Subject: Hematopoietic Stem Cell Transplantation for Germ Cell Tumors	Original Effective Date: 9/17/14
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SUMMARY

Germ cell tumors

Germ cell tumors are a type of tumor that begins in the cells that give rise to sperm or eggs. Germ cell tumors can occur almost anywhere in the body and can be either benign or malignant. These 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. 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. [6 24] According to the International Germ Cell Cancer Collaborative Group (IGCCCG) consensus, risk classification of testicular germ cell tumors are separated by nonseminoma and seminoma diagnosis. There is no poor risk disease in the seminoma category. In nonseminoma, poor prognosis or poor risk disease is indicated by one of the following: mediastinal primary tumor, nonpulmonary visceral metastases, and elevation of any one post-orchiectomy marker (alpha fetal protein [AFP] greater than 10,000 ng/mL, human choriogonadotropin [hCG] greater than 50,000 IU/L, or lactate dehydrogenase [LDH] greater than 10 times the upper limit of normal). [24 25]

Stem Cell Transplantation

Stem-cell transplantation refers to transplantation of hematopoietic stem cells (HSCs) from a donor into a patient. HSCs are immature cells that can develop into any of the three types of blood cells (red cells, white cells or platelets). HSCs are created in the bone marrow and are found in the bone marrow and peripheral blood. There is also a high concentration of HSCs in umbilical-cord blood. Hematopoietic stem-cell transplantation (HSCT) can be either autologous (using the person's own stem cells) or allogeneic (using stem cells from a donor). In allogeneic HSCT, it is preferable for donors to have a human leukocyte antigen (HLA) type that is identical to the recipient. Matching is performed on the basis of variability at three of more loci of the HLA gene (e.g., HLA-A, HLA-B, HLA-DRB1). As HLA variability increases, transplant-related morbidity and mortality, including graft rejection and graft-versus-host disease, also increase.

RECOMMENDATION

All transplants require prior authorization from the Corporate Transplant Department. Solid organ transplant requests will be reviewed by the Corporate Senior Medical Director or qualified clinical designee. If the criteria are met using appropriate NCD and/or LCD guidelines, state regulations and/or MCG policies the Corporate Senior Medical Director's designee can approve the requested transplant.

Members must meet the criteria outlined below for transplantation and the diagnosis must be made by a Hematologist, Oncologist and/or transplant surgeon.

Pre-Transplant Evaluation:

1. General requirements for transplant evaluation include all of the following: [2 4 8 9 12]

- ❑ History and physical examination
- ❑ Psychosocial evaluation and clearance
- ❑ EKG
- ❑ Chest X-ray
- ❑ Cardiac clearance in the presence of any of the following: **[ONE]**
  - chronic smokers
  - > 50 years age
  - those with a clinical or family history of heart disease or diabetes
- ❑ Pulmonary clearance if evidence of pulmonary artery hypertension (PAH)or chronic pulmonary disease
- ❑ Performance Status: [ONE]
  - Karnofsky score 70-100%
  - Eastern Cooperative Oncology Group (ECOG) grade 0-2
- ❑ Neurological exam and clearance for transplant : [ONE]
  - Normal exam by H&P
  - Abnormal neurological exam with positive findings: [ONE]
    - Lumbar puncture normal cytology
    - Lumbar puncture with cytological exam abnormal: CNS disease treated prior to clearance
- ❑ Lab studies:
  - Complete blood count, Kidney profile (blood urea nitrogen, creatinine), electrolytes, calcium, phosphorous, albumin, liver function tests, Coagulation profile (prothrombin time, and partial thromboplastin time)
  - Serologic testing for HIV, Epstein Barr virus, Hepatitis virus B (HBV), and C(HCV), RPR and/or FTA

- ❑ Colonoscopy (if indicated or > age 50) with removal of any polyps
- ❑ GYN examination with Pap smear (if indicated or > age 18) with in the last three year with complete workup and treatment of abnormal results as indicated
- ❑ Dental examination or oral exam showing good dentition and oral care or no abnormality on panorex
- ❑ Mammogram (indicated >40) with complete work up and treatment of abnormal results as indicated

- ❑ *Within the last 12 months the following is required:*

  - Immunizations up to date when indicated: Hepatitis A and Hepatitis B, pneumococcal vaccine, influenza vaccine, tetanus booster)
  - PSA (if applicable) > age 50

Criteria for Hematopoietic Autologous Stem Cell transplantation (HSCT) Transplantation:

1. ***Hematopoietic Autologous stem-cell transplantation (HSCT)*** may be considered medically necessary and may be authorized as salvage therapy for the treatment of germ cell tumors when the following criteria are met: [13 14 19-33]

