

Chronic graft *versus* host disease

Summary

The ability to cure increasing numbers of individuals for malignant and non-malignant diseases with the use of stem cell transplantation has resulted in a growing number of long-term survivors with unique medical issues. Chronic graft *versus* host disease (GvHD) continues to be a significant problem in the allogeneic stem cell transplant setting and, as we continue to use alternative stem cell sources and attempt to modulate the immune system to increase an anti-tumour effect, we will probably see rising numbers of patients with this complication. The capacity to treat this problem and improve both the immediate quality of life as well as long-term effects is imperative and requires the ability of haematologists/oncologists to identify chronic GvHD and its multi-organ system presentations. We describe the risk factors for developing chronic GvHD, its presentation and the current treatment options for both initial therapy and secondary treatment.

Background

Chronic graft *versus* host disease (GvHD) is the most common non-relapse problem affecting long-term survivors of allogeneic haematopoietic cell transplantation (HCT). Of the 60–70% patients receiving human leucocyte antigen (HLA)-identical sibling marrow grafts or alternative donor marrow grafts who survive beyond day 100 develop chronic GvHD (Gilman & Schultz, 2000; Goerner *et al*, 2002; Lee *et al*, 2002a). The incidence of chronic GvHD is lower in children but remains significant. A review of the experience of a single centre, which evaluated patients transplanted for leukaemia using several different regimens for GvHD prophylaxis, had a chronic GvHD rate of 34% (Gustafsson Jernberg *et al*, 2003). A recent evaluation of GvHD following matched sibling or one antigen mismatched-related transplantation by the Children's Cancer Group, in which GvHD prophylaxis was uniform, reported a chronic GvHD rate of 21.2% with 7.3% of the patients with limited disease and the remaining 14% demonstrating extensive disease (Neudorf *et al*, 2004). These patients received methotrexate for GvHD prophylaxis as per the Seattle protocol until day 100. There remains marked heterogeneity in

the GvHD prophylaxis and the stem cell source in the paediatric population making the true estimate of chronic GvHD incidence difficult to quantify.

Patients with chronic GvHD report a significantly decreased quality of life (QOL) with a decreased functional status (Syrjala *et al*, 1993; Duell *et al*, 1997; Sutherland *et al*, 1997; Socie *et al*, 1999). There is minimal data on the life-long complications of chronic GvHD in the paediatric population, including the effects on school performance. Unfortunately, chronic GvHD is becoming a more frequent problem due to the increasing use of alternative donors including haploidentical family members, increasing age limits of transplantation, use of peripheral blood stem cells (PBSC) instead of bone marrow (BM) as the source of the graft, and use of donor lymphocyte infusions (DLI) for treatment of relapse or prophylaxis to prevent relapse in patients at high risk for relapse of their malignancy. While the rate of chronic GvHD has decreased markedly with some alternative donor transplants through the use of antithymocyte globulin (ATG) or Campath, the rate of relapse in these patients remains high. Efforts to modulate the immune system frequently result in GvHD that may improve disease-free survival (DFS) but result in chronic GvHD. Long-term follow-up of adults and children increasingly demonstrate a possible role for chronic GvHD in improving DFS, especially in high-risk malignancies, but may not improve event-free survival (EFS) secondary to complications of GvHD and its treatment (Cutler *et al*, 2001; Gustafsson Jernberg *et al*, 2003; Neudorf *et al*, 2004). The recent publication by the Children's Cancer Group demonstrated the benefit of acute GvHD in relapse-free survival (Neudorf *et al*, 2004), while the role of chronic GvHD in children has been reported from Sweden (Gustafsson Jernberg *et al*, 2003). The price paid for improved DFS may be a marked effect on QOL.

The basic pathophysiology of chronic GvHD remains poorly defined. Most animal models actually more closely mimic non-myeloablative transplants than full ablative allogeneic grafts, making it difficult to know how much the basic immunology of chronic GvHD in the animals relates to chronic GvHD in patients after ablative transplants (Atkinson *et al*, 1982; Beschorner *et al*, 1982; Tutschka *et al*, 1982; Hamilton & Parkman, 1983; DeClerck *et al*, 1986; Nonomura *et al*, 1998; Slayback *et al*, 2000; Zhang *et al*, 2002a). These models most often utilize parent into F₁ hybrid and have shown antibody-mediated damage due to solely T-helper 2 (Th2) cell responses (Okamoto *et al*, 2000). In contrast, both Th1 and Th2 cells have been implicated in humans post-transplant (Reinherz *et al*, 1979; Lichtman *et al*, 1997; Aractingi & Chosidow, 1998;

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Ratanatharathorn *et al*, 2001). Understanding the effect of chronic GvHD in decreased intensity preparative regimens and EFS is being evaluated (Perez-Simon *et al*, 2003). In humans, aberrant recovery of the immune system leading to loss of normal regulation has been felt to cause chronic GvHD. Chronic GvHD may be due to both alloreactive and autoreactive T cells. This view is supported by the higher rates of chronic GvHD following PBSC transplantation (PBSCT) and after DLI and animal models of ciclosporin-induced autologous GvHD (which clinically closely resembles chronic GvHD) (Collins *et al*, 1997; Storek *et al*, 1997; Scott *et al*, 1998; Solano *et al*, 1998; Vigorito *et al*, 1998; Champlin *et al*, 2000; Dazzi *et al*, 2000; Snowden *et al*, 2000; Cutler *et al*, 2001; Morton *et al*, 2001). The autoreactive T cells recognize the class II-associated invariant peptide region of major histocompatibility complex class II molecules (Hess *et al*, 2001). Autoreactive T cells may arise in the allogeneic setting due to thymic injury from acute GvHD, which prevents the deletion of autoreactive clones (Sullivan & Parkman, 1983; Weinberg *et al*, 2001). These autoreactive T lymphocytes can act with interferon- γ to produce the increased collagen deposition seen in chronic GvHD (Parkman, 1998). A role of the host antigen-presenting cell in the development of acute GvHD has been shown in mouse models; however, the role of both the recipient and donor antigen-presenting cells is much less understood (Shlomchik *et al*, 1999; Zhang *et al*, 2002b).

Risk factors

Different groups have found a variety of factors associated with the development of chronic GvHD, with certain factors being found repeatedly (Table I). The most important factor is the development of significant acute GvHD; other risk factors include older age, female donors and male patients, chronic myeloid leukaemia or aplastic anaemia as the reason for transplant, use of mismatched or unrelated donors, infusion of donor lymphocytes, use of PBSC instead of BM, and lack of

T-cell depletion (Storb *et al*, 1983; Ringden *et al*, 1985; Atkinson *et al*, 1990; Bostrom *et al*, 1990; Ochs *et al*, 1994; Carlens *et al*, 1998; Przepiorka *et al*, 2001). There appears to be a very low rate of chronic GvHD after cord blood transplantation, even in patients who have had significant acute GvHD (Wagner *et al*, 2002). The reason for this is not completely understood and may involve a number of factors including decreased reactivity of the donor T cells or other cells within the cord, lower age of the typical recipient and the standard use of ATG and steroids as part of the preparative regimen. As alternative, preparative regimens that do not use ATG are explored and the age of patients able to receive cord transplants rises, second to the increased use of multiple cord units and *ex vivo* expanded products, the rate of both acute and chronic GvHD will need to be monitored.

