Stem-Cell Transplantation for Adult Solid Tumors

**Coverage Policy**

Single or tandem autologous hematopoietic stem-cell transplantation (HSCT) is considered medically necessary for relapsed or refractory testicular and ovarian germ cell tumors.

Up to three autologous HSCT is considered medically necessary as second-line therapy for metastatic germ cell tumors.

EITHER of the following procedures for the treatment of testicular cancer is considered experimental, investigational or unproven:

- autologous HSCT as front-line therapy
- allogeneic HSCT

Hematopoietic stem-cell transplantation for the treatment of ANY of the following solid tumors in an adult is considered experimental, investigational and unproven:

- soft tissue sarcoma
- cancer of the bile duct
- cancer of the cervix
- cancer of the colon and rectum
• cancer of the esophagus
• cancer of the gallbladder
• cancer of the lung
• cancer of the nasopharynx
• cancer of the pancreas
• cancer of the paranasal sinus
• cancer of the prostate
• cancer of the stomach (gastric cancer)
• cancer of the thymus
• cancer of the thyroid
• cancer of the uterus
• epithelial ovarian cancer
• melanoma
• renal cell carcinoma

**Overview**

This Coverage Policy addresses hematopoietic stem-cell transplantation (HSCT) for the treatment of selected solid tumors that occur primarily in adults. These include testicular and ovarian germ cell tumors, soft tissue sarcoma, cancers of the bile duct, cervix, colon and rectum, esophagus, gallbladder, lung, nasopharynx, pancreas, paranasal sinus, prostate, stomach, thymus, thyroid and uterus, epithelial ovarian cancer, melanoma and renal cell carcinoma.

Hematopoietic stem-cell transplantation (HSCT) involves taking hematopoietic stem cells that can regenerate all the blood cells normally produced in the bone marrow from the bone marrow or blood of a donor and infusing them into the person with the disorder, following medication to suppress the immune system. The donor may be the person who is receiving the stem cells (i.e., autologous HSCT) or another person (i.e., allogeneic HSCT).

**General Background**

Solid tumors in adults are a heterogeneous group of disorders encompassing a wide spectrum of body systems. Also called solid neoplasms, some tumors are sensitive to chemotherapy and radiation therapy; however, many are not curable by chemotherapy and responses are often incomplete or not durable. Hematopoietic stem-cell transplantation (HSCT) has been proposed for the treatment of selected solid tumors in adults.

**Stem-Cell Transplantation**

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

Chemotherapeutic dose intensification and autologous HSCT is a strategy that has been proposed as a means to overcome inadequate response to standard dose chemotherapy. Although dose intensification has provided a survival advantage for selected individuals with hematologic malignancies, reviews of the efficacy of high-dose therapy in adult solid tumors have concluded that no role for this approach has been established, even in the diseases most sensitive to chemotherapy and radiation (Murren, 2005; Niebor, 2005).

Theoretically, allogeneic HSCT for solid tumors can induce a graft-versus-tumor (GVT) reaction in which the infused donor cells mount an immune response that eradicates the recipient's cancer cells. Early studies of ablative regimens for treatment of chemotherapy-refractory metastatic solid tumors demonstrated that the high doses of chemotherapy required to ablate the recipient's bone marrow lead to unacceptably high treatment-related mortality (TRM) rates of 20–35% (Arya, 2004). The high TRM associated with standard myeloablative regimens led to the study of nonmyeloablative preparative regimens as conditioning for allogeneic stem-cell transplantation. These studies have not shown improved survival outcomes for participating patients and are
limited by a lack of randomization, small patient populations, and limited follow-up. At this time, insufficient data are available to determine whether GVT effects can occur in most solid tumors (Storb, 2003).

