Hematopoietic Cell Transplantation for Acute Lymphoblastic Leukemia

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Section: Transplants
Place(s) of Service: Outpatient; Inpatient

Precertification is required for this service.

I. Description

Acute lymphoblastic leukemia (ALL) is a heterogeneous disease with different genetic alterations 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). The evidence for autologous or allogeneic HCT in individuals who have childhood ALL in first complete remission but at high risk of relapse, or in second or greater remission, or with refractory ALL, includes randomized controlled trials (RCTs) and an evidence-based systematic review. Relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. Studies suggest that while overall survival did not differ significantly after HCT compared with conventional-dose chemotherapy in most children with standard-risk ALL, HCT 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 American Society for Blood and Marrow Transplantation.

The evidence for autologous or allogenic HCT in individuals, who have adult ALL in first complete remission but at high risk of relapse, or in second or greater remission, or with refractory ALL, includes RCTs and an evidence-based systematic review. Relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. Current evidence and clinical guidelines support the use of autologous HCT for adult patients with high-risk ALL in first complete remission (CR1), or myeloablative allogenic HCT for adult patients with any risk level ALL, whose health status is sufficient to tolerate the procedure. Reduced-intensity conditioning (RIC) allogenic 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 allogenic HCT, but for medical reasons would not tolerate a myeloablative...
conditioning regimen. Additional evidence is necessary to determine whether some patients with ALL and residual disease may benefit from RIC allogenic HCT.

The evidence for the use of allogenic HCT individuals who have relapse after a prior autologous HCT is lacking. Relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. Allogenic 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 supports this use, particularly with RIC regimens, in adults or children.

**Background**

Immunologic compatibility between infused hematopoietic cells and the recipient is not an issue in autologous HCT. However, immunologic compatibility between donor and patient is a critical factor for achieving a good outcome with allogeneic HCT. Compatibility is established by typing of human leukocyte antigen (HLA) using cellular, serologic, or molecular techniques. HLA refers to the tissue type expressed at the HLA A, B, and DR (antigen-D related) 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 (with exception of umbilical cord blood).

**Conventional Preparative Conditioning 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. As a consequence, autologous HCT is typically performed as consolidation therapy when the patient’s disease is in complete remission (CR). Patients who undergo autologous HCT are susceptible to chemotherapy-related toxicities and opportunistic infections before engraftment, but not graft-versus-host disease (GVHD).

The conventional (“classical”) practice of allogeneic 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 pre-engraftment opportunistic infections secondary to loss of endogenous bone marrow function and organ damage and failure caused by the cytotoxic drugs. Furthermore, in any allogeneic HCT, immune suppressant drugs are required to minimize graft rejection and GVHD, which also increases susceptibility of the patient to opportunistic infections.

**Reduced-Intensity Conditioning for Allogeneic HCT**

Reduced-intensity conditioning (RIC) refers to the pretransplant use of lower doses or less intense regimens of cytotoxic drugs or radiation than are used in conventional full-dose myeloablative
conditioning treatments. The goal of RIC is to reduce disease burden 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 allogeneic HCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism, which may be supplemented with donor lymphocyte infusions to eradicate residual malignant cells. For this evidence review, RIC will refer to all conditioning regimens intended to be nonmyeloablative, as opposed to fully myeloablative (conventional) regimens.

**Acute Lymphoblastic Leukemia (ALL)**

**Childhood ALL**

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) CR 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 with only 10% to 15% for those who relapse less than 3 years after treatment. Thus, 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 alterations 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 (WBC) at diagnosis. (3) Certain genetic characteristics of leukemic cells strongly influence prognosis. Clinical and biologic factors predicting clinical outcomes and relapse risk are summarized as follows:

<table>
<thead>
<tr>
<th>PROGNOSTIC 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>
</tbody>
</table>
Hematopoietic Cell Transplantation for Acute Lymphoblastic Leukemia

**Adult ALL**

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 35–40% 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 the outcome differences between the 2 groups. For example, the “good prognosis” genetic abnormalities such as 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 such as the Philadelphia chromosome (t[9;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).

**II. Policy**

**A. Childhood ALL**

1. **Autologous or allogeneic hematopoietic cell transplantation (HCT)** is covered (subject to Administrative Guidelines) to treat childhood acute lymphoblastic leukemia (ALL) in first complete remission but at high risk of relapse. (For definition of high-risk factors, see Policy Guidelines).

