Molina Clinical Policy
Hematopoietic Stem Cell Transplantation for Germ Cell Tumors: Policy No. 194

Last Approval: 10/12/2023
Next Review Due By: October 2024

DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. Policies are not a supplementation or recommendation for treatment; Providers are solely responsible for the diagnosis, treatment, and clinical recommendations for the Member. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (e.g., will be paid for by Molina) for a particular Member. The Member's benefit plan determines coverage – each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their Providers will need to consult the Member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a Member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid Members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this MCP and provide the directive for all Medicare members. References included were accurate at the time of policy approval and publication.

OVERVIEW

Germ cell tumors are a type of tumor that begins in the cells that give rise to sperm or eggs. They can occur almost anywhere in the body and can be either benign or malignant. These tumors are composed primarily of testicular neoplasms (seminomas or non-seminomatous 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 non-seminomatous germ-cell tumors. Germ-cell tumors also are divided into good, intermediate, and poor-risk categories based on histology, site, extent of primary tumor, and serum marker levels. There is no poor risk disease in the seminoma category. In non-seminoma, poor prognosis or poor risk disease is indicated by one of the following: mediastinal primary tumor, non-pulmonary visceral metastases, and elevation of any one post-orchiectomy marker (alpha fetal protein [AFP] greater than 10,000 ng/mL, human choriogonadotropin [hCG] greater than 50,000 IU/L, or lactate dehydrogenase [LDH] greater than 10 times the upper limit of normal). (Cutler, 2022; Holmberg & Sandmaier, 2022; Oh, 2022).

Stem-cell transplantation refers to transplantation of hematopoietic stem cells (HSCs) from a donor into a patient. HSCs are immature cells that can develop into any of the three types of blood cells (red cells, white cells or platelets). HSCs are created in the bone marrow and are found in the bone marrow and peripheral blood. There is also a high concentration of HSCs in umbilical-cord blood. Hematopoietic stem-cell transplantation (HSCT) can be either autologous (using the patient's own stem cells) or allogeneic (donor stem cells donor). Allogeneic HSCT is preferable for donors to have a human leukocyte antigen (HLA) type that is identical to the recipient. Matching is performed on the basis of variability at three of more loci of the HLA gene (e.g., HLA-A, HLA-B, HLA-DRB1). As HLA variability increases, transplant-related morbidity and mortality, including graft rejection and graft-versus-host disease, also increase. (Holmberg & Sandmaier, 2022).

COVERAGE POLICY

All transplants require prior authorization from the Corporate Transplant Department. Solid organ transplant requests will be reviewed by the Corporate Senior Medical Director or qualified clinical designee. All other transplants will be reviewed by the Corporate Senior Medical Director or covering Medical Director. If the criteria are met using appropriate NCD and/or LCD guidelines, State regulations, and/or MCP policies the Corporate Senior Medical Director's designee can approve the requested transplant.

Office visits with participating Providers do NOT require prior authorization. Providers should see the Member in office visits as soon as possible and without delay. Failure to see the Member in office visits may be considered a serious quality of care concern.

Transplant Evaluation

Please see *MCP-323 Pre-Transplant Evaluation* for additional criteria and information.

Components of the transplant evaluation include:

1. History and physical examination; **AND**

2. Psychosocial evaluation and clearance:
    a. Absence of any history of medical treatment non-compliance; **AND**
    b. Member understands surgical risk and post-procedure follow-up required; **AND**
    c. Adequate family and social support; **AND**
    d. No behavioral health disorder by history or psychosocial issues:
        i. If history of behavioral health disorder, no severe psychosis or personality disorder may be present; **AND**
        ii. Mood/anxiety disorder must be excluded or treated, unless actively treated and controlled.

AND

3. EKG; **AND**

4. Chest x-ray; **AND**

5. Cardiac clearance in the presence of any of the following:
    a. Chronic smokers; **OR**
    b. Members > 50 years age; **OR**
    c. Those with a clinical or family history of heart disease or diabetes.

AND

6. Pulmonary clearance if evidence of pulmonary artery hypertension or chronic pulmonary disease; **AND**

7. Neurological exam and clearance for transplant including **ONE** of the following:
    a. Normal neurologic exam; **OR**
    b. Non-life limiting neurological impairment that does not preclude transplant and not caused by hematologic malignancy (e.g. diabetic peripheral neuropathy); **OR**
    c. Abnormal neurological exam with positive findings including **ONE** of the following:
        - Lumbar puncture with normal cytology; **OR**
        - Lumbar puncture with cytological exam abnormal, however central nervous system disease treated prior to clearance.

