Hematopoietic Stem-Cell Transplantation for Acute Lymphoblastic Leukemia

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Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for hematopoietic stem-cell transplantation for acute lymphoblastic leukemia (ALL) when it is determined to be medically necessary because the criteria shown below are met.

When Policy Topic is covered
Childhood ALL
*Autologous* or *allogeneic* hematopoietic stem-cell transplantation (HSCT) may be considered *medically necessary* to treat childhood acute lymphoblastic leukemia (ALL) in first complete remission but at high risk of relapse. (For definition of high-risk factors, see Considerations section.)

*Autologous* or *allogeneic* HSCT may be considered *medically necessary* to treat childhood ALL in second or greater remission or refractory ALL.

*Allogeneic* HSCT is considered *medically necessary* to treat relapsing ALL after a prior *autologous* HSCT.

Adult ALL
*Autologous* HSCT may be considered *medically necessary* to treat adult ALL in first complete remission but at high risk of relapse (for definition of high-risk factors, see Considerations).

*Allogeneic* HSCT may be considered *medically necessary* to treat adult ALL in first complete remission for any risk level (for definition of risk factors, see Considerations).

*Allogeneic* HSCT 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 (RIC) *allogeneic* HSCT 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 Considerations), would be unable to tolerate a standard myeloablative conditioning regimen.

*Allogeneic* HSCT is considered *medically necessary* to treat relapsing ALL after a prior *autologous* HSCT.

When Policy Topic is not covered
Adults
*Autologous* HSCT is *investigational* to treat adult ALL in second or greater remission or those with refractory disease.

Considerations
NOTE: The use of donor leukocyte infusions to treat relapse after high-dose chemotherapy with allogeneic SCT for either children or adults is considered separately in a separate policy.

Reimbursement for Stem Cell collection and storage are considered payable under the Transplant Benefit when billed as a one-time, all-inclusive charge.

Transplant Benefit
The date on which the Transplant Benefit starts accumulating is determined by the transplant coordinator. The Transplant Benefit ends when the Transplant Lifetime Maximum benefit (if applicable) has been exhausted.

Benefits include:
- hospitalization of the recipient for medically recognized transplants from a donor to a transplant recipient;
- evaluation tests requiring hospitalization to determine the suitability of both potential (member's benefits must be verified with regard to the potential donor who does not turn out to be the actual donor) and actual donors, when such tests cannot be safely and effectively performed on an outpatient basis (Note: The member's benefits must be verified with regard to the potential donor who does not turn out to be the actual donor.);
- hospital room, board and general nursing in semi-private rooms;
- special care units, such as coronary and intensive care;
- hospital ancillary services;
- physicians’ services for surgery, technical assistance, administration of anesthetics, and medical care;
- acquisition, preparation, transportation, and storage of organ / tissue / cells;
- diagnostic services;
- drugs which require a prescription by federal law;
- medical and surgical care of the donor (related to the procurement of the organ / tissue / cells) if coverage is not available to the donor from any other source. (Covered services provided to a donor will be applied against the recipient's transplant maximum benefit, if applicable)

If the donor and recipient are both listed on the same (family) policy, BCBSKC charges only one deductible and one coinsurance, if applicable.

In addition to the specific organ criteria, transplant candidates must also meet the following general criteria, including, but not limited to:
- Since compliance is a major factor in transplant graft survival, the patient (or legal guardian) must have the ability to accept and understand the transplant procedure and to maintain compliance with long-term medical management and immunosuppression.
- If applicable, patients with a history of malignancy must have passed the recommended length of time to be considered cured for that specific cancer. A complete metastatic evaluation must be performed before a patient will be considered an acceptable transplant candidate.
- Patients with a history of alcohol or substance abuse must have a six month history of abstinence as evidenced by negative urine or serum drug screens taken randomly.
- The patient must have adequate cardiopulmonary status.
- The patient must be free from active infection.

A covered person is eligible for retransplantation as deemed medically necessary and appropriate by BCBSKC. Review of a retransplantation request will include review of the covered person’s compliance with relevant transplant selection criteria including, but not limited to, adherence to medication regimens, follow-up examinations and abstinence from the use of alcohol and drugs.