2. **Autologous or allogeneic HCT** is covered (subject to Administrative Guidelines) to treat childhood ALL in second or greater remission or refractory ALL.

3. **Allogeneic HCT** is covered (subject to Administrative Guidelines) to treat relapsing ALL after a prior autologous HCT in children.

**B. Adult ALL**

1. **Autologous HCT** is covered (subject to Administrative Guidelines) to treat adult ALL in first complete remission but at high risk of relapse. (For definition of high-risk factors, see Policy Guidelines).

2. **Allogeneic HCT** is covered (subject to Administrative Guidelines) to treat adult ALL in first complete remission for any risk level. (For definition of risk factors, see Policy Guidelines).

3. **Allogeneic HCT** is covered (subject to Administrative Guidelines) to treat adult ALL in second or greater remission, or in adults with relapsed or refractory ALL.

4. **Allogeneic HCT** is covered to treat relapsing adult ALL after a prior autologous HCT.

5. **Reduced-intensity conditioning allogeneic HCT** is covered (subject to Administrative Guidelines) as a treatment of ALL in patients who are in complete marrow and extramedullary first or second remission, and who, for medical reasons (see Policy Guidelines), would be unable to tolerate a standard myeloablative conditioning regimen.

| Immunophenotype | Common, preB | ProB, T-lineage |
III. Policy Guidelines

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, 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 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 >30,000/µL (B cell lineage) or >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 HCT could be curative may be considered candidates for RIC allogeneic HCT. Such patients include those whose age (typically >60 years) or comorbidities (eg, liver or kidney dysfunction, generalized debilitation, prior intensive chemotherapy including autologous or allogeneic HCT, 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 (antigen-D related) loci (on each arm of chromosome 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.

IV. Limitations

A. Autologous HCT is not covered to treat adult ALL in second or greater remission or those with refractory disease as it is not known to be effective in improving health outcomes.
V. Administrative Guidelines

A. Precertification is required for a transplant evaluation and for the transplant itself and should be submitted by the proposed treating facility. To precertify, please complete HMSA’s Precertification Request and mail or fax the form as indicated along with the required documentation.

<table>
<thead>
<tr>
<th>CPT Codes</th>
<th>Description</th>
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<tbody>
<tr>
<td>38204</td>
<td>Management of recipient hematopoietic cell donor search and cell acquisition</td>
</tr>
<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>38208</td>
<td>Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing, per donor</td>
</tr>
<tr>
<td>38209</td>
<td>Thawing of previously frozen harvest with washing, per donor</td>
</tr>
<tr>
<td>38210</td>
<td>Specific cell depletion with harvest, T cell depletion</td>
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<tr>
<td>38211</td>
<td>Tumor cell depletion</td>
</tr>
<tr>
<td>38212</td>
<td>Red blood cell removal</td>
</tr>
<tr>
<td>38213</td>
<td>Platelet depletion</td>
</tr>
<tr>
<td>38214</td>
<td>Plasma (volume) depletion</td>
</tr>
<tr>
<td>38215</td>
<td>Cell concentration in plasma, mononuclear, or buffy coat layer</td>
</tr>
<tr>
<td>38220</td>
<td>Bone marrow; aspiration only</td>
</tr>
<tr>
<td>38221</td>
<td>Bone marrow; biopsy, needle or trocar</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>
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<table>
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<tr>
<th>HCPCS Code</th>
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<tr>
<td>Q0083 - Q0085</td>
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<td>J9000 - J9999</td>
<td>Chemotherapy drugs code range</td>
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<td>Code</td>
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<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>
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**ICD-10-CM** | **Description** |
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<tr>
<td>C91.00-C91.02</td>
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**ICD-10-PCS** | **Description** |
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<td>Administration, circulatory, transfusion, peripheral artery, percutaneous, autologous, code by substance (bone marrow, cord blood or stem cells, hematopoietic)</td>
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<tr>
<td>6A551ZT, 6A551ZV</td>
<td>Extracorporeal Therapies, pheresis, circulatory, multiple, code by substance (cord blood, or stem cells, hematopoietic)</td>
</tr>
</tbody>
</table>

### VI. Scientific Background

This evidence review has been updated periodically with a search of the MEDLINE and EMBASE databases most recently through October 28, 2015.

