



Louisiana

Hematopoietic Cell Transplantation in the Treatment of Germ-Cell Tumors

Policy # 00056

Original Effective Date: 01/28/2002

Current Effective Date: 11/21/2018

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When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider the use of single autologous hematopoietic cell transplantation (HCT) as salvage therapy for germ cell tumors to be **eligible for coverage** when patient selection criteria are met.

Patient Selection Criteria

The use of single autologous hematopoietic cell transplantation (HCT) as salvage therapy for germ-cell tumors may be considered **eligible for coverage** when ANY of the following criteria are met:

- In patients with favorable prognostic factors that have failed a previous course of conventional-dose salvage chemotherapy; OR
- In patients with unfavorable prognostic factors as initial treatment of first relapse (i.e., without a course of conventional-dose salvage chemotherapy) and in patients with platinum-refractory disease.

Based on review of available data, the Company may consider tandem autologous HCT or transplant with sequential high-dose chemotherapy for the treatment of testicular tumors either as salvage therapy or with platinum-refractory disease to be **eligible for coverage**.

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of single autologous hematopoietic cell transplantation (HCT) as salvage therapy to treat patients with germ-cell tumors when patient selection criteria are not met to be **investigational**.*

Based on review of available data, the Company considers autologous hematopoietic cell transplantation (HCT) as a component of first-line treatment for germ-cell tumors to be **investigational**.*

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Based on review of available data, the Company considers allogeneic hematopoietic cell transplantation (HCT) to treat germ-cell tumors, including, but not limited to its use as therapy after a prior failed autologous hematopoietic cell transplantation (HCT) to be **investigational**.*

Policy Guidelines

The favorable and unfavorable prognostic factors are derived from the current National Comprehensive Cancer Network (NCCN) guidelines and the DeVita, Hellman, and Rosenberg's textbook Cancer: Principles and Practice of Oncology.

Patients with favorable prognostic factors include those with a testis or retroperitoneal primary site, a complete response to initial chemotherapy, low levels of serum markers, and low-volume disease. Patients with unfavorable prognostic factors are those with an extratesticular primary site, an incomplete response to initial therapy, high levels of serum markers, high-volume disease, or relapsing mediastinal nonseminomatous germ cell tumors.

Background/Overview

GERM CELL TUMORS

Germ cell tumors are composed primarily of testicular neoplasms as well as ovarian and extragonadal germ cell tumors (no primary tumor in either testis or ovary). Germ cell tumors are classified by their histology, stage, prognosis, and response to chemotherapy.

The most common testicular germ cell tumors are seminomas; all other histologic types are collectively referred to as nonseminomatous tumors. Nonseminomatous tumor types include embryonal cell tumor, yolk sac tumor, and teratomas. Malignant germ cell tumors of ovarian origin are classified as dysgerminomas or nondysgerminomas. Similarly, nondysgerminomas include immature teratomas, embryonal cell tumors, yolk sac tumor, polyembryoma, and mixed germ cell tumors.

Staging

Stage depends on location and extent of the tumor, using the American Joint Committee on Cancer's TNM system. TNM stages, modified by serum concentrations of markers for tumor burden (S0-3) when available, are grouped by similar prognoses. Markers used for germ cell tumors include human β -chorionic gonadotropin, lactate dehydrogenase, and α -fetoprotein. However, most patients with pure seminoma have normal α -fetoprotein concentrations. For testicular tumors, stages IA to B tumors are limited to the testis (no involved nodes or distant metastases) and no marker elevations (S0); stages IIA to C have increasing size and number of tumor-involved lymph nodes, and at least 1 marker moderately elevated above the normal range (S1); and stages IIIA to C have distant metastases and/or marker elevations greater than specified thresholds (S2-3).

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Germ cell tumors also are divided into good-, intermediate-, or poor-risk categories based on histology, site, extent of primary tumor, and serum marker levels. Good-risk pure seminomas can be at any primary site but are without nonpulmonary visceral metastases or marker elevations. Intermediate-risk pure seminomas have nonpulmonary visceral metastases with or without elevated human chorionic gonadotropin and/or lactate dehydrogenase. There are no poor-risk pure seminomas, but mixed histology tumors and seminomas with elevated α -fetoprotein (due to mixture with nonseminomatous components) are managed as nonseminomatous germ cell tumors. Good- and intermediate-risk nonseminomatous germ cell tumors have testicular or retroperitoneal tumors without nonpulmonary visceral metastases, and either S1 (good-risk) or S2 (intermediate) levels of marker elevations. Poor-risk tumors have mediastinal primary tumors, or nonpulmonary visceral metastases, or the highest level (S3) of marker elevations.