As more centres are using PBSCT for their allogeneic patients, exploring chronic GvHD in this setting is gaining in importance. Peripheral blood progenitor cells have been associated with an increased incidence of chronic GvHD (50–90%) in most the studies of HLA-matched sibling transplantation (Storek *et al*, 1997; Scott *et al*, 1998; Solano *et al*, 1998; Vigorito *et al*, 1998; Champlin *et al*, 2000; Snowden *et al*, 2000; Morton *et al*, 2001). A meta-analysis using data from 16 studies reported an increased relative risk (RR) for *extensive* chronic GvHD compared with BM transplantation (Cutler *et al*, 2001). High CD34⁺ counts correlated with an increased risk of chronic GvHD (Zauch *et al*, 2001). The use of stem cell infusions with increasing numbers of CD34⁺ cells to overcome graft rejection in reduced intensity preparative regimens may result in increased chronic GvHD as the use of immunosuppressive therapies is modulated.

Classification of chronic GvHD

Chronic GvHD can be classified according to the type of onset, need for systemic immunosuppressive therapy, or mortality risk. The majority of patients with chronic GvHD have had

Table I. Reported risk factors for chronic graft *versus* host disease (GvHD) according to patient and donor characteristics, haematopoietic stem cell source and post-transplant events.

	Patient	Donor and graft characteristics	Transplant events
Consistently observed	Older age Chronic myeloid leukaemia or aplastic anaemia	Female donor (especially parous) if male patient Mismatched or unrelated PBSC Donor lymphocyte infusions T-cell replete graft	Acute GvHD
Controversial or limited evaluation	CMV seropositive CMV reactivation Splenectomy	Ethnic diversity between donor and patient Lower incidence with umbilical cord blood	Corticosteroids in the acute GvHD prophylaxis regimen High CD34 ⁺ count (PBSC) Lack of methotrexate in acute GvHD prophylaxis (PBSC)

CMV, cytomegalovirus; PBSC, peripheral blood stem cell.

prior acute GvHD. Their disease may evolve directly from acute GvHD ('progressive') that has a grim prognosis, or may follow a period of resolution ('quiescent' or 'interrupted') GvHD, with an intermediate prognosis. Patients may develop chronic GvHD with no history of acute GvHD ('*de novo*') and have a good prognosis. Based on data from the International Bone Marrow Transplant Registry (IBMTR), the distribution of chronic GvHD onset for HLA-matched siblings is 20–30% progressive, 30–40% interrupted and 35% *de novo*. Evaluation of the data regarding the presentation of chronic GvHD is currently being evaluated by the IBMTR. Data from the National Marrow Donor Program (NMDP) for unrelated donor recipients, where the incidence of acute GvHD is higher, shows the spectrum of onset as 19% progressive, 69% interrupted and 12% *de novo* onset (Lee *et al*, 2002a).

The most commonly employed staging system is the 'limited/extensive' classification, proposed by the Seattle group in 1980, based on a retrospective clinical and pathological review of 20 patients with chronic GvHD (Shulman *et al*, 1980). In these patients, mortality correlated best with Karnofsky performance status (Shulman *et al*, 1980). Localized skin involvement with or without hepatic dysfunction (*limited* disease) was associated with less severe disease and fewer infections. Generalized skin involvement or limited disease plus eye involvement, oral involvement, hepatic dysfunction with abnormal liver histology, or involvement of any other target organ was classified as *extensive* disease and was associated with more frequent infections. However, review of data from HLA-matched sibling recipients reported to the IBMTR suggests that transplant centres do not apply the formal definitions accurately, perhaps in part because many patients are unclassifiable by the strict organ criteria (Lee *et al*, 2002a). The Seattle group has developed revised clinical criteria for limited and extensive chronic GvHD in order to clarify ambiguities of the original definition (Table II). 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).

Several investigators have tried to develop improved prognostic grading scales based on larger numbers of observed patients and with survival as the primary end point. Several studies show that thrombocytopenia (platelet count $<100 \times 10^9/l$), progressive onset, skin involvement, poor performance status and gastrointestinal (GI) involvement portend a poorer prognosis (Shulman *et al*, 1980; Wingard *et al*, 1989; Morton *et al*, 1997; Akpek *et al*, 2001a; Lee *et al*, 2002a; Arora *et al*, 2003). The Hopkins model stratified patients into risk categories according to the presence or not of extensive skin involvement, thrombocytopenia and progressive-type onset (Akpek *et al*, 2001a). This model was validated using data from a total of 1108 patients from the IBMTR ($n = 711$), Fred Hutchinson Cancer Center ($n = 188$), University of Nebraska ($n = 60$) and the University

of Minnesota ($n = 149$). Despite significant heterogeneity of the data, for each data set the proposed grading system was able to separate patients into three groups with different survival outcomes.

The IBMTR has also reported a grading system to predict for survival, developed by using data from 1827 HLA-matched sibling marrow recipients reported to the registry (Lee *et al*, 2002a). Karnofsky performance score, diarrhoea, weight loss, and cutaneous and oral involvement were found to be independent prognostic variables, from which a grading scheme was generated. This scheme, the limited/extensive classification system, and a classification based on clinical impression of overall chronic GvHD severity (mild/moderate/severe) was assessed in a parallel analyses of 1092 HLA-matched sibling transplant recipients from the IBMTR and 553 recipients of unrelated donor marrow from the National Marrow Donor Program. The presence of chronic GvHD was associated with fewer relapses (RR = 0.5–0.6) but increased treatment-related mortality (TRM) (RR = 1.8–2.8) in the three analyses. No grading scheme correlated chronic GvHD severity with relapse rates, but all schemes predicted TRM. The survival and DFS of the most favourable chronic GvHD group in each scheme were similar, or better, than those of patients without chronic GvHD. Notably, an overall clinical summary scale of mild, moderate, or severe chronic GvHD was the best predictor of survival based on Akaike's information criterion, a qualitative biostatistical method of comparing prognostic schemes (Lee *et al*, 2002a). However, formal definitions for the mild, moderate and severe categories have not been established (Gaziev *et al*, 2001).

Comparison of the Hopkins and IBMTR reports illustrates the advantages and disadvantages of single institution *versus* registry studies. The Hopkins model has a smaller sample size ($n = 151$) and was based on the consistent diagnostic criteria of a single group of clinicians, but may suffer from referral bias. In contrast, the IBMTR model is based on reports from many centres but is limited by the expertise of those evaluating the patients and the amount of detail that can be captured on specific chronic GvHD manifestations.

Clinical manifestations

Children and adults frequently have very similar presentations of chronic GvHD. Manifestations of 'acute' GvHD can begin after day 100 post-transplant, while classic 'chronic' GvHD can be present before day 100. Differences in presentation, affected organ systems and histological appearance rather than the timing of the onset should be used to make the diagnosis. The median time for the diagnosis of chronic GvHD was 4.5 months after HLA-identical sibling transplant and 4 months after unrelated donor transplant (Lee *et al*, 2002a), with only 5% of cases diagnosed after 1 year. The diagnosis of chronic GvHD requires at least one manifestation that is distinctive for chronic GvHD [e.g. lichenoid oral or vaginal findings, ocular sicca, skin dyspigmentation, scleroderma,

Table II. Original and revised Seattle classification for limited and extensive chronic graft *versus* host disease (GvHD).

