

Hematopoietic Cell Transplantation for Acute Lymphoblastic Leukemia

Effective: January 1, 2019

Next Review: October 2019

Last Review: December 2018

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Transplantation is performed to restore bone marrow function following bone-marrow-toxic doses of chemotherapy.

MEDICAL POLICY CRITERIA

Note: See Appendix I for a glossary of terms.

- I. In **children**, autologous hematopoietic cell transplantation may be considered **medically necessary** to treat any of the following:
 - A. Childhood acute lymphoblastic leukemia (ALL) in first complete remission but at high risk of relapse. (For definition of high-risk factors, see Policy Guidelines)
 - B. Childhood ALL in second or greater remission.
 - C. Refractory ALL.
- II. In **children**, allogeneic hematopoietic cell transplantation may be considered **medically necessary** to treat any of the following:

- A. Childhood acute lymphoblastic leukemia (ALL) in first complete remission but at high risk of relapse. (For definition of high-risk factors, see Policy Guidelines)
 - B. Childhood ALL in second or greater remission.
 - C. Refractory ALL.
 - D. Relapsing ALL after a prior autologous hematopoietic cell transplantation.
- III. Hematopoietic cell transplantation (autologous or allogeneic) is considered **investigational** for pediatric patients who do not meet the medical necessity criteria (I.A-C or II.A-D).
- IV. In **adults**, autologous hematopoietic cell transplantation may be considered **medically necessary** to treat adult acute lymphoblastic leukemia (ALL) in first complete remission but at high risk of relapse (for definition of high-risk factors, see Policy Guidelines).
- V. In **adults**, autologous hematopoietic cell transplantation is considered **investigational** for adult patients who do not meet the medical necessity criterion (IV), including but not limited to the following:
- A. Adult ALL in second or greater remission.
 - B. Refractory ALL.
- VI. In **adults**, allogeneic hematopoietic cell transplantation with myeloablative (conventional) conditioning may be considered **medically necessary** to treat adult patients with any of the following:
- A. ALL in first complete remission for any risk level (for definition of risk factors, see Policy Guidelines).
 - B. ALL in second or greater remissions.
 - C. Relapsed or refractory ALL.
 - D. Relapsing ALL after a prior autologous hematopoietic cell transplantation.
- VII. In **adults**, allogeneic hematopoietic cell transplantation is considered **investigational** for patients who do not meet the medical necessity criteria (VI.A-D).
- VIII. Reduced-intensity conditioning for allogeneic hematopoietic cell transplantation may be considered **medically necessary** as a treatment of ALL in patients who meet *both* of the following criteria:
- A. ALL is in complete marrow and extramedullary first or second remission; AND
 - B. For medical reasons (see Policy Guidelines), would be unable to tolerate a standard myeloablative conditioning regimen.
- IX. Allogeneic hematopoietic cell transplantation using reduced-intensity conditioning is considered **investigational** for patients who do not meet the medical necessity criteria (VIII.A-B).

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

SUBMISSION OF DOCUMENTATION

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and Physical/Chart Notes
- Diagnosis and indication for transplant
- Documentation of Relapse Risk Prognostic Factors
- For patients with a reduced-intensity conditioning (RIC) regimen, documentation supporting reasons patient is unable to tolerate a myeloablative conditioning regimen.

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/ μ L
- 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:

- Poor response to initial therapy including:
 - Poor response to prednisone prophase defined as an absolute blast count of 1,000/ μ L or greater, or
 - Poor treatment response to induction therapy at 6 weeks with high risk having $\geq 1\%$ minimal residual disease measured by flow cytometry)
- All children with T-cell phenotype,
- 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 $>30,000/\mu$ L (B-cell lineage) and $>100,000/\mu$ L (T-cell lineage),
- “Poor prognosis” genetic abnormalities like the Philadelphia chromosome (t(9;22)),
- Extramedullary disease
- Time to attain complete remission longer than 4 weeks (American Society of Hematology Education Program Handbook, 2007).

REDUCED-INTENSITY CONDITIONING (RIC)

Some patients for whom a conventional myeloablative allogeneic hematopoietic cell transplantation (HCT) could be curative may be considered candidates for RIC allogeneic HCT. These include those whose age (typically older than 60 years) or comorbidities (e.g., liver or kidney dysfunction, generalized debilitation, prior intensive chemotherapy, low Karnofsky Performance Status) preclude use of a standard myeloablative conditioning regimen.

Note: Unless otherwise specified in the text of this Policy, it is assumed that the term “allogeneic HCT” refers to the use of a myeloablative pretransplant 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 three of the six major histocompatibility antigens. The majority of patients will have such a donor; however, the risk of graft-versus-host-disease and overall morbidity of the procedure may be severe, and experience with these donors is not as extensive as that with matched donors.

