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Medical Policy Manual Transplant, Policy No. 45.35

Hematopoietic Cell Transplantation for Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma

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Next Review: November 2025
Last Review: October 2024

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

Transplantation is performed to restore normal function following chemotherapy treatment.

MEDICAL POLICY CRITERIA

I. Allogeneic hematopoietic cell transplantation (HCT) 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.

II. Allogeneic HCT is considered **investigational** for the treatment of chronic lymphocytic leukemia or small lymphocytic lymphoma who do not meet Criteria I. above.

III. Single autologous HCT is considered **investigational** for the treatment of chronic lymphocytic leukemia or small lymphocytic lymphoma.

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

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

DEFINITIONS

- **Consolidation therapy:** Treatment that is given after cancer has disappeared following the initial therapy. Consolidation therapy is used to kill any cancer cells that may be left in the body. It may include radiation therapy, a stem cell transplant, or treatment with drugs that kill cancer cells. Also called intensification therapy and postremission therapy.
- **Relapse:** The return of a disease or the signs and symptoms of a disease after a period of improvement.
- **Salvage therapy:** Treatment that is given after the cancer has not responded to other treatments.
- **Tandem transplant:** Refers to a planned second course of high-dose therapy and HCT within six months of the first course.

STAGING AND PROGNOSIS OF CHRONIC LYMPHOCYTIC LEUKEMIA/SMALL LYMPHOCYTIC LYMPHOMA

Two scoring systems are used to determine stage and prognosis of patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (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 CLL/SLL

Rai Stage	Risk	Description	Median Survival, y	Binet Stage	Description	Median Survival, y
0	Low	Lymphocytosis	>10	A	≤3 lymphoid areas, normal hemoglobin and platelets	>10
I	Int	Lymphocytosis + lymphadenopathy	7-9	B	≥3 lymphoid areas, normal hemoglobin and platelets	7
II	Int	Lymphocytosis + splenomegaly ± lymphadenopathy	7-9			
III	High	Lymphocytosis + anemia ± lymphadenopathy or splenomegaly	1.5-5	C	Any number of lymphoid areas, anemia, thrombocytopenia	5
IV	High	Lymphocytosis + thrombocytopenia ± anemia, splenomegaly, or lymphadenopathy	1.5-5			

CLL: chronic lymphocytic leukemia; Int: Intermediate; SLL: small lymphocytic lymphoma.

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 CLL/SLL

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

CLL: chronic lymphocytic leukemia; SLL: small lymphocytic lymphoma.

The National Comprehensive Cancer Network (NCCN) guideline on CLL/SLL stated the following as unfavorable prognostic factors: DNA sequencing with mutated TP53 or ≤2% immunoglobulin heavy-chain variable (IGHV) mutation; interphase cytogenetics with del17p or deletion of 11q (del11q); or complex karyotype (≥3 unrelated chromosome abnormalities in more than 1 cell on karyotype).

REDUCED-INTENSITY CONDITIONING (RIC) FOR ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION (HCT)

Candidates for RIC

Some patients for whom a conventional myeloablative allotransplant could be curative may be considered candidates for RIC allogeneic HCT. 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 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 allogeneic HCT 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 three of the six 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.

LIST OF INFORMATION NEEDED FOR REVIEW

SUBMISSION OF DOCUMENTATION

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and physical/chart notes
- Diagnosis and indication for transplant

CROSS REFERENCES

1. Donor Lymphocyte Infusion for Malignancies Treated with an Allogeneic Hematopoietic Cell Transplant, Transplant, Policy No. 45.03
2. Placental and Umbilical Cord Blood as a Source of Stem Cells, Transplant, Policy No. 45.16
3. Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas, Transplant, Policy No. 45.23
4. Hematopoietic Cell Transplantation for Hodgkin Lymphoma, Policy No. 45.30

BACKGROUND

HEMATOPOIETIC CELL TRANSPLANTATION

Broadly speaking, there are two types of hematopoietic cell transplants (HCT, previously referred to in this policy as a hematopoietic stem cell transplant [HSCT]), autologous and allogeneic. The purpose of an autologous HCT is to treat a disease (e.g. lymphoma) with myeloablative doses of chemotherapy (with or without radiation) that are active against the disease. The recipient's own HCTs (collected previously) are infused after the chemotherapy in order to re-establish normal marrow function. In an allogeneic transplant, the recipient receives HCTs from a donor after myeloablative therapy or non-myeloablative therapy in order to re-establish normal marrow function as well as to use the new blood system as a platform for immunotherapy, a so called "graft versus tumor" effect. Hematopoietic cells 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 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 cells and the recipient is not an issue in autologous HCT. However, immunologic compatibility between donor and patient is a critical factor for achieving a good outcome of allogeneic HST. 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 HCT

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 cells obtained from the patient prior to 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 GVHD.