Omazic et al. (2016) reported an analysis of data for 61 patients with solid cancer who underwent nonmyeloablative (n=23), reduced conditioning (n=36) or myeloablative (n=2) allogeneic HSCT. Two patients received cadaveric donor grafts. Types of solid cancers included in the study were metastatic renal carcinoma (n=22), cholangiocarcinoma (n=17), colon carcinoma (n=15), prostate cancer (n=3), pancreatic adenocarcinoma (n=3), or breast cancer (n=1). All patients with hepatic cholangiocarcinoma and one patient with colon carcinoma (with liver metastases) underwent orthotopic liver transplantation as debulking before HSCT. Three patients with pancreatic cancer underwent Whipple surgery with radical intent. Graft failure occurred in 13 patients (21%). The cumulative incidence of acute graft-versus-host disease (GVHD) of grades II to IV was 47%, and that of chronic GVHD was 32%. Treatment-related mortality at two years was 21%. Five-year cancer-related mortality was 63%; eight-year survival was 12%. Risk factors for mortality were nonmyeloablative conditioning (Hazard ratio [HR] 2.95; p < .001), absence of chronic GVHD (HR, 3.57; p < .001), acute GVHD of grades II to IV (HR, 2.90; p = .002), and HLA-identical transplant (HR, 5.00; p< 0.03). Five-year overall survival rates were 15% and 9% at 10 years. Data do not suggest an enduring benefit of allogeneic HSCT for the indications included in the study.

Hematopoietic stem-cell transplantation (HSCT) for breast cancer is discussed in a separate Coverage Policy (see Related Coverage Policy section). HSCT for the treatment of adult soft tissue sarcomas, cancers of the bile duct, cervix, colon, rectum, esophagus, gallbladder, lung, nasopharynx, pancreas, paranasal sinus, prostate, stomach (gastric cancer), thymus, thyroid, and uterus, epithelial ovarian cancer, malignant melanoma, renal cell carcinoma, and testicular and ovarian germ cell tumors are briefly discussed in this Coverage Policy.

**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. 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

**Adult Soft Tissue Sarcoma:** Soft tissue sarcomas may arise from the mesodermal tissues of the extremities, trunk and retroperitoneum, the head and neck, and rarely in the gastrointestinal stroma. Chemotherapy may be beneficial for patients with advanced sarcoma. Because treatment for this disease is evolving, participation in clinical trials is encouraged.

**Literature Review**

The effectiveness of hematopoietic stem-cell transplantation (HSCT) resulting in improved survival has not been demonstrated in published, peer-reviewed randomized clinical trials (RCT). Professional society/organization support in the form of published consensus guidelines are lacking. The role of HSCT has not yet been established for the treatment of soft tissue sarcomas in adults.
In one phase III RCT, Bui-Nguyen et al. (2012) reported results of 87 patients randomized to receive two doses of standard-dose chemotherapy or two doses of high-dose chemotherapy. The authors report that futility analyses led to study closure. Three-year overall survival (OS) was 49.4% for the standard-dose group versus 32.7% for the patients receiving high-dose therapy. Progression-free survival (PFS) was 32.4% and 14.0%, respectively, for the standard-dose and high-dose groups. High-dose treatment led to higher grades of toxicity. The study failed to demonstrate an OS advantage for patients treated with high-dose therapy and hematopoietic stem-cell transplantation (HSCT).

Peinemann et al. (2011) performed a systematic review of the literature related to non-rhabdomyosarcoma soft tissue sarcoma from 54 studies, reporting on 177 participants who received autologous HSCT and 69 who received standard care. Only one study reported comparative data. All studies had a high-risk of bias. Due to a lack of comparative studies the authors noted it is unclear whether participants with non-rhabdomyosarcoma soft tissue sarcomas have improved survival with high-dose chemotherapy and autologous HSCT.

Peinemann et al. (2014) published an updated systematic review of the literature, comparing the efficacy and adverse events of autologous HSCT following high-dose chemotherapy (HDCT) versus standard-dose chemotherapy (SDCT) in patients with locally advanced or metastatic non-rhabdomyosarcoma soft tissue sarcomas (NRSTS). Two hundred ninety-four individuals with 19 subtypes of malignant NRSTS were evaluated. Sixty-two studies, including one randomized controlled trial were included in the review. Overall survival in the RCT was not statistically significant between autologous HSCT following HDCT versus SDCT. No other comparative study was available. Data do not suggest health benefits of autologous HSCT over treatment with standard dose chemotherapy.

Verma et al. (2008) performed a systematic review of the literature to determine whether first-line dose-intensive chemotherapy supported by growth factor or autologous bone marrow/stem cell transplantation improves response rate, time-to-disease progression, or survival compared with standard-dose chemotherapy in patients with inoperable, locally advanced, or metastatic soft tissue sarcoma. The authors noted that to date only two RCTs have been performed to determine whether growth factor or autologous bone marrow/stem cell transplantation improves survival, response, or time-to-progression compared with standard-dose chemotherapy in the first-line setting. Only one RCT (n=314) reported data on all three outcomes. No significant difference was noted between treatments for response rate (p=.65). One-year PFS was significantly longer in the high-dose arm (p=.03). This analysis was unable to discern any consistent benefits in patients with metastatic unresectable soft tissue sarcoma when doses higher than standard-dose chemotherapy are used in this setting.