AND

8. A Performance Status that includes **ONE** of the following:
    a. Karnofsky score 70-100%; **OR**
    b. Eastern Cooperative Oncology Group (ECOG) Grade 0-2.

AND

9. Lab studies that include:
    a. Complete blood count; kidney profile (blood urea nitrogen, creatinine); electrolytes; calcium; phosphorous; albumin; liver function tests; and coagulation profile (prothrombin time, and partial thromboplastin time);*
    b. Serologic screening for: Human immunodeficiency virus; Epstein Barr virus (; Hepatitis virus B ; Hepatitis C virus; cytomegalovirus ; rapid plasma reagin and/or fluorescent treponemal antibody:*
        - If HIV positive **ALL** of the following must be met:
            i. CD4 count >200 cells/mm-3 for >6 months; **AND**
            ii. Human immunodeficiency virus 11 ribonucleic acid undetectable; **AND**

iii. On stable anti-retroviral therapy >3 months; **AND**
iv. No other complications from acquired immunodeficiency syndrome (e.g., opportunistic infection, including aspergillus, tuberculosis, coccidioides mycosis, resistant fungal infections, Kaposi's sarcoma, or other neoplasm).

c. Urine drug screen if Member has a history of and /or current drug abuse.

AND

10. Colonoscopy (if indicated or if Member is age ≥ 45) with complete workup and treatment of abnormal results as indicated; an initial screening colonoscopy after initial negative screening requires a follow-up colonoscopy every 10 years).*

AND

11. Gynecological examination with Pap smear for women ages ≥ 21 to ≤ 65 years of age or if indicated (not indicated in women who have had a total abdominal hysterectomy or a total vaginal hysterectomy) within the last three years with complete workup and treatment of abnormal results as indicated.

AND

12. Dental examination or oral exam showing good dentition and oral care or no abnormality on panorex or plan for treatment of problem pre- or post-transplant within the last 12 months;

AND

13. Mammogram (if indicated or > age 40) with complete workup and treatment of abnormal results as indicated;*

OR

14. Prostate specific antigen if history of prostate cancer or previously elevated prostate specific antigen with complete workup and treatment of abnormal results as indicated.*

* Participating Centers of Excellence may waive these criteria.

Criteria for Hematopoietic Autologous Stem Cell Transplantation (HSCT)

(Ratko et al., 2012; [1-2] NMDP, n.d.)

Hematopoietic Autologous Stem Cell Transplantation (HSCT) **may be considered medically necessary** and may be authorized as part of salvage therapy for the treatment of germ cell tumors when the following criteria are met:

1. All pre-transplant criteria are met; **AND**

2. **Single** autologous hematopoietic stem-cell transplantation may be considered medically necessary as a treatment of primary germ cell tumors in individuals treated with standard chemotherapy for **ONE** of the following:
   a. A partial or poor initial response; **OR**
   b. Short remission; **OR**
   c. Refractory germ cell tumors; **OR**
   d. Relapsed disease.

OR

3. **Tandem** (or sequential) autologous hematopoietic stem-cell transplantation may be considered medically necessary for the treatment of primary testicular cancer in individuals treated with standard chemotherapy for **ONE** of the following:
   a. A partial response; **OR**
   b. Refractory germ cell tumors; **OR**
   c. Relapsed disease.

OR

4. **Repeat** autologous hematopoietic stem cell transplantation may be considered medically necessary for the treatment of **ONE** of the following:
   a. Primary graft failure; **OR**
   b. Failure to engraft.

AND

5. The requesting transplant recipient is free from **ALL** of the following absolute contraindications:
   a. Cardiac, pulmonary, and nervous system disease that cannot be corrected and is a prohibitive risk for surgery.
   b. Malignant neoplasm with a high risk for reoccurrence, non-curable malignancy (excluding localized skin cancer).
   c. Systemic and/or uncontrolled infection.
   d. AIDS (CD4 count < 200cells/mm^3).
   e. Unwilling or unable to follow post-transplant regimen as documented by history of non-compliance and/or inability to follow through with medication adherence or office follow-up.
   f. Chronic illness, aside from transplant indication, with one year or less life expectancy.
   g. Limited, irreversible rehabilitation potential.
   h. Active untreated substance abuse or misuse (including daily significant cannabis use) requires documentation of a formal substance use disorder evaluation with clear and unambiguous documentation of:
      a. A reasonable expectation that the Member can adequately comply with a complex, post-transplant plan of care; **AND**
      b. The Member is free from addiction for at least 6 months.
   i. Inadequate social/family support.

