Hematopoietic Cell Transplantation for Central Nervous System Embryonal Tumors and Ependymoma

Policy # 00063
Original Effective Date: 01/28/2002
Current Effective Date: 07/08/2024

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 Are 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.*

Autologous Hematopoietic Cell Transplantation

Based on review of available data, the Company may consider autologous hematopoietic cell transplantation (HCT) as consolidation therapy for previously untreated embryonal tumors of the central nervous system (CNS) that show partial or complete response (PR or CR) to induction chemotherapy, or stable disease after induction therapy to be **eligible for coverage**** (See *Note* below).

Based on review of available data, the Company may consider autologous hematopoietic cell transplantation (HCT) to treat recurrent embryonal tumors of the central nervous system (CNS) to be **eligible for coverage.****

Note: In general, use of autologous HCT for previously untreated medulloblastoma has shown no survival benefit for those individuals considered to be at average risk (i.e., patient age older than three years, without metastatic disease, and with total or near total surgical resection [< 1.5 cm^2 residual tumor]) when compared to conventional therapies.

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When Services Are Considered Investigational

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

Autologous Hematopoietic Cell Transplantation

Based on review of available data, the Company considers tandem autologous hematopoietic cell transplantation (HCT) to treat embryonal tumors of the central nervous system (CNS) to be **investigational.***

Allogeneic Hematopoietic Cell Transplantation

Based on review of available data, the Company considers allogeneic hematopoietic cell transplantation (HCT) to treat embryonal tumors of the central nervous system (CNS) to be **investigational.***

Ependymoma

Based on review of available data, the Company considers autologous, tandem autologous and allogeneic hematopoietic cell transplantation (HCT) to treat ependymoma to be **investigational.***

Background/Overview

Central Nervous System Embryonal Tumors

Classification of brain tumors is based on both histopathologic characteristics of the tumor and location in the brain. Central nervous system (CNS) embryonal tumors are more common in children and are the most common brain tumor in childhood. Medulloblastomas account for 20% of all childhood CNS tumors.

Recurrent childhood CNS embryonal tumors is not uncommon and, depending on which type of treatment the patient initially received, autologous hematopoietic cell transplantation (HCT) may be an option. For patients who receive high-dose chemotherapy and autologous HCT for recurrent embryonal tumors, the objective response is 50% to 75%; however, long-term disease control is obtained in fewer than 30% of patients and is primarily seen in patients with a first relapse of localized disease at the time of the relapse.

Ependymoma
Ependymoma is a neuroepithelial tumor that arises from the ependymal lining cell of the ventricles and is, therefore, usually contiguous with the ventricular system. An ependymoma tumor typically arises intracranially in children, while in adults a spinal cord location is more common. Ependymomas have access to the cerebrospinal fluid and may spread throughout the entire neuroaxis. Ependymomas are distinct from ependymoblastomas due to their more mature histologic differentiation.

Hematopoietic Cell Transplantation
Hematopoietic cell transplantation 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]). These cells 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 (GVHD), 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 GVHD.

Reduced-Intensity Conditioning Allogeneic Hematopoietic Cell Transplantation
Reduced-intensity conditioning (RIC) refers to the pretransplant use of lower doses of cytotoxic drugs or less intense regimens of radiotherapy than are used in traditional full-dose myeloablative conditioning treatments. Although the definition of reduced-intensity conditioning 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. Reduced-intensity conditioning 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.

Autologous HCT allows for the escalation of chemotherapy doses above those limited by myeloablation and has been tried in patients with high-risk brain tumors in an attempt to eradicate residual tumor cells and improve cure rates. The use of allo-HCT for solid tumors does not rely on

the escalation of chemotherapy intensity and tumor reduction but rather on a graft-versus-tumor effect. Allo-HCT is not commonly used in solid tumors and may be used if an autologous source cannot be cleared of a tumor or cannot be harvested.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

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

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

High-dose chemotherapy with hematopoietic cell transplantation (HCT) has been investigated as a possible therapy in pediatric patients with brain tumors, particularly in those with high-risk disease. The use of HCT has allowed for a reduction in the dose of radiation needed to treat both average- and high-risk disease with a goal of preserving the quality of life and intellectual functioning.

Summary of Evidence

For individuals who have newly diagnosed central nervous system (CNS) embryonal tumors who receive autologous hematopoietic cell transplantation (HCT), the evidence includes prospective and retrospective studies. Relevant outcomes are overall survival (OS), disease-specific survival (DSS), and treatment-related mortality and morbidity. For pediatric CNS embryonal tumors, an important consideration is whether the use of HCT may allow for a reduction in radiation dose. Data from single-arm studies using high-dose chemotherapy with autologous HCT to treat newly diagnosed CNS embryonal tumors have shown comparable or improved survival (both EFS and OS) compared with historical controls treated with conventional therapy, with or without radiotherapy, particularly