Original Seattle classification (Shulman <i>et al</i> , 1980)	Revised Seattle classification (Lee <i>et al</i> , 2003)
Limited <i>Either or both</i>	Clinical limited
1. Localized skin involvement	1. Oral abnormalities consistent with chronic GvHD, a positive skin or lip biopsy and no other manifestations of chronic GvHD
2. Hepatic dysfunction due to chronic GvHD	2. Mild liver test abnormalities (alkaline phosphatase $\leq 2\times$ upper limit of normal, AST or ALT $\leq 3\times$ upper limit of normal and total bilirubin ≤ 27.3 $\mu\text{mol/l}$) with positive skin or lip biopsy and no other manifestations of chronic GvHD
	3. Less than six papulosquamous plaques, macular–papular or lichenoid rash involving $<20\%$ of body surface area (BSA), dyspigmentation involving $<20\%$ BSA, or erythema involving $<50\%$ BSA, positive skin biopsy and no other manifestations of chronic GvHD
	4. Ocular sicca (Schirmer's test ≤ 5 mm with no more than minimal ocular symptoms), positive skin or lip biopsy and no other manifestations of chronic GvHD
	5. Vaginal or vulvar abnormalities with positive biopsy and no other manifestations of chronic GvHD
Extensive <i>Either</i>	Clinical extensive
1. Generalized skin involvement, or	1. Involvement of two or more organs with symptoms or signs of chronic GvHD, with biopsy documentation of chronic GvHD in any organ
2. Localized skin involvement and/or hepatic dysfunction due to chronic GvHD, plus:	2. Karnofsky or Lansky Clinical Performance scores $<60\%$, $\geq 15\%$ weight loss, and recurrent infections not due to other causes, with biopsy documentation of chronic GvHD in any organ
(a) Liver histology showing chronic aggressive hepatitis, bridging necrosis, or cirrhosis, or	3. Skin involvement more extensive than defined for clinical limited chronic GvHD, confirmed by biopsy
(b) Involvement of eye (Schirmer's test with <5 mm wetting), or	4. Scleroderma or morphea
(c) Involvement of minor salivary glands or oral mucosa demonstrated on labial biopsy, or	5. Onycholysis or onychodystrophy thought to represent chronic GvHD, with documentation of chronic GvHD in any organ
(d) Involvement of any other target organ	6. Decreased range of motion in wrist or ankle extension due to fasciitis caused by chronic GvHD
	7. Contractures thought to represent chronic GvHD
	8. Bronchiolitis obliterans not due to other causes
	9. Positive liver biopsy, or abnormal liver function tests not due to other causes with alkaline phosphatase $>2\times$ upper limit of normal, AST or ALT $>3\times$ upper limit of normal, or total bilirubin >27.3 mmol/l , and documentation of chronic GvHD in any organ
	10. Positive upper or lower GI biopsy
	11. Fasciitis or serositis thought to represent chronic GvHD and not due to other causes

AST, aspartate transaminase; ALT, alanine transaminase; GI, gastrointestinal.

bronchiolitis obliterans (BO), oesophageal web formation]. Whenever possible, biopsies and other diagnostic tests should be pursued to rule out alternative aetiologies such as infections, and confirm the diagnosis of chronic GvHD. In HLA-matched marrow grafting with primarily methotrexate-based prophylaxis, skin (65–80%), mouth (48–72%), liver (40–73%) and eye (18–47%) involvement are most commonly reported. Other less frequently involved organs include GI tract/weight loss (16–26%), lung (10–15%), oesophagus (6–8%) and joints (2–12%) (Sullivan *et al*, 1991; Ochs *et al*, 1994;

Lee *et al*, 2002a). One group (Sullivan *et al*, 1991) reported that PBSC recipients had a similar time to onset and spectrum of organ involvement. Table III outlines the signs, symptoms and histopathological findings associated with chronic GvHD.

Skin and dermal appendages

Chronic GvHD often presents with a lichenoid eruption, an erythematous, papular rash that resembles lichen planus and has no typical distribution pattern. Sclerodermatous GvHD

Table III. Signs, symptoms and clinicopathological findings of chronic graft versus host disease (GVHD).

System	Signs/laboratory findings	Symptoms	Histopathology	Possible interventions
Skin (common)	Hyper- and hypopigmentation, lichen planus (violaceous flat-topped papules), poikiloderma (atrophy, telangiectasias, dyspigmentation), cutaneous ulcers, scleroderma (thickening due to collagen deposition, may cause decreased range of motion and contractures), ichthyosis	Pruritis, lack of flexibility	Lichenoid: hyperkeratosis, focal hypergranulosis, acanthosis, dyskeratotic keratinocytes, vacuolar degeneration, colloid bodies, perivascular and periadnexal lymphoplasmacellular infiltrate Poikiloderma: epidermal atrophy, loss of rete ridges Scleroderma: epidermal atrophy, dermal fibrosis, less inflammation than lichenoid lesion, adnexal structures destroyed Differential diagnosis: drug reaction, eczema	Moisturize, protect from trauma and sun exposure, treat infections Extracorporeal photophoresis
Cutaneous structures	Onchodystrophy, alopecia, loss of sweat glands	Heat sensitivity	Destruction and fibrosis of cutaneous appendages	Nails: consider nail polish Sweat glands: avoid excessive heat, consider swimming for exercise Systemic therapy: tacrolimus may concentrate in liver; however, there is no randomized trial for effectiveness compared with ciclosporin
Liver (common)	Elevated alkaline phosphatase, transaminases, bilirubin	Pruritis	Small bile duct atypia and damage with subsequent necrosis and dropout, moderate lymphocytic infiltrate, cholestasis and ballooning Differential diagnosis: drug toxicity (cholestasis, inflammation), veno-occlusive disease, viral infections, gallstones and infiltrative processes	
Mouth (common)	Lichen planus, erythema, ulcers, xerostomia, dental caries, fibrosis, decreased salivary flow	Food sensitivity, pain, dry mouth, decreased oral range of motion from fibrosis	Mucosal atrophy, lymphoplasmacytic inflammation, increased mucopolysaccharides, fibrosis and destruction of minor salivary glands Differential diagnosis: herpes virus infection, Sjogren's syndrome	Regular dental care (will need endocarditis prophylaxis), avoid foods not tolerated, Nystatin swish and spit if any sign of candidal infection Topical therapy may be used if tolerated
Eyes (common)	Keratoconjunctivitis sicca, corneal ulcerations, Schirmer's test with <5 mm wetting at 5 min	Dry eyes, photophobia, pain	Differential diagnosis: postirradiation xerophthalmia, Sjogren's syndrome	Preservative-free artificial tears or ointment for night, additional recommendations should be made by ophthalmologist
Oesophagus	Oesophageal web, desquamation, ulcerations, strictures, submucosal fibrosis, abnormal motility	Odynophagia, dysphagia, heartburn, retrosternal pain	Differential diagnosis: reflux oesophagitis, infection	Endoscopic/surgical treatment of strictures – may have to be repeated

