



CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all plans administered by CIGNA Companies including plans administered by Great-West Healthcare, which is now a part of CIGNA.

Subject Stem-Cell Transplantation for Testicular Cancer

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Hyperlink to Related Coverage Policies

INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans as well as benefit plans formerly administered by Great-West Healthcare. Please note, the terms of a participant's particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a participant's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a participant's benefit plan document **always supercedes** the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable group benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. Proprietary information of CIGNA. Copyright ©2010 CIGNA

Coverage Policy

CIGNA covers single or tandem high-dose chemotherapy (HDC) followed by autologous hematopoietic stem-cell transplantation (HSCT) as medically necessary for relapsed or refractory testicular cancer.

CIGNA does not cover EITHER of the following procedures for the treatment of testicular cancer because they are considered experimental, investigational or unproven (this list may not be all inclusive):

- HDC followed by autologous HSCT as front-line therapy
- allogeneic HSCT

General Background

Testicular cancer is highly treatable and frequently curable (American Cancer Society [ACS], 2009). Prognosis is based on the type of cancer, the disease stage, and several independent prognostic factors. Ninety percent of testicular cancer is of germ cell origin; two primary types are seminomas, representing 40% of all tumors, and nonseminomas, which represent 60%.

Treatment

Testicular cancer is broadly divided into seminoma and nonseminoma for treatment planning. The type of testicular cancer, stage of disease, and prognostic category are the basis for treatment decisions. Because the biology of testicular germ cell tumors among adolescents and young adult males differs from tumors arising in infants and young boys, treatment guidelines may not apply to both subgroups (National Cancer Institute [NCI], 2009a). Standard first-line treatment options may include surgery, chemotherapy and/or radiation therapy.

For disease that persists despite treatment or has recurred after treatment with standard chemotherapy, prognosis is poor. Salvage chemotherapy regimens can induce long-term complete responses in about 25% of patients who have been previously treated with standard combination chemotherapy (NCI, 2009b). Because standard dose chemotherapy has limited effect in recurrent disease, salvage therapy with high-dose chemotherapy (HDC) with autologous hematopoietic stem-cell transplantation (HSCT) has been proposed.

Stem-Cell Transplantation

Stem-cell transplantation refers to transplantation of hematopoietic stem cells (HSCs) from a donor into a patient. HSC transplantation (HSCT) can be either autologous (using the patient's own stem cells) or allogeneic (using stem cells from a donor).

Autologous HSCT: Metastatic testicular tumors that have not been successfully treated by means of initial chemotherapy are potentially curable with salvage chemotherapy (Einhorn, 2007). The use of HDC with autologous HSCT is based on the hypothesis that major dose escalations of chemotherapy within the myeloablative range may overcome tumor cell resistance and produce a meaningful clinical improvement.

HDC with autologous HSCT has been studied as a first-line treatment for patients with poor-risk testicular cancer; however, several randomized and prospective clinical trials have not demonstrated improved complete response rates or overall survival for this indication compared with standard dose chemotherapy (Droz, 2007; Miki, 2007; Motzer, 2007). The use of conventional-dose chemotherapy remains the standard of care for these individuals (Motzer, 2007).

Droz et al. (2007) reported results of a randomized controlled trial (RCT) involving 115 individuals with metastatic nonseminomatous germ cell tumors who received intensified doses of conventional chemotherapy alone (group A), or followed by autologous HSCT (group B) as first-line treatment. There was no statistically significant difference in complete response (57% and 52%, respectively, for groups A and B), or survival rates. The proportion of patients with nonprogressive disease is similar in both groups (75% and 67%, respectively, for groups A and B). According to the authors, the trial failed to demonstrate an impact on response and survival with the use of high-dose therapy and autologous stem-cell support as first-line treatment.

In another prospective trial, Miki et al. (2007) analyzed the outcomes of 55 patients with advanced testicular germ cell cancer who received first-line HDC with autologous HSCT. All patients were treated with three cycles of conventional chemotherapy as induction. If tumor markers remained elevated patients (n=25) received one course of HDC with autologous HSCT; patients with tumor markers in the normal range did not receive HDC. No patient achieved complete remission after a single dose of HDC; 24 patients (38%) achieved partial remission. This study did not demonstrate improved complete response rates with the use of HDC and autologous HSCT.

