Protocol

Hematopoietic Cell Transplantation for Autoimmune Diseases

(80125)

(Formerly Hematopoietic Stem Cell Transplantation for Autoimmune Diseases)

Medical Benefit		**Effective Date**: 04/01/14	**Next Review Date**: 11/18
Preauthorization	Yes	**Review Dates**: 04/07, 05/08, 01/10, 01/11, 01/12, 01/13, 01/14, 11/14, 11/15, 11/16, 11/17	

Preauthorization is required and must be obtained through Case Management.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

Populations	Interventions	Comparators	Outcomes
Individuals: • With multiple sclerosis	Interventions of interest are: • Hematopoietic cell transplantation	Comparators of interest are: • Conventional medication therapy	Relevant outcomes include: • Overall survival • Health status measures • Quality of life • Treatment-related mortality • Treatment-related morbidity
Individuals: • With systemic sclerosis/ scleroderma	Interventions of interest are: • Hematopoietic cell transplantation	Comparators of interest are: • Conventional medication therapy • Biologic therapy	Relevant outcomes include: • Symptoms • Health status measures • Quality of life • Medication use • Treatment-related mortality • Treatment-related morbidity
Individuals: • With systemic lupus erythematosus	Interventions of interest are: • Hematopoietic cell transplantation	Comparators of interest are: • Conventional medication therapy	Relevant outcomes include: • Overall survival • Symptoms • Quality of life • Treatment-related mortality • Treatment-related morbidity
Individuals: • With juvenile idiopathic or rheumatoid arthritis	Interventions of interest are: • Hematopoietic cell transplantation	Comparators of interest are: • Conventional medication therapy	Relevant outcomes include: • Overall survival • Symptoms • Quality of life • Treatment-related mortality • Treatment-related morbidity

Populations	Interventions	Comparators	Outcomes
Individuals: • With chronic inflammatory demyelinating polyneuropathy	Interventions of interest are: • Hematopoietic cell transplantation	Comparators of interest are: • Conventional medication therapy	Relevant outcomes include: • Overall survival • Symptoms • Health status measures • Quality of life • Treatment-related mortality • Treatment-related morbidity
Individuals: • With type 1 diabetes	Interventions of interest are: • Hematopoietic cell transplantation	Comparators of interest are: • Conventional medication therapy	Relevant outcomes include: • Overall survival • Symptoms • Health status measures • Quality of life • Treatment-related mortality • Treatment-related morbidity
Individuals: • With other autoimmune diseases (e.g., Crohn disease, immune cytopenias, relapsing polychondritis)	Interventions of interest are: • Hematopoietic cell transplantation	Comparators of interest are: • Conventional medication therapy	Relevant outcomes include: • Overall survival • Symptoms • Health status measures • Quality of life • Treatment-related mortality • Treatment-related morbidity

Description

Most patients with autoimmune disorders respond to conventional drug therapies; however, conventional drug therapies are not curative—and a proportion of patients suffer from autoimmune diseases that range from the severe to the recalcitrant to the rapidly progressive. It is in this group of patients with severe autoimmune disease that alternative therapies have been sought, including hematopoietic cell transplantation (HCT).

Summary of Evidence

For individuals with multiple sclerosis who receive HCT, the evidence includes a randomized controlled trial (RCT) and several case series. Relevant outcomes are overall survival, health status measures, quality of life, and treatment-related mortality and morbidity. The phase two RCT compared HCT with mitoxantrone, and the trial reported intermediate outcomes (number of new T2 magnetic resonance imaging lesions); the group randomized to HCT developed significantly fewer lesions than the group receiving conventional therapy. The findings of the case series revealed improvements in clinical parameters following HCT compared with baseline. Adverse event rates were high, and most studies reported treatment-related deaths. Controlled trials (with appropriate comparator therapies) that report on clinical outcomes are needed to demonstrate efficacy. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with systemic sclerosis/scleroderma who receive HCT, the evidence includes RCTs and observational studies. Relevant outcomes are overall survival, symptoms, health status measures, quality of life, and treatment-related mortality and morbidity. The results of the ASTIS trial (N=156) have suggested high-dose chemotherapy plus autologous HCT might 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 HCT recipients than for controls. A smaller RCT (N=19) found that the rate of improvement at 12 months was significantly higher in

the HCT group than in the conventional therapy group. Data from these trials, however, are inconclusive, and additional studies are needed to confirm safety and efficacy. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with systemic lupus erythematosus who receive HCT, the evidence includes case series. Relevant outcomes are overall survival, symptoms, quality of life, and treatment-related mortality and morbidity. Several case series (total N=91 patients) have been published. The largest series (N=50) reported an overall five-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.

