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Pulmonary Chronic Graft versus Host Disease

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Introduction

Since the first report of bone marrow transplantation for cancer treatment in 1950s, painstaking researches have been conducted to bring the dim light of hope to standard treatment nowadays. Advances in prevention and treatment of infectious complications and prevention of acute graft versus host disease (GVHD) led to dramatically improved survival through day 200.[1] The incidence of chronic GVHD was, by contrast, increased in the past 2 decades.[2] Increasing use of peripheral blood stem cell graft and increasing number of patients survived through early phase of transplantation contributed to higher incidence of chronic GVHD over time. Chronic GVHD remains a major late complication involving 30% to 70% of patients. Several risk factors have been identified, including human leucocyte antigen (HLA) mismatch or unrelated donor, donor age, female donor for male recipient, peripheral blood stem cell graft, donor lymphocyte infusion and prior acute GVHD.[3]

Chronic GVHD recognized as an autoimmune reaction affecting various organ systems commonly involves skin, oral mucosa, eyes, liver and gastrointestinal tract. Pulmonary chronic GVHD contributes only 10-20% of cases. However, pulmonary involvement is considered moderate to severe disease because of high morbidity and mortality. In the study of long-term outcomes of hematopoietic stem cell transplant (HSCT) in patients who had survived more than 2 years after transplantation, 15-fold increased risk of late death due to pulmonary dysfunction was reported.[4] Prevention and prompt treatment of pulmonary chronic GVHD is essential to life.

Chronic GVHD: disease definition and diagnosis

Historically, chronic GVHD was defined as manifestations of GVHD that was present (or continued) at 100 days after HSCT or later. Collective data however showed that several distinctive signs of chronic GVHD were not common in acute GVHD. Tissue biopsy from these lesions demonstrated histopathologic findings by which chronic GVHD can be distinguished from acute GVHD. Manifestations of acute GVHD could occur later than 100 days after HSCT. Vice versa, chronic GVHD could also occur before 100 days after HSCT and the overlap of acute and chronic GVHD was also reported. Altogether, new consensus criteria for clinical trials in chronic GVHD was developed by National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease.[5, 6] Current diagnosis of chronic GVHD requires all of the following:

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1. Distinction from acute GVHD.
2. Presence of at least 1 diagnostic clinical sign of chronic GVHD or presence of at least 1 distinctive manifestation confirmed by pertinent biopsy or other relevant tests.[6]
3. Exclusion of other possible diagnoses.

Revision of the criteria in 2014 emphasized the importance of early diagnosis of pulmonary chronic GVHD which usually has limitation to obtain tissue for diagnosis. In this current version, clinical diagnosis of bronchiolitis obliterans syndrome (BOS) plus 1 other distinctive manifestation is sufficient for chronic GVHD diagnosis.

All of the following criteria are needed for clinical diagnosis of BOS[6]:

1. Forced expiratory volume in 1 second/vital capacity ratio (FEV_1/VC) <0.7 or the fifth percentile value as the lower limit of normal (LLN). VC used in the criteria is forced VC or slow VC, whichever is greater.
2. FEV_1 <75% of predicted with ≥ 10% decline over less than 2 years. Post-bronchodilator FEV_1 should be less than 75% of predicted, and the absolute decline for post-bronchodilator values should also be at least 10% over 2 years.
3. Absence of infection in the respiratory tract, documented with investigations directed by clinical symptoms, such as radiologic studies (radiographs or computed tomographic scans) or microbiologic cultures (sinus aspiration, upper respiratory tract viral screen, sputum culture, or bronchoalveolar lavage).
4. One of the 2 supporting features below
   a. Evidence of air trapping or small airway thickening or bronchiectasis on high-resolution chest computed tomography (HRCT), or
   b. Evidence of air trapping by pulmonary function tests: residual volume (RV) > 120% of predicted, or residual volume/total lung capacity (RV/TLC) >95th percentile value as upper limit of normal.

Pathogenesis of chronic GVHD

Chronic GVHD manifests with autoimmune features with multiple organ tissue fibrosis (e.g. lichen planus-like skin or mucosal lesions, scleroderma, esophageal web or bronchiolitis obliterans), while acute GVHD has distinct clinical characteristics such as maculopapular rash, diarrhea and hepatitis.

