Management of chronic graft-versus-host disease

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A B S T R A C T

Chronic graft-*versus*-host disease (cGvHD) is the main cause of long-term morbidity and mortality after allogeneic hematopoietic stem cell transplantation. The complexity of the diagnosis and management of cGvHD and its complications requires a multidisciplinary approach. The National Institute of Health Consensus Development Project distinguishes 3 groups based on the number and severity of organs involvement, with 2-year overall survival of 62%, 86%, and 97% for patients diagnosed with severe, moderate and mild cGvHD, respectively. Systemic therapy is generally considered for patients who meet criteria for moderate-to-severe cGvHD (involvement of 3 or more organs, or with an organ score of 2 or greater in any single organ, or any lung involvement), or for those with less severe disease but with high-risk features. Secondary treatment is generally considered when chronic GvHD shows evidence of progression, no improvement despite treatment during at least 4-8 weeks, when new clinical manifestations develop, or when symptoms worsen during taper of prednisone. There is no current standard of secondary treatment, and "trial-and-error" remains the main way to identify an effective treatment for each individual patient. The choice of agent is likely to depend on the toxicity profile, organ involvement, patient preference and availability. Extracorporeal photopheresis (ECP), mammalian target of rapamycin (mTOR) inhibitors, pentostatin, and rituximab are suggested as second-line treatment options in refractory cGvHD.

Learning goals

At the conclusion of this activity, participants should be able:
- to identify patients diagnosed with cGvHD who require either topical and/or systemic immunosuppressive treatment, as well as those candidates to receive second-line treatment;
- to know the currently available treatment options for both first- and second-line treatment of cGvHD and the most appropriate strategy depending on toxicity profile and organ involvement.

Introduction

Chronic graft-*versus*-host disease (cGvHD) is the main cause of long-term morbidity and mortality after allogeneic hematopoietic stem cell transplantation (alloHSCT) occurring in approximately 50% of transplant recipients. Patients with chronic GvHD (cGvHD) require prolonged immunosuppressive treatment for an average of two years from diagnosis, with 10% of those surviving at least for seven years still requiring immunosuppressive treatment.[1,2] Glucocorticoids with or without calcineurin inhibitors (i.e. cyclosporine or tacrolimus) remain the standard initial treatment, but significant side-effects and unsatisfactory outcomes support the need for more effective and less toxic therapies.

The pathogenesis of chronic GvHD remains elusive. Persistence of allo-reactivity may be due to the expansion of donor T cells which escape deletion mechanisms both in the thymus and in peripheral blood, so that they do not develop immune-tolerance against antigens from the recipient.[3] These lymphocytes may generate direct cytotoxic damage or may produce cytokines which in turn induce activation of B cells and production of auto-antibodies, detected in 11-62% of patients with chronic GvHD, However, direct evidence for the causal relationship of these antibodies in GvHD pathogenesis has not yet been demonstrated, except for the stimulatory anti-platelet-derived growth factor alpha receptor (PDGFR) antibodies in the sclerotic chronic GVHD phenotype.[4]

Incidence and risk factors for developing cGvHD

Median time to develop cGvHD ranges from 200 to 133 days for patients receiving alloHSCT from matched related *versus* mismatched unrelated donor transplants.

Overall, risk profiles are quite similar for both acute and chronic GvHD.[5] In this regard, HLA disparity is one of the most important risk factors for cGvHD, with an incidence ranging from 40% among patients receiving alloHSCT from a matched related donor to up to 70% among those receiving it from a mismatched unrelated donor. Moreover, prior grades 3-4 acute GvHD is the main risk factor for developing cGvHD, with 70-80% incidence among patients who have developed prior acute GvHD. Nevertheless, notable differences are observed for other risk factors between acute and cGvHD, such as a greater

impact of female donor into a male recipient on chronic GvHD compared to acute GvHD, and the strong associations of mobilized peripheral blood cells and of older patient as well as donor age with increased risks for chronic GvHD but not for acute GvHD. This suggests that chronic GvHD is not simply an end stage of acute GvHD. More specifically, regarding the impact of the source of hematopoietic stem cells, the risk of overall and extensive cGvHD varies from 56% and 35% at five years among patients receiving bone marrow transplantation *versus* 73% and 51%, respectively,[6] among those receiving peripheral blood HSCT from matched related donors. These incidences are 41% and 32% for patients receiving bone marrow and 53% and 48% at two years for those receiving peripheral blood from unrelated donors.[7]