Coverage will not be provided for:
- Transplant services when the cost is covered by government, foundation or charitable grants
- The purchase price of organs which are sold rather than donated to the recipient
• An artificial organ

Clinical trials for conditions other than those allowed in this policy may be available in the research setting. However, these trials are considered investigational and/or experimental and therefore contract exclusions.

Note: There are some state mandates in place that require insurance carriers to cover certain clinical trials under very specific guidelines. Please contact your BCBSKC representative for more information.

Relapse Risk Prognostic Factors
Childhood ALL
Adverse prognostic factors in children include the following: age less than 1 year or more than 9 years, male gender, white blood cell 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 prophylaxis 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 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 greater than 35 years, leukocytosis at presentation of >30,000/µL (B cell lineage) and >100,000/µL (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 HSCT. These include those whose age (typically >60 years) or comorbidities (e.g., 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 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, where usually there is sharing of only 3 of the 6 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.

Description of Procedure or Service
Hematopoietic Stem-Cell Transplantation
Hematopoietic stem-cell transplantation (SCT) refers to a procedure in which hematopoietic stem 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. Bone marrow stem cells may be obtained from the transplant recipient (i.e., autologous SCT) or from a donor (i.e., allogeneic SCT). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood and placenta 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). Cord blood is discussed in greater detail in a separate policy.

Background
Immunologic compatibility between infused stem cells and the recipient is not an issue in autologous SCT. However, immunologic compatibility between donor and patient is a critical factor for achieving a good outcome of allogeneic SCT. 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 Hematopoietic HSCT**

The success of autologous HSCT 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 prior to undergoing bone marrow ablation. As a consequence, autologous HSCT is typically performed as consolidation therapy when the patient’s disease is in complete remission. Patients who undergo autologous HSCT are susceptible to chemotherapy-related toxicities and opportunistic infections prior to engraftment, but not GVHD.

The conventional (“classical”) practice of allogeneic SCT 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 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 HSCT, 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 HSCT**

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 as much as possible 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 HSCT 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.

**Acute Lymphoblastic Leukemia (ALL)**

**Childhood ALL**

ALL is the most common cancer diagnosed in children and represents almost 25% of cancers in children younger than 15 years. (1) Complete remission of disease is now typically achieved with pediatric chemotherapy regimens in approximately 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 40–50%
for children whose first remission was longer than 3 years, compared to only 10–15% for those who relapse less than three years following treatment. Thus, HSCT may be a strong consideration in those with short remissions. At present, the comparative outcomes with either autologous or allogeneic HSCT are unknown.

ALL is a heterogeneous disease with different genetic alterations resulting in distinct biologic subtypes. Patients are stratified according to 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 (WBC) at diagnosis. (3) Certain genetic characteristics of the leukemic cells strongly influence prognosis. Clinical and biologic factors predicting clinical outcome can be summarized as follows (2):

<table>
<thead>
<tr>
<th>FACTOR</th>
<th>FAVORABLE</th>
<th>UNFAVORABLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis</td>
<td>1-9 years</td>
<td>&lt;1 or &gt;9 years</td>
</tr>
<tr>
<td>Sex</td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>WBC count</td>
<td>&lt;50,000/µL</td>
<td>≥50,000/µL</td>
</tr>
<tr>
<td>Genotype</td>
<td>Hyperdiploidy (&gt;50 chromosomes) t(12;21) or TEL/AML1 fusion</td>
<td>Hypodiploidy (&lt;45 chromosomes) t(9;22) or BCR/ABL fusion t(4;11) or MLL/AF4 fusion</td>
</tr>
<tr>
<td>Immunophenotype</td>
<td>Common, preB</td>
<td>ProB, T-lineage</td>
</tr>
</tbody>
</table>

**Adult ALL**

ALL accounts for approximately 20% of acute leukemias in adults. Approximately 60%–80% of adults with ALL can be expected to achieve complete remission after induction chemotherapy; however, only 35%–40% can be expected to survive 2 years. (4) Differences in the frequency of genetic abnormalities that characterize adult ALL versus childhood ALL help, in part, to explain the outcome differences between the two groups. For example, the “good prognosis” genetic abnormalities like hyperdiploidy and t(12;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 like the Philadelphia chromosome (t[9;22]) are seen in 25%–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 >30,000/µL (B-cell lineage) and >100,000/µL (T-cell lineage).

