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 in the Treatment of Germ-Cell Tumors

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. Hematopoietic stem cells may be obtained from the transplant recipient (autologous HSCT) or from a donor (allogeneic HSCT). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates. Although cord blood is an allogeneic source, the 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 hematopoietic 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 Class I and Class II loci on chromosome 6. Depending on the disease being treated, an acceptable donor will match the patient at all or most of the HLA loci (with the exception of umbilical cord blood).

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 usually 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 mediated by non-self immunologic effector cells that develop 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 traditional 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 nonrelapse 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 (traditional) regimens.

Germ-Cell Tumors

Germ-cell tumors are composed primarily of testicular neoplasms (seminomas or nonseminomatous tumors) but also include ovarian and extragonadal germ-cell tumors (e.g., retroperitoneal or mediastinal tumors). Germ-cell tumors are classified according to their histology, stage, prognosis, and response to chemotherapy.

Histologies include seminoma, embryonal carcinoma, teratoma, choriocarcinoma, yolk sac tumor, and mixed germ-cell tumors. Seminomas are the most common; all other types are collectively referred to as nonseminomatous germ-cell tumors.

Stage is dependent on location and extent of the tumor, using the American Joint Committee on Cancer's TNM system. TNM stages, modified by serum concentrations of markers for tumor

burden (S0-3) when available, are grouped by similar prognoses. Markers used for germ-cell tumors include human beta-chorionic gonadotropin (hCG), lactate dehydrogenase (LDH), and alpha fetoprotein (AFP). However, most patients with pure seminoma have normal AFP concentrations. For testicular tumors, Stages IA-B have tumors limited to the testis (no involved nodes or distant metastases) and no marker elevations (S0); Stages IIA-C have increasing size and number of tumor-involved lymph nodes, and at least one marker moderately elevated above the normal range (S1); and Stages IIIA-C have distant metastases and/or marker elevations greater than specified thresholds (S2-3).

Germ-cell tumors also are divided into good-, intermediate-, or poor-risk categories based on histology, site, and extent of primary tumor, and on serum marker levels. Good-risk pure seminomas can be at any primary site but are without nonpulmonary visceral metastases or marker elevations. Intermediate-risk pure seminomas have nonpulmonary visceral metastases with or without elevated hCG and/or LDH. There are no poor-risk pure seminomas, but mixed histology tumors and seminomas with elevated AFP (due to mixture with nonseminomatous components) are managed as nonseminomatous germ-cell tumors. Good- and intermediate-risk nonseminomatous germ-cell tumors have testicular or retroperitoneal tumors without nonpulmonary visceral metastases, and either S1 (good risk) or S2 (intermediate) levels of marker elevations. Poor-risk tumors have mediastinal primary tumors, or nonpulmonary visceral metastases, or the highest level (S3) of marker elevations.

Therapy for germ-cell tumors is generally dictated by stage, risk subgroup, and tumor histology. Testicular cancer is divided into seminomatous and nonseminomatous types for treatment planning because seminomas are more sensitive to radiation therapy. Stage I testicular seminomas may be treated by orchiectomy with or without radiation or single-dose carboplatin adjuvant therapy. Nonseminomatous stage I testicular tumors may be treated with orchiectomy with or without retroperitoneal lymph node dissection. Higher stage disease typically involves treatment that incorporates chemotherapy. First-line chemotherapy for good- and intermediate-risk patients with higher-stage disease is usually 3 or 4 cycles of a regimen combining cisplatin and etoposide, with or without bleomycin depending on histology and risk group. Chemotherapy is often followed by surgery to remove residual masses. Second-line therapy often consists of combined therapy with ifosfamide/mesna and cisplatin, plus vinblastine, paclitaxel, or etoposide (if not used for first-line treatment). Patients whose tumors are resistant to cisplatin may receive carboplatin-containing regimens. The probability of long-term continuous complete remission diminishes with each successive relapse.

Regulatory Status:

N/A

Medical Policy Statement

The safety and effectiveness of hematopoietic stem-cell transplantation in the treatment of germ-cell tumors has been established. It may be considered a useful therapeutic option in specified indications.