Table III. *continued.*

System	Signs/laboratory findings	Symptoms	Histopathology	Possible interventions
Intestines	Fibrosis, malabsorption	Diarrhoea, nausea, anorexia, abdominal pain, weight loss	Differential diagnosis: irritable or inflammatory bowel syndrome, infection	Systemic therapy for chronic GvHD Consider use of beclomethasone oral solution Consultation with nutritionist
Lung	Obstructive more than restrictive abnormalities on pulmonary function testing, bronchiolitis obliterans, pneumothoraces, bronchiectasis, pseudomonal colonization, pulmonary infiltrates; air trapping on high resolution CAT scan of chest	Dyspnoea, non-productive cough, wheezing	Bronchiolitis obliterans with granulation tissue plugs and fibrosis obliterating small airways Interstitial pneumonitis	Treat potential underlying infections, investigational agents
Musculoskeletal	Polymyositis, arthritis, fasciitis	Arthralgias, myalgias, weakness	Biopsy non-specific but may have muscle fibre dropout	Systemic therapy of chronic GvHD
Serous	Pericardial, peritoneal and pleural effusions	Clinical syndromes of cardiac tamponade, ascites, dyspnoea	Usually transudative	Systemic therapy of chronic GvHD
Nervous	Entrapment of nerves, peripheral neuropathy, myasthenia gravis	Pain, paresthesias		Systemic therapy of chronic GvHD
Urologic	Cystitis, phimosis	Pain, haematuria		
Vagina	Erythema, lichen-planus like, sicca, strictures, stenosis, ulcers	Pain, dyspareunia, difficulty voiding		May require topical oestrogen, lubricating gel May need dilatation if strictures
Haematopoietic	Thrombocytopenia, neutropenia, eosinophilia, haemolytic anaemia			Systemic therapy of chronic GvHD
Immune system	Lymphoid hypocellularity, hyper- or hypogammaglobulinaemia	Frequent infections, especially sinus, upper respiratory tract		Systemic therapy of chronic GvHD Prophylaxis for <i>Pneumocystis carinii</i> pneumonia and for pneumococcus Delay vaccination until 6 months off immunosuppressive therapy. CDC recommends longer period for live virus vaccines.

CAT, computerized axial tomography; CDC, Disease Control and Prevention.

may involve the dermis and/or the muscular fascia. The skin is thickened, tight and fragile with very poor wound-healing capacity. Alteration in pigmentation, either hypo- or hyperpigmentation, may occur. In severe cases, the skin may blister from poor lymphatic drainage or ulcerate from minor trauma. Because the sclerosis histologically affects the dermis, hair loss and destruction of the sweat glands are common. Individuals are therefore at risk for hyperthermia unless their environment is controlled. Extensive debridement of tissues should be avoided. Unfortunately, skin grafts often fail second to infection or failure of capillaries and lymphatics. Serial assessments should document the extent, type and distribution of skin involvement.

Fingernails and toenails may be affected by chronic GvHD. Nails develop vertical ridges and cracking and are very fragile. Nail problems may persist even after skin changes have resolved. Hair loss in areas of affected skin may also persist after treatment, although recovery of hair is frequently a sign of recovery. Brittle hair often precedes alopecia. Premature greying of hair, eyebrows and eyelashes may occur with chronic GvHD, even in children. The lack of sweat glands may decrease but may be life-long.

Eyes

Ocular GvHD often presents with irritation, burning, dry eyes or photophobia from irreversible destruction of the lacrimal glands. Excessive tearing can be a sign of ocular sicca. Conjunctival GvHD is a rare manifestation of severe chronic GvHD and can be quite refractory to treatment. Protective eyeglasses and sunglasses, frequent lubrication, application of ophthalmic ointment at night, and punctal plugs or cauterization can help symptomatically and prevent further damage. The close collaboration of an experienced ophthalmologist is recommended to prevent long-term effects. Moisture chamber eyeglasses (a prosthetic device coupled to the eyeglasses) can significantly relieve the symptoms of dry eyes (Hart *et al*, 1994). Schirmer's tests can be performed in clinic and are useful to follow chronic GvHD.

Mouth

Oral GvHD usually starts with xerostomia, frequently with a food sensitivity especially to spicy or acidic foods. More advanced disease may cause odynophagia due to extension of damage. Occasionally, a patient may have oesophageal involvement without obvious oral involvement. In mild disease, a physical examination reveals erythema with white plaques that may be confused with thrush or herpetic infections, while extensive lichenoid or hyperkeratotic changes are found in advanced disease (Schubert *et al*, 1984). Pseudo-membranes, large, non-healing ulcers may be found anywhere in the mouth including tongue and palate but are often along the bite lines. Both major and minor salivary dysfunction occurs (Nagler *et al*, 1996). Local infections may cause changes

in symptoms without changes in physical findings. Secondary infections with viruses (especially herpes simplex and human papilloma virus) and yeasts are almost universal and patients usually require treatment as long as their oral disease persists and they remain on immunosuppression. Fibrosis causing decreased oral range of motion is a very late manifestation. Patients with chronic GvHD undergoing dental work should receive antibiotic prophylaxis following recommendations for prevention of endocarditis.

Gastrointestinal tract

Oesophageal symptoms of dysphagia and odynophagia result from desquamation, web and stricture formation, and reflux oesophagitis. Periodic endoscopic dilations and antacid medications may help symptomatically. Stomach and small intestinal pathology are relatively rare. However, many patients have anorexia, nausea, lower abdominal pain, cramping and diarrhoea. Pancreatic insufficiency without characteristic laboratory and radiographic studies may occur, and this syndrome responds to enzyme supplementation (Akpek *et al*, 2001b). Weight loss is common and is probably multifactorial from decreased oral intake, poor absorption, increased resting energy expenditures (Zauner *et al*, 2001) and elevated tumour necrosis factor levels (Imamura *et al*, 1994). The degree of weight loss should be followed closely so appropriate interventions can be instituted. Hopkins reviewed 93 patients with chronic GvHD, and reported malnutrition in 43% and severe malnutrition with a body mass index less than 18.5 in 14% (Jacobsohn *et al*, 2002). Symptoms often improve with successful treatment of GvHD.

Many patients with chronic GvHD have GI complaints that are not necessarily related to their chronic GvHD. When the Hopkins group reviewed 40 patients with chronic GvHD who underwent endoscopy for GI symptoms, over half (59%) were found to have ongoing *acute* GvHD and an additional 27% had both acute and chronic GvHD when biopsies were obtained. Chronic GvHD alone was found in 14% of cases (Akpek *et al*, 2003). Other causes of GI symptoms included infection, drug side effect, motility disorders and malabsorption not related to chronic GvHD but may be secondary to therapies directed at an incorrect diagnosis.

Liver

Hepatic disease typically presents as cholestasis, with laboratory evaluation revealing elevated alkaline phosphatase and/or elevated serum bilirubin. Occasionally, chronic GvHD of the liver presents as a picture of acute hepatitis (Strasser *et al*, 2000). Liver biopsy is required to confirm the diagnosis and is especially important in patients with no other symptoms of chronic GvHD, as viral infection and drug toxicity may mimic GvHD. Cases of isolated hepatic chronic GvHD may be increasing with the use of DLI (Arai *et al*, 2002).