**Childhood ALL**

The evidence review on childhood ALL was initially based on TEC Assessments completed in 1987 and 1990.\(^5\)\(^6\) In childhood ALL, conventional chemotherapy is associated with complete remission (CR) rates of approximately 95%, with long-term durable remissions up to 85%. Therefore, for patients in a CR1) hematopoietic cell transplantation (HCT) is considered only for those with unfavorable risk factors predictive of relapse (see Table 1).
Three randomized controlled trials (RCTs) that compared outcomes of HCT with outcomes with conventional-dose chemotherapy in children with ALL were identified subsequent to the TEC Assessment. The children enrolled in these RCTs were being treated for high-risk ALL in CR1 or for relapsed ALL. These trials reported that overall outcomes after HCT were generally equivalent to overall outcomes after conventional-dose chemotherapy. While HCT administered in CR1 was associated with fewer relapses than conventional-dose chemotherapy, it was also associated with more frequent deaths in remission (ie, from treatment-related toxicity).

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

HCT remains a therapeutic option to manage childhood ALL, especially patients at high risk of relapse or following relapse. This conclusion is supported by a 2012 evidence-based review of the literature sponsored by the American Society for Blood and Marrow Transplantation (ASBMT). Other investigators have recommended that patients be selected for this treatment using risk-directed strategies.

Summary: Childhood ALL

Evidence and reviews of trials have suggested that, while OS and event-free survival (EFS) did not differ significantly between HCT and conventional-dose chemotherapy, HCT remains a therapeutic option to manage childhood ALL, especially patients at high risk of relapse or following relapse.

Adult ALL

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

- For patients in CR1, available evidence suggested survival was equivalent after autologous HCT or conventional-dose chemotherapy. For these patients, the decision between autologous HCT 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 HCT compared with 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. Among 183 high-risk patients in CR1, those with a human leukocyte antigen (HLA)-identical family donor were assigned to allogeneic HCT (n=84); the remaining cases were
randomly assigned to autologous HCT (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 before HCT; 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 HCT arm.

While the utility of allogeneic HCT 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). The ECOG 2993 trial was a Phase III randomized study designed to prospectively define the role of myeloablative allogeneic HCT, autologous HCT, 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=1913) 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 HCT. Patients with the Philadelphia (Ph) chromosome (n=267) who did not have a matched sibling donor could receive an unrelated donor HCT. 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 HCT or consolidation and maintenance chemotherapy.

In ECOG2993, OS at 5-year follow-up of all 1913 patients was 39%; it reached 53% for Ph-negative patients with a donor (n=443) compared with 45% without a donor (n=588) (p=0.01). 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-year 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 HCT, the relapse rate was 24% at 10 years compared with 49% among those who did not undergo HCT (p<0.00005). Among Ph-negative patients with high-risk ALL, the rate of relapse at 10-year follow-up was 37% following allogeneic HCT 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 HCT 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 graft-versus-host-disease (GVHD) and infections. At 2 years, NRM was 36% among high-risk patients with a donor compared with 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 HCT versus 7% in those who received autologous HCT 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% to 46%) for those who had a matched sibling donor versus 25% (95% CI, 12% to 34%) with no donor who received consolidation and maintenance chemotherapy. Although the difference in survival rates was not statistically significant, this analysis demonstrated a moderate superiority of postremission-matched sibling allogeneic HCT 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 HCT was consistently used for all patients who achieved CR1 and who had an HLA-matched sibling donor, irrespective of risk category. A total 433 eligible patients included 288 younger than 55 years, in CR1, and eligible to receive consolidation treatment by an autologous HCT or an allogeneic HCT. Allogeneic HCT was performed in 91 of 96 (95%) with a compatible sibling donor. OS 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 with 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 before 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 HCT in CR1, provided the NRM risk is less than approximately 20% to 25%.