Treatment

Therapy for germ cell tumors is generally dictated by stage, risk subgroup, and tumor histology. Testicular cancer is divided into seminomatous and nonseminomatous types for treatment planning because seminomas are more sensitive to radiotherapy. Stage I testicular seminomas may be treated by orchiectomy with or without radiation or single-dose carboplatin adjuvant therapy. Nonseminomatous stage I testicular tumors may be treated with orchiectomy with or without retroperitoneal lymph node dissection. Higher stage disease typically involves treatment that incorporates chemotherapy. First-line chemotherapy for good- and intermediate-risk patients with higher stage disease is usually 3 or 4 cycles of a regimen combining cisplatin and etoposide, with or without bleomycin depending on histology and risk group. Chemotherapy is often followed by surgery to remove residual masses. Second-line therapy often consists of combined therapy with ifosfamide/mesna and cisplatin, plus vinblastine, paclitaxel, or etoposide (if not used for first-line treatment). Patients whose tumors are resistant to cisplatin may receive carboplatin-containing regimens. The probability of long-term continuous complete remission diminishes with each successive relapse.

Hematopoietic Cell Transplantation

Hematopoietic cell transplantation (HCT) is a procedure in which hematopoietic stem cells are infused to restore bone marrow function in cancer patients who receive bone-marrow-toxic doses of drugs with or without whole body radiotherapy. Hematopoietic stem cells may be obtained from the transplant recipient (autologous HCT) or from a donor (allogeneic HCT). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates. Although cord blood is an allogeneic source, the stem cells in it are antigenically "naive" and thus are associated with a lower incidence of rejection or graft-versus-host disease.

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HCT. However, immunologic compatibility between donor and patient is a critical factor for achieving a good outcome of allogeneic HCT. Compatibility is established by typing of human leukocyte antigens using cellular, serologic, or molecular techniques. Human leukocyte antigen refers to the tissue type expressed at the class I and II loci on chromosome 6. Depending on the disease being treated, an

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acceptable donor will match the patient at all or most of the human leukocyte antigen loci (with the exception of umbilical cord blood).

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

The U.S. FDA regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research, under Code of Federal Regulation (CFR) title 21, parts 1270 and 1271. Hematopoietic stem cells are included in these regulations.

Centers for Medicare and Medicaid Services (CMS)

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Rationale/Source

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

The majority of evidence describes the diagnosis and management of seminomatous and nonseminomatous germ cell tumors.

AUTOLOGOUS HEMATOPOIETIC CELL TRANSPLANTATION AS FIRST-LINE THERAPY FOR GERM CELL TUMORS

Daugaard et al (2011) reported on the outcomes of a randomized phase 3 study comparing standard-dose cisplatin, etoposide, and bleomycin (BEP) with sequential high-dose cisplatin, etoposide, and ifosfamide

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plus stem cell support in previously untreated males with poor-prognosis germ cell cancer. The trial aimed to recruit 222 patients but closed with 137 patients from 27 European oncology centers due to slow accrual. Patients were ages 15 to 50 years and had previously untreated metastatic poor-prognosis nonseminomatous germ cell tumor of testicular or extragonadal origin. Median follow-up was 4.4 years; 66 patients in the BEP group and 65 patients in the transplant group were included in the analysis. Toxicity was more severe in patients who received high-dose chemotherapy (HDC), and toxicity-related deaths were reported for 2 patients who received HDC and in 1 patient in the BEP arm. There was no improvement in complete response (CR) rate in the HDC arm (44.6%) vs the standard-dose arm (33.3%; $p=0.18$). There was no difference in failure-free survival between the 2 groups. At 2 years, failure-free survival rates were 44.8% (95% confidence interval [CI], 32.5% to 56.4%) and 58.2% (95% CI, 48.0% to 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 groups ($p>0.1$). The authors concluded that HDC given as part of first-line therapy does not improve outcomes in patients with poor-prognosis germ cell tumor.