Classification of chronic GVHD by its onset includes: chronic GVHD without preceding acute GVHD (de novo chronic GVHD), chronic GVHD evolving from acute GVHD (progressive chronic GVHD), chronic GVHD following a period of resolution of acute GVHD (interrupted or quiescent chronic GVHD), and concomitant chronic GVHD with acute GVHD features (overlap GVHD). Diverse time relation to acute GVHD and different clinical characteristics suggest different disease mechanisms. However, association between prior acute GVHD and chronic GVHD confirmed by several studies suggests that pathogenesis of chronic GVHD might be influenced by, or share initiating process with, acute GVHD.

Immunocompetent T lymphocytes in donor stem cell preparation are key factor that exert immune response against recipient's tissue. In normal immune individuals, foreign T lymphocytes are effectively rejected. In HSCT patients, compromised immune status caused by conditioning chemotherapy and/or radiation hampers this process. Competent donor T lymphocytes in turn

promote recipient tissue destruction. Pathogenesis of acute GVHD can be simply explained by 3 stages. First, damaged tissue resulted from conditioning regimens releases danger signals, including cryptic proteins and pro-inflammatory cytokines (e.g. tumor necrosis factor [TNF], interleukin [IL]-6, and IL-1). Pathogen associated molecular patterns (PAMPs) are also present due to bacterial translocation caused by damaged gut mucosa. Danger signals and PAMPs, in concert, activate both donor and recipient antigen presenting cells (APCs). Second, the activated APCs present recipient's self-antigens to donor T lymphocytes, resulting in donor T cell activation. In HLA-matched HSCT, donor T cell activation has been explained by the presence of different minor HLAs. Finally, damage to recipient tissue is aggravated mainly by donor cytotoxic T lymphocytes (CTL) and natural killer (NK) cells.

By contrast to acute GVHD, the pathogenesis of chronic GVHD remains poorly understood. Defect in negative selection of autoreactive T lymphocytes can contribute to chronic GVHD. The study in adoptive transfer mouse model demonstrated that donor $CD4^+$ T lymphocytes derived from mice suffering from acute GVHD caused GVHD when adoptively transferred to secondary allogeneic recipient mice.[7] The histopathologic findings were consistent with chronic GVHD. Adoptive transfer of these $CD4^+$ T lymphocytes to autologous mice revealed the same results. Thymectomy was shown to prevent chronic GVHD in mice receiving $CD4^+$ T lymphocytes from mice suffering from chronic GVHD.[8] The $CD4^+$ T lymphocytes derived from chronic GVHD mice were shown reactive to donor antigens. These results implied that autoreactive thymus dependent $CD4^+$ T lymphocytes played central role in chronic GVHD pathogenesis. Several factors can cause thymic damage, including conditioning regimens, prior acute GVHD, and age-related thymic atrophy. This mechanism can explain de novo chronic GVHD, chronic GVHD following an episode of acute GVHD, and increased incidence of chronic GVHD in older age recipients.

Different subsets of $CD4^+$ lymphocytes contribute to development of acute and chronic GVHD. While the role of helper T cells type 1 (Th1 cells) in acute GVHD has been established, knowledge of Th subsets in chronic GVHD is in progress. Expression of Th1 cytokines in tissues of chronic GVHD cases has been reported, but its role in pathogenesis is still unclear.[9] Th2 cytokines were expressed in target organs of mice suffering from chronic GVHD in association with B cell and NK cell expansion.[10] Since chronic GVHD has features resembling autoimmune diseases, common immunologic pathways seem plausible. Th17 has been studied in several autoimmune diseases, including scleroderma. Th17 differentiation has been shown to promote scleroderma in mouse model of chronic GVHD independent of Th1 and Th2 cytokines.[11] T follicular helper (TFH) cells, which augment germinal center B lymphocyte differentiation and class switching, in chronic GVHD patients has been shown phenotypically predominant of Th2/Th17 subtypes.[12] As a result, more B lymphocyte activation and maturation into plasmablasts were promoted.