Finally, other characteristics of the inoculum such as T-cell depletion, either *in vitro* or *in vivo*, as well as the total number of $CD34^+$ cells infused may influence the risk of cGvHD.[8] In this regard, in a recent randomized trial, 12% *versus* 45% of patients developed extensive cGvHD at three years post transplant among those receiving or not ATG, respectively.[9]

Classification and prognostic factors

Classic limited *versus* extensive classification for cGvHD has been overcome by the NIH proposal.[10,11] The National Institute of Health (NIH) Consensus Development Project distinguish 3 groups based on the number and severity of organs involvement. Several studies have demonstrated the prognostic value of this classification, with 2-year overall survival of 62%, 86%, and 97% for patients diagnosed with severe, moderate and mild cGvHD.[12] The International Bone Marrow Transplant Registry (IBMTR) identifies several risk factors predicting survival in patients with cGvHD, including age, prior acute GvHD, time from transplantation to cGvHD, donor type, disease status at transplantation, GvHD prophylaxis, gender mismatch, serum bilirubin, Karnofsky score (KPS), and platelet count. These variables have allowed a cGvHD risk score to be created, and 6 risk groups were identified with 5-year overall survival ranging from to 91% to 4%.[13] In a study by Lee *et al.,* KPS, mouth and skin involvement, diarrhea, and weight loss were found to be important, with high KPS and mouth involvement being favorable prognostic signs, and skin involvement, diarrhea, and weight loss being unfavorable factors.[14] Stewart *et al*. identified HLA mismatch, hyper-bilirubinemia, increased age, thrombocytopenia at cGvHD onset, and progressive onset of disease as risk factors associated with an increased non-relapse mortality in the cGvHD setting.[15] Overall, low platelet count as well as KPS at the time of cGvHD diagnosis together with severity of organ involvement according to NIH (with especial attention to gut or lung) are recognized as the most important prognostic factors in most studies, and allow subgroups of patients with very different outcomes to be identified[16,17] so that therapeutic strategies can be planned according to these factors.

Treatment

The complexity of the diagnosis and management of cGvHD and its complications requires a multidisciplinary approach. A schema of the therapeutic strategies currently available for cGvHD is shown in Figure 1.

