Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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***Current Policy Effective Date: 1/1/13**
(See policy history boxes for previous effective dates)

Title: BMT - Hematopoietic Stem-Cell Transplantation for Acute Lymphoblastic Leukemia

Description / Background

Hematopoietic Stem-Cell Transplantation
Hematopoietic stem-cell transplantation (HSCT) refers to a procedure in which hematopoietic stem cells are infused to restore bone marrow function in cancer patients who receive bone-marrow-toxic doses of cytotoxic drugs, with or without whole-body radiation therapy. Bone marrow stem cells may be obtained from the transplant recipient (i.e., autologous HSCT) or from a donor (i.e., allogeneic HSCT). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood and placenta shortly after delivery of neonates. Although cord blood is an allogeneic source, the stem cells in it are antigenically “naïve” and thus are associated with a lower incidence of rejection or graft-versus-host disease (GVHD).

Immunologic compatibility between infused stem cells and the recipient is not an issue in autologous HSCT. However, immunologic compatibility between donor and patient is a critical factor for achieving a good outcome of allogeneic HSCT. Compatibility is established by typing of human leukocyte antigens (HLA) using cellular, serologic, or molecular techniques. HLA refers to the tissue type expressed at the HLA A, B, and DR loci on each arm of chromosome 6. Depending on the disease being treated, an acceptable donor will match the patient at all or most of the HLA loci.

Conventional Preparative Conditioning for HSCT
The success of autologous HSCT is predicated on the ability of cytotoxic chemotherapy with or without radiation to eradicate cancerous cells from the blood and bone marrow. This permits subsequent engraftment and repopulation of bone marrow space with presumably normal hematopoietic stem cells obtained from the patient prior to undergoing bone marrow ablation. As a consequence, autologous HSCT is typically performed as consolidation therapy when the patient’s disease is in complete remission. Patients who undergo autologous HSCT are

susceptible to chemotherapy-related toxicities and opportunistic infections prior to engraftment, but not GVHD.

The conventional ("classical") practice of allogeneic HSCT involves administration of cytotoxic agents (e.g., cyclophosphamide, busulfan) with or without total-body irradiation at doses sufficient to destroy endogenous hematopoietic capability in the recipient. The beneficial treatment effect in this procedure is due to a combination of initial eradication of malignant cells and subsequent graft-versus-malignancy (GVM) effect that develops after engraftment of allogeneic stem cells within the patient's bone marrow space. While the slower GVM effect is considered to be the potentially curative component, it may be overwhelmed by extant disease without the use of pretransplant conditioning. However, intense conditioning regimens are limited to patients who are sufficiently fit medically to tolerate substantial adverse effects that include pre-engraftment opportunistic infections secondary to loss of endogenous bone marrow function and organ damage and failure caused by the cytotoxic drugs. Furthermore, in any allogeneic HSCT, immune suppressant drugs are required to minimize graft rejection and GVHD, which also increases susceptibility of the patient to opportunistic infections.

Reduced-Intensity Conditioning for Allogeneic HSCT

Reduced-intensity conditioning (RIC) refers to the pretransplant use of lower doses or less intense regimens of cytotoxic drugs or radiation than are used in conventional full-dose myeloablative conditioning treatments. The goal of RIC is to reduce disease burden but also to minimize as much as possible associated treatment-related morbidity and 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 HSCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism, which may be supplemented with donor lymphocyte infusions to eradicate residual malignant cells. For the purposes of this 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

Acute lymphoblastic leukemia (ALL) is the most common cancer diagnosed in children and represents nearly 25% of cancers in children younger than 15 years. (1) Complete remission of disease is now typically achieved with pediatric chemotherapy regimens in approximately 95% of children with ALL, with up to 85% long-term survival rates. Survival rates have improved with the identification of effective drugs and combination chemotherapy through large, randomized trials, integration of presymptomatic central nervous system prophylaxis, and intensification and risk-based stratification of treatment. (2)

