Hematopoietic Cell Transplantation in the Treatment of Germ-Cell Tumors

Policy # 00056
Original Effective Date: 01/28/2002
Current Effective Date: 05/11/2020

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

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

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

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

Patient Selection Criteria

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

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

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

When Services Are Considered Investigational

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

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

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

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

Policy Guidelines

The favorable and unfavorable prognostic factors listed below are derived from the current National Comprehensive Cancer Network guidelines and DeVita et al's textbook *Cancer: Principles and Practice of Oncology* (2015, pp. 988-1004).

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

Background/Overview

Germ Cell Tumors

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

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

immature teratomas, embryonal cell tumors, yolk sac tumor, polyembryoma, and mixed germ cell tumors.

Staging
Stage depends on location and extent of the tumor, using the American Joint Committee on Cancer's TNM system. TNM stages, modified by serum concentrations of markers for tumor burden (S0-3) when available, are grouped by similar prognoses. Markers used for germ cell tumors include human β-chorionic gonadotropin, lactate dehydrogenase, and α-fetoprotein. However, most patients with pure seminoma have normal α-fetoprotein concentrations. For testicular tumors, stages IA to B tumors are limited to the testis (no involved nodes or distant metastases) and no marker elevations (S0); stages IIA to C have increasing size and number of tumor-involved lymph nodes, and at least one 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, extent of the primary tumor, and serum marker levels. Good-risk pure seminomas can be at any primary site but are without nonpulmonary visceral metastases or marker elevations. Intermediate-risk pure seminomas have nonpulmonary visceral metastases with or without elevated human chorionic gonadotropin and/or lactate dehydrogenase. There are no poor-risk pure seminomas, but mixed histology tumors and seminomas with elevated α-fetoprotein (due to the 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
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 a donor (allogeneic HCT [allo-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. HLA 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 HLA 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
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.

FDA or Other Governmental Regulatory Approval

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

Rationale/Source

Therapy for germ cell tumors is generally dictated by several factors, including disease stage, tumor histology, site of tumor primary, and response to chemotherapy. Patients with unfavorable prognostic factors may be candidates for hematopoietic cell transplantation (HCT).

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

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For individuals who have relapsed or refractory germ cell tumors who receive autologous HCT, the evidence includes an RCT and several case series. The relevant outcomes are OS, DSS, and TRM and morbidity. The single published RCT did not find improved outcomes with high-dose chemotherapy (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 high-dose chemotherapy 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 50-60% have consistently been achieved. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have germ cell tumors who receive tandem autologous transplantation and sequential HDC, the evidence includes an RCT, several retrospective cohort studies, and a comparative effectiveness review. The relevant outcomes are OS, DSS, and TRM and morbidity. The RCT reported a higher rate of TRM with sequential HDC compared with single HDC. However, 5five-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 has not shown a benefit in patients with primary mediastinal germ cell tumors. The evidence is insufficient to determine the effects of the technology on health outcomes. However, clinical input supported the use of this approach to salvage treatment.

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

Clinical input obtained in 2010 found strong support for autologous HCT as a treatment of relapsed or refractory germ cell tumors, and for tandem autologous transplant or transplant with sequential HDC as salvage therapy for testicular tumors and as treatment of platinum-refractory testicular tumors. Input was generally consistent with recommendations in national and international guidelines. Thus, these indications may be considered medically necessary.

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, input was received 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 autologous transplant or transplant with sequential HCT is medically necessary for patients as salvage therapy or with platinum-refractory disease; 2 reviewers felt that tandem transplant or sequential high-dose chemotherapy was investigational.

Practice Guidelines and Position Statements

National Comprehensive Cancer Network

Current National Comprehensive Cancer Network guidelines on testicular cancer (v.2.2020) state that second-line chemotherapy regimens for metastatic germ cell tumors include high-dose chemotherapy with stem cell support.

American Society for Blood and Marrow Transplantation

The guidelines by the American Society for Blood and Marrow Transplantation (2015) were published on indications for autologous and allogeneic HCT. Recommendations were intended to describe the current consensus on the 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	C
Germ cell tumor, refractory	N	C

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

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

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			
NCT00432094	Autologous Peripheral Blood Stem Cell Transplant for Germ-Cell Tumors	25	Jan 2020
NCT00936936	High-dose Chemotherapy for Poor-prognosis Relapsed Germ-cell Tumors	68	Nov 2019
NCT02375204	Standard Dose Chemotherapy or High-Dose Chemotherapy and Stem Cell Transplant in Treating Patients with Relapsed or Refractory Germ Cell Tumors	420	Jun 2024

NCT: national clinical trial.

References

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Policy History

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

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10/17/2007	Medical Policy Committee approval. No change to coverage eligibility.
10/01/2008	Medical Director review
10/22/2008	Medical Policy Committee approval. No change to coverage eligibility.
10/01/2009	Medical Policy Committee approval
10/14/2009	Medical Policy Implementation Committee approval. Title changed from "High-Dose Chemotherapy with Stem Cell Support for Germ Cell Tumors" to "Hematopoietic Stem Cell Transplantation in the Treatment of Germ Cell Tumors". No change to coverage eligibility.
10/14/2010	Medical Policy Committee review
10/20/2010	Medical Policy Implementation Committee approval. Terminology changed in coverage statements. Coverage statements changed to indicate that tandem-sequential autologous stem-cell transplantation may be considered eligible for coverage in certain types of testicular cancers.
10/06/2011	Medical Policy Committee review
10/19/2011	Medical Policy Implementation Committee approval. "Based on review of available data, except as noted above for treatment of certain testicular tumors, the Company considers tandem or sequential autologous hematopoietic stem-cell transplantation to treat germ-cell tumors of any stage to be investigational" was deleted from coverage.
10/11/2012	Medical Policy Committee review
10/31/2012	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
03/04/2013	Coding updated
10/03/2013	Medical Policy Committee review
10/16/2013	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
11/06/2014	Medical Policy Committee review
11/21/2014	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
10/29/2015	Medical Policy Committee review
11/16/2015	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

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11/03/2016	Medical Policy Committee review
11/16/2016	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017	Coding update: Removing ICD-10 Diagnosis Codes
11/02/2017	Medical Policy Committee review
11/15/2017	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
11/08/2018	Medical Policy Committee review
11/21/2018	Medical Policy Implementation Committee approval. One policy statement was reworded, from "Tandem or sequential autologous HCT may be considered eligible for coverage for the treatment of testicular tumors either as salvage therapy or with platinum-refractory disease" to "Tandem autologous HCT or transplant with sequential high-dose chemotherapy may be considered eligible for coverage for the treatment of testicular tumors either as salvage therapy or with platinum-refractory disease."
11/07/2019	Medical Policy Committee review
11/13/2019	Medical Policy Implementation Committee approval. No change to coverage.
04/02/2020	Medical Policy Committee review
04/08/2020	Medical Policy Implementation Committee approval. No change to coverage.

Next Scheduled Review Date: 04/2021

Coding

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

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

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

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

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1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.

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

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

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

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NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

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