Systemic therapy is generally considered for patients

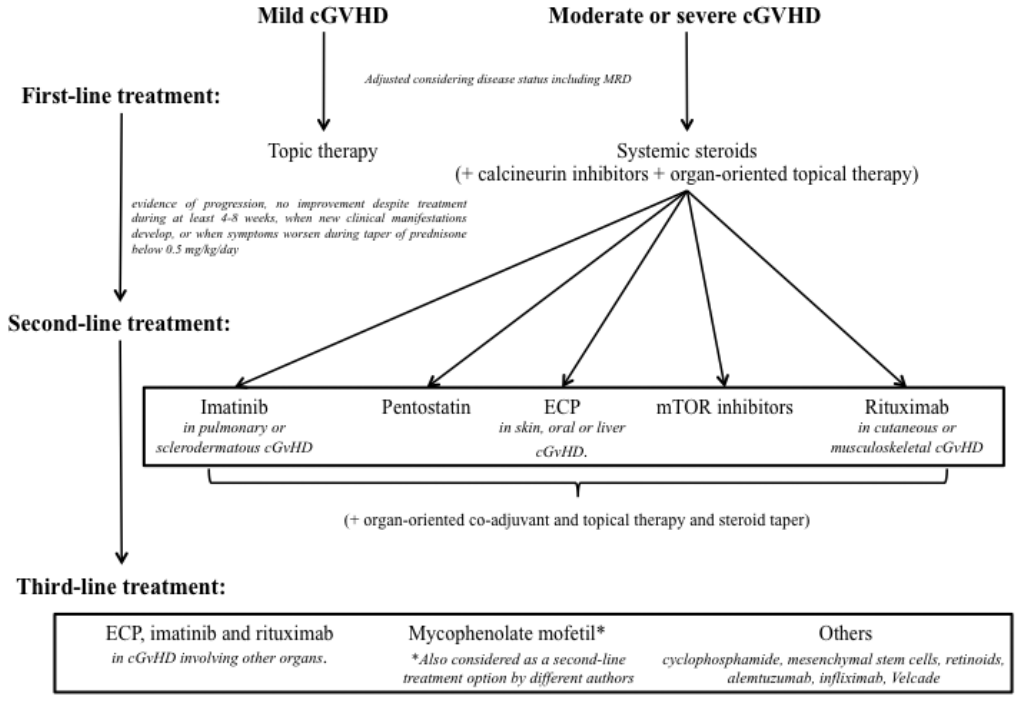

Figure 1. A schema of the therapeutic strategies currently available for cGvHD.

who meet criteria for moderate-to-severe global severity according to the NIH consensus criteria[18-20] (involvement of 3 or more organs, or with an organ score of 2 or greater in any single organ, or any lung involvement), or for those with less severe disease but with high-risk features. Topical therapies may also be used as an adjunct to improve and hasten local response for patients requiring systemic therapy. Symptomatic mild cGvHD is often treated with topical therapies alone. Considering the impact of the management of immunosuppressive therapy not only on GvHD but also on graft-*versus*-leukemia effect, also disease status at transplant and risk of relapse must be considered, in addition to criteria directly related to cGvHD, in order to decide the best therapeutic approach (either systemic and/ or topical treatment) and the best schedule to taper immunosuppression after transplantation.[21-24]

Patients with cGvHD should be reviewed by a team experienced in managing transplant-related complications, which must include a network of specialists to allow for multidisciplinary management.

Initial treatment

Randomized studies for treatment of newly diagnosed chronic GvHD have not demonstrated any benefit from additional agents to glucocorticoids, except for lower rates of avascular necrosis when calcineurin inhibitor (CNI) is added to prednisone in patients with a low-risk profile. In contrast, in patients with high-risk features (extensive cGvHD plus thrombocytopenia), there is an improvement in overall survival using the combination as compared to glucocorticoids alone.[25,26] Thus, the standard initial systemic treatment of chronic GVHD is administration of glucocorticoids (1 mg/kg/day) followed by taper to eventually reach an alternate-day regimen, with or without calcineurin inhibitor, which might be helpful as steroid sparer. The Seattle Group has reported on an alternate day dosing regimen for tapering steroids. This regimen involved using a daily dose of 1 mg/kg for two weeks and subsequently reducing the dose by 25% each week, aiming for a dose of 1 mg/kg on alternate days after 6-8 weeks. In severe cGvHD, this dose may be maintained for 2-3 months and then tapered by 10-20% per month for a total duration of nine months

Secondary treatment

Considering the scarce number of prospective randomized studies available evaluating the efficacy of secondary treatment approaches for cGvHD, evidence is mostly based on non-randomized studies and recommendations based on consensus guidelines. Recently, practical guidelines for cGvHD therapy have been proposed by a joint working group established by the Haemato-Oncology subgroup of the British Committee for Standards in Haematology (BCSH) and the British Society for Bone Marrow Transplantation (BSBMT) and by the German Working Group on Bone Marrow and Blood Stem Cell Transplantation (DAG-KBT) and the German Society of Hematology and Oncology (DGHO), the Austrian Stem Cell Transplant Working Group of the Austrian Society of Hematology and Oncology, the Swiss Blood Stem Cell Transplantation Group (SBST), and the German-Austrian Paediatric Working Group on HSCT.[27,28]

Secondary treatment is generally considered in patients in whom chronic GvHD shows evidence of progression, no improvement despite treatment during at least 4-8 weeks, when new clinical manifestations develop, or when symptoms worsen during taper of prednisone below 0.5 mg/kg/day. There is no current standard of secondary treatment, and "trial-and-error" remains the main way to identify an effective treatment for each patient.[23,27-29] The choice of agent should be based on the toxicity profile, organ involvement, patient preference and availability. Second-line therapy should avoid changing more than one agent at a time, with assessment at 8-12 weeks. Where there is progression within a 4-week period, alternative therapies can be considered, although patients with sclerotic skin disease are likely to take longer to demonstrate response.

