping. Suspected bronchiolitis obliterans requires negative microbiological tests from bronchoalveolar

LEGENDS FOR COLOR SLIDES

Fig 3 (a). Disseminated sclerodermatous skin changes in chronic GVHD. Body skin is atrophic, firm, tight and hyperpigmented

Fig 3 (b). Indurated, sclerotic and white-yellow areas of poorly defined contours on an arm of a patient with chronic GVHD

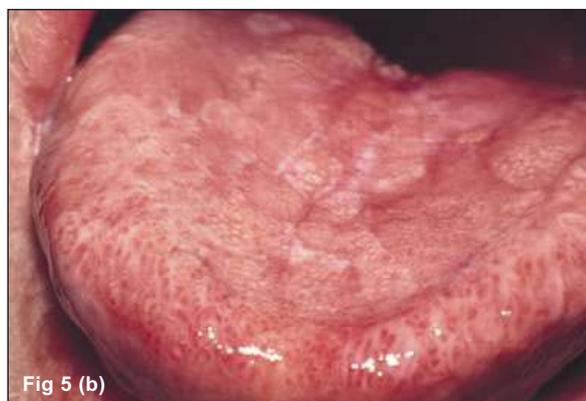
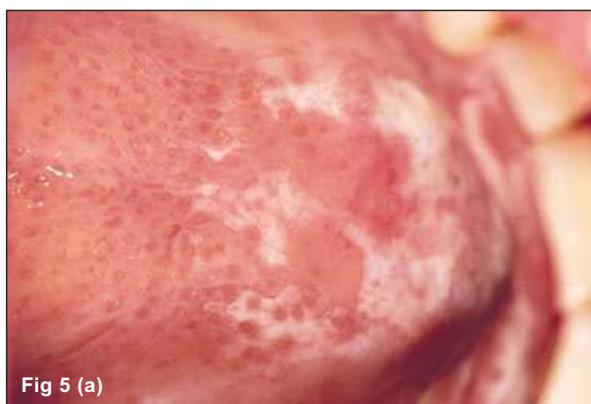
Fig 4. Nails with onychodystrophic features

Fig 5 (a). Heavy lichenoid white plaques due to chronic GVHD. Interspersed among the white plaques are areas of mucosal atrophy and erythema

Fig 5 (b). Complete replacement of normal surface architecture by GVHD-associated oral lichenoid lesions and loss of papilla

Fig 7 (a). Palm with patchy papulosquamous changes and atrophic changes

Fig 7 (b). Arm and part of trunk with brown discoloration with firm, sclerodermatous and atrophic changes on right arm



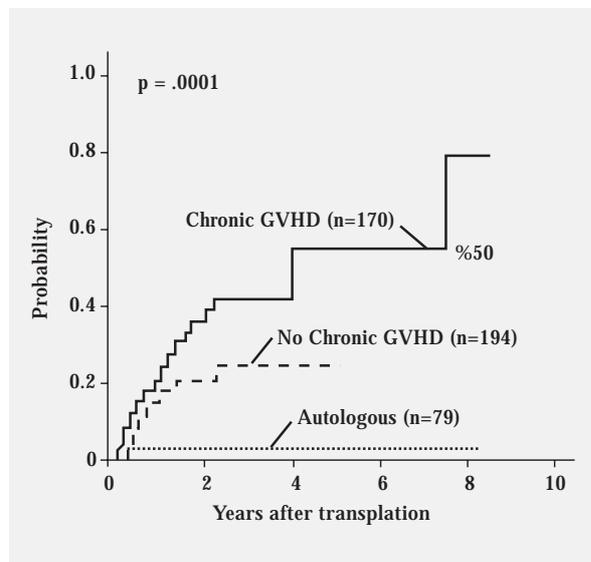


Fig 6. Probability of pulmonary infection after discharge (2,3)

lavage. Transbronchial biopsy is required to confirm the diagnosis of bronchiolitis obliterans in the absence of chronic GVHD involving other organs.

