Regence

Hematopoietic Cell Transplantation in the Treatment of Germ-Cell Tumors

Effective: November 1, 2023

Next Review: August 2024
Last Review: September 2023

IMPORTANT REMINDER

DESCRIPTION

Hematopoietic cell transplantation is performed to restore normal function following chemotherapy treatment.

MEDICAL POLICY CRITERIA

I.   Single autologous hematopoietic cell transplantation may be considered **medically necessary** in the treatment of germ-cell tumors for either of the following (A. or B.):

A.   For patients with *favorable prognostic factors* that have failed a previous course of conventional-dose salvage chemotherapy. 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.; or

B.   For 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. Patients with unfavorable prognostic factors are those with an incomplete response to initial therapy or relapsing mediastinal nonseminomatous germ-cell tumors.

II. Tandem autologous hemopoietic cell transplantation or transplant with sequential high-dose chemotherapy may be considered **medically necessary** in the treatment of testicular tumors, either as salvage therapy or for those with platinum-refractory disease.

III. Hematopoietic cell transplantation is considered **investigational** in the treatment of germ-cell tumors for any of the following:

    A. Autologous hemopoietic cell transplantation as a component of first-line treatment for germ-cell tumors.

    B. Tandem autologous hemopoietic cell transplantation or transplant with sequential high-dose chemotherapy for all other germ-cell tumors of any stage not addressed in Criterion II.

    C. Allogenic hemopoietic cell transplantation for any germ-cell tumors, including, but not limited to its use as therapy after failed autologous hematopoietic cell transplantation.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

DEFINITIONS

- **Consolidation therapy:** Treatment that is given after cancer has disappeared following the initial therapy. Consolidation therapy is used to kill any cancer cells that may be left in the body. It may include radiation therapy, a stem cell transplant, or treatment with drugs that kill cancer cells. Also called intensification therapy and postremission therapy.
- **Relapse:** The return of a disease or the signs and symptoms of a disease after a period of improvement.
- **Salvage therapy:** Treatment that is given after the cancer has not responded to other treatments.
- **Tandem transplant:** Refers to a planned second course of high-dose therapy and HCT within six months of the first course.

LIST OF INFORMATION NEEDED FOR REVIEW

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and physical/chart notes
- Diagnosis and indication for transplant

CROSS REFERENCES

1. Donor Lymphocyte Infusion for Malignancies Treated with an Allogeneic Hematopoietic Cell Transplant, Transplant, Policy No. 45.03
2. Placental and Umbilical Cord Blood as a Source of Stem Cells, Transplant, Policy No. 45.16
3. Hematopoietic Cell Transplantation for Epithelial Ovarian Cancer, Transplant, Policy No. 45.26
4. Hematopoietic Cell Transplantation for Miscellaneous Solid Tumors in Adults, Transplant, Policy No. 45.27

5. [Hematopoietic Cell Transplantation for Solid Tumors of Childhood](), Transplant, Policy No. 45.37

BACKGROUND

HEMATOPOIETIC CELL TRANSPLANTATION

Broadly speaking, there are two types of hematopoietic cell transplants (HCT, previously referred to in this policy as a hematopoietic stem cell transplant [HSCT]), autologous and allogeneic. The purpose of an autologous HCT is to treat a disease (e.g. lymphoma) with myeloablative doses of chemotherapy (with or without radiation) that are active against the disease. The recipient's own HCTs (collected previously) are infused after the chemotherapy in order to re-establish normal marrow function. In an allogeneic transplant, the recipient receives HCTs from a donor after myeloablative therapy or non-myeloablative therapy in order to re-establish normal marrow function as well as to use the new blood system as a platform for immunotherapy, a so called "graft versus tumor" effect. Hematopoietic cells 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 cells in it are antigenically "naïve" and thus are associated with a lower incidence of rejection or graft-versus-host disease (GVHD).

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 (HLA) using cellular, serologic, or molecular techniques. HLA refers to the tissue type expressed at the Class I and Class II loci on chromosome 6. Depending on the disease being treated, an acceptable donor will match the patient at all or most of the HLA loci (with the exception of umbilical cord blood).

