Anthem

Medical Policy

Subject: Hematopoietic Stem Cell Transplantation for Germ Cell Tumors
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Description/Scope

This document addresses hematopoietic stem cell transplantation as a treatment of germ cell tumors (testicular, mediastinal, retroperitoneal, ovarian). Germ cell tumors are neoplasms developed from the reproductive germ cell line.

Note: For epithelial ovarian carcinoma, see TRANS.00031 Hematopoietic Stem Cell Transplantation for Autoimmune Disease and Miscellaneous Solid Tumors.

Position Statement

Medically Necessary:

A *single autologous hematopoietic stem cell transplantation* is considered **medically necessary** as a treatment of primary germ cell tumors* in individuals treated with standard chemotherapy who had **one** of the following results:

A. A partial response; **or**
B. Refractory germ cell tumors; **or**
C. Relapsed disease.

A *planned tandem autologous hematopoietic stem cell transplantation* is considered **medically necessary** as a treatment of primary *testicular cancer* in individuals treated with standard chemotherapy who had one of the following results:

A. A partial response; **or**
B. Refractory germ cell tumors; **or**
C. Relapsed disease.

Note:** Ovarian germ cell tumors* must be distinguished from the far more common epithelial ovarian cancers. For epithelial ovarian carcinoma, please refer to ***TRANS.00031 Hematopoietic Stem Cell Transplantation for Autoimmune Disease and Miscellaneous Solid Tumors.

A *repeat autologous hematopoietic stem cell transplantation* due to primary graft failure or failure to engraft is considered **medically necessary.**

Investigational and Not Medically Necessary:

A *single autologous hematopoietic stem cell transplantation*, in lieu of a course of standard chemotherapy, is considered **investigational and not medically necessary** as initial treatment of poor prognosis germ cell tumors.

A *planned tandem autologous hematopoietic stem cell transplantation* is considered **investigational and not medically necessary** as a treatment of all other non-testicular germ cell tumors.

Allogeneic (ablative and non-myeloablative [mini transplant]) hematopoietic stem cell transplantation is considered **investigational and not medically necessary** as a treatment of germ cell tumors, including but not limited to, use as a therapy after a prior failed high-dose chemotherapy with autologous hematopoietic stem cell support.

A *second or repeat autologous hematopoietic transplant* due to persistent, progressive or relapsed disease is considered **investigational and not medically necessary.**

Hematopoietic stem cell harvesting for a future but unscheduled transplant is considered **investigational and not medically necessary.**

Rationale

Germ cell tumors comprise the vast majority of primary testicular neoplasms, although germ cell tumors can arise in the ovary and in extragonadal locations such as the retroperitoneum or mediastinum. Germ cell tumors can be classified according to their histology, stage, prognosis, or response to chemotherapy. Testicular germ cell tumors are classified as either seminoma or nonseminoma. Histologies of nonseminomatous tumors include embryonal cell carcinoma, teratoma, choriocarcinoma, yolk sac tumor, and mixed germ cell tumors.

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, or 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) (National Comprehensive Cancer Network® [NCCN], 2023).

Autologous Hematopoietic Stem Cell Transplantation as Front-Line Therapy of Germ Cell Tumors

Motzer and colleagues (2007) reported results from a Phase III, multicenter, randomized trial of 219 individuals with poor-prognosis, metastatic germ cell tumors. Participants were assigned to conventional-dose chemotherapy (bleomycin, etoposide and cisplatin [BEP]) (n=111) or randomized to BEP plus high-dose chemotherapy (HDCT) with autologous hematopoietic stem cell transplantation (n=108) as first-line therapy. The 1-year durable complete response (CR) rate was 52% after BEP + HDCT and 48% after BEP alone (p=0.53). The median time-to-treatment failure (TTF) was 23.2 months and 11.3 months for individuals in the BEP + HDCT and BEP

alone cohorts (p=0.40). With a median follow-up of 51 months, there was no difference in survival for individuals treated with BEP + HDCT versus BEP alone (p=0.94). Survival rate was 83% at 1 year and 71% at 2 years. The authors concluded that the routine inclusion of HDCT after two cycles of BEP in first-line treatment for germ cell tumors with metastases and poor predicted outcome to chemotherapy did not improve survival over four cycles of BEP alone. In addition, the authors noted that four cycles of BEP remains the standard of care for intermediate- and poor-risk germ cell tumors.

Droz and colleagues (2007) reported mature results from a randomized controlled trial of treatment naïve individuals with high-volume, metastatic nonseminomatous germ cell tumors. A total of 115 participants were randomized to receive either double-dose cisplatin with vinblastine and bleomycin (PVeBV) in Arm A compared to PVeBV with high dose chemotherapy followed by autologous bone marrow transplantation in Arm B. Both cohorts were equally balanced with 57 participants after 1 individual was deemed ineligible. There was no statistical significance in complete response (57% and 52%) and non-progressive disease (75% and 67%) in all evaluable participants in Arm A and Arm B, respectively. At a median follow-up of 9.7 years, 31 participants (Arm A) and 27 participants (Arm B) showed no evidence of disease. Five-year survival rates were 75% and 61% with 14 and 18 individuals still alive at 10-year follow-up in Arms A and B, respectively. Based on the results of the trial, the authors concluded that a clinical outcome benefit of high dose chemotherapy with autologous hematopoietic stem cell transplantation as front-line therapy was unproven.