Gastrointestinal system

The patients with chronic GVHD may have dysphagia or odynophagia with radiological evidence of stenosis (Barium swallow) or web formation by esophago-gastro-duodenoscopy and occasional, dysmotility. Anorexia, nausea, vomiting, weight loss and diarrhea could be presenting symptoms. Endoscopic biopsy showing characteristic pathological findings is necessary to confirm the diagnosis of chronic GVHD. Weight loss more than 15% body weight not related to other causes is usually a sign of extensive chronic GVHD and is not always associated with gastrointestinal involvement. Malabsorption syndrome is usually present in these patients (4,14,15).

Musculo-skeletal

The patients may have arthralgias involving the large proximal girdle joints although, smaller joints may be also affected. Contractures are usually secondary to scleroderma or fasciitis. Proximal muscle weakness with occasional cramping and elevation of CPK and/or aldolase can be seen. EMG findings are consistent with myositis (16,17). Biopsy is needed to confirm diagnosis if, only an organ is involved. Histological findings

include necrotic fibers, interstitial inflammations and IgG deposits on immunofluorescence staining. Myasthenia gravis has been reported in few cases (Figure 7a and Figure 7b) (18).

Fasciitis

Eosinophilic or sclerosing fasciitis characterized by stiffness with restriction of movement due to inflammation and fibrosis involving the sheaths of tendons can be seen in chronic GVHD (19). Occasionally swelling, erythema and pain may accompany the clinical picture. It usually affects the wrists, forearms and hands, followed by ankles, legs and feet in a less frequent order. Induration may be present on palpation. Patients are unable to extend the wrists without flexing the fingers and the elbows. Cramping is often present.

Hematological findings

Thrombocytopenia (usually $>20,000/\text{mm}^3$) is more often seen in patients with progressive onset of chronic GVHD (20). Thrombocytopenia is a poor prognosis factor if, present at the time of diagnosis of extensive chronic GVHD. Eosinophilia can also be present in patients with chronic GVHD. Recurrent infections (commonly sinusitis) often a sign of severe immunodeficiency are associated with ongoing extensive chronic GVHD. Hypogammaglobulinemia is usually present (i.e., IgG subclasses, IgA) (21).

Infections

Owing to the prolonged time to immunological recovery, infections may be common in patients with chronic GVHD. Treatment of chronic GVHD with steroids and associated hypogammaglobulinemia contribute to this risk. Infections with encapsulated gram-positive bacteria are most common and require daily penicillin or trimethoprim-sulfamethaxazole prophylaxis (3,4,22).

Screening studies for chronic graft-versus-host disease

The median day of diagnosis of chronic GVHD in HLA-identical sibling recipients is 201 days after transplant; in contrast, HLA-non identical related and unrelated donor marrow recipients have an earlier diagnosis and onset. Small number of patients may develop chronic

GVHD after day +500. Screening studies are required to detect early chronic GVHD in all allogenic stem cell and bone marrow transplant recipients 80-100 days after transplantation as well as for patients who are being monitored in long-term follow-up. An updated list of screening studies for chronic GVHD is summarized in table 3. (4,23,24). Long-term follow-up nurses play a significant role in the screening and monitoring studies of patients with chronic GVHD (Figure 8).

Table 3 Screening studies for Chronic Graft-versus-Host Disease
Skin and oral examination
Skin biopsy
Lip biopsy (as clinically indicated)
Schirmer's tear test and slit lamp examination of eyes
Liver function tests
Gynecological evaluation
Weight, muscle /fat store measurement
Karnofsky score or Lansky play index