CONVENTIONAL PREPARATIVE CONDITIONING FOR HCT

The conventional ("classical") practice of allogeneic HCT involves administration of cytotoxic agents (e.g., cyclophosphamide, busulfan) with or without total body radiation at doses sufficient to destroy endogenous hematopoietic capability in the recipient. The beneficial treatment effect in this procedure is due to a combination of initial eradication of malignant cells and subsequent graft-versus-malignancy (GVM) effect mediated by non-self immunologic effector cells that develop after engraftment of allogeneic stem cells within the patient's bone marrow space. While the slower GVM effect is considered to be the potentially curative component, it may be overwhelmed by extant disease without the use of pretransplant conditioning. However, intense conditioning regimens are limited to patients who are sufficiently fit medically to tolerate substantial adverse effects that include pre-engraftment opportunistic infections secondary to loss of endogenous bone marrow function and organ damage and failure caused by the cytotoxic drugs. Furthermore, in any allogeneic HCT, immune suppressant drugs are required to minimize graft rejection and GVHD, which also increases susceptibility of the patient to opportunistic infections.

The success of autologous HCT is predicated on the ability of cytotoxic chemotherapy with or without radiation to eradicate cancerous cells from the blood and bone marrow. This permits subsequent engraftment and repopulation of bone marrow space with presumably normal hematopoietic stem cells obtained from the patient prior to undergoing bone marrow ablation. As a consequence, autologous HCT is typically performed as consolidation therapy when the patient's disease is in complete remission. Patients who undergo autologous HCT are

susceptible to chemotherapy-related toxicities and opportunistic infections prior to engraftment, but usually not GVHD.

REDUCED-INTENSITY CONDITIONING FOR ALLOGENEIC HCT

Reduced-intensity conditioning (RIC) refers to the pretransplant use of lower doses or less intense regimens of cytotoxic drugs or radiation than are used in conventional full-dose myeloablative conditioning treatments. The goal of RIC is to reduce disease burden, but also to minimize as much as possible associated treatment-related morbidity and nonrelapse mortality (NRM) in the period during which the beneficial GVM effect of allogeneic transplantation develops. Although the definition of RIC remains arbitrary, with numerous versions employed, all seek to balance the competing effects of NRM and relapse due to residual disease. RIC regimens can be viewed as a continuum in effects, from nearly totally myeloablative, to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and patient condition. Patients who undergo RIC with allogeneic HCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism, which may be supplemented with donor lymphocyte infusions to eradicate residual malignant cells.

For the purposes of this Policy, the term "reduced-intensity conditioning" will refer to all conditioning regimens intended to be non-myeloablative, as opposed to fully myeloablative (conventional) regimens.

GERM-CELL TUMORS

Germ-cell tumors are composed primarily of testicular neoplasms (seminomas or nonseminomatous tumors) but also include ovarian and extragonadal germ-cell tumors (e.g., retroperitoneal or mediastinal tumors). Germ-cell tumors are classified according to their histology, stage, prognosis, and response to chemotherapy.

Histologies include seminoma, embryonal carcinoma, teratoma, choriocarcinoma, yolk sac tumor, and mixed germ-cell tumors. Seminomas are the most common; all other types are collectively referred to as nonseminomatous germ-cell tumors.

Stage is dependent 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 beta-chorionic gonadotropin (B-hCG), lactate dehydrogenase (LDH), and alpha fetoprotein (AFP). However, most patients with pure seminoma have normal AFP concentrations. For testicular tumors, Stages IA-B have tumors limited to the testis (no involved nodes or distant metastases) and no marker elevations (S0); Stages IIA-C have increasing size and number of tumor-involved lymph nodes, and at least one marker moderately elevated above the normal range (S1); and Stages IIIA-C have distant metastases and/or marker elevations greater than specified thresholds (S2-3).

Germ-cell tumors also are divided into good-, intermediate-, or poor-risk categories based on histology, site, and extent of primary tumor, and on serum marker levels. 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 hCG and/or LDH. There are no poor-risk pure seminomas, but mixed histology tumors and seminomas with elevated AFP (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.

EVIDENCE SUMMARY

The principal outcomes associated with treatment of germ-cell tumors are typically measured in units of survival past treatment: disease-free survival (DFS), a period of time following treatment where the disease is undetectable; progression-free survival (PFS), the duration of time after treatment before the advancement or progression of disease; and overall survival (OS), the period of time the patient remains alive following treatment. Risk of graft-versus-host disease is another primary outcome among patients undergoing allogeneic hematopoietic cell transplantation (HCT). Ideally, in order to understand the impact of HCT for treatment of testicular cancer or any other germ-cell tumor, comparative clinical trials that compare this therapy with standard medical treatment, such as standard chemotherapy regimens, are needed. Further, for treatment of germ-cell tumors, particularly those with a poor prognosis, an understanding of any adverse treatment effects must be carefully weighed against any benefits associated with treatment to understand the net treatment effect.

