Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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***Current Policy Effective Date: 11/1/24**
(See policy history boxes for previous effective dates)

Title: BMT - Hematopoietic Cell Transplantation for Germ-Cell Tumors

Description/Background

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 (T describes the size of the tumor and any spread of cancer into nearby tissue; N describes spread of cancer to nearby lymph nodes; and M describes metastasis (spread of cancer to other parts of the body). 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).

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 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.

HEMATOPOIETIC CELL TRANSPLANTATION

Hematopoietic cell transplantation (HCT) is a procedure in which hematopoietic stem cells are intravenously infused to restore bone marrow and immune function in cancer patients who receive bone-marrow-toxic doses of cytotoxic 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.

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HCT. In allogeneic stem cell transplantation, immunologic compatibility between donor and patient is a critical factor for achieving a successful outcome. Compatibility is established by typing of human leukocyte antigens(HLA) using cellular, serologic, or molecular techniques. Human leukocyte antigen refers to the gene complex expressed at the HLA-A, -B, and -DR (antigen-D related) loci on each arm of chromosome 6. An acceptable donor will match the patient at all or most of the human leukocyte antigen loci.

Conditioning for Hematopoietic Cell Transplantation

Conventional Conditioning

The conventional (“classical”) practice of allo-HCT involves administration of cytotoxic agents (e.g., cyclophosphamide, busulfan) with or without total body irradiation at doses sufficient to cause bone marrow ablation in the recipient. The beneficial treatment effect of this procedure is due to a combination of the initial eradication of malignant cells and subsequent graft-versus-malignancy effect mediated by non-self-immunologic effector cells. While the slower graft-versus-malignancy effect is considered the potentially curative component, it may be overwhelmed by existing disease in the absence of pretransplant conditioning. Intense conditioning regimens are limited to patients who are sufficiently medically fit to tolerate substantial adverse effects. These include opportunistic infections secondary to loss of endogenous bone marrow function and organ damage or failure caused by cytotoxic drugs. Subsequent to graft infusion in allo-HCT, immunosuppressant drugs are required to minimize graft rejection and graft-versus-host disease, which increases susceptibility to opportunistic infections.

The success of autologous HCT is predicated on the potential of cytotoxic chemotherapy, with or without radiotherapy, to eradicate cancerous cells from the blood and bone marrow. This permits subsequent engraftment and repopulation of the bone marrow with presumably normal hematopoietic stem cells obtained from the patient before undergoing bone marrow ablation.

Therefore, autologous HCT is typically performed as consolidation therapy when the patient's disease is in complete remission. Patients who undergo autologous HCT are also susceptible to chemotherapy-related toxicities and opportunistic infections before engraftment, but not graft-versus-host disease.

Reduced-Intensity Conditioning Allogeneic Hematopoietic Cell Transplantation
Reduced-intensity conditioning (RIC) refers to the pretransplant use of lower doses of cytotoxic drugs or less intense regimens of radiotherapy than are used in traditional full-dose myeloablative conditioning treatments. Although the definition of RIC is variable, with numerous versions employed, all regimens seek to balance the competing effects of relapse due to residual disease and non-relapse mortality. The goal of RIC is to reduce disease burden and to minimize associated treatment-related morbidity and non-relapse mortality in the period during which the beneficial graft-versus-malignancy effect of allogeneic transplantation develops. RIC regimens range from nearly total myeloablative to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and patient condition. Patients who undergo RIC with allo-HCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism. In this review, the term *reduced-intensity conditioning* will refer to all conditioning regimens intended to be nonmyeloablative.

Regulatory Status:

The U.S. Food and Drug Administration 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.

Medical Policy Statement

The safety and effectiveness of hematopoietic cell transplantation in the treatment of germ-cell tumors has been established. It may be considered a useful therapeutic option in specified indications.