Motzer et al (2007) reported on a phase 3 prospective, randomized, multicenter trial of 219 previously untreated patients with poor-prognosis germ cell tumors. Median patient age was 28 years. Patients were randomized to conventional chemotherapy (4 cycles of BEP; $n=111$) or 2 cycles of BEP followed by 2 cycles of HDC with autologous hematopoietic cell transplantation (HCT). Median follow-up was 51 months. The 1-year durable CR rate was 52% after BEP plus HDC with HCT, and 48% after BEP alone ($p=0.53$). There was no survival difference at 106 months for patients treated with HDC and HCT (68%) compared with patients treated with conventional chemotherapy (69%).

Droz et al (2007) assessed the impact of HDC plus HCT on the survival of patients with high-volume, previously untreated, metastatic nonseminomatous germ cell tumors. Patients were randomized to 4 cycles every 21 days of vinblastine, etoposide, cisplatin, and bleomycin ($n=57$) or a slightly modified regimen followed by HDC plus autologous HCT ($n=57$). In an intention-to-treat analysis, the CR rates were 56% and 42% for the conventional and HDC groups, respectively ($p=0.099$). Median follow-up was 9.7 years, and no significant difference in OS between groups ($p=0.167$).

Section Summary: Autologous Hematopoietic Cell Transplantation as First-Line Therapy for Germ Cell Tumors

The evidence from several randomized trials found that autologous HCT as first-line therapy for germ cell tumors did not significantly improve outcomes compared with alternative therapy (eg, standard-dose chemotherapy). However, study sample sizes were relatively small and might have been underpowered to detect differences between groups.

AUTOLOGOUS HCT FOR RELAPSED OR REFRACTORY GERM CELL TUMORS

One RCT was identified. In 2005, Pico et al reported on a randomized trial comparing 4 cycles of conventional-dose chemotherapy with 3 cycles of the same regimen followed by carboplatin-based HDC plus autologous HCT in 280 patients who had relapsed after a complete or partial remission following first-

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line therapy with a cisplatin-based regimen. The authors reported no significant differences between treatment arms in 3-year event-free survival or OS. However, the trial began before international consensus had established the current risk group definitions; thus, Pico et al likely included patients now considered to have good prognosis at relapse. Furthermore, while 77% and 86% of patients in the control and experimental arms, respectively, had at least one elevated serum tumor marker, they did not report how highly elevated rates were or compare arms with respect to the marker thresholds that presently determine risk level (S1-3). Finally, HDC in the experimental arm followed 3 cycles of conventional-dose chemotherapy, which differs from most current practice in the United States, in which a single cycle is used before HDC. As a consequence, 38 (28%) of 135 patients randomized to the HDC arm did not receive HDC because of progression, toxicity, or withdrawal of consent.

In addition, several case series were identified. Seftel et al (2011) conducted a multicenter study of consecutive patients undergoing a single autologous HCT for germ cell tumor between 1986 and 2004. For 71 subjects, median follow-up was 10.1 years. Median age was 31 years (range, 16-58 years). Sixty-seven patients had nonseminomatous germ cell tumors and four had seminomatous germ cell tumors. Fifty-seven 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 HCT for relapsed disease after achieving an initial CR. Of these, 24 patients underwent autologous HCT after a first relapse and 4 underwent transplant after a second relapse. An additional 36 patients achieved only an incomplete response after initial therapy and proceeded to autologous HCT after salvage chemotherapy for active residual disease. The OS rate at 5 years was 44.7% (95% CI, 32% to 56.5%) and the EFS rate was 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 good prognosis disease at diagnosis, primary gonadal disease, and response to salvage chemotherapy.

Agarwal et al (2009) reported on their experience at a single center in treating 37 consecutive patients who received HDC and autologous HCT between 1995 and 2005 for relapsed germ cell tumors. Median patient age was 28 years (range, 9-59 years), with 34 males and 3 females. Primary tumor sites included 24 testes/adnexal, 10 chest/neck/retroperitoneal, and 3 CNS. Twenty-nine patients had received prior standard salvage chemotherapy. The 3-year OS rate was 57% (95% CI, 41% to 71%), and the 3-year progression-free survival (PFS) rate was 49% (95% CI, 33% to 64%).

