Regence

Medical Policy Manual Transplant, Policy No. 45.36

Hematopoietic Cell Transplantation for Acute Lymphoblastic Leukemia

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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

Hematopoietic cell transplantation is performed to restore normal function following chemotherapy treatment.

MEDICAL POLICY CRITERIA

I. 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

II. In **children**, allogeneic hematopoietic cell transplantation is considered **not medically necessary** for pediatric patients who do not meet Criterion I. above.

III. In **children**, autologous hematopoietic cell transplantation is considered **not medically necessary**.

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) in minimal-residual disease-negative patients with no available donor or when haploidentical allogeneic HCT is not feasible.

V. In **adults**, autologous hematopoietic cell transplantation is considered **investigational** for adult patients who do not meet 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 **not medically necessary** for patients who do not meet Criteria VI. above.

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), when the patient 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 Criterion VIII. above.

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

POLICY GUIDELINES

DEFINITIONS

- **Consolidation therapy:** 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.

- **Relapse:** The return of a disease or the signs and symptoms of a disease after a period of improvement.
- **Salvage therapy:** Treatment that is given after the cancer has not responded to other treatments.
- **Tandem transplant:** Refers to a planned second course of high-dose therapy and HCT within six months of the first course.

RELAPSE RISK PROGNOSTIC FACTORS

Childhood ALL

Adverse prognostic factors in children include the following:

- Age less than 1 year or more than 9 years
- Biologic male gender
- White blood cell count at presentation above 50,000/µL
- Hypodiploidy (<45 chromosomes)
- t(9:22) or BCR/ABL fusion (Philadelphia chromosome)
- t(4;11) or MLL/AF4 fusion
- 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/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)
- All children with T-cell phenotype,
    a. 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
- 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.

LIST OF INFORMATION NEEDED FOR REVIEW

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 adult patients requesting autologous HCT, minimum residual disease (MRD) status and reason allogeneic transplant is not feasible
- For patients with a reduced-intensity conditioning (RIC) regimen, documentation supporting reasons patient is unable to tolerate a myeloablative conditioning regimen.

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

Broadly speaking, there are two types of hematopoietic cell transplants (HCT, previously referred to in this policy as a hematopoietic stem cell transplant [HSCT]), autologous and allogeneic. The purpose of an autologous HCT is to treat a disease (e.g. lymphoma) with myeloablative doses of chemotherapy (with or without radiation) that are active against the disease. The recipient's own HCTs (collected previously) are infused after the chemotherapy in order to re-establish normal marrow function. In an allogeneic transplant, the recipient receives HCTs from a donor after myeloablative therapy or non-myeloablative therapy in order to re-establish normal marrow function as well as to use the new blood system as a platform for immunotherapy, a so called "graft versus tumor" effect. Hematopoietic cells can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates. Although cord blood is an allogeneic source, the 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 conditioning with 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 pediatric malignancy, with 55.4% of all patients diagnosed younger than 20 years, and an overall median age at diagnosis of 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/µL	≥50,000/µL
Genotype	Hyperdiploidy (>50 chromosomes) t(12;21) or *TEL/AML1* fusion	Hypodiploidy (<45 chromosomes) t(9:22) or *BCR/ABL* fusion t(4;11) or *MLL/AF4* fusion
Immunophenotype	Common, preB	ProB, T-lineage

Adolescents and Young Adults (AYA) ALL

AYA ALL patients are a unique population and may receive treatment based either on pediatric or adult protocols depending on local institutional practices. The age range for AYA varies across studies, and patients treated in pediatric settings may include people up to age 30 years.[1] Cure rates for AYA ALL are less favorable than childhood ALL with five-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;

with remission rates of up to 90% in patients with Ph-positive ALL. However, the 5-year survival of adults with Ph-positive ALL is only 39%.[4] 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/µL (B-cell lineage) and >100,000/µL (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.[5, 6] 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 Policy Guidelines section).

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 three years, compared to only 10% to 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.[7] The literature consisted mainly of retrospective reviews and also included three RCTs.[8-10] 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.[11-13] 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[8]. 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[14-16] and retrospective reviews.[17-23] 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.[16, 24]

ADULT ALL

Systematic Reviews

Shahzad (2023) published a systematic review and meta-analysis comparing outcomes of tyrosine kinase inhibitor (TKI) maintenance therapy with or without allogeneic HCT in adult patients with Ph+ ALL in first remission.[25] Twelve studies were included that involved 1039 patients. Of those, 635 had TKI alone and 404 had allogeneic HCT following TKI. At three years the trend was toward poor overall survival in the TKI alone group, but the difference was not significant (OS; OR 0.67, 95% CI 0.39-1.15, I^2=68%). The TKI alone group also trended toward worse disease-free survival (OR 0.58, 95% CI 0.26-1.29, I^2=76%) and higher relapse rate (RR; OR=2.52, 95% CI 1.66-3.83, I^2=26%).

