Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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Current Policy Effective Date: 3/1/13

Title: BMT- Stem-Cell Transplantation for CNS Embryonal Tumors and Ependymoma

Description / Background

High-dose chemotherapy with hematopoietic stem-cell transplantation (HSCT) has been investigated as a possible therapy in pediatric patients with brain tumors, particularly in patients with disease that is considered high risk. In addition, the use of HSCT has allowed for a reduction in the dose of radiation needed to treat both average and high-risk disease, with preservation of quality of life and intellectual functioning, without compromising survival.

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. Bone-marrow stem cells may be obtained from the transplant recipient (i.e., autologous SCT) or from a donor (i.e., allogeneic SCT). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood and placenta shortly after delivery of neonates.

Hematopoietic Stem-Cell Transplantation for Brain Tumors

Autologous HSCT allows for escalation of chemotherapy doses above those limited by myeloablation and has been tried in patients with high-risk brain tumors in an attempt to eradicate residual tumor cells and improve cure rates. The use of allogeneic HSCT for solid tumors does not rely on escalation of chemotherapy intensity and tumor reduction but rather on a graft-versus-tumor effect. Allogeneic HSCT is not commonly used in solid tumors and may be used if an autologous source cannot be cleared of tumor or cannot be harvested.

CNS Embryonal Tumors

Classification of brain tumors is based on both histopathologic characteristics of the tumor and location in the brain. Central nervous system (CNS) embryonal tumors are more common in children and are the most common brain tumor in childhood. They are primarily composed of undifferentiated round cells, with divergent patterns of differentiation. It has been proposed that these tumors be merged under the term “primitive neuroectodermal tumor” (PNET); however, histologically similar tumors in different locations in the brain demonstrate different molecular

genetic alterations. Embryonal tumors of the CNS include medulloblastoma, medulloepithelioma, supratentorial PNETs (pineoblastoma, cerebral neuroblastoma, ganglioneuroblastoma), ependymoblastoma and atypical teratoid/rhabdoid tumor (AT/RT).

Medulloblastomas account for 20% of all childhood CNS tumors. The other types of embryonal tumors are rare by comparison. Surgical resection is the mainstay of therapy with the goal being gross total resection with adjuvant radiation therapy, as medulloblastomas are very radiosensitive. Treatment protocols are based on risk stratification, as average or high risk. The average-risk group includes children older than 3 years, without metastatic disease, and with tumors that are totally or near totally resected (<1.5 cm^2 of residual disease). The high-risk group includes children aged 3 years or younger, or with metastatic disease, and/or subtotal resection (>1.5 cm^2 of residual disease). (1)

Current standard treatment regimens for average-risk medulloblastoma (postoperative craniospinal irradiation with boost to the posterior fossa followed by 12 months of chemotherapy) have resulted in 5-year overall survival (OS) rates of 80% or better. (1) For high-risk medulloblastoma treated with conventional doses of chemotherapy and radiotherapy, the average event-free survival (EFS) at 5 years ranges from 34–40% across studies. (2) Fewer than 55% of children with high-risk disease survive longer than 5 years. The treatment of newly diagnosed medulloblastoma continues to evolve, and in children under the age of 3 years, because of the concern of the deleterious effects of craniospinal radiation on the immature nervous system, therapeutic approaches have attempted to delay and sometimes avoid the use of radiation and have included trials of higher-dose chemotherapeutic regimens with autologous HSCT.

Supratentorial PNETs (sPNET) are most commonly located in the cerebral cortex and pineal region. The prognosis for these tumors is worse than for medulloblastoma, despite identical therapies. (2) After surgery, children are usually treated similarly to children with high-risk medulloblastoma. Three- to 5-year OS rates of 40–50% have been reported, and for patients with disseminated disease, survival rates at 5 years range from 20–30%. (3)

Recurrent childhood CNS embryonal tumor is not uncommon, and depending on which type of treatment the patient initially received, autologous HSCT may be an option. For patients who receive high-dose chemotherapy and autologous HSCT for recurrent embryonal tumors, objective response is 50–75%; however, long-term disease control is obtained in fewer than 30% of patients and is primarily seen in patients in first relapse with localized disease at the time of relapse. (3)

