MASSACHUSETTS

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Medical Policy

Hematopoietic Cell Transplantation for Acute Lymphoblastic Leukemia

Table of Contents

Policy Number: 076

BCBSA Reference Number: 8.01.32
NCD/LCD: National Coverage Determination (NCD) for Stem Cell Transplantation Formerly 110.8.1 (110.23)

Related Policies

None

Policy

Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity

Childhood Acute Lymphoblastic Leukemia (ALL)
Autologous or allogeneic hematopoietic cell transplantation (HCT) may be considered **MEDICALLY NECESSARY** to treat childhood acute lymphoblastic leukemia (ALL) in first complete remission but at high risk of relapse.*

Autologous or allogeneic HCT may be considered **MEDICALLY NECESSARY** to treat childhood ALL in second or greater remission or refractory ALL.

Allogeneic HCT is considered **MEDICALLY NECESSARY** to treat relapsing ALL after a prior autologous HCT.

Relapse Risk Prognostic Factors
Childhood ALL
*Adverse prognostic factors in children include the following: age younger than 1 year or more than 9 years, male gender, white blood cell (WBC) count at presentation above 50,000/ìL, hypodiploidy (<45 chromosomes), t(9;22) or *BCR/ABL* fusion, t(4;11) or *MLL/AF4* fusion, and ProB or T-lineage immunophenotype. Several risk stratification schema exist, but, in general, the following findings help define children at high risk of relapse: (1) poor response to initial therapy including poor response to prednisone prophase defined as an absolute blast count of 1000/ìL or greater, or poor treatment response to induction therapy at 6 weeks with high risk having ≥1% minimal residual disease measured

by flow cytometry, (2) all children with T- cell phenotype, and (3) patients with either the t(9;22) or t(4;11) regardless of early response measures.

Adult Acute Lymphoblastic Leukemia (ALL)
Autologous HCT may be considered **MEDICALLY NECESSARY** to treat adult ALL in first complete remission but at high risk of relapse.*

Allogeneic HCT may be considered **MEDICALLY NECESSARY** to treat adult ALL in first complete remission for any risk level.*

Allogeneic HCT may be considered **MEDICALLY NECESSARY** to treat adult ALL in second or greater remissions, or in patients with relapsed or refractory ALL.

Reduced-intensity conditioning allogeneic HCT may be considered **MEDICALLY NECESSARY** as a treatment of ALL in patients who are in complete marrow and extramedullary first or second remission, and who, for medical reasons (see below) would be unable to tolerate a standard myeloablative conditioning regimen.

Autologous HCT is **INVESTIGATIONAL** to treat adult ALL in second or greater remission or those with refractory disease.

Allogeneic HCT is considered **MEDICALLY NECESSARY** to treat relapsing ALL after a prior autologous HCT.

Adult ALL
*Risk factors for relapse are less well-defined in adults, but a patient with any of the following may be considered at high risk for relapse: age older than 35 years, leukocytosis at presentation of greater than 30,000/ìL (B-cell lineage) or greater than 100,000/ìL (T-cell lineage), “poor prognosis” genetic abnormalities like the Philadelphia chromosome (t[9;22]), extramedullary disease, and time to attain complete remission longer than 4 weeks.

Reduced-Intensity Conditioning
Some patients for whom a conventional myeloablative allogeneic HSCT could be curative may be considered candidates for RIC allogeneic HCT (see Description section). These include those whose age (typically >60 years) or comorbidities (eg, liver or kidney dysfunction, generalized debilitation, prior intensive chemotherapy including autologous or allogeneic HSCT, low Karnofsky Performance Status) preclude use of a standard myeloablative conditioning regimen.

The ideal allogeneic donors are HLA-identical siblings, matched at the HLA-A, B, and DR loci (6 of 6). Related donors mismatched at 1 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, where usually there is sharing of only 3 of the 6 major histocompatibility antigens. Most 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.

Medicare HMO Blue^{SM} and Medicare PPO Blue^{SM} Members

Medical necessity criteria and coding guidance can be found through the link below.

