

## Corporate Medical Policy

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

**File Name:** hematopoietic\_stem-cell\_transplantation\_in\_the\_treatment\_of\_germ\_cell\_tumor

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**Next CAP Review:** 11/2011

**Last Review:** 11/2011

### Description of Procedure or Service

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#### 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

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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

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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

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**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 for Life-Threatening Conditions.**

## Benefits Application

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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.**

## When Hematopoietic Stem-Cell Transplantation in the Treatment of Germ Cell Tumors is covered

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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.

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

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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

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

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.

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.

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 that 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 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, 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.

## Billing/Coding/Physician Documentation Information

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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](http://www.bcbsnc.com). They are listed in

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the Category Search on the Medical Policy search page.

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

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### **Bone Marrow Transplant for Germ Cell Tumors**

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

BCBSA Medical Policy Reference Manual, 4/30/2000

Specialty Matched Consultant Advisory Panel - 11/2002

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.34, 4/29/2003

Specialty Matched Consultant Advisory Panel - 11/2004

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.34, 7/20/06

Specialty Matched Consultant Advisory Panel - 11/2006

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.34, 9/18/2007

Specialty Matched Consultant Advisory Panel - 11/2008

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

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.34, 4/8/2010

Senior Medical Director 7/2010

National Comprehensive Cancer Network. Testicular cancer. Clinical Practice Guidelines in Oncology. National Comprehensive Cancer Network. V.2.2010. Accessed 7/25/2010 from: [http://www.nccn.org/professionals/physician\\_gls/PDF/testicular.pdf](http://www.nccn.org/professionals/physician_gls/PDF/testicular.pdf)

Specialty Matched Consultant Advisory Panel – 11/2010

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.34, 4/14/2011 Specialty Matched Consultant Advisory Panel – 11/2011

## Policy Implementation/Update Information

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### **Bone Marrow Transplant for Germ Cell Tumors**

1/01 Specialty Matched Consultant Advisory Group.

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.

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- 2/03 Specialty Matched Consultant Advisory Panel review 11/2002. No change in criteria. 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.
- 12/11/06 Specialty Matched Advisory Consultant Panel review 11/6/2006. Added statement regarding clinical trials to "Policy" section. Clarified the first bullet under the "When Covered" section from "HDC and autologous stem cell support may be considered medically necessary as a treatment of germ cell tumors that do not achieve a complete remission. (i.e., refractory germ cell tumors or those exhibiting a partial response to standard chemotherapy)." to "HDC and autologous stem cell support may be considered medically necessary as salvage therapy for patients with germ cell tumors that do not achieve a complete remission. (i.e., refractory germ cell tumors or those exhibiting a partial response or less to standard chemotherapy)." 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 SCT may be considered medically necessary in certain types of testicular cancers. "Guidelines" section revised. References added. (btw)
- 1/4/11 Specialty Matched Consultant Advisory Panel review 11/29/2010. No change to policy statement. 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)

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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)

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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.