The safety and effectiveness of nonmyeloablative or reduced-intensity allogeneic HSCT has also been investigated as treatment for soft tissue sarcoma in adults; however, data from randomized clinical trials are lacking. A well-designed study is required to define the possible role of reduced-intensity stem-cell transplantation for patients with soft tissue sarcoma in whom conventional treatments have failed.

Cancer of the Colon and Rectum: Cancer of the colon and rectum is highly treatable and often curable when localized. Prognosis is related to the degree of penetration of the tumor through the bowel wall and the involvement of lymph nodes.

Literature Review
Although cancer of the colon and rectum may be responsive to chemotherapy in selected individuals, there is insufficient evidence in the published, peer-reviewed scientific literature in the form of high-quality randomized clinical trials to support the safety and effectiveness of hematopoietic stem-cell transplantation (HSCT) for this indication. Further professional society/organization support as evidenced by published consensus guidelines are lacking. The role of this therapy has not been established for the treatment of colon and/or rectal cancer.

Nonmyeloablative allogeneic HSCT has been investigated for the treatment of colorectal cancer in non-randomized clinical trials (Carnevale-Schianca, 2006; Hentschke, 2003). Trials are limited by small patient populations and study design. Disease progression was common after HSCT; however, data suggest the regression of some metastases associated with graft-versus-host disease (GVHD) is suggestive of a graft-versus-tumor (GVT) effect.
Cancer of the Lung:
Although HSCT is the subject of ongoing research, there is insufficient evidence in the published peer-reviewed scientific literature to support the safety and effectiveness for the treatment of NSCLC or SCLC. Improved complete remission rates and prolonged relapse-free survival rates suggest that this approach is promising; however, the role of HSCT has not yet been established. Several randomized studies are ongoing and should help define whether this approach is of value in this disease.

Non-Small Cell Lung Cancer (NSCLC): NSCLC is an aggregate of several different types of cells; some of the most common include epidermoid or squamous carcinoma, adenocarcinoma and large cell carcinoma (NCI, 2017b)

Literature Review for NSCLC
The need for more effective therapy has led to the investigation of autologous HSCT in several non-randomized clinical trials involving small patient populations (De Giorgi, 2008; Schilder, 2000). Response rates were 34%–44% with a median survival of seven to 17 months. It does not appear that high-dose chemotherapy with autologous HSCT improves the response rate or overall survival for patients with NSCLC (Schilder, 2000).

Small Cell Lung Cancer (SCLC):
Without treatment, SCLC has the most aggressive course of any type of pulmonary tumor, with a tendency to be more widely disseminated at time of diagnosis. The median survival is two to four months (NCI, 2017e). Compared to other cell types of lung cancer however, SCLC is more responsive to chemoradiation therapies (NCI, 2017e; Chua, 2004). Approximately 50% of patients with limited-disease SCLC receiving standard doses of combination chemotherapy will achieve clinical remission; although remission rates for patients with extensive disease are only 20%–40% (Chua, 2004).

Literature Review for SCLC
Hematopoietic stem-cell transplantation (HSCT) has been studied in multiple prospective randomized and non-randomized clinical trials, and retrospective studies; however, a consistent survival advantage for patients treated with higher doses of chemotherapy has not been demonstrated (Iwasaki, 2005; Elias, 2002; Rizzo, 2002).

Jiang et al. (2009) performed a meta-analysis of five randomized phase II and III clinical trials involving 641 patients with SCLC. The studies compared intensified chemotherapy with hematopoietic progenitors and control therapy, including chemotherapy and radiation. No significant increase in the odds ratio for response was attributed to the use of intensified chemotherapy (p=0.206). No statistically significantly increase in overall survival was found with the use of intensified chemotherapy compared with control regimens (p=0.432). The use of intensified chemotherapy does not improve outcomes compared with standard therapy in patients with small cell lung cancer.

Epithelial Ovarian Cancer: Ovarian cancer represents tumors of epithelial, germ cell, or sex cord-stromal origin. In general, ovarian tumors are classified according to the kind of cells from which the tumor originated and whether the tumor is benign or cancerous. Identification of the type of cancer is important for treatment and prognosis, as is the stage and grade of tumor. Approximately 90% of ovarian cancer is epithelial in origin and typically occurs in postmenopausal women.