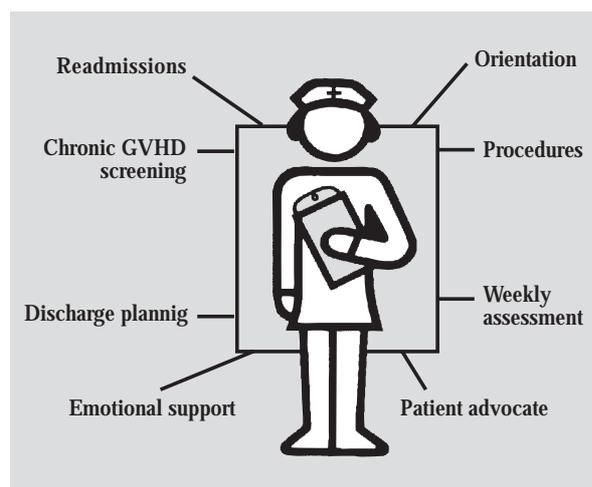


Fig 8. Nurse clinician activities and roles

Laboratory testing and diagnostic indicators of chronic GVHD

Eye

Schirmer's test with a mean value 5 mm at 5 minutes, or values of 6-10 mm in patients who have ocular symptoms, or keratitis detected by slit lamp examination.

Liver

Elevated liver function tests not due to other causes (alkaline phosphatase 2 x upper limit, of normal, AST or ALT >4 x upper limit of normal or total serum bilirubin 2.5).

Lung

New obstructive lung defect defined as an FEV1 <80% of predicted with either an FEF 25-75 <65% of predicted or RV >120% of predicted, or a decrease of FEV1/FVC by >12% within a period of less than 1 year, thought not to be caused by an infectious process, asthma or recurrent aspiration from the sinuses or from gastroesophageal reflux. In the absence of GVHD in any other organ, the diagnosis of bronchiolitis obliterans requires negative microbiological tests from bronchoalveolar lavage, evidence of air trapping by high resolution end-expiratory and end-inspiratory CAT scan of the lung, or confirmation by thoroscopic biopsy.

Esophagus

Esophageal web formation, stricture or dysmotility demonstrated by barium swallow, endoscopy or manometry.

Intestine

Endoscopic findings of mucosal edema, focal erosions, or mucosal sloughing in severe cases, with histological changes of apoptotic epithelial cells and crypt cell drop out.

Muscle

Elevated CPK or aldolase, EMG findings consistent with myositis with biopsy revealing no other etiological process.

Blood

Thrombocytopenia (usually 20,000-100,000/mm³), eosinophilia (>6%), hypogammaglobulinemia, hypergam-

maglobulinemia and autoantibodies may occur in some cases.

Diagnosis of chronic GVHD

Histological documentation of chronic GVHD by skin or other tissue biopsies is necessary for diagnosis. Pathologic findings in the skin include localized epidermal atrophy and dense focal dermal fibrosis in the absence of significant inflammation. In other patients, more generalized histological manifestations are seen with inflammation in eccrine coils and pilar units which lead to fibrosis throughout the dermis. Liver biopsy reveals bile duct damage similar to the histopathologic findings of primary biliary cirrhosis (3,4).

Prevention of chronic GVHD

At least two randomized trials demonstrated that treatment with CSP significantly reduces acute GVHD without altering the rate of chronic GVHD. No difference was observed in the cumulative incidence of chronic GVHD in the transplant recipients given FK506/MTX and those given CSP/MTX prophylaxis.

Standard GVHD prophylaxis with methotrexate (MTX) and cyclosporine (CSP) involves a tapering of CSP doses after day 50 and discontinuation of CSP administration by day 180 (25). With this regimen chronic GVHD tends to occur during the CSP tapering and the ensuing 6 months after discontinuation (26). A prospective randomized clinical trial reported by Kansu, et al (27) compared the incidence of clinical extensive chronic GVHD, transplantation-related mortality, survival and relapse free survival among recipients randomly assigned to receive a 24-month or a 6-month course of cyclosporine prophylaxis after allogeneic transplantation. 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. There were no significant differences between the two groups in developing chronic GVHD, TRM, survival and disease-free survival (27).

Treatment of chronic GVHD

There have been no spontaneous improvement in disabled survivors with clinical extensive chronic GVHD in spite of many years of observation. Treatment of

chronic GVHD usually begins with administration of high dose glucocorticoids and continued administration of cyclosporine or tacrolimus (FK506) originally given for prevention of GVHD after the transplant. Medications used for primary and secondary treatment of chronic GVHD are summarized in table 4.