CROSS REFERENCES

1. [Genetic Testing for Myeloid Neoplasms and Leukemia](#), Genetic Testing, Policy No. 59
2. [Donor Lymphocyte Infusion for Malignancies Treated with an Allogeneic Hematopoietic Cell Transplant](#), Transplant, Policy No. 45.03
3. [Placental and Umbilical Cord Blood as a Source of Stem Cells](#), Transplant, Policy No. 45.16

BACKGROUND

Hematopoietic cell transplantation (HCT, previously referred to in this policy as a hematopoietic stem cell transplant [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. Hematopoietic cells may be obtained from the transplant recipient (i.e., autologous HCT) or from a donor (i.e., allogeneic HCT). 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).

Immunologic compatibility between infused stem 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 of allogeneic HCT. 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 SCT

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

The conventional ("classical") practice of allogeneic HCT 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 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, 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 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 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]

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.^[2] Certain genetic characteristics of the leukemic cells strongly influence prognosis. Clinical and biologic factors predicting clinical outcome can be summarized as follows:^[2]

FACTOR	FAVORABLE	UNFAVORABLE
Age at diagnosis	1-9 years	<1 or >9 years
Sex	Female	Male
WBC count	<50,000/ μ L	\geq 50,000/ μ L
Genotype	Hyperdiploidy (>50 chromosomes) t(12;21) or <i>TEL/AML1</i> fusion	Hypodiploidy (<45 chromosomes) t(9;22) or <i>BCR/ABL</i> fusion t(4;11) or <i>MLL/AF4</i> fusion
Immunophenotype	Common, preB	ProB, T-lineage

Adolescents and Young Adults (AYA) ALL

The age range for AYA varies across studies, but was defined by the National Cancer Institute as 15 to 39 years. AYA ALL patients are a unique population and may receive treatment based either on pediatric or adult protocols depending on local institutional practices.^[4] Cure rates for AYA ALL are less favorable than childhood ALL with 5-year event-free survival (EFS) ranging from 63%-74% for patients treated with pediatric protocols versus 34% to 49% for patients who receive an adult treatment protocol. Differences in the frequency of genetic abnormalities that characterize AYA ALL versus childhood ALL help in part to explain the survival differences between the two groups. For example, the “good prognosis” genetic abnormalities like hyperdiploidy and *TEL-AML1* gene fusion expressed from t(12;21) chromosome translocation are seen much less commonly in AYA ALL, whereas they are some of the most common in childhood ALL. Conversely, “poor prognosis” genetic abnormalities like ALL with *BCR-ABL* (the Philadelphia chromosome [Ph-positive or Ph+ ALL]; translocation t[9;22]) is higher in AYA ALL than in childhood ALL.

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.^[5] As with AYA ALL, favorable cytogenetic subtypes such as hyperdiploidy and t(12;21) are seen much less commonly in adult ALL than in childhood ALL while Ph-positive ALL is seen in 25%–30% of adult ALL but infrequently in childhood ALL (3%). 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/ μ L (B-cell lineage) and >100,000/ μ L (T-cell lineage).

EVIDENCE SUMMARY

CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)

Technology Assessments

The policy on childhood ALL was initially based on BlueCross BlueShield Association (BCBSA) Technology Evaluation Center (TEC) Assessments completed in 1987 and 1990.^[6,7] In childhood ALL, conventional chemotherapy is associated with complete remission rates of about 95%, with long-term durable remissions of 60%. Therefore, for patients in a first complete remission (CR1), hematopoietic cell transplantation (HCT) therapy is considered necessary only in those with risk factors predictive of relapse (see Description section).

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 with early relapse. Thus, HCT may be a strong consideration in those with short remissions. At present, the comparative outcomes with either autologous or allogeneic HCT are unknown.

Systematic Reviews

A 2012 updated systematic review was sponsored by the American Society for Blood and Marrow Transplantation (ASBMT) and included published literature through mid-October 2010 on HCT in children with ALL.^[8] The literature consisted mainly of retrospective reviews and also included three RCTs.^[9-11] In addition, most of the studies were conducted prior to the availability of tyrosine kinase inhibitors (TKIs) and newer chemotherapy drugs with improved event-free survival (EFS). Due to the limited evidence, the recommendations were based on consensus and expert opinion.