**Rationale**

EMBASE electronic databases through April 7, 2014. No new evidence was identified to change the conclusions or Policy statements.

**Childhood ALL**

The policy on childhood acute lymphoblastic leukemia (ALL) was initially based on TEC Assessments completed in 1987 and 1990. (5, 6) In childhood ALL, conventional chemotherapy is associated with complete remission rates of approximately 95%, with long-term durable remissions up to 85%. Therefore, for patients in a first complete remission (CR1), hematopoietic stem-cell transplantation (HSCT) is considered necessary only in those with risk factors predictive of relapse (see Description section).

Three reports describing the results of randomized controlled trials (RCTs) that compared outcomes of HSCT to outcomes with conventional-dose chemotherapy in children with ALL were identified subsequent to the TEC Assessment. (7-9) The children enrolled in the RCTs were being treated for high-risk ALL in CR1 or for relapsed ALL. These studies reported that overall outcomes after HSCT were generally equivalent to overall outcomes after conventional-dose chemotherapy. While HSCT
administered in CR1 was associated with fewer relapses than conventional-dose chemotherapy, it was also associated with more frequent deaths in remission (i.e., from treatment-related toxicity).

A more recently published randomized trial (PETHEMA ALL-93, n=106) demonstrated no significant differences in disease-free survival (DFS) or overall survival rates (OS) at median follow-up of 78 months in children with very high-risk ALL in CR1 who received allogeneic or autologous HSCT versus standard chemotherapy with maintenance treatment. (10) Similar results were observed using either intention-to-treat (ITT) or per-protocol (PP) analyses. However, several study limitations that could have affected outcomes include the relatively small numbers of patients; variations among centers in the preparative regimen used prior to HSCT and time elapsed between complete remission (CR) and undertaking of assigned treatment; and, the use of genetic randomization based on donor availability rather than true randomization for patients included in the allogeneic HSCT arm.

**Summary Childhood ALL**

Clinical evidence and reviews of studies (11, 12) suggest that while OS and event-free survival (EFS) are not significantly different after HSCT compared to conventional-dose chemotherapy, HSCT remains a therapeutic option in the management of childhood ALL, especially for patients considered at high risk of relapse or following relapse. This conclusion is further supported by a 2012 evidence-based systematic review of the literature sponsored by the American Society for Blood and Marrow Transplantation (ASBMT). (13) Other investigators recommend that patients should be selected for this treatment using risk-directed strategies. (14, 15)

**Adult ALL**

The policy on adult ALL was initially based in part on a 1997 TEC Assessment of autologous (not allogeneic) HSCT. (16) This Assessment offered the following conclusions:

- For patients in CR1, available evidence suggested survival was equivalent after autologous HSCT or conventional-dose chemotherapy. For these patients, the decision between autologous HSCT and conventional chemotherapy may reflect a choice between intensive therapy of short duration and longer but less-intensive treatment.
- In other settings, such as in second (CR2) or subsequent remissions, evidence was inadequate to determine the relative effectiveness of autologous HSCT compared to conventional chemotherapy.

**Clinical Studies**

Results that partially conflicted with the ASBMT conclusions in 2006 were obtained in a multicenter (35 Spanish hospitals) randomized trial (PETHEMA ALL-93; n=222) published after the ASBMT literature search. (17) Among 183 high-risk patients in CR1, those with a human leukocyte antigen (HLA)-identical family donor were assigned to allogeneic HSCT (n=84); the remaining cases were randomly assigned to autologous HSCT (n=50) or to delayed intensification followed by maintenance chemotherapy up to 2 years in CR (n=48). At median follow-up of 70 months, the study did not detect a statistically significant difference in outcomes between all 3 arms by both PP and ITT analyses. The PETHEMA ALL-93 trial investigators point out several study limitations that could have affected outcomes, including the relatively small numbers of patients; variations among centers in the preparative regimen used prior to HSCT; differences in risk group assignment; and the use of genetic randomization based on donor availability rather than true randomization for patients included in the allogeneic HSCT arm.

