Hematopoietic Stem-Cell Transplantation for Autoimmune Diseases

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Place(s) of Service: Outpatient; Inpatient

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).

The evidence for HSCT in individuals who have multiple sclerosis includes 1 randomized controlled trial (RCT) and case series. Relevant outcomes are overall survival, health status measures, quality of life, treatment-related mortality and treatment-related morbidity. The phase 2 RCT reported intermediate outcomes (number of new T2 magnetic resonance imaging lesions); the group randomized to HSCT developed significantly fewer lesions than the group receiving conventional therapy. Findings of case series report include improvements in clinical parameters following HSCT. Controlled trials that report on clinical outcomes are needed to demonstrate efficacy. The evidence is insufficient to determine the effects of the technology on health outcomes.

The evidence for HSCT in individuals who have juvenile idiopathic and rheumatoid arthritis includes a registry study. Relevant outcomes are symptoms, quality of life, medication use, treatment-related mortality, and treatment-related morbidity. The registry study included 50 patients and the overall drug-free remission rate was approximately 50%. Additional data are needed from controlled studies to demonstrate efficacy. The evidence is insufficient to determine the effects of the technology on health outcomes.

The evidence for HSCT in individuals who have systemic lupus erythematosus includes case series. Relevant outcomes are overall survival, symptoms, quality of life, treatment-related mortality, and treatment-related morbidity. Several case series have been published. The largest (N=50 patients) found an overall 5-year survival rate of 84% and the probability of disease-free survival was 50%. Additional data are needed from controlled studies to demonstrate efficacy. The evidence is insufficient to determine the effects of the technology on health outcomes.
The evidence for HSCT in individuals who have systemic sclerosis/scleroderma includes RCTs and observational studies. Relevant outcomes are overall survival, symptoms, health status measures, quality of life, treatment-related mortality, and treatment-related morbidity. The results of the ASTIS trial suggest high-dose chemotherapy with autologous HSCT may improve survival among patients with diffuse cutaneous systemic sclerosis compared with pulsed intravenous cyclophosphamide. However, analysis of the internal validity of the trial using U.S. Preventive Services Task Force criteria showed fatal flaws and a poor study rating due to attrition in the control group that could have skewed the survival curve to show better survival for HSCT recipients than for controls. A smaller RCT (N=19) found that the rate of improvement at 12 months was significantly higher in the HSCT group than in the conventional therapy group. Data from these studies are inconclusive; additional studies are needed to confirm safety and efficacy. The evidence is insufficient to determine the effects of the technology on health outcomes.

The evidence for HSCT in individuals who have type 1 diabetes mellitus includes case series. Relevant outcomes are overall survival, symptoms, health status measures, quality of life, treatment-related mortality, and treatment-related morbidity. Several case series evaluated autologous HSCT in patients with new-onset type 1 diabetes; there were no published comparative studies. In the series, although a substantial proportion of patients tended to become insulin free after HSCT, remission rates were high. The evidence is insufficient to determine the effects of the technology on health outcomes.

The evidence for HSCT in individuals who have chronic inflammatory demyelinating polyneuropathy includes case reports. Relevant outcomes are overall survival, symptoms, health status measures, quality of life, treatment-related mortality, and treatment-related morbidity. Additional data are needed from controlled studies to demonstrate efficacy. The evidence is insufficient to determine the effects of the technology on health outcomes.

Background

Autoimmune Diseases
Autoimmune diseases represent a heterogeneous group of immune-mediated disorders, including MS, rheumatoid arthritis (RA), SLE, systemic sclerosis/scleroderma and chronic inflammatory demyelinating polyneuropathy (CIPD). The National Institutes of Health (NIH) estimates that 5% to 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 HSCT. The primary concept underlying use of HSCT for these diseases is that ablating and
“resetting” the immune system can alter the disease process, first inducing a sustained remission that possibly leads to cure.

**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 H SCT 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.

**II. Criteria/Guidelines**

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, type 1 diabetes mellitus and chronic inflammatory demyelinating polyneuropathy as they are not known to improve health outcomes.

III. Administrative Guidelines

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Hematopoietic Stem-Cell Transplantation for Autoimmune Diseases

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| Surgical, lymphatic and hemic systems, extraction, bone marrow, code list |

IV. Scientific Background

This policy has been updated regularly with searches of the MEDLINE database. The most recent literature search was performed through December 10, 2015.

