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Medical Policy Manual

Topic: Hematopoietic Stem-Cell Transplantation for Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma

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IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Hematopoietic Stem Cell Transplantation

Hematopoietic stem cell transplantation (HSCT) refers to a procedure in which hematopoietic stem cells are infused to restore bone marrow function in cancer 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 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.

Conventional Preparative Conditioning for HSCT

The success of *autologous* HSCT 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 prior to undergoing bone marrow ablation. As a consequence, autologous HSCT is typically performed as consolidation therapy when the patient's disease is in complete remission. Patients who undergo autologous HSCT are susceptible to chemotherapy-related toxicities and opportunistic infections prior to engraftment, but not GVHD.

The conventional ("classical") practice of *allogeneic* HSCT 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 mediated by non-self immunologic effector cells that develops after engraftment of allogeneic stem cells within the patient's bone marrow space. While the slower GVM effect is considered to be 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 effects 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 HSCT, immune suppressant drugs are required to minimize graft rejection and GVHD, which also increases susceptibility of the patient to opportunistic infections.

Reduced-Intensity Conditioning for Allogeneic HSCT

Reduced-intensity conditioning (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 non-relapse 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 allogeneic HSCT 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 the purposes of this Policy, the term "reduced-intensity conditioning" will refer to all conditioning regimens intended to be non-myeloablative, as opposed to fully myeloablative (conventional) regimens.

Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma

Chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (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, while in SLL they are generally confined to lymph nodes. The Revised European-American/WHO Classification of Lymphoid Neoplasms considers B-cell CLL and SLL a single disease entity.[1]

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's transformation).[2] 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.[2]

Treatment regimens used for CLL are generally the same as those used for SLL, and outcomes of treatment are comparable for the two diseases. Both low- and intermediate-risk CLL and SLL demonstrate relatively good prognoses with median survivals of 6 to 10 years, while the median survival of high-risk CLL or SLL may be only 2 years (see Policy Guidelines). 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 history prompted investigation of hematopoietic stem-cell transplantation as a possible curative regimen.

MEDICAL POLICY CRITERIA

I. Autologous hematopoietic stem-cell transplantation (HSCT)

Single Autologous HSCT is considered **investigational** for the treatment of the following:

A. Chronic lymphocytic leukemia

B. Small lymphocytic lymphoma

II. Allogeneic HSCT

A. Medically necessary indications

Allogeneic HSCT may be considered **medically necessary** for the treatment of 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.

B. Investigational indications

Allogeneic HSCT is considered **investigational** for the treatment of chronic lymphocytic leukemia or small lymphocytic lymphoma who do not meet the above medical necessity criteria.

III. Tandem HSCT

Tandem HSCT is considered **investigational** for the treatment of chronic lymphocytic leukemia or small lymphocytic lymphoma.

Policy Guidelines

Staging and Prognosis of Chronic Lymphocytic Leukemia (CLL) and Small Lymphocytic Lymphoma (SLL)

Two scoring systems are used to determine stage and prognosis of patients with CLL/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.[3]

Table 1. Rai and Binet Classification for CLL/SLL

RAI STAGE	Risk	Description	BINET STAGE	Description
0	Low	Lymphocytosis	A	2 or fewer lymphoid areas, normal hemoglobin and platelets
I	Intermediate	Lymphocytosis plus lymphadenopathy	B	2 or more lymphoid areas, normal hemoglobin and platelets
II	Intermediate	Lymphocytosis plus hepatomegaly or splenomegaly plus/minus lymphadenopathy		
III	High	Lymphocytosis plus anemia plus/minus hepatomegaly, lymphadenopathy, or splenomegaly	C	Any number of lymphoid areas, anemia, thrombocytopenia
IV	High	Lymphocytosis plus thrombocytopenia plus/minus anemia, hepatomegaly, splenomegaly, or lymphadenopathy		

lymphocytosis = lymphocytes >15 x 10^9/L for 4 wks; anemia = hemoglobin <110 g/L; thrombocytopenia = platelets <100 x 10^9/L

Because prognosis of patients varies 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 CLL/SLL[2]

Community Center	Specialized Center
Advanced Rai or Binet stage	IgVh wild type
Male sex	Expression of ZAP-70 protein
Atypical morphology or CLL/PLL	del 11q22-q23 (loss of ATM gene)
Peripheral lymphocyte doubling time <12 mos	del 17p13 (loss of p53)

CD38+	trisomy 12
Elevated beta2-microglobulin level	Elevated serum CD23
Diffuse marrow histology	Elevated serum tumor necrosis factor-a
Elevated serum lactate dehydrogenase level	Elevated serum thymidine kinase
Fludarabine resistance	

Reduced-Intensity Conditioning for Allogeneic Hematopoietic Stem-Cell Transplantation (HSCT)

Candidates for RIC

Some patients for whom a conventional myeloablative allotransplant could be curative may be considered candidates for RIC allogeneic HSCT. These include those 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 allogeneic HSCT 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 allogeneic HSCT if a complete remission could be re-induced with chemotherapy.