Randomized Controlled Trials

Three reports describing the results of RCTs that compared outcomes of HCT to outcomes with conventional-dose chemotherapy in children with ALL were identified subsequent to the TEC Assessment.^[12-14] 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 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 (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 or overall survival 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^[9]. Similar results were observed using either intention-to-treat (ITT) or per-protocol (PP) analyses. However, the authors pointed 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 HCT and time elapsed between 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 HCT arm.

Nonrandomized Studies

The bulk of the published data for childhood ALL consists of case series^[15-17] and retrospective reviews.^[18-24] While the subjects in these studies had some variation in age (i.e., infants, children, adolescents) and risk factors (e.g., Philadelphia chromosome-positive), the outcomes showed promising results for allogeneic HCT in patients in CR1 at high risk for recurrence,

following relapse and in patients in second or greater remission.

Section Summary

These results suggest that while overall and event-free survival are not significantly different after HCT compared to conventional-dose chemotherapy, HCT 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 the 2012 ASBMT systematic review summarized above. In addition, some investigators recommend that patients should be selected for this treatment using risk-directed strategies.^[17,25]

ADULT ALL

Systematic Reviews

Pidala published a Cochrane systematic review of randomized controlled trials comparing the effect of matched sibling donor vs. no donor status for adults with ALL in first complete remission (CR1).^[26] A total of 14 relevant trials were identified, consisting of a total of 3157 patients. Matched sibling donor allogeneic HCT was superior CR1 therapy in ALL patients aged 15 years or over for overall survival ($p=0.01$), disease-free survival ($p = 0.004$), and reduced relapse risk ($p=0.0004$). The authors cautioned that “these data are based on adult ALL treated with largely total body irradiation-based myeloablative conditioning and sibling donor transplantation and, therefore, cannot be generalized to pediatric ALL, alternative donors including HLA (human leukocyte antigen) mismatched or unrelated donors, or reduced toxicity or non-myeloablative conditioning regimens.

A 2012 evidence-based update of previous evidence reviews sponsored by the American Society for Blood and Marrow Transplantation (ASBMT)^[27,28] included published literature through mid-October 2010.^[29,30] Seven RCTs^[31-37] were included in the review. The ASBMT determined that the evidence supported the following grade A (at least 1 meta-analysis, systematic review, or RCT) conclusions and treatment recommendations:

- Myeloablative allogeneic HCT is an appropriate treatment for adult (<35 years) ALL in first complete remission for all disease risk groups. Allogeneic HCT provided a significant improvement in overall and leukemia-free survival in younger (<35 years), standard risk, Ph-negative ALL patients compared with less intensive chemotherapy regimens. Higher transplant-related mortality in adults over 35 years of age diminished the significant survival advantage.
- Reduced-intensity conditioning may produce similar outcomes to myeloablative regimens, but data were insufficient to make a recommendation. Therefore, reduced-intensity regimens were determined to be appropriate only in adults with ALL in remission who are unsuited for myeloablative conditioning.
- Allogeneic HCT is recommended over chemotherapy for adults with ALL in second complete remission or greater.
- Allogeneic is superior to autologous HCT, though there are insufficient data to determine if this is more apparent in disease risk subgroups including Ph+ ALL.
- There are similar survival outcomes after related and unrelated allogeneic HCT.
- In the absence of a suitable allogeneic donor, autologous HCT may be an appropriate therapy. Although survival outcomes appear similar between autologous HCT and post-remission chemotherapy, the shorter treatment duration with the former is an advantage, but results in a high relapse rate.

- It is appropriate to consider cord blood transplantation for patients with no HLA well-matched donor or those needing an urgent transplant.
- Imatinib therapy before and/or after HCT for Ph+ ALL yields significantly superior overall and leukemia-free survival outcomes.

A meta-analysis published in 2013 included 13 studies (total N = 2962), several of which are described in this Policy.^[38] The results suggest that a matched sibling donor myeloablative HCT improves survival only for younger adults (<35 years old) in CR1 compared to chemotherapy, with an absolute benefit of 10% at 5 years. The analysis also suggests a trend toward inferior overall survival among autologous HCT recipients compared to chemotherapy in CR1 (OR = 1.18; 95% CI, 0.99-1.41, p = 0.06), primarily due to higher treatment-related mortality (TRM) in the autograft patients compared to chemotherapy recipients. These results indicate further study is needed to determine the optimal therapy for adult ALL patients.

Section Summary

Current data from randomized controlled trials indicate post-remission myeloablative allogeneic HCT 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. Even for adults who survive the procedure, there is a significant relapse rate. Nevertheless, current evidence supports the use of myeloablative allogeneic HCT for patients with ALL in CR1 whose health status is sufficient to tolerate the procedure (see Policy Guidelines).