Primary treatment

Initial attempts of treating chronic GVHD were largely unsuccessful. In a prospective placebo-controlled study, prednisone and azathioprine treatment have improved response and decreased disability of chronic GVHD compared to prednisone alone. However, secondary to an increased number of infectious complications in patients treated with prednisone and azathioprine, survival was low at 47% compared to 61% in patients treated with prednisone alone. This analysis included only patients with platelet counts of more than 100,000/cu.mm. Thirty-eight "high-risk" patients were placed on prednisone alone. The non-relapse mortality and survival rates for these patients were 26% and 58%, respectively (28).

The addition of oral CSP in patients at high-risk for GVHD with thrombocytopenia was also studied. Renal toxicity was modest and survival improved and infections decreased with this protocol. Average duration of therapy was 1 to 2 years. However, infections again remained a frequent cause of morbidity and contributed to transplant-related mortality in patients with high-risk chronic GVHD.

In a prospective randomized study, alternating day CSP and prednisone therapy for high-risk chronic GVHD (platelets less than 100,000/mm³) appears to produce a higher response rate compared to CSP alone (29,30). However, the 3-year actuarial survival for the high-risk group remained low at 48% and the non-relapse mortality rate of 35% with the combination therapy. The survival and the non-relapse mortality rates appear not to be significantly different between the two arms of the study (CSP/PRED versus CSP). The 3-year survival was 48% in patients who received primary therapy and infections appeared to be reduced in the long-term survivors.

Arora and co-workers (31) recently suggested to recognize high-risk group with chronic GVHD (age 20

Table 4
Medications used for treatment of chronic GVHD

GENERIC NAME	TRADE NAME	DRUG LEVEL	MAJOR TOXICITIES
Cyclosporine (CSP)	Sandimmune® Neoral®	Range* 150-450 ng/ml by immunoassay in whole blood (TDX, Abbott)	RENAL: increased creatinine, decreased magnesium GI: nausea, vomiting, increased serum bilirubin or transaminase levels, pancreatitis NEUROLOGIC: tremor, paresthesias visual disorder, headache, seizures anxiety, disorientation, depression VASCULAR: hypertension, hemolytic-uremic syndrome, thromboembolism OTHER: hyperglycemia, hypertrichosis, rash, gingival hypertrophy, gynecomastia
Tacrolimus (FK 506)	Prograf®	Range* 10-15 ng/ml by immunoassay in whole blood (IMX, Abbot)	Similar to Cyclosporin toxicities
Mycophenolate Mofetil (MMF)	Cellcept®	Not available for clinical use	GI: vomiting, diarrhea HEMATOLOGIC: neutropenia, anemia
Rapamycin	Rapamune® Sirolimus	Not available for clinical use	HEMATOLOGIC: neutropenia, trombocytopenia
Thalidomide	Thalomid®	Not available for clinical use	TERATOGENIC: birth defects NEUROLOGIC: sedation, sleepiness, peripheral neuropathy (dysesthesias, clumsiness, weakness) GI: constipation HEMATOLOGIC: neutropenia
Azathioprine	Imuran®	Not available for clinical use	HEMATOLOGIC: neutropenia, trombocytopenia GI: constipation, cholestasis, veno-occlusive disease
Clofamizine	Lamprene®	Not available for clinical use	SKIN: discoloration, pruritis EYES: corneal discoloration GI: abdominal and epigastric pain, diarrhea, nausea, vomiting, hepatitis
Acitretin	Soriatane®	Not available for clinical use	MUCOCUTANEOUS: cheilosis, rash, rhinitis, hyperesthesia, paronychia EYES: xerophthalmia HEMATOLOGIC: reticulocytosis METABOLIC: hyperlipidemia, hyperglycemia, increased transaminase levels and CPK OTHER: arthralgia, rigors, occult blood in the stool

**Dose adjustment should be based on evaluation of toxicity and GVHD activity, as well as drug levels*

years or older, progressive onset of disease, platelets $<100,000/\text{mm}^3$, GI involvement and those without a complete response after 6 months) and employ a more intensified regimens to the patients. Novel approaches and more effective treatment modalities should be directed on high-risk patients with chronic GVHD (31).