Systematic Reviews and Meta-Analyses

A meta-analysis published in 2006 pooled evidence from 7 studies of allogeneic HCT published between 1994 and 2005 that included a total of 1274 patients with ALL in CR1. The results showed that regardless of risk category, allogeneic HCT was associated with a significantly longer OS (hazard ratio [HR]=1.29; 95% confidence interval [CI], 1.02 to 1.63, p=0.037) for all patients who had a suitable donor versus patients without a donor who received chemotherapy or autologous HCT. Pooled evidence from patients with high-risk disease showed an increased survival advantage for allogeneic HCT compared to those without a donor (HR=1.42; 95% CI, 1.06 to 1.90, p=0.019). 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 American Society for Blood and Marrow Transplantation (ASBMT) in 2006 addressed the issue of HCT in adults with ALL.\textsuperscript{18} Based on its review of evidence through January 2005, the ASBMT panel recommended HCT as consolidation therapy for adults with high-risk disease in CR1 but not for standard-risk patients. It also recommended HCT for patients in CR2, even though evidence did not include any direct comparisons with alternatives. Based on results from 3 RCTs,\textsuperscript{19-21} the ASBMT panel further concluded that myeloablative allogeneic HCT is superior to autologous HCT 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.\textsuperscript{22} Fourteen trials with treatment assignment based on genetic randomization (total N=3157 patients) were included. Matched sibling donor HCT was associated with a statistically significant OS advantage compared with the no donor group (HR=0.82; 95% CI, 0.77 to 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 to 0.76, \( p < 0.001 \)) and significantly increased nonrelapse mortality (NRM; RR=2.8; 95% CI, 1.66 to 4.73; \( p = 0.001 \)). These results support the conclusions of this evidence review that allogeneic HCT (matched sibling donor) is an effective postremission therapy in adult patients.

In 2012, ASBMT updated its 2005 guidelines for treatment of ALL in adults covering literature to mid-October 2010.\textsuperscript{13} The evidence available at that time supported a grade A treatment recommendation (at least 1 meta-analysis, systematic review, or RCT) that myeloablative allogeneic HCT 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 HCT in patients who do not have a suitable allogeneic stem-cell donor; ASBMT suggested that although survival outcomes appear similar between autologous HCT and postremission chemotherapy, the shorter treatment duration with the former is an advantage. Finally, the ASBMT panel concluded that allogeneic HCT is recommended over chemotherapy for adults with ALL in CR2 or beyond.

A meta-analysis of individual patient data published in 2013 included 13 studies (total N=2962), several of which are compiled in this evidence review.\textsuperscript{23} The results suggested that matched sibling donor myeloablative HCT improves survival only for younger adults (<35 years-old) in CR1 compared with chemotherapy, with an absolute benefit of 10% at 5 years. The analysis also suggested a trend toward inferior OS among autologous HCT recipients compared to chemotherapy in CR1 (odds ratio [OR], 1.18; 95% CI, 0.99 to 1.41, \( p = 0.06 \)), primarily due to higher transplant-related mortality (TRM) in the autograft patients than in chemotherapy recipients. This result does not change the conclusions of this evidence review but indicates further study is needed to determine the optimal therapy for adult ALL patients.

Summary: Adult ALL

Current evidence indicates postremission myeloablative autologous or allogeneic HCT 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 HCT, particularly for older patients. For adults who survive HCT, there is a significant relapse rate. Notwithstanding those caveats, taken together, current evidence and clinical guidelines support the use of autologous HCT
for adult patients with high-risk ALL in CR1, or myeloablative allogeneic HCT for adult patients with any risk level ALL, whose health status is sufficient to tolerate the procedure.

Reduced-Intensity Conditioning (RIC) Allogeneic HCT

The use of reduced-intensity conditioning (RIC) regimens has been investigated as a means to extend the substantial GVL effect of postremission allogeneic HCT to patients who could expect to benefit from this approach but who are ineligible or would not tolerate a fully myeloablative procedure.

A 2014 meta-analysis included data from 5 studies in which RIC conditioning (n=528) was compared with myeloablative conditioning regimens (n=2489) in adult patients with ALL who received allogenic HCT mostly in CR1.28 This analysis of data from nonrandomized studies suggested progression-free survival at 1 to 6 years is significantly lower after RIC conditioning (36%) compared to myeloablative conditioning (41%; OR=0.76; 95% CI, 0.61 to 0.93; p<0.01). However, this was probably offset by the significantly lower NRM in the RIC group than in the myeloablative group (OR=0.76; 95% CI, 0.61 to 0.95), resulting in similar OS (OR=1.03; 95% CI, 0.84 to 1.26; p=0.76). Use of RIC also was associated with lower rates of GVHD but higher rates of relapse compared with myeloablative conditioning (OR=1.77; 95% CI, 1.45 to 2.71; p<0.000).