Daugaard and colleagues (2011) reported the outcomes of a randomized Phase III study comparing standard-dose BEP with sequential high-dose VIP (cisplatin, etoposide, and ifosfamide) plus autologous stem-cell support in previously untreated males with poor-prognosis germ-cell cancer. The study aimed to recruit 222 males but closed with 137 men from 27 European oncology centers due to slow accrual. Subjects were age 15-50 years and had previously untreated metastatic poor-prognosis nonseminomatous germ-cell tumor of either testicular or extragonadal origin. The median follow-up was 4.4 years. Toxicity was more severe for those who were treated with high-dose chemotherapy. Death due to toxicity was reported in 2 individuals who received high-dose chemotherapy and 1 in the BEP arm. There was no improvement in complete response rate in the high-dose chemotherapy arm versus the standard-dose arm (44.6% vs. 33.3%, respectively, p=0.18). There was no difference in failure-free survival between the two groups. At 2 years, failure-free survival was 44.8% (95% confidence interval [CI]: 32.5-56.4) and 58.2% (95% CI: 48.0-71.9), respectively for the standard- and high-dose arms. The difference was not statistically significant (p=0.06). Overall survival (OS) did not differ between the two groups (log-rank p>0.1). The authors concluded that high-dose chemotherapy plus autologous stem-cell support given as part of first-line therapy does not improve outcomes in individuals with poor-prognosis germ-cell tumor.

Autologous Hematopoietic Stem Cell Transplantation as Second-Line or Subsequent Therapy of Germ Cell Tumors

According to Einhorn (2007), an international collaborative group has described cure rates of 90 to 95% for low-risk individuals, 75% for intermediate-risk individuals and 40 to 50% in high-risk individuals with metastatic germ cell tumors. The authors describe a retrospective review of 184 consecutive individuals with progressive metastatic testicular cancer after receiving cisplatin-containing chemotherapy regimens. Disease-free survival (DFS) was the primary endpoint of the analysis. Individuals with primary mediastinal nonseminomatous germ cell tumors were ineligible for the study. A total of 173 participants received two planned courses of high-dose chemotherapy each followed by autologous stem cell transplantations. Eleven individuals received only one cycle of autologous stem cells due to progressive disease, toxicity and salvage surgery. One hundred forty-nine participants had nonseminomatous germ-cell tumors, and 35 had seminoma only. At a median follow-up of 48 months, 116 (63%) participants were continuously disease free. Of these, 104 (90%) had been disease free greater than 2 years. Six additional participants achieved complete remission (CR) after additional therapies. Toxic side effects of high-dose chemotherapy included myelosuppression, mucositis, nausea, peripheral neuropathy and dehydration. There were three treatment related deaths due to hepatic failure and pulmonary toxicities. In addition, 3 individuals that received high-dose chemotherapy and transplantation as a third-line or later therapeutic option developed acute leukemia.

Lazarus and colleagues (2007) reported outcomes from an observational study of single and tandem autologous stem cell transplants from the Center for International Blood and Marrow Transplant Research (CIBMTR) database. Results from 102 individuals with planned tandem autologous stem cell transplants were compared with 198 individuals who did not have a second autologous transplant planned. There was no statistically significant difference between the cohorts for 5-year survival probability of 35% in the planned tandem group versus 42% in the group without a planned second transplant (p=0.29). Additionally, the probability of progression-free survival at 5 years was 34% for the planned tandem group compared to 38% (p=0.50) in the group without a planned second transplant. However, the authors noted a statistically significant difference in lower treatment-related mortality at 1 year of 3% for the planned tandem group versus 10% (p=0.02) in the group without a planned second transplant.

Seftel and colleagues (2011) conducted a long-term multicenter follow-up study of 71 males undergoing a single autologous hematopoietic stem cell transplantation for germ cell tumors between January 1986 and December 2004 after an incomplete response to first-line chemotherapy or relapsed disease. The median follow-up was 10.1 years. OS at 5 years was 44.7% (95% CI, 32.9-56.5%) and EFS is 43.5% (95% CI, 31.4-55.1%). There were seven (10%) treatment-related deaths within 100 days of autologous hematopoietic stem cell transplantation. Three (4.2%) individuals developed secondary malignancies. From a total of 33 relapses, 31 occurred within 2 years of the autologous hematopoietic stem cell transplantation. Two very late relapses were noted 13 and 11 years after hematopoietic stem cell transplantation. In a multivariate analysis, favorable outcome was associated with International Germ Cell Consensus Classification (IGCCC) good prognosis disease at diagnosis, primary gonadal disease and response to salvage chemotherapy. The authors concluded that autologous hematopoietic stem cell transplantation results in successful outcome for a relatively large subgroup of individuals with high-risk germ cell tumors; however, late relapses may occur, even after 10 years. They also noted that further study is required to determine how sequential autologous hematopoietic stem cell transplantation compares with a single autologous stem cell transplantation or with standard dose chemotherapy.