Baek et al (2013) reported on results of a small feasibility study of HDC followed by HCT for patients with relapsed or progressed CNS germ cell tumors. Investigators enrolled 11 patients with nongerminomatous (ie, nonseminomatous) germ cell tumors and 9 patients with germinomatous stem cell tumors, all of whom had received conventional chemotherapy with or without radiotherapy before HCT. Sixteen patients received an initial course of HDC with carboplatin, thiopental, and etoposide followed by HCT, and nine of

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them received a second course of HDC with cyclophosphamide-melphalan followed by a second HCT (see the tandem and sequential HCT for germ cell tumors section next). Twelve patients remained alive at a median follow-up of 47 months (range, 22-90 months), with a 3-year OS probability estimate of 59.1%.

Nieto et al (2015) reported on 43 male patients with poor-risk relapsed or refractory germ cell tumors with received HDC and autologous HCT. Primary tumors were testicular in 32 patients, mediastinal in 7 patients, and retroperitoneal in 4 patients. Median follow-up was 46 months (range, 9-84 months). At follow-up, the relapse-free survival rate was 55.8% and the OS rate was 58.1%. Relapse-free survival rates were 66% in patients with testicular primaries, 28.5% in patients with mediastinal primaries, and 25% in patients with retroperitoneal primaries.

Section Summary: Autologous HCT for Relapsed or Refractory Germ Cell Tumors

The single published RCT did not find improved outcomes with HDC and autologous HCT compared with standard-dose HCT. Case series had sample sizes ranging between 11 and 71 patients each. Three-year OS rates in these case series ranged between 55% and 60%.

TANDEM AUTOLOGOUS HCT AND SEQUENTIAL HDC FOR GERM CELL TUMORS

There is ongoing research into the role of tandem autologous HCT and sequential HDC for germ cell tumors, with a variety of specific chemotherapy regimens.

Lorch et al (2007) compared single- with sequential HDC plus autologous HCT as first or subsequent salvage treatment in patients with relapsed or refractory germ cell tumors. Patients were randomized to two different HDC regimens (arm A, arm B). Most tumors were gonadal primaries; 10% of patients in arm A had retroperitoneal, mediastinal, or CNS primaries, and 11% of patients in arm B had retroperitoneal or mediastinal primaries. This represented the first salvage therapy received for 86% of the patients in arm A and 85% in arm B, whereas 14% in arm A and 15% in arm B had received one or more previous salvage regimens before randomization. A total of 111 (51%) of 216 patients were randomized to sequential high-dose therapy, and 105 (47%) of 216 patients were randomized to single high-dose therapy. The trial was stopped prematurely after recruitment of 216 patients as a result of excess treatment-related mortality in arm B (sequential). There was a planned interim analysis after the inclusion of 50% of the required total number of patients. Survival analyses were performed on an intention-to-treat basis.

At a median follow-up of 36 months, 109 (52%) of 211 patients were alive, and 91 (43%) of 211 patients were progression-free. At 1 year, event-free survival, PFS, and OS 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). Survival rates were not reported separately by primary tumor site. No difference in survival probabilities was found between the single and sequential high-dose regimens; however, sequential high-dose therapy was better tolerated and resulted in fewer treatment-related deaths. Treatment-related deaths, mainly from sepsis and cardiac toxicity, were less frequent in arm A (4/108 [4%] patients) than in arm B (16/103 [16%] patients; $p < 0.01$). The authors attributed the higher rate of treatment-related deaths in arm B

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to the higher dosages per HCT cycle in the arm B regimen compared with arm A, as well as the toxic renal and cardiac effects of cyclophosphamide used in arm B.

Lorch et al (2012) reported long-term results from this trial; 5-year PFS rates were 47% (95% CI, 37% to 56%) in arm A and 45% (95% CI, 35% to 55%) in arm B (hazard ratio [HR], 1.16; 95% CI, 0.79 to 1.70; $p=0.454$). Five-year OS rates were 49% (95% CI, 40% to 59%) in arm A and 39% (95% CI, 30% to 49%) in arm B (HR=1.42; 95% CI, 0.99 to 2.05; $p=0.057$). The authors concluded that patients with relapsed or refractory germ cell tumors could achieve durable long-term survival after single as well as tandem HCT plus sequential HDC and that fewer early deaths related to toxicity translated into superior long-term OS after HCT plus sequential HDC.