A meta-analysis by Owattanapanich (2022) compared outcomes of stem cell transplantations in adults with ALL involving high-risk features or relapse using haploidentical donors versus other stem cell sources, including matched sibling donors, matched unrelated donors, and cord blood transplantations.[26] Twenty-eight studies were included (17 retrospective, 11 prospective). Investigators found no significant differences in OS of haploidentical and other stem cell sources. For haploidentical versus matched donors, the pooled OR was 0.94 (95% CI, 0.79 to 1.12), and for haploidentical versus cord blood, the OR was 1.24 (95% CI, 0.78 to 1.96). The incidence of relapse was significantly higher with matched sibling donor compared to haploidentical donor (OR, 0.69; 95% CI, 0.48 to 0.99). In terms of adverse events, both grade II through IV acute and long-term GVHD were significantly higher in those with haploidentical donors compared to matched sibling donors (OR, 1.78; 95% CI, 1.15 to 2.74; OR, 1.33; 95% CI, 1.00 to 1.77, respectively).

Smith (2022) published a systematic review identifying studies reporting survival in HSCT-receiving patients and apply parametric analyses to predict long-term survival.[27] Twenty-five

relevant studies were identified. Analyses were conducted in 10 studies (n=503; "global" analysis) reporting overall survival (OS) data as Kaplan-Meier curves or at patient level. Four studies (n=217; "subgroup" analysis) measured OS from the point of HSCT. Median OS and five-year survival probability were 11.4 months and 24.4% (95% CI 20.5 to 28.5%) in the global analysis, and 12.0 months and 28.4% (95% CI 22.1 to 34.9%) in the subgroup analysis. The authors report that the risk of death is low beyond four years and newer data appears correlated with improved outcomes.

A systematic review and meta-analysis published by Ponvilawan (2021) compared the efficacy of allogeneic HCT (allo-HCT), autologous HCT (auto-HCT), and chemotherapy alone-all in combination with TKIs in adult Ph-positive ALL patients.[28] A total of 26 cohort studies, of which six were prospective, met inclusion criteria. Patients who received HCT had better overall survival (OS; allo-HCT: pooled odds ratio [OR] =1.61, 95% CI 1.08 to 2.40; I^2=59%; auto-HCT: OR=7.04, 95% CI 1.97 to 25.15; I^2=0%) and disease-free survival (DFS; allo-HCT: OR=3.23, 95% CI 2.00 to 5.23; I^2=62%; auto-HCT: OR=5.78, 95% CI 1.04 to 32.19; I^2=42%) than patients who did not. OS and DFS were not significantly different in patients who received allo-HCT compared to those who received auto-HSCT (pooled OR 1.04; 95% CI 0.74 to 1.44; I^2=0% vs. 1.09; 95% CI 0.79 to 1.49; I^2=0%). There was some indication of publication bias favoring auto-HCT to allo-HCT for OS, but not DFS. There was an increased rate of treatment-related mortality in the allo-HCT group (pooled OR 4.95; 95% CI 1.22 to 20.7; I^2=0%) but a decreased cumulative incidence of relapse (pooled OR 0.39; 95% CI 0.27 to 0.54; I^2=0%).

Wei (2020) published a systematic review that compared allogeneic and autologous HCT in adult patients with Ph-positive ALL who received TKIs.[29] A total of five studies met inclusion criteria (four prospective and one retrospective). The studies were rated as high quality with low risk of bias. Four studies included OS data and were included in the meta-analysis for OS. The difference between groups was statistically significant, with longer OS in patients treated with autologous HCT (hazard ratio [HR]=1.42; 95% CI 1.06 to 1.91; p=0.02). A meta-analysis of data from all five studies indicated that there was no significant difference between groups for relapse-free survival (HR=1.10; 94% CI 0.86 to 1.40; p=0.44) or relapse rate (OR=0.53; 95% CI 0.22 to 1.26; p=0.15). A meta-analysis of the three studies reporting data for treatment-related mortality found that the risk was significantly higher in patients treated with autologous HCT (OR=5.06; 95% CI 1.03 to 24.75; p=0.05).