Donors

The ideal allogeneic donors are HLA-identical siblings, matched at the HLA-A, B, and DR loci (6 of 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, there has been interest in haploidentical donors, typically a parent or a child of the patient, with whom usually there is sharing of only 3 of the 6 major histocompatibility antigens. The majority of patients will have such a donor; however, the risk of GVHD and overall morbidity of the procedure may be severe, and experience with these donors is not as extensive as that with matched donors.

SCIENTIFIC EVIDENCE

Autologous Hematopoietic Stem-Cell Transplantation (HSCT)

Several systematic reviews and technology assessments have been published on the use of autologous HSCT in CLL or SLL.

Systematic Reviews/Technology Assessments

This policy initially was based on two TEC Assessments, one from 1999 on autologous hematopoietic stem-cell transplantation (autologous HSCT) for chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL)[4,5], and the other from 2002 on allogeneic hematopoietic stem-cell transplantation (allogeneic HSCT) to treat CLL or SLL.[5] Both documents indicated that existing data were insufficient to permit scientific conclusions regarding the use of either procedure, limited by inter-study heterogeneity in patient's baseline characteristics, procedural differences, sample size, and short follow-up.

- A systematic review of autologous HSCT for CLL or SLL included nine studies (tot[al] n=361, of which 292 were transplanted) identified from a search of MEDLINE databases from 1966 to September 2006.[6] Studies were included if they were full-publication English language reports of prospective randomized, non-randomized, or single-arm design. The analysis suggested that while autologous HSCT may achieve significant clinical response rates (74%–100%) with relatively low treatment-related mortality (0–9%), molecular remissions are typically short lived, with subsequent relapse. Overall survival ranged from 68% at three years' follow-up to 58% at six years. Secondary myelodysplasia and myelodysplastic syndrome that may progress to frank acute myelogenous leukemia has been reported in 5%–12% of patients in some studies of autologous HSCT, which suggests caution in considering this approach, especially given the indolent nature of CLL or SLL. The authors of the review concluded that in the absence of randomized, comparative studies, it is uncertain whether autologous HSCT is superior to conventional chemotherapy (or current chemo-immunotherapy) combinations as first-line consolidation treatment in CLL or SLL patients, regardless of disease risk, or as salvage therapy in those with relapsed disease.

- Several non-systematic reviews discuss uncertainties with respect to the type of transplant (autologous vs. allogeneic), the intensity of pretransplant conditioning, the optimal timing of transplantation in the disease course, the baseline patient characteristics that best predict likelihood of clinical benefit from transplant, and the long-term risks of adverse outcomes.[7-11]

Randomized Controlled Trials (RCTs)

- The conclusions of the systematic review of autologous HSCT outlined above are congruent with results of a Phase III randomized trial by Michallet and colleagues published in 2010 that compared autologous HSCT (n=112) or post-induction observation (n=111) for consolidation in patients with CLL who were in complete remission (CR; 59% of total) or very good partial remission (PR; 27% of total) following fludarabine-containing induction therapy.[12] Patient age ranged from 31-65 years, with Binet stage A progressive (14%), B (66%), and C (20%) disease. None were known to have 17p deletion, 45% were known to not carry 17p deletion, but that status was unknown in 54% of all patients. The primary outcome, median event-free survival (EFS), was 51 months (range: 40-62 months) in the autograft group, compared to 24 months (range: 17-32 months) in the observed group; the 5-year EFS was 42% and 24%, respectively ($p<0.001$). The relapse rate at 5-year follow-up was 54% in the autograft group versus 76% in the observational group ($p<0.001$); median time to relapse requiring therapy or to death (whichever came first) was 65 months (range: 59-71 months) and 40 months (range: 25-56 months), respectively ($p=0.002$). Overall survival probability at 5 year follow-up was 86% (95% confidence interval [CI]: 77-94%) in the autograft arm, versus 84% (95% CI: 75-93%) in the observation arm ($p=0.77$), with no evidence of a plateau in the curves. There was no significant difference in NRM between groups, 4% in the autologous HSCT group and 0% in the observation group ($p=0.33$). Myelodysplastic syndrome (MDS) was observed at follow-up in 3 patients receiving an autograft and in 1 patient in the observational group.

