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Medical Policy Manual

Topic: Hematopoietic Stem-Cell Transplantation in the Treatment of Germ-Cell Tumors

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IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Hematopoietic Stem-Cell Transplantation

Hematopoietic stem-cell transplantation (HSCT) refers to a procedure in which hematopoietic stem cells are infused to restore bone marrow function in cancer patients who receive bone-marrow-toxic doses of cytotoxic drugs with or without whole body radiation therapy. Hematopoietic stem cells may be obtained from the transplant recipient (autologous HSCT) or from a donor (allogeneic HSCT). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates. Although cord blood is an allogeneic source, the stem cells in it are antigenically "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 HSCT. However, immunologic compatibility between donor and patient is a critical factor for achieving a good outcome of allogeneic HSCT. 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 HSCT

The success of autologous HSCT 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 HSCT is typically performed as consolidation therapy when the patient's disease is in complete remission. Patients who undergo autologous HSCT are susceptible to chemotherapy-related toxicities and opportunistic infections prior to engraftment, but usually not GVHD.

The conventional ("classical") practice of allogeneic HSCT 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 HSCT, immune suppressant drugs are required to minimize graft rejection and GVHD, which also increases susceptibility of the patient to opportunistic infections.

Reduced-Intensity Conditioning for Allogeneic HSCT

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 HSCT 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 (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.

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 radiation therapy. 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.

MEDICAL POLICY CRITERIA

I. Autologous hematopoietic stem-cell transplantation (HSCT)

A. Single autologous hematopoietic stem-cell transplantation may be considered **medically necessary** as salvage therapy for germ-cell tumors:

1. In 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.[1,2]

2. In patients with *unfavorable prognostic factors* as initial treatment of first relapse (i.e., without a course of conventional-dose salvage chemotherapy) and in patients with platinum-refractory disease.

   Patients with unfavorable prognostic factors are those with an incomplete response to initial therapy[3] or relapsing mediastinal nonseminomatous germ-cell tumors.[2]

B. Autologous hematopoietic stem-cell transplantation is considered **investigational** as a component of first-line treatment for germ-cell tumors.

II. Allogeneic HSCT

Allogeneic HSCT is considered **investigational** to treat germ-cell tumors, including, but not limited to its use as therapy after a prior failed autologous hematopoietic stem-cell transplantation.

III. Tandem HSCT

A. Tandem (or sequential) *autologous* hematopoietic stem-cell transplantation may be considered **medically necessary** for the treatment of testicular tumors either as salvage therapy or with platinum-refractory disease.

B. Tandem (or sequential) *autologous* hematopoietic stem-cell transplantation is considered **investigational** to treat all other germ-cell tumors of any stage.

SCIENTIFIC EVIDENCE

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 stem cell transplantation (HSCT). Ideally, in order to understand the impact of HSCT 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 Stem-Cell Transplantation (HSCT) as Front-Line Therapy

The evidence on autologous HSCT as a first-line treatment of germ cell tumors consists of randomized, comparative studies.

Randomized Controlled Trials

- Daugaard and colleagues 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.[4] 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. Toxicity was more severe in the patients who received high-dose chemotherapy, and toxic death was reported in 2 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 2 years, failure-free survival was 44.8% (95% confidence interval [CI]: 32.5-56.4) and 58.2% (95% CI: 48.0-71.9), respectively for the standard and high-dose arms. The difference was not statistically significant (p=0.06). Overall survival 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 and colleagues reported on a Phase III prospective, randomized, multicenter trial of 219 previously untreated patients with poor-prognosis germ-cell tumors.[5] The median patient age was 28 years. Patients were randomized to receive either conventional chemotherapy (4 cycles of standard BEP) (n=111), or 2 cycles of BEP followed by 2 cycles of high-dose chemotherapy with autologous HSCT. Median follow-up was 51 months. One-year durable complete response rate was 52% after BEP and high-dose chemotherapy with HSCT, and 48% after BEP alone (p=0.53). There was no survival difference at 106 months for patients treated with high-dose chemotherapy and HSCT compared to the patients treated with conventional chemotherapy (68% and 69%, respectively).

- Droz and colleagues assessed the impact of high-dose chemotherapy with HSCT on the survival of patients with high-volume, previously untreated, metastatic nonseminomatous germ-cell tumors.[6] 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 HSCT (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 overall survival (OS) was observed (p=0.167).

Overall, the evidence indicates no overall survival benefit with HSCT compared to conventional treatment as a fist-line therapy in patients with germ-cell tumors.