In principle, less immunosuppressive therapy is preferable when treating cGvHD, and thus agents being identified as ineffective should be discontinued to avoid side-effects. In addition, immunosuppression should be reduced as soon as disease control has been achieved. Thus far, no controlled trial has shown evidence for a beneficial impact of a 3-agent treatment in first-line therapy.[29-31] Moreover, a retrospective analysis performed by Mitchell *et al*.[32] demonstrated a decline in quality of life in the presence of multi-agent treatment independent of severity of cGvHD. To be confident about success or failure of each immunosuppressive agent applied, the Consensus Conference advised that a base-line NIH-style comprehensive organ assessment be obtained to serve as a comparison for follow-up evaluations. In addition, reasons for treatment changes including progression of symptoms, toxic side-effects, or patient's request should be documented.

In many studies on second-line treatment of cGvHD, drugs like mycophenolate mofetil (MMF), sirolimus or ECP were combined with continuous steroid administration. Thus, the contribution of steroids to the reported response rates in these studies remains uncertain. Because steroid-sparing is an important goal in cGvHD patients, their dose is usually reduced once symptoms of cGvHD are resolved and steroids may be stopped before dose reduction of other immunosuppressants. If cGvHD flares during steroid taper, increasing the dose by 1 or 2 taper steps may be enough to control symptoms.

Dignan *et al*. summarizes currently available approaches as follows.[28]

- Extracorporeal photopheresis (ECP) may be considered as a second-line treatment in skin, oral or liver cGvHD.
- Mammalian target of rapamycin (mTOR) inhibitors are suggested as a second-line treatment option in refractory cGvHD.
- Pentostatin is suggested as a second-line treatment option in refractory cGvHD.
- Rituximab is suggested as a second-line treatment option in refractory cutaneous or musculoskeletal cGvHD.
- Imatinib is suggested as a second-line treatment option in refractory pulmonary or sclerodermatous cGvHD.
- ECP, imatinib and rituximab may be considered as third-line treatment options in cGvHD involving other organs.
- The following agents are suggested as third-line treatment options in refractory chronic GvHD: MMF, methotrexate, pulsed corticosteroids.

- There is insufficient evidence, at present, to support recommendations to use the following agents in the management of chronic GvHD: cyclophosphamide, mesenchymal stem cells, thalidomide, retinoids, alemtuzumab, infliximab, etanercept, clofazimine, alefacept, daclizumab, basiliximab, hydroxychloroquine, thoracoabdominal irradiation.
- Azathioprine is not recommended in the management of chronic GvHD due to the risk of oral malignancy.

Extracorporeal photopheresis: extracorporeal photopheresis (ECP) has been widely used as a second-line therapy for the treatment of mucocutaneous cGvHD, with consistently high complete response rates of up to 80% with cutaneous manifestations, and significant improvement in sclerodermatous skin involvement.[33] Flowers *et al*.[34] published the first multicenter, randomized controlled, prospective phase II trial of ECP in the treatment of patients with cGvHD. The study used percentage improvement in total skin scores after 12 weeks of ECP treatment as the primary end point. The percentage in total skin score involved from baseline was not significantly reduced in the ECP arm compared to the non-ECP arm. By contrast, the proportion of patients who had at least a 50% reduction in steroid dose and at least a 25% decrease in total skin score was 8.3% in the ECP arm at week 12 and 0% in the control arm (P=0.04).

A UK consensus statement on the use of ECP in cGvHD suggested that patients with cutaneous, mucous membrane and hepatic manifestations of cGvHD should be given priority for this treatment as it is particularly efficacious in this setting. This consensus group recommended a treatment schedule of two ECP treatments on two consecutive days every two weeks with less frequent monthly treatment in those who respond.[35] No benefit has been demonstrated for more regular treatments. The median number of ECP cycles in a UK study was 15 (30 treatments) and the median duration of treatment was 330 days.[33]

Rituximab: a number of retrospective studies published covering more than 100 patients were pooled in a meta-analysis showing an overall response of 0.66 (95% confidence interval 50.57-0.74). Response rates were 13-100% for cGvHD of the skin, 0-83% for cGvHD of the oral mucosa, 0-66% for cGvHD of the liver, and 0-38% for cGvHD of the lung. Common adverse events were related to infusion reactions or infectious complications.[36] In the majority of the studies, investigators used the dose of 375 mg/m^2 once a week for 4-8 infusions. In contrast, von Bonin *et al*.[37] using substantially lower doses of 50 mg/m^2/ week for four weeks in 11 patients with steroid refractory cGvHD and 2 with post-transplant autoimmune disorders (glomerulonephritis and immune-thrombocytopenia), observed similar efficacy with an overall response rate of 69% including 3 patients (23%) with complete remission.