- ❑ **Single** autologous hematopoietic stem-cell transplantation may be considered medically necessary for the following: [ONE]
  - In patients with favorable prognostic factors that have failed a previous course of conventional-dose salvage chemotherapy; and: [ALL]
    - testicular primary site; and
    - a complete response to initial chemotherapy; and
    - low levels of serum markers (e.g. AFP, hCG, and LDH); and
    - low volume disease

    OR

  - In patients with unfavorable prognostic factors and have disease recurrence with: [ONE]
    - an incomplete response to prior chemotherapy; or
    - high levels of serum markers; or
    - high-volume disease; or
    - extratesticular primary; or
    - late relapse

- ❑ **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. [19 22 27 28 33]

AND

- ❑ ***No absolute contraindications:***
  - Cardiac, pulmonary, and nervous system disease that cannot be corrected and is a prohibitive risk for surgery
  - Malignant neoplasm outside the liver with a high risk for reoccurrence, non-curable malignancy (excluding localized skin cancer)
  - Systemic and/or uncontrolled infection
  - AIDS (CD4 count < 200cells/mm3)
  - Unwilling or unable to follow post-transplant regimen
  - Documented history of non-compliance including inability to follow through with medication adherence or office follow-up
  - Chronic illness with one year or less life expectancy

- Active alcohol and/or other substance abuse (to remove as a contraindication there must be 6 months of documented abstinence through participation in a structured alcohol/substance abuse program with regular meeting attendance and negative random drug testing)
- Limited, irreversible rehabilitation potential
- No adequate social/family support

CONTINUATION OF THERAPY

A review for any stem cell transplantation procedure is valid for one year from the time the request was approved. Due to potential lengthy organ donor waiting time, an annual review of clinical information should be conducted to evaluate any changes in the member's clinical status.

COVERAGE EXCLUSIONS [7 14 34]

1. Autologous stem cell transplantation when the above criteria are not met.
2. Autologous hematopoietic stem-cell transplantation is considered investigational for first-line treatment of germ-cell tumors.
3. Allogeneic HSCT is considered investigational to treat germ-cell tumors and as therapy after a previously failed autologous hematopoietic stem-cell transplantation.
4. Tandem (or sequential) autologous hematopoietic stem-cell transplantation is considered investigational to treat all other germ-cell tumors of any stage.
5. Hematopoietic stem cell collection, storage and freezing for a future unplanned transplant is not covered

6. Relative contraindications to stem cell transplantation include all of the following:
   - ❑ poor cardiac function (ejection fraction < 50%)
   - ❑ poor liver function (bilirubin > 2.0mg/dl and transaminases greater than two times normal), unless related to AML
   - ❑ poor renal function (creatinine clearance < 60ml/min)
   - ❑ poor pulmonary function [diffusion capacity (DLCO) < 60% of predicted]
   - ❑ active central nervous system involvement
   - ❑ If HIV positive all of the following are met:
     - CD4 count >200 cells/mm-3 for >6 months
     - HIV-1 RNA undetectable
     - On stable anti-retroviral therapy >3 months
     - No other complications from AIDS (e.g., opportunistic infection, including aspergillus, tuberculosis, coccidioides mycosis, resistant fungal infections, Kaposi's sarcoma, or other neoplasm)
   - ❑ Meeting all other criteria for transplantation
   - ❑ an active infection with any ONE of the following:
     - hepatitis B virus (HBV)
     - hepatitis C virus (HCV)
     - human T-cell lymphotropic virus (HTLV)-1
   - ❑ Karnofsky rating <70% ; OR
   - ❑ Eastern Cooperative Oncology Group (ECOG) performance status >2
   - ❑ Meeting all other criteria for transplantation

SUMMARY OF MEDICAL EVIDENCE

First Line Therapy with auHSCT: Randomized trials have been published regarding high dose chemotherapy (HDC) with autologous HSCT as a front-line treatment for patients with poor-risk testicular cancer; however these trials have not demonstrated improved complete response rates or overall survival (OS) when used as initial therapy compared with standard dose chemotherapy. The standard of care for these individuals is conventional-dose chemotherapy. [16 17 18]

Single auHSCT:

Seftel et al. (2011) 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 (CNS) disease, and 1 presented with retroperitoneal disease. In all, 28 patients underwent autologous HSCT for relapsed disease after achieving an initial 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. OS at 5 years was 44.7% (95% CI: 32% to 56.5%) and EFS, 43.5% (95% CI: 31.4% to 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. [29]

