The following Protocol contains medical necessity criteria that apply for this service. It is applicable to Medicare Advantage products unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Preauthorization is required and must be obtained through Case Management. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient’s contract at the time the services are rendered.

Description

Hematopoietic stem-cell transplantation (HSCT) 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 HSCT) or from a donor (i.e., allogeneic HSCT). 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 graft-versus-host disease (GVHD).

Background

Immunologic compatibility between infused stem cells and the recipient is not an issue in autologous HSCT. However, immunologic compatibility between donor and patient is a critical factor for achieving a good outcome of allogeneic HSCT. 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, C, 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 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 HSCT 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 nonrelapse 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 Protocol, the term “reduced-intensity conditioning” 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 and 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 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 three 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>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>
<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 two 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 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 25–30% 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).

Policy (Formerly Corporate Medical Guideline)

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 Policy Guidelines.)

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 Policy Guidelines).

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

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 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 Policy Guidelines), would be unable to tolerate a standard myeloablative conditioning regimen.

Autologous HSCT is investigational to treat adult ALL in second or greater remission or those with refractory disease.

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

Policy Guideline

Relapse Risk Prognostic Factors

Childhood ALL

Adverse prognostic factors in children include the following: age less than one year or more than nine 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 prophase defined as an absolute blast count of 1000/µL or greater, or poor treatment response to induction therapy at six 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 four 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 older than 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 (six of six). 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 three of the six 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.

**Benefit Application**

Individual transplant facilities may have their own additional requirements or protocols that must be met in order for the patient to be eligible for a transplant at their facility.

**Medicare Advantage**

If a transplant is needed, we arrange to have the transplant center review and decide whether the patient is an appropriate candidate for the transplant.

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. Some of this Protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.
References

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.


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.