While the utility of allogeneic HSCT for postremission therapy in patients with high-risk ALL has been established, its role in those who do not have high-risk features has been less clear. This question has been addressed by the International ALL trial, a collaborative effort conducted by the Medical Research Council (MRC) in the United Kingdom and the Eastern Cooperative Oncology Group (ECOG) in the United States (MRC UKALL XII/ECOG E2993). (18) The ECOG 2993 trial was a Phase III randomized study designed to prospectively define the role of myeloablative allogeneic HSCT, autologous HSCT,
and conventional consolidation and maintenance chemotherapy for adult patients up to age 60 years with ALL in CR1. This study is the largest RCT in which all patients (total n=1,913) received essentially identical therapy, irrespective of their disease risk assignment. After induction treatment that included imatinib mesylate for Philadelphia chromosome-positive patients, all patients who had an HLA-matched sibling donor (n=443) were assigned to receive an allogeneic HSCT. Patients with the Philadelphia (Ph) chromosome (n=267) who did not have a matched sibling donor could receive an unrelated donor HSCT. Patients who did not have a matched sibling donor or were older than 55 years (n=588) were randomly allocated to receive a single autologous HSCT or consolidation and maintenance chemotherapy.

In ECOG2993, OS at 5-year follow-up of all 1,913 patients was 39%; it reached 53% for Ph-negative patients with a donor (n=443) compared to 45% without a donor (n=588) (p=0.01). (18) Analysis of Ph-negative patient outcomes according to disease risk showed a 5-year OS of 41% among patients with high-risk ALL and a sibling donor versus 35% of high-risk patients with no donor (p=0.2). In contrast, OS at 5-years follow-up was 62% among standard risk Ph-negative patients with a donor and 52% among those with no donor, a statistically significant difference (p=0.02). Among Ph-negative patients with standard risk disease who underwent allogeneic HSCT, the relapse rate was 24% at 10-years, compared to 49% among those who did not undergo HSCT (p<0.00005). Among Ph-negative patients with high-risk ALL, the rate of relapse at 10-year follow-up was 37% following allogeneic HSCT versus 63% without a transplant (p<0.00005), demonstrating the potent graft-versus-leukemia (GVL) effect in an allogeneic transplantation. This evidence clearly shows a significant long-term survival benefit associated with postremission allogeneic HSCT in standard risk Ph-negative patients, an effect previously not demonstrated in numerous smaller studies. Failure to demonstrate a significant OS benefit in high-risk Ph-negative cases can be attributed to a high nonrelapse mortality (NRM) rate at 1 and 2 years, mostly due to GVHD and infections. At 2 years, NRM was 36% among high-risk patients with a donor compared to 14% among those who did not have a donor. Among standard risk cases, the NRM rate at 2 years was 20% in patients who underwent allogeneic HSCT versus 7% in those who received autologous HSCT or continued chemotherapy.

In a separate report on the Ph-positive patients in ECOG2993, an ITT analysis (n=158) showed 5-year OS of 34% (95% CI: 25-46%) for those who had a matched sibling donor versus 25% (95% CI: 12-34%) with no donor who received consolidation and maintenance chemotherapy. (19) Although the difference in survival rates was not statistically significant, this analysis demonstrated a moderate superiority of postremission-matched sibling allogeneic HSCT over chemotherapy in patients with high-risk ALL in CR1, in concordance with this policy.

The Dutch HOVON cooperative group reported results combined from 2 successive randomized trials in previously untreated adult patients with ALL aged 60 years or younger, in which myeloablative allogeneic HSCT was consistently used for all patients who achieved CR1 and who had an HLA-matched sibling donor, irrespective of risk category. (20) A total 433 eligible patients included 288 younger than 55 years, in CR1, and eligible to receive consolidation treatment by an autologous HSCT or an allogeneic HSCT.