AND

6. The requesting transplant recipient should be evaluated carefully and potentially treated if any of the relative contraindications below are present. (Irreversible lung disease patients require consultation and clearance by a Pulmonologist prior to consideration of transplantation).
   a. Smoking, documentation supporting free from smoking for 6 months; **OR**
   b. Active peptic ulcer disease; **OR**
   c. Active gastroesophageal reflux disease; **OR**
   d. Cerebrovascular accident (CVA) with long term impairment that is not amendable to rehabilitation or a patient with CVA/transient ischemic attack within past 6 months; **OR**
   e. Obesity with body mass index of >30 kg/m^2 may increase surgical risk; **OR**
   f. Chronic liver disease such as Hepatitis B/C/D, or cirrhosis which increases the risk of death from sepsis and hepatic failure requires consultation by a gastroenterologist or hepatologist; **OR**
   g. Gall bladder disease requires ultrasound of the gall bladder with treatment prior to transplantation.

Continuation of Therapy

When extension of a previously approved transplant authorization is requested, review using updated clinical information is appropriate.

1. If Molina Healthcare has authorized prior requests for transplantation **ALL** of the following information is required for medical review:
   a. Presence of no absolute contraindication as listed above; **AND**
   b. History and physical within the last 12 months; **AND**
   c. Kidney profile within the last 12 months; **AND**
   d. Cardiac update if history of cardiac disease within two years (≥ 50 years of age); **AND**
   e. Psychosocial evaluation or update within the last 12 months; **AND**

f. Per initial and updated history and physical, any other clinically indicated tests and/or scans as determined by transplant center physician or Molina Medical Director.

2. If authorized prior requests for transplantation were obtained from another insurer, **ALL** of the following information is required for medical review:
   a. Authorization letter/documentation from previous insurer; **AND**
   b. Presence of no absolute contraindication as listed above; **AND**
   c. History and physical within the last 12 months; **AND**
   d. Cardiac update if history of cardiac disease within two years (≥ 50 years of age); **AND**
   e. Psychosocial evaluation or update within the last 12 months; **AND**
   f. Per initial and updated history and physical, any other clinically indicated tests and/or scans as determined by transplant center physician or Molina Medical Director.

Limitations and Exclusions ([1-2] **NC**CN**, 2022**)

1. Autologous stem cell transplantation when the above criteria are not met.
2. A single autologous hematopoietic stem-cell transplantation is considered investigational for first-line treatment of poor prognosis germ-cell tumors.
3. Allogeneic HSCT is considered investigational to treat germ-cell tumors as therapy after a previously failed autologous hematopoietic stem-cell transplantation.
4. A second or repeat autologous hematopoietic transplant due to persistent, progressive or relapsed disease is considered investigational.
5. Tandem (or sequential) autologous hematopoietic stem-cell transplantation is considered investigational to treat all other germ-cell tumors of any stage.
6. Hematopoietic stem cell collection, storage and freezing for a future unplanned transplant is not covered.

DOCUMENTATION REQUIREMENTS. Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational, or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

SUMMARY OF MEDICAL EVIDENCE

First Line Therapy with auHSCT

Randomized trials have been published regarding high dose chemotherapy (HDC) with autologous HSCT as a front-line treatment for patients with poor-risk testicular cancer; however, these trials have not demonstrated improved complete response rates or overall survival (OS) when used as initial therapy compared with standard dose chemotherapy. The standard of care for these individuals is conventional-dose chemotherapy. (Daugaard et al., 2011; Mackall et al., 2009; Droz et al., 2007). Evidence is developing for the use of HDC with autologous stem cell transplant in the pediatric population. An ongoing Phase III trial, TIGER trial (NCT 02375204) aims to compare the overall survival of patients treated with conventional dose chemotherapy or the HDCT plus AuHSCT as initial salvage treatment of children with relapsing or refractory germ cell tumors, Lew et al., (2023).

