Protocol

Hematopoietic Cell Transplantation for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

(80115)

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

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 chronic lymphocytic leukemia or small lymphocytic lymphoma and markers of poor-risk disease	Interventions of interest are: • Allogeneic hematopoietic cell transplantation	Comparators of interest are: • Chemotherapy and/or immunotherapy	Relevant outcomes include: • Overall survival • Disease-specific survival • Change in disease status • Treatment-related mortality • Treatment-related morbidity
Individuals: • With chronic lymphocytic leukemia or small lymphocytic lymphoma	Interventions of interest are: • Autologous hematopoietic cell transplantation	Comparators of interest are: • Chemotherapy and/or immunotherapy	Relevant outcomes include: • Overall survival • Disease-specific survival • Change in disease status • Treatment-related mortality • Treatment-related morbidity

DESCRIPTION

Risk stratification of patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) guides therapy decisions, which may include hematopoietic cell transplantation (HCT) for those with poor-risk features.

SUMMARY OF EVIDENCE

For individuals who have CLL or SLL and markers of poor-risk disease who receive allogeneic hematopoietic cell transplantation (allo-HCT), the evidence includes single-arm prospective and registry-based studies as well as a TEC Assessment. Relevant outcomes are overall survival, disease-specific survival, change in disease status, and treatment-related mortality and morbidity. Data have suggested that allo-HCT can provide long-term disease control and overall survival in patients with poor-risk CLL or SLL. High rates of treatment-related morbidity discourage this approach in lower risk disease, particularly among older patients whose health status typically precludes the use of myeloablative conditioning. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have CLL or SLL who receive autologous HCT, the evidence includes randomized controlled trials (RCTs), systematic reviews, and a TEC Assessment. Relevant outcomes are overall survival, disease-specific survival, change in disease status, and treatment-related mortality and morbidity. Autologous HCT is feasible in younger patients but is not curative, particularly in those with poor-risk CLL. Studies of autologous HCT published to date have not shown improvement in overall survival in patients with CLL or SLL, and results must be considered in the context of improved outcomes with the use of newer chemoimmunotherapy agents. Furthermore, evidence from the European Intergroup RCT has suggested quality-of-life issues are important in selecting patients for autologous HCT and may dictate the management course for patients who are otherwise candidates for this approach. The evidence is insufficient to determine the effects of the technology on health outcomes.

POLICY

Allogeneic hematopoietic cell transplantation is considered **medically necessary** to treat chronic lymphocytic leukemia or small lymphocytic lymphoma in patients with markers of poor-risk disease (see Policy Guidelines). Use of a myeloablative or reduced-intensity pretransplant conditioning regimen should be individualized based on factors that include patient age, the presence of comorbidities, and disease burden.

Autologous hematopoietic cell transplantation is considered **investigational** to treat chronic lymphocytic leukemia or small lymphocytic lymphoma.

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.

STAGING AND PROGNOSIS OF CHRONIC LYMPHOCYTIC LEUKEMIA OR SMALL LYMPHOCYTIC LYMPHOMA

Two scoring systems are used to determine stage and prognosis of patients with CLL or SLL. As outlined in Table 1, the Rai and Binet staging systems classify patients into three risk groups with different prognoses, and are used to make therapeutic decisions.

Table 1. Rai and Binet Classification for Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma

Rai Stage	Risk	Description	Median Survival (y)	Binet Stage	Description	Median Survival (y)
0	Low	Lymphocytosis	> 10	A	three or fewer lymphoid areas, normal hemoglobin and platelets	> 10
I	Intermediate	Lymphocytosis plus lymphadenopathy	7-9	B	three or more lymphoid areas, normal hemoglobin and platelets	7
II	Intermediate	Lymphocytosis plus splenomegaly plus/minus lymphadenopathy	7-9			
III	High	Lymphocytosis plus anemia plus/minus lymphadenopathy or splenomegaly	1.5-5	C	Any number of lymphoid areas, anemia, thrombocytopenia	5
IV	High	Lymphocytosis plus thrombocytopenia plus/	1.5-5			

Rai Stage	Risk	Description	Median Survival (y)	Binet Stage	Description	Median Survival (y)
		minus anemia, spleno-megaly or lymphadenopathy				

Because prognoses of patients vary within the different Rai and Binet classifications, other prognostic markers are used in conjunction with staging to determine clinical management. These are summarized in Table 2, according to availability in clinical centers.