Inclusionary and Exclusionary Guidelines

Inclusions:

- *Single autologous* hematopoietic cell transplantation as salvage therapy[a] for germ-cell tumors in the following situations:
  - In individuals with *favorable* prognostic factors that have failed a previous course of conventional-dose salvage chemotherapy; or
  - In individuals with *unfavorable* prognostic factors as initial treatment of first relapse (i.e., without a course of conventional-dose salvage chemotherapy) and in individuals with platinum-refractory disease.
- *Tandem*[b] *autologous* hematopoietic cell transplantation *or sequential high-dose chemotherapy* for the treatment of germ-cell tumors either as salvage therapy[a] or with platinum-refractory disease.

[a] *The term salvage therapy describes therapy given to individuals with refractory or relapsed disease. Salvage therapy includes individuals who do not achieve a complete response, have progressive disease or refractory disease with first-line of chemotherapy or who relapse after achieving a complete response with first-line induction chemotherapy.*

[b] *Tandem transplant refers to a planned second course of high-dose therapy and HCT within 6 months of the first course.*

Exclusions:

- *Autologous* hematopoietic cell transplantation as a component of first-line treatment for germ-cell tumors
- *Allogeneic* hematopoietic cell transplantation to treat germ-cell tumors, including, but not limited to its use as therapy after a prior failed autologous hematopoietic cell transplantation.
- All other indications not listed in the inclusions.

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure)*

Established codes: (autologous only)

38206	38207	38208	38209	38210	38211
38212	38213	38214	38215	38232	38241
38243	S2150				

Other codes (investigational, not medically necessary, etc.): (allogeneic only) ***(Italicized/bolded * codes can be used for both auto and allogeneic transplants. If used for allogeneic transplant they would be considered experimental/investigational.)***

38204	38205	***38207****	***38210****	***38211****	***38212****
38213*	***38214****	***38215****	38230	38240	38242
38243*	81267	81268	81370	81371	81372
81373	81374	81375	81376	81377	81378
81379	81380	81381	81382	81383	86812
86813	86816	86817	86821	S2140	S2142
S2150*					

POTENTIAL CONTRAINDICATIONS FOR TRANSPLANT:

Note: Final patient eligibility for transplant is subject to the judgment and discretion of the requesting transplant center.

The selection process for approved tissue transplants is designed to obtain the best result for each patient. Therefore, relative contraindications to HCT may include, but are not limited to:

- Poor cardiac function: Ejection fraction should be greater than 45% with no overt symptoms of congestive heart failure.
- Poor pulmonary function: Pulmonary function tests must be greater than or equal to 50% of predicted value.

- Poor renal function: Renal creatinine clearance should be greater than 40 ml/min or creatinine must be less than or equal to 2mg/dl.
- Poor liver function: There should be no history of severe chronic liver disease
- Presence of HIV or an active form of hepatitis B, hepatitis C or human T-cell lymphotropic virus (HTLV-1).

Clinical documentation supplied to the health plan must demonstrate that attending staff at the transplant center have considered all contraindications as part of their overall evaluation of potential organ transplant recipient and have decided to proceed.

Rationale

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 1 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.

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

Clinical Context and Therapy Purpose

The purpose of autologous hematopoietic cell transplantation (HCT) transplantation in individuals who have previously untreated germ cell tumors is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICOs were used to select literature to inform this review.

Populations

The relevant population(s) of interest are individuals with previously untreated germ cell tumors.

Interventions

The therapy being considered is autologous HCT.

Comparators

The following practices are currently being used to make decisions about treatment of previously untreated germ cell tumors: standard-dose chemotherapy. 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.

Outcomes

The general outcomes of interest are overall survival, disease-specific survival, change in disease status, treatment-related mortality.

Individuals with previously untreated germ cell tumors have been considered for HCT in the setting of remission after induction therapy. If a transplant were to be performed follow-up would be intensive weekly to monthly surveillance during the first year after transplant and life-long if there is a successful transplant.