The analysis of autoantibodies in HSCT patients has revealed association between positivity of autoantibody and development of chronic GVHD, especially in extensive disease.[13] The presence of autoantibody was also associated with an increase in number of B lymphocytes recovered from peripheral blood of HSCT patients. These results suggested a role of B lymphocytes and autoreactive antibodies in chronic GVHD pathogenesis. Roles of B lymphocytes has been highlighted in a murine study. Deposition of

$CD4^+$ T lymphocytes, B lymphocytes and alloantibodies was demonstrated in target organs of mice suffering from chronic GVHD.[14] When mature B lymphocyte deficient donor mice were used, recipient mice showed better pulmonary function comparing with mice with chronic GVHD. Treatment with lymphotoxin-beta receptor immunoglobulin, which disrupted germinal center formation, also improved pulmonary function in murine chronic GVHD model. These results have thereby emphasized a role of B lymphocytes in chronic GVHD and bronchiolitis obliterans development.

Pathological findings in pulmonary chronic GVHD

According to the NIH consensus criteria 2014, bronchiolitis obliterans syndrome (BOS) diagnosed by lung biopsy is classified as a diagnostic feature for chronic GVHD.[6] The term BOS was used to described a clinical syndrome of dyspnea on exertion with new onset of obstructive ventilator defect caused by underlying pathology consistent with obliterative bronchiolitis. Clinically diagnosed BOS without lung biopsy alone is not sufficient to diagnose chronic GVHD. Cryptogenic organizing pneumonia (COP) is another form of pulmonary involvement mentioned in the literature. However, COP is only considered a manifestation of chronic GVHD when the diagnosis has already been established. In other words, no other lung pathology besides obliterative bronchiolitis is capable of diagnosing chronic GVHD.

The pathologic findings of obliterative bronchiolitis consist of subepithelial expansion of fibrous tissue resulting in constriction of bronchiolar lumen. Aggregation of foamy macrophages and distal mucostasis are also present secondarily to obliterative bronchiolitis.[15] BOS is frequently confusing with COP because of its old name; bronchiolitis obliterans-organizing pneumonia (BOOP). These two entities should be distinguished from each other, since they possess different pathological characteristics. COP is characterized by plugs of granulation tissue in distal airspaces. While BOS is diagnostic of chronic GVHD, COP is associated with both acute and chronic GVHD. Additionally, COP is predictive of more favorable outcomes. Other non-diagnostic concomitant findings include bronchiectasis, pleuropulmonary fibroelastosis (PPFE), non-specific interstitial pneumonia (NSIP) and veno-occlusive disease.[16]

Clinical manifestations and HRCT findings of pulmonary chronic GVHD

Since the manifestations of pulmonary chronic GVHD are non-specific, diagnosis of this condition requires high index of suspicion in patients at risk, pulmonary function test results, high resolution computed tomography (HRCT), and sometimes lung biopsy. In early stage, patients may complain of dyspnea on exertion, nonproductive cough or wheezing. However, many patients present with abnormal pulmonary function tests without any symptom. Early diagnosis of pulmonary chronic GVHD therefore needs regular screening of pulmonary function tests. Late disease can present with exercise intolerance or limited activities. Pneumothorax and pneumomediastinum are not common, but indicate poor prognosis.

BOS is characterized by a new onset of obstructive ventilatory defect after HSCT. Median time from HSCT to the onset of BOS was 465 days (range 77 to 3,212 days) in one study.[17] The onset is usually insidious with progression to dyspnea on exertion and nonproductive cough. Fever is not common, and suggests accompanying infection. Chest radiographic findings of

BOS are generally non-specific, including infiltrates, hyperinflation or merely normal image. In early stage, HRCT may be unremarkable or reveal hyperinflation. Bronchiectasis is subsequently demonstrated as the disease progresses. Mosaic attenuation, featured as areas of decreased attenuation mingle with areas of normal or increased attenuation, is a characteristic of BOS. Air trapping is demonstrated in 56% of cases as accentuation of decreased attenuation on expiratory scans.[18]

COP is characterized by clinical manifestations similar to pneumonia without response to antibiotic therapy. Patients generally present with subacute onset of fever, nonproductive cough and dyspnea. HRCT typically shows airspace consolidations with predominant peribronchovascular and peripheral distribution. However, immunocompromised patients may manifest with nodules or ground glass opacity. Differential diagnosis of infectious pneumonia necessitates bronchoalveolar lavage to exclude possibility of infection.

