Hematopoietic Stem-Cell Transplantation for Autoimmune Diseases

I. Description

Most patients with autoimmune disorders respond to conventional therapies. However, these drugs are not curative, and a proportion of patients will have severe, recalcitrant, or rapidly progressive disease. It is in this group of patients with severe autoimmune disease that alternative therapies have been sought, including hematopoietic stem-cell transplantation (HSCT).

Initial studies focused on using HSCT as salvage therapy for refractory autoimmune diseases. More recent experience has better helped to define which patients are most likely to benefit from HSCT. Thus the field has shifted to the use of HSCT earlier in the disease course before irreversible organ damage and to the use of safer and less intense nonmyeloablative conditioning regimens.

The experience with HSCT and autoimmune disorders has been predominantly with autologous transplants, and a number of published clinical reports with follow-up have demonstrated the safety and in some patients (particularly those with systemic sclerosis, systemic lupus erythematosus [SLE], and multiple sclerosis [MS]) the impact of HSCT in selected autoimmune diseases.

Although some of the initial results have been promising, this field continues to evolve. Many trials (randomized and nonrandomized) are currently recruiting or ongoing comparing the use of HSCT with conventional therapy for most of the diseases addressed in this policy; the results of these trials will further define the role of HSCT in the management of these diseases. Thus, use of HSCT for these autoimmune diseases is considered investigational.

Background

Autoimmune Diseases

Autoimmune diseases represent a heterogeneous group of immune-mediated disorders, including multiple sclerosis (MS), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic sclerosis/scleroderma and chronic inflammatory demyelinating polyneuropathy (CIPD). The
National Institutes of Health (NIH) estimates that 5–8% of Americans have an autoimmune disorder.

The pathogenesis of autoimmune diseases is not well-understood but appears to involve underlying genetic susceptibility and environmental factors that lead to loss of self-tolerance, culminating in tissue damage by the patient’s own immune system (T cells).

Immune suppression is a common treatment strategy for many of these diseases, particularly the rheumatic diseases (e.g., RA, SLE, and scleroderma). Most patients with autoimmune disorders respond to conventional therapies, which consist of anti-inflammatory agents, immunosuppressants, and immunomodulating drugs. However, these drugs are not curative, and a proportion of patients will have severe, recalcitrant, or rapidly progressive disease. It is in this group of patients with severe autoimmune disease that alternative therapies have been sought, including hematopoietic stem-cell transplantation (HSCT).

HSCT in autoimmune disorders raises the question of whether ablating and “resetting” the immune system can alter the disease process and sustain remission and possibly lead to cure.

Hematopoietic Stem-Cell Transplantation

Hematopoietic stem-cell transplantation (HSCT) refers to a procedure in which hematopoietic stem cells are infused to restore bone marrow function in patients who receive bone-marrow-toxic doses of cytotoxic drugs with or without whole-body radiation therapy. Hematopoietic stem cells may be obtained from the transplant recipient (autologous HSCT) or from a donor (allogeneic HSCT). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates. Although cord blood is an allogeneic source, the stem cells in it are antigenically “naïve” and thus, are associated with a lower incidence of rejection or graft-versus-host disease (GVHD).

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HSCT. However, immunologic compatibility between donor and patient is a critical factor for achieving a good outcome of allogeneic HSCT. Compatibility is established by typing of human leukocyte antigens (HLA) using cellular, serologic, or molecular techniques. HLA refers to the tissue type expressed at the class I and class II loci on chromosome 6. Depending on the disease being treated, an acceptable donor will match the patient at all or most of the HLA loci (with the exception of umbilical cord blood).

Autologous Stem-Cell Transplantation for Autoimmune Diseases

The goal of autologous HSCT in patients with autoimmune diseases is to eliminate self-reactive lymphocytes (lymphoablative) and generate new self-tolerant lymphocytes. This approach is in contrast to destroying the entire hematopoietic bone marrow (myeloablative), as is often performed in autologous HSCT for hematologic malignancies. However, there is currently no standard conditioning regimen for autoimmune diseases and both lymphoablative and
myeloablative regimens are used. The efficacy of the different conditioning regimens has not been compared in clinical trials.

Currently, for autoimmune diseases, autologous transplant is preferred over allogeneic, in part because of the lower toxicity of autotransplant relative to allogeneic, the GVHD associated with allogeneic transplant, and the need to administer post-transplant immunosuppression after an allogeneic transplant.

**Allogeneic Stem-Cell Transplantation for Autoimmune Diseases**

The experience of using allogeneic HSCT for autoimmune diseases is currently limited but has two potential advantages over autologous transplant. First, the use of donor cells from a genetically different individual could possibly eliminate genetic susceptibility to the autoimmune disease and potentially result in a cure. Second, there exists a possible graft-versus-autoimmune effect, in which the donor T cells attack the transplant recipient’s autoreactive immune cells.