Autologous HSCT for Relapsed or Refractory Germ-Cell Tumors

Similar to that reported for autologous HSCT as first-line treatment, evidence on the use of autologous HSCT for salvage treatment in germ cell tumors consists of a randomized controlled trial and several non-randomized case series.

Randomized Controlled Trials

In 2005, Pico and colleagues reported on a randomized trial comparing 4 cycles of conventional-dose chemotherapy to 3 cycles of the same regimen followed by carboplatin-based high-dose chemotherapy plus autologous HSCT in 280 patients who had relapsed after a complete or partial remission following first-line therapy with a cisplatin-based regimen.[7] The authors reported no significant differences between treatment arms in 3-year event-free survival (EFS) and OS. However, the study began before international consensus established the current risk group definitions;[8] 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 3 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.

Non-randomized Trials

- Agarwal and colleagues reported their experience at Stanford in treating 37 consecutive patients who received high-dose chemotherapy and autologous HSCT between 1995 and 2005 for relapsed germ-cell tumors.[9] 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 3 year progression-free survival was 49% (95% CI: 33–64%).

- Seftel and colleagues conducted a multicenter cohort study of consecutive patients undergoing a single autologous HSCT for germ-cell tumor between January 1986 and December 2004.[10] 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 HSCT for relapsed disease after achieving an initial complete response (CR). Of these, 24 patients underwent autologous HSCT 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 HSCT after salvage chemotherapy for active residual disease. Overall survival at 5 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 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 (IGCCC) good prognosis disease at diagnosis, primary gonadal disease, and response to salvage chemotherapy.

Although the evidence on the use of autologous HSCT for salvage treatment in germ cell tumors is limited, the long-term EFS and OS rates are high enough to suggest a benefit to adding HSCT as a component to salvage treatment, in this patient population.

Tandem Autologous HSCT

Apart from a systematic review, evidence on the treatment of germ cell tumors with tandem autologous HSCT consists of case series and other non-randomized studies.

Systematic Review

A comparative effectiveness review conducted for the Agency for Healthcare Research and Quality (AHRQ) on the use of HSCT in the pediatric population concluded that, for germ-cell tumors, the body of evidence on overall survival with tandem HSCT compared with single HSCT for the treatment of relapsed pediatric germ-cell tumors was insufficient to draw conclusions.[11]

Non-randomized Trials

- Lazarus and colleagues reported the results of autologous HSCT in relapsed testicular/germ-cell cancer from registry data from the Center for International Blood and Marrow Transplant Research.[12] Patients with mediastinal primaries were excluded. Data included 300 patients from 76 transplant centers in 8 countries who received either a single transplant or tandem autologous HSCT between 1989 and 2001. Of the 300 patients, 102 received tandem, and 198 single planned autologous HSCT. PFS and OS at 1, 3, and 5 years was similar for both groups. The probability of PFS at 5 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 5-year OS was 35% (95% CI: 25–46%) versus 42% (95% CI: 35–49%), respectively; p=0.29.

- Lorch and colleagues compared single versus sequential high-dose chemotherapy with autologous HSCT as first or subsequent salvage treatment in patients with relapsed or refractory germ-cell tumors.[13] 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 1 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 HSCT 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 HSCT in pretreated patients with germ cell tumors than single HSCT.

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 HSCT and that fewer early deaths related to toxicity translated into superior long-term OS after sequential HSCT.[14]

- Lotz and colleagues reported the results of a Phase II study on 3 consecutive cycles of high-dose chemotherapy regimens supported by autologous HSCT in 45 poor-prognosis patients with relapsed germ-cell tumors.[15] 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 3-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 2 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 and colleagues 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 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 et al. 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.[17]

Available evidence on the use of tandem autologous HSCT is primarily focused on patients with testicular germ-cell cancer and is sufficient, in this particular group, to suggest treatment benefit with transplant. Additional, comparative clinical trials are needed to demonstrate whether tandem autologous HSCT is efficacious in patients with non-testicular germ-cell tumors.

Allogeneic HSCT for Germ-Cell Tumors

There are scant data in the literature to support the use of allogeneic HSCT in the treatment of germ-cell tumors.[18]

Clinical Practice Guidelines

National Comprehensive Cancer Network (NCCN)

The 2013 NCCN guidelines for the treatment of testicular cancer state that if a patient with favorable prognostic factors (defined as "testicular primary site, prior complete response to first line therapy, low levels of post-orchiectomy serum markers and low volume disease"), experiences an incomplete response to conventional-dose salvage chemotherapy therapy or relapses after salvage chemotherapy, high-dose chemotherapy with autologous stem cell support is the preferred option (category 2A).[1] Patients with unfavorable prognostic factors for conventional-dose salvage therapy (e.g. "an incomplete response to first line therapy, high levels of serum markers, high volume disease and presence of extratesticular primary tumor") and patients requiring third-line salvage therapy are considered for treatment with high-dose chemotherapy plus autologous stem cell support (category 2B). The guidelines do not address the use of tandem or sequential HSCT in the treatment of testicular tumors.