AUTOLOGOUS HEMATOPOIETIC CELL TRANSPLANTATION AS FIRST-LINE THERAPY

Randomized Controlled Trials

Daugaard (2011) reported the outcomes of a randomized Phase III study comparing standard-dose BEP (cisplatin, etoposide, and bleomycin) to sequential high-dose VIP (cisplatin, etoposide, and ifosfamide) plus stem-cell support in previously untreated males with poor-prognosis germ-cell cancer.[1] The study aimed to recruit 222 patients but closed with 137 patients from 27 European oncology centers due to slow accrual. Patients were age 15-50 years and had previously untreated metastatic poor-prognosis nonseminomatous germ-cell tumor of either 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 the patients who received high-dose chemotherapy, and toxic death was reported in two patients who received high-dose chemotherapy and one 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 two 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 did not differ between the two groups (log-rank p>0.1). The authors concluded that high-dose chemotherapy given as part of first-line therapy does not improve outcomes in patients with poor-prognosis germ-cell tumor.

Motzer (2007) reported on a Phase III prospective, randomized, multicenter trial of 219 previously untreated patients with poor-prognosis germ-cell tumors.[2] The median patient age was 28 years. Patients were randomized to receive either conventional chemotherapy (four cycles of standard BEP) (n=111), or two cycles of BEP followed by two cycles of high-dose chemotherapy with autologous HCT. Median follow-up was 51 months. One-year durable complete response rate was 52% after BEP and high-dose chemotherapy with HCT, and 48% after BEP alone (p=0.53). There was no survival difference at 106 months for patients treated

with high-dose chemotherapy and HCT compared to the patients treated with conventional chemotherapy (68% and 69%, respectively).

Droz (2007) assessed the impact of high-dose chemotherapy with HCT on the survival of patients with high-volume, previously untreated, metastatic nonseminomatous germ-cell tumors.[3] Patients were randomized to four cycles every 21 days of vinblastine, etoposide, cisplatin and bleomycin (n=57) or a slightly modified regimen followed by high-dose chemotherapy and autologous HCT (n=57). In an intention-to-treat analysis, there were 56% and 42% complete responses in the conventional and high-dose chemotherapy groups, respectively (p=0.099). Median follow-up was 9.7 years, and no significant difference between OS was observed (p=0.167).

AUTOLOGOUS HCT FOR RELAPSED OR REFRACTORY GERM-CELL TUMORS

Randomized Controlled Trial

In 2005, Pico reported on a randomized trial comparing four cycles of conventional-dose chemotherapy to three cycles of the same regimen followed by carboplatin-based high-dose chemotherapy plus autologous HCT in 280 patients who had relapsed after a complete or partial remission following first-line therapy with a cisplatin-based regimen.[4] The authors reported no significant differences between treatment arms in three-year event-free survival (EFS) and OS. However, the study began before international consensus established the current risk group definitions;[5] thus, Pico and colleagues likely included some 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 these were and did not compare arms with respect to the marker thresholds that presently determine risk level (S1-3). Finally, high-dose chemotherapy in the experimental arm followed three cycles of conventional-dose chemotherapy, which differs from most current practice in the U.S., where a single cycle is used prior to high-dose chemotherapy. As a consequence, 38 of 135 (28%) randomized to the high-dose chemotherapy arm did not receive high-dose chemotherapy because of progression, toxicity, or withdrawal of consent.

Nonrandomized Studies

Zschäbitz (2018) reported a retrospective analysis of the experience of two referral centers using high dose chemotherapy and autologous stem cell transplantation (HDCT/ASCT) for relapsed or refractory germ cell tumors.[6] Forty-six patients treated with HDCT/ASCT between 2000–2016 were identified; 52% of whom were categorized as poor risk by the International Prognostic Factors Study Group (IPFSG) prognosis score. HDCT/ASCT was performed as the first salvage regimen in 67% of patients. Further consolidation therapy after HDCT/ASCT was performed with 41% of patients undergoing resection of residual tumor. In patients who were in complete remission after HDCT/ASCT and in those who received residual tumor resection or radiotherapy as consolidation median progression free survival (mPFS) was 17.7 months (range 2–185; 95% CI: n.a.) and median overall survival (mOS) had not been reached with 64% of patients being alive at a median follow up time of 41 months. Median PFS and OS in patients who did not achieve a complete response was 3.3 months (95% CI: 1 1.0–5.5) and 6.4 months (95% CI: 5.6–7.2) in those who had no further consolidation treatment.