**Multiple Sclerosis**

MS is the most common autoimmune disease for which autologous HSCT is being studied. Following initial promising clinical experience, more than 350 consecutive cases have been reported by the EBMT over the last decade. Most patients who underwent autologous HSCT for MS in the early studies had secondary progressive MS, and relatively fewer had relapsing remitting disease, with a Kurtzke Expanded Disability Status Scale (EDSS) of 3.0–9.5 at the time of HSCT. Improvements in supportive care and patient selection have contributed to improved outcomes, with a significant reduction in treatment-related mortality to 1.3% seen during 2001–2007. It is now generally accepted that administering HSCT relatively early in the course of the disease to reduce inflammation before irreversible neuronal damage occurs is important. Current studies target MS patients with active disease and worsening disability, as evidenced clinically by relapse, change in EDSS, and/or inflammatory activity seen on magnetic resonance imaging (MRI) and who have failed at least one approved first-line immunomodulatory MS therapy for enrollment. Follow-up of several years will be needed to evaluate outcomes of these clinical trials.

A systematic review published in 2011 evaluated the safety and efficacy of autologous HSCT in patients with progressive MS refractory to conventional medical treatment. Eight case series were included that met the inclusion criteria for the primary outcome of progression-free survival (PFS) with a median follow-up of at least 2 years. An additional 6 studies were included for a summary of mortality and morbidity. For the 8 case series, there was substantial heterogeneity across studies. The majority of patients (77%) had secondary progressive MS, although studies also included those with primary progressive, progressive-relapsing, and relapse-remitting disease. Numbers of patients across studies ranged between 14 and 26. The studies differed in the types and intensities of conditioning regimens used prior to HSCT, with 5 studies using an intermediate-intensity regimen, while the other 3 used high-intensity regimens. All of the studies were rated of moderate quality. The estimated rate of long-term PFS of patients receiving intermediate-intensity conditioning regimen was 79.4% (95% confidence interval [CI]: 69.9–86.5%) with a median follow-up of 39 months, while the estimate for patients who received a high-dose regimen was 44.6%
(95% CI: 26.5-64.5%) at a median follow-up of 24 months. Of the 14 studies that reported on adverse events, 13 were case series; from these, a total of 7 treatment-related deaths were recorded; 6 non-treatment-related deaths occurred, 5 associated with disease progression.

A review published in 2010 summarizes the experience with HSCT and MS. A small number of patients have undergone autologous HSCT for the rare malignant form of MS, which is characterized by very active inflammatory disease with high relapse rates leading to a rapid progression of disabilities from the onset. These patients had persistent disease activity despite numerous different treatments. All patients but one were relapse-free without the need for ongoing immunosuppression after autologous HSCT with up to 66 months of follow-up. One patient experienced a mild relapse that improved with conventional treatment. All of the patients had remarkable improvement in their functional abilities.

Most patients who have undergone autologous HSCT have had poor prognosis MS, which manifests as frequent relapses or the early onset of the secondary progressive (SPMS) phase of the illness within 3 to 5 years of diagnosis. Studies are mainly case series that report the outcomes of autologous HSCT in MS patients with ongoing disease activity that is refractory to conventional disease-modifying agents. There has not been a “standard” transplant regimen, and different mobilization and conditioning regimens have been used throughout the published series. Clinical relapses were reported following autologous HSCT in one series, but overall, there has been an absence of ongoing acute episodic inflammatory disease activity in most reports. Evidence of ongoing chronic disease activity was seen in 14–76% of cases in the different series, with median follow-up between 1.5 to 3 years. Although the frequency of progression seems to be similar to what might be expected from historical controls, in many of the transplant studies, between 5% and 60% of patients actually had significant and sustained improvement in their disability score, and MS PFS seems to level off with increasing length of follow-up after autologous HSCT, a change from the expected natural history of progressive disabilities increasing with time.

Burt and colleagues have transplanted 21 patients with relapsing-remitting MS with ongoing relapses during treatment with interferon. (13) The conditioning regimen was nonmyeloablative. With a median follow-up of 37 months, 16 patients remained free of relapse, whereas 17 of the 21 patients had a 1-point or greater improvement in their EDSS score.

The EBMT Autoimmune Diseases Working Party database reported new data from a retrospective survey of 178 patients with MS who underwent autologous HSCT following one of several different preparative regimens. Overall, at median follow-up of about 42 months, the disease remained stable or improved in 63% of cases and worsened in 37%. Autologous HSCT was associated with significantly better PFS in a subset of younger patients (i.e., younger than 40 years of age) affected by severe, progressive MS who received autologous HSCT within 5 years from diagnosis compared to those older than 40 years. The authors suggest that autologous HSCT could be considered after failure of conventional treatments in patients with rapidly progressing MS.