Summary

Autologous Hematopoietic Stem-Cell Transplantation (HSCT)

Salvage therapy plays a role in patients with germ-cell tumors who are either refractory to cisplatin or who relapse after initial treatment.[9] The timing for the use of high-dose chemotherapy and HSCT instead of standard salvage chemotherapy is less well defined, with patient heterogeneity playing a role in the overall outcome.[9] Studies have been limited in their attempts to stratify patients into various prognostic groups to identify those who are high-risk, as only 30% of patients with germ-cell tumors require salvage treatment.[9] The use of autologous HSCT as first-line therapy has not been shown to be superior to standard chemotherapy; its use as first-line therapy is therefore considered investigational. However, for patients who fail standard salvage therapy, HSCT remains the treatment of choice, and this indication is considered to be medically necessary.

Allogeneic HSCT

Insufficient evidence has been published to date on the use of allogeneic HSCT in the treatment of germ-cell tumors. Pending publication of high-quality evidence to support the use of this therapy in the treatment of these tumors, use of allogeneic HSCT is considered investigational.

Tandem Autologous HSCT

The role of tandem or sequential autologous transplants has been investigated in several studies, including a comparative effectiveness review from the Agency for Healthcare Research and Quality. Although findings from these publications indicate that tandem or sequential HSCT may have the potential to provide survival benefit in some patients with germ cell tumors, available evidence to date is limited by heterogeneous patient populations, different salvage treatment settings (i.e., first versus subsequent salvage therapy), and the lack of an accepted prognostic tool to risk-stratify patients.

Therefore, at present, the use of tandem or sequential HSCT is considered medically necessary only in the treatment of testicular tumors either as salvage therapy or in patients with platinum-refractory disease. Treatment benefit with tandem autologous HSCT has not been clearly identified in patients with other germ-cell tumors; thus HSCT for these indications is considered investigational.

REFERENCES

1. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Testicular cancer. V.1.2013. [cited 07/30/2013]; Available from: http://www.nccn.org/professionals/physician_gls/pdf/testicular.pdf
2. Bosl, G. Devita, Hellman and Rosenberg's Cancer Principles and Practice of Oncology. 8th (Ed): Lippincott Williams and Wilkins; 2008, chapter 41, pp. 1463-85.
3. Bernstein, IL, Li, JT, Bernstein, DI, et al. Allergy diagnostic testing: an updated practice parameter. *Ann Allergy Asthma Immunol*. 2008 Mar;100(3 Suppl 3):S1-148. PMID: 18431959
4. Daugaard, G, Skoneczna, I, Aass, N, et al. A randomized phase III study comparing standard dose BEP with sequential high-dose cisplatin, etoposide, and ifosfamide (VIP) plus stem-cell support in males with poor-prognosis germ-cell cancer. An intergroup study of EORTC, GTCSG, and Grupo Germinal (EORTC 30974). *Ann Oncol*. 2011 May;22(5):1054-61. PMID: 21059637
5. Motzer, RJ, Nichols, CJ, Margolin, KA, et al. Phase III randomized trial of conventional-dose chemotherapy with or without high-dose chemotherapy and autologous hematopoietic stem-cell rescue as first-line treatment for patients with poor-prognosis metastatic germ cell tumors. *J Clin Oncol*. 2007 Jan 20;25(3):247-56. PMID: 17235042
6. Droz, JP, Kramar, A, Biron, P, et al. Failure of high-dose cyclophosphamide and etoposide combined with double-dose cisplatin and bone marrow support in patients with high-volume metastatic nonseminomatous germ-cell tumours: mature results of a randomised trial. *Eur Urol*. 2007 Mar;51(3):739-46; discussion 47-8. PMID: 17084512
7. Pico, JL, Rosti, G, Kramar, A, et al. A randomised trial of high-dose chemotherapy in the salvage treatment of patients failing first-line platinum chemotherapy for advanced germ cell tumours. *Ann Oncol*. 2005 Jul;16(7):1152-9. PMID: 15928070
8. International Germ Cell Consensus Classification: a prognostic factor-based staging system for metastatic germ cell cancers. International Germ Cell Cancer Collaborative Group. *J Clin Oncol*. 1997 Feb;15(2):594-603. PMID: 9053482
9. Agarwal, R, Dvorak, CC, Stockerl-Goldstein, KE, Johnston, L, Srinivas, S. High-dose chemotherapy followed by stem cell rescue for high-risk germ cell tumors: the Stanford experience. *Bone Marrow Transplant*. 2009 Apr;43(7):547-52. PMID: 18997833
10. Seftel, MD, Paulson, K, Doocey, R, et al. Long-term follow-up of patients undergoing auto-SCT for advanced germ cell tumour: a multicentre cohort study. *Bone Marrow Transplant*. 2011 Jun;46(6):852-7. PMID: 21042312
11. Ratko TA, Belinson SE, Brown HM et al. Hematopoietic stem-cell transplantation in the pediatric population. Comparative Effectiveness Review No 48. (Prepared by the Blue Cross and Blue Shield Association Technology Evaluation Center Evidence-based Practice Center under Contract No. HHSA 290-2007-10058.) AHRQ Publication No. 12-EHC018-EF. Rockville, MD: Agency for Healthcare Research and Quality. February 2012. [cited 08/2012]; Available from: www.effectivehealthcare.ahrq.gov/reports/final.cfm
12. Lazarus, HM, Stiff, PJ, Carreras, J, et al. Utility of single versus tandem autotransplants for advanced testes/germ cell cancer: a center for international blood and marrow transplant research (CIBMTR) analysis. *Biol Blood Marrow Transplant*. 2007 Jul;13(7):778-89. PMID: 17580256

