Subject: Hematopoietic Stem Cell Transplantation for Chronic Lymphoblastic Leukemia (CLL) and Small Lymphocytic Lymphoma (SLL)	Original Effective Date: 7/29/2014
Policy Number: MCP-188	**Revision Date(s):** 6/2/2015, 7/27/2017
Review Date: 12/16/2015, 6/15/2016, 7/10/2018, 6/19/2019	
MCPC Approval Date: 9/19/2017, 7/10/2018, 6/19/2019	

DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (i.e., will be paid for by Molina) for a particular member. The member's benefit plan determines coverage. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this Molina Clinical Policy (MCP) document and provide the directive for all Medicare members.[1]

DESCRIPTION OF PROCEDURE/SERVICE/PHARMACEUTICAL

Chronic Lymphoblastic Leukemia and Small Lymphocytic Lymphoma (SLL)

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. [23] 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.

In this disorder, lymphocyte counts in the blood are usually greater than or equal to 5,000/mm3 with a characteristic immunophenotype (CD5- and CD23-positive B cells). The clinical course of this disease progresses from an indolent lymphocytosis without other evident disease to one of generalized lymphatic enlargement with concomitant pancytopenia. There is usually an insidious onset, with diagnosis often resulting from incidental blood tests. Symptoms are usually nonspecific, and include fatigue, anorexia, weight loss, dyspnea on exertion, or a sense of abdominal fullness from an enlarging spleen. Late symptoms include susceptibility to bacterial, viral and fungal infection. Complications of pancytopenia, including hemorrhage and infection, represent a major cause of death in these patients. Immunological aberrations, including Coombs-

positive hemolytic anemia, immune thrombocytopenia, and depressed immunoglobulin levels may all complicate the management of CLL/SLL. Treatment ranges from periodic observation with treatment of infectious, hemorrhagic, or immunologic complications to a variety of therapeutic options, including steroids, alkylating agents, purine analogs, combination chemotherapy, monoclonal antibodies, and transplantation. For patients with progressing CLL/SLL, treatment with conventional doses of chemotherapy is not curative. Selected patients may be treated with allogeneic stem cell transplantation.

CLL is staged according to 2 common systems, the Rai and Binet. The Rai system has 5 stages of disease advancement from 0 through IV and the Binet system has 3 stages A through C (A overlaps with Rai 0, I, and II; B with I and II; and C with III and IV). Patients in stages I/II are considered as having intermediate-risk / early-stage disease, and those in stages III/IV as having high-risk / advanced-stage disease.

Stem Cell Transplantation

Stem-cell transplantation refers to transplantation of hematopoietic stem cells (HSCs) from a donor into a patient. HSCs are immature cells that can develop into any of the three types of blood cells (red cells, white cells or platelets). HSCs are created in the bone marrow and are found in the bone marrow and peripheral blood. There is also a high concentration of HSCs in umbilical-cord blood. Hematopoietic stem-cell transplantation (HSCT) can be either autologous (using the person's own stem cells) or allogeneic (using stem cells from a donor). In allogeneic HSCT, it is preferable for donors to have a human leukocyte antigen (HLA) type that is identical to the recipient. Matching is performed on the basis of variability at three of more loci of the HLA gene (e.g., HLA-A, HLA-B, HLA-DRB1). As HLA variability increases, transplant-related morbidity and mortality, including graft rejection and graft-versus-host disease, also increase.

Donor Lymphocyte Infusion

Following an allogeneic hematopoietic stem cell transplant, donor lymphocyte infusion is a form of adoptive immunotherapy and may be requested to induce a graft versus leukemia, or graft versus tumor, response without requiring the recipient to undergo additional high-dose chemotherapy. Donor lymphocytes are collected from the original donor through leukapheresis. This collection is an outpatient procedure for the donor. The lymphocytes are then either infused via vein into the recipient or are frozen for a more clinically appropriate time.