Ependymoma

Ependymoma is a neuroepithelial tumor that arises from the ependymal lining cell of the ventricles and is, therefore, usually contiguous with the ventricular system. In children, the tumor typically arises intracranially, while in adults, a spinal cord location is more common. Ependymomas have access to the cerebrospinal fluid and may spread throughout the entire neuroaxis. Ependymomas are distinct from ependymoblastomas due to their more mature histologic differentiation. Initial treatment of ependymoma consists of maximal surgical resection followed by radiotherapy. Chemotherapy usually does not play a role in the initial treatment of ependymoma. However, disease relapse is common, typically occurring at the site of origin. Treatment of recurrence is problematic; further surgical resection or radiation therapy is usually not possible. Given the poor response to conventional-dose chemotherapy, high-dose chemotherapy with autologous HSCT has been investigated as a possible salvage therapy. Peripheral neuroblastoma and Ewing’s sarcoma may be considered PNETs but differ due to their neuroepithelial origins.

Medical Policy Statement

- **Embryonal tumors of the CNS**
  The safety and effectiveness of specified *autologous* stem cell transplants for embryonal tumors of the central nervous system have been established. It may be considered a useful therapeutic tool when indicated for patients who meet established patient selection guidelines.

- **Ependymoma**
  Autologous, *tandem autologous and allogeneic hematopoietic* stem-cell transplants are experimental and investigational for the treatment of ependymoma. They have not been scientifically demonstrated to improve patient clinical outcomes better than conventional treatment.

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)

Embryonal tumors of the CNS

Inclusions:

- *Autologous* hematopoietic stem-cell transplantation for previously untreated embryonal tumors of the central nervous system (CNS) that show partial or complete response to induction chemotherapy, or stable disease after induction therapy.
- *Autologous* hematopoietic stem-cell transplantation for the treatment of recurrent embryonal tumors of the CNS.

Exclusions:

- *Tandem* autologous hematopoietic stem-cell transplant for the treatment of embryonal tumors of the CNS.
- *Allogeneic* hematopoietic stem-cell transplantation for the treatment of embryonal tumors of the CNS.

Ependymoma

Inclusions:

N/A

Exclusions:

- Autologous, tandem autologous and allogeneic hematopoietic stem-cell transplants are experimental and investigational for the treatment of ependymoma.

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 (Note: These codes may be established or investigational based on the diagnosis of embryonal tumor of the CNS or ependymoma. Please refer to medical policy statement)

38204	38205	38207	38208	38209	38210
38211	38212	38213	38214	38215	38220
38221	38230	38232	38240	38242	81267
81268	81270	81271	81272	81273	81274
81275	81276	81277	81278	81279	81280
81281	81282	81283	86812	86813	86816
86817	86821	86822	S2140	S2142	S2150

Regulatory Status:

N/A

Rationale

CNS Embryonal Tumors
Newly diagnosed
Chintagumpala and colleagues reviewed event-free survival (EFS) of 16 patients with newly diagnosed supratentorial primitive neuroectodermal tumor (sPNET) treated with risk-adapted craniospinal irradiation and subsequent high-dose chemotherapy with autologous hematopoietic stem-cell transplantation (HSCT) between 1996 and 2003. (4) Eight patients were considered at average risk and 8 were at high risk (defined as the presence of residual tumor larger than 1.5 cm^2 or disseminated disease in the neuroaxis). Median age at diagnosis was 7.9 years (range: 3–21 years). Seven patients had pineal PNET. After a median follow-up of 5.4 years, 12 patients were alive. Five-year EFS and overall survival (OS) for the patients with average-risk disease were 75% (+/- 17%) and 88% (+/- 13%), respectively, and for the high-risk patients 60% (+/- 19%) and 58% (+/- 19%), respectively. No treatment-related toxicity deaths were reported. The authors concluded that high-dose chemotherapy with stem-cell support after risk-adapted craniospinal irradiation allows for a reduction in the dose of radiation needed to treat nonmetastatic, average-risk sPNET, without compromising EFS.