Allogeneic HSCT was performed in 91 of 96 (95%) with a compatible sibling donor. Overall survival at 5-year follow-up was 61% ± 5% among all patients with a donor and 47% ± 5% among those without a donor (p=0.08). The cumulative incidence of relapse at 5-year follow-up among all patients was 24% ± 4% (SE) in those with a donor versus 55% ± 4% (SE) in those (n=161) without a donor (p<0.001). Among patients stratified by disease risk, those in the standard risk category with a donor (n=50) had 5-year OS of 69% ± 7% and relapse rate at 5 years of 14% ± 5% compared to 49% ± 6% and 52% ± 5%, respectively, among those (n=88) without a donor (p=0.05). High-risk patients with a donor (n=46) had 5-year OS of 53% ± 8% and relapse at 5 years of 34% ± 7%, versus 41% ± 8% and 61% ± 7%, respectively, among those with no donor (n=3; p=0.50). NRM rates among standard risk patients were 16% ± 5% among those with a donor and 2% ± 2% among those without a donor; in high-risk patients, NRM rates were 15% ± 7% and 4% ± 3%, respectively, among those with and without a donor.
The HOVON studies were analyzed as from remission evaluation prior to consolidation whereas the ECOG2993 data were analyzed and presented as from diagnosis, which complicates direct comparison of their outcomes. To facilitate a meaningful comparison, the HOVON data were reanalyzed according to donor availability from diagnosis. This showed a 5-year OS rate of 60% in standard-risk patients with a donor in the HOVON study, which is very similar to the 62% OS observed in standard-risk patients with a donor in the ECOG2993 trial. Collectively, these results suggest that patients with standard-risk ALL can expect to benefit from allogeneic HSCT in CR1, provided the NRM risk is less than approximately 20% to 25%. (20)

**Systematic Reviews and Meta-Analyses**

A meta-analysis published in 2006 pooled evidence from 7 studies of allogeneic HSCT published between 1994 and 2005 that included a total of 1,274 patients with ALL in CR1. (21) The results showed that regardless of risk category, allogeneic HSCT was associated with a significant OS advantage (hazard ratio [HR]: 1.29; 95% confidence interval [CI]: 1.02-1.63, p=0.037) for all patients who had a suitable donor versus patients without a donor who received chemotherapy or autologous HSCT. Pooled evidence from patients with high-risk disease showed an increased survival advantage for allogeneic HSCT compared to those without a donor (HR: 1.42; 95% CI: 1.06-1.90, p=0.019). None of the studies in this meta-analysis showed significant benefit of allogeneic HSCT for patients who did not have high-risk disease, nor did the meta-analysis. However, the individual studies were relatively small, the treatment results were not always comparable, and the definitions of high-risk disease features varied across all studies.

An evidence-based systematic review sponsored by the ASBMT in 2006 addressed the issue of HSCT in adults with ALL. (22) Based on its review of evidence available through January 2005, the ASBMT panel recommended HSCT as consolidation therapy for adults with high-risk disease in CR1 but not for standard-risk patients. It also recommended HSCT for patients in CR2, although evidence is not available to directly compare outcomes with alternatives. Based on results from 3 RCTs, (23-25) the ASBMT panel further concluded that myeloablative allogeneic HSCT is superior to autologous HSCT in adult patients in CR1, although available evidence did not permit separate analyses in high-risk versus low-risk patients.

A meta-analysis from the Cochrane group in 2011 evaluated the evidence for the efficacy of matched sibling stem-cell donor versus no donor status for adults with ALL in CR1. (26) A total of 14 trials with treatment assignment based on genetic randomization including a total of 3,157 patients were included in this analysis. Matched sibling donor HSCT was associated with a statistically significant overall survival advantage compared to the no donor group (HR: 0.82; 95% CI: 0.77-0.97, p=0.01). Patients in the donor group had a significantly lower rate of primary disease relapse than those without a donor (risk ratio [RR]: 0.53; 95% CI: 0.37-0.76, p=0.0004) and significantly increased nonrelapse mortality (RR: 2.8; 95% CI: 1.66-4.73, p=0.001). These results support the conclusions of this policy, that allogeneic HSCT (matched sibling donor) is an effective postremission therapy in adult patients.

In 2012, the ASBMT published an update to the 2006 guidelines for treatment of ALL in adults. (27) An electronic search of the literature extended to mid-October 2010. The evidence available at that time supported a grade A treatment recommendation (at least 1 meta-analysis, systematic review, or RCT) that myeloablative allogeneic HSCT is an appropriate treatment for adult ALL in CR1 for all risk groups. Further, the ASBMT panel indicated a grade A treatment recommendation for autologous HSCT in patients who do not have a suitable allogeneic stem-cell donor; they suggested that although survival outcomes appear similar between autologous HSCT and postremission chemotherapy, the shorter treatment duration with the former is an advantage. Finally, the ASBMT panel concluded that allogeneic HSCT is recommended over chemotherapy for adults with ALL in CR2 or beyond.