Suleiman and colleagues (2013), in a subsequent small study at the same center as the Einhorn trial, evaluated outcomes of 12 individuals with recurrent primary mediastinal nonseminomatous germ cell tumors after initial treatment with cisplatin-containing combination chemotherapy (a group excluded from their previous study). Participants received two consecutive courses of high dose chemotherapy (carboplatin and etoposide) followed by hematopoietic stem cell transplantation. Outcomes of tandem transplant for primary mediastinal nonseminomatous germ cell tumors were generally poor compared to testes cancer, with a median survival of 11 months (range, 4-52 months). However, 3 of 12 subjects achieved a complete remission, 1 subject remained disease free at 50 months of follow up, and 1 remained free of disease following tandem hematopoietic stem cell transplantation and subsequent mediastinal surgery at 52 months of follow-up.

A large single center retrospective analysis (Adra, 2017) performed at Indiana University consisted of 364 individuals with relapsed germ cell tumor with disease progression after cisplatin-based combination therapy. The primary tumor site was testis in the majority of persons (n=316). Other tumor sites were retroperitoneum (n=28) and mediastinum (n=20). Median age of those treated was 32 years (range, 17 to 70 years) and ECOG performance status at treatment initiation was 0-1. Of the 364 total subjects, 341 were treated with the planned two consecutive courses of HDCT consisting of 700 mg/m^2 carboplatin and 750 mg/m^2 etoposide, each for 3 consecutive days, and each followed by peripheral blood stem cell transplantation (PBSCT). Treatment was limited to a single course of HDCT in 23 subjects due to progressive disease or toxicity. At a median follow-up of 3.3 years, the 2-year progression-free survival (PFS) was 60% (95% CI, 55% to 65%) and the 2-year OS was 66% (95% CI, 60% to 70%). Of the 143 persons who had disease

recurrence after HDCT, the median time to relapse was 4.3 months (range, 1 to 30 months). Overall, 363 individuals had received HDCT as second-line therapy with a 2-year PFS of 63% (95% CI, 57% to 68%), and 61 individuals received HDCT as third-line or subsequent therapy with a 2-year PFS of 49% (95% CI, 36% to 61%). There were 9 treatment-related deaths and secondary leukemia developed in 5 individuals. The authors concluded that HDCT followed by PBSCT was an effective salvage therapy for relapsed germ cell tumor; however, there were both short- and long-term quality of life issues that occurred as a result of HDCT.

Sequential Autologous Hematopoietic Stem Cell Transplantation

Lotz and colleagues (2005) reported the results of a Phase II study of three consecutive cycles of high-dose chemotherapy regimens supported by autologous hematopoietic stem cell transplantation in 45 individuals with poor-prognosis and relapsed germ cell tumors. From March 1998 to September 2001 (median follow-up, 31.8 months), 45 individuals (median age, 28 years) were enrolled. Most (76%) had testicular primaries; 13% had mediastinal primaries; 11% retroperitoneal, hepatic or unknown. A total of 22 individuals received the complete course. Twenty-five individuals died from progression and 5 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 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 those with a Beyer score greater than two did not benefit from this approach, confirming that highly refractory cases and particularly those with resistant/refractory primary mediastinal germ cell tumors do not benefit from high-dose chemotherapy. The authors also stated that better selection criteria have to be fulfilled in forthcoming studies.

Feldman and colleagues (2010) studied the efficacy of the TI-CE regimen consisting of paclitaxel [T] plus ifosfamide [I] followed by three high-dose cycles of carboplatin [C] plus etoposide [E] with stem-cell support in individuals with germ cell tumors predicted to have a poor prognosis with conventional-dose salvage therapy. A total of 107 individuals with advanced GCTs with progressive disease post chemotherapy and unfavorable prognostic features (extragonadal primary site, incomplete response [IR] to first-line therapy, or relapse/IR to ifosfamide-cisplatin-based conventional-dose salvage) participated in this prospective, single-institution, phase II trial. The major findings included a 52% 5-year OS and 47% 5-year DFS. Among the 107 participants, 50 deaths occurred including 2 (2%) treatment-related deaths (grade 5 toxicities). The treatment related deaths consisted of one fatal cerebral hemorrhage and one fatal pulmonary hemorrhage. In addition, all participants experienced grade 4 neutropenia.

Further research is needed surrounding the treatment of relapsed/refractory metastatic germ cell tumors and additional study is planned (Feldman, 2011; Rashid, 2012; Tan, 2019). In the NCCN clinical practice guideline (CPG) for testicular cancer (V1.2023) the Panel concludes that it is not currently known whether high-dose chemotherapy is better than conventional-dose chemotherapy in the second-line setting for patients with relapsed disease, the NCCN Panel recommends clinical trial enrollment for these participants. An international group of investigators will compare conventional-dose therapy consisting of paclitaxel, ifosfamide, and cisplatin (TIP) with sequential high-dose therapy (TI-CE with stem-cell support) for relapsed/refractory germ cell tumors in a global randomized prospective trial (TIGER trial). Subjects who have failed initial cisplatin-based therapy will be eligible and all prognostic groups are to be included. The primary endpoint will be OS and approximately 420 participants will be required over 4 years. As a result of this phase 3 study, investigators plan to answer questions and resolve uncertainties that exist surrounding the treatment of relapsed/refractory germ cell tumors. At the time of this writing, the TIGER trial (NCT02375204) is still recruiting participants with an estimated enrollment of 420 individuals and primary completion date of June 2024.