Pulmonary function tests

Key elements for the diagnosis of pulmonary chronic GVHD include spirometry. Current definition requires FEV_1/FVC ratio of 0.7 and FEV_1 75% of predicted value. Due to nonspecific symptoms, diagnosis of BOS is usually delayed. The study of screening spirometry in allogeneic HSCT revealed that FEV_1 was decreased below the diagnostic margin at the diagnosis of noninfectious pulmonary complications.[19] Despite a scheduled spirometry at day 100, 1 year and 2 years, median FEV_1 at the diagnosis is 58% of predicted. The results suggest that the initiation of substantial decline in pulmonary function is long before clinically recognized. A retrospective study of longitudinal change of FEV_1 in HSCT patients who were eventually diagnosed BOS demonstrated rapid FEV_1 decline 6 months prior to the diagnosis of BOS.[20] Mean estimated rates of FEV_1 decline per months were 6.8% and 6.71% of the predicted in 2 cohorts. The rates of FEV_1 decline in the same 2 cohorts were reduced to 0.04% and 0.12% of the predicted after the treatment of BOS. These results emphasize a prominent role of early detection and prompt treatment in limiting progression of pulmonary function impairment.

Scheduled pulmonary function tests are currently recommended for the early detection of pulmonary chronic GVHD. Spirometry, lung volume measurement by whole-body plethysmography and diffusion capacity for carbon monoxide (DLco) should be performed at baseline within 2 weeks before the conditioning regimen. Subsequent tests should be performed every 3 months after transplantation for 2 years and every 6 months after then. Additional tests are needed when the patients develop respiratory symptoms without concomitant infections, and after the initiation of treatment of pulmonary chronic GVHD.[21] Interval and frequency of the tests vary depending on institutional preference and availability of pulmonary function test facilities.

Besides the cruciality of pretransplant pulmonary function tests in diagnosis of chronic GVHD, as the baseline values are compared with those of subsequent tests in order to define BOS, they are also useful for prognostication. Several studies reported association of posttransplant pulmonary function decline and abnormal pretransplant pulmonary function parameters. A retrospective study in long-term survivors after myeloablative HSCT revealed that abnormal pretransplant FEV_1, VC and DLco were predictive for the decline of those parameters in the first year posttransplant.[22] There was no association between abnormal pretransplant parameters and the decline in

the third and fifth year. Significant decrease of FEV_1 and FVC at the fifth year posttransplant was however demonstrated in patients who were diagnosed chronic GVHD including those without diagnosis of BOS. A composite score of pretransplant FEV_1 and DLco, the so-called lung function score, was also proposed a predictor for survival of HSCT patients.[23]

Although the diagnostic criteria for BOS has been established, an eminent limitation in their sensitivity thwarts detection of BOS cases in earlier stage. A potential BOS stage (BOS 0-p) has proved the ability to predict BOS in lung transplant patients.[24] The role of BOS 0-p in prediction of BOS in HSCT has also been studied. BOS 0-p is defined by a 10-19% decrease in FEV_1 or a 25% decrease in mid-expiratory flow rate ($FEF_{25–75}$) from baseline but not otherwise meet the criteria for BOS. A retrospective cohort of allogeneic HSCT demonstrated BOS 0-p as a potential predictor of BOS with hazard ratio of 3.22.[25] Eighty-five percent of BOS cases met the criteria of BOS 0-p before the diagnosis of BOS. Median FEV_1 and $FEF_{25–75}$ presented as % of predicted at BOS 0-p diagnosis was 81% and 65%, respectively. Development of BOS 0-p within 2 years posttransplant was able to predict BOS with the sensitivity of 85%, specificity 78%, positive predictive value 29% and negative predictive value 97%. The screening of BOS 0-p in 2 years allows identification of cases with low probability to develop BOS.

National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease published the 2014 report including statements concerning pulmonary function tests for diagnosis (as described above) and for severity grading of chronic GVHD.[6] Chronic GVHD potentially involves multiple organs. A clinical scoring of organ systems was designed to confer meaningful information about disease extent and severity. Furthermore, a clinical scoring can be used for monitoring the response to treatment. FEV_1 (% of predicted) is stratified in to 4 levels; ≥ 80%, 60-79%, 40-59% and ≤ 39%. The scores for each level are 0, 1, 2 and 3, respectively. Whenever pulmonary function test results are not available, the score will be substituted with respiratory symptom score.