Fangusaro and colleagues reported outcomes for 43 children with newly diagnosed sPNET treated prospectively on two serial studies (Head Start 1 [HS1] and Head Start 2 [HS2]) between

1991 and 2002 with intensified induction chemotherapy followed by myeloablative chemotherapy and autologous HSCT. (2) There were no statistical differences between HS1 and HS2 patient demographics. After maximal surgical resection, patients underwent induction chemotherapy. If, after induction, the disease remained stable or there was partial or complete response, patients underwent myeloablative chemotherapy with autologous HSCT (n=32). Patients with progressive disease at the end of induction were not eligible for consolidation. Five-year EFS and OS were 39% (95% confidence interval [CI]: 24–53%) and 49% (95% CI: 33–62%), respectively. Patients with non-pineal tumors did significantly better than patients with pineal PNETs (2-year and 5-year EFS of 57% vs. 23% and 48% vs. 15%, respectively and 2-year and 5-year OS of 70% vs. 31% and 60% vs. 23%, respectively). Sixty percent of survivors were alive without exposure to radiation therapy.

Dhall and colleagues reported outcomes for children younger than 3 years of age at diagnosis of nonmetastatic medulloblastoma, after being treated with 5 cycles of induction chemotherapy and subsequent myeloablative chemotherapy and autologous HSCT. (5) Twenty of 21 children enrolled completed induction chemotherapy, of which 14 had a gross total surgical resection and 13 remained free of disease at the completion of induction chemotherapy. Of 7 patients with residual disease at the beginning of induction, all achieved a complete radiographic response to induction chemotherapy. Of the 20 patients who received consolidation chemotherapy, 18 remained free of disease at the end of consolidation. In patients with gross total tumor resection, 5-year EFS and OS were 64% (+/- 13) and 79% (+/- 11), respectively, and for patients with residual tumor, 29% (+/- 17) and 57% (+/-19), respectively. There were 4 treatment-related deaths. The need for craniospinal irradiation was eliminated in 52% of the patients, and 71% of survivors avoided irradiation completely, with preservation of quality of life and intellectual functioning.

Gajjar and colleagues reported the results of risk-adapted craniospinal radiotherapy followed by high-dose chemotherapy and autologous HSCT in 134 children with newly diagnosed medulloblastoma. (6) After tumor resection, patients were classified as having average-risk disease (n=86), defined as ≤ 1.5 cm^2 residual tumor and no metastatic disease, or high-risk disease (n=48), defined as greater than 1.5 cm^2 residual disease or metastatic disease localized to the neuroaxis. A total of 119 children completed the planned protocol. Five-year OS was 85% (95% CI: 75–94%) among the average-risk cases and 70% (95% CI: 54–84%) in the high-risk patients. Five-year EFS was 83% (95% CI: 73–93%) and 70% (95% CI: 55–85%) for average- and high-risk patients, respectively. No treatment-related deaths were reported.

Lee and colleagues retrospectively reviewed the medical records of 13 patients diagnosed with atypical teratoid/rhabdoid tumor (AT/RT) who were treated at their institute at Seoul National Children's University Hospital (Korea). (7) The median age was 12 months (range: 3–67 months), and 7 patients were younger than 1-year old at the time of diagnosis. Three patients (23%) underwent high-dose chemotherapy and autologous HSCT. The authors assessed the impact on OS in these 3 patients, as compared to the remaining 10 patients undergoing other chemotherapy regimens. No statistical difference in OS was observed between these 2 groups (p=0.36); however, the median survival was reported to be higher in the HSCT group (15 months) compared to the non-HSCT group (9 months). (7)

National Cancer Institute (NCI) Clinical Trial Database (PDQ®)

- A Phase III study of combination chemotherapy, radiation therapy, and an autologous peripheral blood stem-cell transplant in treating young patients with AT/RT (NCT00653068, COG-ACNS0333) is active. The primary purpose of this multi-center study (being undertaken

in 87 trial sites across the U.S., Australia, and Canada) is to determine the EFS and OS of children (birth to 21 years of age) with AT/RT treated with surgery, high-dose chemotherapy combined with HSCT, and radiation therapy. Expected enrollment is 70 patients, with an estimated trial completion date of June 2017.