An individual patient data meta-analysis published in 2013 included 13 studies (total N = 2962), several of which are compiled in this Policy. The results suggest that a matched sibling donor myeloablative HSCT improves survival only for younger adults (<35 years old) in CR1 compared to chemotherapy,
with an absolute benefit of 10% at 5 years. (28) The analysis also suggests a trend toward inferior overall survival among autologous HSCT recipients compared to chemotherapy in CR1 (OR = 1.18; 95% CI, 0.99-1.41, p = 0.06), primarily due to higher TRM in the autograft patients compared to chemotherapy recipients. This result does not change the conclusions of this Policy but indicates further study is needed to determine the optimal therapy for adult ALL patients.

**Summary: Adult ALL**

Current evidence indicates post-remission myeloablative autologous or allogeneic HSCT is an effective therapeutic option for a large proportion of adults with ALL in CR1. However, the increased morbidity and mortality from GVHD limit use of allogeneic HSCT, particularly for older patients. For adults who survive the procedure, there is a significant relapse rate. Notwithstanding those caveats, taken together, current evidence and clinical guidelines support the use of autologous HSCT for adult patients with high-risk ALL in CR1, or myeloablative allogeneic HSCT for adult patients with any risk level ALL, whose health status is sufficient to tolerate the procedure (see Considerations).

**Reduced-Intensity Conditioning (RIC) Allogeneic HSCT**

The use of RIC regimens has been investigated as a means to extend the substantial GVL effect of postremission allogeneic HSCT to patients who could expect to benefit from this approach but who are ineligible or would not be able to tolerate a fully myeloablative procedure. In a multicenter single-arm study of patients (n=43, median age 19 years; range: 1–55 years) in CR2, a 3-year OS rate of 30% was achieved, with 100-day and NRM rates of 15% and 21%, respectively. Despite achievement of complete donor chimerism in 100% of the patients, 28 (65%) had leukemic relapse, with 67% ultimately succumbing to their disease. (29)

A registry-based study included 97 adult patients (median age 38 years, range 17–65 years) who underwent RIC and allogeneic HSCT to treat ALL in CR1 (n=28), beyond CR1 (CR2/CR3, n=26/5) and advanced or refractory disease (n=39). (30) With median follow-up of approximately 3 years, in the overall population 2-year OS was 31%, with NRM of 28% and relapse rate of 51%. In patients transplanted in CR1, OS was 52%; in CR2/CR3, it was 27%; in patients with advanced or refractory ALL, OS was 20%. This evidence suggests RIC and allogeneic HSCT have some efficacy as salvage therapy in high-risk ALL.

RIC for allogeneic HSCT was investigated in a prospective Phase II study that included 37 consecutive adults (median age 45 years, range: 15-63 years) with high-risk ALL (43% Ph-positive, 43% high white blood cell [WBC]) in CR1 (81%) or CR2 (19%) who were ineligible to receive a myeloablative allogeneic HSCT because of age, organ dysfunction, low Karnofsky performance status (<50%) or the presence of infection. (31) Patients received stem cells from a matched sibling (n=27) or matched unrelated donor (n=10). Postremission RIC conditioning consisted of fludarabine and melphalan, with graft-versus-host disease (GVHD) prophylaxis (cyclosporine or tacrolimus, plus methotrexate). All Ph-positive patients also received imatinib prior to HSCT. The 3-year cumulative incidence of relapse was 19.7% ± 6.9%; that of NRM was 17.7% ± 6.9%. The 3-year cumulative OS rate was 64.1% ± 8.6%, with DFS rate of 62.6% ± 8.5% at the same point. After a median follow-up of 36 months (range 121-96 months), 25 (67.6%) of patients remained alive, 24 (96%) of whom remained in continuous CR.