REDUCED-INTENSITY CONDITIONING (RIC) ALLOGENEIC HCT

There is a substantial graft-versus-malignancy (GVM) effect of postremission allogeneic SCT. RIC regimens have been investigated as a means to extend this GVM effect to patients who could benefit from this procedure but who are ineligible or would not tolerate a fully myeloablative procedure.

Systematic Review

A systematic review published by Abdul Wahid^[39] in 2014 included a meta-analysis of data from five studies in which RIC conditioning (n=528) was compared with myeloablative conditioning regimens (n=2489) in adult patients with ALL who received allogeneic HCT mostly in CR1. This analysis of data from nonrandomized studies suggests progression-free survival at 1 to 6 years was significantly lower after RIC conditioning (36%) compared with 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 non-relapse mortality in the RIC group compared with the myeloablative group (OR=0.76; 95% CI, 0.61 to 0.95), resulting in similar overall survival (OR=1.03; 95% CI, 0.84 to 1.26; p=0.76). The 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). Studies included in the review were limited by the small number of studies, inter-study heterogeneity for GVHD data, and publication bias for progression-free survival.

Nonrandomized Studies

Rosko (2017) used Center for International Blood and Marrow Transplant Research registry data to examine the effectiveness of RIC HCT in adults 55 years or older with B-cell ALL and

explored prognostic factors associated with long-term outcomes.^[40] The authors evaluated 273 participants with B-cell ALL with disease status in CR1 (71%), CR2 or beyond (17%), and primary induction failure/relapse (11%) who underwent RIC HCT between 2001 and 2012. Among patients with available cytogenetic data, 50% were Ph-positive. The three-year OS rate was 38% (95% CI, 33% to 44%). The three-year cumulative incidences of non-relapse mortality and relapse were 25% (95% CI, 20% to 31%) and 47% (95% CI, 41% to 53%), respectively.

In a multicenter single-arm study of patients (n=43, median age 19 years; range: 1–55) in second complete remission (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.^[41]

A registry-based study included 97 adult patients (median age 38 years, range 17–65) who underwent RIC and allogeneic HCT to treat ALL in CR1 (n=28), beyond CR1 (CR2/CR3, n=26/5), and advanced or refractory disease (n=39).^[42] With median follow-up of about 3 years, in the overall population 2-year OS was 31%, with non-relapse mortality 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%. These data suggest RIC and allogeneic HCT have some efficacy as salvage therapy in high-risk ALL.

RIC for allogeneic SCT 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 WBC) in CR1 (81%) or CR2 (19%) who were ineligible to receive a myeloablative allogeneic HCT because of age, organ dysfunction, low Karnofsky performance status (<50%), or the presence of infection.^[43] 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 GVHD prophylaxis (cyclosporine or tacrolimus, plus methotrexate). All Ph-positive patients also received imatinib prior to HCT. 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, among whom 24 (96%) 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 HCT with a fludarabine-based RIC regimen.^[44] This study represents the first large cooperative group study to be published in this setting. Among the 17 ALL cases, 4 were in CR2, 12 in CR3, and 1 had secondary ALL. All patients were heavily pretreated, including previous myeloablative allogeneic or autologous HCT, 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 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. Treatment-related mortality was not reported by disease, nor was HCT-related morbidities. However, these data do suggest allogeneic HCT with RIC

can be used in children with high-risk ALL and achieve some long-term survival in patients with no therapeutic recourse.

Section Summary

Based on currently available data and clinical input, there is sufficient evidence to conclude that RIC allogeneic HCT may be beneficial in patients who demonstrate complete marrow and extramedullary first or second remission, but who, for medical reasons, would be unable to tolerate a myeloablative conditioning regimen. Additional data are necessary to determine whether some patients with ALL and residual disease may benefit from RIC allogeneic HCT.

ALLOGENEIC TRANSPLANT AFTER PRIOR FAILED AUTOLOGOUS TRANSPLANT

A 2000 BCBSA TEC Assessment focused on allogeneic HCT after a prior failed autologous HCT, in the treatment of a variety of malignancies, including ALL.^[45] The BCBSA TEC Assessment found that data were inadequate to permit conclusions about outcomes of this treatment strategy. Since the TEC assessment, there continues to be a lack of strong evidence on allogeneic HCT in this circumstance. However, it has gained support in the clinical setting as it is potentially curative and has been shown to be of clinical benefit in other hematologic malignancies.