Recent reviews summarize the research to date using HSCT to treat a number of autoimmune diseases.

In 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 MS (n=379), systemic sclerosis (n=207), SLE (n=92), RA (n=88), juvenile idiopathic arthritis (n=70), idiopathic thrombocytopenic purpura (n=23), and Crohn’s disease (n=23).

Multiple Sclerosis

Only 1 randomized controlled trial (RCT) evaluating HSCT for treatment of MS has been published, but this trial did not report clinical outcomes. No controlled trials with contemporaneous control groups were identified that reported clinical end points such as overall survival (OS), progression-free survival (PFS), or disability status as their primary outcomes. The 2015 RCT by Mancardi et al was originally designed as a phase 3 study reporting on disability progression. However, due to low patient enrollment, the protocol was amended as a phase 2 study with the primary outcome of cumulative number of new T2 magnetic resonance imaging (MRI) lesions in the 4 years after treatment. Eligibility for the trial was secondary progressive or relapsing-remitting MS, a documented worsening during the last year, and lack of response to conventional therapy. A total of 21 patients were randomized to autologous HSCT (n=9) or medical therapy (mitoxantrone) (n=12). Follow-up data were not available on 4 patients; missing data was imputed in the intention-to-treat analysis of the primary outcome. The median number of new T2 MRI lesions was 2.5 in the HSCT group and 8 in the conventional therapy group (rate ratio, 0.21; 95% confidence interval, 0.10 to 0.48, p<0.001). Among secondary outcomes, the annualized relapse rate was significantly lower in the HSCT group (0.19) than in the conventional therapy group (0.6), but there was no statistically significant difference between groups in the rate of disease progression or change in disability status.

The remaining published literature consists of case series. In 2010, Pasquini et al published data on more than 350 consecutive cases included in the EBMT database. Most patients who underwent
autologous HSCT for MS in the early years had secondary progressive MS, and relatively fewer had relapsing remitting disease, with Kurtzke Expanded Disability Status Scale (EDSS) scores of 3.0 to 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 to 2007. Thinking at the time was that administering HSCT relatively early in the course of the disease to reduce inflammation before irreversible neuronal damage occurs was 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.

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 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% to 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% to 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 2012 study by Shevchenko et al reported the results of a prospective, open-label, single-center study that analyzed the safety and efficacy of autologous HSCT with reduced-intensity conditioning regimen in 95 patients with different types of MS. Patients underwent early, conventional, and salvage/late transplantation. Efficacy was evaluated based on clinical and quality-of-life (QOL) outcomes. No transplantation-related deaths were observed. All patients, except 1, responded to 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 and 73% in the group after conventional/salvage transplant (p=0.01). No active, new, or enlarging lesions on MRI were found in patients without disease progression. All patients who did not have disease progression were off therapy throughout the posttransplantation period. HSCT was accompanied by a significant improvement in QOL, with statistically significant changes in most QOL parameters (p<0.05). A 2015 subsequent publication reported on 64 patients participating in this trial who had at least 36 months of follow-up (median, 62 months). (Another 35 patients had shorter follow-up and the remainder were lost to follow-up.) Thirty (47%) of the 64 patients improved at least 0.5 point on the EDSS score compared with baseline. Among the other patients, 29 (45%) were stable and 5 (7%) experienced worsening disease.
In 2012, 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 to 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 to 12 months confirmed Expanded Disability Status Scale improvement greater than 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.

A 2015 single-center case series by Burt et al reported on 151 patients, 123 with relapsing-remitting MS and 28 with secondary progressive MS. Patients were treated with nonmyeloablative HSCT between 2003 and 2014. Six patients were not included in the outcome analysis. The remaining 145 patients were followed for a median of 2 years (range, 6 months to 5 years). There were no treatment-related deaths. The primary outcome was change in the EDSS score. A decrease of at least 1.0 point was considered significant improvement and an increase of at least 1.0 point was considered significant progression. There was statistically significant improvement in EDSS score for the group as a whole compared with the pretransplant mean score of 4.0, decreasing to a mean EDSS score of 2.5 at 3, 4, and 5 years. In post hoc analysis, patients most likely to have statistically significant improvements in EDSS score were those with relapsing-remitting MS, with duration of disease of 10 years or less, and those without sustained fever during HSCT.