A multicenter prospective study published in 2010 involved 47 pediatric patients (median age 11 years, range: 2-20 years) with hematologic cancers, including ALL (n=17), who underwent allogeneic HSCT with a fludarabine-based RIC regimen. (32) It represents the first large cooperative group study to be published in this setting. Among the 17 cases, 4 were in CR2, 12 in CR3, and 1 had secondary ALL. All patients were heavily pretreated, including previous myeloablative allogeneic or autologous HSCT, but these were not individually reported. While most data were presented in aggregate, some survival findings were specified, showing EFS of 35% and OS of 37% at 2-year follow-up for the ALL patients. Although most patients lived only a few months after relapse or rejection, some were long-term survivors after further salvage treatment. Among those, 1 ALL patient received chemotherapy and
donor lymphocyte infusion (DLI) for low chimerism and relapse and was reported alive 1 year following DLI and 3 years from HSCT. A second ALL case, who rejected an initial mismatched-related donor graft, underwent a second RIC regimen using the same donor and was alive with moderate chronic GVHD more than 3 years after HSCT. Treatment-related mortality was not reported by disease, nor were HSCT-related morbidities. However, this evidence suggests allogeneic HSCT with RIC can be used in children with high-risk ALL and achieve some long-term survival in patients with no therapeutic recourse.

**Summary: RIC Allogeneic HSCT**

Based on currently available evidence and clinical input as noted in the following section, RIC allogeneic HSCT may be considered medically necessary in patients who demonstrate complete marrow and extramedullary first or second remission, could be expected to benefit from a myeloablative allogeneic HSCT, and who, for medical reasons, would be unable to tolerate a myeloablative conditioning regimen. Additional evidence is necessary to determine whether some patients with ALL and residual disease may benefit from RIC allogeneic HSCT.

**Allogeneic Transplant after Prior Failed Autologous Transplant**

A 2000 TEC Assessment focused on allogeneic HSCT after a prior failed autologous HSCT, in the treatment of a variety of malignancies, including ALL. (33) The TEC Assessment found that evidence was inadequate to permit conclusions about outcomes of this treatment strategy. Published evidence was limited to small, uncontrolled clinical series with short follow-up. Updated literature searches have not identified strong evidence to permit conclusions on this use of HSCT.

**Overall Summary**

Clinical study results summarized above suggest that while OS and EFS are not significantly different after autologous HSCT compared to conventional-dose chemotherapy in most children with standard risk ALL, HSCT remains a therapeutic option for patients considered at high risk of relapse. This conclusion is further supported by an evidence-based systematic review of the literature sponsored by the ASBMT. It has been recommended that patients should be selected for this treatment using risk-directed strategies.

Evidence indicates post-remission myeloablative allogeneic HSCT is an effective therapeutic option for a large proportion of adults with ALL. However, the increased morbidity and mortality from GVHD limit its use, particularly for older patients. Further, for adults who survive the procedure, there is a significant relapse rate. Notwithstanding those caveats, taken together, current evidence supports the use of myeloablative allogeneic HSCT for patients with ALL in CR1 whose health status is sufficient to tolerate the procedure.

RIC allogeneic HSCT may be considered medically necessary in patients who demonstrate complete marrow and extramedullary first or second remission, and who could be expected to benefit from a myeloablative allogeneic HSCT, but for medical reasons would be unable to tolerate a myeloablative conditioning regimen. Additional evidence is necessary to determine whether some patients with ALL and residual disease may benefit from RIC allogeneic HSCT.

Strong evidence is unavailable to permit conclusions on the use of allogeneic HSCT following failure of an autologous HSCT and clinical trials are unlikely. However, allogeneic HSCT after failed autologous HSCT has been shown to be of clinical benefit in other hematologic malignancies and is potentially curative. In addition, clinical input supports this use, particularly with RIC regimens, in adults or children. Therefore, an allogeneic HSCT after a prior failed autologous HSCT may be considered medically necessary.

**Clinical Input Received through Physician Specialty Societies and Academic Medical Centers**
In response to requests, input was received from 1 physician specialty society (2 reviewers) and 2 academic medical centers while this policy was under review in 2008. While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted. There was strong consensus among reviewers that reduced-intensity conditioning allogeneic HSCT was of value in patients who were in complete remission. With this exception, there was general support for the policy statements.

In 2013, input was received from two academic medical centers, one medical society, and three physicians from Blue Distinction Centers. In general, clinical input supported most existing policy statements. However, most reviewers disagreed that allogeneic HSCT is considered investigational to treat relapsing ALL after a prior autologous HSCT in either children or adults. Given a scarcity of evidence on this topic, with no substantial trials likely to be forthcoming, and that RIC allogeneic HSCT is considered medically necessary to treat ALL in second or greater remission or relapsed or refractory ALL, the policy statements were revised to medical necessity for this indication in children and adults.