Pretransplant Evaluation

The goal of the pretransplant evaluation is to assess the ability of a patient to tolerate the surgery, post-operative immunosuppression, and transplant care. An extensive cardiopulmonary evaluation, screening for occult infection or cancer, and psychosocial evaluation is standard. Specific testing varies depending upon the patient's age, medical history, and transplant center practice. In addition, while a certain battery of tests may initiate the work up, more testing may be indicated depending upon the condition of the patient or the initial test results. In addition to a standard medical evaluation the initial assessment should include a psychological and social support evaluation to identify issues that may impair a successful outcome after transplantation. These include a lack of information about the nature of the transplant procedure and post-transplant care, drug or alcohol dependence, compliance with complex medical and behavior regimens. The assessment includes education of

the family and the support network of the patient because compliance with complex medical and behavior treatment is critical after any organ transplant procedure. Recipients must be able to incorporate complicated medications, follow-up appointments, and frequent laboratory visits into their schedules. Having an adequate support network aware of these requirements will encourage patient compliance and long-term success.

RECOMMENDATION

All transplants require prior authorization from the Corporate Transplant Department. Solid organ transplant requests will be reviewed by the Corporate Senior Medical Director or qualified clinical designee. All other transplants will be by the Corporate Senior Medical Director or covering Medical Director. If the criteria are met using appropriate NCD and/or LCD guidelines, state regulations and/or MCP policies the Corporate Senior Medical Director's designee can approve the requested transplant.

Members must meet UNOS/OPTN policies and guidelines for pretransplantation evaluation and listing criteria and the diagnosis must be made by a Specialist in the Disease and or Transplant Surgeon.

Pre-Transplant Evaluation: [2-9]

Criteria for transplant evaluation include all of the following:

- ❑ History and physical examination
- ❑ Psychosocial evaluation and clearance:
  - No behavioral health disorder by history or psychosocial issues:
    - ➢ if history of behavioral health disorder, no severe psychosis or personality disorder
    - ➢ mood/anxiety disorder must be excluded or treated
    - ➢ member has understanding of surgical risk and post procedure compliance and follow-up required
  - Adequate family and social support
- ❑ EKG
- ❑ Chest x-ray
- ❑ Cardiac clearance in the presence of any of the following:
  - o chronic smokers
  - o > 50 years age
  - o those with a clinical or family history of heart disease or diabetes
- ❑ Pulmonary clearance if evidence of pulmonary artery hypertension (PAH) or chronic pulmonary disease
- ❑ Neurological exam and clearance for transplant: [ONE]
  - o Normal exam by H&P
  - o Abnormal neurological exam with positive findings: [ONE]
    - ➢ Lumbar puncture normal cytology
    - ➢ Lumbar puncture with cytological exam abnormal: CNS disease treated prior to clearance
- ❑ Performance Status : [ONE]
  - o Karnofsky score 70-100%; or
  - o Eastern Cooperative Oncology Group (ECOG) grade 0-2

- ❑ Lab studies:
  - *Complete blood count, Kidney profile (blood urea nitrogen, creatinine), electrolytes, calcium, phosphorous, albumin, liver function tests, Coagulation profile (prothrombin time, and partial thromboplastin time)
  - *Serologic screening for HIV, Epstein Barr virus (EBV), Hepatitis virus B (HBV), and Hepatitis C(HCV), cytomegalovirus (CMV), RPR and/or FTA:
    - If HIV positive all of the following are met:
      - CD4 count >200 cells/mm-3 for >6 months
      - HIV-1 RNA undetectable
      - On stable anti-retroviral therapy >3 months
      - No other complications from AIDS (e.g., opportunistic infection, including aspergillus, tuberculosis, coccidioides mycosis, resistant fungal infections, Kaposi's sarcoma, or other neoplasm)
    - If abnormal serology need physician plan to address and/or treatment as indicated
  - UDS (urine drug screen) if patient is current or gives a history of past drug abuse
- ❑ *Colonoscopy (if indicated or if patient is 50 ≥ older should have had an initial screening colonoscopy, after initial negative screening requires follow up colonoscopy every ten years) with complete workup and treatment of abnormal results as indicated
- ❑ *GYN examination with Pap smear for women ≥ 21 to ≤ 65 years of age or indicated (not indicated in women who have had a TAH or TVH) with in the last three year with complete workup and treatment of abnormal results as indicated