ALL is a heterogeneous disease with different genetic alterations resulting in distinct biologic subtypes. Patients are stratified according to certain clinical and genetic risk factors that predict outcome, with risk-adapted therapy tailoring treatment based on the predicted risk of relapse. (3) Two of the most important factors predictive of risk are patient age and white blood cell count (WBC) at diagnosis. (3) Certain genetic characteristics of the leukemic cells strongly

influence prognosis. Clinical and biologic factors predicting clinical outcome can be summarized as follows (2):

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

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. (4) Differences in the frequency of genetic abnormalities that characterize adult ALL versus childhood ALL help, in part, to explain the outcome differences between the 2 groups. For example, the “good prognosis” genetic abnormalities such as hyperdiploidy and t(12;21) are seen much less commonly in adult ALL, whereas they are some of the most common in childhood ALL. Conversely, “poor prognosis” genetic abnormalities such as the Philadelphia chromosome (t(9;22)) are seen in 25–30% 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) and greater than 100,000/µL (T-cell lineage).

Regulatory Status:

N/A

Medical Policy Statement

The safety and effectiveness of hematopoietic stem-cell transplantation for acute lymphoblastic leukemia has been established. It may be considered a useful therapeutic option for patients meeting patient selection criteria.

Contraindications

Absolute and relative contraindications represent situations where proceeding with transplant may not be advisable in the context of limited organ/tissue availability. Contraindications may evolve over time as transplant experience grows in the medical community. Clinical documentation supplied to the health plan *must* demonstrate that attending staff at the transplant center have considered *all* contraindications as part of their overall evaluation of potential organ transplant recipients and have decided to proceed.

Relative contraindications:

The selection process for approved tissue transplants is designed to obtain the best result for each patient. Therefore, relative contraindications to HSCT may include, but are not limited to:

- Poor cardiac function: Ejection fraction should be greater than 45% with no overt symptoms of congestive heart failure.
- Poor pulmonary function: Pulmonary function tests must be greater than or equal to 50% of predicted value.
- Poor renal function: Renal creatinine clearance should be greater than 40 ml/min or creatinine must be less than or equal to 2mg/dl.
- Poor liver function: There should be no history of severe chronic liver disease
- Presence of HIV or an active form of hepatitis B, hepatitis C or human T-cell lymphotropic virus (HTLV-1).

Inclusionary and Exclusionary Guidelines (Clinically based guidelines that may support individual consideration and pre-authorization decisions)

Children:

Inclusions:

- *Allogeneic* or *autologous* hematopoietic stem-cell transplantation (SCT) children with childhood acute lymphoblastic leukemia (ALL) in *first* complete remission but at high risk of relapse.
- A*utologous* or *allogeneic* hematopoietic SCT may be considered **medically necessary** to treat childhood ALL in *second or greater* remission or *refractory* ALL.

Exclusions:

Allogeneic hematopoietic SCT to treat relapsing ALL after a prior *autologous* SCT.

Adults:

Inclusions:

- A*utologous* hematopoietic SCT to treat adult ALL in first complete remission but at high risk of relapse.
- A*llogeneic* hematopoietic SCT to treat adult ALL in first complete remission for any risk level.
- A*llogeneic* hematopoietic SCT to treat adult ALL in second or greater remissions, or in patients with relapsed or refractory ALL.
- Reduced-intensity conditioning *allogeneic* hematopoietic SCT as a treatment of ALL in patients who are in complete marrow and extramedullary first or second remission, and who, for medical reasons would be unable to tolerate a standard myeloablative conditioning regimen.

Exclusions:

- A*utologous* hematopoietic SCT to treat adult ALL in second or greater remission or those with refractory disease.
- *Allogeneic* hematopoietic SCT to treat relapsing ALL after a prior *autologous* SCT.