Table 2. Markers of Poor Prognosis in Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma

Community Center	Specialized Center
Advanced Rai or Binet stage	IgVh wild type
Male sex	Expression of ZAP-70 protein
Atypical morphology or CLL or SLL	del (11q22-q23) (loss of ATM gene)
Peripheral lymphocyte doubling time < 12 months	del (17p13)/variant TP53
CD38 positive	Trisomy 12
Elevated β_2-microglobulin level	Elevated serum CD23
Diffuse marrow histology	Elevated serum tumor necrosis factor-α
Elevated serum lactate dehydrogenase level	Elevated serum thymidine kinase
Fludarabine resistance	

IgVH: immunoglobulin heavy-chain variable-region

An expert panel convened by the American Society for Blood and Marrow Transplantation was queried about criteria used to define high-risk CLL, as part of the process for developing 2016 guidelines. Panelists responded that criteria are presence of del17P and/or TP53 variants (100%) and presence of complex karyotype (67%).

REDUCED-INTENSITY CONDITIONING FOR ALLOGENEIC HCT

Some patients for whom a conventional myeloablative allotransplant could be curative may be considered candidates for reduced-intensity conditioning (RIC) allo-HCT. These include those patients whose age (typically older than 60 years) or comorbidities (e.g., liver or kidney dysfunction, generalized debilitation, prior intensive chemotherapy, low Karnofsky Performance Status) preclude use of a standard myeloablative conditioning regimen. A patient who relapses following a conventional myeloablative allo-HCT could undergo a second myeloablative procedure if a suitable donor is available and his or her medical status would permit it. However, this type of patient would likely undergo RIC prior to a second allo-HCT if a complete remission could be reinduced with chemotherapy.

The ideal allogeneic donors are human leukocyte antigen (HLA)-identical siblings, matched at the HLA-A, -B, and -DR loci (six of six) on each arm of chromosome 6. Related donors mismatched at one locus are also considered suitable donors. A matched, unrelated donor identified through the National Marrow Donor Registry is typically the next option considered. Recently, haploidentical donors, typically a parent or a child of the patient, with whom usually there is sharing of only three of the six major histocompatibility antigens, have been under investigation as a stem-cell source. Most patients will have such a donor; however, the risk of graft-versus-host disease (GVHD) and overall morbidity of the procedure may be severe, and experience with these donors is not as extensive as that with matched donors.

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

CHRONIC LYMPHOCYTIC LEUKEMIA AND SMALL CELL LYMPHOMA

CLL and SLL are neoplasms of hematopoietic origin characterized by the accumulation of lymphocytes with a mature, generally well-differentiated morphology. In CLL, these cells accumulate in blood, bone marrow, lymph nodes, and spleen; in SLL they are generally confined to lymph nodes. The Revised European-American/World Health Organization Classification of Lymphoid Neoplasms considers B-cell CLL and SLL a single disease entity.

CLL and SLL share many common features and are often referred to as blood and tissue counterparts of each other, respectively. Both tend to present as asymptomatic enlargement of the lymph nodes, tend to be indolent in nature, but can undergo transformation to a more aggressive form of disease (e.g., Richter transformation). The median age at diagnosis of CLL is approximately 72 years, but it may present in younger individuals, often as poor-risk disease with significantly reduced life expectancy.

Treatment regimens used for CLL are generally the same as those used for SLL, and treatment outcomes are comparable for both diseases. Both low- and intermediate-risk CLL and SLL demonstrate relatively good prognoses, with median survivals of six to 10 years; however, the median survival of high-risk CLL or SLL may only be two years. Although typically responsive to initial therapy, CLL and SLL are rarely cured by conventional therapy, and nearly all patients ultimately die of their disease. This natural disease history prompted investigation of HCT as a possible curative regimen.

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 from a donor (allogeneic HCT [allo-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 (GVHD). 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 of allo-HCT. 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 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.

Conditioning for HCT

Conventional Conditioning for HCT

The conventional practice of allo-HCT involves administration of cytotoxic agents (e.g., 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 (GVM) effect that develops after engraftment of allogeneic stem cells within the patient's bone marrow space. The slower GVM effect is

considered the potentially curative component, but 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 effects that include preengraftment opportunistic infections secondary to loss of endogenous bone marrow function and organ damage and failure caused by the cytotoxic drugs. Furthermore, in any allo-HCT, immunosuppressant drugs are required to minimize graft rejection and GVHD, 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 radiation 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 before engraftment, but not GVHD.

Reduced-Intensity Conditioning for Allo-HCT

RIC refers to the pretransplant use of lower doses or less intense regimens of cytotoxic drugs or radiation 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 nonrelapse mortality (NRM) in the period during which the beneficial GVM effect of allogeneic transplantation develops. Although the definition of RIC remains arbitrary, with numerous versions employed, all seek to balance the competing effects of NRM and relapse due to residual disease. RIC regimens can be viewed as a continuum in effects, from nearly totally myeloablative to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and patient condition. Patients who undergo RIC with allo-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 protocol, 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 the Code of Federal Regulation title 21, parts 1270 and 1271. Hematopoietic cells are included in these regulations.

RELATED PROTOCOL

Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas

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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