I. POLICY

Single autologous hematopoietic stem-cell transplantation may be considered medically necessary as salvage therapy for germ-cell tumors:

- 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. (See Policy Guidelines for prognostic factors.)

Tandem or sequential autologous hematopoietic stem-cell transplantation may be considered medically necessary for the treatment of testicular tumors either as salvage therapy or with platinum-refractory disease.

Autologous hematopoietic stem-cell transplantation is considered investigational as a component of first-line treatment for germ-cell tumors. There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this procedure.

Allogeneic hematopoietic stem-cell transplantation is considered investigational to treat germ-cell tumors, including, but not limited to its use as therapy after a prior failed autologous hematopoietic stem-cell transplantation. There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this procedure.

Policy Guidelines

The favorable and unfavorable prognostic factors listed below are derived from the current National Comprehensive Cancer Network (NCCN) guidelines (1) and DeVita, Hellman, and Rosenberg’s textbook Cancer: Principles and Practice of Oncology. (2)
Patients with favorable prognostic factors include those with a testis or retroperitoneal primary site, a complete response 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.

Cross-references:

MP-9.038  Hematopoietic Stem-Cell Transplantation for Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma
MP-9.039  Hematopoietic Stem-Cell Transplantation for Chronic Myelogenous Leukemia
MP-9.040  Hematopoietic Stem-Cell Transplantation for Acute Myeloid Leukemia
MP-9.041  Hematopoietic Stem-Cell Transplantation for Acute Lymphoblastic Leukemia
MP-9.042  Hematopoietic Stem-Cell Transplantation for Non-Hodgkin Lymphoma
MP-9.043  Hematopoietic Stem-Cell Transplantation for Hodgkin Lymphoma
MP-9.044  Hematopoietic Stem-Cell Transplantation for Plasma Cell Dyscrasias, Including Multiple Myeloma and POEMS Syndrome
MP-9.045  Hematopoietic Stem-Cell Transplantation for Primary Amyloidosis
MP-9.046  Hematopoietic Stem-Cell Transplantation for Waldenstrom Macroglobulinemia
MP-9.047  Hematopoietic Stem-Cell Transplantation for Epithelial Ovarian Cancer
MP-9.048  Hematopoietic Stem-Cell Transplantation Miscellaneous Solid Tumors in Adults
MP-9.049  Hematopoietic Stem-Cell Transplantation for Breast Cancer
MP-9.050  Hematopoietic Stem-Cell Transplantation for CNS Embryonal Tumors and Ependymoma
MP-9.053  Hematopoietic Stem-Cell Transplantation for Autoimmune Diseases
MP-9.054  Hematopoietic Stem-Cell Transplantation for Solid Tumors of Children
MP-9.055  Allogeneic HSCT for Genetic Diseases and Acquired Anemias
MP-9.056  Allogeneic Stem-Cell Transplantation for Myelodysplastic Syndromes and Myeloproliferative Neoplasms

II. PRODUCT VARIATIONS

This policy is applicable to all programs and products administered by Capital BlueCross unless otherwise indicated below.

BlueJourney HMO*  BlueJourney PPO*  FEP PPO**
**III. DESCRIPTION/BACKGROUND**

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 hematopoietic stem-cell transplantation.

**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). Cord blood is discussed in greater detail in MP 9.001.

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.

IV. RATIONALE

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

Daugaard 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 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 assessed the impact of high-dose chemotherapy with HSCT on the survival of patients with high-volume, previously untreated, metastatic nonseminomatomous germ-cell tumors. (5) 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 (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).

Overall, the evidence from multiple randomized trials indicates that autologous HSCT is not superior to alternative therapy as initial therapy for germ-cell tumors.

**Autologous HSCT for relapsed or refractory germ-cell tumors**

The evidence related to the use of autologous HSCT for relapsed or treatment-refractory germ-cell tumors consists of one RCT and several nonrandomized observational studies.

In 2005, Pico et al. 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. 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 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 et al. 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 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.

Agarwa et al. 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. (8) 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%).