The conventional ("classical") practice of *allogeneic* 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 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 HCT, 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 HCT

Reduced-intensity conditioning (RIC) refers to conditioning with 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 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 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 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). The median age at diagnosis of CLL is approximately 72 years.[1]

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 two 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 cell transplantation as a possible curative regimen.

EVIDENCE SUMMARY

AUTOLOGOUS HEMATOPOIETIC CELL TRANSPLANTATION (HCT)

Systematic Reviews

A 2015 systematic review of autologous HCT as front-line consolidation in CLL included a literature search through November 2014.[2] Four RCTs in adult patients were included in the review. Outcomes included OS, PFS, EFS, and harms (adverse events, treatment-related mortality and secondary malignancies). Four studies met inclusion criteria, with 301 patients randomized to the autologous HCT arm and 299 to the control arm using front-line therapy without HCT as consolidation. Autologous HCT did not result in a statistically significant improvement in OS (hazard ratio [HR], 0.91; 95% confidence interval [CI] 0.62 to 1.33) or in PFS (HR=0.70; 95% CI 0.32 to 1.52). There was a statistically significant improvement in EFS favoring autologous HCT (HR=0.46; 95% CI 0.26 to 0.83). There was not a higher rate of secondary malignancy or treatment-related mortality associated with autologous HCT.

This policy initially was based on two TEC Assessments, one from 1999 on autologous hematopoietic cell transplantation (autologous HCT) for chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL)[3, 4], and the other from 2002 on allogeneic hematopoietic cell transplantation (allogeneic HCT) to treat CLL or SLL.[4] 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 HCT for CLL or SLL included nine studies (total n=361, of which 292 were transplanted) identified from a search of MEDLINE databases from 1966 to September 2006.[5] 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 HCT may achieve significant clinical response rates (74% to 100%) with relatively low treatment-related mortality (0 to 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% to 12% of patients in some studies of autologous HCT, 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 HCT 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.[6-10]

Randomized Controlled Trials (RCTs)

The conclusions of the systematic review of autologous HCT outlined above are congruent with results of a Phase III randomized trial by Michallet published in 2010 that compared autologous HCT (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.[11] 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 to 32 months) in the observed group; the five-year EFS was 42% and 24%, respectively ($p<0.001$). The relapse rate at five-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 to 71 months) and 40 months (range: 25 to 56 months), respectively ($p=0.002$). Overall survival probability at five-year follow-up was 86% (95% CI 77 to 94%) in the autograft arm, versus 84% (95% CI 75 to 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 HCT group and 0% in the observation group ($p=0.33$). Myelodysplastic syndrome (MDS) was observed at follow-up in three patients receiving an autograft and in one patient in the observational group.

In a 2013 follow-up report of the Michallet trial, the authors presented quality of life (QoL) findings in the two years after randomization.[12] Two secondary analyses were performed to further investigate the impact of HCT and relapse on QoL. In the primary analysis, the authors demonstrate an adverse impact of HCT on QoL which was largest at four months and continued throughout the first year after randomization. Further, a sustained adverse impact of relapse on QoL was observed which worsened over time. Thus, despite better disease control by autologous HCT, the side effects turned the net effect towards inferior QoL in the first year and comparable QoL in the following two years after randomization.