A multicenter, single-arm study of patients (N=43; median age 19 years; range, 1–55 years) in CR2 reported a 3-year OS rate of 30%, with 100-day mortality and NRM rates of 15% and 21%, respectively. Despite achievement of complete donor chimerism in 100% of 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 HCT to treat ALL in CR1 (n=28), in CR2 and CR3 (n=26/5), and advanced or refractory disease (n=39). (30) With median follow-up of nearly 3 years, in the overall population, 2-year OS was 31%, with an NRM rate of 28% and a relapse rate of 51%. In patients with HCT in CR1, OS was 52%; in CR2 and CR3,OS was 27%; in patients with advanced or refractory ALL, OS was 20%. This evidence suggests RIC and allogeneic HCT have some efficacy as salvage therapy in high-risk ALL.

RIC for allogeneic HCT was investigated in a prospective phase 2 study of 37 consecutive adults (median age, 45 years; range, 15-63 years) with high-risk ALL (43% Ph-positive, 43% high white blood cell) in CR1 (81%) or CR2 (19%) who were ineligible for myeloablative allogeneic HCT 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 consisted of fludarabine and melphalan, with GVHD prophylaxis (cyclosporine or tacrolimus, plus methotrexate). All Ph-positive patients also received imatinib before HCT. The 3-year cumulative incidence of relapse was 19.7% ± 6.9%; the NRM rate 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 were alive, 24 (96%) of whom remained in CR.

A 2009 multicenter prospective study involved 47 pediatric patients (median age, 11 years; range, 2-20 years) with hematologic cancers, including ALL (n=17), who underwent allogeneic HCT with a fludarabine-based RIC regimen.32 (It represents the first large cooperative group study to be
Among the 17 ALL cases, 4 were in CR2, 12 in CR3, and 1 had secondary ALL. All patients were heavily pretreated, which included previous myeloablative allogeneic or autologous HCT, but these treatments were not individually reported. While most data were 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, who received chemotherapy and donor lymphocyte infusion (DLI) for low chimerism and relapse, was reported alive 1 year following DLI and 3 years from HCT. 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 HCT. Neither transplant-related mortality nor HCT-related morbidities were reported by disease. However, this evidence suggests allogeneic HCT with RIC can be used in children with high-risk ALL and can facilitate long-term survival in patients with no therapeutic recourse.

Summary: RIC Allogeneic HCT

Based on currently available evidence and clinical input as noted in the Supplemental Information section, RIC allogeneic HCT may benefit patients who demonstrate complete marrow and extramedullary CR1 or CR2, could be expected to benefit from a myeloablative allogeneic HCT, 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 HCT.

Allogeneic Transplant after Failed Autologous Transplant

A 2000 TEC Assessment focused on allogeneic HCT, after a failed autologous HCT, in the treatment of a variety of malignancies, including ALL. 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 HCT.

Clinical Input Received through Physician Specialty Societies and Academic Medical Centers

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.

In 2013, input was received from 2 academic medical centers, 1 medical society, and 3 physicians from Blue Distinction Centers. In general, clinical input supported most existing policy statements. However, most reviewers disagreed that allogeneic HCT is considered investigational to treat relapsing ALL after a prior autologous HCT 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 HCT 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

National Comprehensive Cancer Network (NCCN) clinical practice guidelines for ALL indicate allogeneic HCT is appropriate for consolidation treatment of most poor risk (eg, Ph1+, relapsed or refractory) patients with ALL. These guidelines are silent on the use of autologous HCT, but are otherwise generally consistent with this evidence review. However, NCCN guidelines now stratify treatment by the categories of adolescent and young adult (age 15-39 years) and adult (≥ age 40 years), rather than by more traditional children (≤ 18 years) and adult categories (≥ 18 years).

VII. Important Reminder

The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii’s Patients’ Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4), generally accepted standards of medical practice and review of medical literature and government approval status. HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA’s determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

VIII. References


27. Cornelissen JJ, van der Holt B, Verhoef GE et al. Myeloablative allogeneic versus autologous stem cell transplantation in adult patients with acute lymphoblastic leukemia in first remission:


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.
