Medical Policy

Hematopoietic Cell Transplantation for Acute Lymphoblastic Leukemia

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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
BCR-ABL1 Testing in Chronic Myelogenous Leukemia and Acute Lymphoblastic Leukemia, #612

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/µL, 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/µL 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 BlueSM and Medicare PPO BlueSM Members**

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

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

**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**.

<table>
<thead>
<tr>
<th>Product Type</th>
<th>Prior Authorization Requirement</th>
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</thead>
<tbody>
<tr>
<td>Commercial Managed Care (HMO and POS)</td>
<td>Prior authorization is required.</td>
</tr>
<tr>
<td>Commercial PPO and Indemnity</td>
<td>Prior authorization is required.</td>
</tr>
<tr>
<td>Medicare HMO BlueSM</td>
<td>Prior authorization is required.</td>
</tr>
<tr>
<td>Medicare PPO BlueSM</td>
<td>Prior authorization is required.</td>
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</tbody>
</table>

**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**

<table>
<thead>
<tr>
<th>CPT codes:</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>38205</td>
<td>Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic</td>
</tr>
<tr>
<td>38206</td>
<td>Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous</td>
</tr>
<tr>
<td>38230</td>
<td>Bone marrow harvesting for transplantation; allogeneic</td>
</tr>
<tr>
<td>38232</td>
<td>Bone marrow harvesting for transplantation; autologous</td>
</tr>
<tr>
<td>38240</td>
<td>Bone marrow or blood-derived peripheral stem-cell transplantation; allogeneic</td>
</tr>
<tr>
<td>38241</td>
<td>Bone marrow or blood-derived peripheral stem-cell transplantation; autologous</td>
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</table>

**HCPCS Codes**

<table>
<thead>
<tr>
<th>HCPCS codes:</th>
<th>Code Description</th>
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<tbody>
<tr>
<td>S2140</td>
<td>Cord blood harvesting for transplantation, allogeneic</td>
</tr>
<tr>
<td>S2142</td>
<td>Cord blood-derived stem-cell transplantation, allogeneic</td>
</tr>
<tr>
<td>S2150</td>
<td>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)</td>
</tr>
</tbody>
</table>

**ICD-10-PCS Procedure Codes**

| ICD-10-PCS procedure codes: | Code Description |
ACUTE LYMPHOBLASTIC LEUKEMIA

Childhood Acute Lymphoblastic Leukemia

Acute lymphoblastic leukemia (ALL) is the most common cancer diagnosed in children; it represents nearly 25% of cancers in children younger than 15 years.\(^1\) Complete remission of disease is now typically achieved with pediatric chemotherapy regimens in 95% 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 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 to only 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 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 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 Acute Lymphoblastic Leukemia

ALL accounts for 20% of acute leukemias in adults. Between 60% and 80% of adults with ALL can be expected to achieve CR after induction chemotherapy; however, only 35% to 40% can be expected to survive 2 years. Differences in the frequency of genetic abnormalities that characterize adult ALL versus childhood ALL help, in part, explain differences in outcomes between the 2 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 30,000/μL (B-cell lineage) or greater than 100,000/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 subsequent graft-versus-malignancy (GVM) effect 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 preengraftment 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 GVHD, which also increases susceptibility of the patient to opportunistic infections.

Reduced-Intensity Conditioning for Allo-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 and to minimize as much as possible associated treatment-related morbidity and nonrelapse mortality (NRM) when 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 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 outcome. Therapy may include hematopoietic cell transplantation (HCT).

For individuals who have childhood ALL in first complete remission at high risk of relapse, subsequent remission, or refractory ALL who receive autologous or allogeneic HCT, the evidence includes randomized controlled trials (RCTs) and systematic reviews. Relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. For children with high risk ALL in first complete remission (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, 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 first complete remission or subsequent remission, or refractory ALL who receive autologous or allogeneic HCT, the evidence includes RCTs and systematic reviews. Relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. Current evidence supports the use of autologous HCT for adults with high-risk ALL in first complete remission, or myeloablative allogeneic HCT (allo-HCT) for adults with any risk level ALL, whose health status is sufficient to tolerate the procedure. Reduced-intensity conditioning (RIC) 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 relapse after a prior autologous HCT for ALL who receive allo-HCT, the evidence includes case series and systematic reviews. Relevant outcomes are overall survival, disease specific survival, and treatment-related mortality and morbidity. Evidence Street Assessments have identified only small case series with short-term follow-up, which were 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 use of allogeneic HCT to treat relapsing ALL after a failed prior autologous HCT, particularly with RIC regimens, in adults or children. Thus, this indication may be considered medically necessary.

**Policy History**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
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<tbody>
<tr>
<td>1/2019</td>
<td>Outpatient prior authorization is required for all commercial products including Medicare Advantage. Effective 1/1/2019.</td>
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<tr>
<td>2/2018</td>
<td>New references added from BCBSA National medical policy.</td>
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<tr>
<td>1/2018</td>
<td>Clarified coding information.</td>
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<tr>
<td>5/2017</td>
<td>New references added from BCBSA National medical policy.</td>
</tr>
<tr>
<td>6/2017</td>
<td>New references added from BCBSA National medical policy.</td>
</tr>
<tr>
<td>2/2017</td>
<td>New references added from BCBSA National medical policy.</td>
</tr>
<tr>
<td>5/2016</td>
<td>BCBSA National medical policy review.</td>
</tr>
<tr>
<td></td>
<td>“Hematopoietic stem cell transplantation (HSCT)” was replaced with “hematopoietic cell transplantation (HCT)” in the policy statements and title. 5/1/2016</td>
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<tr>
<td>8/2015</td>
<td>Added coding language.</td>
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<tr>
<td>7/2015</td>
<td>New references added from BCBSA National medical policy.</td>
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<tr>
<td>5/2014</td>
<td>Updated Coding section with ICD10 procedure and diagnosis codes, effective 10/2015.</td>
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Investigational indications for autologous hematopoietic stem-cell transplantation clarified; medically necessary indications for allogeneic hematopoietic stem-cell transplantation clarified.


12/2012 Updated to add new CPT code 38243.


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

References


29. Mohty M, Labopin M, Tabrizzi R, et al. Reduced intensity conditioning allogeneic stem cell transplantation for adult patients with acute lymphoblastic leukemia: a retrospective study from the