CPT / HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure)*

Established codes:

38204	38205	38206	38208	38209	38210
38211	38212	38213	38214	38215	38220
38221	38230	38232	38240	38241	S2140
S2142	S2150				

Other codes (investigational, not medically necessary, etc.):

N/A

Rationale

Childhood ALL

The policy on childhood acute lymphoblastic leukemia (ALL) was initially based on TEC Assessments completed in 1987 and 1990. (5, 6) In childhood ALL, conventional chemotherapy is associated with complete remission rates of approximately 95%, with long-term durable remissions of 60%. Therefore, for patients in a first complete remission (CR1), hematopoietic stem-cell transplantation (HSCT) 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, HSCT may be a strong consideration in those with short remissions. At present, the comparative outcomes with either autologous or allogeneic HSCT are unknown.

Three reports describing the results of randomized controlled trials (RCTs) that compared outcomes of HSCT to outcomes with conventional-dose chemotherapy in children with ALL were identified subsequent to the TEC Assessment. (7-9) 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 HSCT were generally equivalent to overall outcomes after conventional-dose chemotherapy. While HSCT 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 (DFS) or overall survival rates (OS) at median follow-up of 78 months in children with very high-risk ALL in CR1 who received allogeneic or autologous HSCT versus standard chemotherapy with maintenance treatment. (10) Similar results were observed using either intention-to-treat (ITT) or per-protocol (PP) analyses. However, the authors point out several study limitations that could have affected outcomes, including the relatively small numbers of patients; variations among centers in the preparative regimen used prior to HSCT and time elapsed between complete remission (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 HSCT arm.

These results, and reviews of other studies (11, 12) suggest that while OS and event-free survival (EFS) are not different after HSCT compared to conventional-dose chemotherapy, HSCT remains an important therapeutic option in the management of childhood ALL, especially for patients considered at high risk of relapse. This conclusion is further supported by an evidence-based systematic review of the literature sponsored by the American Society for Blood and Marrow Transplantation (ASBMT). (13) Other investigators recommend that patients should be selected for this treatment using risk-directed strategies. (14, 15)

Adult ALL

The policy on adult ALL was initially based in part on a 1997 TEC Assessment of autologous (not allogeneic) HSCT. (16) This Assessment offered the following conclusions:

- For patients in CR1, available data suggested survival was equivalent after autologous HSCT or conventional-dose chemotherapy. For these patients, the decision between autologous HSCT and conventional chemotherapy may reflect a choice between intensive therapy of short duration and longer but less-intensive treatment.
- In other settings, such as in second (CR2) or subsequent remissions, data were inadequate to determine the relative effectiveness of autologous HSCT compared to conventional chemotherapy.

A subsequent evidence-based systematic review sponsored by ASBMT addressed the issue of HSCT in adults with ALL. (17) Based on its review of evidence available through January 2005, the ASBMT panel recommended HSCT as consolidation therapy for adults with high-risk disease in CR1 but not for standard-risk patients. It also recommended HSCT for patients in CR2, although data are not available to directly compare outcomes with alternatives. Based on results from 3 RCTs, (18-20) the ASBMT panel further concluded that myeloablative allogeneic HSCT is superior to autologous HSCT in adult patients in CR1, although available data did not permit separate analyses in high-risk versus low-risk patients.

Results that partially conflicted with the ASBMT conclusions were obtained in a multicenter (35 Spanish hospitals) randomized trial (PETHEMA ALL-93; n=222) published after the ASBMT literature search. (21) Among 183 high-risk patients in CR1, those with a human leukocyte antigen (HLA)-identical family donor were assigned to allogeneic HSCT (n=84); the remaining cases were randomly assigned to autologous HSCT (n=50) or to delayed intensification followed by maintenance chemotherapy up to 2 years in CR (n=48). At median follow-up of 70 months, the study did not detect a statistically significant difference in outcomes between all 3 arms by both PP and ITT analyses. The PETHEMA ALL-93 trial investigators point out several study limitations that could have affected outcomes, including the relatively small numbers of patients; variations among centers in the preparative regimen used prior to HSCT; differences in risk group assignment; and the use of genetic randomization based on donor availability rather than true randomization for patients included in the allogeneic HSCT arm.