Baek et al. reported results of a small feasibility study of high-dose chemotherapy followed by HSCT for patients with relapsed or progressed central nervous system germ-cell tumors. (9) The authors enrolled 11 patients with nongerminomatous (i.e., nonseminomatous) germ cell tumors and 9 patients with germinomatous stem cell tumors, all of whom had received conventional chemotherapy with or without radiation before HSCT. Sixteen patients received an initial course of high-dose chemotherapy with carboptatin, thiopental, and etoposide followed by HSCT, and 9 of those received a second course of high-dose chemotherapy with cyclophosphamide-melphalan followed by a second HSCT (see “Tandem and sequential HSCT for germ-cell tumors”, below). Twelve patients remained alive at a median follow up of 47 months (range 22-90), with a probability of 3-year overall survival of 59.1% (± 11.2%).

Tandem and sequential HSCT for germ-cell tumors

There is ongoing research into the role of tandem and sequential HSCT for germ-cell tumors, with a variety of specific chemotherapy regimens.

Lorch et al. 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. (10) 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.

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. (11)

Lazarus et al. 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. (12) 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.

Lotz et al. 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. (13) 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 5 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 et al. 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 (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.

Caveats regarding the Einhorn et al study include 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.

In a subsequent study from the same center as the Einhorn et al. study, Suleiman et al. evaluated the outcomes for 12 patients with recurrent primary mediastinal nonseminomatous germ-cell tumors after initial treatment with cisplatin-containing combination chemotherapy, a population excluded from their previous study, who were treated with tandem HSCT. Patients received 2 consecutive courses of high dose chemotherapy (carboplatin and etoposide) followed by HSCT. Overall outcomes were poor, with a median survival of 11 months (range 4-52 months), but 3 out of 12 patients achieved a complete remission. One patient remained free of disease at 50 months of follow up, and one patient remained free of disease after tandem HSCT and subsequent mediastinal surgery at 52 months of follow up.

Pal et al. reported 5-year follow up results from a retrospective case series of 48 patients with relapsed germ-cell tumors who were enrolled in a study to evaluate the effectiveness of two sequential cycles of high-dose chemotherapy (paclitaxel, etoposide, and carboplatin in the first cycle, followed by dose of high-dose paclitaxel, ifosfamide, and carboplatin) followed by HSCT. Forty-three patients (91.5%) had nonseminomatous histology. Most patients (n=39) had received 2 prior chemotherapy regimens; 6 patients had received 3 prior regimens. Thirty-four patients had intermediate risk classification by the Beyer score and the remainder had high risk
classification. Of the 48 patients enrolled, 17 received only 1 course of high-dose chemotherapy, 11 due to progressive disease, 5 due to toxicities, and one due to a severe fungal infection. A total of 17 patients of the 48 enrolled were alive and progression free at a median of 123.2 months (range: 51.6-170.2); twenty-five patients died, most (n=23) due to disease progression. Of the 23 patients who were alive after receiving per-protocol therapy, 18 were contacted for interviews at a median 115.6 months (range: 38.9-185.9) post-enrollment and underwent a cancer-related quality of life assessment with the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (QLQ-C30). The overall average score on the QLQ-C30 was 87.04 (standard deviation: 14.64); the authors compared quality of life scores in this cohort to a separate cohort of 150 patients with germ-cell tumors who received chemotherapy, and reported that patients in their cohort had significantly higher global health score (87.04 vs 75.62, P=0.02), but a lower physical functioning score (68.9 vs 92.7, P=0.0001.) The authors conclude that tandem high-dose chemotherapy followed by HSCT is a reasonable option for relapsed germ-cell tumors, with long term survivors demonstrating a reasonable quality of life.

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. (17)

**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.18

**Ongoing and Unpublished Clinical Trials**

Table 1 summarizes key ongoing clinical trials of HSCT for therapy of germ-cell tumors.

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None<sup>a</sup>

NCT: national clinical trial.
<sup>a</sup> Denotes industry-sponsored or cosponsored trial.
Clinical Input Received From Physician Specialty Societies and Academic Medical Centers
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.