In summary, rituximab may be considered as a second-line treatment of musculoskeletal and skin cGvHD or as a third-line option in cGvHD involving other organs.

Imatinib: it is likely that imatinib exerts its effect by dual inhibition of transforming growth factor b (TGF-b) and platelet-derived growth factor (PDGF) pathways.

A retrospective study reported a 50% response rate (2 complete responses, 5 partial responses) in 14 patients with refractory sclerotic GvHD.[38]

Olivieri *et al*.[39] reported a 79% response rate (7 complete responses, 8 partial responses) at six months in a prospective pilot study of 19 patients with refractory disease. Complete or partial responses were observed in 7 of 11 patients with mild pulmonary cGvHD. Overall survival at 18 months was 85%. The initial dose used was 100–200 mg, which was subsequently titrated to 400 mg if well tolerated. No data on the benefit of other tyrosine kinase inhibitors besides imatinib are currently available.

Imatinib may be used as a second-line option for sclerodermoid or pulmonary cGvHD or as a third-line option for cGvHD involving other organs.

Pentostatin: pentostatin (deoxycoformicin) is a nucleoside analog that irreversibly inhibits adenosine deaminase, an enzyme expressed in lymphocytes that mediates recycling of purines. Jacobsohn *et al*.[40] performed a phase II study in 58 patients with refractory cGvHD given pentostatin at 4 mg/m^2 every second week for a median of 12 doses. The overall response rate was 55% with major responses in 31 patients. Toxicity was minimal, with nausea as the most frequent adverse effect and severe infections grades III-IV in 20% of patients. Survival at two years was 70%. A phase II trial in 51 children with steroid-refractory cGvHD was subsequently published by the same group.[41] Application of pentostatin resulted in an overall response rate of 53%, including a 59% response rate in sclerosis. In 25% of patients, toxicity of the compound required discontinuation of treatment. Overall survival at one year was 84%.

Application of a 4 mg/m^2 dose of pentostatin every second week for three months is recommended and the dose must be adjusted based on renal function and blood cell counts As infections were reported as the most frequent complication of pentostatin application in cGvHD, the compound should not be given in patients with active or recurrent infections or with pulmonary cGvHD.

Mammalian target of rapamycin inhibitors (mTOR): sirolimus and everolimus, exert their action by forming a complex with the mammalian target of rapamycin (mTOR). Sirolimus has been evaluated in second-line treatment of cGvHD in several phase II trials including a total of 112 patients mostly in combination with calcineurin inhibitors and response rates ranged between 56% and 81%.[42-44] Similar results were reported on use of everolimus in combination with steroids and in part with azathioprine.[45]

Because mTOR possibly interfere with wound healing, they should be used with caution in patients with cutaneous or mucosal ulcers. In view of the reported side-effects of mTOR (including thrombotic microangiopathy when combined with calcineurin inhibitors), close monitoring of blood counts, trough levels, and serum chemistry is advisable. mTOR inhibitors are effective options for cGvHD treatment with an acceptable toxicity profile as long as low therapeutic drug trough levels are maintained (4-8 ng/mL). A loading dose of mTOR should be avoided in salvage therapy.