Epithelial ovarian cancer demonstrates a high response rate to standard-dose chemotherapy and several clinical studies have identified a relationship between dose intensity and response. The use of high-dose chemotherapy (HDC) with HSCT has been proposed based on the hypothesis that major dose escalations within the myeloablative range are needed to overcome tumor cell resistance and produce a meaningful clinical improvement. However, the use of HSCT remains controversial (Armstrong, 2008; Papadimitriou, 2007). The effectiveness of single or sequential HDC with autologous HSCT has not been proven in several randomized controlled clinical trials (RCT) (Papadimitriou, 2007; Mobus, 2007; Goncalves, 2006; Stiff, 2004), or retrospective comparison of outcomes achieved with HDC compared with standard dose therapy (Stiff, 2000).

Literature Review
To date the effectiveness of single or sequential high-dose chemotherapy followed by autologous or allogeneic HSCT has not been demonstrated by published, peer-reviewed high-quality clinical trial data. Although it remains an area of clinical investigation, the role of this therapy has not yet been established for this indication.

Papadimitriou et al. (2007) compared the effectiveness and tolerability of HDC and autologous HSCT as a consolidation approach in women with chemosensitive advanced epithelial ovarian cancer. Eighty patients who achieved their first complete remission after six cycles of standard dose chemotherapy were randomly assigned to receive high-dose melphalan or other treatment. Patients not assigned to the high-dose arm were considered the control arm. Of the 37 patients assigned to receive the high-dose therapy, eleven patients (29%) did not receive high-dose therapy. In an intent-to-treat analysis, there were no significant differences between the two arms in time to progression (p=0.59) or overall survival (p=0.38). The use of high-dose chemotherapy failed to yield a statistically significant improvement in outcome.

In another RCT involving 58 women with stage III or stage IV persistent or recurrent ovarian cancer, participants were assigned to receive one of two high-dose chemotherapy treatment regimens; both were followed by autologous HSCT. No significant differences were noted in overall or progression-free survival rates between regimens (Stiff, 2004).

In other studies, limited by uncontrolled design and/or small participant populations, high response rates were noted; however, response rates and survival durations were short (Armstrong, 2008; Bengala, 2004; Donato, 2004). Additionally, in a prospective trial by Schilder et al. (2003), individuals with advanced ovarian cancer who had undergone surgical treatment but had not had previous chemotherapy received HDC followed by autologous HSCT. Complete response rates were low (12.5%); 11 of 45 cycles of the protocol therapy resulted in hospitalizations. High treatment-related morbidity and low efficacy of the therapy did not support continuing, and the study was closed early.

**Sequential High-Dose Chemotherapy (HDC) and Autologous Hematopoietic Stem-Cell Transplantation (HSCT):** Sequential cycles of HDC followed by autologous HSCT have also been proposed for the treatment of individuals with stage III and IV epithelial ovarian cancer. Sequential HDC involves performing multiple cycles of chemotherapy followed by a single HSCT. This therapy potentially allows an increase in the total dose of chemotherapy that can be given; however, some patients are unable to tolerate the side effects of the chemotherapy cycle and transplantation process and are therefore unable to complete multiple cycles.

The outcomes achieved in an RCT as well as several case series do not support a clear advantage of sequential HDC and autologous HSCT compared with conventional dose chemotherapy alone (Mobus, 2007; Goncalves, 2006; Ikeba, 2004; Boiko, 2001; Prince, 2001; Schilder, 2001).

**Allogeneic HSCT:** In theory, the graft-versus-tumor effect from allogeneic HSCT may cause regression of disease in patients with solid tumors; however, there are scarce data in the published, peer-reviewed scientific literature regarding the use of allogeneic HSCT for epithelial ovarian cancer. Studies are limited to small-case series and retrospective analyses. Patient selection has primarily targeted patients with advanced refractory disease who have exhausted all other options, including previous treatment with high-dose chemotherapy with autologous HSCT. Reported outcomes include slow disease regression followed by disease relapse in a majority of patients (Bay, 2010; Donato, 2004; Hanel, 2003).

**Germ Cell Tumors (GCTs)**

**Testicular:** Highly treatable and frequently curable, 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% of GCTs (American Cancer Society [ACS], 2016). Treatment decisions are based on the type of testicular cancer, stage of disease, and prognostic category. 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], 2017d).