- A Phase III study of radiation therapy and combination chemotherapy followed by autologous stem-cell transplant in patients with newly diagnosed medulloblastoma, supratentorial primitive neuroectodermal tumor, or atypical teratoid rhabdoid tumor (NCT00085202, SJCRH-SJMB03) is active. The purpose of the study is to compare 2 different regimens of radiation therapy when given together with chemotherapy and autologous stem-cell transplant. Projected accrual is 413 patients, and estimated date of study completion is September 2016.
- A Phase III pilot study of induction chemotherapy followed by consolidation myeloablative chemotherapy comprising thiotepa and carboplatin with or without etoposide followed by autologous hematopoietic stem cell rescue in pediatric patients with previously untreated malignant brain tumors (NCT00392886; CHLA-HEAD-START-III) is closed. The study compares 2 alternative induction regimens prior to myeloablative chemotherapy and stem cell rescue. Expected enrollment was 120 patients, with an estimated trial completion date in December 2010. The publication date of this study is presently unknown.
- A Phase III randomized study of intensive induction chemotherapy comprising vincristine, etoposide, cyclophosphamide, and cisplatin with or without high-dose methotrexate and leucovorin followed by consolidation chemotherapy comprising carboplatin and thiotepa and peripheral blood stem-cell rescue in pediatric patients with newly diagnosed supratentorial primitive neuroectodermal tumors or high-risk medulloblastoma (NCT00336024, COG-ACNS0334) is suspended. The study was intended to compare the response rate of induction therapy with or without methotrexate and leucovorin. Expected enrollment is 96 patients, with an estimated trial completion date of September 2018.

Recurrent

Raghuram and colleagues performed a systematic review of the literature regarding the outcome of patients with relapsed sPNET treated with high-dose chemotherapy and autologous HSCT.(8) Eleven observational studies published before 2010 met their inclusion criteria; 4 of these were prospective case-series. The 11 studies consisted of 46 patients diagnosed with relapsed sPNET or pineoblastoma who received autologous HSCT for treatment of relapse. Of those, 15 patients were children younger than 3 years of age, and 15 were pineoblastomas. With a median follow-up of 40 months (range 3-123 months) 15 patients were reported alive. Thirteen patients (of 15 survivors) did not receive craniospinal irradiation. The 12-month OS rate of the cohort was 44.2 ± 7.5 months. Twelve-month OS for children younger than 36 months was 66.7 ± 12.2 months, while for older children, 12-month OS was 27.8 ± 10.6 ($p=0.003$). Twelve-month OS was 20.0 ± 10.3 for those patients with pineoblastoma versus 54.6 ± 9.0 for those with non-pineal sPNETs ($p<0.001$). Cox regression analysis revealed pineal location as the only independent adverse prognostic factor. (8) Based on these pooled results, high-dose chemotherapy with HSCT might lead to survival primarily in younger children with relapsed sPNET, even in the absence of concomitant use of radiotherapy, whereas the outcome in older children and/or in a pineal location is poor with this modality.

Dunkel and colleagues report an expanded series with longer follow-up using autologous HSCT for previously irradiated recurrent medulloblastoma. (9,10) Twenty-five patients were treated between 1990 and 1999 and consisted of 18 males and 7 females with a median age at diagnosis of 11.5 years (range: 4.2-35.5 years). Median age at the time of HSCT was 13.8 years (range: 7.6-44.7 years). All patients had previously received postoperative external beam

radiation with (n=15) or without (n=10) chemotherapy. The median time from diagnosis to disease relapse or progression was 29.8 months (range 5.3-114.7 months). Stage at the time of relapse was M0 n=6, M1 n=1, M2 n=8, M3 n=10 (M0=no evidence of subarachnoid or hematogenous metastasis, M1=tumor cells found in cerebrospinal fluid, M2=intracranial tumor beyond primary site, M3=gross nodular seeding in spinal subarachnoid space). High-dose chemotherapy prior to HSCT consisted of carboplatin, thiotepa and etoposide. Treatment-related mortality was 12% within 30 days of transplant. Tumor recurred in 16 patients at a median of 8.5 months after HSCT (range: 2.3-58.5 months). Median overall survival (OS) was 26.8 months (95% CI: 11.9-51.1 months) and event-free survival (EFS) and OS at 10 years post-HSCT was 24% for both (95% CI: 9.8-41.7%). The authors concluded that this retrieval strategy provides long-term EFS for some patients with previously irradiated recurrent medulloblastoma.