Study Selection

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with preference for prospective studies.
- To assess longer term outcomes and adverse effects, single-arm studies that capture longer periods of follow up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Randomized Clinical Trials

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 plus stem cell support in previously untreated males with poor-prognosis germ cell cancer.(1) 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=.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=.06). Overall survival (OS) did not differ between groups (p>.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 III prospective, randomized, multicenter trial of 219 previously untreated patients with poor-prognosis germ cell tumors.(2) 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 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=.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.(3) 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=.099). Median follow-up was 9.7 years, and no significant difference in OS between groups (p=.167).

Section Summary: Autologous Hematopoietic Cell Transplantation as First-Line Therapy for Germ Cell Tumors
For individuals who have previously untreated germ cell tumors who receive autologous HCT as first-line therapy, the evidence includes RCTs. 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 (e.g., standard-dose chemotherapy). Study sample sizes were relatively small and might have been underpowered to detect differences between groups.

AUTOLOGOUS HEMATOPOIETIC CELL TRANSPLANT FOR RELAPSED OR REFRACTORY GERM CELL TUMORS

Clinical Context and Therapy Purpose
The purpose of autologous stem cell transplantation in patients who have relapsed, or refractory germ cell tumors is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does autologous stem cell transplantation used as treatment of relapsed or refractory germ cell tumors improve net health outcomes?

The following PICO was used to select literature to inform this review.

Populations
The relevant population(s) of interest are individuals with relapsed or refractory germ cell tumors.

Interventions
The therapy being considered is autologous HCT.

Comparators
The following practices are currently being used to make decisions about the treatment of previously untreated germ cell tumors: standard-dose chemotherapy. 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.

Outcomes
The general outcomes of interest are overall survival, disease-specific survival, change in disease status, and treatment-related mortality.

If a transplant were to be performed follow-up would be intensive weekly to monthly surveillance during the first year after transplant and life-long if there is a successful transplant.

Study Selection
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with preference for prospective studies.
- To assess longer term outcomes and adverse effects, single-arm studies that capture longer periods of follow up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Randomized Controlled Trials
Pico et al (2005) reported on a randomized trial comparing four 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-line therapy with a cisplatin-based regimen.(4) The authors reported no significant differences between treatment arms in 3-year event-free survival or OS. However, the trial began before international consensus (5) 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 1 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.

Case Series

Zschäbitz et al (2018) reported a retrospective analysis of the experience of 2 referral centers using high dose chemotherapy (HDC) and autologous stem cell transplantation (ASCT) for relapsed or refractory germ cell tumors.(6) Forty-six patients treated with HDC/ASCT between 2000–2016 were identified; 52% of whom were categorized as poor risk by the International Prognostic Factors Study Group (IPFSG) prognosis score. HDC/ASCT was performed as the first salvage regimen in 67% of patients. Further consolidation therapy after HDC/ASCT was performed with 41% of patients undergoing resection of residual tumor. In patients who were in complete remission after HDC/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 months; 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 progression free survival (PFS) and OS inpatients who did not achieve a complete response was 3.3 months (95% CI: 1.0–5.5 months) and 6.4 months (95% CI: 5.6–7.2 months) in those who had no further consolidation treatment.

Adra et al (2017) reported a retrospective analysis of a single institution experience of using high dose chemotherapy and autologous stem cell transplantation (HDC/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 2 consecutive courses of HDC consisting of 700 mg/m^2 carboplatin and 750 mg/m^2 etoposide, each for 3 consecutive days, and each followed by peripheral blood stem cell transplant. At a median follow-up of 3.3 years, patients with pure seminoma had the highest cure rate, with a 2-year PFS of 90% (95% CI, 81% to 95%). Remissions were achieved in poor prognosis patients who received HDC as third-line or subsequent therapy (2-year PFS, 49%) and in patients with platinum-refractory disease (2-year PFS, 33%). Adverse events were notable with 9 treatment related deaths due to infectious complications, hepatic failure and secondary leukemia.

Nieto et al (2015) reported on 43 male patients with poor-risk relapsed or refractory germ cell tumors with received 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.

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.(9) 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 9 of 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%.

Seftel et al (2011) conducted a multicenter study of consecutive patients undergoing a single autologous HCT for germ cell tumor between 1986 and 2004.(10) 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 4 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 event-free survival 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.