Standard first-line treatment options may include surgery, standard-dose chemotherapy and/or radiation therapy (NCI, 2017d). For disease that persists despite treatment or has recurred after treatment with standard-dose chemotherapy, prognosis is poor; however, salvage chemotherapy regimens can induce long-term complete
responses in about 25% of patients in this treatment group (National Cancer Institute [NCI], 2017d). Because standard dose chemotherapy has limited effect in recurrent disease, salvage therapy with autologous HSCT has been proposed.

**Ovarian:** Malignant germ cell tumors account for approximately 3% to 5% of ovarian malignancies and primarily occur in teens and young adults with a peak age in the early 20s. Tumor types include dysgerminomas, immature teratomas, embryonal tumors, and endodermal sinus (yolk-sac) tumors. Because they are so rare, treatment of malignant germ cell tumors is based largely on the experience with the more common testicular germ cell tumors (Morgan, 2013). Recurrent/persistent disease after platinum-based therapy may be salvaged with high-dose chemotherapy and stem-cell rescue (National Comprehensive Cancer Network Guidelines™ [NCCN Guidelines™], 2017; Morgan, 2013).

**Literature Review**
Several randomized controlled clinical trial data have not demonstrated improved health outcomes with the use of high-dose chemotherapy and autologous HSCT as a front-line therapy. Although data are not robust, the use of single or tandem HDC with autologous HSCT is considered an acceptable therapy for the treatment of individuals with refractory or relapsed testicular and ovarian germ cell tumors. For metastatic germ-cell tumors, three cycles of high-dose chemotherapy, each cycle followed by HSCT, is considered an appropriate second-line treatment option.

**Autologous Hematopoietic Stem-Cell Transplantation (HSCT):** The use of 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.

**Autologous HSCT as First-Line Therapy:** High dose chemotherapy (HDC) with autologous HSCT has been studied as a front-line treatment for patients with poor-risk testicular cancer; however, randomized (Daugaard, 2011; Droz, 2007, Motzer, 2007) and prospective clinical trials (Miki, 2007) have not demonstrated improved complete response rates or overall survival (OS) when used as initial therapy compared with standard dose chemotherapy. Conventional-dose chemotherapy remains the standard of care for these individuals (Motzer, 2007).

In a phase III randomized controlled trial Daugaard et al. (2011) compared the efficacy of one cycle of standard-dose cisplatin, etoposide, and ifosfamide (VIP) chemotherapy plus three cycles of high-dose VIP chemotherapy followed by autologous HSCT versus four cycles of standard-dose cisplatin, etoposide, and bleomycin (BEP) chemotherapy. One hundred thirty-one individuals with previously untreated metastatic poor-prognosis germ-cell cancer were included in this analysis. The complete response rates (p=0.18) and failure-free survival rates (p=0.060) did not differ between the two treatment arms.

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.

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).

**Autologous HSCT for Relapsed or Refractory Disease:** Metastatic testicular tumors that have not been successfully treated by means of initial chemotherapy are potentially curable with salvage chemotherapy.
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. Improved overall- and disease-free survival rates have been demonstrated in several prospective and retrospective studies (Agawala, 2011; Lorch, 2011; Einhorn, 2007; Lotz, 2005; Schmoll, 2003).

The National Comprehensive Cancer Network ([NCCN™], 2017) notes that HDC with autologous HSCT is the preferred third-line option in incomplete response or relapses after second-line conventional dose chemotherapy. Published results of case controlled studies show modest improvement with the use of this therapy for relapsed or recurrent disease (Einhorn, 2007; Vaena, 2003).

Although the effectiveness of planned tandem cycles of HDC followed by autologous HSCT has not been proven in randomized controlled clinical trials, it 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).

**Autologous HSCT for Metastatic Germ Cell Tumors**

Use of three cycles of high-dose chemotherapy followed by autologous HSCT has been investigated as a second-line therapy for metastatic GCTs in a number of prospective, observational clinical trials (Feldman, 2015; Feldman, 2010; Kondagunta, 2007; Motzer, 2000). Complete response rates range from 42% -57% in these studies. Feldman et al. (2010) reported five-year overall- (OS) and disease-free-survival (DFS) rates of 52% and 48%, respectively.