Within the last 12 months:

- ❑ Dental examination or oral exam showing good dentition and oral care or no abnormality on panorex or plan for treatment of problems pre or post-transplant
- ❑ *Mammogram (if indicated or > age 40) with complete workup and treatment of abnormal results as indicated
- ❑ *PSA if history of prostate cancer or previously elevated PSA with complete workup and treatment of abnormal results as indicated

Participating Centers of Excellence may waive these criteria

Criteria for Hematopoietic Allogeneic Stem Cell transplantation (HSCT) Transplantation: [2-9 26-28]

1. ***Hematopoietic Allogeneic stem-cell transplantation (HSCT)*** *ablative (must be* ≤ 55 years of age *or non-myeloablative (must be* ≤ 75 years of age) from a human leukocyte antigen (HLA)-matched donor (i.e., at least six out of eight match of the HLA-A, HLA-B, HLA-C and HLA-DRB1 markers) or from cord blood when there are no matched sibling or unrelated donors (i.e. at least four out of six match of the HLA-A, HLA-B and HLA-DRB-1 markers) may be authorized for the treatment of chronic lymphocytic/lymphoblastic leukemia (CLL) and small lymphocytic lymphoma (SLL) when ALL of the following criteria are met: **[ALL]**

   - ❑ All pre-transplant criteria are met; and
   - ❑ Responsive to salvage chemotherapy after having failed fludarabine based therapy; and

- ❑ *Rai stage III-IV disease with any of the following high risk factors for relapse: **[ONE]**:
  - High-risk cytogenetics or molecular features (e.g., del(11q) or del(17p); ZAP70, CD38 positivity; unmutated Ig VHmutational status)
  - Short initial remission
  - Poor initial response
  - Richter's transformation to diffuse large cell lymphoma
  - Leukocyte count greater than 50 x109/L

Note: Rai Staging System [6]

- **Stage 0:** CLL is characterized by absolute lymphocytosis (>15,000/mm^3) without adenopathy, hepatosplenomegaly, anemia, or thrombocytopenia.
- **Stage I**: CLL is characterized by absolute lymphocytosis with lymphadenopathy without hepatosplenomegaly, anemia, or thrombocytopenia.
- **Stage II**: CLL is characterized by absolute lymphocytosis with either hepatomegaly or splenomegaly with or without lymphadenopathy.
- **Stage III:** CLL is characterized by absolute lymphocytosis and anemia (hemoglobin <11 g/dL) with or without lymphadenopathy, hepatomegaly, or splenomegaly.
- **Stage IV**: CLL is characterized by absolute lymphocytosis and thrombocytopenia (<100,000/mm^3) with or without lymphadenopathy, hepatomegaly, splenomegaly, or anemia.

AND

- ❑ The requesting transplant recipient should not have any of the following **absolute contraindications**:
  - Cardiac, pulmonary, and nervous system disease that cannot be corrected and is a prohibitive risk for surgery
  - Malignant neoplasm with a high risk for reoccurrence, non-curable malignancy (excluding localized skin cancer)
  - Systemic and/or uncontrolled infection
  - AIDS (CD4 count < 200cells/mm3)
  - Unwilling or unable to follow post-transplant regimen
    - ◊ Documented history of non-compliance
    - ◊ Inability to follow through with medication adherence or office follow-up
  - Chronic illness with one year or less life expectancy
  - Limited, irreversible rehabilitation potential
  - Active untreated substance abuse issues, requires documentation supporting free from addiction for minimally 6 months if previous addiction was present
  - No adequate social/family support

- ❑ The requesting transplant recipient should be evaluated carefully and potentially treated if the following **relative contraindications** are present:
  - Irreversible lung disease patients require consultation and clearance by a Pulmonologist prior to consideration of transplantation, this includes the following:
  - Smoking, documentation supporting free from smoking for 6 months

- Active peptic ulcer disease
- Active gastroesophageal reflux disease
- CVA with long term impairment that is not amendable to rehabilitation or a patient with CVA/transient ischemic attack within past 6 months
- Obesity with body mass index of >30 kg/m^2 may increase surgical risk
- Chronic liver disease such as Hepatitis B/C/D, or cirrhosis which increases the risk of death from sepsis and hepatic failure requires consultation by a gastroenterologist or hepatologist
- Gall bladder disease requires ultrasound of the gall bladder with treatment prior to transplantation