13. Lorch, A, Kollmannsberger, C, Hartmann, JT, et al. Single versus sequential high-dose chemotherapy in patients with relapsed or refractory germ cell tumors: a prospective randomized multicenter trial of the German Testicular Cancer Study Group. *J Clin Oncol*. 2007 Jul 1;25(19):2778-84. PMID: 17602082
14. Lorch, A, Kleinhans, A, Kramar, A, et al. Sequential versus single high-dose chemotherapy in patients with relapsed or refractory germ cell tumors: long-term results of a prospective randomized trial. *J Clin Oncol*. 2012 Mar 10;30(8):800-5. PMID: 22291076
15. Lotz, JP, Bui, B, Gomez, F, et al. Sequential high-dose chemotherapy protocol for relapsed poor prognosis germ cell tumors combining two mobilization and cytoreductive treatments followed by three high-dose chemotherapy regimens supported by autologous stem cell transplantation. Results of the phase II multicentric TAXIF trial. *Ann Oncol*. 2005 Mar;16(3):411-8. PMID: 15659420
16. Einhorn, LH, Williams, SD, Chamness, A, Brames, MJ, Perkins, SM, Abonour, R. High-dose chemotherapy and stem-cell rescue for metastatic germ-cell tumors. *N Engl J Med*. 2007 Jul 26;357(4):340-8. PMID: 17652649
17. Shamash, J, Stebbing, J, Powles, T. Germ-cell tumors. *N Engl J Med*. 2007 Oct 25;357(17):1771-2; author reply 3-4. PMID: 17960020
18. Goodwin, A, Gurney, H, Gottlieb, D. Allogeneic bone marrow transplant for refractory mediastinal germ cell tumour: possible evidence of graft-versus-tumour effect. *Intern Med J*. 2007 Feb;37(2):127-9. PMID: 17229257
19. BlueCross BlueShield Association Medical Policy Reference Manual "High-Dose Chemotherapy and Hematopoietic Stem-Cell Support as a Treatment of Germ-Cell Tumors." Policy No. 8.01.35

CROSS REFERENCES

Donor Lymphocyte Infusion for Malignancies Treated with an Allogeneic Hematopoietic Stem-Cell Transplant, Transplant, Policy No. 45.03

Placental and Umbilical Cord Blood as a Source of Stem Cells, Transplant, Policy No. 45.16

Hematopoietic Stem-Cell Transplantation for Epithelial Ovarian Cancer, Transplant, Policy No. 45.26

Hematopoietic Stem-Cell Transplantation for Miscellaneous Solid Tumors in Adults, Transplant, Policy No. 45.27

Hematopoietic Stem-Cell Transplantation for Solid Tumors of Childhood, Transplant, Policy No. 45.37

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

CODES	NUMBER	DESCRIPTION
		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	Bone marrow; aspiration only
	38221	Bone marrow; biopsy, needle or trocar
	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	J9000–J9999	Chemotherapy drugs code range
	Q0083–Q0085	Chemotherapy administration code range
	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)