Fassas and colleagues reported the long-term results of a Phase I/II study conducted in a single center that investigated the effect of HSCT in the treatment of MS. The authors reported on the
clinical and MRI outcomes of 35 patients with aggressive MS treated with HSCT after a median follow-up period of 11 (range 2-15) years. Disease PFS at 15 years was 44% for patients with active central nervous system (CNS) disease and 10% for those without (p=0.01); median time to progression was 11 years (95% CI: 0-22) and 2 years (0-6). Improvements by 0.5-5.5 (median 1) Expanded Disability Status Scale (EDSS) points were observed in 16 cases lasting for a median of 2 years. In 9 of these patients, EDSS scores did not progress above baseline scores. Two patients died, at 2 months and 2.5 years, from transplant-related complications. Gadolinium-enhancing lesions were significantly reduced after mobilization but were maximally and persistently diminished post-HSCT. The authors concluded that HSCT should be reserved for aggressive cases of MS, still in the inflammatory phase of the disease, and for the malignant form, in which it can be life-saving, and that HSCT can result in PFS rates of 25% and can have an impressive and sustained effect in suppressing disease activity on MRI.

Shevchenko and colleagues reported the results of a prospective Phase II open-label single-center study which analyzed the safety and efficacy of autologous HSCT with reduced-intensity conditioning regimen in 95 patients with different types of MS. The patients underwent early, conventional, and salvage/late transplantation. The efficacy was evaluated based on clinical and quality-of-life outcomes. No transplantation-related deaths were observed. All of the patients, except one, responded to the treatment. At long-term follow-up (mean 46 months), the overall clinical response in terms of disease improvement or stabilization was 80%. The estimated PFS at 5 years was 92% in the group after early transplant versus 73% in the group after conventional/salvage transplant (p=0.01). No active, new, or enlarging lesions in MRI were registered in patients without disease progression. All patients who did not have disease progression were off therapy throughout the post-transplantation period. HSCT was accompanied by a significant improvement in quality of life with statistically significant changes in the majority of quality-of-life parameters (p<0.05).

Mancardi and colleagues reported their experience with 74 consecutive patients with MS treated with autologous HSCT with an intermediate intensity conditioning regimen in the period from 1996 to 2008. Clinical and MRI outcomes were reported. The median follow-up period was 48.3 months (range=0.8-126). Two patients (2.7%) died from transplant-related causes. After 5 years, 66% of patients remained stable or improved. Among patients with a follow-up longer than 1 year, 8 out of 25 subjects with a relapsing-remitting course (31%) had a 6-12 months confirmed Expanded Disability Status Scale improvement >1 point after HSCT, as compared with 1 out of 36 (3%) patients with a secondary progressive disease course (p=0.009). Among the 18 cases with a follow-up longer than 7 years, 8 (44%) remained stable or had a sustained improvement, while 10 (56%), after an initial period of stabilization or improvement with a median duration of 3.5 years, showed a slow disability progression.

Bowen and colleagues reported the long-term safety and effectiveness of high-dose immunosuppressive therapy followed by autologous HSCT in advanced MS. (18) Neurologic examinations, brain MRI and cerebrospinal fluid (CSF) for oligoclonal bands (OCB) were serially evaluated. There were 26 patients with a mean Expanded Disability Status Scale (EDSS) of 7.0; 17 with secondary progressive MS, 8 with primary progressive, and 1 with relapsing/remitting.
follow up was 48 months after HSCT. The 72-month probability of worsening ≥1.0 EDSS point was 0.52 (95% CI: 0.30-0.75). Five patients had an EDSS at baseline of ≤6.0; 4 of them had not failed treatment at last study visit. OCB in CSF persisted with minor changes in the banding pattern. Four new or enhancing lesions were seen on MRI, all within 13 months of treatment. In this population with high baseline EDSS, a significant proportion of patients with advanced MS remained stable for as long as 7 years after transplant. Non-inflammatory events may have contributed to neurologic worsening after treatment. HSCT may be more effective in patients with less advanced relapsing/remitting MS.

Systemic Sclerosis/Scleroderma

A recent review summarized the clinical studies that have been performed using conventional therapy, as well as those using autologous HSCT in the treatment of systemic sclerosis. Ongoing randomized trials are also discussed.