Respiratory tract

Bronchiolitis obliterans is a late manifestation of chronic GvHD. Patients typically present with a cough, wheezing, dyspnoea on exertion or with a history of recurrent bronchitis or sinusitis (Clark *et al*, 1989). Pulmonary function testing shows new obstructive lung defects defined by a forced expiratory volume in 1 s (FEV1) <80% of predicted or a decrease of FEV1/forced vital capacity by $\geq 10\%$ within a period of less than 1 year, not explained by infection, asthma or recurrent aspiration from the sinuses or from gastroesophageal reflux. A measurement of the diffusion capacity for carbon monoxide (DLCO) should also be performed and may aid in differentiating the role of decreased chest wall movement in patients with concomitant sclerodermatous GvHD. The ability to obtain pulmonary function tests on younger children with the advent of new technology may aid in our understanding of the role of GvHD in the younger child who may be transplanted during the time of normal lung development. Studies to evaluate these children are in the nascent stage. In the absence of chronic GvHD in any other organ, the diagnosis of BO requires negative microbiological tests from bronchoalveolar lavage, evidence of air trapping by high-resolution end-expiratory and end-inspiratory computerized axial tomography scan of the lungs, or confirmation by lung biopsy showing granulation tissue and scarring obliterating the small airways. Although low immunoglobulin levels and chronic GvHD are associated with BO, a randomized trial of prophylactic immunoglobulin replacement did not decrease the incidence of BO (Sullivan *et al*, 1996). Patients with BO have minimal response to therapy and a very poor prognosis; serial pulmonary function tests can quantify the degree of respiratory compromise. BO organizing pneumonia (BOOP) not due to infections may also represent a manifestation of chronic GvHD (Freudenberger *et al*, 2003). Patients with BOOP should be carefully evaluated for the presence of chronic GvHD manifestation in other organs. BOOP may respond to the initiation of corticosteroids and require a slow taper. Successful lung transplantation has been performed in a small number of patients with end-stage pulmonary chronic GvHD (Boas *et al*, 1994; Rabitsch *et al*, 2001). Outside of HCT, an underlying autoimmune process is implicated by the association of BO with lung transplantation, collagen vascular diseases and viral infections (Holland *et al*, 1988; Philit *et al*, 1995).

Even without BO, pulmonary sicca and bronchiectasis lead to frequent infections and bacterial colonization, often with *Pseudomonas* species. Patients with chronic GvHD are also at risk for chronic sinopulmonary disease, which may be relatively asymptomatic given the extent of involvement. The sinuses should be considered as a potential fever source in any patient with chronic GvHD. The smoking habits of patients, especially adolescents, should be reviewed and the individual and caregivers should be counselled about the risks of smoking and of passive smoking (Socie *et al*, 2001).

Musculoskeletal system

Muscle cramps are a common complaint, although the pathophysiology is not understood. Myositis, with tender muscles and elevated muscle enzymes, may start as a proximal myopathy, but is rare and does not explain the frequent complaints of severe cramps. Fascial involvement in sclerodermatous GvHD is usually associated with skin changes, but may develop with normal, but fixed overlying skin (Janin *et al*, 1994). Fasciitis often affects forearms and legs causing significant limitations in range of motion and joint contractures. Patients with a restricted range of motion often benefit from a regular programme of physical therapy and deep muscle-fascial massage. Serial assessments of joints should document the patients' range of motion.

Haematopoietic system

Cytopenias are common in chronic GvHD patients. They may be a result of stromal damage or due to autoimmune processes. Thrombocytopenia at the time of chronic GvHD diagnosis has been associated with a poor prognosis (Sullivan *et al*, 1988a; Anasetti *et al*, 1989; Akpek *et al*, 2001a). Peripheral blood thrombopoietin concentrations may be decreased secondary to BM stromal cell damage (Hirayama *et al*, 2003). Eosinophilia may be seen and may be an indicator of chronic GvHD activity.

Other organ systems

Pericardial and pleural effusions can cause compressive loss of function and may require drainage and sclerosis. Peripheral oedema may be severe. Myasthenia gravis and peripheral neuropathy have also been attributed to chronic GvHD. Women may develop vaginal or vulvar lichenoid changes, ulcers, web formation and strictures, and should have a biopsy to confirm the diagnosis if no other organs are involved (Spinelli *et al*, 2003). Topical corticosteroids can be effective treatment for vaginal chronic GvHD, and mechanical or surgical dilation may be necessary for the relief of symptoms.

In paediatrics, chronic GvHD and its treatment can inhibit growth. Children frequently experience catch-up growth if growth plates remain open once chronic GvHD is controlled and immunosuppression tapered; however, their full predicted height, based on parental heights, may not be reached. Maintaining adequate nutrition is essential and evaluation of growth and, in particular, head circumference is required. Possible underlying endocrine deficiencies should be evaluated and corrected when possible. Dietary supplementation is frequently needed in severe cases. It is imperative to maintain as much range of motion as possible at involved joints. Chronic GvHD involvement of heart, kidney and central nervous system is questionable despite occasional rare reports.

Immunodeficiency

Chronic GvHD causes profound immune dysfunction (Siadak & Sullivan, 1994; Storek *et al*, 1996; Sherer & Shoenfeld, 1998; Maury *et al*, 2001), and most chronic GvHD deaths are attributable to infection. Defects in mucosal integrity, immunosuppressive medications, and reduced number and function of mature T and B cells contribute to the high case fatality rate from bacterial, fungal and viral pathogens (Siadak & Sullivan, 1994; Storek *et al*, 1996; Sherer & Shoenfeld, 1998; Maury *et al*, 2001). Functional asplenia with an increased susceptibility to encapsulated bacteria, particularly pneumococcus, is common, and circulating Howell-Jolly bodies may be seen on peripheral blood smears (Kulkarni *et al*, 2000). Patients are also at high risk for invasive fungal infections and *Pneumocystis carinii* pneumonia (Kulkarni *et al*, 2000; Chen *et al*, 2003).

Evaluation and diagnosis of chronic GvHD

Many patients will have returned to the care of their primary haematologist/oncologist when chronic GvHD develops. Therefore, all clinicians who care for individuals following a stem cell transplant must be aware of the clinical picture of chronic GvHD as patients have frequently returned to their referring institutions. While not every rash or GI complaint represents GvHD, the accurate and timely diagnosis of chronic GvHD is an important first step in its successful treatment. It is important to confirm the diagnosis of chronic GvHD and rule out other potential causes of rashes, diarrhoea, or liver function test abnormalities such as drug reactions or infection. Subtle manifestations of chronic GvHD may go undiagnosed for months and frequently results in decreased function, markedly affecting the activities of daily living including the ability to eat and dress oneself. However, symptoms are frequently downplayed until they become unbearable. For example, the diagnosis of fasciitis without skin changes may be difficult to recognize, but systematic assessment of range of motion of wrists and ankles may detect early signs before permanent disability. In addition, pulmonary function testing at 3 months and at 1 year after transplant may detect early signs of BO before symptoms become apparent.

The care for patients with possible chronic GvHD requires a multidisciplinary team of health care workers and co-operation of the patient and caregivers. Patients should be evaluated at a centre familiar with chronic GvHD and should return periodically for re-evaluations. In addition to physicians and nurses, patients should be evaluated by a physical therapist, a nutritionist, an occupational therapist and an ophthalmologist. Additional evaluations should depend on the organ system involved and the mode of therapy chosen.