In 2019, the American Society for Transplantation and Cellular Therapy (ASTCT; previously the American Society for Blood and Marrow Transplantation [ASBMT]) published an updated systematic review of Hematopoietic Cell Transplantation in the Treatment of Adult Acute Lymphoblastic Leukemia.[30] The ASTC determined that the evidence supported the following grade A (at least one meta-analysis, systematic review, or RCT rated as high-quality) treatment recommendations:

- Allogeneic HCT should be offered for adults with standard-risk Ph-negative ALL in CR1.
- Allogeneic HCT should be offered for adults with high-risk Ph-negative ALL in CR1.
- Allogeneic HCT should not be considered for AYA with otherwise standard-risk, MRD-negative Ph-negative ALL in CR1 if treated with pediatric-inspired regimens.
- Allogeneic HCT should be considered for AYA for Ph-negative ALL in CR1 with high-risk features or persistent MRD after induction.
- Autologous HCT should not be offered for Ph-negative ALL in CR1.

Pidala published a 2011 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).[31] 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 meta-analysis published by Gupta in 2013 included 13 studies (total n=2962), several of which are described in this Policy.[32] 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 five 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 to 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.

Dinmohamed (2016) reviewed survival trends among adults with ALL who underwent HCT between 1989 and 2012.[33] Data were available on 1833 patients. Survival rates increased significantly over time in all age groups (18-24, 25-39, 40-59, 60-69, and ≥70 years old). For the most recent period (2007 to 2012), five-year relative survival rates by age group were 75%, 57%, 37%, 22%, and 5%, respectively.

Non-randomized Studies

Aleshina (2022) published a non-randomized study in which the selection is limited to patients with auto-HSCT vs chemotherapy (ChT) only.[34] All T-cell ALL patients who achieved complete response (CR) were brought to randomization after the informed consent to one of two groups: auto-HSCT vs ChT only. Two hundred and sixty-seven Ph-negative ALL adult patients were included from Dec 2016 until Apr 2022. 111 patients had T-cell ALL, 74% were male, and median age was 31. Eighty-seven T-ALL patients were randomized: 43 patients to ChT, and 44 to auto-HSCT. For transplanted patients: time from complete response to transplant was 7 months. didn't detect differences in DFS and PR (67% vs 78%, and 25% vs 22% auto-HSCT vs ChT). Auto-HSCT does not improve DFS in T-ALL with MRD after induction. In both auto-HSCT and only ChT groups with MRD persistence after induction have poor DFS (MRD-: 86% vs 81% and MRD+: 67% and 40%, respectively ChT vs auto-HSCT). The authors report that there is not enough evidence that auto-HSCT could improve long-term result for T-cell ALL.

Several recent studies have evaluated changes in survival rates over time. A 2017 multicenter clinical trial from Europe reported on 4859 adults with ALL in CR1 treated with allo-HCT from either a matched sibling donor (n=2681) or an unrelated donor (n=2178).[35] Survival rates generally improved over time (ie, from 1993-2002 to 2008-2012). For the period 2008 to 2012, 2-year OS rates after matched sibling donor HCT were 76% for 18- to 25-year-olds, 69% for 26- to 35-year-olds and 36- to 45-year-olds, and 60% for 46- to 55-year-olds. During that time, 2-year OS rates after unrelated donor HCT were 66% for 18- to 25-year-olds, 70% for 26- to 35-year-olds, 61% for 36- to 45-year-olds, and 62% for 46- to 55-year-olds.

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[36] 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 one to six 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

Lee (2020) reported a retrospective analysis of RIC allogeneic HCT in patients with ALL unfit for myeloablation.[37] A total of 78 patients were included. Median follow-up was 22 months. Two-year estimates of relapse-free survival and OS were 57.4% (95% CI 42.1 to 70.0%) and 68.7% (95% CI 55.4 to 78.8%), respectively. Cumulative incidences of relapse and non-relapse mortality were 42.9% and 19.6%, respectively. Three deaths were due to engraftment failure, four to infectious complications, and four to chronic GVHD. One case of central nervous system relapse was reported. GVHD occurred in 41.7% of patients and Grade II to IV GVHD occurred in 21.1%.

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.[38] 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 to 55) in second complete remission (CR2), a three-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.[39]

A registry-based study included 97 adult patients (median age 38 years, range 17 to 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).[40] With median follow-up of about three years, in the overall population two-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.[41] 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 three-year cumulative incidence of relapse was 19.7% + 6.9%, that of NRM was 17.7% + 6.9%. The three-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 to 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 to 20 years) with hematologic cancers, including ALL (n=17), who underwent allogeneic HCT with a fludarabine-based RIC regimen.[42] This study represents the first large cooperative group study to be published in this setting. Among the 17 ALL cases, four were in CR2, 12 in CR3, and one 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 two-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, one ALL patient received chemotherapy and donor lymphocyte infusion (DLI) for low chimerism and relapse and was reported alive one year following DLI and three 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 three 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.