Patients with chronic GVHD should be included in treatment protocols. In those patients without this option available, alternate-day prednisone and CSP appears to be the treatment of choice. But in newly diagnosed patients with extensive chronic GVHD after similar medications and dose levels, daily prednisone (1mg/kg) and daily CSP (10mg/kg) should be started. If there is no flare of the clinical chronic GVHD, steroid taper should be started first followed by CSP taper by 25% per week to alternate-day dose schedule. The patient must be examined every two to three months and doses should be adjusted according to response criteria. When the patient has a complete recovery of extensive chronic GVHD, then a gradual taper schedule has to be made and dose reductions to be advised every two weeks. Total therapy period may last 9 to 12 months. If the patient does not respond by 3 to 6 months or progress on treatment, then salvage (secondary) therapy protocols must be considered (4,32).

Secondary treatment

Salvage therapy is indicated in patients who do not respond and/or fail the primary therapy.

In chronic GVHD, long-term immunosuppression has been shown to increase disability-free survival and despite treatment with cyclosporine (CSP) and prednisone, patients with high-risk chronic GVHD have poor survival (33,34). In addition, report by Flowers et al. (35), suggested that chronic GVHD after PBSCT may be more protracted and less responsive to current treatment regimens than chronic GVHD seen after bone marrow transplantation. In her study, number of successive treatments needed to control chronic GVHD was higher after PBSCT than after BMT ($p=0.03$) (35).

The major problem in the treatment of chronic GVHD is when disease shows progression while the patients are still receiving CSP and prednisone. Salvage therapeutic modalities have to be considered in the early

course to treat extensive chronic GVHD.

Response criteria to therapy and definition of failure is summarized below. Azathioprine, alternating CSP/prednisone and thalidomide give similar survival rates, approximately 75% rate in patients in whom initial steroid therapy fails. The medications used in the secondary salvage treatment of chronic GVHD are summarized in the table 4.

At present time, on standard salvage treatment for patients who do not respond to their first-line chronic GVHD therapy, several pharmacologic agents are currently being tested in clinical trials aimed at the salvage treatment of high-risk or refractory chronic GVHD. For these patients clinicians must seek Phase I/II trials.

Mycophenolate mofetil (MMF) is a potent immunosuppressive agent that selectively inhibits proliferation of T and B cells. Experimental studies in canine models demonstrated a synergistic effect of the allograft recipients. Large randomized study from the Seattle group in standard risk patients with extensive chronic GVHD ($n=305$) showed a better outcome using the combination of CSP plus prednisone as compared to prednisone alone. Results of using MMF as salvage therapy showed 11% CR and 41% PR (36).

Tacrolimus (FK506) has been given to patients with steroid-resistant disease and has a better activity for patients with liver disease than those on CSP. Tacrolimus and MMF have both shown some effectiveness in treating patients who have not been helped by CSP and prednisone.

Thalidomide also showed some efficacy in the primary treatment of patients with high-risk chronic GVHD as well as those with refractory disease (37). A randomized trial with thalidomide was conducted in high-risk chronic GVHD patients comparing thalidomide (25 patients) with placebo (25 patients) given in combination with either CSP or tacrolimus (FK506) with prednisone (38). In this trial, large number of patients had to discontinue thalidomide due to neutropenia and neurologic symptoms. The authors did not find any evidence that thalidomide improved the survival of high-risk clinical extensive chronic GVHD patients.

Recently a larger clinical trial of thalidomide as

salvage therapy for chronic GVHD has been reported. Response was observed in 20% of patients treated with thalidomide. Controlled studies are underway to investigate the efficacy of FK-506, MMF and rapamycin as a salvage therapy in chronic GVHD patients who failed the primary treatment.