Third-line treatment

Based on the evidence currently available, Dignan *et al*.[28] suggest that the previously mentioned agents might be considered as a second-line treatment, while MMF, methotrexate or pulsed corticosteroids, among others, are suggested as third-line treatment options in refractory chronic GvHD. This differentiation is not considered by Wolff *et al*.[27]

Mycophenolate mofetil: since the first publication of a case series with 26 patients at Johns Hopkins, mycophenolate mofetil (MMF) is increasingly used in salvage therapy for refractory cGvHD.[46] Reported response rates range between 40% and 75%. Most of the improvements have been observed in patients with limited disease and steroid sparing was observed.[47,48] Nevertheless, some limitations in the use of MMF as salvage therapy have to be considered, such as side-effects, including gastrointestinal discomfort, diarrhea, hematologic toxicity or infections. In addition, MMF treatment can result in histopathological changes of the gut mucosa, which may mimic intestinal GVHD.[49]

Retinoids: based on the successful use of retinoids in systemic sclerosis, and their inhibitory effect of the synthesis of fibroblasts, as well as their potential effect on regulatory T cells,[50] the efficacy of etretinate was evaluated in 32 patients with refractory sclerodermatous cGvHD by Marcellus *et al*.[51] Twenty of 27 evaluable patients showed improvement, including softening of the skin, flattening of cutaneous lesions, increased range of motion, and improved performance status. Overall, etretinate was well tolerated; however, skin breakdown and/ or ulceration led to treatment discontinuation in 6 patients. Other frequent side-effects are hyperlipidemia, increase in transaminases and teratogenicity. Acitretin or isotretinoin may be suitable alternatives to etretinate.

Others: methotrexate, pulsed corticosteroids, cyclophosphamide, mesenchymal stem cells, alemtuzumab, infliximab, etanercept, clofazimine, alefacept, daclizumab, basiliximab, hydroxychloroquine, have been tested in phase II trials with a wide range of efficacy.

Management of specific forms of cGvHD and organ involvement

Although a review of the approaches to treat specific organ involvement would be too long for the purpose of this manuscript, it is worth mentioning some of the therapeutic options to manage, particularly severe forms of cGvHD, either due to their adverse impact on survival or to their difficult management in order to obtain any response.

Gastrointestinal cGvHD: gastrointestinal (GI) cGvHD affects up to 60% of patients after HSCT. In the cGvHD setting, diagnostic features for the GI tract include esophageal web, stricture, or concentric rings documented by endoscopy or a barium contrast radiograph. Symptoms of anorexia, nausea, vomiting, and diarrhea are not considered diagnostic of cGvHD, but are common symptoms in patients with the condition.[18] Wasting syndrome can be a manifestation of cGvHD, but is often multifactorial and may result from decreased caloric intake, poor absorption, increased resting energy expenditures, and hypercatabolism. In view of the wide differential diagnosis, patients with diarrhea without associated jaundice or rash suggestive of GvHD should be investigated by both upper (with duodenal aspirate and biopsies) and lower (flexible sigmoidoscopy and biopsy) gastrointestinal endoscopy in preference to colonoscopy alone. Therefore, if empirical treatment for suspected GvHD is not rapidly effective, systematic investigation is required and referral to a gastroenterologist should be considered.

Intestinal involvement is usually more severe and difficult to treat as compared with other target organs. In this regard, presence of chronic diarrhea and/or weight loss are identified as poor prognostic factors according to an IBMTR study.[14]

In patients with established GVHD in whom other causes of diarrhea have been excluded, supportive care with anti-diarrheal agents including loperamide, codeine or octreotide may be helpful in addition to systemic immunosuppression.

Beclomethasone dipropionate (BDP) is a topically active corticosteroid with relatively low absorption from the GI mucosa into systemic circulation. BDP was administered to 33 patients with biopsy-proven GI cGvHD for a minimum of 16 weeks. Of those patients receiving BDP as the first-line of treatment, 22 (84.6%) achieved complete remission (CR) and 2 (7.7%) achieved a partial response (PR). Nevertheless, only 7 (27%) patients had maintained the response at last follow up, whereas 19 (73%) finally relapsed or progressed. In the case of the patients who received BDP as a second- or third-line treatment, 3 (42.9%) achieved CR and 2 (28.6%) PR. For the whole series of patients, 13 patients (39.4%) were not receiving immunosuppressive treatment at last follow up.[52] Thus, it might be considered a therapeutic option which may both avoid further immunosuppression and allow systemic steroid sparing.