In the earlier publication, Dunkel and colleagues reported the outcomes of 23 patients with recurrent medulloblastoma treated with high-dose carboplatin, thiotepa and etoposide. (10) Seven patients were event-free survivors at a median of 54 months, with OS estimated at 46% at 36 months. HSCT was expected to be most effective with minimal disease burden. Thus, Dunkel and colleagues suggested increased surveillance for recurrence or aggressive surgical debulking at the time of recurrence. The authors also acknowledged the potential for effects of patient selection bias on their results, since not all patients eligible for the protocol were enrolled.

Grodman et al. reported outcomes of 8 patients with relapsed medulloblastoma with metastasis (n=7) and relapsed germinoma (n=1) who received dose-intensive chemotherapy with autologous HSCT. (11) Mean age was 12.9 years (range: 5–27.8 years). Mean survival post-transplant was 4.8 years (range: 8–160+ months). The 2-year and 5-year OS rates were 75% and 50%, respectively.

Gill and colleagues reported outcomes for 23 adult patients (18 years or older) treated for recurrent embryonal CNS tumors between 1976 and 2004, comparing high-dose chemotherapy with autologous HSCT (n=10) with an historic control group of patients treated with conventional-dose chemotherapy (n=13). (12) In the HSCT group, 6 patients received tandem autologous transplants. Autologous HSCT was associated with increased survival (p=0.044) and a longer time to disease progression (TTP) (p=0.028). Median TTP for the conventional versus HSCT group was 0.58 years and 1.25 years, respectively. Median survival was 2.00 years and 3.47 years, respectively. There were no long-term survivors in the conventional chemotherapy group. With a median follow-up of 2.9 years, 5 of the HSCT patients were alive, 4 without disease progression. In a comparison of outcomes between the patients who received a single versus tandem transplant, there was improvement in TTP favoring tandem transplant (p=0.046), but no difference in survival was observed (p=0.132).

Tandem Transplant

Park and colleagues reported the results of tandem double high-dose chemotherapy with autologous HSCT in 6 children younger than 3 years of age with newly diagnosed AT/RT. (13) No treatment-related death occurred during the tandem procedure, and 5 (of 6) patients were alive at a median follow-up of 13 months (range 7-64) from first HSCT. Although 3 patients remained progression-free after tandem HSCT, the effectiveness of this modality is unclear, because all survivors received radiotherapy, as well as tandem HSCT. (13) .

Sung and colleagues reported the results of a single or tandem double high-dose chemotherapy with autologous HSCT in 25 children with newly diagnosed high-risk or relapsed

medulloblastoma or PNET following surgical resection. (14) Three-year EFS for patients in complete remission (CR) or partial remission (PR) and less than PR at first high-dose chemotherapy was 67% or 16.7%, respectively. For 19 cases in CR or PR at first high-dose chemotherapy, 3-year EFS was 89% in the tandem double group and 44% in the single high-dose chemotherapy group, respectively. Four treatment-related deaths occurred, and in 4 of 8 young children, craniospinal radiotherapy was successfully withheld without relapse.

Allogeneic Transplant
The use of allogeneic HSCT for CNS embryonal tumors consists of rare case reports with mixed results. (15-17). According to the National Cancer Institute (NCI) Clinical Trial Database (PDQ®), no Phase III randomized trials using HSCT for recurrent embryonal CNS tumors are identified.

Ependymoma
Literature regarding autologous HSCT for the treatment of ependymoma primarily consists of small case series. Sung and colleagues reported the results of tandem double high-dose chemotherapy with autologous HSCT in 5 children younger than 3 years of age with newly diagnosed anaplastic ependymoma. (18) All patients were alive at median follow-up of 45 months (range 31–62) from diagnosis, although tumor progressed at the primary site in one patient. No significant endocrine dysfunction occurred except for hypothyroidism in one patient, and one patient had significant neurologic injury from primary surgical treatment. (18) The results of this very small case series indicate that treatment with tandem HSCT is feasible in very young children with anaplastic ependymoma and that this strategy might also be a possible option to improve survival in these patients without unacceptable long-term toxicity. Further studies with larger patient cohorts are needed to confirm these results.

