Protocol

Hematopoietic Cell Transplantation for Acute Lymphoblastic Leukemia

(80132)

Medical Benefit		**Effective Date**: 07/01/14	**Next Review Date**: 07/19
Preauthorization	Yes	**Review Dates**: 04/07, 05/08, 05/09, 03/10, 03/11, 03/12, 03/13, 07/13, 07/14, 07/15, 07/16, 07/17, 07/18	

Preauthorization is required and must be obtained through Case Management.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. 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.

Populations	Interventions	Comparators	Outcomes
Individuals: • With childhood ALL in first complete remission at high risk of relapse, remission, or refractory ALL	Interventions of interest are: • Autologous hematopoietic cell transplantation	Comparators of interest are: • Conventional-dose chemotherapy	Relevant outcomes include: • Overall survival • Disease-specific survival • Treatment-related mortality • Treatment-related morbidity
Individuals: • With childhood ALL in first complete remission at high-risk of relapse, remission, or refractory ALL	Interventions of interest are: • Allogeneic hematopoietic cell transplantation	Comparators of interest are: • Conventional-dose chemotherapy	Relevant outcomes include: • Overall survival • Disease-specific survival • Treatment-related mortality • Treatment-related morbidity
Individuals: • With adult ALL in first complete remission, subsequent remission, or refractory ALL	Interventions of interest are: • Autologous hematopoietic cell transplantation	Comparators of interest are: • Conventional-dose chemotherapy	Relevant outcomes include: • Overall survival • Disease-specific survival • Treatment-related mortality • Treatment-related morbidity
Individuals: • With adult ALL in first complete remission, subsequent remission, or refractory ALL	Interventions of interest are: • Allogeneic hematopoietic cell transplantation	Comparators of interest are: • Conventional-dose chemotherapy	Relevant outcomes include: • Overall survival • Disease-specific survival • Treatment-related mortality • Treatment-related morbidity
Individuals: • Who relapse after a prior autologous hematopoietic cell transplantation for acute lymphoblastic leukemia	Interventions of interest are: • Allogeneic hematopoietic cell transplantation	Comparators of interest are: • Conventional-dose chemotherapy	Relevant outcomes include: • Overall survival • Disease-specific survival • Treatment-related mortality • Treatment-related morbidity

ALL: Acute lymphoblastic leukemia

DESCRIPTION

Acute lymphoblastic leukemia (ALL) is a heterogeneous disease with different genetic variations resulting in

distinct biologic subtypes. Patients are stratified to risk-adapted therapy according to certain clinical and genetic risk factors that predict outcome. Therapy may include hematopoietic cell transplantation (HCT).

SUMMARY OF EVIDENCE

For individuals who have childhood ALL in first complete remission (CR1) at high-risk of relapse, remission, or refractory ALL who receive autologous HCT, the evidence includes randomized controlled trials (RCTs) and systematic reviews. Relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. For children with high-risk ALL in CR1 or with relapsed ALL, studies have suggested that HCT is associated with fewer relapses but higher death rates due to treatment-related toxicity. However, for a subset of high-risk patients in second complete remission or beyond or with relapsed disease, autologous HCT is a treatment option. This conclusion is further supported by an evidence-based systematic review and position statement from the American Society for Blood and Marrow Transplantation. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have childhood ALL in CR1 at high-risk of relapse, remission, or refractory ALL who receive allogeneic HCT (allo-HCT), the evidence includes RCTs and systematic reviews. Relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. For children with high-risk ALL in CR1 or with relapsed ALL, studies have suggested that allo-HCT is associated with fewer relapses but higher death rates due to treatment-related toxicity. However, for a subset of high-risk patients in second complete remission or beyond or with relapsed disease, allo-HCT is a treatment option. This conclusion is further supported by an evidence-based systematic review and position statement from the American Society for Blood and Marrow Transplantation. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have adult ALL in CR1, subsequent remission, or refractory ALL who receive autologous HCT, the evidence includes RCTs and systematic reviews. Relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. Current evidence supports the use of autologous HCT for adults with high-risk ALL in CR1, whose health status is sufficient to tolerate the procedure. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have adult ALL in CR1, or subsequent remission or refractory ALL who receive allo-HCT, the evidence includes RCTs and systematic reviews. Relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. Current evidence supports the use of myeloablative allo-HCT for adults with any risk level ALL, whose health status is sufficient to tolerate the procedure. Reduced-intensity conditioning allo-HCT may be considered for patients who demonstrate complete marrow and extramedullary first or second remission and who could be expected to benefit from a myeloablative allo-HCT, but for medical reasons would not tolerate a myeloablative conditioning regimen. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have relapsed after a prior autologous HCT for ALL who receive allo-HCT, the evidence includes case series and systematic reviews. Relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. Evidence reviews have identified only small case series with short-term follow-up, which were considered inadequate evidence of benefit. The evidence is insufficient to determine the effects of the technology on health outcome.

POLICY

CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)

Autologous or allogeneic hematopoietic cell transplantation (HCT) may be considered **medically necessary** to treat childhood ALL in first complete remission but at high risk of relapse. (For definition of high-risk factors, see Policy Guidelines.)

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

Allogeneic HCT is considered **medically necessary** to treat relapsing ALL after a prior *autologous* HCT in children.

ADULT ALL

Autologous HCT 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 HCT may be considered **medically necessary** to treat adult ALL in first complete remission for any risk level (for definition of risk factors, see Policy Guidelines).

Allogeneic HCT may be considered **medically necessary** to treat adult ALL in second or greater remission or in adults with relapsed or refractory ALL.