Criteria for Repeat Allogeneic Stem Cell Transplantation:

2. ***Hematopoietic Allogeneic stem cell transplantation*** *(ablative or non-myeloablative)* may be authorized after *the first prior stem cell transplantation* has occurred only one time for members with CLL/SLL who meet all of the above criteria for transplant and have any of the following **:[ONE]**

   - ❑ primary graft failure indicated by no signs of engraftment* by 42 days after the transplant; **OR**
   - ❑ failure to engraft*; **AND**
   - ❑ a suitable allogeneic donor has been identified if applicable

   ***Note:** Engraftment is defined as the first 3 consecutive days on which the absolute neutrophil count (ANC) exceeds 5 x 10^9/L or > ANC500at any time after transplantation.*[5]

Criteria for Donor Lymphocyte Infusion (DLI):

3. ***Donor lymphocyte infusion (DLI)***, ***collection and cryopreservation*** may be authorized following a medically necessary allogeneic hematopoietic stem cell transplant: [11 12 26]
   - ❑ For incomplete chimerism and disease relapse in the setting of incomplete chimerism (defined as incomplete donor stem cell grafting in the recipient's bone marrow);
     AND
   - ❑ Donor lymphocytes must be collected from the original hematopoietic stem cell donor

CONTINUATION OF THERAPY

When extension of a previously approved transplant authorization is requested, review using updated clinical information is appropriate.

- ❑ If Molina Healthcare has authorized prior requests for transplantation, the following information is required for medical review: [ALL]
  - Presence of no absolute contraindication as listed above;
  - History and physical within the last 12 months;
  - Kidney profile within the last 12 months;
  - Cardiac update if history of cardiac disease within two years (≥ 50 years of age);
  - Psychosocial evaluation or update within the last 12 months;
  - Per initial and updated history and physical, any other clinically indicated tests and/or scans as determined by transplant center physician or Molina Medical Director.

- ❑ If authorized prior requests for transplantation were obtained from another insurer, the following information is required for medical review: [ALL]
  - Authorization letter/documentation from previous insurer;
  - Presence of no absolute contraindication as listed above;
  - History and physical within the last 12 months;
  - Cardiac update if history of cardiac disease within two years (≥ 50 years of age);
  - Psychosocial evaluation or update within the last 12 months;
  - Per initial and updated history and physical, any other clinically indicated tests and/or scans as determined by transplant center physician or Molina Medical Director.

COVERAGE EXCLUSIONS [2-9]

1. Allogeneic (ablative or non-myeloablative) stem cell transplantation when the above criteria are not met.
2. Patients with refractory progressive disease occurring more than 12 months after the discontinuation of treatment [6]
3. Autologous stem cell transplantation in individuals with CLL or SLL
4. Hematopoietic stem cell collection, storage and freezing for a future unplanned transplant is not covered

SUMMARY OF MEDICAL EVIDENCE [10-25]

There are currently no randomized trials that report the outcomes of high-dose chemotherapy (HDC) followed by stem cell transplant compared to conventional therapy however, 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. There is a lack of randomized trials that report the outcomes of high-dose chemotherapy followed by autologous stem cell transplant compared to conventional therapy. A summary of the most relevant medical evidence is outlined below.

In the peer reviewed literature there are six published non-randomized studies involving 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. The majority of patients in these series were 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). [17] 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. [15-20]