Treatment of pulmonary chronic GVHD

The goals for treatment of chronic GVHD are to relieve symptoms, to terminate ongoing inflammation which ultimately leads to preservation of affected organ functions, and to reverse the process of structural change. Unfortunately, the latter has not been achieved so far. Current therapeutic concepts consist of anti-inflammatory drugs to prevent further tissue injury while awaiting immunologic tolerance to occur. Treatment strategies therefore focus on early case identification. Treatment provided at the early stage before extensive organ damage may engender more favorable outcomes. According to the consensus statement of National Institute of Health in 2014, symptomatic mild chronic GVHD is generally managed with topical therapy. Systemic immunosuppressive treatments should be considered in moderate to severe chronic GVHD defined by involvement of 3 or more organs, or at least 1 organ (not lung) with a score of 2, or lung involvement with a score of 1. It is notable that the presence of pulmonary chronic GVHD warrants systemic therapy.[6] Due to limited number of pulmonary chronic GVHD, most of the evidence derived from studies in chronic GVHD in general. We will also discuss several studies of treatment specific to pulmonary chronic GVHD, i.e., azithromycin, inhaled corticosteroids, and montelukast.

Corticosteroids

Systemic corticosteroids has remained the most effective therapeutic agent in chronic GVHD. Several publications specifically reported the outcome of pulmonary chronic GVHD patients. A retrospective study in bone marrow HSCT patients with pathologically confirmed BO showed 49% response to treatment defined by 10% improvement of FEV_1 and sustained reduction of dyspnea and cough.[17] Various treatment regimens were used in the study, but all included systemic corticosteroids. From 47 patients, 6 were treated with intravenous antithymocyte globulin 15 mg/kg for 5 days, bolus intravenous methylprednisolone 250 mg/m^2 twice a day for 5 days and then weekly for 8 weeks at 15 mg/kg, prednisone 60 mg/m^2 once a day, and intravenous cyclosporine 1.5 mg/kg every 12 hours. Twenty-seven patients were treated with weekly bolus methylprednisolone 15 mg/kg for 8 weeks, prednisone 0.5 mg/kg every other day, and either oral cyclosporine 6.25 mg/kg every 12 hours or azathioprine 0.5 mg/kg/day. Fourteen patients were treated with oral prednisone 1 mg/kg/day alone or with cyclosporine or azathioprine. Response rate in each group ranged from 33% to 55%. Reports from other experienced centers revealed consistent benefit of high dose corticosteroid in BOS.[26, 27] It has been noted that most of the data was derived from pediatric and young adult patients, and there was no randomized trial for the efficacy of systemic corticosteroids in pulmonary chronic GVHD. Nevertheless, systemic corticosteroids is generally embraced in chronic GVHD treatment. The standard dose is 1 mg/kg/day of prednisone or equivalent dose of methylprednisolone with gradual tapering dose after the objective response.[28]

Owing to the high rate of relapse in moderate to severe chronic GVHD and significant toxicity of systemic corticosteroids, combinations with other immunosuppressive drugs are usually used in order to spare the corticosteroid effects. So far, no other single immunosuppressive drug or combination regimen has been proven being superior efficacy to systemic corticosteroids.

Azathioprine

Early treatment of chronic GVHD with a combination of prednisone and azathioprine has failed to demonstrate survival benefit comparing with prednisone plus placebo group. The treatment response rate was equivalent, but prednisone plus azathioprine group showed significantly increased nonrelapse mortality.[29] The major cause of the mortality was infection. It is noteworthy that, at the time this study was published, supportive care was not as effective as nowadays. Recent retrospective study of patients underwent allogeneic HSCT between 2004 and 2012 showed that addition of azathioprine improved overall survival of chronic GVHD patients as compared to prednisone alone.[30] The benefit of azathioprine in chronic GVHD in current context should be reconsidered. However, caution must be exercised, since azathioprine use in chronic GVHD treatment has been reported as an independent risk of squamous-cell cancers, especially when it was used for longer than 12 months.[31]

Calcineurin inhibitors

Cyclosporine is an immunosuppressive drug commonly used in the prophylaxis against graft rejection in solid organ transplantation, and also in the prophylaxis against acute GVHD after HSCT. The role of cyclosporine in the treatment of chronic GVHD has been studied. A randomized trial was designed to compare the outcomes of chronic GVHD patients between the treatment with prednisone alone versus a combination

of prednisone and cyclosporine.[32] No survival benefit of added cyclosporine was demonstrated. There was no significant difference in cumulative nonrelapse mortality at 5 years. However, patients who received a combination therapy of prednisone and cyclosporine developed avascular necrosis significantly less than those received prednisone alone. Cyclosporine is currently used for chronic GVHD treatment in order to avoid complications related to corticosteroid treatment.

