

## ***Hematopoietic Cell Transplantation for Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma***

**Effective:** January 1, 2019

**Next Review:** September 2019

**Last Review:** December 2018

### **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 bone marrow function following bone-marrow-toxic doses of chemotherapy.

### **MEDICAL POLICY CRITERIA**

**Notes:** See Appendix I for glossary of terms.

- I. Allogeneic 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 the above medical necessity criteria.
- III. Single Autologous HCT is considered **investigational** for the treatment of the following:

- A. Chronic lymphocytic leukemia
  - B. 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

### 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 PG1, the Rai and Binet staging systems classify patients into three risk groups with different prognoses and are used to make therapeutic decisions.

**Table PG1. 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 PG2, according to availability in clinical centers.

**Table PG2. Markers of Poor Prognosis in CLL/SLL**

Community Center	Specialized Center
<ul style="list-style-type: none"> <li>• Advanced Rai or Binet stage</li> <li>• Male sex</li> <li>• Atypical morphology or CLL/SLL</li> <li>• Peripheral lymphocyte doubling time &lt;12 mo</li> <li>• CD38<sup>+</sup></li> </ul>	<ul style="list-style-type: none"> <li>• IgVh wild type</li> <li>• Expression of ZAP-70 protein</li> <li>• del 11q22-q23 (loss of <i>ATM</i> gene)</li> <li>• del 17p13/mutation <i>TP53</i></li> <li>• Trisomy 12</li> </ul>

Community Center	Specialized Center
<ul style="list-style-type: none"> <li>• Elevated <math>\beta_2</math>-microglobulin level</li> <li>• Diffuse marrow histology</li> <li>• Elevated serum lactate dehydrogenase level</li> <li>• Fludarabine resistance</li> </ul>	<ul style="list-style-type: none"> <li>• Elevated serum CD23</li> <li>• Elevated serum tumor necrosis factor-<math>\alpha</math></li> <li>• Elevated serum thymidine kinase</li> </ul>

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

## 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.

## 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

Hematopoietic cell transplantation (HCT, previously referred to in this policy as a hematopoietic stem cell transplant [HSCT]) refers to a procedure in which hematopoietic 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 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 “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 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 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.<sup>[1]</sup>

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, but it may present in younger individuals, often as poor-risk disease with significantly reduced life expectancy.<sup>[2]</sup>

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.<sup>[3]</sup> 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)<sup>[4,5]</sup>, and the other from 2002 on allogeneic hematopoietic cell transplantation (allogeneic HCT) to treat CLL or SLL.<sup>[5]</sup> 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.<sup>[6]</sup> 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%–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 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.<sup>[7-11]</sup>

### **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.<sup>[12]</sup> 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 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: 59-71 months) and 40 months (range: 25-56 months), respectively (p=0.002). Overall survival probability at five-year follow-up was 86% (95% 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 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.<sup>[13]</sup> 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.<sup>[14]</sup> 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, 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%, 100%) in the observation arm, and 96% (95% CI: 90%, 100%) in the HCT arm (p=0.73). The estimated HR for death was 1.2 (95% CI: 0.3, 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.<sup>[15]</sup>

Brion (2012) compared the use of autologous HCT versus treatment with the CHOP (cyclophosphamide, hydroxydaunorubicin, Oncovin, prednisone) chemotherapy regimen among 86 previously untreated patients (ages 18 to 60) with CLL.<sup>[16]</sup> 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.<sup>[15]</sup> 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**

Khafan-Dabaja (2018) reported the results of a systematic review comparing the efficacy of myeloablative and reduced intensity conditioning (RIC) allogeneic HCT.<sup>[17]</sup> 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**

In a 2018 retrospective chart review, van Gorkom reported on CLL patients receiving allogeneic HCT from a haploidentical donor.<sup>[18]</sup> 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.<sup>[19-24]</sup> 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%–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%–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: 27-65 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).<sup>[25]</sup> 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<sup>[26-30]</sup> have since been published, an example of which is the 20-year cohort study reported by Toze in 2012.<sup>[31]</sup> 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 offer the following on the use of HCT in CLL/SLL:<sup>[2]</sup>

*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 relapsed/refractory therapy in patients without del(17p)/mut TP53, allogeneic HCT may be considered if without significant comorbidities. In those with del(17p)/mut TP53 who respond to first-line therapy and have a complex karyotype, allogeneic HCT may also be considered.