A meta-analysis published in 2006 pooled data from 7 studies of allogeneic HSCT published between 1994 and 2005 that included a total of 1,274 patients with ALL in CR1. (22) The results showed that regardless of risk category, allogeneic HSCT was associated with a significant OS advantage (hazard ratio [HR]: 1.29; 95% confidence interval [CI]: 1.02, 1.63, p=0.037) for all patients who had a suitable donor versus patients without a donor who received chemotherapy or autologous HSCT. Pooled data from patients with high-risk disease showed an increased survival advantage for allogeneic HSCT compared to those without a

donor (HR: 1.42; 95% CI: 1.06-1.90, p=0.019). None of the studies in this meta-analysis showed significant benefit of allogeneic HSCT for patients who did not have high-risk disease, nor did the meta-analysis. However, the individual studies were relatively small, the treatment results were not always comparable, and the definitions of high-risk disease features varied across all studies.

A subsequent meta-analysis from the Cochrane group evaluated the evidence for the efficacy of matched sibling stem-cell donor versus no donor status for adults with ALL in CR1. (23) A total of 14 trials with treatment assignment based on genetic randomization including a total of 3,157 patients were included in this analysis. Matched sibling donor HSCT was associated with a statistically significant overall survival advantage compared to the no donor group (HR: 0.82; 95% CI: 0.77, 0.97, p=0.01). Patients in the donor group had a significantly lower rate of primary disease relapse than those without a donor (risk ratio [RR]: 0.53; 95% CI: 0.37, 0.76, p=0.0004) and significantly increased non-relapse mortality (RR: 2.8; 95% CI: 1.66, 4.73, p=0.001). These results support the conclusions of this policy, that allogeneic HSCT (matched sibling donor) is an effective postremission therapy in adult patients.

While the utility of allogeneic HSCT for postremission therapy in patients with high-risk ALL has been established, its role in those who do not have high-risk features has been less clear. This question has been addressed by the International ALL trial, a collaborative effort conducted by the Medical Research Council (MRC) in the United Kingdom and the Eastern Cooperative Oncology Group (ECOG) in the United States (MRC UKALL XII/ECOG E2993). (24) The ECOG 2993 trial was a Phase III randomized study designed to prospectively define the role of myeloablative allogeneic HSCT, autologous HSCT, and conventional consolidation and maintenance chemotherapy for adult patients up to age 60 years with ALL in CR1. This study is the largest RCT in which all patients (total n=1,913) received essentially identical therapy, irrespective of their disease risk assignment. After induction treatment that included imatinib mesylate for Philadelphia chromosome-positive patients, all patients who had an HLA-matched sibling donor (n=443) were assigned to receive an allogeneic HSCT. Patients with the Philadelphia (Ph) chromosome (n=267) who did not have a matched sibling donor could receive an unrelated donor HSCT. Patients who did not have a matched sibling donor or were older than 55 years (n=588) were randomly allocated to receive a single autologous HSCT or consolidation and maintenance chemotherapy.

In ECOG2993, OS at 5-year follow-up of all 1,913 patients was 39%; it reached 53% for Ph-negative patients with a donor (n=443) compared to 45% without a donor (n=588) (p=0.01). (24) Analysis of Ph-negative patient outcomes according to disease risk showed a 5-year OS of 41% among patients with high-risk ALL and a sibling donor versus 35% of high-risk patients with no donor (p=0.2). In contrast, OS at 5-years follow-up was 62% among standard risk Ph-negative patients with a donor and 52% among those with no donor, a statistically significant difference (p=0.02). Among Ph-negative patients with standard risk disease who underwent allogeneic HSCT, the relapse rate was 24% at 10-years, compared to 49% among those who did not undergo HSCT (p<0.00005). Among Ph-negative patients with high-risk ALL, the rate of relapse at 10-year follow-up was 37% following allogeneic HSCT versus 63% without a transplant (p<0.00005), demonstrating the potent graft-versus-leukemia (GVL) effect in an allogeneic transplantation. These data clearly show a significant long-term survival benefit associated with postremission allogeneic HSCT in standard risk Ph-negative patients, an effect previously not demonstrated in numerous smaller studies. Failure to demonstrate a significant OS benefit in high-risk Ph-negative cases can be attributed to a high non-relapse mortality (NRM) rate at 1 and 2 years, mostly due to GVHD and infections. At 2 years, NRM was 36%