**Allogeneic HSCT:** There are scarce data in the published, peer-reviewed scientific literature regarding the safety or effectiveness of allogeneic hematopoietic stem-cell transplantation (HSCT) with myeloablative or nonmyeloablative conditioning regimens for the treatment of testicular cancer and the effectiveness of this treatment is unknown.

**Renal Cell Carcinoma:** Renal cell carcinoma, also known as renal adenocarcinoma, kidney cancer or hypernephroma, is a form of cancer that affects the renal tubules. Because of the lack of curative therapy for metastatic disease and the promise of targeted therapies patients should be considered for the many ongoing clinical trials testing single or combination therapies (NCI, 2017b). Hematopoietic stem-cell transplantation (HSCT) has also been proposed as a treatment for renal cell carcinoma.

**Literature Review**

High treatment-related toxicity remains an obstacle to the safety and effectiveness of HSCT for renal cell carcinoma. Optimal patient selection criteria, most effective conditioning regimen, and strategies to exploit the graft-versus-tumor effect continue to be identified. While promising, there is insufficient evidence to demonstrate the safety and effectiveness of allogeneic HSCT for this indication. The role of this therapy has not yet been established for renal cell carcinoma.

**Autologous HSCT:** Data are lacking in the published, peer-reviewed scientific literature regarding the safety and/or effectiveness of autologous HSCT for the treatment of renal cell carcinoma. At this time the role of this therapy has not been established.

**Allogeneic HSCT:** The NCI (2017d) notes responses to cytotoxic chemotherapy generally have not exceeded 10% for any regimen that has been studied in adequate numbers of patients.

In a retrospective analysis, Nakayama et al. (2007) studied 99 patients with metastatic renal cell carcinoma to characterize the natural history of the disease, identify prognostic factors, and compare outcomes in patients who did (n=23) or did not (n=76) undergo allogeneic HSCT. For those who did not undergo transplantation, patients with poor performance status and brain metastasis were excluded for the purposes of comparison with...
the transplant group. Overall response rate (i.e. complete and partial response) in the transplant group was 26%; of these, 17% achieved complete response. Treatment-related mortality was 17% and 26% at 100 days and 12 months after transplant, respectively. At a median of seven months, 74% of patients had died in the transplant group. At a median follow-up of 17.4 months, overall survival rates were comparable in the transplant and non-transplant groups (p=.92).

In theory, allogeneic hematopoietic stem-cell transplantation (HSCT) for solid organ malignancies may induce a graft-versus-tumor reaction. The high treatment-related mortality and suggestion of a graft-versus-tumor effect associated with myeloablative preparative regimens has led to the study of reduced-intensity and nonmyeloablative preparative regimens as conditioning for allogeneic stem-cell transplantation. In several nonrandomized case series and retrospective analyses with small patient populations, complete donor chimerism was observed in the majority of patients. Response rates were variable at 0%–42%. Despite reduced intensity or nonmyeloablative conditioning, treatment-related mortality rates are 12%–33%, primarily from graft-versus-host disease (Bregni, 2009; Peres, 2007; Yun, 2007; Barkholt, 2006; Artz, 2005; Massenkeil, 2004; Bregni, 2002; Rini, 2002; Childs, 2000). One-year survival rates are 18%–59%; there are scarce data regarding long-term outcomes.

Other Solid Tumors: High-quality published peer-reviewed clinical trial data are lacking to support the safety and effectiveness of HSCT for the treatment of autologous or allogeneic HSCT for the treatment of cancers of the bile duct, cervix, esophagus, gallbladder, melanoma, nasopharynx, pancreas, paranasal sinus, prostate, stomach (gastric cancer), thymus, thyroid, or uterus. Further there is a lack of professional society/organization support in the form of published consensus guidelines for the use of HSCT. At this time the role of HSCT has not been established.

Professional Societies/Organizations
National Cancer Institute (NCI):
Malignant Germ Cell Tumors: The NCI (2017a) notes that HDC with autologous stem cell rescue has been explored in adults with recurrent testicular germ cell tumors (GCTs). This therapy has been reported to cure adult patients with relapsed testicular GCTs, even as third-line therapy and in cisplatin-refractory patients. While several other studies support this approach, others do not. Salvage attempts using HDC regimens may be of little benefit if the patient is not clinically disease free at the time of HSCT.

Regarding ovarian germ cell cancer in adults, the NCI (2017b) notes that high-dose chemotherapy and autologous marrow rescue is a potential therapy.