Several studies have focused on patients with aggressive MS. In 2011, Fassas and colleagues reported the long-term results of 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 years (range: 2 to 15 years), on the clinical and MRI outcomes of 35 patients with aggressive MS treated with HSCT. 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 to 22 years) and 2 years (0 to 6), respectively. Improvements by 0.5 to 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.

2014 multicenter case series by Burman et al reported on 48 patients with aggressive relapsing-remitting MS, defined as disease with high relapse frequency, and who failed conventional therapy. Patients underwent autologous HSCT. At the 5-year follow-up, relapse-free survival was 87% and the EDSS score PFS (EDSS deterioration of <0.5 points) was 77%. The rate of disease-free survival (no relapses, no new MRI lesions, no EDSS score progression) was 68%.
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 III 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 to 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 to 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 two 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 to 0.74) at 2 years and 0.34 (95% CI: 0.16 to 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) of the control group.

An open-label, randomized, controlled Phase II 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 (i.e., 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 and colleagues 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 to 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 (i.e., >25%) decrease (i.e., 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 and colleagues 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. 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 to 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 and colleagues reported on their experience with autologous HSCT for systemic sclerosis in 26 consecutive patients scheduled for HSCT between 1997 and 2009. 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 and colleagues published the results of the largest single-center series of this treatment in SLE available in the U.S. Between April 1997 through January 2005, they enrolled 50 patients (mean age: 30 years [SD=10.9 years]; 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 and colleagues 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 PFS were used to assess
the efficacy and toxicities of the treatment. The median follow-up time was 89 months (range: 33 to 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.

**Juvenile Idiopathic Arthritis**
A 2008 review article by Saccardi and colleagues summarizes the experience thus far with juvenile idiopathic and RA as follows: 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**
Several case series were identified evaluating autologous HSCT in patients with new-onset type 1 diabetes; there were no published comparative studies. In the series, although a substantial proportion of patients tended to become insulin-free after HSCT, remission rates were high. In 2015, Xiang et al published data on 128 patients ages 12 to 35 years who had been diagnosed with type 1 diabetes no more than 6 weeks before study enrollment. After a mean follow-up of 28.5 months (range, 15-38 months), 71 patients (55%) were considered to be insulin-free. These patients had a mean remission period of 14.2 months (SD=6.1 months). The other 57 patients (45%) were insulin-dependent. The latter group includes 27 patients with no response to treatment and another 30 patients who relapsed after a transient remission period. Adverse events included ketoacidosis and renal dysfunction (1 patient each); there was no transplant-related mortality. In multiple logistic regression analysis, factors independently associated with becoming insulin-free after autologous HSCT were younger age at onset of diabetes, lower tumor necrosis factor α, and higher fasting C peptid.

A 2015 case series by Snarski et al reported on 24 patients with a diagnosis of type 1 diabetes within 6 weeks of enrollment who underwent autologous HSCT.27 Patients had a mean age of 26.5 years (range, 18-34 years). After treatment, 20 of 23 patients (87%) went into diabetes remission, defined as being insulin-free with normoglycemia for at least 9.5 months. Median time of remission was 31 months (range, 9.5-80 months). Mean insulin doses remained significantly lower than baseline doses at 2 and 3 years, but the insulin doses returned to pre-HSCT levels at years 4 and 5.
Among patients (n=20) remaining in follow-up at the time of data analysis for publication, 4 (20%) remained insulin-free. Adverse events include neutropenic fever in 12 patients (50%). There were 4 cases of sepsis, including a fatal case of Pseudomonas aeruginosa sepsis. There was also 1 case of pulmonary emphysema after insertion of a central venous catheter.

In 2009, 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 to 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. After a mean follow-up of 29.8 months (range: 7 to 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 to 52 months), and 8 patients relapsed and resumed low-dose insulin. In the continuously insulin-independent group, HbA1c levels were less than 7.0%. There was no transplant-related mortality.

Other Autoimmune Diseases
Phase II/III protocols are being developed for Crohn disease. For the remaining autoimmune diseases (including immune cytopenias, relapsing polychondritis, and others), the sample sizes are too small to draw conclusions.

REGULATORY STATUS
The U.S. Food and Drug Administration regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research, under Code of Federal Regulation (CFR) title 21, parts 1270 and 1271. Hematopoietic stem cells are included in these regulations.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 1.