Therapy for chronic GvHD is highly immunosuppressive and must be continued for a prolonged time. It is imperative to confirm the diagnosis before initiating therapy. The diagnosis of chronic GvHD is often based on clinical findings only. It is important to obtain a biopsy of the affected organ

when possible, as there are often many potential aetiologies for the abnormalities. A pathologist experienced in the histological diagnosis of GvHD and variations seen in acute and chronic GvHD should review the case. The diagnosis of chronic GvHD was conventionally made after day 100 post-transplant, although there is no biological reason for this. Evaluations of patients may reveal the presence of findings consistent with chronic GvHD prior to day 100 post-SCT, and acute and chronic GvHD may be present concurrently. The initial presentation of chronic GvHD after day 500 post-SCT is rare. The median time of diagnosis of chronic GvHD is day 201 after HLA-identical sibling transplant, day 159 after mismatched-related transplant, and day 133 after an unrelated donor transplant (Sullivan *et al*, 1991). Recent IBMTR/NMDP data showed that the median time of diagnosis of chronic GvHD is 4.5 months after HLA-identical sibling transplant and 4 months after unrelated donor transplant, with only 5% of cases diagnosed after 1 year (Lee *et al*, 2002a).

There is a tendency to assume that problems post-transplant are due to chronic GvHD. In reviewing 123 patients referred to Johns Hopkins for the management of refractory chronic GvHD, we found that nine patients had no evidence of ever having chronic GvHD and that 26 additional patients had inactive disease (Jacobsohn *et al*, 2001). Individuals are frequently begun and continued on immunosuppressive therapy without an objective response, placing them at high risk for infection. Unfortunately, there is no reliable laboratory indicator of the onset or progress of chronic GvHD. Thus, it is important to have a high index of suspicion and to carefully evaluate abnormalities in patients after allogeneic grafts and carefully document improvements following the initiation of treatment strategies.

Once chronic GvHD is diagnosed, intermittent evaluation at an experienced centre can help guide management. In a series of 123 patients referred to Johns Hopkins for the management of refractory chronic GvHD, nine patients were judged to never have had chronic GvHD and 26 patients had inactive disease (Jacobsohn *et al*, 2001). Restaging with the use of the Schirmer's test, pulmonary function tests, gynecological evaluation, liver function, complete blood counts and medical photographs, if skin involvement is present is helpful to assess the extent of the disease. A morbidity scale can be used to record the severity of manifestation of the chronic GvHD at the time of diagnosis, whenever therapy is changed, and at yearly intervals if treatment continues or if manifestations of chronic GvHD persist.

Prevention

Although acute GvHD is a predictor for development of chronic GvHD, successful efforts to decrease acute GvHD have not resulted in decreased rates of chronic GvHD. The two notable exceptions are T-cell depletion and use of umbilical cord blood as a stem cell source, as lower rates of both acute and chronic GvHD are observed with these approaches

(Kurtzberg *et al*, 1996; Gluckman *et al*, 1997). Specific attempts to decrease chronic GvHD rates through prolonging the ciclosporin administration, addition of immunoglobulin or thalidomide, and preemptive treatment on the basis of subclinical chronic GvHD found in skin and lip biopsies (Sullivan *et al*, 1988b; Loughran *et al*, 1990; Gluckman *et al*, 1997) have proved unsuccessful. The use of decreased doses of ATG at the time of the preparative regimen may decrease the rate of chronic GvHD in addition to chronic GvHD without a decrease in the rate of engraftment (Meijer *et al*, 2003).

Treatment of chronic GvHD

The most frequent life-threatening complication of chronic GvHD and its treatment is infection, therefore patient education and infection prophylaxis are very important components of chronic GvHD management. Infection is the leading cause of death in patients with chronic GvHD. The US Department of Health and Human Services Centers for Disease Control and Prevention (CDC) have suggested guidelines for prevention of opportunistic infections among haematopoietic stem cell transplant recipients. The strength of the recommendations is based on current literature in the field and can be found at the web site of CDC (http://www.cdc.gov/mmwr/mmwr_rr.html) (Centers for Disease Control and Prevention, Infectious Disease Society of America & American Society of Blood and Marrow Transplantation, 2000). Briefly, prophylaxis against *P. carinii* should be administered to all patients undergoing treatment of chronic GvHD for 6 months after discontinuation of immunosuppressive medications. Life-long splenic dysfunction occurs with chronic GvHD, and prophylaxis against encapsulated bacteria is recommended. The guidelines published by the American Heart Association for endocarditis prophylaxis (Dajani *et al*, 1997) should be followed when patients are undergoing dental or other invasive procedures. Patients treated with topical steroids for oral GvHD should be treated with clotrimazole troches or nystatin swishes to prevent oral candidiasis. Patients at risk for late cytomegalovirus (CMV) disease (receiving systemic corticosteroids) should have CMV activity monitored closely, and treatment initiated on reactivation. Patients should receive prophylactic acyclovir for prevention of varicella zoster virus infection during the first year after the transplant and later if systemic immunosuppression is still needed to control chronic GvHD. Some centres administer intravenous immunoglobulin (IgG) to patients with hypogammaglobulinaemia (if levels are <4 g/l) to maintain serum IgG levels >5 g/l. Post-transplant vaccination guidelines are available on the centres for CDC web site (http://www.cdc.gov/mmwr/mmwr_rr.html) (Centers for Disease Control and Prevention, Infectious Disease Society of America & American Society of Blood and Marrow Transplantation, 2000). Patients with chronic GvHD should not receive live virus vaccinations such as measles, mumps, rubella, varicella or the new inhaled influenza vaccine. Respiratory syncytial virus prophylaxis should be discussed

for patients with lung disease who are at risk for acquiring infections, such as young children in day care.

The most widely employed first line therapy for treatment of chronic GvHD is a ciclosporin A (CSA) and prednisone regimen. Sullivan *et al* (1988b) reported that prednisone alone was superior to prednisone plus azathioprine for primary treatment of patients with standard-risk extensive chronic GvHD. However, in patients classified as high risk on the basis of platelet counts less than $100 \times 10^9/l$, treatment with prednisone alone resulted in only 26% 5-year survival. When a similar group of patients was treated with alternating day CSA and prednisone, the 5-year survival exceeded 50% (Sullivan *et al*, 1988a). After this encouraging report, most centres, including our own, adopted this regimen for initial treatment of all patients, not just those deemed at high risk. Patients start treatment with daily prednisone at 1 mg/kg/d and daily CSA at 10 mg/kg/d, given twice a day with CSA adjusted for renal status and concomitant drug use based on serum drug levels. If chronic GvHD is stable or improving after 2 weeks, prednisone is tapered by 25% per week to a target dose of 1 mg/kg every other day. After successful completion of this steroid taper, CSA is reduced by 25% per week to alternate day dosing of 10 mg/kg/d divided twice a day, every other day. If the disease has completely resolved, patients are slowly weaned from both medications after 9 months, with dose reductions approximately every 2 weeks. Patients with incomplete responses are kept on therapy for three more months and then re-evaluated. If patients fail to respond by 3 months or demonstrate progressive disease, salvage regimens are warranted (Vogelsang, 2001). Many centres use tacrolimus in place of ciclosporin in front line therapy and some favour it for the treatment of liver GvHD. Many centres have begun to utilize sirolimus for the treatment of chronic GvHD as well, based on the growing experience in the solid organ transplant setting.

