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

**Description of Procedure or Service**

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).

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).

**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...
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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.

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.

Policy

**BCBSNC will provide coverage for Hematopoietic Stem-Cell Transplantation in the Treatment of Germ Cell Tumors when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.**

Some patients may be eligible for coverage under clinical trials. Refer to the policy on Clinical Trial Services.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

Some health benefit plans may exclude benefits for transplantation.
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**When Hematopoietic Stem-Cell Transplantation in the Treatment of Germ Cell Tumors is covered**

1. 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.)

2. 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.

**When Hematopoietic Stem-Cell Transplantation in the Treatment of Germ Cell Tumors is not covered**

1. Autologous hematopoietic stem-cell transplantation is considered *investigational* as a component of first-line treatment for germ-cell tumors.

2. 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.

**Policy Guidelines**

Refer to the individual member’s benefit booklet for prior review requirements.

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 cell transplantation (HCT).

For individuals who have previously untreated germ cell tumors who receive first-line treatment with autologous HCT, the evidence includes randomized controlled trials (RCTs). Relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. The available trials found that autologous HCT as initial therapy for germ cell tumors did not significantly improve outcomes compared with alternative therapy (e.g., standard-dose chemotherapy). Study sample sizes were relatively small and may have been underpowered to detect differences between groups. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have relapsed or refractory germ cell tumors who receive autologous HCT, the evidence includes 1 RCT and several case series. Relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. The RCT did not find significant differences in outcomes between autologous HCT plus high-dose chemotherapy and standard-dose chemotherapy. Case series found 3-year overall survival rates that ranged from 55% to 60%; these studies lacked comparison groups. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with germ cell tumors who receive tandem or sequential HCT, the evidence includes 1 RCT, several retrospective cohort studies, and a comparative effectiveness review. Relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. The RCT found a higher rate of treatment-related mortality with sequential HCT than with single HCT. However,
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5-year survival outcomes did not differ significantly between groups. Overall, the available studies have included heterogeneous patient populations, in different salvage treatment settings (ie, first vs subsequent salvage therapy), and have lacked a universally accepted prognostic scoring system to risk-stratify patients. Tandem or sequential HCT has not shown benefit in patients with primary mediastinal germ cell tumors. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have germ cell tumors who receive allogeneic HCT, the evidence includes a case report. Relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. There were no RCTs or non-RCTs evaluating allogeneic HCT for germ cell tumors. One 2007 case report described successful treatment of a refractory mediastinal germ cell tumor with allogeneic HCT. The evidence is insufficient to determine the effects of the technology on health outcomes.

Clinical input obtained in 2010 found strong support for autologous HCT as a treatment of relapsed or refractory germ cell tumors, and for tandem or sequential HCT as salvage therapy for testicular tumors and as treatment of platinum-refractory testicular tumors. The clinical input is generally consistent with recommendations in national and international guidelines. Thus, these indications may be considered medically necessary.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

*Applicable service codes: 38205, 38206, 38230, 38232, 38240, 38241, 38242, 38243, S2150

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

*Bone Marrow Transplant for Germ Cell Tumors*

- TEC Assessment, July, 1999; Volume 14, No. 11

*Policy name changed to Hematopoietic Stem-Cell Transplantation in the Treatment of Germ Cell Tumors*
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Senior Medical Director 7/2010


Policy Implementation/Update Information
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**Bone Marrow Transplant for Germ Cell Tumors**


2/01 Original policy issued.

7/01 Statement removed under when not covered section, "It should be noted that ovarian germ cell tumors must be distinguished from the far more common epithelial ovarian cancers. High-dose therapy for ovarian epithelial cancer is considered investigational." Refer to policy on Epithelial Ovarian Cancer. Removed "ovarian" from key words and medical term definitions.

Codes 86812-86822 removed; codes 38231 and 86915 deleted and codes 38242, 38205 and 38206 added to the Billing/Coding section. System coding changes.

1/04 Benefits Application and Billing/Coding sections updated for consistency.

2/04 Individual CPT codes listed for CPT code ranges 38240-38242 under Billing/Coding section.

7/29/04 HCPCS code S2150 added to Billing/Coding section.

12/23/04 Specialty Matched Advisory Consultant Panel review 11/29/04. No changes to criteria. Revised Description of Procedure or Service section. Added information to Policy Guidelines section to provide additional information related to "refractory" and "partial response". Policy number added Policy Key Words section. "Hematopoietic" and "Opportunistic" added to Definitions. References added.

12/22/08 Specialty Matched Consultant Advisory Panel review 11/13/08. Added additional wording in the "When Not Covered" section, no change in policy intent. References added. (btw)

6/22/10 Policy Number(s) removed. (amw)

**Policy name changed to Hematopoietic Stem-Cell Transplantation in the Treatment of Germ Cell Tumors**

8/31/10 Policy name changed from “Bone Marrow Transplant for Germ Cell Tumors” to “Hematopoietic Stem-Cell Transplantation in the Treatment of Germ Cell Tumors”. Removed reference to "Bone Marrow Transplant, high dose chemotherapy and stem cell support" and inserted "hematopoietic stem-cell transplantation" throughout policy as appropriate. Senior Medical Director Review 7/25/2010. Policy statements reworded extensively. Policy statements changed to indicate that tandem-sequential autologous...
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SCT may be considered medically necessary in certain types of testicular cancers. “Guidelines” section revised. References added. (btw)


7/1/11 Removed statement under the “When Not Covered” section that indicated “Except as noted above for treatment of certain testicular tumors, tandem or sequential autologous hematopoietic stem-cell transplantation is considered investigational to treat germ-cell tumors of any stage.” Medical Director review 6/13/2011. Reference added. (btw)

1/10/12 Specialty Matched Consultant Advisory Panel review 11/30/2011. No change to policy. (btw)

2/21/12 New 2012 CPT code, 38232, added to Billing/Coding section. (btw)

6/29/12 Reference added. (btw)


6/11/13 Added the following statements to the Description section; “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.” Removed the following statements from the Policy Guidelines section; “Refractory is defined as less than 50% reduction in tumor burden measured by serial computed tomography (CT) scans or levels of circulating tumor markers, such as alpha fetoprotein. Partial response is defined as least a 50% reduction in tumor burden.” Reference added. No change to policy intent. Senior Medical Director review 5/18/2013. (btw)

12/10/13 Specialty Matched Consultant Advisory Panel review 11/20/2013. No change to policy intent. (btw)

5/27/14 Policy Guidelines updated. References updated. Updated reference policy title from “Clinical Trial Services for Life Threatening Conditions” to “Clinical Trial Services”. No changes to Policy Statements. (mco)

12/9/14 Specialty Matched Consultant Advisory Panel review 11/24/2014. No change to policy intent. (lpr)

7/1/15 Reference update. No change to policy statement. (lpr)

12/30/15 Specialty Matched Consultant Advisory Panel review 11/18/2015. Reference added. No change to policy statement. (lpr)

12/30/16 Policy Guidelines updated. Specialty Matched Consultant Advisory Panel review 11/30/2016. No change to policy intent. (lpr)

2/24/17 Revised Description and Policy Guidelines sections. Reference added. No change to policy intent. (lpr)
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12/15/17   Specialty Matched Consultant Advisory Panel review 11/29/2017. No change to policy statement. (lpr)

12/14/18   Specialty Matched Consultant Advisory Panel review 11/28/2018. Reference added. No change to policy statement. (lpr)

12/31/19   Specialty Matched Consultant Advisory Panel review 11/20/2019. Reference added. No change to policy statement. (lpr)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.