- A subsequent prospective, randomized clinical trial assessed the efficacy of autologous HSCT in previously untreated CLL patients.[13] A total of 244 patients (181 males) of median age 56 years (range 31-66 years) had Binet stage B (n=185) or C (n=56) disease. Among enrollees, 237 started planned therapy, 6 of whom discontinued. All 231 patients underwent induction chemotherapy; 103 (45%) entered CR and were randomly allocated to autologous HSCT (n=52) or observation (n=53). The 3-year estimated OS rates were 98% (95% CI: 94%, 100%) in the observation arm, and 96% (95% CI: 90%, 100%) in the HSCT arm ($p=0.73$). The estimated HR for death was 1.2 (95% CI: 0.3, 3.8) in the HSCT arm relative to the observation arm ($p=0.82$). During the 36 months after

randomization, HSCT was associated, on average, with an extra 9 months without clinical symptoms or blood signs of CLL progression (32 ± 1 month) compared with observation (23 ± 2 months).

An editorial that accompanied this report, and which also cited the results from the Michallet et al. study (described above) concluded that autologous HSCT in CLL may prolong time to progression and event-free survival, but that because OS is not improved, autologous HSCT remains investigational for CLL/SLL patients.[14]

- Brion and colleagues compared the use of autologous HSCT versus treatment with the CHOP (cyclophosphamide, hydroxyldaunorubicin, Oncovin, prednisone) chemotherapy regimen among 86 previously untreated patients (ages 18 to 60) with CLL.[15] The primary outcome was progression-free survival, with overall survival measured as a secondary outcome (all on an intent-to-treat basis). Due to the development of new therapeutic options (such that CHOP is no longer considered first-line treatment for CLL), the study was closed to new patients in 2004 (at which point power calculations indicated that an additional 44 patients would have been needed to see treatment differences between the two groups where there were any). Interpretation of results from this study is thus limited by the potential lack of statistical power to find treatment differences.

One limitation of the studies cited above is that the standard treatment for CLL has evolved since the initiation of these trials, indicating therefore that all patients may have improved survival statistics from those reported here.[14] Nevertheless, it is not clear that this limitation would necessarily bias results in favor of the autologous transplant group.

Allogeneic HSCT

Given that autologous HSCT based on myeloablative conditioning regimens has not been demonstrated to be a curative treatment of CLL/SLL, alternative modalities have been sought. Allogeneic HSCT has been under investigation for the past two decades based on a potent graft-versus-leukemia (GVL) effect expressed as a permanently active cellular immune therapy in the recipient, independent of chemotherapy-related cytotoxicity. Allogeneic HSCT may include use of myeloablative or reduced-intensity pretransplant conditioning regimens.

Non-randomized Studies

- Six published non-randomized studies involved a total of 328 patients with advanced CLL who underwent reduced-intensity conditioning (RIC) allogeneic HSCT using conditioning regimens that included fludarabine in various combinations that included cyclophosphamide, busulfan, rituximab, alemtuzumab, and total body irradiation.[16-21] The majority of patients in these series were heavily pretreated, with a median 3–5 courses of prior regimens. Among individual studies, 27%–57% of patients had chemo-refractory disease, genetic abnormalities including del 17p13, del 11q22, and VH unmutated, or a combination of those characteristics. A substantial proportion in each study (18%–67%) received stem cells from a donor other than an HLA-identical sibling. Reported non-relapse mortality (NRM), associated primarily with graft-versus-host disease (GVHD) and its complications, ranged from 2% at 100 days to 26% overall at median follow-up that ranged from 1.7 years to 5 years. Overall survival rates ranged from 48%–70%, at follow-up that ranged from 2–5 years. Similar results were reported for progression-free survival, 34%–58% at 2–5 years' follow-up. Very similar results were reported from a Phase II study published in 2010 of RIC allogeneic HSCT in patients with poor-risk CLL (n=90; median age 53 years, range: 27-65 years), defined as having 1 of the following: refractoriness or early relapse (i.e., less than 12 months) after purine-analog

therapy; relapse after autologous HSCT; or, progressive disease in the presence of an unfavorable genetic marker (11q or 17p deletion, and/or unmutated IgVh status and/or usage of the VH3-21 gene).[22] With a median follow-up of 46 months, 4-year NRM, EFS, and OS were 23%, 42%, and 65%, respectively. EFS was similar for all genetic subsets, including those with a 17p deletion mutation.