Lazarus et al (2007) reported on the results of autologous HCT for relapsed testicular/germ cell cancer using 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 a single or a tandem autologous HCT between 1989 and 2001. Of the 300 patients, 102 received tandem and 198 received single planned autologous HCT. PFS and OS rates at 1, 3, and 5 years were similar for both groups. The probability of PFS at 5 years for the tandem transplant group was 34% (95% CI, 25% to 44%) vs 38% (95% CI, 31% to 45%) for the single transplant group ($p=0.50$). The probability of 5-year OS was 35% (95% CI, 25% to 46%) vs 42% (95% CI, 35% to 49%), respectively ($p=0.29$).

Lotz et al (2005) reported on the results of a phase 2 study on 3 consecutive cycles of HDC regimens supported by autologous HCT in 45 poor-prognosis patients with relapsed germ cell tumors. From 1998 to 2001 (median follow-up, 31.8 months), 45 patients (median age, 28 years) were enrolled. Most patients (76%) had testicular primaries; 13% had mediastinal primaries; 11% had retroperitoneal, hepatic, or unknown. Of all patients, 22 received the complete course. Twenty-five patients died from disease progression and five from treatment toxicity. The overall response rate was 37.7%, including an 8.9% CR rate. Median OS was 11.8 months. The 3-year OS and PFS rates were both 23.5%. Authors used the Beyer prognostic score to predict the outcome of HDC and concluded that patients with a Beyer score greater than two did not benefit from this approach, confirming that highly refractory patients and particularly patients with resistant or refractory primary mediastinal germ cell tumors do not benefit from HDC.

Einhorn et al (2007) reported retrospectively on a series of 184 patients, treated between 1996 and 2004, with 2 consecutive cycles of HDC for metastatic testicular cancer that had progressed (relapsed) after receiving cisplatin-containing combination chemotherapy. Patients with primary mediastinal nonseminomatous germ cell tumors or tumors with late relapse (≥ 2 years after previous therapy) were excluded. The patient population included those with initial International Germ Cell Consensus Classification stage defined as low risk (39%), intermediate-risk (21%), and high-risk (41%) and both platinum-sensitive and refractory disease at the beginning of HDC. Results from this experienced center showed that, of the 184 patients, 116 had complete remission of disease without relapse during a median

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follow-up of 48 months. Of the 135 patients who received the treatment as second-line therapy (ie, first salvage setting), 94 (70%) were disease-free during follow-up; 22 (45%) of 49 patients who received treatment as third-line or later therapy were disease-free. Of 40 patients with cancer refractory to standard-dose platinum, 18 (45%) were disease-free. Caveats to the Einhorn study included the lack of a validation set for the prognostic scoring system used; the unanswered question of the role of high-dose vs conventional-dose chemotherapy in the first salvage setting; and the lack of a universally accepted prognostic scoring system in this setting.

In a subsequent study from the same center as the Einhorn study, Suleiman et al (2013) evaluated outcomes for 12 patients with recurrent primary mediastinal nonseminomatous germ cell tumors after initial treatment with cisplatin-containing combination chemotherapy, a population excluded from their previous study, who were treated with tandem HCT. Patients received 2 consecutive courses of HDC (carboplatin and etoposide) followed by HCT. Overall outcomes were poor, with a median survival of 11 months (range, 4-52 months), but 3 of 12 patients achieved a CR. One patient remained disease-free at 50 months of follow-up, and one remained disease-free after tandem HCT and subsequent mediastinal surgery at 52 months of follow-up.