Until recently, there was no data on the effectiveness of this regimen in standard risk patients. Flowers (2002) reviewed the success of initial combination therapy for patients treated in the 1980s. She reported a non-relapse mortality of 21% in standard risk patients ($n = 126$) and 39% in high-risk patients ($n = 111$), defined by progressive onset or thrombocytopenia. Successful discontinuation of all immunosuppressive medications eventually occurred for 60% of standard risk patients and 40% of high-risk patients (Flowers, 2002). Koc *et al* (2002) reported the long awaited results of a study comparing prednisone alone to prednisone plus CSA in patients with extensive chronic GvHD without thrombocytopenia. In this trial ($n = 287$ evaluated patients), the cumulative incidence of TRM, survival, relapse, need for secondary chronic GvHD therapy and discontinuation of immunosuppressive medications were not significantly different between the two arms. Intriguingly, survival without recurrent malignancy was better in the prednisone-only arm ($P = 0.03$), although the incidence of avascular necrosis was also higher. Thus, there is no evidence that initial combination therapy improved control of

chronic GvHD in patients with platelet counts greater than $100 \times 10^9/l$. 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. Currently, two large randomized trials are planned or underway for front line therapy. One trial, through the Children's Oncology Group, is looking at the addition of hydroxychloroquine to ciclosporin or tacrolimus plus prednisone. The other multicentred trial, organized by the Fred Hutchinson Cancer Research Center, is examining the addition of mycophenolate mofetil to prednisone plus calcineurin inhibitor in patients with *extensive* chronic GvHD or high-risk features. Table IV reviews the published trials of initial treatment for chronic GvHD.

Secondary therapies

If patients fail to respond or progress through steroid-based therapy then secondary therapy is indicated. Steroid-refractory

chronic GvHD is formally defined as either failure to improve after at least 2 months, or progression after 1 month of standard immunosuppressive therapy including corticosteroids and ciclosporin (Parker *et al*, 1995; Browne *et al*, 2000). 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 included 40 or fewer patients. Reported response rates are usually based on four categories: complete (resolution of all chronic GvHD manifestations), partial ($\geq 50\%$ but less than complete organ responses), no response ($< 50\%$ response) and progression (worsening while on therapy) (Vogelsang *et al*, 1992; Parker *et al*, 1995). Table V provides information about salvage therapies in chronic GvHD. Single institution experiences of the use of extracorporeal photopheresis have been reported for patients with extensive skin GvHD with promising results and this technique is now being extended to the treatment of children, resulting in an increased 5-year survival and undoubtedly an increase in QOL (Messina *et al*, 2003; Seaton *et al*, 2003). A multicentre, randomized trial with extracorporeal

Table IV. Primary therapy for chronic graft *versus* host disease (GvHD).

Treatment	<i>n</i>	Comments	Conclusions
Group I: untreated, Group II: corticosteroids and/or anti-thymocyte globulin, Group III: corticosteroids and cyclophosphamide, procarbazine, or azathioprine	52	Sequential study, alive and free of disability: untreated 15%, corticosteroids and/or ATG 23%, combination therapy 71%	Most effective regimen was corticosteroids and azathioprine (Sullivan <i>et al</i> , 1981)
Corticosteroids \pm azathioprine	179	Standard risk patients were randomized, high risk patients given single agent prednisone, 40% of patients in each group had subclinical disease only	Higher mortality from infection if azathioprine part of initial treatment regimen. In high risk patients (platelet count $< 100 \times 10^9/l$), prednisone alone resulted in 26% survival (Sullivan <i>et al</i> , 1988b)
Alternating day corticosteroids and ciclosporin	61	Phase II design, high-risk extensive chronic GvHD, 40 given primary therapy, 21 given salvage therapy, long-term survival $> 50\%$ compared with historical control of 26%	Alternating day, combination therapy better (Sullivan <i>et al</i> , 1988a)
Cyclosporine, steroids \pm thalidomide	54	Randomized, unblinded trial, patients with extensive chronic GvHD	Closed early (target enrolment $n = 134$) after interim analysis showed slow accrual and higher response rates in both arms than projected (Arora <i>et al</i> , 2001)
Steroids, ciclosporin or tacrolimus \pm thalidomide	51	Randomized, placebo-controlled trial of thalidomide added to standard upfront therapy in higher risk patients with thrombocytopenia or progressive presentation	Closed early (target enrolment $n = 132$) after interim analysis showed slow accrual and only 42% probability of reaching statistical significance by enrolling remainder of patients (Koc <i>et al</i> , 2000)
Steroids \pm ciclosporin	287	Randomized, unblinded trial, enrolled 1985–92	DFS was lower in the combination arm (HR 1.51, 95% CI 1.03–2.21, $P = 0.03$) in multivariate analysis. Transplant-related mortality, relapse, secondary chronic GvHD therapy rates and discontinuation of all immunosuppressive therapy were not different (Koc <i>et al</i> , 2002)

ATG, antithymocyte globulin; DFS, disease-free survival; HR, hazard ratio.

Table V. Secondary therapy for chronic GvHD.

Agent	Published success rate	Hypothesized mechanism of action	Side effects	References
High-dose corticosteroids	48% major response rate ($n = 56$)	Lympholytic at these doses	Infection, glucose intolerance, osteoporosis, avascular necrosis, cataracts, psychological effects including psychosis, insomnia	Alpek <i>et al</i> (2001c)
Tacrolimus (Prograf)	35% response rate ($n = 39$)	Binds to FKBP-12 (FK binding protein) and inhibits T-lymphocyte activation, concentrates in liver	Renal dysfunction, neurotoxicity, hypertension	Tzakis <i>et al</i> (1991), Carnevale-Schianca <i>et al</i> (2000)
Mycophenolate mofetil (Cellcept)	46% objective response ($n = 26$)	Prodrug of mycophenolic acid that is a non-competitive reversible inhibitor of inosine monophosphate dehydrogenase. Cytostatic for T and B lymphocytes, as they lack salvage pathways	Nausea, vomiting, diarrhoea, neutropenia	Basara <i>et al</i> (1998), Mookerjee <i>et al</i> (1999)
Rapamycin (Rapamune)	Not available	Binds to FKBP-12 and mTOR (mammalian target of rapamycin) to inhibit cytokine-driven T-cell proliferation	Hyperlipidemia, hypertension, rash	
Extracorporeal photopheresis	33–80% ($n = 11$ –18)	Induces apoptosis in alloreactive T cells, normalization of CD4/CD8 ratios by decreasing CD8 cells, increases natural killer cells, decreases dendritic cells	Gastrointestinal upset, potential need for central i.v. access	Dall'Amico <i>et al</i> (1997), Greinix <i>et al</i> (1998), Child <i>et al</i> (1999), Alcindor <i>et al</i> (2001)
Psoralen and UVA (PUVA)	40% CR, 38% PR ($n = 11$ –40)	Interferes with antigen presentation and inflammatory cytokine production by Langerhan's cells, increases IL-10	Increase in skin cancer, phototoxicity, nausea, hepatotoxicity	Eppinger <i>et al</i> (1990), Jampel <i>et al</i> (1991), Kapoor <i>et al</i> (1992)
UVB radiation	Case series	Treats epidermis only, induces IL-10 in human epidermal cells	Increase in skin cancer, phototoxicity	Enk <i>et al</i> (1998)
Thalidomide	9–42% CR rate ($n = 14$ –80)	Anti-inflammatory and immunosuppressive properties	Neuropathy, somnolence, constipation, neutropenia	Vogelsang <i>et al</i> (1992), Parker <i>et al</i> (1995), Rovelli <i>et al</i> (1998), Browne <i>et al</i> (2000)
Etretinate (no longer available), acitretin (Soriatane)	74% improvement ($n = 27$)	Synthetic vitamin A derivative, may affect production of cytokines	Skin scaling, breakdown, nail cracking, xerosis, cheilitis, pruritis, rare pseudotumour cerebri	Marcellus <i>et al</i> (1999)
Azathioprine (Imuran)	Not available	Cleaved to mercaptopurine	Gastrointestinal symptoms, neutropenia, thrombocytopenia	Gilman <i>et al</i> (2000)
Hydroxychloroquine (Plaquenil)	9% CR and 44% PR ($n = 40$)	Interferes with antigen processing and presentation, proliferation, TNF- α production, and cytotoxicity, synergistic with ciclosporin and tacrolimus <i>in vitro</i>	Gastrointestinal symptoms, rare retinal toxicity	