In response to requests, input was received 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. 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.

Summary of Evidence
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 hematopoietic stem-cell transplantation (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-dose chemotherapy and HSCT as first-line therapy has not been shown to be superior to standard salvage therapy; HSCT remains the treatment of choice for patients who fail standard salvage therapy.

The role of tandem or sequential autologous transplants in relapsed disease has been investigated in one Phase II study, one randomized study, several retrospective series, 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.

Practice Guidelines and Position Statements
National Comprehensive Cancer Network (NCCN) Guidelines (19)

NCCN guidelines (v.1.2015) 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.

V. DEFINITIONS

NA

VI. BENEFIT VARIATIONS

The existence of this medical policy does not mean that this service is a covered benefit under the member's contract. Benefit determinations should be based in all cases on the applicable contract language. Medical policies do not constitute a description of benefits. A member’s individual or group customer benefits govern which services are covered, which are excluded, and which are subject to benefit limits and which require preauthorization. Members and providers should consult the member’s benefit information or contact Capital for benefit information.

VII. DISCLAIMER

Capital’s medical policies are developed to assist in administering a member’s benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member’s benefit information, the benefit information will govern. Capital considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.
Allogeneic hematopoietic stem-cell transplantation is investigational to treat germ-cell tumors:

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Covered when medically necessary:

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<tr>
<th>CPT Codes</th>
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<tr>
<td>38204</td>
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<td>38212</td>
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</tr>
</tbody>
</table>

Bone marrow or blood-derived stem cells (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation and related complications including pheresis and cell preparation/storage; marrow ablative therapy; drugs; supplies; hospitalization with outpatient follow-up; medical/surgical, diagnostic, emergency, and rehabilitative services; and the number of days of pre- and post-transplant care in the global definition.

<table>
<thead>
<tr>
<th>ICD-10-CM Diagnosis Codes</th>
<th>Description</th>
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<tbody>
<tr>
<td>C38.1</td>
<td>Malignant Neoplasm of anterior Mediastinum</td>
</tr>
<tr>
<td>C38.2</td>
<td>Malignant Neoplasm of posterior Mediastinum</td>
</tr>
<tr>
<td>C48.0</td>
<td>Malignant neoplasm of retroperitoneum</td>
</tr>
<tr>
<td>C56.1</td>
<td>Malignant Neoplasm of Right Ovary</td>
</tr>
<tr>
<td>C56.2</td>
<td>Malignant Neoplasm of Left Ovary</td>
</tr>
<tr>
<td>C62.01</td>
<td>Malignant neoplasm of undescended right testis</td>
</tr>
<tr>
<td>C62.02</td>
<td>Malignant neoplasm of undescended left testis</td>
</tr>
<tr>
<td>C62.11</td>
<td>Malignant neoplasm of descended right testis</td>
</tr>
</tbody>
</table>
C62.12 | Malignant neoplasm of descended left testis

*If applicable, please see Medicare LCD or NCD for additional covered diagnoses.

IX. REFERENCES


Other Sources:

X. Policy History

<table>
<thead>
<tr>
<th>Policy Number</th>
<th>History</th>
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<tr>
<td>MP 9.052</td>
<td>CAC 5/20/14 Minor. Information on HSCT in the Treatment of Germ-Cell Tumors was extracted from MP 9.037 Autologous and Allogeneic Stem Cell Transplantation (which was retired) and this new separate policy created. No change to policy statements. References updated. Policy guidelines and Rationale section added. Policy coded.</td>
</tr>
<tr>
<td></td>
<td>CAC 6/2/15 Consensus review. No change to policy statements. References and rationale updated. Codes reviewed.</td>
</tr>
<tr>
<td></td>
<td>CAC 5/31/16 Consensus review. No change to policy statements. References and rationale reviewed. Coding reviewed.</td>
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<td></td>
<td>Admin update 1/1/17: Product variation section reformatted.</td>
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