Table 1. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ongoing</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>NCT00288626</td>
<td>A Phase II Study of High-Dose Immunosuppressive Therapy (HDIT) Using Carmustine, Etoposide, Cytarabine, and Melphalan (BEAM) and Thymoglobulin, and Autologous CD34+ Hematopoietic Stem Cell Transplant (HCT) for the Treatment of Poor Prognosis Multiple Sclerosis. Interim 3 year data reported in 2015; the study is ongoing to 5 years</td>
<td>25</td>
<td>Aug 2015</td>
</tr>
<tr>
<td>NCT00114530</td>
<td>A Randomized, Open-Label, Phase II Multicenter Study of High- Dose Immunosuppressive Therapy Using Total Body Irradiation, Cyclophosphamide, ATGAM, and Autologous</td>
<td>75</td>
<td>Dec 2017</td>
</tr>
</tbody>
</table>
Hematopoietic Stem-Cell Transplantation for Autoimmune Diseases

| NCT00273364 | Hematopoietic Stem Cell Therapy for Patients With Inflammatory Multiple Sclerosis Failing Alternate Approved Therapy: A Randomized Study | 110 | Dec 2017 |
| NCT00278629 | Non-myeloablative Autologous Hematopoietic Stem Cell Transplantation in Patients With Chronic Inflammatory Demyelinating Polyneuropathy: A Phase II Trial | 80 | Dec 2017 |

NCT: national clinical trial.

Summary
Please refer to description.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

A review of the guidelines from the American Academy of Neurology (AAN) and the American College of Rheumatology found no mention of stem cell transplantation in guidelines for multiple sclerosis, lupus, rheumatoid arthritis, or juvenile idiopathic arthritis. For example, guidelines from AAN published in 2002 and reaffirmed in 2008 on disease-modifying therapies in multiple sclerosis did not discuss stem cell transplantation.

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
There are numerous autoimmune diseases and the Centers for Medicare and Medicaid Services has not issued a national coverage determination (NCD) for stem cell transplantation for each disease. A general NCD for stem cell transplantation (110.8.1) states the following:

“Note: This may not be an exhaustive list of all applicable Medicare benefit categories for this item or service.

Item/Service Description

A. General

Stem-cell transplantation is a process in which stem cells are harvested from either a patient’s (autologous) or donor’s (allogeneic) bone marrow or peripheral blood for intravenous infusion. Autologous stem cell transplants (AuSCT) must be used to effect hematopoietic reconstitution following severely myelotoxic doses of chemotherapy (HDCT) and/or radiotherapy used to treat various malignancies. Allogeneic stem-cell transplants may be used to restore function in recipients having an inherited or acquired deficiency or defect. Hematopoietic stem cells are
multi-potent stem cells that give rise to all the blood cell types; these stem cells form blood and immune cells. A hematopoietic stem cell is a cell isolated from blood or bone marrow that can renew it, differentiate to a variety of specialized cells, can mobilize out of the bone marrow into circulating blood, and can undergo programmed cell death, called apoptosis - a process by which cells that are unneeded or detrimental self-destruct.

The Centers for Medicare & Medicaid Services (CMS) is clarifying that bone marrow and peripheral blood stem-cell transplantation is a process which includes mobilization, harvesting, and transplant of bone marrow or peripheral blood stem cells and the administration of high-dose chemotherapy or radiotherapy prior to the actual transplant. When bone marrow or peripheral blood stem-cell transplantation is covered, all necessary steps are included in coverage. When bone marrow or peripheral blood stem-cell transplantation is noncovered, none of the steps are covered.

Indications and Limitations of Coverage

1. Allogeneic Hematopoietic Stem Cell Transplantation (HSCT)

Allogeneic hematopoietic stem cell transplantation (HSCT) is a procedure in which a portion of a healthy donor's stem cell or bone marrow is obtained and prepared for intravenous infusion.

a. Nationally Covered Indications

The following uses of allogeneic HSCT are covered under Medicare:

i. Effective for services performed on or after August 1, 1978, for the treatment of leukemia, leukemia in remission, or aplastic anemia when it is reasonable and necessary,

ii. Effective for services performed on or after June 3, 1985, for the treatment of severe combined immunodeficiency disease (SCID) and for the treatment of Wiskott-Aldrich syndrome.

iii. Effective for services performed on or after August 4, 2010, for the treatment of Myelodysplastic Syndromes (MDS) pursuant to Coverage with Evidence Development (CED) in the context of a Medicare-approved, prospective clinical study.