The results of the Autologous Stem Cell Transplantation International Scleroderma (ASTIS) trial (ISRCTN54371254) were published in June 2014. ASTIS was a Phase 3 randomized controlled trial (RCT) conducted in 10 countries at 29 centers with access to an EBMT-registered transplant facility. A total of 156 patients were recruited between March 2001 and October 2009. Individual patients were eligible if they were between 18 and 65 years of age; had diffuse cutaneous systemic sclerosis according to American Rheumatism Association criteria, with maximum duration of 4 years; minimum modified Rodnan skin score (mRSS) of 15 (range, 0-51 with higher scores indicating more severe skin thickening); and, involvement of heart, lungs, or kidneys. Patients were randomly allocated to receive high-dose chemotherapy (intravenous cyclophosphamide 200 mg/kg over 4 consecutive days and intravenous rabbit antithymocyte globulin 7.5 mg/kg total dose over 3 consecutive days) followed by CD34+ selected autologous HSCT support (n=79) or 12 monthly treatments with intravenous pulsed cyclophosphamide (750 mg/m2). Median follow-up was 5.8 years (interquartile range, 4.1-7.8 years). The primary end point was event-free survival, defined as the time in days from randomization until the occurrence of death due to any cause or the development of persistent major organ failure (heart, lung, kidney). Main secondary end points included treatment-related mortality, toxicity, and disease-related changes in mRSS, organ function, body weight, and quality-of-life scores. The internal validity (risk of bias) of ASTIS was assessed according to the United States Preventive Services Task Force (USPSTF) criteria for randomized trials. The study was rated as “poor” quality according to this framework because it has 2 fatal flaws: outcome assessment was not masked to patients or assessors, and 18 of 75 (24%) of the control group discontinued intervention because of death, major organ failure, adverse events, or nonadherence. Furthermore, the article states that crossover was allowed after the second year, but whether any patients did so and were analyzed as such is not mentioned. Finally, the authors report that the use of unspecified concomitant medications or other supportive care measures were allowed at the discretion of the investigators, adding further uncertainty to the results.

A total of 53 primary end point events were recorded: 22 in the HSCT group (19 deaths and 3 irreversible organ failures; 8 patients died of treatment-related causes in the first year, 9 of disease
progression, 1 of cerebrovascular disease, 1 of malignancy) and 31 in the control group (23 deaths and 8 irreversible organ failures [7 of whom died later]; 19 patients died of disease progression, 4 of cardiovascular disease, 5 of malignancy, 2 of other causes). The data show patients treated with HSCT experienced more events in the first year but appeared to have better long-term event-free survival than the controls, as the Kaplan-Meier curves for overall survival (OS) cross at about 2 years after treatment with OS at that time estimated at 85%. According to data from the Kaplan-Meier curves, at 5 years, OS was an estimated 66% in the control group and about 80% the HSCT group (p value unknown). Time-varying hazard ratios (modeled with treatment x time interaction) for event-free survival were 0.35 (95% CI, 0.15-0.74) at 2 years and 0.34 (95% CI, 0.16-0.74) at 4 years, supporting a benefit of HSCT versus pulsed cyclophosphamide. Severe or life-threatening grade 3 or 4 adverse events were reported in 51 (63%) of the HSCT group compared with 30 (37% by intention-to-treat, p=0.002).

An open-label, randomized, controlled phase 2 trial (ASSIST) assessed the safety and efficacy of autologous nonmyeloablative HSCT compared with the standard of care cyclophosphamide. Nineteen consecutively enrolled patients who were younger than 60 years of age with diffuse systemic sclerosis, mRSS of more than 14, and internal organ involvement or restricted skin involvement (mRSS <14) but coexistent pulmonary involvement were randomly allocated 1:1 by use of a computer-generated sequence to receive HSCT, 200 mg/kg intravenous cyclophosphamide, and rabbit antithymocyte globulin or to 1.0 g/m² intravenous cyclophosphamide once per month for 6 months. The primary outcome was improvement at 12 months’ follow-up, defined as a decrease in mRSS (<25% for those with initial mRSS >14) or an increase in forced vital capacity by more than 10%. Patients in the control group with disease progression (>25% increase in mRSS or decrease of >10% in forced vital capacity) despite treatment with cyclophosphamide could switch to HSCT 12 months after enrollment. No deaths occurred in either group during follow-up. Patients allocated to HSCT (n=10) improved at or before 12 months of follow-up, compared with none of the 9 allocated to cyclophosphamide (p<0.001). Treatment failure (ie, disease progression without interval improvement), occurred in 8 of 9 controls, compared with none of the 10 patients treated by HSCT (p<0.001). After long-term follow-up (mean, 2.6 years) of patients who were allocated to HSCT, all but 2 patients had sustained improvement in mRSS and forced vital capacity, with a longest follow-up of 60 months. Seven patients allocated to receive cyclophosphamide switched treatment groups at a mean of 14 months after enrollment and underwent HSCT without complication, and all improved after HSCT. Four of these patients followed for at least 1 year had a mean decrease in mRSS points from 27 (SD=15.5) to 15 (SD=7.4), an increase in forced vital capacity from 65% (SD=20.6) to 76% (SD=26.5) and an increase in total lung capacity from 81% (SD=14.0) to 88% (SD=13.9%). Data for 11 patients with follow-up to 2 years after HSCT suggested that the improvements in mRSS (p<0.001) and forced vital capacity (p<0.03) persisted.