Section Summary: Autologous HCT for Relapsed or Refractory Germ Cell Tumors
For individuals who have relapsed or refractory germ cell tumors who receive autologous HCT, the evidence includes an RCT and several case series. The single published RCT did not find improved outcomes with HDC and autologous HCT compared with standard-dose HCT. Case series had a wide range of sample sizes. Progression-free and OS rates varied by prior treatment experience, prognostic factors, number of HDC and autologous stem cell transplantation cycles and whether additional consolidation treatment such as radiation therapy was included. However, 2- and 3-year progression free survival rates of 50 to 60% have consistently been achieved.

TANDEM AUTOLOGOUS HEMATOPOIETIC CELL TRANSPLANT AND SEQUENTIAL HIGH DOSE CHEMOTHERAPY FOR GERM CELL TUMORS

Clinical Context and Therapy Purpose
The purpose of tandem autologous HCT in individuals who have germ cell tumors is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations
The relevant population(s) of interest are individuals with germ cell tumors.

Interventions

The therapy being considered is tandem autologous HCT including the use of sequential HDC.

Comparators
The following practices are currently being used to make decisions about treatment of previously untreated germ cell tumors: standard dose chemotherapy and single autologous HCT.

Outcomes
The general outcomes of interest are overall survival, disease-specific survival, change in disease status, and treatment-related mortality.

If a transplant were to be performed, the follow-up would be intensive weekly to monthly surveillance during the first year after transplant and life-long if there is a successful transplant.

Study Selection
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with preference for prospective studies.
- To assess longer term outcomes and adverse effects, single-arm studies that capture longer periods of follow up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded

Review of Evidence

Randomized Controlled Trials
Lorch et al (2007) compared single HDC with sequential HDC plus autologous HCT as first or subsequent salvage treatment in patients with relapsed or refractory germ cell tumors.(11) Patients were randomized to 2 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 1 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; $p<.01$). The authors attributed the higher rate of treatment-related deaths in arm B 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 study reported 5-year PFS as 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).(12) 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=.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.

Nonrandomized Clinical Trials
Lotz et al (2005) reported on the results of a Phase II study on 3 consecutive cycles of HDC regimens supported by autologous HCT in 45 poor-prognosis patients with relapsed germ-cell tumors.(13) 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% retroperitoneal, hepatic, or unknown. Of all patients, 22 received the complete course. Twenty-five patients died from progression and 5 from toxicity. The overall response rate was 37.7%, including an 8.9% complete response rate. The median OS was 11.8 months. The 3-year survival and PFS rate was 23.5%. Authors used the Beyer prognostic score to predict the outcome of high-dose chemotherapy and concluded that patients with a Beyer score greater than 2 did not benefit from this approach, confirming that highly refractory patients and particularly patients with resistant or refractory primary mediastinal germ-cell tumors do not benefit from HDC.

Tiersten et al (2006) investigated (1) the tolerability of a high-dose chemotherapy (HDC) regimen with autologous hematopoietic stem cell support in individuals with pretreated advanced ovarian cancer, and (2) the maximum-tolerated dose (MTD) of topotecan in this setting. Advanced ovarian cancer individuals previously treated with platinum-based first-line therapy were enrolled. After autologous hematopoietic stem cell mobilization and harvesting, subjects received 3 consecutive cycles of HDC with autologous hematopoietic stem cell support. Cycle 1 was carboplatin area under the concentration curve 20 and paclitaxel 250 mg/m^2. Cycle 2 was topotecan starting at 5 mg/m^2, dose escalated in 2 mg/m^2 increments, and etoposide 600 mg/m^2. Cycle 3 was thiotepa 500 mg/m^2. After each cycle, autologous hematopoietic stem cells were infused. Granulocyte colony stimulating factor (5 microg/kg/day) was administered until neutrophil recovery occurred. Seventeen patients were enrolled; safety was evaluated in all individuals. The most common nonhematologic toxicity was grade 3 mucositis (44%). Engraftment of autologous hematopoietic stem cells was successful in all individuals after each cycle, and no treatment-related deaths occurred. Of 14 patients with measurable disease, 5 (36%) had complete responses, 2 (14%) had partial responses, and 4 (29%) had stable disease. The median progression-free and overall survivals were 7 and 18 months, respectively. The MTD of topotecan was not reached. Authors determined that the tolerability and activity of this regimen in individuals with advanced ovarian cancer warrant further investigation.