The MDS refers to a group of diverse blood disorders in which the bone marrow does not produce enough healthy, functioning blood cells. These disorders are varied with regard to clinical characteristics, cytologic and pathologic features, and cytogenetics. The abnormal production of blood cells in the bone marrow leads to low blood cell counts, referred to as cytopenias, which are a hallmark feature of MDS along with a dysplastic and hypercellular-appearing bone marrow.

Medicare payment for these beneficiaries will be restricted to patients enrolled in an approved clinical study. In accordance with the Stem Cell Therapeutic and Research Act of 2005 (US Public Law 109-129) a standard dataset is collected for all allogeneic transplant patients in the United States by the Center for International Blood and Marrow Transplant Research. The elements in this
dataset, comprised of two mandatory forms plus one additional form, encompass the information we require for a study under CED.

A prospective clinical study seeking Medicare payment for treating a beneficiary with allogeneic HSCT for MDS pursuant to CED must meet one or more aspects of the following questions:

- **Prospectively, compared to Medicare beneficiaries with MDS who do not receive HSCT, do Medicare beneficiaries with MDS who receive HSCT have improved outcomes as indicated by:**
  - Relapse-free mortality,
  - Progression-free survival,
  - relapse, and
  - overall survival?

- **Prospectively, in Medicare beneficiaries with MDS who receive HSCT, how do International Prognostic Scoring System (IPSS) score, patient age, cytopenias and comorbidities predict the following outcomes:**
  - Relapse-free mortality,
  - Progression-free survival,
  - relapse, and
  - overall survival?

- **Prospectively, in Medicare beneficiaries with MDS who receive HSCT, what treatment facility characteristics predict meaningful clinical improvement in the following outcomes:**
  - Relapse-free mortality,
  - Progression-free survival,
  - relapse, and
  - overall survival?

In addition, the clinical study must adhere to the following standards of scientific integrity and relevance to the Medicare population:

a. The principal purpose of the research study is to test whether a particular intervention potentially improves the participants’ health outcomes.

b. The research study is well supported by available scientific and medical information or it is intended to clarify or establish the health outcomes of interventions already in common clinical use.

c. The research study does not unjustifiably duplicate existing studies.

d. The research study design is appropriate to answer the research question being asked in the study.

e. The research study is sponsored by an organization or individual capable of executing the proposed study successfully.

f. The research study is in compliance with all applicable Federal regulations concerning the protection of human subjects found at 45 CFR Part 46.
g. All aspects of the research study are conducted according to appropriate standards of scientific integrity (see http://www.icmje.org).

h. The research study has a written protocol that clearly addresses, or incorporates by reference, the standards listed here as Medicare requirements for CED coverage.

i. The clinical research study is not designed to exclusively test toxicity or disease pathophysiology in healthy individuals. Trials of all medical technologies measuring therapeutic outcomes as one of the objectives meet this standard only if the disease or condition being studied is life threatening as defined in 21 CFR §312.81(a) and the patient has no other viable treatment options.

j. The clinical research study is registered on the ClinicalTrials.gov Web site by the principal sponsor/investigator prior to the enrollment of the first study subject.

k. The research study protocol specifies the method and timing of public release of all pre-specified outcomes to be measured including release of outcomes if outcomes are negative or study is terminated early. The results must be made public within 24 months of the end of data collection. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors (http://www.icmje.org). However a full report of the outcomes must be made public no later than 3 years after the end of data collection.

l. The research study protocol must explicitly discuss subpopulations affected by the treatment under investigation, particularly traditionally underrepresented groups in clinical studies, how the inclusion and exclusion criteria effect enrollment of these populations, and a plan for the retention and reporting of said populations on the trial. If the inclusion and exclusion criteria are expected to have a negative effect on the recruitment or retention of underrepresented populations, the protocol must discuss why these criteria are necessary.

m. The research study protocol explicitly discusses how the results are or are not expected to be generalizable to the Medicare population to infer whether Medicare patients may benefit from the intervention. Separate discussions in the protocol may be necessary for populations eligible for Medicare due to age, disability or Medicaid eligibility.