National Coverage Determinations (NCDs)

National Coverage Determination (NCD) for Stem Cell Transplantation Formerly 110.8.1 (110.23)

Note: To review the specific NCD, please remember to click "accept" on the CMS licensing agreement at the bottom of the CMS webpage.

Prior Authorization Information

Inpatient

- For services described in this policy, precertification/preauthorization **IS REQUIRED** for all products if the procedure is performed **inpatient**.

Outpatient

- For services described in this policy, see below for products where prior authorization **might be required** if the procedure is performed **outpatient**.

	Outpatient
Commercial Managed Care (HMO and POS)	Prior authorization is **required**.
Commercial PPO and Indemnity	Prior authorization is **required**.
Medicare HMO Blue℠	Prior authorization is **required**.
Medicare PPO Blue℠	Prior authorization is **required**.

CPT Codes / HCPCS Codes / ICD Codes

Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

The above medical necessity criteria MUST be met for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

CPT Codes

CPT codes:	Code Description
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
38240	Bone marrow or blood-derived peripheral stem-cell transplantation; allogeneic
38241	Bone marrow or blood-derived peripheral stem-cell transplantation; autologous

HCPCS Codes

HCPCS codes:	Code Description
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)

ICD-10-PCS Procedure Codes

ICD-10-PCS procedure codes:	Code Description
30233G0	Transfusion of Autologous Bone Marrow into Peripheral Vein, Percutaneous Approach
30233G1	Transfusion of Nonautologous Bone Marrow into Peripheral Vein, Percutaneous Approach
30243G0	Transfusion of Autologous Bone Marrow into Central Vein, Percutaneous Approach
30243G1	Transfusion of Nonautologous Bone Marrow into Central Vein, Percutaneous Approach
30263G0	Transfusion of Autologous Bone Marrow into Central Artery, Percutaneous Approach
30263G1	Transfusion of Nonautologous Bone Marrow into Central Artery, Percutaneous Approach
3E03305	Introduction of Other Antineoplastic into Peripheral Vein, Percutaneous Approach
3E04305	Introduction of Other Antineoplastic into Central Vein, Percutaneous Approach
3E05305	Introduction of Other Antineoplastic into Peripheral Artery, Percutaneous Approach
3E06305	Introduction of Other Antineoplastic into Central Artery, Percutaneous Approach
30233Y0	Transfusion of Autologous Hematopoietic Stem Cells into Peripheral Vein, Percutaneous Approach
30243Y0	Transfusion of Autologous Hematopoietic Stem Cells into Central Vein, Percutaneous Approach
30233Y1	Transfusion of Nonautologous Hematopoietic Stem Cells into Peripheral Vein, Percutaneous Approach
30243Y1	Transfusion of Nonautologous Hematopoietic Stem Cells into Central Vein, Percutaneous Approach
30263Y1	Transfusion of Nonautologous Hematopoietic Stem Cells into Central Artery, Percutaneous Approach
30233X1	Transfusion of Nonautologous Cord Blood Stem Cells into Peripheral Vein, Percutaneous Approach
30243X1	Transfusion of Nonautologous Cord Blood Stem Cells into Central Vein, Percutaneous Approach
30263X1	Transfusion of Nonautologous Cord Blood Stem Cells into Central Artery, Percutaneous Approach

Description

Acute Lymphoblastic Leukemia

Childhood Acute Lymphoblastic Leukemia

ALL is the most common cancer diagnosed in children; it represents nearly 25% of cancers in children younger than 15 years.[1] Remission of disease is now typically achieved with pediatric chemotherapy regimens in 98% of children with ALL, with up to 85% long-term survival rates. Survival rates have improved with the identification of effective drugs and combination chemotherapy through large randomized trials, integration of presymptomatic central nervous system prophylaxis, and intensification and risk-based stratification of treatment.[2] The prognosis after the first relapse is related to the length of the original remission. For example, leukemia-free survival is 40% to 50% for children whose first remission was longer than 3 years compared with 10% to 15% for those who relapse less than 3 years after treatment. Thus, hematopoietic cell transplantation (HCT) may be a strong consideration in those with short remissions. At present, the comparative outcomes with autologous or allogeneic HCT (allo-HCT) are unknown.