Vonk et al reported the long-term results of 28 patients with severe diffuse cutaneous systemic sclerosis who underwent autologous HSCT from 1998 to 2004. There was 1 transplant-related death and 1 death due to progressive disease, leaving 26 patients for evaluation. After a median follow-up of 5.3 years (range, 1-7.5 years), 81% (n=21/26) of the patients demonstrated a clinically beneficial response. Skin sclerosis was measured with a modified Rodnan skin score, and a
significant (ie, >25%) decrease (ie, improvement) was achieved in 19 of 26 patients after 1 year and in 15 of 16 after 5 years. At inclusion into the study, 65% of patients had significant lung involvement; all pulmonary function parameters remained stable after transplant at 5 and 7 year follow-up. Analyzing World Health Organization (WHO) performance status, which reflects the effect of HSCT on the combination of functional status, skin, lung, heart, and kidney involvement, the percentage of patients with a performance score of 0 increased to 56% compared with 4% at baseline. Estimated survival at 5 years was 96.2% (95% CI, 89% to 100%) and at 7 years was 84.8% (95% CI, 70.2% to 100%), and event-free survival, (survival without mortality, relapse, or progression of systemic sclerosis resulting in major organ dysfunction) was 64.3% (95% CI, 47.9% to 86%) at 5 years and 57.1% (95% CI, 39.3% to 83%) at 7 years. For comparison, an international meta-analysis published in 2005 estimated the 5-year mortality rate in patients with severe systemic sclerosis at 40%.

Nash et al reported the long-term follow-up of 34 patients with diffuse cutaneous systemic sclerosis with significant visceral organ involvement who were enrolled in a multi-institutional pilot study between 1997 and 2005 and underwent autologous HSCT.22 Of the 34 patients, 79% survived 1 year and were evaluable for response (there were 8 transplant-related deaths and 4 systemic sclerosis-related deaths). Seventeen of the 27 (63%) evaluable patients had sustained responses at a median follow-up of 4 years (range, 1-8 years). Skin biopsies showed a statistically significant decrease in dermal fibrosis compared with baseline (p<0.001) and, in general, lung, heart, and kidney function remained stable. Overall function as assessed in 25 patients by the modified Health Assessment Questionnaire Disability Index showed improvement in 19, and disease response was observed in the skin of 23 of 25 and lungs of 8 of 27 patients. Estimated OS and progression-free survival (PFS) were both 64% at 5 years.

Henes et al reported on their experience with autologous HSCT for systemic sclerosis in 26 consecutive patients scheduled for HSCT between 1997 and 2009.23 The major outcome variable was the response to treatment (reduction of mRSS by 25%) at 6 months. Secondary end points were TRM and PFS. At 6 months, significant skin and lung function improvement of the mRSS was achieved in 78.3% of patients. The overall response rate was 91%, as some patients improved even after month 6. Three patients died between mobilization and conditioning treatment, 2 due to severe disease progression and 1 whose death was considered treatment-related. Seven patients experienced a relapse during the 4.4 years of follow-up. PFS was 74%. Four patients died during follow-up, and the most frequent causes of death were pulmonary and cardiac complications of systemic sclerosis. The authors concluded that autologous HSCT resulted in significant improvement in most patients with systemic sclerosis.

Systemic Lupus Erythematosus

Burt et al published the results of the largest single-center series of this treatment in SLE available in the United States.24 Between April 1997 through January 2005, they enrolled 50 patients (mean age, 30 years, SD=10.9; 43 women, 7 men) with SLE refractory to standard immunosuppressive therapies and either organ- or life-threatening visceral involvement in a single-arm trial. All subjects
had at least 4 of 11 American College of Rheumatology criteria for SLE and required more than 20 mg per day of prednisone or its equivalent in spite of use of cyclophosphamide. Patients underwent autologous SCT following a lymphoablative conditioning regimen. Two patients died after mobilization, yielding a treatment-related mortality of 4% (2/50). After a mean follow-up of 29 months (range, 6 months to 7.5 years), overall 5-year survival was 84%, and the probability of disease-free survival was 50%. Several parameters of SLE activity (described in the 2001 TEC Assessment) improved, including renal function, SLE Disease Activity Index (DAI) score, antinuclear antibody, anti-ds DNA, complement, and carbon monoxide diffusion lung capacity. The investigators suggest these results justify a randomized trial comparing immunosuppression plus autologous SCT versus continued standard of care.