Adra (2017) reported a retrospective analysis of a single institution experience of using high dose chemotherapy and autologous stem cell transplantation (HDCT/ASCT) for relapsed or

refractory germ cell tumors.[7] Between 2004 and 2014, there were 364 consecutive patients with germ cell tumors who progressed after cisplatin-based combination chemotherapy; 341 received two consecutive courses of HDCT consisting of 700 mg/m2 carboplatin and 750 mg/m2 etoposide, each for three consecutive days, and each followed by peripheral blood stem cell transplant. At a median follow-up of 3.3 years, patients with pure seminoma had the highest cure rate, with a two-year PFS of 90% (95% CI, 81% to 95%). Remissions were achieved in poor prognosis patients who received HDCT as third-line or subsequent therapy (two-year PFS, 49%) and in patients with platinum-refractory disease (two-year PFS, 33%). Adverse events were notable with nine treatment related deaths due to infectious complications, hepatic failure and secondary leukemia.

In 2015, Nieto reported on 43 male patients with poor-risk relapsed or refractory germ cell tumors with received high-dose chemotherapy (HDC) and autologous HCT.[8] 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.

In 2014, Berger reported on a retrospective comparison of 143 patients with relapsed or refractory germ-cell cancer undergoing first salvage treatment with conventional-dose (CD-CX, n=48) or high-dose chemotherapy with autologous cell transplantation (HD-CX, n=95).[9] The aim of the study was to evaluate prognostic risk factors according to the International Prognostic Factors Study Group (IPFSG) criteria and the efficacy of salvage treatment. The IPFSG categories (very low risk 13/143, low risk 36/143, intermediate risk 66/143, high risk 22/143, and very high risk 6/143) significantly correlated with OS (p=0.025) after initial salvage treatment. Vital carcinoma found in secondary resected lesions was more prevalent following CD-CX compared to HD-CX, 22/29 vs. 22/45, (p=0.021) respectively. In addition, second relapse rate was higher in the CD-CX group (75%) compared to the HD-CX group (44%), resulting in a shorter median PFS (8 vs.42 months); however, no difference in OS was observed between treatment groups.

Baek (2013) reported results of a small feasibility study of HDC followed by HCT for patients with relapsed or progressed CNS germ-cell tumors.[10] The authors enrolled 11 patients with nongerminomatous (i.e., nonseminomatous) germ-cell tumors and 9 patients with germinomatous stem-cell tumors, all of whom had received conventional chemotherapy with or without radiation before HCT. Sixteen patients received an initial course of HDC with carboplatin, thiopental, and etoposide followed by HCT, and nine of those received a second course of HDC with cyclophosphamide-melphalan followed by a second HCT. Twelve patients were alive at a median follow-up of 47 months (range, 22-90 months), with a probability of three-year OS of 59.1% (± 11.2%).

Seftel (2011) conducted a multicenter cohort study of consecutive patients undergoing a single autologous HCT for germ-cell tumor between January 1986 and December 2004.[11] Of 71 subjects, median follow-up was 10.1 years. The median age was 31 years (range 16–58 years). A total of 67 of the patients had nonseminomatous germ-cell tumors and 4 had seminomatous germ-cell tumors. A total of 57 patients had primary gonadal disease and 14 had primary extragonadal disease. Of the latter, 11 patients presented with primary mediastinal disease, 2 presented with primary central nervous system disease, and 1 presented with retroperitoneal disease. In all, 28 patients underwent autologous HCT for

relapsed disease after achieving an initial complete response (CR). Of these, 24 patients underwent autologous HCT after a first relapse, whereas 4 patients underwent transplant after a second relapse. An additional 36 patients achieved only an incomplete response after initial therapy and proceeded to autologous HCT after salvage chemotherapy for active residual disease. Overall survival at five years was 44.7% (95% CI: 32.9–56.5%) and EFS 43.5% (95% CI: 31.4–55.1%). 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 two years of the transplant. Two very late relapses occurred 13 and 11 years after transplant. In a multivariate analysis, a favorable outcome was associated with International Germ Cell Consensus Classification (IGCCC) good prognosis disease at diagnosis, primary gonadal disease, and response to salvage chemotherapy.