A retrospective study from the EBMT registry analyzed 368 chronic lymphocytic leukemia patients who underwent allogeneic hematopoietic stem cell transplantation. There were 198 human leukocyte antigen (HLA)-identical siblings; among unrelated transplants, 31 were well matched in high resolution (well matched unrelated donor, WMUD), and 139 were mismatched (MM), including 30 matched in low resolution; 266 patients (72%) received reduced-intensity conditioning and 102 (28%) received standard. According to the EBMT risk score, 11% were in scores 1-3, 23% in score 4, 40% in score 5, 22% in score 6 and 4% in score 7. There was no difference in overall survival (OS) at 5 years between HLA-identical siblings (55% (48-64)) and WMUD (59% (41-84)), P=0.82. In contrast, OS was significantly worse for MM (37% (29-48) P=0.005) due to a significant excess of transplant-related mortality. Also OS worsened significantly when EBMT risk score increased. HLA matching had no significant impact on relapse (siblings: 24% (21-27); WMUD: 35% (26-44), P=0.11 and MM: 21% (18-24), P=0.81); alemtuzumab T-cell depletion and stem cell source (peripheral blood) were associated with an increased risk. In conclusion, the findings support the use of WMUD as equivalent alternative to HLA-matched sibling donors for allogeneic HSCT in CLL, and justify the application of EBMT risk score in this disease. [23]

Magni and colleagues (2014) reported results from a phase III multic-enter randomized controlled trial (RCT) that investigated the use of rituximab, fludarabine and cyclophosphamide (R-FC) compared to high-dose sequential (R-HDS) chemotherapy followed by an autologous SCT (ASCT) as frontline treatment for individuals with CLL. A total of 96 individuals were randomized and 48 participants were assigned to each group. There was no statistically significant improvement in PFS and OS between the groups after 5 years of follow-up. The PFS for the R-HDS group was 60.4% and 65.1% (p=0.66) for the R-FC group. The OS was similar for the R-HDS group (88.0%) compared to the R-FC group (88.1%). The authors concluded that the use of upfront ASCT should not be recommended compared to optimal chemoimmunotherapy regimens. There is a lack of additional randomized trials that report the outcomes of high-dose chemotherapy followed by autologous stem cell transplant compared to conventional therapy. [23]

A 2015 systematic review of autologous HCT as front-line consolidation in CLL included a literature search through November 2014. Four randomized controlled trials (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. [25]

Professional Organizations [2-9]

The National Comprehensive Cancer Network (NCCN) guidelines for Non-Hodgkin's Lymphoma do not include autologous or tandem HSCT as a therapeutic option in CLL or SLL. NCCN indicates that allogeneic HSCT may be considered for select patients refractory to small molecule inhibitor therapy in patients without significant comorbidities and in those with high-risk disease [Rai high risk, or del17p]). Allogeneic transplant is not considered a treatment option for refractory CLL or disease relapse within 12-24 months after initial purine analogue-based therapy.[7]

Toronto (ON) Cancer Care Ontario Program Advisory Panel on Bone Marrow and Stem Cell Transplantation, and the Hematology Disease Site Group: Stem Cell Transplantation for adults with CLL is recommended for the following subsets: [4]

- Allogeneic stem cell transplantation is an option for selected patients with CLL, including those with high-risk cytogenetics who have failed purine analog therapy.
- Autologous stem cell transplantation is not recommended for patients with CLL.
- Qualifying Statement: The management of CLL is in evolution with the emergence of new treatment options, including targeted therapy. These options must be considered when recommending stem cell transplantation.

CODING INFORMATION: THE CODES LISTED IN THIS POLICY ARE FOR REFERENCE PURPOSES ONLY. LISTING OF A SERVICE OR DEVICE CODE IN THIS POLICY DOES NOT IMPLY THAT THE SERVICE DESCRIBED BY THIS CODE IS A COVERED OR NON-COVERED. COVERAGE IS DETERMINED BY THE BENEFIT DOCUMENT. THIS LIST OF CODES MAY NOT BE ALL INCLUSIVE.