Single auHSCT

Lazarus et al. (2007) conducted a multicenter cohort study of consecutive patients undergoing a single autologous HSCT for germ-cell tumor between January 1986 and December 2004. 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 (CNS) disease, and 1 presented with retroperitoneal disease. In all, 28 patients underwent autologous HSCT for relapsed disease after achieving an initial 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. OS at 5 years was 44.7% (95% CI: 32% to 56.5%) and EFS, 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 (IGCCC) good prognosis disease at diagnosis, primary gonadal disease, and response to salvage chemotherapy.

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

In summary, improved overall- and disease-free survival rates have been demonstrated in one randomized controlled study and several prospective and retrospective studies. Durable complete remissions may be achieved with salvage therapy including HDC followed by autologous HSCT in a small subset of individuals. (Agawala et al., 2011; Agawala et al., 2009; Lazarus et al., 2007; Lorch et al., 2007; Einhorn et al., 2007).

Tandem auHSCT

Lotz, et al. (2005) 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. 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 indicate that better selection criteria have to be fulfilled in forthcoming studies.

Lorch, et al. compared single- versus sequential HDC with autologous HSCT as first or subsequent salvage treatment in patients with relapsed or refractory germ-cell tumors. 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. 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). Long-term results were reported in 2012 from this study indicated 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). Results showed 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. (Lorch et al., 2012; Lorch et al., 2011; Gilligan et al., 2010).

Lazarus, et al. (2007) 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. 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.

In summary, the role of tandem or sequential autologous transplants in relapsed testicular germ cell tumors has been assessed in one Phase II study, one randomized study, several retrospective series and a comparative effectiveness

review from the Agency for Healthcare Research and Quality. Tandem or sequential HSCT may provide survival benefit, and the randomized study showed lower treatment-related mortality with sequential HSCT compared with single HSCT.

National and Specialty Organizations

The **American Society for Transplantation and Cellular Therapy (ASTCT)** published a policy statement regarding *Generic Immunosuppressants in Hematopoietic Cell Transplantation*. A Task Force of the ASBMT's Executive Committee evaluated the use of generic immunosuppressants in HCT. Issues examined included drug bioequivalence, drug safety, and pharmacoeconomics in HCT. An overview of generic immunosuppressants is offered as well as using these in non-HCT settings. (Cutler et al., 2011).

The **National Marrow Donor Program (NMDP)** has published the following guidance: *Disease-Specific HCT Indications and Outcomes Data; Engraftment; HLA Matching; Patient Eligibility for HCT; Transplant Consultation Timing; and Treatment Before Transplant.* ([1-6] NMDP, n.d.).

The **National Cancer Institute (NCI)** (2022) published PDQs for *Ovarian Germ Cell Tumors* and *Testicular Cancer Treatment.*

The **National Comprehensive Cancer Network (NCCN)** (2023) *Clinical Practice Guidelines in Oncology for Testicular Cancer* indicate that Patients with disease relapse following first-line therapy, or those who do not experience a durable complete response to first-line therapy, should receive second-line therapy. Second line options include enrollment in a clinical trial (preferred) or conventional chemotherapy (TIP or VeIP) or high dose chemotherapy (carboplatin plus etoposide followed by autologous transplant. The *Clinical Practice Guidelines in Oncology for Ovarian Cancer* indicates that high-dose chemotherapy with stem cell support is an acceptable therapy for those with residual or recurrent malignant germ-cell tumors.

CODING & BILLING INFORMATION

CPT (Current Procedural Terminology) Codes

CPT	Description
	Collection Codes
38206	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous
38232	Bone marrow harvesting for transplantation; autologous
	Cell Processing Services
38207	Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage
38208	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing, per donor
38209	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing, per donor
38210	Transplant preparation of hematopoietic progenitor cells; specific cell depletion within harvest, T-cell depletion
38211	Transplant preparation of hematopoietic progenitor cells; tumor cell depletion
38212	Transplant preparation of hematopoietic progenitor cells; red blood cell removal
38213	Transplant preparation of hematopoietic progenitor cells; platelet depletion
38214	Transplant preparation of hematopoietic progenitor cells; plasma (volume) depletion
38215	Transplant preparation of hematopoietic progenitor cells; cell concentration in plasma, mononuclear, or buffy coat layer
	Cell infusion codes
38241	Hematopoietic progenitor cell (HPC); autologous transplantation
38243	Hematopoietic progenitor cell (HPC); HPC boost