ALL is a heterogeneous disease with different genetic variations resulting in distinct biologic subtypes. Patients are stratified by certain clinical and genetic risk factors that predict an outcome, with risk-adapted therapy tailoring treatment based on the predicted risk of relapse.[3] Two of the most important factors

predictive of risk are patient age and white blood cell count at diagnosis.[3] Certain genetic characteristics of leukemic cells strongly influence prognosis. Clinical and biologic factors predicting clinical outcomes and relapse risk are summarized in the Policy Guidelines section.[2]

Adult ALL
ALL accounts for 20% of acute leukemias in adults. Between 60% and 80% of adults with ALL can be expected to achieve a complete response after induction chemotherapy; however, only 35% to 40% can be expected to survive 2 years.[4] Differences in the frequency of genetic abnormalities that characterize adult ALL vs childhood ALL help, in part, explain differences in outcomes between the two groups. For example, the "good prognosis" genetic abnormalities, such as hyperdiploidy and translocation of chromosomes 12 and 21, are seen much less commonly in adult ALL, whereas they are some of the most common in childhood ALL. Conversely, "poor prognosis" genetic abnormalities such as the Philadelphia chromosome (translocation of chromosomes 9 and 22) are seen in 25% to 30% of adult ALL but infrequently in childhood ALL. Other adverse prognostic factors in adult ALL include age greater than 35 years, poor performance status, male sex, and leukocytosis at presentation of greater than 30000/μL (B-cell lineage) or greater than 100000/μL (T-cell lineage).

Conditioning for HCT
Conventional 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 stem cells obtained from the patient before undergoing bone marrow ablation. Patients who undergo autologous HCT are susceptible to chemotherapy-related toxicities and opportunistic infections before engraftment, but not graft-versus-host disease.

The conventional ("classical") practice of allo-HCT involves administration of cytotoxic agents (eg, 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 the subsequent graft-vs-malignancy effect that develops after engraftment of allogeneic stem cells within the patient's bone marrow space. While the slower graft-versus-malignancy 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 allo-HCT, immune suppressant drugs are required to minimize graft rejection and graft-versus-host disease, which also increases the susceptibility of the patient to opportunistic infections.

Reduced-Intensity Conditioning for Allo-HCT
RIC refers to the pretransplant use of lower doses or less intense regimens of cytotoxic drugs or radiotherapy that are used in conventional full-dose myeloablative conditioning treatments. The goal of RIC is to reduce disease burden and to minimize as much as possible associated treatment-related morbidity and nonrelapse mortality when the beneficial graft-versus-malignancy effect of allogeneic transplantation develops. Although the definition of RIC remains arbitrary, with numerous versions employed, all seek to balance the competing effects of nonrelapse mortality and relapse due to residual disease. RIC regimens can be viewed as a continuum of effects, from nearly totally myeloablative, to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and patient condition. Patients who undergo RIC with allo-HCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism, which may be supplemented with donor lymphocyte infusions to eradicate residual malignant cells. For this evidence review, RIC will refer to all conditioning regimens intended to be nonmyeloablative, as opposed to fully myeloablative (conventional) regimens.

Summary

Acute lymphoblastic leukemia (ALL) is a heterogeneous disease with different genetic variations resulting in distinct biologic subtypes. Patients are stratified to risk-adapted therapy according to certain clinical and genetic risk factors that predict an outcome. Therapy may include hematopoietic cell transplantation (HCT).