Lorch and colleagues (2012) studied long-term survival rates of individuals with relapsed or refractory germ cell tumors following treatment with single or sequential high-dose chemotherapy. Between November 1999 and November 2004, 211 persons with relapsed or refractory germ cell tumors were randomly assigned to treatment with either one cycle of cisplatin 100 mg/m^2, etoposide 375 mg/m^2, and ifosfamide 6 g/m^2 (VIP) plus three cycles of high-dose carboplatin 1500 mg/m^2 and etoposide 1500 mg/m^2 (CE, arm A) or three cycles of VIP plus one cycle of high-dose carboplatin 2200 mg/m^2, etoposide 1800 mg/m^2, and cyclophosphamide 6400 mg/m^2 (CEC, arm B) followed by autologous stem-cell re-infusion (Lorch, 2007). Long-term PFS and OS were compared 6 years after the last person was randomized. Overall, 108 and 103 individuals were randomly assigned to arms A and B, respectively. The study was terminated prematurely due to excess treatment-related mortality in arm B (14%) compared with that in arm A (4%). As of December 2010, 9 (5%) of 211 subjects were lost to follow-up; 94 (45%) of 211 remained alive and 88 (94%) of 94 were progression free. At 5 years, PFS was 47% in arm A and 45% in arm B and OS was 49% in arm A and 39% in arm B.

In a small retrospective case series, Lewin and colleagues (2014) analyzed records of 17 men from a single Australian center who received HDCT with autologous stem cell transplantation for relapsed germ cell tumors. Baseline characteristics, treatment-related toxicity and survival were analyzed. Median age was 34 (21-46), with 41% having primary refractory disease and 53% with high/very high risk disease. Two subjects received two cycles and 15 received three cycles of HDCT-autologous stem cell transplantation. The most commonly used regimen was paclitaxel/ifosfamide followed by high-dose carboplatin/etoposide (TI-CE; n=12). The median duration of grade 4 (G4) neutropenia was 11 days (range 9-17) with febrile neutropenia in 90% resulting in four intensive care unit admissions (8%). Median duration of G4 thrombocytopenia was 10 days (range 8-19) requiring a median of two pooled platelets bags (range 0-33) per episode. Transplant-related mortality occurred in 1 individual (veno-occlusive disease). Twenty-seven per cent of HDCT-autologous stem cell cycles were associated with grade 3 mucositis. Two-year PFS and OS rates were 59% and 71%. Subjects who received HDCT-autologous stem cell transplantation as second or subsequent relapse fared worse than those treated with HDCT-autologous stem cell transplantation at first relapse. Three-year OS for those who received TI-CE at first relapse was 90%. This case series was limited by a small sample size.

Other Considerations

The NCCN (V1.2023) CPG for testicular cancer assigns a 2A recommendation to the second-line/third-line chemotherapy regimen consisting of paclitaxel, ifosfamide, carboplatin, and etoposide administered with peripheral blood stem cell support at 14-21 day intervals for three cycles. The NCCN 2A category is based upon lower-level evidence and uniform NCCN consensus that the intervention is appropriate.

In 2015, the American Society for Blood and Marrow Transplantation (Majhail and colleagues) issued guidelines for autologous and allogeneic hematopoietic cell transplantation. Definitions used for classifying indications were: standard of care (S); standard of care, clinical evidence available (C); standard of care, rare indication (R); Developmental (D); and not generally recommended (N). Indications for hematopoietic cell transplantation in adults (generally 18 years of age and above) include the following classifications for germ cell tumors:

- Germ cell tumor, relapse (N for allogeneic, C for autologous)
- Germ cell tumor, refractory (N for allogeneic, C for autologous)

Indications for hematopoietic cell transplantation in children (generally less than 18 years of age) include the following classifications for germ cell tumors:

- Germ cell tumor, relapse (D for allogeneic, C for autologous)

- Germ cell tumor, refractory (D for allogeneic, C for autologous)

Hematopoietic stem cell transplant (HSCT) is an important therapeutic modality for many malignant and nonmalignant hematologic diseases and its applicability continues to expand as its use in established therapies is refined and new indications are identified. In addition, the number of individuals who could benefit from HSCT has increased due to advancements, such as reduced intensity conditioning regimens, which have made HSCT safer (Majhail, 2015). However, the risks associated with transplant-associated morbidity and mortality remain significant. Most transplant centers utilize forums, boards or conferences where the treatment options of individual HSCT candidates are discussed (Majhail, 2015). Okamoto (2017) notes:

> The medical decision-making process for a transplant procedure is complex which requires assessing several factors besides the underlying indication for transplantation. Those include patient/disease factors, and transplant factors such as planed conditioning/graft-versus-host disease (GVHD) prophylaxis and stem cell source. Patient factors include their overall health and comorbidities, prior therapies, and how patients responded to those therapies, age, and disease/disease risk.