Following Richter's transformation, for clonally related diffuse large B-cell lymphoma, following chemotherapy, consider allogeneic HCT when chemotherapy sensitive.

### **AMERICAN SOCIETY FOR BLOOD AND MARROW TRANSPLANTATION (ASBMT) RECOMMENDATIONS**

In 2016, the ASBMT published evidence based clinical practice recommendations based on majority consensus vote.<sup>[32]</sup> For standard-risk CLL, the recommendation is to offer an allo-HCT when there is lack of response or evidence of disease progression after B-cell receptor (BCR) inhibitors. For high-risk CLL, the recommendation is for allo-HCT: for patients showing an objective response to BCR inhibitors or to a clinical trial; for patients showing an objective response to BCL-2 inhibitors, or to a clinical after demonstrating refractory disease to prior therapies including BCR inhibitors; for patients who failed to respond or progressed after BCL-2 inhibitors; for patients with documented Richter transformation who demonstrate an objective response to treatment; and for patients with purine-analogue relapsed or refractory disease.

## **SUMMARY**

### **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.

### **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.

### **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.

---

## **REFERENCES**

1. Campo, E, Swerdlow, SH, Harris, NL, Pileri, S, Stein, H, Jaffe, ES. The 2008 WHO classification of lymphoid neoplasms and beyond: evolving concepts and practical applications. *Blood*. 2011 May 12;117(19):5019-32. PMID: 21300984
2. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. V.1.2019. [cited 9/14/2018]; Available from: [https://www.nccn.org/professionals/physician\\_gls/pdf/cll.pdf](https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf)
3. Reljic, T, Kumar, A, Djulbegovic, B, Kharfan-Dabaja, MA. High-dose therapy and autologous hematopoietic cell transplantation as front-line consolidation in chronic lymphocytic leukemia: a systematic review. *Bone marrow transplantation*. 2015 Aug;50(8):1144. PMID: 26242579
4. TEC Assessment 1999. "High Dose Chemotherapy plus Autologous Stem Cell Transplant to Treat Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma." BlueCross BlueShield Association Technology Evaluation Center, Vol. 14, Tab 20.
5. TEC Assessment 2002. "High Dose Chemotherapy plus Allogeneic Stem Cells to Treat Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma." BlueCross BlueShield Association Technology Evaluation Center, Vol. 17, Tab 4.
6. Kharfan-Dabaja, MA, Kumar, A, Behera, M, Djulbegovic, B. Systematic review of high dose chemotherapy and autologous haematopoietic stem cell transplantation for chronic lymphocytic leukaemia: what is the published evidence? *Br J Haematol*. 2007 Oct;139(2):234-42. PMID: 17897299
7. Abbott, BL. Chronic lymphocytic leukemia: recent advances in diagnosis and treatment. *Oncologist*. 2006 Jan;11(1):21-30. PMID: 16401710
8. Dreger, P, Brand, R, Michallet, M. Autologous stem cell transplantation for chronic lymphocytic leukemia. *Semin Hematol*. 2007 Oct;44(4):246-51. PMID: 17961723