Song et al reported on the efficacy and toxicity of autologous stem-cell transplantation for 17 patients with SLE after 7 years follow-up. The probabilities of OS and progression-free survival (PFS) were used to assess the efficacy and toxicities of the treatment. The median follow-up time was 89 months (range, 33-110 months). The probabilities of 7-year OS and PFS were 82.4%±9.2% and 64.7%±11.6%, respectively. The principal adverse events included allergy, infection, elevation of liver enzymes, bone pain, and heart failure. Two patients died due to severe pneumonia and heart failure at 33 and 64 months after transplantation, respectively. The authors concluded that their 7-year follow-up results suggest that autologous HSCT seems beneficial for SLE patients.

**Chronic Inflammatory Demyelinating Polyneuropathy**

Several review articles have summarized experience with HSCT in treatment of chronic inflammatory demyelinating polyneuropathy (CIDP).26-28 In general, evidence comprises a few case reports describing outcomes of autologous HSCT in patients who failed standard treatments such as corticosteroids, intravenous immunoglobulins, and plasma exchange.

**Type 1 Diabetes Mellitus**

Couri et al reported the results of a prospective Phase 1/2 study of autologous HSCT in 23 patients with type 1 diabetes mellitus (age range, 13-31 years) diagnosed in the previous 6 weeks by clinical findings with hyperglycemia and confirmed by measurement of serum levels of antiglutamic acid decarboxylase antibodies.29 Enrollment was November 2003 to April 2008, with follow-up until December 2008. After a mean follow-up of 29.8 months (range, 7-58 months) following autologous nonmyeloablative HSCT, C-peptide levels increased significantly (C-peptide is a measure of islet cell mass, and an increase after HSCT indicates preservation of islet cells), and most patients achieved insulin independence with good glycemic control. Twenty patients without previous ketoacidosis and not receiving corticosteroids during the preparative regimen became insulin-free. Twelve patients maintained insulin independence for a mean of 31 months (range, 14-52 months), and 8 patients relapsed and resumed low-dose insulin. In the continuously insulin-independent group, HbA1c levels were less than 7.0% and mean area under the curve (AUC) C-peptide levels increased significantly from 225.0 (SE=75.2) ng/mL per 2 hours pretransplantation to 785.4 (SE=90.3) ng/mL per 2 hours at 24 months posttransplantation (p<0.001) and to 728.1 (SE=144.4) ng/mL per 2 hours at 36 months (p=0.001). In the transiently insulin-independent group, mean AUC of C-peptide levels...
also increased from 148.9 (SE=75.2) ng/mL per 2 hours pretransplantation to 546.8 (SE=96.9) ng/mL per 2 hours at 36 months (p=0.001), which was sustained at 48 months. In this latter group, 2 patients regained insulin independence after treatment with sitagliptin (Januvia®), which was associated with an increase in C-peptide levels. There was no transplant-related mortality.

Other Autoimmune Diseases

Phase 2/3 protocols are being developed for Crohn disease. For the remaining autoimmune diseases (including immune cytopenias, relapsing polychondritis, and others), the numbers are too small to draw conclusions, with further phase 1/2 pilot studies proceeding.

Ongoing and Unpublished Clinical Trials

A Phase III randomized trial (Stem Cell Therapy for Patients With Multiple Sclerosis Failing Interferon A Randomized Study) is recruiting participants to study the effect of autologous peripheral blood HSCT in patients with relapsing MS versus U.S. Food and Drug Administration (FDA)-approved standard of care. Primary endpoint is disease progression. Patients will be followed for 5 years after randomization. Estimated enrollment is 110, and estimated study completion date is January 2013 (NCT00273364).

The Phase II randomized ASTIMS trial evaluating autologous HSCT in severe cases of MS was terminated due to difficulty in accruing patients and lack of funds.

The High-Dose Immunosuppression and Autologous Transplantation for Multiple Sclerosis (HALT-MS) Study is a Phase II nonrandomized, uncontrolled trial to determine the effectiveness of autologous HSCT for the treatment of poor prognosis (relapsing-remitting or secondary progressive) MS. The primary outcome measure is time to treatment failure. Estimated enrollment is 25, and estimated study completion date is September 2015 (NCT00288626).

The Canadian MS-BMT Phase II study is to determine the effect of autologous HSCT on early-stage MS. Estimated enrollment is 24. Enrollment completed July 2009.

The SCOT trial is a randomized Phase 2 study comparing HSCT and pulsed cyclophosphamide. Primary outcome measure is the global rank composite score at 54 months postrandomization (which includes measures of event-free survival, death, lung function, and skin score). Crossover to the HSCT arm is not allowed. The trial is still recruiting, with an estimated enrollment of 114 patients with an estimated study completion date of June 2016 (NCT00114530)
Three nonrandomized, open-label Phase 2 trials are recruiting patients, ongoing or completed studying the effectiveness of autologous HSCT in patients with SLE: one with an estimated enrollment of 9 and study completion date of October 2013 (NCT00076752), another with an estimated enrollment of 30 and study completion date of April 2014 (NCT00750971), and a third with an estimated enrollment of 52 and study completion date of April 2012 (NCT00271934).