Recently, a Phase II trial was reported in 29 patients with steroid refractory chronic GVHD (median age 42 years, range 18-69) utilizing tacrolimus (FK-506) combination with sirolimus (Rapamycin) (39). The onset of chronic GVHD at study enrollment included 15 relapsing (52%), 12 progressive (42%) and 2 (7%) de novo cases. All patients had failed multiple previous lines of immunosuppression prior to sirolimus (Rapamycin) (39). The overall response was 68% (n=18) with 5 CR and 13 PR. Of the remaining patients, 6 failed to respond, 3 had progressive disease and 2 patients were not evaluable. The authors concluded that combination therapy with sirolimus and tacrolimus is an active regimen for the treatment of steroid-refractory chronic GVHD particularly in patients with steroid-refractory scleroderma (39).

Use of PUVA has been explored in patients with refractory cutaneous chronic GVHD. In patients who have isolated skin involvement who do not present without scleroderma, PUVA should be considered as a first line therapy. Morphea have been shown to be successfully treated with PUVA alone. This type of treatment currently lacks randomized studies and there is a great need for new randomized prospective trials with PUVA.

Extracorporeal photochemotherapy (Photopheresis, ECP)

ECP is a new treatment option for the management of steroid refractory chronic GVHD over the past few years. ECP involves ex vivo exposure of leukapheresed peripheral blood mononuclear cells to ultraviolet A light in the presence of a DNA-intercalating agent, 8-methoxypsoralen, with subsequent reinfusion of the treated cells. The total number of lymphocytes treated ex-vivo per cycle has been estimated to be approximately 10% of circulating lymphocytes, with an energy delivered by ultraviolet light of 2 J/cm² per cell (40). ECP is effective in treating cutaneous T-cell lymphoma, sclero-

derma and alloreactivity in solid organ and bone marrow allografts (41). In patients with GVHD, ECP appears to induce tolerance to alloreactive T-cell responses by modulating dendritic cells (42).

Clinical response to ECP in patients with chronic GVHD was first reported by Rosetti et al. (43) in 1996. Besides the previously described effect of ECP on T-cell subsets, a direct effect on circulating antigen-presenting dendritic cells and natural killer cell populations has been demonstrated (44,45). Clinical response to ECP was associated not only with normalization of skewed CD4/CD8 ratios but also with an increase in CD3(-)/CD56(+) natural killer cells and a decrease in the number of CD80(+) and CD123(+) circulating dendritic cells (44,45). While DC-1 type dendritic cells predominate in the allograft recipient before the initiation of therapy, most ECP-treated patients demonstrate a shift from DC-1 to DC-2 type dendritic cells. This phenomenon leads to a shift from Th1 (interleukin-2, interferon-gamma) to Th2 (IL-4, IL-10) cytokine profile following photopheresis, indicating that it can alter alloreactivity in chronic GVHD by affecting allo-targeted effector T-cell function via modulation of antigen-presenting cells (44,45).

Besides the well known efficacy of ECP in the setting of chronic GVHD, recent studies suggest that it can also be effective in controlling steroid refractory acute GVHD involving skin and liver (46-52). ECP is not recommended for patients with grade IV acute GVHD or gut involvement (52). The ECP procedure is performed using the UVAR photopheresis system (Therakos, West Chester, PA, USA) with a mean treatment time of 3.5 hours. Use of a pheresis catheter is not always necessary. ECP is initiated in patients with steroid-refractory GVHD when the white blood cell count is over 1x10⁹/L and if there is no signs of acute infection. Patients are treated on 2 consecutive days (one cycle) at 1- to 2-week intervals until improvement and thereafter every 2 to 4 weeks until maximal response (52). Then, ECP was tapered on an individual basis.

Definition of response

No response or progression (failure): Deterioration of chronic GVHD in at least one organ after 9-12 months

of therapy without improvement in other organs. This also includes those patients who are stable but who have persisting Karnofsky or Lansky scores less than 50%.