Although efficacy of tacrolimus in the first line treatment of chronic GVHD has not been clearly elucidated, its role in salvage regimen has been prospectively studied. Small proportion of patients was benefited from substitution of tacrolimus for cyclosporine after failure of the first line treatment.[33] Chronic GVHD patients who failed cyclosporine plus prednisone regimen were treated with tacrolimus plus prednisone. From 39 patients recruited, 8 patients (20%) showed response to treatment; 5 were in complete response and 3 in stable disease after 3 years of follow-up.

Mycophenolate mofetil (MMF)

Case series reports showed benefit of mycophenolate mofetil (MMF) in the treatment of corticosteroid-refractory chronic GVHD. A randomized trial has been done to prove the benefit of MMF added-on in the initial treatment of chronic GVHD.[34] MMF or placebo was given to the patients diagnosed as chronic GVHD within 14 days of the initial treatment. Most of the participants already received corticosteroid plus one calcineurin inhibitor. There was no significant difference in the mortality between MMF arm and placebo arm, but the MMF arm showed higher rate of treatment failure. Efficacy of MMF in the treatment of BOS cannot be directly concluded, since this study excluded the patients with BOS. However, the study failed to demonstrate reduction in the rate of newly diagnosed BOS after being enrolled in the MMF arm.

Azithromycin

Anti-inflammatory effects of macrolide antibiotics have been established. Several guidelines related to chronic airway diseases embraced macrolides as an add-on therapy. In BOS complicating lung transplantation, administration of azithromycin regimens showed efficacy in improvement of FEV_1 and FVC comparing to the placebo.[35] Because of similar pathogenesis, azithromycin use in BOS complicating HSCT has been studied. Significant improvement of FEV_1 and FVC has been demonstrated in a preliminary open-label, single-arm study.[36] From 153 HSCT patients, 8 patients who later developed obstructive airway disease and their classical HRCT findings consistent with BO were given 500 mg of azithromycin per day for three days, followed by 250 mg of azithromycin three times a week for 12 weeks. At the end of the study period, mean FEV_1 improvement of 0.28 L (95% CI; 0.10 to 0.44) and mean FVC improvement 0.41 L (95% CI; 0.16 to 0.65) were observed. Despite promising results from the preliminary study, a randomized placebo-controlled trial in BOS after HSCT patients has failed to demonstrate significant improvement of pulmonary function parameters and respiratory symptoms after a three-month period of 250 mg daily dose of azithromycin.[37] Recently, a randomized placebo-controlled trial to investigate the effect of early administration of azithromycin before the onset of BOS revealed that the azithromycin prophylaxis resulted in worse outcome.[38] The trial was early terminated due to the higher mortality rate and the hematological relapse rate at two years in azithromycin arm. The mechanisms underlying these unanticipated outcomes remain to be elucidated. According to the trial protocol, azithromycin

was given since the first day of the conditioning regimen and was continued for 2 years. It was proposed that azithromycin might interfere with the conditioning regimen, or with the immune response against the residual leukemic cells. Thus, azithromycin for the prophylaxis of pulmonary chronic GVHD is considered harmful. In addition, there was, so far, no concrete evidence to suggest azithromycin for the treatment of pulmonary chronic GVHD.

Inhaled corticosteroids and bronchodilators

The potential effects of inhaled corticosteroids for BOS after HSCT have been demonstrated in a retrospective study including 17 patients with constrictive bronchiolitis who received high-dose inhaled fluticasone propionate (500 to 940 µg twice daily).[39] Addition of inhaled fluticasone propionate resulted in more clinical benefit comparing to the previous observational study, in which only systemic immunosuppressive therapy was given. Inhaled fluticasone propionate seemed to stabilize FEV_1 at 6 months after the treatment. A prospective, randomized, double-blind, placebo-controlled trial has revealed positive effects of combined inhaled corticosteroid and bronchodilator.[40] Thirty-two patients with BOS after HSCT were randomly allocated to budesonide/formoterol arm and placebo arm. After one month of the treatment, significantly increased FEV_1 was demonstrated in budesonide/formoterol arm comparing with the placebo.