among high-risk patients with a donor compared to 14% among those who did not have a donor. Among standard risk cases, the NRM rate at 2 years was 20% in patients who underwent allogeneic HSCT versus 7% in those who received autologous HSCT or continued chemotherapy.

In a separate report on the Ph-positive patients in ECOG2993, an ITT analysis (n=158) showed 5-year OS of 34% (95% CI: 25-46%) for those who had a matched sibling donor versus 25% (95% CI: 12-34%) with no donor who received consolidation and maintenance chemotherapy. (25) Although the difference in survival rates was not statistically significant, this analysis demonstrated a moderate superiority of postremission-matched sibling allogeneic HSCT over chemotherapy in patients with high-risk ALL in CR1, in concordance with this policy.

The Dutch HOVON cooperative group reported results combined from 2 successive randomized trials in previously untreated adult patients with ALL aged 60 years or younger, in which myeloablative allogeneic HSCT was consistently used for all patients who achieved CR1 and who had an HLA-matched sibling donor, irrespective of risk category. (26) A total 433 eligible patients included 288 younger than 55 years, in CR1, and eligible to receive consolidation treatment by an autologous HSCT or an allogeneic HSCT. Allogeneic HSCT was performed in 91 of 96 (95%) with a compatible sibling donor. Overall survival at 5-year follow-up was 61% +/- 5% among all patients with a donor and 47% +/- 5% among those without a donor (p=0.08). The cumulative incidence of relapse at 5-year follow-up among all patients was 24% +/- 4% (SE) in those with a donor versus 55% +/- 4% (SE) in those (n=161) without a donor (p<0.001). Among patients stratified by disease risk, those in the standard risk category with a donor (n=50) had 5-year OS of 69% +/- 7% and relapse rate at 5 years of 14% +/- 5% compared to 49% +/- 6% and 52% +/- 5%, respectively, among those (n=88) without a donor (p=0.05). High-risk patients with a donor (n=46) had 5-year OS of 53% +/- 8% and relapse at 5 years of 34% +/- 7%, versus 41% +/- 8% and 61% +/- 7%, respectively, among those with no donor (n=3; p=0.50). NRM rates among standard risk patients were 16% +/- 5% among those with a donor and 2% +/- 2% among those without a donor; in high-risk patients, NRM rates were 15% +/- 7% and 4% +/- 3%, respectively, among those with and without a donor.

The HOVON studies were analyzed as from remission evaluation prior to consolidation whereas the ECOG2993 data were analyzed and presented as from diagnosis, which complicates direct comparison of their outcomes. To facilitate a meaningful comparison, the HOVON data were reanalyzed according to donor availability from diagnosis. This showed a 5-year OS rate of 60% in standard-risk patients with a donor in the HOVON study, which is very similar to the 62% OS observed in standard-risk patients with a donor in the ECOG2993 trial. Collectively, these results suggest that patients with standard-risk ALL can expect to benefit from allogeneic HSCT in CR1, provided the NRM risk is less than approximately 20% to 25%. (26)

Current data indicate postremission myeloablative allogeneic HSCT 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. Notwithstanding those caveats, taken together, current evidence supports the use of myeloablative allogeneic HSCT for patients with ALL in CR1 whose health status is sufficient to tolerate the procedure (see Policy Guidelines).