There are a number of clinical assessment and prognostic tools which evaluate individuals based upon multiple factors. The earlier, simpler tools, such as the Charlson Comorbidity Index (CCI) were useful in predicting outcomes, but lacked the sensitivity of subsequent tools such as the HCT-specific comorbidity index (HCT-CI) The HCT-CI score has been validated in multiple HSCT settings to independently predict non-relapse mortality (NRM) rates by weighting 17 relevant comorbidities. The HCT-CI was further enhanced by the incorporation of some laboratory biomarkers into an augmented version. While these tools provide valuable prognostic information, the decision to transplant is unique to each individual and needs to include a specific risk-benefit analysis in partnership with the individual's physicians and other caregivers.

Summary

At this time there is insufficient evidence to support the efficacy of high-dose chemotherapy with allogeneic stem cell transplant or non-myeloablative conditioning regimens as treatment of germ cell tumors. Additionally, there is insufficient evidence to support the efficacy of three or more cycles of autologous stem cell support.

There are no data from controlled studies that investigated the efficacy of planned cycles (tandem) of HDC followed by stem cell support (auto/auto or auto/allo) for the treatment of germ cell tumors other than in individuals with testicular cancer that meet specified criteria. Therefore, conclusions regarding the net efficacy of such planned tandem protocols could not be reached.

Background/Overview

Germ cell tumors are usually treated with one or a combination of modalities including surgery, chemotherapy and radiation therapy. Treatment is determined by the histology and stage of disease in combination with other factors. Autologous stem cell transplantation has been utilized as a salvage therapeutic option.

Testicular cancer is a disease in which cells in one or both testicles become cancerous and begin to grow uncontrollably. Seminomas and non-seminomas are the two main types of testicular germ cell tumors. If not treated or removed, these cancerous cells will eventually form a growth or tumor that can spread to other parts of the body. Testicular cancer most often develops in young and middle aged men and is highly treatable if detected early. According to the National Cancer Institute (NCI), in 2022, approximately 9910 new cases of testicular cancer will be diagnosed in the United States.

Ovarian cancers may arise from different cell lines. Ovarian germ cell tumors include dysgerminoma. According to the American Cancer Society (ACS), in 2022, approximately 19,880 new cases of ovarian cancer will be diagnosed in the United States and 12,810 estimated deaths. Ovarian germ cell tumors are aggressive and uncommon tumors often occurring in young women and adolescent girls. If the tumor is identified and treated early, it can be curable.

High-dose chemotherapy (HDC) involves the administration of cytotoxic agents using doses several times greater than the standard therapeutic dose. In some cases, whole body or localized radiotherapy is also given and is included in the term HDC when applicable. The rationale for HDC is that many cytotoxic agents act according to a steep dose-response curve. Thus, small increments in dosage will result in relatively large increases in tumor cell kill. Increasing the dosage also increases the incidence and severity of adverse effects related primarily to bone marrow ablation (for example, opportunistic infections, hemorrhage, or organ failure). Bone marrow ablation is the most significant side effect of HDC. As a result, HDC is accompanied by a re-infusion of hematopoietic stem cells, which are primitive cells capable of replication and formation into mature blood cells, in order to repopulate the marrow. The potential donors of stem cells include:

1. Autologous - Stem cells can be harvested from the individual's own bone marrow or peripheral blood
2. Allogeneic - Stem cells harvested from a histocompatible donor

   (**Note:** this document does not require a specific level of histocompatibility be present as part of the medical necessity evaluation)

Donor stem cells, either autologous or allogeneic, can be collected from either the bone marrow or the peripheral blood. Stem cells may be harvested from the peripheral blood using a pheresis procedure. To increase the number of stem cells in the peripheral circulation, donors may be pretreated with a course of chemotherapy or hematopoietic growth factors, or both.

In addition, blood harvested from the umbilical cord and placenta shortly after delivery of neonates contains stem and progenitor cells. Although cord blood is an allogeneic source, these stem cells are antigenically "naïve" and thus, are associated with a lower incidence of rejection or graft versus host disease.

Immunologic compatibility between donor and recipient is a critical factor for achieving a good outcome of allogeneic bone marrow transplantation. 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 HLA A, B, and DR loci on the long arm of chromosome 6.

The most appropriate stem cell source for a particular individual depends upon his or her disease, treatment history, and the availability of a compatible donor. The most appropriate source of stem cells for each individual must balance the risks of graft failure and re-infusion of malignant cells in autologous procedures, the risks of graft rejection, and graft versus host disease in allogeneic procedures.