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)

Inclusions:

- *Single autologous* hematopoietic stem-cell transplantation as salvage therapy for germ-cell tumors in the following situations:
  - In patients with *favorable* prognostic factors that have failed a previous course of conventional-dose salvage chemotherapy; or
  - In patients with *unfavorable* prognostic factors as initial treatment of first relapse (i.e., without a course of conventional-dose salvage chemotherapy) and in patients with platinum-refractory disease.
- *Tandem or sequential autologous* hematopoietic stem-cell transplantation for the treatment of testicular tumors either as salvage therapy or with platinum-refractory disease.

Exclusions:

- *Autologous* hematopoietic stem-cell transplantation as a component of first-line treatment for germ-cell tumors
- *Allogeneic* hematopoietic stem-cell to treat germ-cell tumors, including, but not limited to its use as therapy after a prior failed autologous hematopoietic stem-cell transplantation.
- All other indications not listed in the inclusions.

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	38206	38208	38209	38210	38211
38212	38213	38214	38215	38220	38221
38232	38241	S2150			

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

38205	38230	38240	S2140	S2142

Rationale

Autologous hematopoietic stem-cell transplantation (HSCT) as front-line therapy of germ-cell tumors

Daugaard and colleagues reported the outcomes of a randomized Phase III study comparing standard-dose BEP (cisplatin, etoposide and bleomycin) to sequential high-dose VIP (cisplatin, etoposide and ifosfamide) plus stem-cell support in previously untreated males with poor-prognosis germ-cell cancer. (3) The study aimed to recruit 222 patients but closed with 137 patients from 27 European oncology centers due to slow accrual. Patients were age 15-50 years and had previously untreated metastatic poor-prognosis nonseminomatous germ-cell tumor of either testicular or extragonadal origin. Median follow-up was 4.4 years. Toxicity was more severe in the patients who received high-dose chemotherapy, and toxic death was reported in 2 patients who received high-dose chemotherapy and one in the BEP arm. There was no improvement in complete response rate in the high-dose chemotherapy arm versus the standard-dose arm (44.6% vs. 33.3%, respectively, p=0.18). There was no difference in failure-free survival between the two groups. At 2 years, failure-free survival was 44.8% (95% confidence interval [CI]: 32.5-56.4) and 58.2% (95% CI: 48.0-71.9), respectively, for the standard and high-dose arms. The difference was not statistically significant (p=0.06). Overall survival did not differ between the two groups (log-rank p>0.1). The authors concluded that high-dose chemotherapy given as part of first-line therapy does not improve outcomes in patients with poor-prognosis germ-cell tumor.

Motzer and colleagues reported on a Phase III prospective, randomized, multicenter trial of 219 previously untreated patients with poor-prognosis germ-cell tumors. (4) The median patient age was 28 years. Patients were randomized to receive either conventional chemotherapy (4 cycles of BEP) (n=111), or 2 cycles of BEP followed by 2 cycles of high-dose chemotherapy with autologous HSCT. Median follow-up was 51 months. One-year durable complete response rate was 52% after BEP and high-dose chemotherapy with HSCT, and 48% after BEP alone (p=0.53). There was no survival difference at 106 months for patients treated with high-dose chemotherapy and HSCT compared to the patients treated with conventional chemotherapy (68% and 69%, respectively).

Droz and colleagues assessed the impact of high-dose chemotherapy with HSCT on the survival of patients with high-volume, previously untreated, metastatic nonseminomatous germ-cell tumors. (5) Patients were randomized to four cycles every 21 days of vinblastine,

etoposide, cisplatin and bleomycin (n=57) or a slightly modified regimen followed by high-dose chemotherapy and autologous HSCT (n=57). In an intention-to-treat (ITT) analysis, there were 56% and 42% complete responses in the conventional and high-dose chemotherapy groups, respectively (p=0.099). Median follow-up was 9.7 years, and no significant difference between overall survival (OS) was observed (p=0.167).

Autologous HSCT for relapsed or refractory germ-cell tumors

Agarwal and colleagues reported their experience at Stanford in treating 37 consecutive patients who received high-dose chemotherapy and autologous HSCT between 1995 and 2005 for relapsed germ-cell tumors. (6) The median patient age was 28 years (range: 9–59 years), with 34 males and 3 females. Primary tumor sites included 24 testes/adnexal, 10 chest/neck/retroperitoneal, and 3 central nervous system (CNS). Twenty-nine of the patients had received prior standard salvage chemotherapy. Three-year OS was 57% (95% CI: 41-71%), and 3-year progression-free survival (PFS) was 49% (95% CI: 33–64%).

In 2005, Pico and colleagues reported on a randomized trial comparing 4 cycles of conventional-dose chemotherapy to 3 cycles of the same regimen followed by carboplatin-based high-dose chemotherapy plus autologous HSCT in 280 patients who had relapsed after a complete or partial remission following first-line therapy with a cisplatin-based regimen. (7) The authors reported no significant differences between treatment arms in 3-year event-free survival (EFS) and OS. However, the study began before international consensus (8) established the current risk group definitions; thus, Pico and colleagues likely included some patients now considered to have good prognosis at relapse. Furthermore, while 77% and 86% of patients in the control and experimental arms, respectively, had at least one elevated serum tumor marker, they did not report how highly elevated these were and did not compare arms with respect to the marker thresholds that presently determine risk level (S1-3). Finally, high-dose chemotherapy in the experimental arm followed 3 cycles of conventional-dose chemotherapy, which differs from most current practice in the U.S., in which a single cycle is used prior to high-dose chemotherapy. As a consequence, 38 of 135 (28%) randomized to the high-dose chemotherapy arm did not receive high-dose chemotherapy because of progression, toxicity, or withdrawal of consent.

Seftel and colleagues conducted a multicenter cohort study of consecutive patients undergoing a single autologous HSCT for germ-cell tumor between January 1986 and December 2004. (9) Of 71 subjects, median follow-up was 10.1 years. The median age was 31 years (range 16–58 years). A total of 67 of the patients had nonseminomatous germ-cell tumors and 4 had seminomatous germ-cell tumors. A total of 57 patients had primary gonadal disease and 14 had primary extragonadal disease. Of the latter, 11 patients presented with primary mediastinal disease, 2 presented with primary central nervous system disease, and 1 presented with retroperitoneal disease. In all, 28 patients underwent autologous HSCT for relapsed disease after achieving an initial complete response (CR). Of these, 24 patients underwent autologous HSCT after a first relapse, whereas 4 patients underwent transplant after a second relapse. An additional 36 patients achieved only an incomplete response after initial therapy and proceeded to autologous HSCT after salvage chemotherapy for active residual disease. Overall survival at 5 years was 44.7% (95% CI: 32.9–56.5%) and EFS 43.5% (95% CI: 31.4–55.1%). There were 7 (10%) treatment-related deaths within 100 days of transplant. Three (4.2%) patients developed secondary malignancies. Of 33 relapses, 31 occurred within 2 years of the transplant. Two very late relapses occurred 13 and 11 years after transplant. In a multivariate analysis, a favorable outcome was associated with

International Germ Cell Consensus Classification (IGCCC) good prognosis disease at diagnosis, primary gonadal disease, and response to salvage chemotherapy.

Tandem and sequential HSCT for germ-cell tumors

Lazarus and colleagues reported the results of autologous HSCT in relapsed testicular/germ-cell cancer from registry data from the Center for International Blood and Marrow Transplant Research. (10) Patients with mediastinal primaries were excluded. Data included 300 patients from 76 transplant centers in 8 countries who received either a single transplant or tandem autologous HSCT between 1989 and 2001. Of the 300 patients, 102 received tandem, and 198 single planned autologous HSCT. PFS and OS at 1, 3, and 5 years was similar for both groups. The probability of PFS at 5 years for the tandem transplant group was 34% (95% CI: 25–44%) versus 38% (95% CI: 31–45%) in the single transplant group; p=0.50. The probability of 5-year OS was 35% (95% CI: 25–46%) versus 42% (95% CI: 35–49%), respectively; p=0.29.

Lorch and colleagues compared single versus sequential high-dose chemotherapy with autologous HSCT as first or subsequent salvage treatment in patients with relapsed or refractory germ-cell tumors. (11) Between November 1999 and November 2004, patients planned to be recruited in a prospective, randomized, multicenter trial comparing one cycle of cisplatin, etoposide, and ifosfamide (VIP) plus 3 cycles of high-dose carboplatin and etoposide (CE; arm A) versus 3 cycles of VIP plus one cycle of high-dose carboplatin, etoposide and cyclophosphamide (CEC; arm B). The majority of the tumors were gonadal primaries; ten percent of patients in arm A had retroperitoneal, mediastinal or central nervous system (CNS) primaries, and 11% of patients in arm B had retroperitoneal or mediastinal primaries. This represented the first salvage therapy received in 86% of the patients in arm A and 85% in arm B, whereas 14% (arm A) and 15% (arm B) had received one or more previous salvage regimens prior to randomization. One-hundred-eleven (51%) of 216 patients were randomly assigned to sequential high-dose therapy, and 105 (47%) of 216 patients were randomly assigned to single high-dose therapy. The study was stopped prematurely after recruitment of 216 patients as a result of excess treatment-related mortality (TRM) in arm B. There was a planned interim analysis after the inclusion of 50% of the required total number of patients. Survival analyses were performed on an ITT basis.

With a median follow-up time of 36 months, 109 (52%) of 211 patients were alive, and 91 (43%) of 211 patients were progression free. At 1 year, event-free, progression-free, and overall survival rates were 40%, 53%, and 80%, respectively, in arm A compared with 37%, 49%, and 61%, respectively, in arm B (p>0.05 for all comparisons). Survival rates were not reported separately by primary site of the tumor. No difference in survival probabilities was found between the single and sequential high-dose regimens; however, sequential high-dose therapy was better tolerated and resulted in fewer treatment-related deaths. Treatment-related deaths, mainly as a result of sepsis and cardiac toxicity, were less frequent in arm A (4 of 108 patients, 4%) compared with arm B (16 of 103 patients, 16%; p<0.01). The authors state that the higher treatment-related deaths observed in arm B likely were due to the higher dosages per HSCT cycle in the arm B regimen compared to arm A, and the toxic renal and cardiac effects of cyclophosphamide used in arm B. The authors conclude that sequential treatment at submaximal doses of carboplatin and etoposide might be less toxic and safer to deliver HSCT in pretreated patients with germ-cell tumors than single HSCT.

Lotz and colleagues reported the results of a Phase II study on 3 consecutive cycles of high-dose chemotherapy regimens supported by autologous HSCT in 45 poor-prognosis patients

with relapsed germ-cell tumors. (12) From March 1998 to September 2001 (median follow-up, 31.8 months), 45 patients (median age, 28 years) were enrolled. Most of the patients (76%) had testicular primaries; 13% had mediastinal primaries; 11% retroperitoneal, hepatic, or unknown. Of all patients, 22 received the complete course. Twenty-five patients died from progression and five from toxicity. The overall response rate was 37.7%, including an 8.9% complete response rate. The median OS was 11.8 months. The 3-year survival and PFS rate was 23.5%. The authors used the “Beyer” prognostic score to predict the outcome of high-dose chemotherapy and concluded that patients with a Beyer score greater than 2 did not benefit from this approach, confirming that highly refractory patients and particularly patients with resistant/refractory primary mediastinal germ-cell tumors do not benefit from high-dose chemotherapy. The authors also state that better selection criteria have to be fulfilled in forthcoming studies.

Einhorn and colleagues reported retrospectively on a series of 184 patients, treated between 1996 and 2004, with 2 consecutive cycles of high-dose chemotherapy for metastatic testicular cancer that had progressed (relapsed) after receiving cisplatin-containing combination chemotherapy. (13) Patients with primary mediastinal nonseminomatous germ-cell tumors or tumors with late relapse (2 or greater years after previous therapy) were excluded. The patient population included those with initial International Germ Cell Cancer Collaborative Group (IGCCCG) stage defined as low risk (39%), intermediate risk (21%), and high risk (41%) and both platinum-sensitive and refractory disease at the beginning of high-dose chemotherapy. Results from this experienced center showed that of the 184 patients, 116 had complete remission of disease without relapse during a median follow-up of 48 months. Of the 135 patients who received the treatment as second-line therapy (i.e., first salvage setting), 94 (70%) were disease-free during follow-up; 22 (45%) of 49 patients who received treatment as third-line or later therapy were disease-free. Of 40 patients with cancer that was refractory to standard-dose platinum, 18 (45%) were disease-free.

Letters to the editor regarding the Einhorn et al. study noted the lack of a validation set for the prognostic scoring system used in the study, the unanswered question of the role of high-dose versus conventional-dose chemotherapy in the first salvage setting, and the lack of a universally accepted prognostic scoring system in this setting. (14)

A comparative effectiveness review conducted for the Agency for Healthcare Research and Quality (AHRQ) on the use of HSCT in the pediatric population concluded that, for germ-cell tumors, the body of evidence on overall survival with tandem HSCT compared to single HSCT for the treatment of relapsed pediatric germ-cell tumors was insufficient to draw conclusions. (15)

Allogeneic HSCT for germ-cell tumors

There are scant data in the literature to support the use of allogeneic HSCT in the treatment of germ-cell tumors. (16)

Summary

Salvage therapy plays a role in patients with germ-cell tumors who are either refractory to cisplatin or who relapse after initial treatment. (6) The timing for the use of high-dose chemotherapy and HSCT instead of standard salvage chemotherapy is less well-defined, with patient heterogeneity playing a role in the overall outcome. (6) Studies have been limited trying to stratify patients into various prognostic groups to identify those who are high-risk, as only

30% of patients with germ-cell tumors require salvage treatment. (6) The use of high-dose chemotherapy and HSCT as first-line therapy has not been shown to be superior to standard chemotherapy; HSCT remains the treatment of choice for patients who fail standard salvage therapy. (6)

The role of tandem or sequential autologous transplants in relapsed disease has been investigated in one Phase II study, one randomized study, two retrospective series (one single-center experience and one registry data from multiple centers), and a comparative effectiveness review for AHRQ. Tandem or sequential HSCT may provide survival benefit, and the randomized study showed lower treatment-related mortality with sequential HSCT compared to single HSCT. However, studies have included heterogeneous patient populations, in different salvage treatment settings (i.e., first versus subsequent salvage therapy) and have suffered from the lack of a universally accepted prognostic scoring system to risk-stratify patients. Tandem or sequential HSCT has not shown benefit in patients with primary mediastinal germ-cell tumors. Strong clinical support was received from clinical experts in support of the use of tandem or sequential HSCT in the salvage or platinum-refractory setting.

National Comprehensive Cancer Network (NCCN) Guidelines (17)
The 2012 (v.1.2012) NCCN guidelines for the treatment of testicular cancer state that if a patient with favorable prognostic factors (defined as testicular primary site, prior complete response to first-line therapy, low levels of serum markers and low volume disease) has disease recurrence after prior chemotherapy, high-dose chemotherapy is an option, or if a patient with disease recurrence undergoes conventional-dose chemotherapy and experiences an incomplete response or relapses, high-dose chemotherapy with autologous stem-cell support is category 2A recommendation. Patients with unfavorable prognostic factors (e.g., an incomplete response to prior chemotherapy, high levels of serum markers, high-volume disease, extratesticular primary or late relapse) and disease recurrence are considered for treatment with high-dose chemotherapy plus autologous stem cell support (category 2B). The guidelines do not address the use of tandem or sequential HSCT in the treatment of testicular tumors.

National Cancer Institute (NCI) Clinical Trial Database (PDQ®)
A search of the National Cancer Institute's Physician Data Query database identified the following Phase III randomized study:

- Salvage Using Cisplatin, Etoposide, and Ifosfamide (PEI) or Vinblastine, Ifosfamide, and Cisplatin (VeIP) With or Without High-Dose Carboplatin, Etoposide, and Cyclophosphamide, Followed by Autologous Bone Marrow and/or Peripheral Blood Stem-Cell Transplantation in Male Patients With Germ-Cell Tumors in Relapse or First Partial Remission (NCT00002566). Expected enrollment is 280 patients. Trial status is unknown.

Clinical Input Received Through Physician Specialty Societies and Academic Medical Centers
In response to requests, Blue Cross Blue Shield Association received input from 3 physician specialty societies, 3 academic medical centers, and 5 Blue Distinction Centers for Transplants® while this policy was under review for March 2010. 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 general agreement with the policy statements regarding the use of single autologous HSCT as salvage therapy, the use of autologous HSCT as first-line treatment, and the use of allogeneic HSCT. Seven of the reviewers felt that tandem or sequential HSCT is medically necessary for patients as salvage therapy or with platinum-refractory disease; 2 reviewers felt that tandem or sequential HSCT was investigational; 2 stated that commenting on this was beyond his/her area of expertise.

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 7/27/12.

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.

Other

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 specifically addressing hematopoietic stem cell transplantation for germ-cell tumors.

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: 7/27/12.

Section 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 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 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
- 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 July 27, 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	• Policy formatted to mirror BCBSA • Added “relative contraindications” to inclusionary/exclusionary section.

Next Review Date: 4th Qtr, 2013

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: BMT - HEMATOPOIETIC STEM-CELL TRANSPLANTATION IN THE TREATMENT OF GERM-CELL TUMORS

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	Follow guidelines for commercial members

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.