Lung disease: bronchiolitis obliterans syndrome (BOS) is a potentially fatal complication that occurs among recipients of allogeneic lung and hematopoietic stem cell transplantation. It is defined as the development of new fixed airflow obstruction that usually occurs within the first two years after alloHSCT but may develop as late as 4-5 years after transplantation.[53] Prevalence estimates based on the NIH Consensus Criteria indicate that BOS has a prevalence of 5.5% among all alloHSCT recipients, and 14% among long-term survivors who develop cGvHD.[54]

The NIH consensus guidelines included spirometric guidelines for diagnosing BOS: FEV1 less than 75% of predicted and FEV1/forced vital capacity (FVC) ratio less than 0.7.[11] Given the potential adverse events associated with high-dose corticosteroid therapy, one should try to identify significant declines in airflow by requiring that the FEV1 is decreased by at least 10% since pre-transplant, and that the FEV1/vital capacity (VC) ratio uses the slow VC to minimize using falsely decreased FVCs among the severely obstructed patients. Confirmation of BOS requires the participation of a clinician experienced with this specialized patient population, guided by a full complement of diagnostic tests, including lung volume measurements, thoracic computed tomography (CT) scan, and microbiological evaluation

The dismal overall survival for BOS patients is approximately 15%. The initial systemic treatment is typically prednisone given at 1 mg/kg of body weight per day for two weeks, with subsequent taper over four weeks to a dose of 1 mg/kg every other day with appropriate antimicrobial prophylaxis. In view of the dismal results of BOS therapy, some recommend more intensive prednisone regimes with delay of tapering to every other day dosing for several months. For those not responding, pulsed steroids or imatinib should be considered.

The poor response to standard cGvHD therapy further highlights the need for rigorous clinical trials to identify potential beneficial therapeutic inventions for at-risk

patients. The hope is that improved early screening for BOS in HCT patients may prevent further decline prior to the patient meeting the full criteria for BOS.[55]

Inhaled corticosteroids (fluticasone dipropionate) and additional immune modifiers such as montelukast and azithromycin are currently being studied for efficacy in the treatment of the disease.

Scleroderma: sclerotic graft-*versus*-host disease (GvHD) represents a distinctive phenotype of chronic GvHD often associated with severe disability and morbidity after allogeneic hematopoietic cell transplantation. ScGvHD of the skin includes several cutaneous presentations characterized by inflammation and progressive fibrosis of the dermis and subcutaneous tissues. These changes can resemble morphea, systemic sclerosis, or eosinophilic fasciitis and may or may not occur in the setting of concurrent overlying epidermal GVHD. When severe, ScGvHD can result in contractures, severe wasting, and chest wall restriction. Additionally, skin ulceration and poor wound healing associated with skin fibrosis can cause significant morbidity and increases the risk of infection. The mean onset of sclerotic skin changes following transplant is late (529 days); 7% of patients presented with sclerosis at the time of initial systemic treatment for chronic GvHD, and the cumulative incidence of sclerosis increased to 20% at three years. ScGvHD responds poorly to topical interventions and is often resistant to systemic therapy. Many therapies have been employed, including calcineurin inhibitors, steroids, antimetabolites, biological agents, hydroxychloroquine, and ECP and imatinib mesilate. The latter has biological activity against both PDGF and TGF-β signaling pathways. Both cytokines have been implicated in the pathogenesis of scleroderma, a disease that closely resembles ScGVH.

Conclusions

In summary, the management of patients with cGvHD requires a multidisciplinary approach. Systemic therapy should be considered for patients who meet criteria for moderate-to-severe global severity according to the NIH consensus criteria or for those with less severe disease but with high-risk features. Topical therapies are useful for symptomatic mild cGvHD but also as an adjunct to improve and hasten local response for patients requiring systemic therapy. In this regard, systemic immunosuppression must also be tailored considering disease status at transplant and risk of relapse. The standard initial systemic treatment of chronic GvHD is administration of glucocorticoids with or without calcineurin inhibitors. Secondary treatment is generally considered in patients in whom chronic GVHD shows evidence of progression, no improvement despite treatment during at least 4-8 weeks, when new clinical manifestations develop, or when symptoms worsen during taper of prednisone below 0.5 mg/kg/day. The choice of agent should be based on the toxicity profile, organ involvement, patient preference and availability.

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