<u>Reduced-Intensity Conditioning (RIC) Allogeneic HSCT</u>

The use of RIC regimens has been investigated as a means to extend the substantial GVL effect of postremission allogeneic HSCT to patients who could expect to benefit from this approach but who are ineligible or would not be able to tolerate a fully myeloablative procedure. In a multicenter single-arm study of patients (n=43, median age 19 years; range: 1–55 years) in 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. (27)

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

RIC for allogeneic HSCT 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 white blood cell [WBC]) in CR1 (81%) or CR2 (19%) who were ineligible to receive a myeloablative allogeneic HSCT because of age, organ dysfunction, low Karnofsky performance status (<50%) or the presence of infection. (29) 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 graft-versus-host disease (GVHD) prophylaxis (cyclosporine or tacrolimus, plus methotrexate). All Ph-positive patients also received imatinib prior to HSCT. 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, 24 (96%) of whom 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 HSCT with a fludarabine-based RIC regimen. (30) It represents the first large cooperative group study to be published in this setting. Among the 17 cases, 4 were in CR2, 12 in CR3, and 1 had secondary ALL. All patients were heavily pretreated, including previous myeloablative allogeneic or autologous HSCT, 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 HSCT. 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 HSCT. Treatment-related mortality was not reported by disease, nor were HSCT-related morbidities. However, these data do suggest allogeneic HSCT with RIC can be used in children with high-risk ALL and achieve some long-term survival in patients with no therapeutic recourse.

Thus, based on currently available data and clinical input as noted in the following section, RIC allogeneic HSCT may be considered medically necessary in patients who demonstrate

complete marrow and extramedullary first or second remission, could be expected to benefit from a myeloablative allogeneic HSCT, and 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 HSCT.

Allogeneic Transplant after Prior Failed Autologous Transplant

A 2000 TEC Assessment focused on allogeneic HSCT after a prior failed autologous HSCT, in the treatment of a variety of malignancies, including ALL. (31) The TEC Assessment found that data were inadequate to permit conclusions about outcomes of this treatment strategy. Published evidence was limited to small, uncontrolled clinical series with short follow-up. Updated literature searches have not identified any additional evidence to permit conclusions on this use of HSCT.

Summary

Clinical study results summarized above suggest that while OS and EFS are not different after HSCT compared to conventional-dose chemotherapy in most children with standard risk ALL, HSCT remains an important therapeutic option for patients considered at high risk of relapse. This conclusion is further supported by an evidence-based systematic review of the literature sponsored by the ASBMT. It has been recommended that patients should be selected for this treatment using risk-directed strategies.

Current data indicate postremission myeloablative allogeneic HSCT 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. Further, for adults who survive the procedure, there is a significant relapse rate. Notwithstanding those caveats, taken together, current evidence supports the use of myeloablative allogeneic HSCT for patients with ALL in CR1 whose health status is sufficient to tolerate the procedure (see Policy Guidelines). RIC allogeneic HSCT may be considered medically necessary in patients who demonstrate complete marrow and extramedullary first or second remission, could be expected to benefit from a myeloablative allogeneic HSCT, and 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 HSCT. Evidence is insufficient to permit conclusions on the use of allogeneic HSCT following failure of autologous HSCT.

Clinical Input Received through Physician Specialty Societies and Academic Medical Centers

In response to requests, Blue Cross Blue Shield Association received input from 1 physician specialty society (2 reviewers) and 2 academic medical centers while this policy was under review in 2008. While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted. There was strong consensus among reviewers that reduced-intensity conditioning allogeneic HSCT was of value in patients who were in complete remission. With this exception, there was general support for the policy statements.

National Comprehensive Cancer Network Guidelines

The 2011 National Comprehensive Cancer Network clinical practice guidelines for non-Hodgkin's lymphoma indicate autologous or allogeneic HSCT is appropriate for treatment of

poor-risk patients with lymphoblastic lymphoma (i.e., when disease is considered to be systemic). (32) These guidelines are generally consistent with this policy.