Pal et al (2013) reported on 5-year follow-up results for 48 patients with relapsed germ cell tumors enrolled in a retrospective case series to evaluate the effectiveness of 2 sequential cycles of chemotherapy with paclitaxel, etoposide, and carboplatin in the first cycle, high-dose paclitaxel, ifosfamide, and carboplatin in the second, followed by HCT. Forty-three (91.5%) patients had nonseminomatous histology. Most patients (n=39) had received 2 prior chemotherapy regimens; 6 patients had received 3 prior regimens. Thirty-four patients had intermediate-risk classification by the Beyer score and the remainder had high-risk classification. Of the 48 patients enrolled, 17 received only 1 course of paclitaxel, etoposide, and carboplatin, 11 due to progressive disease, 5 due to toxicities, and 1 due to a severe fungal infection. Seventeen of the 48 patients enrolled were alive and progression-free at a median of 123.2 months (range, 51.6-170.2 months); 25 died, most (n=23) due to disease progression. Of the 23 patients alive after receiving per-protocol therapy, 18 were contacted for interviews at a median 115.6 months (range, 38.9-185.9 months) postenrollment and underwent a cancer-related quality-of-life assessment with the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire–Core 30. The overall average score on the questionnaire was 87.04; the authors compared quality-of-life scores in this cohort with a separate cohort of 150 patients who had germ cell tumors who received chemotherapy; authors reported that patients in their cohort had significantly higher global health scores (87.04 vs 75.62, $p=0.02$), but lower physical functioning scores (68.9 vs 92.7, $p<0.001$). The authors concluded that tandem HDC followed by HCT would be a reasonable treatment option for relapsed germ cell tumors, with long-term survivors demonstrating a reasonable quality of life.

A 2012 comparative effectiveness review, conducted for the Agency for Healthcare Research and Quality, on the use of HCT in the pediatric population concluded that, for germ cell tumors, the body of evidence on OS with tandem HCT compared with single HCT was insufficient to draw conclusions.

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Section Summary: Tandem Autologous HCT and Sequential for Germ Cell Tumors

One RCT compared tandem HCT with single vs sequential HDC for germ cell tumors. This RCT showed higher treatment-related mortality with sequential HDC than with single HDC. Five-year survival outcomes, however, did not show significant differences between groups. Observational studies have included heterogeneous patient populations, in different salvage treatment settings (ie, first vs subsequent salvage therapy), and lacked a universally accepted prognostic scoring system to risk-stratify patients.

ALLOGENEIC HCT FOR GERM CELL TUMORS

No RCTs or nonrandomized comparative studies evaluating allogeneic HCT for germ cell tumors were identified. One 2007 case report has described successful treatment of a refractory mediastinal germ cell tumor with allogeneic HCT.

Section Summary: Allogeneic HCT for Germ Cell Tumors

There is a lack of comparative studies evaluating allogeneic HCT for germ cell tumors. Only a single case report was identified.

SUMMARY OF EVIDENCE

For individuals who have previously untreated germ cell tumors who receive autologous HCT as first-line therapy, the evidence includes randomized controlled trials (RCTs). Relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. Results from the RCTs have shown that autologous HCT as initial therapy for germ cell tumors did not significantly improve outcomes compared with alternative therapy (eg, standard-dose chemotherapy). Study sample sizes were relatively small and might have been underpowered to detect differences between groups. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have relapsed or refractory germ cell tumors who receive autologous HCT, the evidence includes an RCT and several case series. Relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. The RCT did not find significant differences in outcomes between autologous HCT plus HDC and standard-dose chemotherapy. Case series found 3-year overall survival rates that ranged from 55% to 60%; these studies lacked comparison groups. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have germ cell tumors who receive tandem autologous transplantation and sequential HDC, the evidence includes an RCT, several retrospective cohort studies, and a comparative effectiveness review. Relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. The RCT reported a higher rate of treatment-related mortality with sequential HDC compared with single HDC. However, 5-year survival outcomes did not differ significantly between groups. Overall, the available studies have included heterogeneous patient populations, in different salvage treatment settings (ie, first vs subsequent salvage therapy), and have lacked a universally accepted prognostic scoring system

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Louisiana

Hematopoietic Cell Transplantation in the Treatment of Germ-Cell Tumors

Policy # 00056

Original Effective Date: 01/28/2002

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to risk-stratify patients. Tandem autologous transplant or transplant with sequential HDC has not shown a benefit in patients with primary mediastinal germ cell tumors. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have germ cell tumors who receive allogeneic HCT, the evidence includes a case report. Relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. There were no RCTs or nonrandomized comparative studies evaluating allogeneic HCT for germ cell tumors. One 2007 case report has described successful treatment of a refractory mediastinal germ cell tumor with allogeneic HCT. The evidence is insufficient to determine the effects of the technology on health outcomes.