- Additional non-randomized studies[23-26] have since been published, an example of which is the 20-year cohort study reported by Toze and colleagues in 2012.[27] The researchers reported similar outcomes (OS of 63% at two years and 55% at five years) among a group of 49 consecutive patients treated with allogeneic HSCT who were unresponsive to initial disease treatment.

Although randomized controlled trials are lacking, available evidence from non-randomized trials is sufficient to suggest the possibility of long-term survival with allogeneic HSCT among patients with poor prognosis disease.

Tandem HSCT

The literature search failed to identify studies of tandem HSCT for CLL/SLL.

Clinical Practice Guidelines

National Comprehensive Cancer Network (NCCN)

Current NCCN guidelines for Non-Hodgkin's Lymphoma do not include autologous or tandem HSCT as a therapeutic option in CLL or SLL.[28] NCCN indicates that allogeneic HSCT (conditioning regimen unspecified) may be considered, preferably in a clinical trial, for select patients (those younger than age 70 years with high-risk disease [Rai high risk, or del17p]) or as salvage treatment in those with progressive or relapsed disease.

Summary

Autologous Hematopoietic Stem-Cell Transplantation (HSCT)

Autologous HSCT is feasible in younger patients, but is not curative, particularly in those with poor-risk chronic lymphocytic leukemia (CLL). Results from multiple randomized controlled trials do not suggest it results in prolongation of overall survival, compared with conventional therapy; therefore, the use of autologous HSCT in patients with CLL/ small lymphocytic lymphoma (SLL) is considered investigational.

Allogeneic HSCT

A substantial body of evidence from single-arm prospective and registry-based studies suggests allogeneic HSCT can provide long-term disease control and overall survival in patients with poor-risk disease; therefore, in select patients allogeneic HSCT may be considered medically necessary.

Tandem HSCT

It is not possible to reach conclusions about the impact of tandem hematopoietic stem-cell transplantation on health outcomes as there are no published clinical studies of this treatment for CLL/SLL. Therefore its use for these indications is considered investigational.

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CROSS REFERENCES

Donor Lymphocyte Infusion for Malignancies Treated with an Allogeneic Hematopoietic Stem-Cell Transplant, Transplant, Policy No. 45.03

Placental and Umbilical Cord Blood as a Source of Stem Cells, Transplant, Policy No. 45.16

Hematopoietic Stem Cell Transplantation for Non-Hodgkin Lymphomas, Transplant, Policy No. 45.23

Hematopoietic Stem-Cell Transplantation for Hodgkin Lymphoma, Policy No. 45.30

CODES	NUMBER	DESCRIPTION
CPT	38204	Management of recipient hematopoietic cell donor search and cell acquisition
	38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection, allogeneic
	38206	;autologous
	38207	Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage
	38208	;thawing of previously frozen harvest, without washing, per donor
	38209	;thawing of previously frozen harvest with washing, per donor
	38210	;specific cell depletion with harvest, T cell depletion
	38211	;tumor cell depletion
	38212	;red blood cell removal
	38213	;platelet depletion
	38214	;plasma (volume) depletion
	38215	;cell concentration in plasma, mononuclear, or buffy coat layer
	38220	Bone marrow; aspiration only
	38221	Bone marrow; biopsy, needle or trocar
	38230	Bone marrow harvesting for transplantation; allogeneic
	38232	Bone marrow harvesting for transplantation; autologous
	38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor
	38241	;autologous transplantation
	38243	;HPC boost
	38242	Allogeneic lymphocyte infusions

CODES	NUMBER	DESCRIPTION
HCPCS	J9000–J9999	Chemotherapy drugs code range
	Q0083–Q0085	Chemotherapy administration code range
	S2140	Cord blood harvesting for transplantation; allogeneic
	S2142	Cord blood derived stem-cell transplantation, allogeneic
	S2150	Bone marrow or blood-derived peripheral stem-cell harvesting and transplantation, allogeneic or autologous, including pheresis, high-dose chemotherapy, and the number of days of post-transplant care in the global definition (including drugs; hospitalization; medical surgical, diagnostic and emergency services)