HCPCS(Healthcare Common Procedure Coding System) Code

HCPCS	Description

S2150	Bone marrow or blood-derived stem cells (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation, and related complications; including pheresis and cell preparation/storage; marrow ablative therapy; drugs; supplies; hospitalization with outpatient follow-up; medical/surgical, diagnostic, emergency, and rehabilitative services; and the number of days of pre-and post-transplant care in the global definition

CODING DISCLAIMER. Codes listed in this policy are for reference purposes only and may not be all-inclusive. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry standard coding practices for all submissions. When improper billing and coding is not followed, Molina has the right to reject/deny the claim and recover claim payment(s). Due to changing industry practices, Molina reserves the right to revise this policy as needed.

APPROVAL HISTORY

10/12/2023	Policy reviewed, changes to criteria include age for colonoscopy reduced to 45 years, addition of non-life limiting neurological impairment criteria and substance use to absolute contraindications, and removal of abnormal serology criteria and cannabis use section. Updated Overview, Summary of Medical Evidence, and References. IRO Peer Review on September 25, 2023, by a practicing, board-certified physician with specialties in Pediatrics and Pediatric Hematology/Oncology.
10/12/2022	Policy reviewed, no changes to criteria, included section on marijuana use.
10/13/2021	Policy reviewed, no changes to criteria, updated references.
9/16/2020	Policy reviewed, no changes.
9/18/2019	Policy reviewed, no changes.
9/13/2018	Policy reviewed, no changes.
12/13/2017	Removed favorable and unfavorable prognostic factors for single auto transplant. Tandem transplant criteria updated; repeat transplant criteria added and professional guidelines and references updated.
9/15/2016	Policy reviewed, no changes.
6/2/2015	Updated pre-transplant criteria, continuation of therapy, absolute and relative contraindications and coding sections.
9/17/2014	New policy.

REFERENCES

1. Adra N, Abonour R, Althouse SK, et al. High-dose chemotherapy and autologous peripheral-blood stem-cell transplantation for relapsed metastatic germ cell tumors: the Indiana University experience. J Clin Oncol. 2017 Apr 1;35(10):1096-1102. doi: 10.1200/JCO.2016.69.5395.
2. Agarwal R, Dvorak CC, Stockerl-Goldstein KE, et al. 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. doi: 10.1038/bmt.2008.364.
3. Agawala AK, Perkins SM, Abonour R, et al. Salvage chemotherapy with high-dose carboplatin and etoposide with peripheral blood stem cell transplant in patients with relapsed pure seminoma. Am J Clin Oncol. 2011 Jun;34(3):286-8. doi: 10.1097/COC.0b013e3181d6b518.
4. Centers for Medicare and Medicaid Services (CMS). Medicare coverage database. National coverage determination (NCD) – Stem cell transplantation 110.23. Effective Date January 27, 2016. Accessed September 13, 2023. https://www.cms.gov/medicare-coverage-database/search.aspx.
5. Cutler C, Kesselheim A, Gabardi S, et al. Generic immunosuppressants in hematopoietic cell transplantation. Biol Blood Marrow Transplant. 2011 Mar;17(3):285-90. doi: 10.1016/j.bbmt.2010.11.006. Epub 2010 Nov 16. PMID: 21087678.
6. Cutler C. Long-term care of the adult hematopoietic cell transplantation survivor. Updated January 14, 2022. Accessed September 15, 2023. www.uptodate.com.
7. 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):1054-1061. doi: 10.1093/annonc/mdq575.
8. 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 randomized trial. Eur Urol. 2007 Mar;51(3):739-46; discussion 747-8. doi: 10.1016/j.eururo.2006.10.035.
9. Eastern Cooperative Oncology Group (ECOG) Performance Status. Accessed September 15, 2023. https://ecog-acrin.org/resources/ecog-performance-status/.
10. Einhorn HL, Williams SD, Chamness A, et al. High-dose chemotherapy and stem-cell rescue for metastatic germ-cell tumors. N Engl J Med. 2007 Jul 26;357(4):340-8. doi: 10.1056/NEJMoa067749.
11. Gilligan TD, Seidenfeld J, Basch EM, et al. American Society of Clinical Oncology clinical practice guideline on uses of serum tumor markers in adult males with germ cell tumors. J Clin Oncol. 2010 Jul 10;28(20):3388-404. doi: 10.1200/JCO.2009.26.4481.
12. Gilligan, T., Richie, J. Initial risk-stratified treatment for advanced testicular germ cell tumors. Updated June 13, 2023. Accessed September 17, 2023. www.uptodate.com.
13. Holmberg HJ, Sandmaier BM. Determining eligibility for autologous/allogenic hematopoietic cell transplantation. Updated February 21, 2022. Accessed September 13, 2023. www.uptodate.com.
14. 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. doi:

10.1016/j.bbmt.2007.02.013.
15. Lew CZ, Liu HC, Hou JY, Huang TH, Yeh TC. Pediatric Extracranial Germ Cell Tumors: Review of Clinics and Perspectives in Application of Autologous Stem Cell Transplantation. Cancers (Basel). 2023 Mar 27;15(7):1998. doi: 10.3390/cancers15071998. PMID: 37046659; PMCID: PMC10093083.
16. Lorch A, Bascoul-Mollevi C, Kramar A, et al. Conventional-dose versus high-dose chemotherapy as first salvage treatment in male patients with metastatic germ cell tumors: Evidence from a large international database. J Clin Oncol. 2011 Jun 1;29(16):2178-84. doi: 10.1200/JCO.2010.32.6678.
17. 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. doi: 10.1200/JCO.2011.38.6391.
18. 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. doi: 10.1200/JCO.2006.09.2148.
19. 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. UROGENITAL TUMORS| VOLUME 16, ISSUE 3, P411-418, MARCH 01, 2005. https://doi.org/10.1093/annonc/mdi087.
20. Mackall C, Fry T, Gress R, et al. Background to hematopoietic cell transplantation, including post-transplant immune recovery. Bone Marrow Transplant. 2009 Oct;44(8):457-62. doi: 10.1038/bmt.2009.255.
21. [1]National Cancer Institute (NCI). Ovarian germ cell tumors treatment (PDQ). Updated July 8, 2022. Accessed September 18, 2023. http://www.cancer.gov/cancertopics/pdq/treatment/ovarian-germ-cell/HealthProfessional.
22. [1]National Comprehensive Cancer Network (NCCN). Clinical practice guidelines in oncology: Ovarian Cancer (including fallopian tube cancer and primary peritoneal cancer (ver. 3.2022). Updated July 25, 2022. Accessed August 17, 2022. https://www.nccn.org/guidelines/category_1.
23. [1]National Marrow Donor Program (NMDP). Disease-specific HCT indications and outcomes data. Accessed September 2, 2023. https://bethematchclinical.org/transplant-indications-and-outcomes/disease-specific-indications-and-outcomes/.
24. [2]National Cancer Institute (NCI). Testicular cancer treatment (PDQ). Updated March 9, 2023. Accessed September 19, 2023. https://www.cancer.gov/types/testicular/hp/testicular-treatment-pdq.
25. [2]National Comprehensive Cancer Network (NCCN). Clinical practice guidelines in oncology: Testicular cancer (ver. 1.2023). Accessed September 9, 2023. https://www.nccn.org/guidelines/category_1.
26. [2]National Marrow Donor Program (NMDP). Engraftment. Accessed September 12, 2023. https://bethematch.org/patients-and-families/life-after-transplant/physical-health-and-recovery/engraftment/.
27. [3]National Marrow Donor Program (NMDP). HLA matching. Accessed September 12, 2023. https://bethematch.org/patients-and-families/before-transplant/find-a-donor/hla-matching/.
28. [4]National Marrow Donor Program (NMDP). Patient eligibility for HCT. Accessed September 2, 2023. https://bethematchclinical.org/transplant-indications-and-outcomes/eligibility/.
29. [5]National Marrow Donor Program (NMDP). Transplant consultation timing. Accessed September 2, 2023. https://bethematchclinical.org/transplant-indications-and-outcomes/referral-timing-guidelines/.
30. [6]National Marrow Donor Program (NMDP). Treatment before transplant. Accessed September 2, 2023. https://bethematch.org/patients-and-families/before-transplant/treatment-before-transplant/.
31. Ratko TA, Belinson SE, Brown HM, et al. Hematopoietic Stem-Cell Transplantation in the Pediatric Population [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2012 Feb. Report No.: 12-EHC018-EF. PMID: 22439159.