Tandem high-dose or non-myeloablative chemotherapy with autologous or allogeneic stem cell support is the planned administration of two cycles of high-dose chemotherapy, alone or with total body irradiation, each of which is followed by re-infusion of stem cells. Despite treatment with high-dose chemotherapy, many individuals with advanced malignancies eventually relapse, indicating the presence of residual neoplastic cells. The hypothesis is that eradication of residual tumor cells can be achieved using multiple cycles of myeloablative or non-myeloablative chemotherapy with stem cell support.

Definitions

Ablative: A very high dose of a treatment, calculated to kill a tumor.

Allogeneic stem cells: Stem cells harvested from a histocompatible donor.

Autologous stem cells: Stem cells harvested from the individual's own bone marrow or peripheral blood.

Bone marrow: A spongy tissue located within flat bones, including the hip and breast bones and the skull. This tissue contains stem cells, the precursors of platelets, red blood cells, and white cells.

Chemosensitive: Showing tumor response to the most recent chemotherapy regimen.

Chemotherapy: The medical treatment of a disease, particularly cancer, with drugs or other chemicals. Chemotherapy may vary by disease and stage.

Chimerism: Cell populations derived from different individuals; may be mixed or complete.

Complete response/remission (CR): The disappearance of all signs of cancer in response to treatment; this does not always mean the cancer has been cured; also called a complete response.

Cytotoxic: Destructive to cells.

ECOG (Eastern Cooperative Oncology Group) Performance Status: A scale used to determine the individual's level of functioning; this scale may also be referred to as the WHO (World Health Organization) or Zubrod score; based on the following scale:

0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Deceased

Failure to engraft: When the bone marrow infused during a bone marrow transplant does not take or is not accepted by the recipient.

Graft versus host disease: A life-threatening complication of bone marrow transplants in which the donated marrow causes an immune reaction against the recipient's body.

Hematopoietic stem cells: Primitive cells capable of replication and formation into mature blood cells in order to repopulate the bone marrow.

High-dose or myeloablative chemotherapy (HDC): The administration of cytotoxic agents using doses several times greater than the standard therapeutic dose.

HLA (human leukocyte antigen): A group of protein molecules located on bone marrow cells that can provoke an immune response.

Karnofsky Score: A measure of the individual's overall physical health, judged by their level of activity; the score uses the following scale:

100%	Normal, no complaints, no signs of disease
90%	Capable of normal activity, few symptoms or signs of disease
80%	Normal activity with some difficulty, some symptoms or signs
70%	Caring for self, not capable of normal activity or work
60%	Requiring some help, can take care of most personal requirements
50%	Requires help often, requires frequent medical care
40%	Disabled, requires special care and help
30%	Severely disabled, hospital admission indicated but no risk of death
20%	Very ill, urgently requiring admission, requires supportive measures or treatment
10%	Moribund, rapidly progressive fatal disease processes
0%	Death

Lansky Score: A measure of the individuals overall physical health, judged by their level of activity; the score uses the following scale:

100	Fully active, normal
90	Minor restrictions in physically strenuous activity
80	Active, but tires more quickly
70	Both greater restriction of and less time spent in play activity
60	Up and around, but minimal active play; keeps busy with quieter activities
50	Gets dressed but lies around much of the day, no active play but able to participate in all quiet play and activities
40	Mostly in bed; participates in quiet activities
30	In bed; needs assistance even for quiet play
20	Often sleeping; play entirely limited to very passive activities
10	No play; does not get out of bed
0	Unresponsive

Non-myeloablative chemotherapy: Less intense chemotherapy conditioning regimens, which rely more on immunosuppression than cytotoxic effects to permit engraftment of donor cells.

Partial response: Showing at least a 50% reduction in tumor burden.

Poor prognosis (germ cell tumor): There is no poor prognosis or poor risk disease in the seminoma category of germ cell tumors. In nonseminoma, poor prognosis or poor risk disease is indicated by any 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).

Primary graft failure: Occurs when the bone marrow infused during a bone marrow transplant does not take or is not accepted by the recipient.

Refractory: Tumors that show less than 50% reduction in tumor burden in response to chemotherapy upon or during the course(s) of chemotherapy.

Relapse: The return of signs and symptoms of cancer after a period of improvement.

Tandem transplant: Planned infusion (transplant) of previously harvested hematopoietic stem cells with a repeat hematopoietic stem cell infusion (transplant) that is performed within 6 months of the initial transplant. This is distinguished from a repeat transplantation requested or performed more than 6 months after the first transplant, and is used as salvage therapy after failure of initial transplantation or relapsed disease.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services may be Medically Necessary when criteria are met:

CPT	
38206	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous
38207-38215	Transplant preparation of hematopoietic progenitor cells [includes codes 38207, 38208, 38209, 38210, 38211, 38212, 38213, 38214, 38215; when specified as autologous]
38232	Bone marrow harvesting for transplantation; autologous
38241	Hematopoietic progenitor cell (HPC); autologous transplantation
HCPCS	
S2150	Bone marrow or blood-derived peripheral 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 [when specified as autologous]
ICD-10 Procedure	
	Autologous transplantation
30233G0-30243G0	Transfusion of autologous bone marrow into peripheral or central vein, percutaneous approach [includes codes 30233G0, 30243G0]
30233Y0-30243Y0	Transfusion of autologous hematopoietic stem cells into peripheral or central vein, percutaneous approach [includes codes 30233Y0, 30243Y0]
	Pheresis [when specified as autologous]
6A550ZV	Pheresis of hematopoietic stem cells, single
6A551ZV	Pheresis of hematopoietic stem cells, multiple
ICD-10 Diagnosis	
C38.1-C38.3	Malignant neoplasm of mediastinum
C48.0	Malignant neoplasm of retroperitoneum
C56.1-C56.9	Malignant neoplasm of ovary [specified as germ cell]
C62.00-C62.92	Malignant neoplasm of testis
C78.1	Secondary malignant neoplasm of mediastinum
C78.6	Secondary malignant neoplasm of retroperitoneum and peritoneum
C79.60-C79.63	Secondary malignant neoplasm of ovary
C79.82	Secondary malignant neoplasm of genital organs [specified as testis]

When services are Investigational and Not Medically Necessary:
For the procedure codes listed above when criteria are not met or when the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

When Services are also Investigational and Not Medically Necessary:
For the procedure and diagnosis codes listed below when describing a procedure indicated in the Position Statement section as investigational and not medically necessary.

CPT	
38204	Management of recipient hematopoietic progenitor cell donor search and cell acquisition
38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic
38207-38215	Transplant preparation of hematopoietic progenitor cells [includes codes 38207, 38208, 38209, 38210, 38211, 38212, 38213, 38214, 38215; when specified as allogeneic]
38230	Bone marrow harvesting for transplantation; allogeneic
38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor
38243	Hematopoietic progenitor cell (HPC); HPC boost
HCPCS	
S2150	Bone marrow or blood-derived peripheral 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 [when specified as allogeneic]
S2142	Cord blood-derived stem cell transplantation, allogeneic
ICD-10 Procedure	
	Allogeneic transplantation

30233G2-30243G4	Transfusion of allogeneic bone marrow, related, unrelated or unspecified into peripheral or central vein, percutaneous approach [includes codes 30233G2, 30233G3, 30233G4, 30243G2, 30243G3, 30243G4]
30233U2-30243U4	Transfusion of allogeneic T-cell depleted hematopoietic stem cells, related, unrelated or unspecified into peripheral or central vein, percutaneous approach [includes codes 30233U2, 30233U3, 30233U4, 30243U2, 30243U3, 30243U4]
30233X2-30243X4	Transfusion of allogeneic cord blood stem cells, related, unrelated or unspecified into peripheral or central vein, percutaneous approach [includes codes 30233X2, 30233X3, 30233X4, 30243X2, 30243X3, 30243X4]
30233Y2-30243Y4	Transfusion of allogeneic hematopoietic stem cells, related, unrelated or unspecified into peripheral or central vein, percutaneous approach [includes codes 30233Y2, 30233Y3, 30233Y4, 30243Y2, 30243Y3, 30243Y4]
	Pheresis [when specified as allogeneic]
6A550ZV	Pheresis of hematopoietic stem cells, single
6A551ZV	Pheresis of hematopoietic stem cells, multiple

ICD-10 Diagnosis

C38.1-C38.3	Malignant neoplasm of mediastinum
C48.0	Malignant neoplasm of retroperitoneum
C56.1-C56.9	Malignant neoplasm of ovary [specified as germ cell]
C62.00-C62.92	Malignant neoplasm of testis
C78.1	Secondary malignant neoplasm of mediastinum
C78.6	Secondary malignant neoplasm of retroperitoneum and peritoneum
C79.60-C79.63	Secondary malignant neoplasm of ovary
C79.82	Secondary malignant neoplasm of genital organs [specified as testis]

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Mini-Transplant
Non-Myeloablative Stem Cell Transplant
Peripheral Blood Stem Cell
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Stem Cell Transplant (SCT)

Document History

Status	Date	Action
Revised	11/09/2023	Medical Policy & Technology Assessment Committee (MPTAC) review. Revised formatting of Position Statement. Updated References and Websites.
Reviewed	11/10/2022	MPTAC review. Updated Rationale, Background, References and Websites sections.
Reviewed	11/11/2021	MPTAC review. Updated Rationale, Background, References and Websites sections.
	10/01/2021	Updated Coding section with 10/01/2021 ICD-10-CM and ICD-10-PCS changes; added diagnosis code C79.63, removed open approach procedure codes deleted 09/30/2021.
Reviewed	11/05/2020	MPTAC review. Updated Rationale, Background, References and Websites sections.
Reviewed	11/07/2019	MPTAC review. Updated Rationale, Background, References and Websites sections.
	10/01/2019	Updated Coding section with 10/01/2019 ICD-10-PCS changes; added 30230U2-30243U4; removed 30250G0-30263G1, 30250X1-30263Y1 deleted 09/30/2019.
Reviewed	11/08/2018	MPTAC review.
Reviewed	10/31/2018	Hematology/Oncology Subcommittee review. Updated Rationale, Background, References and Websites sections.
Revised	11/02/2017	MPTAC review.
Revised	11/01/2017	Hematology/Oncology Subcommittee review. The document header wording updated from “Current Effective Date” to “Publish Date”. In the Position Statement, removed the requirement that individuals must meet the “Individual Selection Criteria for all diagnoses” Updated Rationale, Background, References and Websites sections.
Reviewed	05/04/2017	MPTAC review.
Reviewed	05/03/2017	Hematology/Oncology Subcommittee review. Rationale, Background and References sections updated. Formatting updated in Individual Selection Criteria section of Position Statement.
	10/01/2016	Updated Coding section with 10/01/2016 ICD-10-PCS procedure code changes.
Reviewed	05/05/2016	MPTAC review.
Reviewed	05/04/2016	Hematology/Oncology Subcommittee review. Rationale, Background and References sections updated. Removed ICD-9 codes from Coding section.
Reviewed	05/07/2015	MPTAC review.
Reviewed	05/06/2015	Hematology/Oncology Subcommittee review. Rationale, Background, Definition and References sections updated.