Agarwal (2009) reported their experience at Stanford in treating 37 consecutive patients who received high-dose chemotherapy and autologous HCT between 1995 and 2005 for relapsed germ-cell tumors.[12] The 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 central nervous system (CNS). Twenty-nine of the patients had received prior standard salvage chemotherapy. Three-year OS was 57% (95% CI: 41-71%) and three-year progression-free survival was 49% (95% CI: 33–64%).

TANDEM AUTOLOGOUS HCT AND SEQUENTIAL HDC FOR GERM CELL TUMORS

Systematic Review

A comparative effectiveness review conducted for the Agency for Healthcare Research and Quality (AHRQ) on the use of HCT in the pediatric population concluded that, for germ-cell tumors, the body of evidence on overall survival with tandem HCT compared with single HCT for the treatment of relapsed pediatric germ-cell tumors was insufficient to draw conclusions.[13]

Nonrandomized Studies

Lazarus (2007) reported the results of autologous HCT in relapsed testicular/germ-cell cancer from registry data from the Center for International Blood and Marrow Transplant Research.[14] Patients with mediastinal primaries were excluded. Data included 300 patients from 76 transplant centers in eight countries who received either a single transplant or tandem autologous HCT between 1989 and 2001. Of the 300 patients, 102 received tandem, and 198 single planned autologous HCT. PFS and OS at one, three, and five years was similar for both groups. The probability of PFS at five years for the tandem transplant group was 34% (95% CI: 25–44%) versus 38% (95% CI: 31–45%) in the single transplant group; p=0.50. The probability of five-year OS was 35% (95% CI: 25–46%) versus 42% (95% CI: 35–49%), respectively; p=0.29.

Lorch (2007) compared single versus sequential HDC with autologous HCT as first or subsequent salvage treatment in patients with relapsed or refractory germ-cell tumors.[15] Between November 1999 and November 2004, patients planned to be recruited in a prospective, randomized, multicenter trial comparing one cycle of cisplatin, etoposide and ifosfamide (VIP) plus three cycles of high-dose carboplatin and etoposide (CE; arm A) versus three cycles of VIP plus one cycle of high-dose carboplatin, etoposide and cyclophosphamide (CEC; arm B). The majority of the tumors were gonadal primaries; ten percent 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 in

86% of the patients in arm A and 85% in arm B, whereas 14% (arm A) and 15% (arm B) had received one or more previous salvage regimens prior to randomization. One-hundred-eleven (51%) of 216 patients were randomly assigned to sequential high-dose therapy, and 105 (47%) of 216 patients were randomly assigned to single high-dose therapy. The study was stopped prematurely after recruitment of 216 patients as a result of excess treatment-related mortality in arm B. There was a planned interim analysis after the inclusion of 50% of the required total number of patients. Survival analyses were performed on an intent-to-treat basis.

With a median follow-up time of 36 months, 109 (52%) of 211 patients were alive, and 91 (43%) of 211 patients were progression free. At one year, event-free, progression-free, and overall survival rates were 40%, 53%, and 80%, respectively, in arm A compared with 37%, 49%, and 61%, respectively, in arm B (p >0.05 for all comparisons). Survival rates were not reported separately by primary site of the tumor. 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 as a result of sepsis and cardiac toxicity, were less frequent in arm A (four of 108 patients, 4%) compared with arm B (16 of 103 patients, 16%; p <0.01). The authors state that the higher treatment-related deaths observed in arm B likely were due to the higher dosages per HCT cycle in the arm B regimen compared to arm A, and the toxic renal and cardiac effects of cyclophosphamide used in arm B. The authors conclude that sequential treatment at submaximal doses of carboplatin and etoposide might be less toxic and safer to deliver HCT in pretreated patients with germ cell tumors than single HCT.