For individuals with juvenile idiopathic or rheumatoid arthritis who receive HCT, the evidence includes registry data. Relevant outcomes are symptoms, quality of life, medication use, and treatment-related mortality and morbidity. The registry included 50 patients with juvenile idiopathic or rheumatoid arthritis. 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.

For individuals with chronic inflammatory demyelinating polyneuropathy who receive HCT, the evidence includes case reports. Relevant outcomes are overall survival, symptoms, health status measures, quality of life, and treatment-related mortality and 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.

For individuals with type 1 diabetes who receive HCT, the evidence includes case series and a meta-analysis of 22 studies. Relevant outcomes are overall survival, symptoms, health status measures, quality of life, and treatment-related mortality and morbidity. While a substantial proportion of patients tended to become insulin-free after HCT, remission rates were still high. The meta-analysis further revealed that HCT is more effective in patients with type 1 diabetes and when HCT is administered soon after the diagnosis. Certain factors limit the conclusions that can be drawn about the overall effectiveness of HCT in treating diabetes; those factors are: heterogeneity in the stem cell types, cell number infused, and infusion methods. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with other autoimmune diseases (e.g., Crohn disease, immune cytopenias, relapsing polychondritis) who receive HCT, the evidence includes small retrospective studies. Relevant outcomes are overall survival, symptoms, health status measures, quality of life, and treatment-related mortality and 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.

Policy

Autologous or allogeneic hematopoietic cell transplantation is considered **investigational** as a treatment of autoimmune diseases including, but not limited to, the following:

- multiple sclerosis
- systemic sclerosis/scleroderma
- systemic lupus erythematosus
- juvenile idiopathic and rheumatoid arthritis
- chronic inflammatory demyelinating polyneuropathy
- type 1 diabetes mellitus.

Medicare Advantage

If a transplant is needed, we arrange to have the transplant center review and decide whether the patient is an appropriate candidate for the transplant.

Background

Autoimmune Diseases

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

The pathogenesis of autoimmune diseases is not well understood, but it 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).

Treatment

Immune suppression is a common treatment strategy for many of these diseases, particularly the rheumatic diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, scleroderma). Most patients with autoimmune disorders respond to conventional therapies, which consist of anti-inflammatory agents, immunosuppressants, and immunomodulating drugs; however, conventional drug therapies are not curative, and a proportion of patients suffer from autoimmune diseases that range from severe to recalcitrant to rapidly progressive. It is for this group of patients with severe autoimmune disease that alternative therapies have been sought, including HCT. The primary concept underlying use of HCT for these diseases is that ablating and "resetting" the immune system can alter the disease process, by inducing a sustained remission that possibly leads to cure.[1]

HEMATOPOIETIC CELL TRANSPLANTATION

HCT is a procedure in which hematopoietic stem cells are infused to restore bone marrow function in cancer patients who receive bone-marrow-toxic doses of drugs with or without whole body radiotherapy. Hematopoietic stem cells may be obtained from the transplant recipient (autologous HCT) or a donor (allogeneic HCT). 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 "naive" and thus are associated with a lower incidence of rejection or graft-versus-host disease. Cord blood is discussed in detail in the Placental and Umbilical Cord Blood as a Source of Stem Cells Protocol.

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HCT. However, immunologic compatibility between donor and patient is critical for achieving a good outcome with allogenic HCT. Compatibility is established by typing of human leukocyte antigens (HLAs) using cellular, serologic, or molecular techniques. HLA refers to the tissue type expressed at the HLA-A, -B, and -DR loci on each arm of 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 Cell Transplantation - The goal of autologous HCT in patients with autoimmune diseases is to eliminate self-reactive lymphocytes (lymphoablation) and generate new self-tolerant lymphocytes.[2] This approach is in contrast to destroying the entire hematopoietic bone marrow (myeloablation), as is often performed in autologous HCT for hematologic malignancies.[2] However, no standard conditioning regimen exists for autoimmune diseases, and both lymphoablative and myeloablative regimens are used.[1] The efficacy of the different conditioning regimens has not been compared in clinical trials.[1]

Currently, for autoimmune diseases, autologous transplant is preferred over allogeneic, in part because of the lower toxicity of autotransplant relative to allogeneic, the graft-versus-host disease associated with allogeneic transplant, and the need to administer posttransplant immunosuppression after an allogeneic transplant.[1]

Allogeneic Cell Transplantation - The experience of using allogeneic HCT for autoimmune diseases is currently limited[1] 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.[1]

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 title 21, parts 1270 and 1271. Hematopoietic stem cells are included in these regulations.

Related Protocol

Plasma Exchange

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

References

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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