In a subsequent prospective, randomized clinical trial, Sutton (2011) assessed the efficacy of autologous HCT in previously untreated CLL patients.[13] A total of 244 patients (181 males) of median age 56 years (range 31 to 66 years) had Binet stage B (n=185) or C (n=56) disease. Among enrollees, 237 started planned therapy, six of whom discontinued. All 231 patients underwent induction chemotherapy; 103 (45%) entered complete remission (CR) and were randomly allocated to autologous HCT (n=52) or observation (n=53). The three-year estimated OS rates were 98% (95% CI 94% to 100%) in the observation arm, and 96% (95% CI 90% to 100%) in the HCT arm ($p=0.73$). The estimated HR for death was 1.2 (95% CI 0.3 to 3.8) in the HCT arm relative to the observation arm ($p=0.82$). During the 36 months after randomization, HCT was associated, on average, with an extra nine 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 study (described above) concluded that autologous HCT in CLL may prolong time to progression and event-free survival, but that because OS is not improved, autologous HCT remains investigational for CLL/SLL patients.[14]

Brion (2012) compared the use of autologous HCT 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 HCT

Given that autologous HCT based on myeloablative conditioning regimens has not been demonstrated to be a curative treatment of CLL/SLL, alternative modalities have been sought. Allogeneic HCT 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 HCT may include use of myeloablative or reduced-intensity pretransplant conditioning regimens.

Systematic Reviews

Kharfan-Dabaja (2018) reported the results of a systematic review comparing the efficacy of myeloablative and reduced intensity conditioning (RIC) allogeneic HCT.[16] Studies that enrolled at least 10 patients with CLL receiving allogeneic HCT were included and evaluated for methodological quality. Forty-eight studies met inclusion criteria, none of which were comparative. Results were reported using Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. High heterogeneity between studies was found for those reporting on myeloablative allogeneic HCT for event/progression-free survival, OS, non-relapse mortality, and chronic GVHD, but not for CR or acute GVHD. Among prospective studies investigating allogeneic RCT, heterogeneity was low to moderate, whereas among retrospective studies heterogeneity was moderate to high. Results reported for RIC and myeloablative conditioning were OS (60% [95% CI 56 to 65%] and 51% [95% CI 42 to 61%]), event/progression-free survival (46% [95% CI 41 to 52%] and 41% [95% CI 32 to 50%]), CR (66% [95% CI 57 to 74%] and 58% [95% CI 48 to 67%]), non-relapse mortality (23% [95% CI 19 to 27%] and 32% [95% CI 21 to 44%]), grade 2-4 acute GVHD (46% [95% CI 41 to 52%] and 46% [95% CI 40 to 52%]), and chronic GVHD (all grades; 55% [95% CI 46 to 63%] and 59% [95% CI 46 to 71%]) respectively. A limitation of this study is that not all outcomes were extractable from all included studies and for some outcomes very few studies were available.

Nonrandomized Studies

Aytan (2021) published the results of a retrospective analysis of overall and progression-free survival in high-risk CLL patients who received allogeneic HCT compared with those nontransplant patients from a single center.[17] The estimated cumulative overall survival was 72.6 ± 15 and 84.3 ± 13 months in the nontransplant (n=20) and transplant (n=13) groups, respectively. The five-year overall and progression-free survival rates in the transplant group were 57.3% and 36.0% and in the nontransplant group 40% and 20.6%, respectively. Transplant, relapse, and Binet stage were independent predictors of overall survival.

Helbig (2019) reported outcomes of allogeneic HCT in 30 CLL patients.[18] HLA-matched related donor stem cell grafts were received by 23 patients and matched unrelated donors or HLA-mismatched grafts were received by 7 patients. RIC and MAC regimens were similarly

distributed, with 24 patients receiving RIC and five receiving MAC. Median follow-up for survivors was 6.8 years. Progression-free and overall survival were 56% and 60%, respectively, at three years. For RIC patients, three-year progression-free and overall survival were 64% and 72%, respectively.

In a 2018 retrospective chart review, van Gorkom reported on CLL patients receiving allogeneic HCT from a haploidentical donor.[19] Data from 117 patients from the European Group for Blood and Marrow Transplantation registry were analyzed to determine outcomes following haploidentical allogeneic HCT and the effect of post-transplantation cyclophosphamide. OS was 48% and 38% at two and five years, respectively. Non-relapse mortality occurred in 40% of patients at two years, with most dying from transplantation-related causes. Cumulative incidence of relapse was 22% and 26% at two and five years, respectively. No outcomes were significantly different between those who received post-transplantation cyclophosphamide and those that did not. The authors concluded that the results with haploidentical allogeneic HCT are similar to historical data from HCT with HLA-matched donors. Given this, they suggest that haploidentical HCT should be considered in high-risk patients when an HLA-matched donor is not available.