Kilari et al (2018) analyzed outcomes and prognostic factors in 2,395 male stem cell transplant (SCT) recipients for relapsed germ cell tumors (primary extragonadal) between 1990 and 2015 in 225 centers. Outcomes were compared by SCT year: 1990-94 (N = 288), 1995-99 (N = 351), 2000-04 (N = 376), 2005-09 (N = 509) and 2010-15 (N = 871). A recent subset (n = 267,

2000-2015) with detailed disease- and transplant-related data was further analyzed with a multivariate (MVA) Cox proportional hazards model. Median age at SCT was 31 (11-76) years and 49% received SCT within 12 months of diagnosis consistent with early relapse/primary refractory germ cell tumor. 26% had primary extragonadal GCT; 1,167 (49%) had intent to tandem transplant. The median follow up was 51 (3-313) months. Day 100 non-relapse mortality was statistically similar at 8% in 1990-94 (vs. 4% in 2010-15) but 3-year progression-free survival (PFS) improved from 24 (18-31)% in 1990-94 to 47 (43-50)% in 2010-15 ($p < 0.0001$) and 3-year survival (OS) from 35 (29-40)% to 54 (50-57)% in 2010-15 ($p < 0.0001$). Compared with single SCT, tandem transplant recipients were younger 31 (16-62) vs 34 (13-76), with lower Hematopoietic Cell Transplantation-Comorbidity Index, more likely to undergo SCT after 1 line of chemotherapy (28% vs 9%), and within 1 year of diagnosis (51% vs 38%). tandem transplant was preferred over single SCT over time (48% of SCT were tandem transplant in 2000-04 vs. 81% in 2010-15). In MVA, non-seminoma histology, residual tumor at SCT, receipt of > 1 line of pre-SCT chemotherapy and single SCT (vs. tandem transplant), were associated with worse PFS and OS. Year of SCT was not significant when adjusted for these covariates. In this large longitudinal cohort, improvements in PFS and OS were observed. SCT earlier in disease course and tandem SCT were associated with superior outcomes.

Observational Studies

Agrawal et al (2021) reported retrospectively on a series of 445 patients, treated between 2004 and 2017, for metastatic germ cell tumors that had progressed (relapsed) after receiving cisplatin-etopside-based combination chemotherapy and tandem HCT.(14) Patients were excluded from the study if they had late relapse germ cell tumors, defined as ≥2 years after previous therapy. Patients received 2 consecutive courses of HDC (carboplatin and etoposide) followed by HCT. The primary outcome was 2-year PFS in patients <40 years old (n=329) and in patients ≥40 years old (n=116). The 2-year PFS in patients <40 years old was 58.7% versus 59.6% in patients ≥40 years old (p=.76). The OS for patients <40 years old was 63.9% versus 61.5% in patients ≥40 years old (p=.93).It was concluded that patient age was not an independent predictor of treatment outcomes.

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.(15) 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=.29).

Einhorn et al (2007) reported retrospectively on a series of 184 patients, treated between 1996 and 2004, with 2 consecutive cycles of high-dose chemotherapy for metastatic testicular cancer that had progressed (relapsed) after receiving cisplatin-containing combination chemotherapy.(16) 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 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. Caveats regarding the Einhorn et al study include 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.

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.(17) 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 1 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.(18) 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) 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 (EORTC QLQ-C30). 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=.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 (AHRQ) 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 to single HCT was insufficient to draw conclusions.(19)

Section Summary: Tandem Autologous HCT and Sequential HDC for Germ Cell Tumors
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. 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 (i.e., first versus subsequent salvage therapy), and have lacked a universally accepted prognostic scoring system to risk-stratify patients. Tandem autologous transplant or transplant with sequential HDC may provide benefit in some individuals with primary mediastinal germ cell tumors.

ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANT FOR GERM CELL TUMORS

Clinical Context and Therapy Purpose
The purpose of allogeneic HCT in individuals who have germ cell tumors is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with germ cell tumors.

Interventions
The therapy being considered is allogeneic HCT.

Comparators
The following practices are currently being used to make decisions about treatment of previously untreated germ cell tumors: standard-dose chemotherapy and autologous HCT.

Outcomes
The general outcomes of interest are OS, DSS, change in disease status, and treatment-related mortality.

If a transplant were to be performed, the follow-up would be intensive weekly to monthly surveillance during the first year after transplant and life-long if there is a successful transplant.

Study Selection
Methodologically credible studies were selected using the following principles:
- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse effects, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

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 gem cell tumor with allogeneic HCT.(20)

Section Summary: Allogeneic HCT for Germ Cell Tumors
For individuals who have germ cell tumors who receive allogeneic HCT, the evidence includes a case report. 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.

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 (e.g., 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 that the technology results in an improvement in the net health outcome.

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 single published RCT did not find improved outcomes with HDC and autologous HCT compared with standard-dose HCT. Case series had a wide range of sample sizes. Progression-free and overall survival rates varied by prior treatment experience, prognostic factors, number of HDC/AUSCT cycles and whether additional consolidation treatment such as radiation therapy was included. However, 2- and 3-year progression-free survival rates of 50% to 60% have consistently been achieved. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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 to risk-stratify patients. Tandem autologous transplant or transplant with sequential HDC may provide benefit in some patients with primary mediastinal germ cell tumors. The evidence is sufficient to determine that the technology may result in an improvement in health outcome.

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 gem cell tumor with allogeneic HCT. The

evidence is insufficient to determine that the technology results in an improvement in health outcome.

Supplemental Information

CLINICAL INPUT FROM PHYSICIAN SPECIALTY SOCIETIES AND ACADEMIC MEDICAL CENTERS

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, Blue Cross Blue Shield Association received input from 3 physician specialty societies, 3 academic medical centers, and 5 Blue Distinction Centers for Transplants while this policy was under review in 2010. There was general agreement with the policy statements regarding the use of single autologous hematopoietic cell transplantation (HCT) as salvage therapy, the use of autologous HCT as first-line treatment, and the use of allogeneic HCT. Seven reviewers felt that tandem or sequential HCT is medically necessary for patients as salvage therapy or with platinum-refractory disease; 2 reviewers felt that tandem or sequential HCT was investigational.

PRACTICE GUIDELINES AND POSITION STATEMENTS

National Comprehensive Cancer Network (NCCN) Guidelines

Current NCCN guidelines on ovarian cancer (v2.2024) state that high-dose chemotherapy with stem cell support is among preferred regimens as potentially curative therapy for recurrent malignant germ cell tumors. (21)

Current National Comprehensive Cancer Network guidelines on testicular cancer (v1.2024) state that second-line chemotherapy regimens for metastatic germ cell tumors include high-dose chemotherapy with stem cell support.(22)

American Society for Transplantation and Cellular Therapy

The guidelines by the American Society for Transplantation and Cellular Therapy (2020) were published on indications for autologous and allogeneic HCT.(23) Recommendations were intended to describe the current consensus on use of HCT within and outside of the clinical trial setting. Recommendations on germ cell tumors are listed in Table 1.

Table 1. 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	S
Germ cell tumor, refractory	N	S

HCT: hematopoietic cell transplantation, C: clinical evidence available, standard of care; D: developmental (i.e., promising); N: not generally recommended, S: standard of care.

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

Not applicable.

ONGOING AND UNPUBLISHED CLINICAL TRIALS

Some currently unpublished trials that might influence this policy are listed in Table 2.

