Protocol

Hematopoietic Cell Transplantation for Waldenström Macroglobulinemia

(80154)

Medical Benefit		**Effective Date**: 04/01/13	**Next Review Date**: 07/21
Preauthorization	Yes	**Review Dates**: 04/07, 05/08, 01/10, 01/11, 09/11, 09/12, 09/13, 07/14, 07/15, 07/16, 07/17, 07/18, 07/19, 07/20	

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.

RELATED PROTOCOLS

Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas

Placental and Umbilical Cord Blood as a Source of Stem Cells

Populations	Interventions	Comparators	Outcomes
Individuals: • With Waldenström macroglobulinemia	Interventions of interest are: • Hematopoietic cell transplantation	Comparators of interest are: • Chemotherapy • Targeted therapy drugs • Biologic therapy drugs	Relevant outcomes include: • Overall survival • Change in disease status • Quality of life • Treatment-related mortality • Treatment-related morbidity

DESCRIPTION

Hematopoietic cell transplantation (HCT) 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 drugs with or without whole body radiotherapy. Hematopoietic stem cells may be obtained from the transplant recipient (autologous HCT) or from 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.

SUMMARY OF EVIDENCE

For individuals who have Waldenström macroglobulinemia who receive HCT, the evidence includes case series. Several retrospective series have evaluated HCT for Waldenström macroglobulinemia. Analyses of registry data have found five-year overall survival rates of 52% after allogeneic HCT and 68.5% after autologous HCT. The total number of patients studied is small and there is a lack of published controlled studies. The evidence is insufficient to determine the effects of the technology on health outcomes.

Clinical input obtained in 2011 and national and international clinical guidelines support the use of autologous HCT as salvage therapy for patients with chemosensitive Waldenström macroglobulinemia. Allogeneic HCT is recommended in the context of clinical trials. Thus, autologous HCT may be considered medically necessary as salvage therapy for patients with chemosensitive Waldenström macroglobulinemia. Allogeneic HCT for patients with Waldenström macroglobulinemia is considered investigational.

POLICY

Autologous hematopoietic cell transplantation may be considered **medically necessary** as salvage therapy of chemosensitive Waldenström macroglobulinemia.

Allogeneic hematopoietic cell transplantation is considered **investigational** to treat Waldenström macroglobulinemia.

POLICY GUIDELINES

Individual transplant facilities may have their own additional requirements or protocols that must be met in order for the patient to be eligible for a transplant at their facility.

MEDICARE ADVANTAGE

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

BACKGROUND

WALENSTRÖM MACROGLOBULINEMIA

Waldenström macroglobulinemia (WM) is a clonal disorder of B lymphocytes that accounts for 1% to 2% of hematologic malignancies, with an estimated 1,500 new cases annually in the United States. Symptoms include weakness, headaches, stroke-like symptoms (confusion, loss of coordination), vision problems, excessive bleeding, unexplained weight loss, and frequent infections. The median age of WM patients is 63 to 68 years, with men comprising 55% to 70% of cases. Median survival of WM ranges from five to ten years, with age, hemoglobin concentration, serum albumin level, and b2-microglobulin level as predictors of outcome.

The Revised European American Lymphoma and World Health Organization classification and a consensus group formed at the Second International Workshop on Waldenström's Macroglobulinemia recognize WM primarily as a lymphoplasmacytic lymphoma with an associated immunoglobulin M (IgM) monoclonal gammopathy. The definition also requires the presence of a characteristic pattern of bone marrow infiltration with small lymphocytes demonstrating plasmacytic differentiation with variable cell surface antigen expression. The Second International Workshop indicated no minimum serum concentration of IgM is necessary for a diagnosis of WM.

Treatment

The goal of therapy for patients with WM is to achieve symptomatic relief and reduce organ damage without compromising quality of life. Treatment of WM is indicated only in symptomatic patients and should not be initiated solely on the basis of serum IgM concentration. Clinical and laboratory findings that indicate the need for therapy of diagnosed WM include a hemoglobin concentration less than 10 g/dL; platelet count less than

100,000/mL; significant adenopathy or organomegaly; symptomatic Ig-related hyperviscosity (>50 g/L); severe neuropathy; amyloidosis; cryoglobulinemia; cold-agglutinin disease; or evidence of disease transformation.

Primary chemotherapeutic options in patients that may undergo autologous hematopoietic cell transplantation (HCT) often combine rituximab with other agents (e.g., dexamethasone, cyclophosphamide, bortezomib, bendamustine), but other agents may also be used including purine analogues (cladribine, fludarabine). Plasma exchange is indicated for acute treatment of symptomatic hyperviscosity, cyclophosphamide, busulfan) with or without total body irradiation at doses sufficient to destroy endogenous hematopoietic capability in the recipient. The beneficial treatment effect in this procedure is due to a combination of initial eradication of malignant cells and subsequent graft-versus-malignancy effect that develops after engraftment of allogeneic stem cells within patients' bone marrow space. While the slower graft-versus-malignancy effect is considered the potentially curative component, it may be overwhelmed by extant disease without the use of pretransplant conditioning. However, intense conditioning regimens are limited to patients who are sufficiently fit medically to tolerate substantial adverse events that include pre-engraftment opportunistic infections secondary to loss of endogenous bone marrow function and organ damage and failure caused by the cytotoxic drugs. Furthermore, in any allogeneic HCT, immune suppressant drugs are required to minimize graft rejection and graft-versus-host disease, which also increases susceptibility of the patient to opportunistic infections.

The success of autologous HCT is predicated on the ability of cytotoxic chemotherapy with or without radiotherapy to eradicate cancerous cells from the blood and bone marrow. This permits subsequent engraftment and repopulation of bone marrow space with presumably normal hematopoietic stem cells obtained from the patient before undergoing bone marrow ablation. As a consequence, autologous HCT is typically performed as consolidation therapy when the patient's disease is in complete remission. Patients who undergo autologous HCT are susceptible to chemotherapy-related toxicities and opportunistic infections prior to engraftment, but not graft-versus-host disease.

Reduced-Intensity Conditioning for Allogeneic HCT

Reduced-intensity conditioning (RIC) refers to the pretransplant use of lower doses or less intense regimens of cytotoxic drugs or radiotherapy than are used in conventional full-dose myeloablative conditioning treatments. The goal of RIC is to reduce disease burden but also to minimize as much as possible associated treatment-related morbidity and non-relapse mortality in the period during which the beneficial graft-versus-malignancy effect of allogeneic transplantation develops. Although the definition of RIC remains arbitrary, with numerous versions employed, all seek to balance the competing effects of non-relapse mortality and relapse due to residual disease. RIC regimens can be viewed as a continuum in effects, from nearly totally myeloablative to minimally myeloablative with lympho-ablation, with intensity tailored to specific diseases and patient condition. Patients who undergo RIC with allogeneic HCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism, which may be supplemented with donor lymphocyte infusions to eradicate residual malignant cells. For this evidence review, the term reduced-intensity conditioning will refer to all conditioning regimens intended to be nonmyeloablative, as opposed to fully myeloablative (conventional) regimens.

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.

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