Long-term results from this study reported five-year PFS as 47% (95% CI, 37%-56%) in arm A and 45% (95% CI, 35%-55%) in arm B (hazard ratio, 1.16; 95% CI, 0.79-1.70; p=.454). Five-year OS was 49% (95% CI, 40%-59%) in arm A and 39% (95% CI, 30%-49%) in arm B (hazard ratio, 1.42; 95% CI, 0.99-2.05; p=.057). The authors concluded that patients with relapsed or refractory germ-cell tumors can achieve durable long-term survival after single as well as sequential HCT and that fewer early deaths related to toxicity translated into superior long-term OS after sequential HCT.[16]

Lotz (2005) reported the results of a Phase II study on three consecutive cycles of high-dose chemotherapy regimens supported by autologous HCT in 45 poor-prognosis patients with relapsed germ-cell tumors.[17] From March 1998 to September 2001 (median follow-up, 31.8 months), 45 patients (median age, 28 years) were enrolled. Most of the patients (76%) had testicular primaries; 13% had mediastinal primaries; 11% retroperitoneal, hepatic or unknown. Of all patients, 22 received the complete course. Twenty-five patients died from progression and five from toxicity. The overall response rate was 37.7%, including an 8.9% complete response rate. The median OS was 11.8 months. The three-year survival and PFS rate was 23.5%. The authors used the "Beyer" prognostic score to predict the outcome of high-dose chemotherapy and concluded that patients with a Beyer score greater than two did not benefit from this approach, confirming that highly refractory patients and particularly patients with resistant/refractory primary mediastinal germ cell tumors do not benefit from high-dose chemotherapy. The authors also state that better selection criteria have to be fulfilled in forthcoming studies.

Einhorn (2007) reported retrospectively on a series of 184 patients, treated between 1996 and 2004, with two consecutive cycles of high-dose chemotherapy for metastatic testicular cancer that had progressed (relapsed) after receiving cisplatin-containing combination chemotherapy.[18] Patients with primary mediastinal nonseminomatous germ cell tumors or

tumors with late relapse (two or more years after previous therapy) were excluded. The patient population included those with initial International Germ Cell Cancer Collaborative Group (IGCCCG) stage defined as low risk (39%), intermediate risk (21%) and high risk (41%), and both platinum-sensitive and refractory disease at the beginning of high-dose chemotherapy. Results from this experienced center showed that of the 184 patients, 116 had complete remission of disease without relapse during a median follow-up of 48 months. Of the 135 patients who received the treatment as second-line therapy (i.e., 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 that was refractory to standard-dose platinum, 18 (45%) were disease-free.

Letters to the editor regarding the Einhorn study noted the lack of a validation set for the prognostic scoring system used in the study, the unanswered question of the role of high-dose versus conventional-dose chemotherapy in the first salvage setting, and the lack of a universally accepted prognostic scoring system in this setting.[19]

In a subsequent study from the same center as the Einhorn study, Suleiman (2013) evaluated the outcomes for 12 patients, excluded from the previous study, with recurrent primary mediastinal nonseminomatous germ-cell tumors after initial treatment with cisplatin-containing combination chemotherapy, who were treated with tandem HCT.[20] Patients received two 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 complete remission (CR; 10, 15, and 50 months' duration). One patient remained free of disease at 50 months of follow up, and one remained free of disease after tandem HCT and subsequent mediastinal surgery at 52 months of follow-up.

Pal (2013) reported five-year follow up results from a retrospective case series of 48 patients with relapsed germ-cell tumors who were enrolled in a study to evaluate the effectiveness of two sequential cycles of HDC (paclitaxel, etoposide, and carboplatin in the first cycle, followed by dose of high-dose paclitaxel, ifosfamide, and carboplatin) followed by HCT.[21] Forty-three patients (91.5%) had nonseminomatous histology. Most patients (n=39) had received two prior chemotherapy regimens; six patients had received three 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 one course of HDC, 11 due to progressive disease, 5 due to toxicities, and 1 due to a severe fungal infection. A total of 17 patients of the 48 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 who were alive after receiving per-protocol therapy, 18 were contacted for interviews at a median 115.6 months (range, 38.9- 185.9 months) post-enrollment 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 (QLQ-C30). The overall average score on the questionnaire was 87.04 (standard deviation=14.64); the authors compared quality-of-life scores in this cohort to a separate cohort of 150 patients with germ-cell tumors who received chemotherapy, and 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=0.0001.) The authors conclude that tandem HDC followed by HCT is a reasonable option for relapsed germ-cell tumors, with long-term survivors demonstrating a reasonable quality of life.