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

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

Reduced-intensity conditioning *allogeneic* HCT 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.

POLICY GUIDELINES

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.

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 (less than 45 chromosomes), translocation involving chromosomes 9 and 22 t(9;22) or BCR/ABL fusion, translocation involving chromosomes 4 and 11 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% or higher minimal residual disease measured by flow cytometry, 2) all children with T-cell phenotype and 3) patients with either the t(9;22) or t(4;11) regardless of early response measures.

Adult ALL

Risk factors for relapse are less well defined in adults, but a patient with any of the following may be considered at high risk for relapse: age older than 35 years, leukocytosis at presentation of greater than 30,000/µL (B-cell

lineage) or greater than 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 allo-HCT could be curative may be considered candidates for reduced-intensity conditioning (RIC) allo-HCT (see Background section). Such patients 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 HCT, low Karnofsky Performance Status score) preclude the use of a standard myeloablative conditioning regimen.

The ideal allogeneic donors are human leukocyte antigen (HLA)–identical siblings, matched at the HLA-A, -B, and DR (antigen-D related) loci on each arm of chromosome 6. Related donors mismatched at 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. Most patients will have such a donor. The risk of morbidity (e.g., graft-versus host disease [GVHD]) may be higher than with HLA matched donors; however, as medical treatments improve, the risks of GVHD with haploidentical donors are approaching those similar to HLA-matched donors.

MEDICARE ADVANTAGE

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

BACKGROUND

ACUTE LYMPHOBLASTIC LEUKEMIA

Childhood ALL

ALL is the most common cancer diagnosed in children; it represents nearly 25% of cancers in children younger than 15 years.[1] Remission of disease is now typically achieved with pediatric chemotherapy regimens in 98% 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 the 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 with 10% to 15% for those who relapse less than three years after treatment. Thus, HCT may be a strong consideration in those with short remissions. At present, the comparative outcomes with autologous or allo-HCT are unknown.

ALL is a heterogeneous disease with different genetic variations resulting in distinct biologic subtypes. Patients are stratified by certain clinical and genetic risk factors that predict outcome, with risk-adapted therapy tailoring treatment based on the predicted risk of relapse.[3] Two of the most important factors predictive of risk are patient age and white blood cell count at diagnosis.[3] Certain genetic characteristics of leukemic cells strongly influence prognosis. Clinical and biologic factors predicting clinical outcomes and relapse risk are summarized in the Policy Guidelines section.[2]

Adult ALL

ALL accounts for 20% of acute leukemias in adults. Between 60% and 80% of adults with ALL can be expected to

achieve a complete response after induction chemotherapy; however, only 35% to 40% can be expected to survive two years.[4] Differences in the frequency of genetic abnormalities that characterize adult ALL vs. childhood ALL help, in part, explain differences in outcomes between the two groups. For example, the "good prognosis" genetic abnormalities, such as hyperdiploidy and translocation of chromosomes 12 and 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 (translocation of chromosomes 9 and 22) are seen in 25% to 30% of adult ALL but infrequently in childhood ALL. Other adverse prognostic factors in adult ALL include age greater than 35 years, poor performance status, male sex, and leukocytosis at presentation of greater than 30,000/µL (B-cell lineage) or greater than 100,000/µL (T-cell lineage).

CONDITIONING FOR HCT

Conventional Conditioning for HCT

The success of autologous HCT is predicated on the ability of cytotoxic chemotherapy with or without radiation to eradicate cancerous cells from the blood and bone marrow. This permits subsequent engraftment and repopulation of bone marrow space with presumably normal hematopoietic stem cells obtained from the patient before undergoing bone marrow ablation. Patients who undergo autologous HCT are susceptible to chemotherapy-related toxicities and opportunistic infections before engraftment, but not graft-versus-host disease.

The conventional ("classical") practice of allo-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-vs.-malignancy effect that develops after engraftment of allogeneic stem cells within the patient's bone marrow space. While the slower graft-versus-malignancy 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 preengraftment opportunistic infections secondary to loss of endogenous bone marrow function and organ damage and failure caused by the cytotoxic drugs. Furthermore, in any allo-HCT, immune suppressant drugs are required to minimize graft rejection and graft-versus-host disease, which also increases the susceptibility of the patient to opportunistic infections.

Reduced-Intensity Conditioning (RIC) for Allo-HCT

RIC refers to the pretransplant use of lower doses or less intense regimens of cytotoxic drugs or radiotherapy that are used in conventional full-dose myeloablative conditioning treatments. The goal of RIC is to reduce disease burden and to minimize as much as possible associated treatment-related morbidity and nonrelapse mortality when the beneficial graft-versus-malignancy effect of allogeneic transplantation develops. Although the definition of RIC remains arbitrary, with numerous versions employed, all seek to balance the competing effects of nonrelapse mortality and relapse due to residual disease. RIC regimens can be viewed as a continuum of effects, from nearly totally myeloablative, to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and patient condition. Patients who undergo RIC with allo-HCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism, which may be supplemented with donor lymphocyte infusions to eradicate residual malignant cells. For this protocol, RIC will refer to all conditioning regimens intended to be nonmyeloablative, as opposed to fully myeloablative (conventional) regimens.

REGULATORY STATUS

The U.S. Food and Drug Administration regulates human cells and tissues intended for implantation, transplan-

tation, or infusion through the Center for Biologics Evaluation and Research, under Code of Federal Regulation, title 21, parts 1270 and 1271. Hematopoietic stem cells are included in these regulations.

RELATED PROTOCOL

Genetic Testing for Leukemia and Lymphoma

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.

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