Consistent with section 1142 of the Social Security Act, the Agency for Health Research and Quality (AHRQ) supports clinical research studies that CMS determines meet the above-listed standards and address the above-listed research questions.

The clinical research study should also have the following features:

- It should be a prospective, longitudinal study with clinical information from the period before HSCT and short- and long-term follow-up information.
- Outcomes should be measured and compared among pre-specified subgroups within the cohort.
- The study should be powered to make inferences in subgroup analyses.
- Risk stratification methods should be used to control for selection bias. Data elements to be used in risk stratification models should include:

Patient selection:
- Patient age at diagnosis of MDS and at transplantation
• Date of onset of MDS
• Disease classification (specific MDS subtype at diagnosis prior to preparative/conditioning regimen using World Health Organization (WHO) classifications). Include presence/absence of refractory cytopenias
• Comorbid conditions
• IPSS score (and WHO-adapted Prognostic Scoring System (WPSS) score, if applicable) at diagnosis and prior to transplantation
• Score immediately prior to transplantation and one year post-transplantation
• Disease assessment at diagnosis at start of preparative regimen and last assessment prior to preparative regimen Subtype of MDS (refractory anemia with or without blasts, degree of blasts, etc.)
• Type of preparative/conditioning regimen administered (myeloablative, non-myeloablative, reduced–intensity conditioning)
• Donor type
• Cell source
• IPSS Score at diagnosis

Facilities must submit the required transplant essential data to the Stem-Cell Therapeutics Outcomes Database.

b. Nationally Non-Covered Indications

Effective for services performed on or after May 24, 1996, allogeneic HSCT is not covered as treatment for multiple myeloma.

2. Autologous Stem-Cell Transplantation (AuSCT)

Autologous stem-cell transplantation (AuSCT) is a technique for restoring stem cells using the patient's own previously stored cells.

a. Nationally Covered Indications

i. Effective for services performed on or after April 28, 1989, AuSCT is considered reasonable and necessary under §1862(a)(1)(A) of the Social Security Act (the Act) for the following conditions and is covered under Medicare for patients with:
• Acute leukemia in remission who have a high probability of relapse and who have no human leucocyte antigens (HLA)-matched;
• Resistant non-Hodgkin’s lymphomas or those presenting with poor prognostic features following an initial response;
• Recurrent or refractory neuroblastoma; or
• Advanced Hodgkin’s disease who have failed conventional therapy and have no HLA-matched donor.

ii. Effective October 1, 2000, single AuSCT is only covered for Durie-Salmon Stage II or III patients that fit the following requirements:
• Newly diagnosed or responsive multiple myeloma. This includes those patients with previously untreated disease, those with at least a partial response to prior chemotherapy
(defined as a 50% decrease either in measurable paraprotein [serum and/or urine] or in bone marrow infiltration, sustained for at least 1 month), and those in responsive relapse; and,

- Adequate cardiac, renal, pulmonary, and hepatic function.
  
  iii. Effective for services performed on or after March 15, 2005, when recognized clinical risk factors are employed to select patients for transplantation, high-dose melphalan (HDM) together with AuSCT is reasonable and necessary for Medicare beneficiaries of any age group with primary amyloid light chain (AL) amyloidosis who meet the following criteria:

  - Amyloid deposition in 2 or fewer organs; and,
  - Cardiac left ventricular ejection fraction (EF) greater than 45%.

b. Nationally Non-Covered Indications

Insufficient data exist to establish definite conclusions regarding the efficacy of AuSCT for the following conditions:

- Acute leukemia not in remission;
- Chronic granulocytic leukemia;
- Solid tumors (other than neuroblastoma);
- Up to October 1, 2000, multiple myeloma;
- Tandem transplantation (multiple rounds of AuSCT) for patients with multiple myeloma;
- Effective October 1, 2000, non primary AL amyloidosis; and,
- Effective October 1, 2000, thru March 14, 2005, primary AL amyloidosis for Medicare beneficiaries age 64 or older.

In these cases, AuSCT is not considered reasonable and necessary within the meaning of §1862(a)(1)(A) of the Act and is not covered under Medicare.

B. Other

All other indications for stem cell transplantation not otherwise noted above as covered or non-covered nationally remain at Medicare Administrative Contractor discretion.

(This NCD last reviewed August 2010.)

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

30. American Academy of Neurology and the MS Council for Clinical Practice Guidelines. Disease modifying