CPT	Description
	Collection Codes
38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic
38206	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous
38230	Bone marrow harvesting for transplantation; allogeneic
38232	Bone marrow harvesting for transplantation; autologous
	Cell Processing Services
38207	Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage
38208	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing
38209	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing
38210	Transplant preparation of hematopoietic progenitor cells; specific cell depletion within harvest, T-cell depletion
38211	Transplant preparation of hematopoietic progenitor cells; tumor cell depletion
38212	Transplant preparation of hematopoietic progenitor cells; red blood cell removal
38213	Transplant preparation of hematopoietic progenitor cells; platelet depletion
38214	Transplant preparation of hematopoietic progenitor cells; plasma (volume) depletion
38215	Transplant preparation of hematopoietic progenitor cells; cell concentration in plasma, mononuclear, or buffy coat layer
	Cell infusion codes
38240	Bone marrow or blood-derived peripheral stem cell transplantation; allogeneic
38241	Bone marrow or blood-derived peripheral stem cell transplantation; autologous
38242	Bone marrow or blood-derived peripheral stem cell transplantation; allogeneic donor lymphocyte infusions
38243	Bone marrow or blood-derived peripheral stem cell transplantation; allogeneic hematopoietic cellular transplant boost

HCPCS	Description
S2140	Cord blood harvesting for transplantation, allogeneic
S2142	Cord blood derived stem-cell transplantation, allogeneic

S2150	Bone marrow or blood-derived stem cells (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation, and related complications; including pheresis and cell preparation/storage; marrow ablative therapy; drugs; supplies; hospitalization with outpatient follow-up; medical/surgical, diagnostic, emergency, and rehabilitative services; and the number of days of pre-and post-transplant care in the global definition

ICD-10	Description: [For dates of service on or after 10/01/2015]
C91.1-C91.12	Chronic lymphocytic leukemia of B-cell type

RESOURCE REFERENCES

Government Agency

1. Centers for Medicare & Medicaid Services. NCD for Stem Cell Transplantation (110.8.1). 2010. Accessed at: http://www.cms.gov/medicare-coverage-database/

Professional Society Guidelines

2. American Society for Blood and Marrow Transplantation (ASBMT). Practice Guidelines. Indications for Autologous and Allogeneic Hematopoietic Cell Transplantation. Accessed at: http://asbmt.org/practice-resources/practice-guidelines
3. Eastern Cooperative Oncology Group (ECOG) Performance Status. Accessed at: http://www.ecog.org/general/perf_stat.html
4. Imrie K, Rumble RB, Crump M, Advisory Panel on Bone Marrow and Stem Cell Transplantation, Hematology Disease Site Group. Stem cell transplantation in adults: recommendations. Toronto (ON): Cancer Care Ontario Program in Evidence-based Care; 2009 Jan 30. 78 p. Accessed at: https://www.cancercare.on.ca/common/pages/UserFile.aspx?serverId=6&path=/File%20Database/CCO%20Files/PEBC/pebc_stemcell.pdf
5. National Bone Marrow Donor Program:
    - HLA Matching Requirements. Accessed at: http://marrow.org/Patient/Transplant_Process/Search_Process/HLA_Matching__Finding_the_Best_Donor_or_Cord_Blood_Unit.aspx
    - Treatment before transplant. Accessed at: https://bethematch.org/for-patients-and-families/getting-a-transplant/treatment-before-transplant/
    - Measuring Engraftment. Accessed at: http://marrow.org/Patient/Transplant_Process/Days_0-30/Measuring_Engraftment.aspx
6. National Cancer Institute. Chronic Lymphoblastic Leukemia PDQ 2019. Accessed at: http://www.cancer.gov/cancertopics/pdq/treatment/CLL/healthprofessional
7. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (V.4.2019). Accessed at: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp
8. National Marrow Donor Program (NMDP):
    - CLL Transplant Outcomes. Accessed at: https://bethematchclinical.org/Transplant-Indications-and-Outcomes/Disease-Specific-Indications-and-Outcomes/CLL/
    - Patient Eligibility for HCT. Accessed at: https://bethematchclinical.org/Transplant-Indications-and-Outcomes/Eligibility/
9. National Marrow Donor Program® (NMDP) and the American Society for Blood and Marrow Transplantation (ASBMT) referral guidelines: Recommended Timing for Transplant Consultation. Accessed at: http://marrow.org/Physicians/When_to_Transplant/Referral_Guidelines.aspx