Motzer (2007) reported outcomes of a Phase III prospective, randomized, multicenter trial involving 219 previously untreated male patients with intermediate- or poor-risk germ cell tumor. Patients were randomized to either conventional-dose chemotherapy alone (n=111) or conventional-dose chemotherapy plus HDC and autologous HSCT (n=108). The one-year durable complete response rates were 48% and 52% after conventional chemotherapy and HDC, respectively. There was no difference in survival at 106 months for patients treated with conventional chemotherapy compared with HDC plus autologous HSCT (69% and 68%, respectively).

Use of HDC and autologous HSCT for refractory or relapsed testicular cancer is considered an acceptable treatment option. Durable complete remissions may be achieved with salvage therapy including HDC followed by autologous HSCT in a small percentage of individuals with relapsed or refractory testicular cancer. Improved overall and disease-free survival rates have been demonstrated in several prospective and retrospective studies (Einhorn, 2007; Lotz, 2005; Schmoll, 2003; Vaena, 2003; Vuky, 2002; Bhatia, 2000). Subsequent HDC with autologous HSCT is possibly curative in 15–20% of individuals who have failed second-line therapy, (Small, 2004). Patients with unfavorable prognostic features for conventional-dose salvage therapy and patients

requiring third-line salvage therapy may be considered for treatment with high-dose chemotherapy (HDC) plus autologous hematopoietic stem-cell transplantation (HSCT) (National Comprehensive Cancer Network [NCCN], 2009). Published results of case controlled studies show modest improvement with the use of this therapy for relapsed or recurrent disease (Einhorn, 2007; Vaena, 2003; Hartman, 2001).

Although the effectiveness of this therapy has not been proven in randomized controlled clinical trials, planned tandem cycles of HDC followed by autologous HSCT may also be used in the setting of recurrent disease. In a multicenter trial Pico et al. (2005) randomly assigned 280 patients to receive either four cycles of standard dose chemotherapy or three cycles of the same chemotherapy followed by HDC. Complete and partial response rates were similar in both arms (56% and 56%, respectively). No significant improvement in three-year event-free survival was noted with the use of HDC compared with standard-dose (35% versus 42%, respectively). Despite the lack of efficacy data, it has been estimated that 30% of patients with recurrent disease undergo tandem autotransplants (Lazarus, 2007). Although data are not robust, the use of tandem HDC with autologous HSCT is considered an acceptable therapy for the treatment of individuals with refractory or relapsed testicular cancer.

Allogeneic HSCT: There is scarce data in the published, peer-reviewed scientific literature regarding the use of allogeneic HSCT with myeloablative or non-myeloablative conditioning regimens for the treatment of testicular cancer and the effectiveness of this treatment is unknown. The evidence is insufficient to demonstrate improved outcomes with the use of this therapy for the treatment of testicular cancer. The role of this therapy in the treatment of testicular cancer has not yet been established.

Contraindications

Many factors affect the outcome of a tissue transplant; the selection process is designed to obtain the best result for each individual. The presence of any significant comorbid conditions which would significantly compromise clinical care and chances of survival is a contraindication to transplant. According to the NCI (2009), radiation therapy and/or chemotherapy for patients with testicular cancer may be associated with an increase in cardiovascular morbidity. Relative contraindications to HSCT include, but are not limited to:

- poor cardiac function (ejection fraction < 45%)
- poor liver function (bilirubin > 2.0 mg/dl and transaminases greater than two times normal)
- poor renal function (creatinine clearance < 50 ml/min)
- poor pulmonary function (diffusion capacity [DLCO] < 60% of predicted)
- **EITHER** of the following:
 - presence of human immunodeficiency virus
 - an active form of **ANY ONE** of the following:
 - hepatitis B
 - hepatitis C
 - HTLV-1
- Karnofsky rating <60% and/or Eastern Cooperative Oncology Group (ECOG) performance status>2

Professional Societies/Organizations

European Germ Cell Cancer Consensus Group (EGCCCG): On behalf of the EGCCCG, Schmoll et al. (2004) noted that for patients with advanced disease it has not yet been proven that HDC plus autologous hematopoietic stem cell support given as first-line therapy increases survival; therefore HDC must not be used outside of a clinical trial.