No phase 2 or 3 clinical trials were identified using HSCT in juvenile idiopathic or RA.

One nonrandomized, Phase 2 clinical trial is recruiting patients to study nonmyeloablative autologous HSCT in patients with CIDP (NCT00278629). It is estimated the study will be complete in December 2014.

Three Phase 1/2 and 2 Phase 2 trials are recruiting patients with type 1 diabetes mellitus for autologous HSCT (NCT00315133, NCT01121029, NCT00807651, NCT01341899, NCT1285934). The status of 1 Phase 2 and 1 Phase 2/3 trial for patients with type 2 diabetes mellitus for autologous HSCT is unknown. (NCT00644241, NCT01065298)

II. Policy

Autologous or allogeneic hematopoietic stem-cell transplantation is not covered as a treatment of autoimmune diseases, including, but not limited to multiple sclerosis, juvenile idiopathic and rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis/scleroderma, and type 1 diabetes mellitus and chronic inflammatory demyelinating polynuropathy as they are not known to improve health outcomes.

III. Administrative Guidelines

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<td>Allogeneic hematopoietic stem-cell transplant without purging</td>
</tr>
<tr>
<td>41.06</td>
<td>Cord blood stem-cell transplant</td>
</tr>
<tr>
<td>41.07</td>
<td>Autologous hematopoietic stem-cell transplant with purging</td>
</tr>
<tr>
<td>41.08</td>
<td>Allogeneic hematopoietic stem-cell transplant with purging</td>
</tr>
<tr>
<td>41.09</td>
<td>Autologous bone marrow transplant with purging</td>
</tr>
<tr>
<td>41.91</td>
<td>Aspiration of bone marrow from donor for transplant</td>
</tr>
<tr>
<td>99.79</td>
<td>Other therapeutic apheresis (includes harvest of stem cells)</td>
</tr>
</tbody>
</table>

**HCPCS Code**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q0083 - Q0085</td>
<td>Chemotherapy, administer code range</td>
</tr>
<tr>
<td>J9000 - J9999</td>
<td>Chemotherapy drug code range</td>
</tr>
<tr>
<td>S2150</td>
<td>Bone marrow or blood-derived peripheral stem-cell harvesting and transplantation, allogeneic or autologous, including pheresis, high-dose chemotherapy, and the number of days of post-transplant care in the global definition (including drugs; hospitalization; medical surgical, diagnostic, and emergency services)</td>
</tr>
</tbody>
</table>
ICD-10 codes are provided for your information. These will not become effective until 10/01/2015.

<table>
<thead>
<tr>
<th>ICD-10-PCS</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>30243G0, 30243X0, 30243Y0</td>
<td>Percutaneous transfusion, central vein, bone marrow or stem cells, autologous, code list</td>
</tr>
<tr>
<td>30243G1, 30243X1, 30243Y1</td>
<td>Percutaneous transfusion, central vein, bone marrow or stem cells, nonautologous, code list</td>
</tr>
<tr>
<td>07DQ0ZZ, 07DQ3ZZ, 07DR0ZZ, 07DR3ZZ, 07DS0ZZ, 07DS3ZZ</td>
<td>Surgical, lymphatic and hemic systems, extraction, bone marrow, code list</td>
</tr>
</tbody>
</table>

### IV. Scientific Background

This policy has been updated regularly with searches of the MEDLINE database. The most recent literature search was performed for the period August 31, 2013 through September 15, 2014.

Recent reviews summarize the experience to date with hematopoietic stem-cell transplantation (HSCT) and autoimmune diseases.

As of March 2009, patients with an autoimmune disease registered in the European Group for Blood and Marrow Transplantation/European League Against Rheumatism (EBMT/EULAR) database who have undergone HSCT include a total of 1,031 with the clinical indications of multiple sclerosis (MS) (n=379), systemic sclerosis (n=207), systemic lupus erythematosus (SLE) (n=92), rheumatoid arthritis (RA) (n=88), juvenile idiopathic arthritis (n=70), idiopathic thrombocytopenic purpura (n=23), and Crohn’s disease (n=23).

**Clinical Trials**

Three nonrandomized, open-label Phase II trials are recruiting patients, ongoing or completed studying the effectiveness of autologous HSCT in patients with SLE: one with an estimated enrollment of 9 and study completion date of April 2018 (NCT00076752), another with an estimated enrollment of 30 and study completion date of April 2014 (NCT00750971), and a third with an estimated enrollment of 52 and study completion date of April 2012 (NCT00271934).