9. Gine, E, Moreno, C, Esteve, J, Montserrat, E. The role of stem-cell transplantation in chronic lymphocytic leukemia risk-adapted therapy. *Best Pract Res Clin Haematol*. 2007 Sep;20(3):529-43. PMID: 17707838
10. Kharfan-Dabaja, MA, Anasetti, C, Santos, ES. Hematopoietic cell transplantation for chronic lymphocytic leukemia: an evolving concept. *Biol Blood Marrow Transplant*. 2007 Apr;13(4):373-85. PMID: 17382245
11. Gribben, JG. Role of allogeneic hematopoietic stem-cell transplantation in chronic lymphocytic leukemia. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2008 Oct 20;26(30):4864-5. PMID: 18794537
12. Michallet, M, Dreger, P, Sutton, L, et al. Autologous hematopoietic stem cell transplantation in chronic lymphocytic leukemia: results of European intergroup randomized trial comparing autografting versus observation. *Blood*. 2011 Feb 3;117(5):1516-21. PMID: 21106985
13. de Wreede, LC, Watson, M, van Os, M, et al. Improved relapse-free survival after autologous stem cell transplantation does not translate into better quality of life in chronic lymphocytic leukemia: lessons from the randomized European Society for Blood and Marrow Transplantation-Intergroup study. *American journal of hematology*. 2014 Feb;89(2):174-80. PMID: 24123244
14. Sutton, L, Chevret, S, Tournilhac, O, et al. Autologous stem cell transplantation as a first-line treatment strategy for chronic lymphocytic leukemia: a multicenter, randomized, controlled trial from the SFGM-TC and GFLLC. *Blood*. 2011 Jun 9;117(23):6109-19. PMID: 21406717
15. Montserrat, E, Gribben, JG. Autografting CLL: the game is over! *Blood*. 2011 Jun 9;117(23):6057-8. PMID: 21659550
16. Brion, A, Mahe, B, Kolb, B, et al. Autologous transplantation in CLL patients with B and C Binet stages: final results of the prospective randomized GOELAMS LLC 98 trial. *Bone marrow transplantation*. 2012 Apr;47(4):542-8. PMID: 21725374
17. Kharfan-Dabaja, MA, Moukalled, N, Reljic, T, El-Asmar, J, Kumar, A. Reduced intensity is preferred over myeloablative conditioning allogeneic HCT in chronic lymphocytic leukemia whenever indicated: A systematic review/meta-analysis. *Hematology/oncology and stem cell therapy*. 2018 Jun;11(2):53-64. PMID: 29197550
18. van Gorkom, G, van Gelder, M, Eikema, DJ, et al. Outcomes of haploidentical stem cell transplantation for chronic lymphocytic leukemia: a retrospective study on behalf of the chronic malignancies working party of the EBMT. *Bone marrow transplantation*. 2018;53(3):255-63. PMID: 29255169
19. Brown, JR, Kim, HT, Li, S, et al. Predictors of improved progression-free survival after nonmyeloablative allogeneic stem cell transplantation for advanced chronic lymphocytic leukemia. *Biol Blood Marrow Transplant*. 2006 Oct;12(10):1056-64. PMID: 17084369
20. Delgado, J, Thomson, K, Russell, N, et al. Results of alemtuzumab-based reduced-intensity allogeneic transplantation for chronic lymphocytic leukemia: a British Society of Blood and Marrow Transplantation Study. *Blood*. 2006 Feb 15;107(4):1724-30. PMID: 16239425
21. Dreger, P, Brand, R, Hansz, J, et al. Treatment-related mortality and graft-versus-leukemia activity after allogeneic stem cell transplantation for chronic lymphocytic leukemia using intensity-reduced conditioning. *Leukemia*. 2003 May;17(5):841-8. PMID: 12750695
22. Khouri, IF, Saliba, RM, Admirand, J, et al. Graft-versus-leukaemia effect after non-myeloablative haematopoietic transplantation can overcome the unfavourable