Reviewed	05/15/2014	MPTAC review.
Reviewed	05/14/2014	Hematology/Oncology Subcommittee review. Rationale, Background and Reference sections updated.
Reviewed	05/09/2013	MPTAC review.
Reviewed	05/08/2013	Hematology/Oncology Subcommittee review. Rationale and Reference sections updated.
	01/01/2013	Updated Coding section with 01/01/2013 CPT changes.
Reviewed	05/10/2012	MPTAC review.
Reviewed	05/09/2012	Hematology/Oncology Subcommittee review. Rationale, Reference and Background sections updated.
	01/01/2012	Updated Coding section with 01/01/2012 CPT changes.
Revised	05/19/2011	MPTAC review.
Revised	05/18/2011	Hematology/Oncology Subcommittee review. Removed duplicative investigational and not medically necessary statement regarding a non-myeloablative allogeneic hematopoietic transplantation (mini-transplant). Rationale, Background, Definitions, Reference, and Index sections updated.
Revised	05/13/2010	MPTAC review.
Revised	05/12/2010	Hematology/Oncology Subcommittee review. Removed investigational and not medically necessary indication for epithelial ovarian cancer and referred user to TRANS.00031 for criteria. Clarified autologous hematopoietic stem cell transplant criteria (single and tandem). Added “relapse” as a criterion for single transplant, and “partial response” as a criterion for tandem transplant. Reformatted investigational and not medically necessary statement for single autologous stem cell transplant and removed “treatment following first relapse”. Clarified investigational and not medically necessary hematopoietic stem cell harvest language. Updated rationale, background, websites and references.
Reviewed	11/19/2009	MPTAC review.
Reviewed	11/18/2009	Hematology/Oncology Subcommittee review. Modified title. Updated rationale, references and websites.
Revised	11/20/2008	MPTAC review.
Revised	11/19/2008	Hematology/Oncology Subcommittee review. Updated rationale, references, coding and websites. Clarified Patient Selection Criteria.
	01/01/2008	Updated Coding section with 01/01/2008 HCPCS changes; removed HCPCS G0267 deleted 12/31/2007.
Reviewed	11/29/2007	MPTAC review.
Reviewed	11/28/2007	Hematology/Oncology Subcommittee review. Updated rationale, references, coding and websites. No change to policy position. The phrase “investigational/not medically necessary” was clarified to read “investigational and not medically necessary.”
Revised	12/07/2006	MPTAC review.
Revised	12/06/2006	Hematology/Oncology Subcommittee review. Addition of medical necessity statement for primary graft failure.
Revised	06/08/2006	MPTAC review.
Revised	06/07/2006	Hematology/Oncology Subcommittee review. Revision to general patient selection criteria.
Revised	12/01/2005	MPTAC review.
Revised	11/30/2005	Hematology/Oncology Subcommittee review. Eliminated age requirements and revised general patient selection criteria.
	11/22/2005	Added reference for Centers for Medicare and Medicaid Services (CMS) – National Coverage Determination (NCD).
Reviewed	07/14/2005	MPTAC review.
Revised	04/28/2005	MPTAC review. Revision based on Pre-merger Anthem and Pre-merger WellPoint Harmonization.

Pre-Merger Organizations	Last Review Date	Document Number	Title
Anthem, Inc.	10/28/2004	TRANS.00002	Stem Cell Transplant following Chemotherapy for Malignant Diseases
WellPoint Health Networks, Inc.	12/02/2004	7.11.02	Autologous Bone Marrow Transplantation or Peripheral Blood Stem Cell Support (PBSCS) for Malignancies
	12/02/2004	Clinical Guideline	Bone Marrow Transplants Germ Cell Tumors

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Applicable to Commercial HMO members in California: When a medical policy states a procedure or treatment is investigational, PMGs should not approve or deny the request. Instead, please fax the request to Anthem Blue Cross Grievance and Appeals at fax # 818-234-2767 or 818-234-3824. For questions, call G&A at 1-800-365-0609 and ask to speak with the Investigational Review Nurse.

Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The member’s contract benefits in effect on the date that services are rendered must be used. Medical Policy, which addresses medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.