**Juvenile Arthritis**

A review article by Saccardi et al. summarizes the experience thus far with juvenile idiopathic and rheumatoid arthritis (RA) as follows (27): More than 50 patients with juvenile idiopathic arthritis have been reported to the EBMT Registry. The largest cohort study initially used one conditioning regimen, and thereafter, a modified protocol. Overall drug-free remission rate was approximately 50%. Some late relapses have been reported, and only partial correction of growth impairment has been seen. The frequency of HSCT for RA has decreased significantly since 2000, due to the introduction of new biologic therapies. Most patients who have undergone HSCT have had persistence or relapse of disease activity within 6 months of transplant.
**Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)**

Several review articles have summarized experience with HSCT in treatment of CIDP. In general, evidence comprises a few case reports describing outcomes of autologous HSCT in patients who failed standard treatments such as corticosteroids, intravenous immunoglobulins, and plasma exchange.

**Type 1 Diabetes Mellitus**

Couri and colleagues reported the results of a prospective Phase I/II study of autologous HSCT in 23 patients with type 1 diabetes mellitus (age range, 13-31 years) diagnosed in the previous 6 weeks by clinical findings with hyperglycemia and confirmed by measurement of serum levels of antiglutamic acid decarboxylase antibodies. (31) Enrollment was November 2003-April 2008, with follow-up until December 2008. After a mean follow-up of 29.8 months (range, 7-58 months) following autologous nonmyeloablative HSCT, C-peptide levels increased significantly (C-peptide is a measure of islet cell mass, and an increase after HSCT indicates preservation of islet cells), and the majority of patients achieved insulin independence with good glycemic control. Twenty patients without previous ketoacidosis and not receiving corticosteroids during the preparative regimen became insulin-free. Twelve patients maintained insulin independence for a mean of 31 months (range, 14-52 months), and 8 patients relapsed and resumed low-dose insulin. In the continuously insulin-independent group, HbA1c levels were less than 7.0% and mean area under the curve (AUC) C-peptide levels increased significantly from 225.0 (standard error [SE]: 75.2) ng/mL per 2 hours pretransplantation to 785.4 (SE: 90.3) ng/mL per 2 hours at 24 months post-transplantation (p<0.001) and to 728.1 (SE: 144.4) ng/mL per 2 hours at 36 months (p=0.001). In the transiently insulin-independent group, mean AUC of C-peptide levels also increased from 148.9 (SE: 75.2) ng/mL per 2 hours pretransplantation to 546.8 (SE: 96.9) ng/mL per 2 hours at 36 months (p=0.001), which was sustained at 48 months. In this latter group, 2 patients regained insulin independence after treatment with sitagliptin (Januvia®), which was associated with an increase in C-peptide levels. There was no transplant-related mortality.

**Clinical Trials**

Three Phase I/II and two Phase II trials are recruiting patients with type 1 diabetes mellitus for autologous HSCT (NCT00315133, NCT01121029, NCT00807651, NCT01341899, NCT1285934). The status of one Phase II and one Phase II/III trial for patients with type 2 diabetes mellitus for autologous HSCT is unknown. (NCT00644241, NCT01065298).

**Other Autoimmune Diseases**

Phase II/III protocols are being developed for Crohn’s disease. For the remaining autoimmune diseases (including immune cytopenias, relapsing polychondritis, and others), the numbers are too small to draw conclusions, with further Phase I/II pilot studies proceeding. (32)
Summary

Initial studies focused on using hematopoietic stem-cell transplantation (HSCT) as salvage therapy for end-stage treatment of refractory autoimmune diseases. More recent experience has better helped to define which patients are most likely to benefit from HSCT, and the field has shifted to the use of HSCT earlier in the disease course before irreversible organ damage and to the use of safer and less intense nonmyeloablative conditioning regimens.

The experience with HSCT and autoimmune disorders has been predominantly with autologous transplants, and a number of published clinical reports with follow-up have demonstrated the safety and in some patients (particularly those with systemic sclerosis, systemic lupus erythematosus [SLE], and multiple sclerosis [MS]) the impact of HSCT in selected autoimmune diseases.

Although some of the initial results have been promising, this field continues to evolve. Many trials (randomized and nonrandomized) are currently recruiting or ongoing comparing the use of HSCT to conventional therapy for most of the diseases addressed in this policy; the results of these trials will further define the role of HSCT in the management of these diseases. Thus, use of HSCT for these autoimmune diseases is considered investigational.

V. Important Reminder

The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii’s Patients’ Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4), generally accepted standards of medical practice and review of medical literature and government approval status. HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA’s determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

VI. References


3. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). High-dose lymphoablative therapy (HDLT) with or without stem cell rescue for treatment of severe autoimmune diseases. TEC Assessments 2000; Vol 15, Tab 1.

4. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). High-dose lymphoablative therapy (HDLT) with or without stem-cell rescue for treatment of severe autoimmune diseases. TEC Assessments 2001; Vol 16, Tab 14.


