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

Policy Number: MM.07.020
Line(s) of Business: HMO; PPO
Section: Transplants
Place(s) of Service: Outpatient; Inpatient

Precertification is required for this service.

I. Description

**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.

II. Criteria/Limitations

A. Single autologous hematopoietic stem-cell transplantation is covered (subject to Limitations/Exclusions and Administrative Guidelines) as salvage therapy for germ-cell tumors:
   1. In patients with favorable prognostic factors that have failed a previous course of conventional-dose salvage chemotherapy; or
   2. 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.)

B. Tandem or sequential autologous hematopoietic stem-cell transplantation is covered (subject to Limitations/Exclusions and Administrative Guidelines) for the treatment of testicular tumors either as salvage therapy or with platinum-refractory disease.

C. Autologous hematopoietic stem-cell transplantation is not covered as a component of first-line treatment for germ-cell tumors.

D. Allogeneic hematopoietic stem-cell transplantation is not covered to treat germ-cell tumors, including, but not limited to its use as therapy after prior failed autologous hematopoietic stem-cell transplantation.

III. Policy Guidelines

A. The favorable and unfavorable prognostic factors listed below are derived from the current National Comprehensive Cancer Network (NCCN) guidelines (1) and the DeVita, Hellman, and Rosenberg’s textbook Cancer Principles and Practice of Oncology. (2)

B. 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.
IV. Limitations/Exclusions

The patient must be an appropriate candidate for transplant. This is defined as:
A. Adequate cardiopulmonary status
B. Absence of active infection
C. No history of malignancy within 5 years of transplantation, excluding nonmelanomatous skin cancers
D. Documentation of patient compliance with medical management

V. Administrative Guidelines

Precertification is required for this service as well as for any transplant evaluations. To precertify, please complete HMSA's Precertification Request and mail or fax the form as indicated along with the required documentation.

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<td>38212</td>
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VI. Scientific Background

**Autologous HSCT as front-line therapy of germ-cell tumors**

Motzer and colleagues reported on a phase III prospective, randomized, multicenter trial of 219 previously untreated patients with poor-prognosis germ-cell tumors. (3) The median patient age was 28 years. Patients were randomized to receive either conventional chemotherapy (4 cycles of standard bleomycin, etoposide, and cisplatin [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. (4) 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 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 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. (5) 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. Twenty-nine of the patients had received prior standard salvage chemotherapy. Three year overall survival was 57% (95% CI: 41-71%) and 3 year progression-free survival 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. (6) The authors reported no significant differences between treatment arms in 3-year event-free survival and overall survival. However, the study began before international consensus (7) 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., 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.

**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. (8) 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. Progression-free and overall survival at 1, 3, and 5 years was similar for both groups. The probability of progression-free survival 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 overall survival 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. (9) 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 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; ten percent 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 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 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 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 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 (four 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. (10) 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 overall survival was 11.8 months. The 3-year survival and progression-free survival 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. (11) 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 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. (12)

**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. (13)

**National Comprehensive Cancer Network (NCCN) Guidelines** (1)
The 2010 (v.1.2010) 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), experiences an incomplete response to conventional-dose salvage chemotherapy therapy or relapses after salvage chemotherapy, high-dose chemotherapy with autologous stem cell support is the preferred option. Patients with unfavorable prognostic factors for conventional-dose salvage therapy (e.g. an incomplete response to first line therapy) and patients requiring third-line salvage therapy 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 2 Phase III randomized studies that are ongoing but not recruiting patients:
- Standard VIP followed by sequential high-dose VIP and stem-cell rescue versus bleomycin, etoposide, and cisplatin (BEP) in chemotherapy-naive men ages 16–50 years with poor-prognosis germ-cell cancer (protocols EORTC-30974, NCT00003941). This trial is organized by the European Organization for Research and Treatment of Cancer and expects to accrue 222 patients within 2 years.
- 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.

**Physician Specialty Society and Academic Medical Center Input**
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. 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.

Summary
Salvage therapy plays a role in patients with germ-cell tumors who are either refractory to cisplatin or who relapse after initial treatment. (5) 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. (5) Studies have been limited trying to stratify patients into various prognostic groups to identify those that are high-risk, as only 30% of patients with germ-cell tumors require salvage treatment. (5) 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. (5)

The role of tandem or sequential autologous transplants has been investigated in one Phase II study, one randomized study, and two retrospective series (one single-center experience and one registry data from multiple centers). 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. Policy statement regarding tandem or sequential HSCT for the treatment of testicular tumors is changed to medically necessary.

VII. Important Reminder
The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii’s Patients’ Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4), generally accepted standards of medical practice and review of medical literature and government approval status. HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician
disagrees with HMSA’s determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

VIII. References