Montelukast

The effects of montelukast, a leukotriene receptor antagonist, in chronic GVHD were observed in a preliminary prospective study.[41] Nineteen patients with extensive chronic GVHD without improvement after the standard immunosuppressive treatments were recruited. A 10-mg daily dose of montelukast was supplemented. Dosage of immunosuppressive drugs was reduced when the clinical response was achieved. Overall response rate was 79% in recruited patients. The improvement was not organ specific as evident in involved organs, including skin, liver, gastroinstestinal tract and lungs. Although a randomized controlled study is still needed to confirm the efficacy of montelukast in chronic GVHD, it has been embraced in studies of combination therapy for pulmonary chronic GVHD.

The first combination is inhaled fluticasone propionate, oral azithromycin and oral montelukast, so-called FAM regimen.[42] In a single-arm, open-labeled study, 36 patients with BOS diagnosed after HSCT were enrolled. All the patients were given prednisone 1 mg/kg/day with scheduled tapering. Inhaled fluticasone propionate 440 µg twice daily dose, oral azithromycin 250 mg daily dose for 3 days per week and oral montelukast 10 mg/day were given to all patients. Stabilized lung function at 3 months, as defined by less than 10% reduction of absolute FEV_1, was reported in 84% of patients. Among these, 37% showed 10% or more increase of FEV_1. At 3 months, 50% reduction of systemic corticosteroid dose was achieved in 48% of patients. This study has suggested the efficacy of FAM regimen in stabilization of lung function and steroid sparing in patients with BOS after HSCT.

A combination of budesonide/formoterol, montelukast and N-acetylcysteine has been reported to improve lung function and symptom score in pulmonary chronic GVHD.[43] Data of the patients with BOS after HSCT treated according to the same protocol were retrospectively reviewed. Sixty-one patients who were treated, in addition to immunosuppressive therapy, with a combination of budesonide/formoterol, montelukast and N-acetylcysteine were analyzed. After 3 months

of the combination treatment, significant increase of FEV_1 and decrease of residual volume were observed (mean FEV_1 increase 220 mL and mean residual volume decrease 200 mL).

Extracorporeal chemophototherapy

Extracorporeal chemophototherapy or photopheresis (ECP) is an immunomodulatory therapy consisting of exposure of apheresis blood to 8-methoxypsoralen and ultraviolet light and re-infusion of the ex vivo treated cells to the patient. Ultraviolet light induces apoptosis of mononuclear cells photosensitized by 8-methoxypsoralen. The proposed mechanism of ECP for chronic GVHD is that apoptotic lymphocytes are phagocytosed by antigen presenting cells which subsequently promote differentiation of regulatory T lymphocytes.[44]

ECP is considered for treatment of refractory chronic GVHD. In a cohort which included patients with severe BOS after HSCT, ECP was reported to slow the rate of FEV_1 decline and reduce corticosteroid requirement.[45] All the patients already received corticosteroids and FAM regimen, but FEV_1 trajectory continued. Scheduled ECP sessions were done for at least 12 months. After 3 months, 7 from 8 patients had stable or improved FEV_1. However, only 2 from 8 patients maintained stable FEV_1 until the end of a 12-month period. Prednisone dose was reduced 71% after 12 months of ECP. Further study is needed to identify patients who would gain the most benefit of ECP.

Conclusion

Globally increased use of HSCT and advance in early post HSCT care lead to growing number of chronic GVHD cases. Although pulmonary involvement of chronic GVHD is not common, it is a serious complication of HSCT due to its high mortality. Thus far, the mainstay of treatment depends on systemic corticosteroids with second immunosuppressive drug in order to reduce adverse effects of systemic corticosteroids. Additional treatment with fluticasone, azithromycin and montelukast helps stabilize pulmonary function. Nevertheless, significant number of patients have progressive disease. ECP has been shown to stabilize pulmonary function for months, but the decline in pulmonary function continues in majority of patients. In refractory cases, some receive lung transplantation, others succumb. More investigations in the pathogenesis and the efficacy of new drugs are needed to cure pulmonary chronic GVHD and increase quality of life.

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