Ursodeoxycholic acid (Actigal)	33% decreased in bilirubin levels, but not sustained off therapy (<i>n</i> = 12)	Replaces native human bile acids, reduces class I human leucocyte antigen expression on hepatocytes	Diarrhoea, abdominal pain, headache	Fried <i>et al</i> (1992)
Clofazimine (Lamprone)	55% PR (<i>n</i> = 22)	Atypical immunomodulatory effects	Abdominal cramping, hyperpigmentation	Lee <i>et al</i> (1997)
Antithymocyte globulin	Not available	<i>In vivo</i> T-cell depletion	Anaphylaxis, serum sickness	
Daclizumab (Zenapax)	Not available	Humanized anti-IL-2 receptor antibody	None	
Infliximab (Remicade)	Reported in abstracts	Chimaeric IgG monoclonal antibody, binds to TNF- α and prevents binding with receptors	Hypersensitivity reactions, infections	
2-deoxycoformycin (Pentostatin)	Reported in abstracts	Inhibits adenosine deaminase	Nausea, vomiting, myelosuppression, rash, headache	
Rituximab (Rituxan)	Case report	Chimaeric anti-CD20 monoclonal antibody	Allergic reactions	Ratanatharathorn <i>et al</i> (2000)
Total lymphoid radiation	Case series		Leucopenia	Socie <i>et al</i> (1990), Bullorsky <i>et al</i> (1993)
Topical azathioprine	Case report	Purine analogue metabolized to 6-mercaptopurine	Rash, fever, pancreatitis, arthralgias, malaise, nausea, diarrhoea, pancytopenia, hepatitis, infections, malignancy	Epstein <i>et al</i> (2000)
Topical tacrolimus	Case series	0.1% ointment	Localized skin burning, pruritis, irritation	Aoyama <i>et al</i> (1995)
Ophthalmic ciclosporin	Case series	1% solution	None	Kiang <i>et al</i> (1998)
Intravenous lidocaine	Case report	Vascular and anti-inflammatory properties	Seizures, drowsiness, tremors, hypotension	Voltairelli <i>et al</i> (2001)

IL; interleukin; CR, complete remission; PR, partial remission; TNF- α , tumour necrosis factor alpha.

photopheresis is currently being conducted in the United States and Europe for patients with corticosteroid-dependent or refractory chronic GvHD with skin involvement.

Impact of chronic GvHD on major transplantation outcomes

Non-relapse mortality

Chronic GvHD is the major cause of non-relapse mortality in patients surviving more than 2 years following allogeneic transplantation, and the increasing severity of chronic GvHD is associated with higher non-relapse mortality rates (Socie *et al*, 1999).

Infection from a broad array of pathogens is the major cause of death, followed by progressive organ failure from chronic GvHD involvement. *De novo* chronic GvHD occurs later than the other forms of chronic GvHD and does not seem to adversely affect survival (Sullivan *et al*, 1981; Weiden *et al*, 1981). In aplastic anaemia and refractory anaemia 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 (Deeg *et al*, 1998; Goerner *et al*, 2002).

Graft versus malignancy effect

Chronic GvHD is associated with lower relapse rates in both early and advanced stage leukaemia (Weiden *et al*, 1979, 1981; Sullivan *et al*, 1989; Horowitz *et al*, 1990; Ringden *et al*, 1997; Brunet *et al*, 2001; Lee *et al*, 2002a). However, the nature of this graft *versus* malignancy effect is poorly understood, and it is not known whether the protective effect relies on development of overt chronic GvHD or is durable once chronic GvHD resolves (Sullivan *et al*, 1989). Recent observational data suggest that increased severity of chronic GvHD is not associated with a decreased relapse risk.

Nevertheless, studies examining preventive and treatment strategies should carefully follow relapse rates, especially in situations where disease is advanced or cure is thought to be heavily reliant on an intact graft *versus* malignancy effect. For example, eradication of Philadelphia chromosome-positive cells in patients with chronic myeloid leukaemia was correlated with development of chronic GvHD in one study (Pichert *et al*, 1995).

Impact on functional status and quality of life

Chronic GvHD is associated with substantial QOL deficits, particularly in the areas of physical and functional status (Syrjala *et al*, 1993; Chiodi *et al*, 2000; Heinonen *et al*, 2001; Lee *et al*, 2002b). In addition, patients with chronic GvHD report more specific symptoms such as rashes, mouth sores and frequent infections than unaffected individuals (Schmidt

et al, 1993; Sutherland *et al*, 1997). Social and emotional functioning and satisfaction with transplantation are relatively preserved, although chronic GvHD is associated with decreased general health status, sexual inactivity and loss of employment in long-term survivors (Sullivan *et al*, 1981; Wingard *et al*, 1991; Andrykowski *et al*, 1995; Marks *et al*, 1999; Socie *et al*, 2001; Lee *et al*, 2002b). In addition, long-term treatment with corticosteroids for chronic GvHD may result in compromised QOL due to the significant morbidity associated to this treatment. A 30-item survey allowing patient self-report of chronic GvHD symptoms has been validated (Lee *et al*, 2002b).

Future directions

Efforts to prevent the development of chronic GvHD, including the use of immunoglobulin and thalidomide, have been unsuccessful (Chao *et al*, 1996; Sullivan *et al*, 1996). Likewise, trials of prolonged administration of CSA found no difference in chronic GvHD or mortality when CSA was given for 24 months rather than 6 months (Kansu *et al*, 2001). Current transplantation practices, including the use of DLI and PBSC, older patient age and the increasing use of unrelated and mismatched stem cell donors make it likely that chronic GvHD is going to be a progressively more common problem. Ongoing research to further characterize the pathogenesis of this disease is crucial to the development of new therapeutic approaches, while well-organized, multicentre trials are needed to test clinical questions. As the repertoire of possible treatment options and clinical trials for treatment of these patients expands, the need to identify and enrol patients on clinical trials grows.

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