National Cancer Institute Clinical Trials Database (PDQ®)
A search of the NCI PDQ database in December 2011 identified 17 active Phase II/III trials that involve stem-cell support for adult patients with ALL (Available online at: http://www.cancer.gov/clinicaltrials/search/results?protocolsearchid=7147167).
Twenty trials were identified for pediatric ALL (Available online at: http://www.cancer.gov/clinicaltrials/search/results?protocolsearchid=9873567).

Government Regulations

National:

National Coverage Determination (NCD) for Stem Cell Transplantation (110.8.1), Effective Date of this Version 8/4/10, Implementation Date 11/10/10, Retrieved from: http://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=45&ncdver=5&bc=AgAAgAAAAAAA&, Accessed 7/31/12.

Indications and Limitations of Coverage

1. **Allogeneic Hematopoietic Stem Cell Transplantation (HSCT)**
   Allogeneic hematopoietic stem cell transplantation (HSCT) is a procedure in which a portion of a healthy donor's stem cell or bone marrow is obtained and prepared for intravenous infusion.
   a. Nationally Covered Indications
      The following uses of allogeneic HSCT are covered under Medicare:
      i. Effective for services performed on or after August 1, 1978, for the treatment of leukemia, leukemia in remission, or aplastic anemia when it is reasonable and necessary,
      ii. Effective for services performed on or after June 3, 1985, for the treatment of severe combined immunodeficiency disease (SCID) and for the treatment of Wiskott-Aldrich syndrome.
      iii. Effective for services performed on or after August 4, 2010, for the treatment of Myelodysplastic Syndromes (MDS) pursuant to Coverage with Evidence Development (CED) in the context of a Medicare-approved, prospective clinical study.

2. **Autologous Stem Cell Transplantation (AuSCT)**
   Autologous stem cell transplantation (AuSCT) is a technique for restoring stem cells using the patient's own previously stored cells.
   a. Nationally Covered Indications
      i. Effective for services performed on or after April 28, 1989, AuSCT is considered reasonable and necessary under §l862(a)(1)(A) of the Social Security Act (the Act) for the following conditions and is covered under Medicare for patients with:
         - Acute leukemia in remission who have a high probability of relapse and who have no human leucocyte antigens (HLA)-matched;
         - Resistant non-Hodgkin's lymphomas or those presenting with poor prognostic features following an initial response;
         - Recurrent or refractory neuroblastoma; or
         - Advanced Hodgkin's disease who have failed conventional therapy and have no HLA-matched donor.

ii. Effective October 1, 2000, single AuSCT is only covered for Durie-Salmon Stage II or III patients that fit the following requirements:
   - Newly diagnosed or responsive multiple myeloma. This includes those patients with previously untreated disease, those with at least a partial response to prior chemotherapy (defined as a 50% decrease either in measurable paraprotein [serum and/or urine] or in bone marrow infiltration, sustained for at least 1 month), and those in responsive relapse; and,
   - Adequate cardiac, renal, pulmonary, and hepatic function.

iii. Effective for services performed on or after March 15, 2005, when recognized clinical risk factors are employed to select patients for transplantation, high dose melphalan (HDM) together with AuSCT is reasonable and necessary for Medicare beneficiaries of any age group with primary amyloid light chain (AL) amyloidosis who meet the following criteria:
   - Amyloid deposition in 2 or fewer organs; and,
   - Cardiac left ventricular ejection fraction (EF) greater than 45%.

b. Nationally Non-Covered Indications

Insufficient data exist to establish definite conclusions regarding the efficacy of AuSCT for the following conditions:

- Acute leukemia not in remission;
- Chronic granulocytic leukemia;
- Solid tumors (other than neuroblastoma);
- Up to October 1, 2000, multiple myeloma;
- Tandem transplantation (multiple rounds of AuSCT) for patients with multiple myeloma;
- Effective October 1, 2000, non primary AL amyloidosis; and,
- Effective October 1, 2000, thru March 14, 2005, primary AL amyloidosis for Medicare beneficiaries age 64 or older.

In these cases, AuSCT is not considered reasonable and necessary within the meaning of §l862(a)(1)(A) of the Act and is not covered under Medicare.