Agarwal et al. (2009) reported their experience at Stanford in treating 37 consecutive patients who received HDC and autologous HSCT between 1995 and 2005 for relapsed germ-cell tumors. The median patient age was 28 years (range, 9-59 years), with 34 males and three females. Primary tumor sites included 24 testes/adnexal, 10 chest/neck/retroperitoneal, and 3 CNS. Twenty-nine of the patients had received prior standard salvage chemotherapy. Three-year OS was 57% (95% CI: 41% to 71%), and 3-year PFS was 49% (95% CI: 33% to 64%). [31]

Summary: Improved overall- and disease-free survival rates have been demonstrated in one randomized controlled study and several prospective and retrospective studies. Durable complete remissions may be achieved with salvage therapy including HDC followed by autologous HSCT in a small subset of individuals. [20-21 29 31 32]

Tandem auHSCT:

Lotz et al. (2005) 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.[15]

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 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 indicate that better selection criteria have to be fulfilled in forthcoming studies. [22]

Lorch et al. (2007 [30] & 2012 [27]) compared single- versus sequential HDC with autologous HSCT as first or subsequent salvage treatment in patients with relapsed or refractory germ-cell tumors. 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. 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).[30] Long-term results were reported in 2012 from this study indicated five-year PFS as 47% (95% CI, 37%-56%) in arm A and 45% (95% CI, 35%-55%) in arm B (hazard ratio, 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 (hazard ratio, 1.42; 95% CI, 0.99-2.05; p=.057). Results showed 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. [27]

Lazarus et al. (2007) 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. 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. [28]

Summary: The role of tandem or sequential autologous transplants in relapsed testicular germ cell tumors has been assessed in one Phase II study, one randomized study, several retrospective series and a comparative effectiveness review from the Agency for Healthcare Research and Quality. Tandem or sequential HSCT may provide survival benefit, and the randomized study showed lower treatment-related mortality with sequential HSCT compared with single HSCT. [19 22 27 28 33]

Professional Organizations

National Comprehensive Cancer Network (NCCN): [13 14]

The NCCN Clinical Practice Guidelines in Oncology for Testicular Cancer (2014) indicate 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, HDC is an option, or if a patient with disease recurrence undergoes conventional-dose chemotherapy and experiences an incomplete response or relapses, HDC 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 HDC 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.

In the Clinical Practice Guidelines in Oncology for Ovarian Cancer (2014) indicates that high-dose chemotherapy with stem cell support is an acceptable therapy for those with residual or recurrent malignant germ-cell tumors.

CODING INFORMATION: THE CODES LISTED IN THIS POLICY ARE FOR REFERENCE PURPOSES ONLY. LISTING OF A SERVICE OR DEVICE CODE IN THIS POLICY DOES NOT IMPLY THAT THE SERVICE DESCRIBED BY THIS CODE IS A COVERED OR NON-COVERED. COVERAGE IS DETERMINED BY THE BENEFIT DOCUMENT. THIS LIST OF CODES MAY NOT BE ALL INCLUSIVE.

CPT	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
38210	Transplant preparation of hematopoietic progenitor cells; specific cell depletion within harvest, T-cell depletion
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
38215	Transplant preparation of hematopoietic progenitor cells; cell concentration in plasma, mononuclear, or buffy coat layer
38230	Bone marrow harvesting for transplantation
38232	Bone marrow harvesting for transplantation; autologous
38241	Bone marrow or blood-derived peripheral stem cell transplantation; autologous
38242	Bone marrow or blood-derived peripheral stem cell transplantation; allogeneic donor lymphocyte infusions

HCPCS	Description
S2140	Cord blood harvesting for transplantation, allogeneic

S2142	Cord blood derived stem-cell transplantation, allogeneic
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 of pre-and post-transplant care in the global definition

ICD-9	Description
158.0	Malignant neoplasm of retroperitoneum
164.2	Malignant neoplasm of anterior mediastinum
164.3	Malignant neoplasm of posterior mediastinum
183.0	Malignant neoplasm of ovary
186-186.9	Malignant neoplasm of testis

ICD-10	Description
C48.0	Malignant neoplasm of retroperitoneum
C56-C56.9	Malignant neoplasm of ovary
C62-C62.92	Malignant neoplasm of testis

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DISCLAIMER

This Medical Guidance is intended to facilitate the Utilization Management process. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (i.e., will be paid for by Molina) for a particular member. The member's benefit plan determines coverage. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member's benefit plan to determine if there are any exclusions or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid members. CMS's Coverage Database can be found on the following website: http://www.cms.hhs.gov/center/coverage.asp.

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this Molina medical coverage guidance (MCG) document and provide the directive for all Medicare members.

CMS does have a NCD called Stem Cell Transplantation (110.8.1); however this NCD does not address the treatment of germ cell tumors. [1]