Partial response: After 9-12 months of therapy the patient is clinically stable or improved in at least one evaluable organ without deterioration in others. If still a partial response after 18 months to 24 months, the patient is declared a failure. Patients with improvement of skin and other organ involvement, but persistent active oral involvement will be considered partial responders.

Complete response: After 9-12 months of therapy the patient is well and has resolution of all symptoms and signs of active GVHD. Patients with complete response in all organs, but have persistent ocular sicca, will be considered complete responders. Clinical responders should be divided into two categories: (a) Those with clinical and histologically complete responses including biopsies showing no active chronic GVHD, and (b) those patients with complete clinical response but persistent histological involvement, including those with biopsy positive for GVHD.

Flare: Treatment is reduced or stopped after achieving a complete response but active chronic GVHD returns requiring systemic therapy. Every patient should be evaluated by a physician to judge chronic GVHD activity at 2-3 and 5-6 months of therapy. Physical and neurologic examinations, weight, laboratory examinations and doses of immunosuppressive drugs must be recorded. If flare of chronic GVHD occurs, physical findings, laboratory findings, dates and treatment instituted must also be recorded.

Measurement of response

Involvement of the skin (surface area, hair and nails), oral cavity, eyes (Schirmer's test), liver (serum bilirubin and alkaline phosphatase), gut (weight loss, malabsorption, volume of diarrhea, cramps or bleeding), musculoskeletal (range of motion, CPK, aldolase) will be measured before and 3 month intervals through the completion of the treatment. A brief guideline to evaluate and record the response is summarized below.

Skin: To evaluate response in the skin, a "Grid" approach should be used. Comparative photographs may

also be used to assess treatment response. Skin is considered to be improved if there is a 25% decrease of the surface areas involved by rash, sclerosis, lichenoid or dyspigmentation; regrowth of hair in previous sclerotic areas; softening of the skin in >25% of previous involved areas or, increased range of motions by >25% in one or more joints without deteriorations in others.

Liver: Liver disease is considered improved if; there is a decrease in serum bilirubin to less than 2 mg/dl for patients with baseline values of 2 to 4 mg/dl, or; decrease of >2mg%/dl for patients with baseline values of 4 to 8 mg/dl, or; >25% decrease to <200 mg/dl for patients with baseline values >300 mg/dl.

Gut: Gut disease is considered improved if there is a cessation of weight loss or weight gain (i.e. >1 kg) in a 3 month interval, or; resolution of diarrhea, or; decrease in the three day average stool volume by >500 ml with clearing of cramps and bleeding, if present, and/or; clearing of any cramps and bleeding is considered as evidence of improvement in patients who have diarrhea volumes <500 ml but not in patients who have changed diarrhea volumes >500 ml.

Supportive care

Topical steroids can be used in oral, vaginal, or penile lesions of chronic GVHD. Ocular sicca may respond to retinoic acid, and oral sicca may respond to pilocarpine. In addition to use of artificial tears, ligation of lacrimal puncti is necessary for patients with severe dry eyes. Muscular cramps and carpal spasm may be relieved by clonazepam, klonipin or beclofen. In patients with liver function abnormalities and refractory hepatic chronic GVHD, bile acid replacement therapy with ursodeoxycholic acid (UDCA) can be beneficial.

For patients on long-term steroids, estrogen replacement in women, high calcium and vitamin-D intake, daily exercise, annually bone density studies and anti-osteoporosis agents are important to reduce the bone loss. Weight bearing exercise is necessary to maintain skeletal muscle mass and can help improve cardiovascular function. Walking should be done carefully to avoid harm to the joints.

Pre-menopausal females prior to transplant should

receive gonadal replacement therapy following transplant. Women who decline estrogen therapy or for whom replacement is inappropriate, such as persons with a history of breast cancer, should be treated with calcitonin. Males with low total and free testosterone may benefit from depo-testosterone injections.

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