Table 2. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02375204	A Randomized Phase III Trial Comparing Conventional-Dose Chemotherapy Using Paclitaxel, Ifosfamide, and Cisplatin (TIP) with High-Dose Chemotherapy Using Mobilizing Paclitaxel Plus Ifosfamide Followed by High-Dose Carboplatin and Etoposide (TI-CE) as First Salvage Treatment in Relapsed or Refractory Germ Cell Tumors	420	Jun 2024
NCT00936936	High-dose Chemotherapy for Poor-prognosis Relapsed Germ-cell Tumors	64	Mar 2024
Unpublished			
NCT00432094	Autologous Peripheral Blood Stem Cell Transplant for Germ-Cell Tumors	23	Mar 2021

NCT: national clinical trial.

Government Regulations

National:

There are numerous autoimmune diseases and the Centers for Medicare and Medicaid Services have not issued a national coverage determination (NCD) for stem cell transplantation for each disease. CMS has a general NCD for stem cell transplantation.

Medicare National Coverage Determinations Manual 100-3, Chapter 1, Part 2, Section 110.23, "Stem Cell Transplantation." Effective date: 03/06/24; Implementation Date: 10/07/24

A. General

Stem cell transplantation is a process in which stem cells are harvested from either a patient's (autologous) or donor's (allogeneic) bone marrow or peripheral blood for intravenous infusion. Autologous stem cell transplantation (AuSCT) is a technique for restoring stem cells using the patient's own previously stored cells. AuSCT must be used to effect hematopoietic reconstitution following severely myelotoxic doses of chemotherapy (HDC) and/or radiotherapy used to treat various malignancies. Allogeneic hematopoietic stem cell transplantation (HSCT) is a procedure in which a portion of a healthy donor's stem cell or bone marrow is obtained and prepared for intravenous infusion. Allogeneic HSCT may be used to restore function in recipients having an inherited or acquired deficiency or defect. Hematopoietic stem cells are multi-potent stem cells that give rise to all the blood cell types; these stem cells form blood and immune cells. A hematopoietic stem cell is a cell isolated from blood or bone marrow that can renew itself, differentiate to a variety of specialized cells, can mobilize out of the bone marrow into circulating blood, and can undergo programmed cell death, called apoptosis - a process by which cells that are unneeded or detrimental will self-destruct.

The Centers for Medicare & Medicaid Services (CMS) is clarifying that bone marrow and peripheral blood stem cell transplantation is a process which includes mobilization, harvesting, and transplant of bone marrow or peripheral blood stem cells and the administration of high

dose chemotherapy or radiotherapy prior to the actual transplant. When bone marrow or peripheral blood stem cell transplantation is covered, all necessary steps are included in coverage. When bone marrow or peripheral blood stem cell transplantation is non-covered, none of the steps are covered.

Indications and Limitations of Coverage

B. Nationally Covered Indications

I. Allogeneic Hematopoietic STEM CELL Transplantation (HSCT)

- Does not mention germ cell tumors

II. Autologous STEM CELL Transplantation (AuSCT)

- Does not mention germ cell tumors

C. Nationally Non-Covered Indications

I. Allogeneic Hematopoietic STEM CELL Transplantation (HSCT)

- Does not mention germ cell tumors

II. Autologous STEM CELL Transplantation (AuSCT)

Insufficient data exist to establish definite conclusions regarding the efficacy of AuSCT for the following conditions:

- Solid tumors (other than neuroblastoma);

In these cases, AuSCT is not considered reasonable and necessary within the meaning of §l862(a)(1)(A) of the Act and is not covered under Medicare.

D. Other

All other indications for STEM CELL TRANSPLANTATION not otherwise noted above as covered or non-covered remain at local Medicare Administrative Contractor discretion.

(This NCD last reviewed March 2024.)