PRACTICE GUIDELINE SUMMARY

The following U.S. professional associations have published position statements for the diagnosis and treatment of ALL:

THE NATIONAL COMPREHENSIVE CANCER NETWORK GUIDELINES

Guidelines from the National Comprehensive Cancer Network (NCCN) (v1.2018) for ALL are generally consistent with this policy.^[4] However, the NCCN guidelines stratify treatment according to the categories adolescent and young adult (age 15-39 years) and adult (age 40 or more years), rather than the more traditional categorization of children (18 years or younger) and adult categories (18 or more years).

THE AMERICAN SOCIETY FOR BLOOD AND MARROW TRANSPLANTATION (ASBMT)

The 2012 ASBMT systematic reviews and guidelines for adults^[30] and children^[46] are summarized above. As noted, these guidelines were developed by consensus and expert opinion, and are generally consistent with this policy.

SUMMARY

AUTOLOGOUS HCT

Current research suggests that autologous hematopoietic cell transplantation (HCT) may be considered a therapeutic option in the treatment of acute lymphoblastic leukemia (ALL) in select patients. Therefore, autologous HCT may be considered medically necessary when criteria are met. However, the evidence is insufficient to permit conclusions about the safety and effectiveness of HCT for ALL patients who do not meet the medical necessity criteria; therefore, HCT is considered investigational for those patients.

ALLOGENEIC HCT WITH MYELOABLATIVE CONDITIONING

Current research indicates myeloablative allogeneic hematopoietic cell transplantation (HCT) is an effective therapeutic option for a large proportion of patients with acute lymphoblastic leukemia (ALL). Therefore, myeloablative allogeneic HCT may be considered medically necessary when criteria are met. However, adverse effects from graft versus host disease (GVHD) can be severe, particularly for older or debilitated patients, and there is a significant relapse rate. Therefore, the use of myeloablative allogeneic HCT is considered investigational for patients with ALL who do not meet the medical necessity criteria.

REDUCED-INTENSITY CONDITIONING FOR ALLOGENEIC HCT

Current research is sufficient to determine that reduced intensity conditioning (RIC) allogeneic hematopoietic cell transplantation (HCT) may be considered medically necessary in patients with acute lymphoblastic leukemia (ALL) in complete first or second remission who, for medical reasons, would be unable to tolerate a conventional myeloablative conditioning regimen. Current evidence is insufficient to permit conclusions about the safety and effectiveness of RIC allogeneic HCT for all other ALL patients. Additional studies are necessary to determine which, if any, of these patients are most likely to benefit from this treatment regimen. Therefore, allogeneic HCT using RIC is considered investigational for patients with ALL who do not meet the medical necessity criteria.

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CODES

Codes	Number	Description
CPT	38204	Management of recipient hematopoietic cell donor search and cell acquisition
	38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection, allogeneic
	38206	;autologous
	38207	Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage
	38208	;thawing of previously frozen harvest, without washing, per donor
	38209	;thawing of previously frozen harvest with washing, per donor
	38210	;specific cell depletion with harvest, T cell depletion
	38211	;tumor cell depletion
	38212	;red blood cell removal
	38213	;platelet depletion
	38214	;plasma (volume) depletion
	38215	;cell concentration in plasma, mononuclear, or buffy coat layer
	38220	Diagnostic bone marrow; aspiration(s)
	38221	Diagnostic bone marrow; biopsy(ies)
	38222	Diagnostic bone marrow; biopsy(ies) and aspiration(s)
	38230	Bone marrow harvesting for transplantation; allogeneic
	38232	Bone marrow harvesting for transplantation; autologous
38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor	
38241	;autologous transplantation	
38243	;HPC boost	
38242	Allogeneic lymphocyte infusions	
HCPCS	J9000– J9999	Chemotherapy drugs code range
	Q0083– Q0085	Chemotherapy administration code range
	S2140	Cord blood harvesting for transplantation; allogeneic
	S2142	Cord blood derived stem-cell transplantation, allogeneic
	S2150	Bone marrow or blood-derived peripheral stem-cell harvesting and transplantation, allogeneic or autologous, including pheresis, high-dose chemotherapy, and the number of days of post-transplant care in the global

APPENDIX I: Glossary of Terms used in this Policy

consolidation therapy¹ - Treatment that is given after cancer has disappeared following the initial therapy. Consolidation therapy is used to kill any cancer cells that may be left in the body. It may include radiation therapy, a stem cell transplant, or treatment with drugs that kill cancer cells. Also called intensification therapy and postremission therapy.

relapse² - The return of a disease or the signs and symptoms of a disease after a period of improvement.

salvage therapy³ - Treatment that is given after the cancer has not responded to other treatments.

tandem transplant⁴ – Refers to a planned second course of high-dose therapy and HCT within six months of the first course.

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