**National Comprehensive Cancer Network Guidelines**

The latest National Comprehensive Cancer Network clinical practice guidelines for acute lymphoblastic leukemia indicate allogeneic HSCT is appropriate for consolidation treatment of most poor-risk (e.g., Ph1+, relapsed or refractory) patients with ALL. (34) These guidelines are silent on the use of autologous HSCT, but are otherwise generally consistent with this policy. However, the NCCN guidelines now stratify treatment according to the categories adolescent and young adult (age 15-39 years) and adult (age 40 or more years), rather than in more traditional children (18 years or younger) and adult categories (18 or more years).

**National Cancer Institute Clinical Trials Database (PDQ®)**

A search of the NCI PDQ database in late April 2014 identified 18 active Phase II/III trials that involve stem-cell support for adult patients with ALL (Available online at: http://www.cancer.gov/clinicaltrials/search/results?protocolsearchid=7147167 ).

Fifteen trials were identified for pediatric ALL (Available online at: http://www.cancer.gov/clinicaltrials/search/results?protocolsearchid=9873567 ).

**References**


33. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Salvage high-dose chemotherapy with allogeneic stem-cell support for relapse or incomplete remission following high-dose chemotherapy with autologous stem-cell transplantation for hematologic malignancies. TEC Assessments 2000; Volume 15, Tab 9.


**Billing Coding/Physician Documentation Information**

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<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>38204</td>
<td>Management of recipient hematopoietic progenitor cell donor search and cell acquisition</td>
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<tr>
<td>38205</td>
<td>Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogenic</td>
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<td>38206</td>
<td>Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous</td>
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<td>38208</td>
<td>Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing</td>
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<tr>
<td>38209</td>
<td>Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing</td>
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<td>38210</td>
<td>Transplant preparation of hematopoietic progenitor cells; specific cell depletion within harvest, T-cell depletion</td>
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<td>38211</td>
<td>Transplant preparation of hematopoietic progenitor cells; tumor cell depletion</td>
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<td>38212</td>
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<td>Transplant preparation of hematopoietic progenitor cells; plasma (volume) depletion</td>
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86812  HLA typing; A, B, or C, single antigen
86813  HLA typing; A, B, or C, multiple antigens
86816  HLA typing; DR/DQ single antigen
86817  HLA typing; DR/DQ multiple antigens
86821  HLA typing; lymphocyte culture, mixed (MLC)
86822  HLA typing; lymphocyte culture, primed (PLC)
Q0083  Chemotherapy administration by other than infusion technique only (e.g., subcutaneous, intramuscular, push), per visit
Q0084  Chemotherapy administration by infusion technique only, per visit
Q0085  Chemotherapy administration by both infusion technique and other technique(s) (e.g., subcutaneous, intramuscular, push), per visit
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 28 days of post-transplant care (including drugs; hospitalization; medical surgical, diagnosis and emergency services)

Additional Policy Key Words
N/A

Policy Implementation/Update Information

<table>
<thead>
<tr>
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<th>Description</th>
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<td>New policy.</td>
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<tr>
<td>8/1/03</td>
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<td>7/1/04</td>
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<tr>
<td>4/1/06</td>
<td>Considerations section revised to include general criteria.</td>
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<td>7/1/07</td>
<td>No policy statement changes. References updated.</td>
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<td>No policy statement changes.</td>
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<td>12/11/08</td>
<td>Interim update. Policy statement added that RIC allogeneic SCT may be considered medically necessary in select patients in complete remission. Policy title changed to state “Acute Lymphoblastic Leukemia.”</td>
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<td>7/1/09</td>
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<td>Policy statement regarding treatment of adult ALL in first complete remission but at high risk of relapse split to address allogeneic and autologous transplant separately, but there was no change in the intent of the policy.</td>
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<td>7/1/13</td>
<td>Revised policy statements that allogeneic HSCT may be considered medically necessary following a failed autologous HSCT in children or adult patients.</td>
</tr>
<tr>
<td>7/1/14</td>
<td>No policy statement changes.</td>
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