Local:

There is no local coverage determination specifically addressing hematopoietic cell transplantation for germ-cell tumors.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- BMT – Hematopoietic Cell Transplantation for Acute Lymphoblastic Leukemia
- BMT – Hematopoietic Cell Transplantation for Acute Myeloid Leukemia and Blastic plasmacytoid dendritic cell neoplasm (BPDCN)
- BMT – Hematopoietic Cell Transplantation for Autoimmune Diseases
- BMT – Hematopoietic Cell Transplantation for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma – Autologous and Allogeneic

- BMT – Hematopoietic Cell Transplantation for Chronic Myeloid Leukemia
- BMT – Hematopoietic Cell Transplantation (HCT) for CNS Tumors, Embryonal Tumors and Ependymoma
- BMT – Hematopoietic Cell Transplantation for Epithelial Ovarian Cancer
- BMT – Hematopoietic Cell Transplantation for Genetic Diseases and Acquired Anemias, Allogeneic
- BMT – Hematopoietic Cell Transplantation for Hodgkin Lymphoma
- BMT – Hematopoietic Cell Transplantation for Miscellaneous Solid Tumors in Adults
- BMT – Hematopoietic Cell Transplantation for Myelodysplastic Syndromes and Myeloproliferative Neoplasms, Allogeneic
- BMT – Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas
- BMT – Hematopoietic Cell Transplantation for Plasma Cell Dyscrasias, Including Multiple Myeloma and POEMS Syndrome
- BMT – Hematopoietic Cell Transplantation for Primary Amyloidosis
- BMT – Hematopoietic Cell Transplantation for Solid Tumors of Childhood
- BMT – Hematopoietic Cell Transplantation for Waldenström's Macroglobulinemia
- BMT – Malignant Astrocytomas and Gliomas (Autologous)
- Donor Lymphocyte Infusion for Malignancies Treated with an Allogeneic Hematopoietic Stem-Cell Transplant
- Orthopedic Applications of Stem-Cell Therapy (Including Allografts and Bone Substitutes used with Autologous Bone Marrow)

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through May 29, 2024, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
1/1/13	10/16/12	10/16/12	• Policy formatted to mirror BCBSA • Added “relative contraindications” to inclusionary/exclusionary section.
3/1/14	12/10/13	1/6/14	Routine maintenance. Updated rationale and references
9/1/15	6/19/15	7/16/15	Routine maintenance. Updated rationale and references.
9/1/16	6/21/16	6/21/16	Routine maintenance
9/1/17	6/20/17	6/20/17	Routine maintenance
9/1/18	6/19/18	6/19/18	Routine maintenance
11/1/19	8/20/19		Routine maintenance
11/1/20	8/18/20		Routine maintenance
11/1/21	8/17/21		Routine maintenance
11/1/22	8/16/22		Routine maintenance
11/1/23	8/15/23		• Routine maintenance • Clarified dual-use codes (both autologous and allogeneic) and updated cover sheet and internal coding section of policy to align. o Code 38204 listed as Established on the cover sheet, but listed on the internal coding section of the policy under Investigational. This code was moved from the Est codes section to the Investigational section on the cover sheet. o Codes 38208 and 38209 listed as EST on the cover sheet but listed as E/I on the internal coding section of the policy. These 2 codes added to EST on the internal coding section of the policy. o Code 38243 in the non-covered internal section italicized/bolded* as this code

			applies to both autologous and allogeneic. o Added code and nomenclature for 38242 in the non-covered section on the cover page. This code is in the internal section as non-covered (correctly) as it is allogeneic. o Added code 81383 to the internal section as non-covered as it is on the front covered page as E/I. o Updated cover page of other codes section with (Italicized/bolded* codes can be used for both auto and allogeneic transplants. If used for allogeneic transplant they would be considered experimental/investigational.) Added the italicized/bolded* codes to the cover sheet to be in alignment with internal code section. o Vendor/NA (ky)
11/1/24	8/20/24		• Routine maintenance • Vendor: N/A (ky/slp) • Criteria added for tandem transplant

Next Review Date: 3rd Qtr, 2025

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: BMT - HEMATOPOIETIC CELL TRANSPLANTATION FOR GERM-CELL TUMORS

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered; criteria apply
BCNA (Medicare Advantage)	Refer to the Medicare information under the Government Regulations section of this policy.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage