Hematopoietic Stem-Cell Transplantation in the Treatment of Germ-Cell Tumors

Policy # 00056
Original Effective Date: 01/28/2002
Current Effective Date: 10/16/2013

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- Benefits are available in the member’s contract/certificate, and
- Medical necessity criteria and guidelines are met.

Based on review of available data, the Company may consider the use of single autologous hematopoietic stem-cell transplantation (HSCT) as salvage therapy to treat patients with germ-cell tumors to be eligible for coverage when patient selection criteria are met.

Patient Selection Criteria
The use of single autologous hematopoietic stem-cell transplantation (HSCT) as salvage therapy for germ-cell tumors may be considered eligible for coverage when ANY of the following criteria are met:

- 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.

When Services Are Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- Benefits are available in the member’s contract/certificate, and
- Medical necessity criteria and guidelines are met.

Based on review of available data, the Company may consider tandem or sequential autologous hematopoietic stem-cell transplantation (HSCT) for the treatment of testicular tumors either as salvage therapy or with platinum-refractory disease to be eligible for coverage.

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of single autologous hematopoietic stem-cell transplantation (HSCT) as salvage therapy to treat patients with germ-cell tumors when patient selection criteria are not met to be investigational.*
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Based on review of available data, the Company considers autologous hematopoietic stem-cell transplantation (HSCT) as a component of first-line treatment for germ-cell tumors to be investigational.*

Based on review of available data, the Company considers allogeneic hematopoietic stem-cell transplantation (HSCT) to treat germ-cell tumors, including, but not limited to its use as therapy after a prior failed autologous hematopoietic stem-cell transplantation (HSCT) to be investigational.*

Note: The favorable and unfavorable prognostic factors are derived from the current National Comprehensive Cancer Network (NCCN) guidelines and the DeVita, Hellman, and Rosenberg’s textbook Cancer Principles and Practice of Oncology.

Patients with favorable prognostic factors include those with a testis or retroperitoneal primary site, a complete response (CR) to initial chemotherapy, low levels of serum markers and low volume disease. Patients with unfavorable prognostic factors are those with an incomplete response to initial therapy or relapsing mediastinal nonseminomatous germ-cell tumors.

Background/Overview
Therapy for germ-cell tumors is generally dictated by several factors, including disease stage, tumor histology, site of tumor primary and response to chemotherapy.

Patients with unfavorable prognostic factors may be candidates for HSCT.

Hematopoietic Stem-Cell Transplantation
Hematopoietic stem-cell transplantation 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. Human leukocyte antigens 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.

Conventional Preparative Conditioning for Hematopoietic Stem-Cell Transplantation
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.
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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 Hematopoietic Stem-Cell Transplantation

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. Reduced-intensity conditioning 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.
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Stage is dependent on location and extent of the tumor, using the American Joint Committee on Cancer’s Classification of Malignant Tumours (TNM) system. The 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 three or four 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.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

High-dose chemotherapy with autologous stem cell support (AuSCS) is a procedure and thus not subject to FDA regulation. The chemotherapeutic agents used during this procedure, however, require and have been given FDA approval for conventional-dose administration. High-dose administration of these approved agents is an off label use. Once a product has been approved for marketing, a physician may prescribe it for uses or patient populations not included in approved labeling. The FDA states that accepted medical practice may include drug use that is not indicated in approved drug labeling.
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The FDA does regulate devices related to the harvesting of stem cells.

Rationale/Source
Autologous Hematopoietic Stem-Cell Transplantation 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. 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 CR 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 (OS) did not differ 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 (OS) 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. The median patient age was 28 years. Patients were randomized to receive either conventional chemotherapy (4 cycles of standard 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 CR 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. Patients were randomized to 4 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 analysis, there were 56% and 42% CRs in the conventional and high-dose chemotherapy groups, respectively (p = 0.099). Median follow-up was 9.7 years, and no significant difference between OS was observed (p = 0.167).

Autologous Hematopoietic Stem-Cell Transplantation 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. 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).
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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 four cycles of conventional-dose chemotherapy to three 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. 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 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 three cycles of conventional-dose chemotherapy, which differs from most current practice in the U.S., where 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. 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 CNS disease, and 1 presented with retroperitoneal disease. In all, 28 patients underwent autologous HSCT for relapsed disease after achieving an initial 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 in CR 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 Hematopoietic Stem-Cell Transplantation 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. Patients with mediastinal primaries were excluded. Data included 300 patients from 76 transplant centers in eight 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. Progression-free and OS at 1, 3, and 5 years was similar for both groups. The probability of PFS at five years for the tandem transplant group was 34% (95% CI: 25–44%) versus 38% (95% CI: 31–45%) in the single transplant group;
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\[ p = 0.50. \] 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. Between November 1999 and November 2004, patients planned to be recruited in a prospective, randomized, multicenter trial comparing one cycle of VIP plus three cycles of high-dose carboplatin and etoposide (CE; arm A) versus three cycles of VIP plus one cycle of high-dose carboplatin, etoposide and cyclophosphamide (CEC; arm B). The majority of the tumors were gonadal primaries; 10\% of patients in arm A had retroperitoneal, mediastinal or 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 1 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 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 intent-to-treat 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 OS 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 were 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.

Long-term results from this study reported 5-year PFS as 47\% (95\% CI: 37-56\%) in arm A and 45\% (95\% CI: 35-55\%) in arm B (hazard ratio, [HR] = 1.16; 95\% CI: 0.79-1.70; \( p = .454 \)). Five-year OS was 49\% (95\% CI: 40-59\%) in arm A and 39\% (95\% CI: 30-49\%) in arm B (HR = 1.42; 95\% CI: 0.99-2.05; \( p = .057 \)). The authors concluded that patients with relapsed or refractory germ-cell tumors can achieve durable long-term survival after single, as well as sequential HSCT and that fewer early deaths related to toxicity translated into superior long-term OS after sequential HSCT.

Lotz and colleagues reported the results of a Phase II study on three consecutive cycles of high-dose chemotherapy regimens supported by autologous HSCT in 45 poor-prognosis patients with relapsed germ-cell tumors. 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
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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% CR 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 two 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. Patients with primary mediastinal nonseminomatous germ cell tumors or tumors with late relapse (two 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 Einhorn’s 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.

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 OS with tandem HSCT compared to single HSCT for the treatment of relapsed pediatric germ-cell tumors was insufficient to draw conclusions.

Allogeneic Hematopoietic Stem-Cell Transplantation 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.

Summary
Salvage therapy plays a role in patients with germ-cell tumors who are either refractory to cisplatin or who relapse after initial treatment. 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. 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. The use of high-
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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.

The role of tandem or sequential autologous transplants has been investigated in one Phase II study, 1 randomized study, and 2 retrospective series (1 single-center experience and 1 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 Guidelines
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 CR 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 AuSCS (category 2B). The guidelines do not address the use of tandem or sequential HSCT in the treatment of testicular tumors.

Ongoing Clinical Trials
National Cancer Institute Clinical Trial Database
A search of the National Cancer Institute’s (NCIs) Physician Data Query (PDQ®)† database identified the following Phase III randomized study:
- Salvage Using Cisplatin, Etoposide, and Ifosfamide (PEI) or Vinblastine, Ifosfamide, and Cisplatin (VelP) 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.

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Coding
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12/06/2001  Medical Policy Committee review
01/28/2002  Managed Care Advisory Council approval
06/24/2002  Format revision. Policy addresses only Germ Cell Tumors. Replaces high dose chemotherapy with hematopoietic stem cell support.
03/31/2004  Medical Director review
04/20/2004  Medical Policy Committee review. Format revision. No substance change to policy.
04/26/2004  Managed Care Advisory Council approval
05/03/2005  Medical Director review
05/17/2005  Medical Policy Committee review. Format revision. Policy statement corrected to reflect "that HDC and autologous SCS as initial treatment (i.e., in lieu of an initial course of conventional chemotherapy) of poor-risk germ cell tumors or as initial treatment of a first relapse (i.e., in lieu of a course of conventional chemotherapy) is investigational".
05/23/2005  Managed Care Advisory Council approval
05/03/2006  Medical Director review
05/17/2006  Medical Policy Committee approval. Format revision, including addition of FDA and or other governmental regulatory approval and rationale/source. Coverage eligibility unchanged.
10/10/2007  Medical Director review
10/17/2007  Medical Policy Committee approval. No change to coverage eligibility.
10/01/2008  Medical Director review
10/22/2008  Medical Policy Committee approval. No change to coverage eligibility.
10/01/2009  Medical Policy Committee approval
10/14/2009  Medical Policy Implementation Committee approval. Title changed from "High-Dose Chemotherapy with Stem Cell Support for Germ Cell Tumors" to "Hematopoietic Stem Cell Transplantation in the Treatment of Germ Cell Tumors". No change to coverage eligibility.
10/14/2010  Medical Policy Committee review
10/20/2010  Medical Policy Implementation Committee approval. Terminology changed in coverage statements. Coverage statements changed to indicate that tandem-sequential autologous stem-cell transplantation may be considered eligible for coverage in certain types of testicular cancers.
10/06/2011  Medical Policy Committee review
10/19/2011  Medical Policy Implementation Committee approval. "Based on review of available data, except as noted above for treatment of certain testicular tumors, the Company considers tandem or sequential autologous hematopoietic stem-cell transplantation to treat germ-cell tumors of any stage to be investigational" was deleted from coverage.

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Hematopoietic Stem-Cell Transplantation in the Treatment of Germ-Cell Tumors

Policy # 00056
Original Effective Date: 01/28/2002
Current Effective Date: 10/16/2013

10/11/2012 Medical Policy Committee review
10/31/2012 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
03/04/2013 Coding updated
10/03/2013 Medical Policy Committee review
10/16/2013 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
Next Scheduled Review Date: 10/2014

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:
   A. whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
   B. whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
      1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
      2. credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
      3. reference to federal regulations.

**Medically Necessary (or “Medical Necessity”) - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:
   A. in accordance with nationally accepted standards of medical practice;
   B. clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
   C. not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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