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 described successful treatment of a refractory mediastinal gem cell tumor with allogeneic HCT.[22]

AMERICAN SOCIETY FOR BLOOD AND MARROW TRANSPLANTATION

In 2015, guidelines by the American Society for Blood and Marrow Transplantation were published on indications for autologous and allogeneic HCT. Recommendations were intended to describe the current consensus on use of HCT within and outside of the clinical trial setting.[23] Recommendations on germ cell tumors are listed in Table 1.

Table 1. ASBMT Recommendations on Allogeneic and Autologous HCT

Indications	Allogeneic HCT	Autologous HCT
Pediatric		
Germ cell tumor, relapse	D	C
Germ cell tumor, refractory	D	C
Adult		
Germ cell tumor, relapse	N	C
Germ cell tumor, refractory	N	C

ASBMT: American Society for Blood and Marrow Transplantation; C: clinical evidence available, standard of care; D: developmental (ie promising); HCT: hematopoietic cell transplantation N: not generally recommended.

NATIONAL COMPREHENSIVE CANCER NETWORK (NCCN)

Guidelines from NCCN (1.2023) offer the following on the use of HCT in testicular cancer:[24]

> *All recommendations are category 2A unless otherwise indicated. Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.*

In patients requiring second-line therapy for metastatic germ cell tumors, recommendations include administration of specific-high dose chemotherapy regimens with peripheral blood stem cell support at 14- to 21-day intervals for three cycles.

AUTOLOGOUS HEMATOPOIETIC CELL TRANSPLANTATION

It appears that autologous hematopoietic cell transplantation (HCT) may improve long-term event-free and overall survival rates help when included as a component of salvage treatment for people with germ-cell tumors. Therefore, single autologous hematopoietic cell transplantation may be considered medically necessary as salvage therapy for germ-cell tumors in patients who meet policy criteria.

There is not enough research to know if or how well autologous hematopoietic cell transplantation (HCT) works as a first line therapy to treat people with germ-cell tumors. This does not mean that it does not work, but more research is needed to know. Therefore, use of autologous HCT as first-line therapy is considered investigational.

TANDEM AUTOLOGOUS HEMATOPOIETIC CELL TRANSPLANTATION AND TRANSPLANT WITH SEQUENTIAL HIGH-DOSE CHEMOTHERAPY

It appears that tandem autologous hematopoietic cell transplantation (HCT) or transplant with sequential high-dose chemotherapy may improve overall health outcomes for patients with testicular tumors as a salvage therapy, or for those with platinum-refractory disease. Therefore, tandem autologous HCT or transplant with sequential high-dose chemotherapy may be considered medically necessary when policy criteria are met. Due to a lack of evidence and clinical practice guidelines, use of tandem autologous HCT or transplant with sequential high-dose chemotherapy as a treatment for other germ-cell tumors is considered investigational.

ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION

There is not enough research to know if or how well allogeneic hematopoietic cell transplantation (HCT) works to improve overall health outcomes for people with germ-cell tumors. This does not mean that it does not work, but more research is needed to know. Therefore, use allogeneic HCT as first-line therapy for any germ-cell tumors is considered investigational.

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CODES

Codes	Number	Description
CPT	38204	Management of recipient hematopoietic cell donor search and cell acquisition
	38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection, allogeneic
	38206	;autologous
	38207	Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage
	38208	;thawing of previously frozen harvest, without washing, per donor
	38209	;thawing of previously frozen harvest with washing, per donor
	38210	;specific cell depletion with harvest, T cell depletion
	38211	;tumor cell depletion
	38212	;red blood cell removal
	38213	;platelet depletion
	38214	;plasma (volume) depletion
	38215	;cell concentration in plasma, mononuclear, or buffy coat layer
	38220	Diagnostic bone marrow; aspiration(s)
	38221	Diagnostic bone marrow; biopsy(ies)
	38222	Diagnostic bone marrow; biopsy(ies) and aspiration(s)
	38230	Bone marrow harvesting for transplantation; allogeneic
	38232	Bone marrow harvesting for transplantation; autologous
	38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor
	38241	;autologous transplantation
	38243	;HPC boost
	38242	Allogeneic lymphocyte infusions
HCPCS	S2140	Cord blood harvesting for transplantation; allogeneic
	S2142	Cord blood derived stem-cell transplantation, allogeneic
	S2150	Bone marrow or blood-derived peripheral stem-cell harvesting and transplantation, allogeneic or autologous, including pheresis, high-dose chemotherapy, and the number of days of post-transplant care in the global definition (including drugs; hospitalization; medical surgical, diagnostic and emergency services)