For individuals who have childhood ALL in first complete remission (CR1) at high-risk of relapse, remission, or refractory ALL who receive autologous HCT, the evidence includes randomized controlled trials (RCTs) and systematic reviews. The relevant outcomes are overall survival (OS), disease-specific survival (DSS), and treatment-related mortality (TRM) and morbidity. For children with high-risk ALL in CR1 or with relapsed ALL, studies have suggested that HCT is associated with fewer relapses but higher death rates due to treatment-related toxicity. However, for a subset of high-risk patients in second complete remission or beyond or with relapsed disease, autologous HCT is a treatment option. This conclusion is further supported by an evidence-based systematic review and position statement from the American Society for Blood and Marrow Transplantation. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have childhood ALL in CR1 at high-risk of relapse, remission, or refractory ALL who receive allogeneic HCT (allo-HCT), the evidence includes RCTs and systematic reviews. The relevant outcomes are OS, DSS, and TRM and morbidity. For children with high-risk ALL in CR1 or with relapsed ALL, studies have suggested that allo-HCT is associated with fewer relapses but higher death rates due to treatment-related toxicity. However, for a subset of high-risk patients in second complete remission or beyond or with relapsed disease, allo-HCT is a treatment option. This conclusion is further supported by an evidence-based systematic review and position statement from the American Society for Blood and Marrow Transplantation. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have adult ALL in CR1, subsequent remission, or refractory ALL who receive autologous HCT, the evidence includes RCTs and systematic reviews. The relevant outcomes are OS, DSS, and TRM and morbidity. Current evidence supports the use of autologous HCT for adults with high-risk ALL in CR1, whose health status is sufficient to tolerate the procedure. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have adult ALL in CR1 or subsequent remission or refractory ALL who receive allo-HCT, the evidence includes RCTs and systematic reviews. The relevant outcomes are OS, DSS, and TRM and morbidity. Current evidence supports the use of myeloablative allo-HCT for adults with any risk level ALL, whose health status is sufficient to tolerate the procedure. Reduced-intensity conditioning allo-HCT may be considered for patients who demonstrate complete marrow and extramedullary first or second remission and who could be expected to benefit from a myeloablative allo-HCT, but for medical reasons would not tolerate a myeloablative conditioning regimen. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have relapsed after a prior autologous HCT for ALL who receive allo-HCT, the evidence includes case series and systematic reviews. The relevant outcomes are OS, DSS, and TRM and morbidity. Evidence reviews have identified only small case series with short-term follow-up, which was considered inadequate evidence of benefit. The evidence is insufficient to determine the effects of the technology on health outcome.

Allo-HCT after failed autologous HCT has been shown to be of clinical benefit in other hematologic malignancies and is potentially curative. In addition, clinical input has supported the use of allo- HCT to treat relapsing ALL after a failed, prior autologous HCT, particularly with reduced-intensity conditioning regimens, in adults or children. Thus, this indication may be considered medically necessary.

Policy History

Date	Action
3/2019	BCBSA National medical policy review. Description, summary and references updated. Policy statements unchanged.
1/2019	Outpatient prior authorization is required for all commercial products including Medicare Advantage. Effective 1/1/2019.
2/2018	New references added from BCBSA National medical policy.
1/2018	Clarified coding information.
5/2017	New references added from BCBSA National medical policy.
6/2017	New references added from BCBSA National medical policy.
2/2017	New references added from BCBSA National medical policy.
5/2016	BCBSA National medical policy review. "Hematopoietic stem cell transplantation (HSCT)" was replaced with "hematopoietic cell transplantation (HCT)" in the policy statements and title. 5/1/2016
8/2015	Added coding language.
7/2015	New references added from BCBSA National medical policy.
5/2014	Updated Coding section with ICD10 procedure and diagnosis codes, effective 10/2015.
4/2014	Investigational indications for autologous hematopoietic stem-cell transplantation clarified; medically necessary indications for allogeneic hematopoietic stem-cell transplantation clarified.
11/2013	BCBSA National medical policy review. New medically necessary indications described. Effective 11/1/2013.
12/2012	Updated to add new CPT code 38243.
11/2011-4/2012	Medical policy ICD 10 remediation: Formatting, editing and coding updates. No changes to policy statements.
7/2011	Reviewed - Medical Policy Group - Hematology and Oncology. No changes to policy statements.
9/2010	Reviewed - Medical Policy Group - Hematology and Oncology. No changes to policy statements.
9/1/2010	Medical policy 076 effective 9/1/2010 describing covered and non-covered indications.

Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:

Medical Policy Terms of Use
Managed Care Guidelines
Indemnity/PPO Guidelines
Clinical Exception Process
Medical Technology Assessment Guidelines

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