A retrospective cohort study by Trujillo et al (2021) assessed 42 pediatric patients (median age, 11 years; range, 2 to 17 years) with high-risk leukemias, including ALL (n=26).[43] Patients who underwent allo-HCT with a cyclophosphamide-based RIC regimen between 2012 and

2017 in the Colombian study center were included. Overall, 33% of the patients were in CR1, 50% were in CR2, 14% were in CR3, and 3% had refractory disease. Patients with ALL were all previously treated with Berlin-Frankfurt-Munich (BFM)-based chemotherapy. Most of the data were aggregated, however, some survival findings were specified for ALL. The study found that there were no statistically significant differences in OS or EFS between patients with ALL and those with acute myelogenous leukemia (AML). Overall the study found that between those positive or negative for pre-HCT minimal residual disease, or based on pre-HCT remission status, there was also no statistically significant difference in OS or EFS. Median duration for follow-up was 45 months and OS and EFS for the study group at 36 months were 56% and 46%, respectively.

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.[44] 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) for pediatric and adult ALL (v 3.2023) indicate allogeneic hematopoietic cell transplantation (allo-HCT) is appropriate for postremission consolidation treatment, with the recommendation to “strongly consider early transplant evaluation and donor search” during initial workup for all adolecscent and young adult patients with ALL.[45] The guidelines state that for appropriately fit older adults with ALL who are achieving remission, “consideration of autologous or reduced-intensity allogeneic stem cell transplantation may be appropriate.” Additionally, the guidelines for pediatric ALL state that “Allogeneic HSCT has demonstrated improved clinical outcomes in pediatric ALL patients with evidence of certain high-risk features and/or persistent disease.[1] In addition, survival rates appear to be comparable regardless of the stem cell source (matched related, matched unrelated, cord blood, or haploidentical donor).” The guidelines state that the benefit of allogenic HCT in infants is still controversial.

THE AMERICAN SOCIETY FOR TRANSPLANTATION AND CELLULAR THERAPY

The 2019 American Society for Transplantation and Cellular Therapy (ASTCT; previously the American Society for Blood and Marrow Transplantation [ASBMT]) systematic reviews and guidelines for adults[30] and children[46] are summarized above.

In 2020, updated guidelines from the ASTCT on indications for autologous and allogeneic HCT were published.[47] Recommendations were intended to describe the current consensus on the use of HCT in and out of the clinical trial setting. Recommendations on ALL are listed in Table 1.

Table 1. Guidelines for Autologous and Allogeneic HCT Indication

Indication	Children (Age <18 Years)		Adults (Age ≥18 Years)	
	Allogeneic HCT	Autologous HCT	Allogeneic HCT	Autologous HCT
First complete response, standard-risk	N	N	S	N
First complete response, high-risk	S	N	S	N
Second complete response	S	N	S	N
At least third complete response	C	N	S	N
Not in remission	C*	N	S*	N

C: clinical evidence available; HCT: hematopoietic cell transplantation; N: not generally recommended; S: standard of care.

SUMMARY

CHILDREN

Current research indicates allogeneic hematopoietic cell transplantation (HCT) is an effective therapeutic option for a large proportion of patients with acute lymphoblastic leukemia (ALL). Therefore, allogeneic HCT may be considered medically necessary when criteria are met. However, allogeneic hematopoietic cell transplantation is not clinically appropriate when criteria are not met. Therefore, the use of hematopoietic cell transplantation (HCT) is considered not medically necessary for pediatric patients with ALL who do not meet the medical necessity criteria.

Autologous hematopoietic cell transplantation (HCT) is not clinically appropriate in children with acute lymphoblastic leukemia (ALL). Therefore, the use of autologous HCT is considered not medically necessary for pediatric patients with ALL.

ADULTS

Autologous HCT

Autologous hematopoietic cell transplantation (HCT) is not clinically appropriate in adults with acute lymphoblastic leukemia (ALL). Therefore, the use of autologous HCT is considered not medically necessary for adult patients with ALL.

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, allogeneic hematopoietic cell transplantation is not clinically appropriate when criteria are not met. Therefore, the use of myeloablative

allogeneic HCT is considered not medically necessary 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	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 definition (including drugs; hospitalization; medical surgical, diagnostic and emergency services)

Date of Origin: *May 2010*