Six published nonrandomized studies involved a total of 328 patients with advanced CLL who underwent RIC allogeneic HCT using conditioning regimens that included fludarabine in various combinations that included cyclophosphamide, busulfan, rituximab, alemtuzumab, and total body irradiation.[20-25] The majority of patients in these series were heavily pretreated, with a median three to five 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% to 67%) received stem cells from a donor other than an HLA-identical sibling. Reported 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% to 70%, at follow-up that ranged from two to five years. Similar results were reported for progression-free survival, 34%–58% at two to five years' follow-up. Very similar results were reported from a Phase II study published in 2010 of RIC allogeneic HCT in patients with poor-risk CLL (n=90; median age 53 years, range: 27 to 65 years), defined as having one of the following: refractoriness or early relapse (i.e., less than 12 months) after purine-analog therapy; relapse after autologous HCT; 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).[26] With a median follow-up of 46 months, four-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 nonrandomized studies[27-31] have since been published, an example of which is the 20-year cohort study reported by Toze in 2012.[32] 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 HCT who were unresponsive to initial disease treatment.

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

TANDEM HCT

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

PRACTICE GUIDELINE SUMMARY

NATIONAL COMPREHENSIVE CANCER NETWORK (NCCN) GUIDELINES

Guidelines from NCCN (v.1.2025) offer the following on the use of HCT in CLL/SLL.[1]

All recommendations are category 2A unless otherwise indicated. Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

For CLL/SLL without del(17p)/mut TP53: Allogeneic HCT is a treatment option (clinical trial preferred) in patients without significant comorbidities and with relapsed or refractory disease after third-line therapy with BTK inhibitor and venetoclax-based regimens.

For CLL/SLL with del(17p)/mut TP53: Allogeneic HCT is a treatment option (clinical trial preferred) in patients without significant comorbidities for second-line and subsequent therapy for relapse after treatment with BTK inhibitor and venetoclax-based regimens if there was response to first-line therapy.

AMERICAN SOCIETY FOR TRANSPLANTATION AND CELLULAR THERAPY

In 2020, the ASTCT (formerly the American Society for Blood and Marrow Transplantation(published evidence-based clinical practice recommendations.[33] For high-risk CLL in first or greater remission allogeneic HCT is the standard of care (S). For the subtype T-cell prolymphocytic leukemia, allogeneic HCT is the standard of care (S) (autologous HCT is standard of care, rare indication(R)). For the subtype B cell prolymphocytic leukemia, allogeneic and autologous HCT are the standard of care, rare indication (R). For CLL with transformation to high-grade lymphoma autologous HCT is the standard of care (S) and allogeneic HCT is the standard of care with clinical evidence available (C).

SUMMARY

ALLOGENEIC HCT

Research suggests allogeneic HCT can provide long-term disease control and overall survival in patients with poor-risk disease; therefore, in select patients, when criteria are met, allogeneic HCT may be considered medically necessary in patients with chronic lymphocytic leukemia (CLL)/ small lymphocytic lymphoma (SLL). There is not enough research to show that allogeneic HCT improves outcomes when criteria are not met. Therefore, the use of allogeneic HCT is considered investigational when policy criteria are not met.

AUTOLOGOUS HEMATOPOIETIC CELL TRANSPLANTATION

Research suggests that autologous hematopoietic cell transplantation (HCT) is feasible in younger patients, but is not curative, particularly in those with poor-risk chronic lymphocytic leukemia (CLL). Research does not suggest improved overall survival, compared with conventional therapy; therefore, the use of autologous HCT in patients with CLL/ small lymphocytic lymphoma (SLL) is considered investigational.

TANDEM HCT

There is no research on tandem HCT for chronic lymphocytic leukemia (CLL)/ small lymphocytic lymphoma (SLL). More research is needed to know the impact of tandem

hematopoietic cell transplantation on health outcomes for people with CLL/SLL. Therefore, the use of tandem HCT for CLL/SLL is considered investigational.

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CODES

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
	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
	38242	Allogeneic lymphocyte infusions
HCPCS	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)

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