Mason and colleagues reported on a case series of 15 patients with recurrent ependymoma. (19) Five patients died of treatment-related toxicities, 8 died from progressive disease, and 1 died of unrelated causes. After 25 months, 1 patient remains alive, but with tumor recurrence. The authors concluded that their high-dose regimen of thiotepa and etoposide was not an effective treatment of ependymoma. Grill and colleagues similarly reported a disappointing experience in 16 children treated with a thiotepa-based high-dose regimen. (20)

A small series reported 5-year EFS of 12% (+/- 6%) and OS of 38% (+/- 10%) among 29 children younger than 10 years of age who received autologous HSCT following intensive induction chemotherapy to treat newly diagnosed ependymoma. (21) Importantly, radiation-free survival was only 8% (+/- 5%) in these cases. The results of these series, although limited in size, further suggest HSCT is not superior to other previously reported chemotherapeutic approaches.

National Cancer Institute (NCI) Clinical Trial Database (PDQ®)
A Phase III pilot study of induction chemotherapy followed by consolidation myeloablative chemotherapy comprising thiotepa and carboplatin with or without etoposide followed by autologous hematopoietic stem cell rescue in pediatric patients with previously untreated malignant brain tumors, including ependymomas, (NCT00392886; CHLA-HEAD-START-III) is currently recruiting patients. The study compares 2 alternative induction regimens prior to myeloablative chemotherapy and stem cell rescue. Accrual will be 120 patients, with an estimated trial completion date in December 2010. The publication date of this study is presently unknown.

National Comprehensive Cancer Network (NCCN) Practice Guidelines 2010

NCCN guidelines on treating CNS tumors do not address the use of autologous HSCT in treating ependymomas and do not address embryonal tumors in general. (22)

Summary
Data from single-arm studies using autologous HSCT to treat newly diagnosed CNS embryonal tumors have shown an improved survival benefit (both event-free and overall), particularly in patients with disease that is considered high-risk. In addition, the use of autologous HSCT has allowed for a reduction in the dose of radiation needed to treat both average and high-risk disease, with preservation of quality of life and intellectual functioning, without compromising survival.

Data from single-arm studies using autologous HSCT to treat recurrent CNS embryonal tumors have shown improved survival benefit for some patients.

More data on the use of tandem and allogeneic transplants for CNS embryonal tumors are needed.

The use of HSCT for ependymoma has not shown a survival benefit compared to the use of conventional approaches, and the policy statement regarding ependymoma remains investigational.

Government Regulations

National:

110.8.1 - Stem Cell Transplantation (Various Effective Dates Below)
(Rev. 127, Issued: 10-08-10, Effective: 08-04-10, Implementation: 11-10-10)
The Centers for Medicare & Medicaid Services (CMS) is clarifying that bone marrow and peripheral blood stem cell transplantation is a process which includes mobilization, harvesting, and transplant of bone marrow or peripheral blood stem cells and the administration of high dose chemotherapy or radiotherapy prior to the actual transplant. When bone marrow or peripheral blood stem cell transplantation is covered, all necessary steps are included in coverage. When bone marrow or peripheral blood stem cell transplantation is non-covered, none of the steps are covered.

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.

Local:

Wisconsin Physician's Service (WPS), National Coverage Decision, "Bone Marrow or Stem Cell Transplantation." Contractor HONC-009, available at http://www.wpsmedicare.com/part_b/policy/active/national/_files/honc009.pdf

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Allogeneic Hematopoietic Stem Cell Transplantation (HSCT)

Nationally Covered Indications

The following uses of allogeneic (HSCT) bone marrow transplantation are covered under Medicare:

- 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; and
- 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.
- 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.

Nationally Noncovered Indications

Effective for services performed on or after May 24, 1996, allogeneic stem cell transplantation is not covered as treatment for multiple myeloma.

B. **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.

Nationally Covered Indications

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 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.

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.

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%.

Nationally Noncovered 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.

Other

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

Michigan Department of Community Health:

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 Lymphoblastic Leukemia
- 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 Genetic Diseases and Acquired Anemias
- 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 November 15, 2012, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
3/1/12	12/13/11	1/31/12	Joint policy established; topic pulled out from combined joint policies on autologous and allogeneic bone marrow/stem cell transplants
3/1/13	12/11/12	12/31/12	Routine update. References added. No change in policy status.

Next Review Date: 4th Qtr, 2013

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: BMT- STEM-CELL TRANSPLANTATION FOR CNS EMBRYONAL TUMORS AND EPENDYMOMA

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered; criteria apply.
BCNA (Medicare Advantage)	Covered; criteria apply.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.
BlueCaid	Covered; criteria apply.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- 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.