Small Cell Lung Cancer: The NCI (2017e) notes the role of dose intensification in patients with small cell lung cancer remains unclear. Although early studies showed that under-treatment compromised outcome and suggested that early dose intensification may improve survival, later studies examining the use of colony-stimulating factors to support dose-intensified chemotherapy have yielded conflicting results.

Testicular Cancer: The NCI (2017d) notes that autologous hematopoietic stem-cell transplantation, (HSCT) has been used in uncontrolled case series for adults with recurrent testicular cancer. 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.

The National Comprehensive Cancer Network™ (NCCN™): The NCCN publishes guidelines for the treatment of adults only.

Testicular Cancer: Clinical Practice Guidelines in Oncology for Testicular Cancer note that second line therapy for metastatic germ cell tumors includes high-dose chemotherapy followed by autologous peripheral blood stem-cell support or two or three cycles.

Ovarian Cancer: In the Clinical Practice Guidelines in Oncology for Ovarian Cancer regarding malignant germ-cell tumors, the NCCN notes high-dose chemotherapy is an acceptable therapy residual or recurrent disease.
The American Board of Internal Medicine’s (ABIM) Foundation Choosing Wisely® Initiative (2014): No relevant statements.

Use Outside of the US:
Cancer Care Ontario: On behalf of the Sarcoma Disease Site Group of Cancer Care Ontario’s Program in Evidence-Based Care, Verma et al. (2008) published a clinical practice guideline for Dose-Intensive Chemotherapy with Growth Factor or Autologous Bone Marrow or Stem-Cell Transplant Support in First-Line Treatment of Advanced or Metastatic Adult Soft Tissue Sarcoma. The recommendations note:

- Dose-intensive chemotherapy with growth factor support is not recommended in the first-line treatment of patients with inoperable locally advanced or metastatic soft tissue sarcoma.
- The data are insufficient to support the use of high dose chemotherapy with autologous bone marrow or stem-cell transplantation as first-line treatment in this group of patients.
- Eligible patients should be encouraged to enter clinical trials assessing novel approaches or compounds.

Coding/Billing Information

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Autologous

Considered Medically Necessary when used to report autologous bone marrow or blood-derived stem cell procedures for the treatment of relapsed or refractory testicular and ovarian germ cell tumors:

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<td>Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage</td>
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<td>38208</td>
<td>Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing, per donor</td>
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<td>S2150</td>
<td>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</td>
</tr>
</tbody>
</table>

Considered Experimental/Investigational/Unproven when used to report allogeneic bone marrow or blood-derived stem cell procedures for the treatment of testicular cancer:
<table>
<thead>
<tr>
<th>CPT* Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>38205</td>
<td>Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic</td>
</tr>
<tr>
<td>38207</td>
<td>Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage</td>
</tr>
<tr>
<td>38208</td>
<td>Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing, per donor</td>
</tr>
<tr>
<td>38209</td>
<td>Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing, per donor</td>
</tr>
<tr>
<td>38210</td>
<td>Transplant preparation of hematopoietic progenitor cells; specific cell depletion within harvest, T-cell depletion</td>
</tr>
<tr>
<td>38212</td>
<td>Transplant preparation of hematopoietic progenitor cells; red blood cell removal</td>
</tr>
<tr>
<td>38213</td>
<td>Transplant preparation of hematopoietic progenitor cells; platelet depletion</td>
</tr>
<tr>
<td>38214</td>
<td>Transplant preparation of hematopoietic progenitor cells; plasma (volume) depletion</td>
</tr>
<tr>
<td>38215</td>
<td>Transplant preparation of hematopoietic progenitor cells; cell concentration in plasma, mononuclear, or Buffy coat layer</td>
</tr>
<tr>
<td>38230</td>
<td>Bone marrow harvesting for transplantation, allogeneic</td>
</tr>
<tr>
<td>38240</td>
<td>Hematopoietic progenitor cell (HPC); allogeneic transplantation, per donor</td>
</tr>
<tr>
<td>38242</td>
<td>Allogeneic lymphocyte infusions</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
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<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>S2140</td>
<td>Cord blood harvesting for transplantation, allogeneic</td>
</tr>
<tr>
<td>S2142</td>
<td>Cord blood-derived stem cell transplantation, allogeneic</td>
</tr>
<tr>
<td>S2150</td>
<td>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</td>
</tr>
</tbody>
</table>


**References**


with chimerism conversion but transplantation has high toxicity. Bone Marrow Transplant. 2004 Aug;34(4):309-16.


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