National Cancer Institute (NCI): The NCI (2009) notes HDC with autologous HSCT is under clinical investigation for Stage III nonseminoma for selected patients with bulky disease. The NCI also notes HDC with autologous marrow transplantation has also been used in uncontrolled case series in the setting of recurrent disease. However, a randomized controlled trial comparing conventional doses of salvage chemotherapy with HDC with autologous marrow rescue showed more toxic effects and treatment-related deaths in the high-dose arm without any improvement in response rate or overall survival.

National Comprehensive Cancer Network (NCCN): The NCCN (2009) notes high-dose chemotherapy (HDC) with autologous stem-cell support is the preferred option for individuals with stages IIC and IIIA-C nonseminoma who have an incomplete response or have relapsed after salvage therapy. Individuals with unfavorable prognostic features for conventional chemotherapy (i.e., an incomplete response to first-line therapy) and patients requiring third-line salvage therapy are considered for treatment with HDC and plus autologous HSCT.

Summary

The published, peer-reviewed scientific literature supports the safety and effectiveness of high-dose chemotherapy (HDC) with autologous hematopoietic stem-cell transplantation (HSCT) for selected individuals with testicular cancer. Data are lacking regarding the safety and effectiveness of allogeneic HSCT for the treatment of testicular cancer; at this time, the role of this therapy has not been established for this indication.

Coding/Billing Information

Note: This list of codes may not be all-inclusive.

Covered when medically necessary:

| CPT ^{®*} Codes | Description |
|-------------------------|---|
| 38206 | Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous |
| 38207 | Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage |
| 38208 | Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing |
| 38209 | Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing |
| 38211 | Transplant preparation of hematopoietic progenitor cells; tumor cell depletion |
| 38212 | Transplant preparation of hematopoietic progenitor cells; red blood cell removal |
| 38213 | Transplant preparation of hematopoietic progenitor cells; platelet depletion |
| 38214 | Transplant preparation of hematopoietic progenitor cells; plasma (volume) depletion |
| 38230 | Bone marrow harvesting for transplantation |
| 38241 | Bone marrow or blood-derived peripheral stem cell transplantation; autologous |

| HCPCS Codes | Description |
|--------------------|--|
| S2150 [†] | 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 or pre-and post-transplant care in the global definition |

†Note: Covered when medically necessary when used to report autologous bone marrow or blood-derived stem cell procedures.

| ICD-9-CM Diagnosis Codes | Description |
|--------------------------|--|
| 186.0-186.9 | Malignant neoplasm of testis |
| 233.6 | Carcinoma in situ of other and unspecified male genital organs |

Experimental/Investigational/Unproven/Not Covered for the treatment of testicular cancer:

| CPT* Codes | Description |
|------------|---|
| 38205 | Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic |
| 38210 | Transplant preparation of hematopoietic progenitor cells; specific cell depletion within harvest, T-cell depletion |
| 38215 | Transplant preparation of hematopoietic progenitor cells ; cell concentration in plasma, mononuclear, or buffy coat layer |
| 38240 | Bone marrow or cord blood-derived peripheral stem-cell transplantation; allogeneic |
| 38242 | Bone marrow or blood-derived peripheral stem cell transplantation; allogeneic donor lymphocyte infusions |

| HCPCS Codes | Description |
|-------------|--|
| S2142 | Cord blood-derived stem-cell transplantation, allogeneic |

*Current Procedural Terminology (CPT®) © 2010 American Medical Association: Chicago, IL.

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Policy History

| Pre-Merger Organizations | Last Review Date | Policy Number | Title |
|---------------------------------|-------------------------|----------------------|--|
| CIGNA HealthCare | 3/15/2008 | 0323 | Stem-Cell Transplant for Testicular Cancer |

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