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Policy History

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|------------|--|
| 12/06/2001 | Medical Policy Committee review |
| 01/28/2002 | Managed Care Advisory Council approval |
| 06/24/2002 | Format revision. Policy addresses only Germ Cell Tumors. Replaces high dose chemotherapy with hematopoietic stem cell support. |
| 03/31/2004 | Medical Director review |
| 04/20/2004 | Medical Policy Committee review. Format revision. No substance change to policy. |
| 04/26/2004 | Managed Care Advisory Council approval |
| 05/03/2005 | Medical Director review |
| 05/17/2005 | Medical Policy Committee review. Format revision. Policy statement corrected to reflect "that HDC and autologous SCS as initial treatment (i.e., in lieu of an initial course of conventional chemotherapy) of poor-risk germ cell tumors or as initial treatment of a first relapse (i.e., in lieu of a course of conventional chemotherapy) is investigational". |
| 05/23/2005 | Managed Care Advisory Council approval |
| 05/03/2006 | Medical Director review |
| 05/17/2006 | Medical Policy Committee approval. Format revision, including addition of FDA and or other governmental regulatory approval and rationale/source. Coverage eligibility unchanged. |
| 10/10/2007 | Medical Director review |
| 10/17/2007 | Medical Policy Committee approval. No change to coverage eligibility. |
| 10/01/2008 | Medical Director review |
| 10/22/2008 | Medical Policy Committee approval. No change to coverage eligibility. |
| 10/01/2009 | Medical Policy Committee approval |

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10/14/2009 Medical Policy Implementation Committee approval. Title changed from "High-Dose Chemotherapy with Stem Cell Support for Germ Cell Tumors" to "Hematopoietic Stem Cell Transplantation in the Treatment of Germ Cell Tumors". No change to coverage eligibility.

10/14/2010 Medical Policy Committee review

10/20/2010 Medical Policy Implementation Committee approval. Terminology changed in coverage statements. Coverage statements changed to indicate that tandem-sequential autologous stem-cell transplantation may be considered eligible for coverage in certain types of testicular cancers.

10/06/2011 Medical Policy Committee review

10/19/2011 Medical Policy Implementation Committee approval. "Based on review of available data, except as noted above for treatment of certain testicular tumors, the Company considers tandem or sequential autologous hematopoietic stem-cell transplantation to treat germ-cell tumors of any stage to be investigational" was deleted from coverage.

10/11/2012 Medical Policy Committee review

10/31/2012 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

03/04/2013 Coding updated

10/03/2013 Medical Policy Committee review

10/16/2013 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

11/06/2014 Medical Policy Committee review

11/21/2014 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

08/03/2015 Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.

10/29/2015 Medical Policy Committee review

11/16/2015 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

11/03/2016 Medical Policy Committee review

11/16/2016 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

01/01/2017 Coding update: Removing ICD-10 Diagnosis Codes

11/02/2017 Medical Policy Committee review

11/15/2017 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

11/08/2018 Medical Policy Committee review

11/21/2018 Medical Policy Implementation Committee approval. One policy statement was reworded, from "Tandem or sequential autologous HCT may be considered eligible for coverage for the treatment of testicular tumors either as salvage therapy or with platinum-refractory disease" to "Tandem autologous HCT or transplant with sequential high-dose chemotherapy may be considered eligible for coverage for the treatment of testicular tumors either as salvage therapy or with platinum-refractory disease."

Next Scheduled Review Date: 11/2019

Coding

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Code Type	Code
CPT	38204, 38205, 38206, 38207, 38208, 38209, 38210, 38211, 38212, 38213, 38214, 38215, 38230, 38232, 38240, 38241, 38242, 38243
HCPCS	S2140, S2142, S2150
ICD-10 Diagnosis	C38.1-C38.8, C48.0, C56.1-C56.9, C62.00-C62.02, C62.10-C62.12, C62.90-C62.91

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
 - 1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
 - 2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
 - 3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

- A. In accordance with nationally accepted standards of medical practice;
- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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