All other indications for stem cell transplantation not otherwise noted above as covered or non-covered nationally remain at local contractor discretion.

Local:

There is no local coverage determination on this topic.

Michigan Department of Community Health:

Medicaid Provider Manual, Version Date: April 1, 2012, Retrieved from http://www.mdch.state.mi.us/dch-medicaid/manuals/MedicaidProviderManual.pdf, Accessed: 7/31/12.

6.6 Transplants

Heart, bone marrow, liver, lung, simultaneous pancreas/kidney and pancreas transplants are reimbursed at the hospital's Medicaid cost to charge ratio.

- Organ acquisition costs are reimbursed at 100% of charges when billed using either revenue code 0811 or 0812. This applies to heart, kidney, liver, lung, simultaneous pancreas/kidney, or pancreas transplants. This does not apply to bone marrow transplants. All bone marrow transplant charges are reimbursed at the hospital's cost to charge ratio.

- The letter of authorization for the transplant from the Office of Medical Affairs (OMA) or MHP must be attached to all transplant claims, otherwise, payment is denied.
- Indicate "PA letter submitted" in the Remarks Section of the submitted claim.
- For other transplant services not described by a specific DRG, identify in the Remarks Section the type of transplant that has been performed (i.e., small bowel transplant).
- If the donor and beneficiary are both Medicaid eligible, the services must be billed under each beneficiary's respective ID Number. If only the beneficiary is Medicaid eligible, bill services for both donor and beneficiary under the Medicaid beneficiary's ID Number.

All other insurance resources must be exhausted before Medicaid is billed. If Medicare eligibility is denied, the denial notice must be submitted with the claim.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- BMT – Autologous, for Malignant Astrocytomas and Gliomas
- BMT – Hematopoietic Stem Cell Transplantation for Breast Cancer
- BMT – Hematopoietic Stem Cell Transplantation for Treatment of Multiple Myeloma
- BMT – Hematopoietic Stem Cell Transplantation for Acute Myeloid Leukemia
- BMT – Hematopoietic Stem Cell Transplantation for Autoimmune Diseases
- BMT – Hematopoietic Stem Cell Transplantation for Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma - Autologous or Allogeneic
- BMT – Hematopoietic Stem Cell Transplantation for Chronic Myelogenous Leukemia
- BMT – Hematopoietic Stem Cell Transplantation for CNS Embryonal Tumors and Ependymoma
- BMT – Hematopoietic Stem Cell Transplantation for Epithelial Ovarian Cancer
- BMT – Hematopoietic Stem Cell Transplantation for Hodgkin Lymphoma
- BMT – Hematopoietic Stem Cell Transplantation for Miscellaneous Solid Tumors in Adults
- BMT – Hematopoietic Stem Cell Transplantation for Non-Hodgkin Lymphomas
- BMT – Hematopoietic Stem Cell Transplantation for Primary Amyloidosis
- BMT – Hematopoietic Stem Cell Transplantation for Solid Tumors of Childhood
- BMT – Hematopoietic Stem Cell Transplantation for Waldenström's Macroglobulinemia
- BMT – Hematopoietic Stem Cell Transplantation in the Treatment of Germ-Cell Tumors
- Donor Lymphocyte Infusion for Malignancies Treated with an Allogeneic Hematopoietic Stem-Cell Transplant

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through August 2, 2012, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
1/1/13	10/16/12	10/16/12	• Topic split out from former combined BMT policies. • Policy formatted to mirror BCBSA. • Added “relative contraindications” to inclusionary/exclusionary section.

Next Review Date: 4th Qtr, 2013

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: HEMATOPOIETIC STEM-CELL TRANSPLANTATION FOR ACUTE LYMPHOBLASTIC LEUKEMIA

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered; criteria apply.
BCNA (Medicare Advantage)	Refer to Medicare section.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.
Blue Cross Complete of Michigan	Refer to Medicare section.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.