- expression of ZAP-70 in refractory chronic lymphocytic leukaemia. *Br J Haematol*. 2007 May;137(4):355-63. PMID: 17456058
23. Schetelig, J, Thiede, C, Bornhauser, M, et al. Evidence of a graft-versus-leukemia effect in chronic lymphocytic leukemia after reduced-intensity conditioning and allogeneic stem-cell transplantation: the Cooperative German Transplant Study Group. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2003 Jul 15;21(14):2747-53. PMID: 12860954
  24. Sorrow, ML, Storer, BE, Sandmaier, BM, et al. Five-year follow-up of patients with advanced chronic lymphocytic leukemia treated with allogeneic hematopoietic cell transplantation after nonmyeloablative conditioning. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2008 Oct 20;26(30):4912-20. PMID: 18794548
  25. Dreger, P, Dohner, H, Ritgen, M, et al. Allogeneic stem cell transplantation provides durable disease control in poor-risk chronic lymphocytic leukemia: long-term clinical and MRD results of the German CLL Study Group CLL3X trial. *Blood*. 2010 Oct 7;116(14):2438-47. PMID: 20595516
  26. Brunner, AM, Kim, HT, Coughlin, E, et al. Outcomes in Patients Age 70 or Older Undergoing Allogeneic Hematopoietic Stem Cell Transplantation for Hematologic Malignancies. *Biol Blood Marrow Transplant*. 2013 Jun 18. PMID: 23791626
  27. Dreger, P, Schnaiter, A, Zenz, T, et al. TP53, SF3B1, and NOTCH1 mutations and outcome of allotransplantation for chronic lymphocytic leukemia: six-year follow-up of the GCLLSG CLL3X trial. *Blood*. 2013 Apr 18;121(16):3284-8. PMID: 23435461
  28. Richardson, SE, Khan, I, Rawstron, A, et al. Risk-stratified adoptive cellular therapy following allogeneic hematopoietic stem cell transplantation for advanced chronic lymphocytic leukaemia. *Br J Haematol*. 2013 Mar;160(5):640-8. PMID: 23293871
  29. Brown, JR, Kim, HT, Armand, P, et al. Long-term follow-up of reduced-intensity allogeneic stem cell transplantation for chronic lymphocytic leukemia: prognostic model to predict outcome. *Leukemia*. 2012 Aug 14. PMID: 22955330
  30. Machaczka, M, Johansson, JE, Remberger, M, et al. High incidence of chronic graft-versus-host disease after myeloablative allogeneic stem cell transplantation for chronic lymphocytic leukemia in Sweden: graft-versus-leukemia effect protects against relapse. *Med Oncol*. 2013 Dec;30(4):762. PMID: 24214180
  31. Toze, CL, Dalal, CB, Nevill, TJ, et al. Allogeneic haematopoietic stem cell transplantation for chronic lymphocytic leukaemia: outcome in a 20-year cohort. *Br J Haematol*. 2012 Jul;158(2):174-85. PMID: 22640008
  32. Kharfan-Dabaja, MA, Kumar, A, Hamadani, M, et al. Clinical Practice Recommendations for Use of Allogeneic Hematopoietic Cell Transplantation in Chronic Lymphocytic Leukemia on Behalf of the Guidelines Committee of the American Society for Blood and Marrow Transplantation. *Biol Blood Marrow Transplant*. 2016 Sep 19. PMID: 27660167
  33. BlueCross BlueShield Association Medical Policy Reference Manual "Hematopoietic Stem-Cell Transplantation for Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma." Policy No. 8.01.15

## 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
38220	Diagnostic bone marrow; aspiration(s)
38221	Diagnostic bone marrow; biopsy(ies)
38222	Diagnostic bone marrow; biopsy(ies) and aspiration(s)
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
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)

#### APPENDIX I: Glossary of Terms used in this Policy

**consolidation therapy**<sup>1</sup> - 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**<sup>2</sup> - The return of a disease or the signs and symptoms of a disease after a period of improvement.

**salvage therapy**<sup>3</sup> - Treatment that is given after the cancer has not responded to other treatments.

**tandem transplant**<sup>4</sup> – Refers to a planned second course of high-dose therapy and HCT within six months of the first course.

1. NCI Dictionary of Cancer Terms | <https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=45654> | Accessed Sep 25 2018

2. NCI Dictionary of Cancer Terms | <https://www.cancer.gov/publications/dictionaries/cancer-terms?CdrID=45866> | Accessed Sep 25 2018
3. NCI Dictionary of Cancer Terms | <https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=44176> | Accessed Sep 25 2018
4. NCCN Guidelines Version 2.2018 Multiple Myeloma | [https://www.nccn.org/professionals/physician\\_gls/pdf/myeloma.pdf](https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf) | Accessed Sep 25 2018

*Date of Origin: May 2010*