Peer Reviewed Publications

10. C Mackall, T Fry, R Gress, K Peggs, J Storek and A Toubert. Background to hematopoietic cell transplantation, including post-transplant immune recovery. Bone Marrow Transplant 44: 457-462; doi:10.1038/bmt.2009.255
11. Collins RH, Goldstein S, Giralt S, et al. Donor leukocyte infusions in acute lymphocytic leukemia. Bone Marrow Transplant. 2000; 26(5): 511-516. Accessed at: http://www.nature.com/bmt/journal/v26/n5/full/1702555a.html
12. Mackinnon S. American Society of clinical Oncology (ASCO). Donor Lymphocyte Infusion after Allogeneic Stem Cell Transplantation. 2008. Accessed at: http://www.asco.org/ascov2/Education+&+Training/Educational+Book?&vmview=edbk_detail_view&confID=55&abstractID=54
13. Gribben J. Stem cell transplantation in chronic lymphocytic leukemia. Biol Blood Marrow Transplant. Jan 2008; 15(1 Suppl): 53–58. Accessed at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2668540/
14. Campo E. Swerdlow S et al. The 2008 WHO classification of lymphoid neoplasms and beyond: evolving concepts and practical applications. Blood. May 2011;19:117. Accessed at: http://bloodjournal.hematologylibrary.org/content/117/19/5019?sso-checked=1
15. 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
16. 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
17. 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
18. 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
19. 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. J Clin Oncol. 2003 Jul 15;21(14):2747-53. PMID: 12860954
20. Sorror, 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. J Clin Oncol. 2008 Oct 20;26(30):4912-20. PMID: 18794548
21. 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
22. Kharfan-Dabaja MA(1), Pidala J, et al. Comparing efficacy of reduced-toxicity allogeneic hematopoietic cell transplantation with conventional chemo-(immuno) therapy in patients with relapsed or refractory CLL: a Markov decision analysis. Bone Marrow Transplant. 2012 Sep;47(9):1164-70. doi: 10.1038/bmt.2012.71. Epub 2012 May 7.
23. Michallet M1, Sobh M, Milligan D, Morisset S, et al. The impact of HLA matching on long-term transplant outcome after allogeneic hematopoietic stem cell transplantation for CLL: a retrospective study from the EBMT registry. Leukemia. 2010 Oct ;24(10):1725-31. doi: 10.1038/leu.2010.165. Epub 2010 Aug 12.

24. Magni M, Di Nicola M, Patti C, et al. Results of a randomized trial comparing high-dose chemotherapy plus Auto-SCT and R-FC in CLL at diagnosis. Bone Marrow Transplant. 2014; 49(4):485-491.
25. Reljic T, Kumar A, Djulbegovic B, et al. High-dose therapy and autologous hematopoietic cell transplantation as front-line consolidation in chronic lymphocytic leukemia: a systematic review. Bone Marrow Transplant. Aug 2015;50(8):1144. PMID 26242579

Other Resources

26. UpToDate: Waltham, MA: Walters Kluwer Health; 2019.
- Negrin C. Immunotherapy for the prevention and treatment of relapse following hematopoietic cell transplantation.
- Negrin R, Rai K. Hematopoietic cell transplantation in chronic lymphocytic leukemia.
- Rai K. Overview of the treatment of chronic lymphocytic leukemia.
- Rai K. Selection of initial therapy for symptomatic or advanced chronic lymphocytic leukemia.
- Rai K. Treatment of relapsed or refractory chronic lymphocytic leukemia.
- Cutler C. The approach to hematopoietic cell transplantation survivorship.
- Chao NG. Selection of an umbilical cord blood graft for hematopoietic cell transplantation.
- Deeg HJ, Sandmaier B. Determining eligibility for allogeneic hematopoietic cell transplantation.

27. McKesson InterQual Criteria for Procedures: InterQual Hematopoietic Transplantation, Allogeneic Stem Cell; 2018.
28. DynaMed Plus [Internet]. Ipswich (MA): EBSCO Information Services. 1995-2019. Chronic Lymphoblastic Leukemia.

Review/Revision History:

7/29/14: Policy created

6/2/15: Updated pre-transplant criteria, continuation of therapy, absolute and relative contraindications and coding sections.

6/15/16: Policy reviewed, no changes

7/27/17: Updated professional society guidelines, references and summary of medical evidence sections.

7/10/18, 6/19/19: Policy reviewed, updated references