in patients with a disease considered high-risk. In a retrospective comparative study, survival in patients receiving high-dose chemotherapy with HCT and delayed craniospinal irradiation (CSI) was comparable with survival in those receiving upfront CSI. Overall, data from these observational studies have suggested HCT may allow reduced doses of CSI without worsening survival outcomes. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have recurrent or relapsed CNS embryonal tumors who receive autologous HCT, the evidence includes prospective and retrospective single-arm studies and a systematic review of these studies. Relevant outcomes are OS, DSS, and treatment-related mortality and morbidity. For recurrent/relapsed CNS embryonal tumors, survival outcomes after HCT vary, and survival is generally very poor for tumors other than medulloblastoma. Data from some single-arm studies using autologous HCT to treat recurrent CNS embryonal tumors have shown comparable or improved survival compared with historical controls treated with conventional therapy for certain patients. The results of a 2012 systematic review of observational studies in patients with relapsed supratentorial PNET suggested that a subgroup of infants with the chemosensitive disease might benefit from autologous HCT, achieving survival without the use of radiotherapy, whereas outcomes in older children and/or in the pineal location are poor with this modality. However, a relatively large prospective multicenter study has reported that HCT was not associated with improved survival outcomes in patients who had a good response to therapy. Overall, data from these single-arm studies have suggested HCT may be associated with improved survival outcomes in select patients, although data for some tumor types are limited (eg, atypical teratoid/rhabdoid tumors). The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have CNS embryonal tumors who receive tandem autologous HCT, the evidence includes prospective and retrospective single-arm studies. Relevant outcomes are OS, DSS, and treatment-related mortality and morbidity. Less evidence specifically addresses the use of tandem autologous HCT for CNS embryonal tumors. The available single-arm studies are very small but appear to report OS and EFS rates comparable with single autologous HCT. Tandem transplants might allow reduced doses of craniospinal irradiation, with the goal of avoiding long-term radiation damage. However, most studies used standard-dose irradiation, making the relative benefit of tandem autologous HCT uncertain. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have CNS embryonal tumors who receive allogeneic HCT, the evidence includes case reports. Relevant outcomes are OS, DSS, and treatment-related mortality and morbidity. The available evidence is limited. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have ependymoma who receive autologous HCT, the evidence includes relatively small case series. Relevant outcomes are OS, DSS, and treatment-related mortality and morbidity. The available case series do not report higher survival rates for patients with ependymoma treated with HCT compared with standard therapies. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Supplemental Information

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

National Comprehensive Cancer Network

Current National Comprehensive Cancer Network (NCCN; v.2.2022) guidelines on treating central nervous system tumors make the following recommendations about hematopoietic cell transplant (HCT):

- For medulloblastoma and supratentorial primitive neuroectodermal tumor, high-dose chemotherapy with autologous HCT for localized recurrent disease with maximum safe resection is a category 2A recommendation (based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate).

American Society for Blood and Marrow Transplantation

In 2015, the American Society for Blood and Marrow Transplantation (now referred to as the American Society for Transplantation and Cellular Therapy) published consensus guidelines on the use of HCT to treat specific conditions, in both clinical trial and clinical practice settings. These

guidelines were updated in 2020. Neither the 2015 nor the 2020 guidelines address HCT in treatment of ependymomas. The tumors addressed in this review for which the Society has provided recommendations are listed in Table 1.

Table 1. Recommendations for Use of Autologous and Allogeneic Hematopoietic Cell Transplantation in Pediatric patients (<18 years)

Condition	Treatment Option	2015 Recommendation	2020 Recommendation
Neuroblastoma, high-risk or relapse	Allogeneic HCT	Developmental	Developmental
	Autologous HCT	Standard of care	Standard of care; tandem autologous HCT recommended over single transplant
Medulloblastoma, high-risk	Allogeneic HCT	Not generally recommended	Not generally recommended
	Autologous HCT	Standard of care, clinical evidence available	Standard of care, clinical evidence available
Other malignant brain tumors	Allogeneic HCT	Not generally recommended	Not generally recommended
	Autologous HCT	Standard of care, clinical evidence available	Standard of care, clinical evidence available

HCT: hematopoietic cell transplantation

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

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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 ongoing or unpublished trials that might influence this review are listed in Table 2.

Table 2. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT00336024	A Phase III Randomized Trial for the Treatment of Newly Diagnosed Supratentorial PNET and High-Risk Medulloblastoma in Children < 36 Months Old With Intensive Induction Chemotherapy With Methotrexate Followed by Consolidation With Stem Cell Rescue Versus the Same Therapy Without Methotrexate	91	Dec 2016 (active, not recruiting)

NCT: national clinical trial.

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12/06/2001	Medical Policy Committee review
01/28/2002	Managed Care Advisory Council approval
05/07/2004	Medical Director review
05/18/2004	Medical Policy Committee review. Format revision. High-Dose Chemotherapy with Hematopoietic Stem-cell Support for Primitive Neuroectodermal policy developed separately from current HDC with Hematopoietic Stem-cell Support policy. No substance change to policy.
06/28/2004	Managed Care Advisory Council approval
05/03/2005	Medical Director review
05/17/2005	Medical Policy Committee review. Patient Selection criteria added to policy.
05/23/2005	Managed Care Advisory Council approval
08/03/2005	Medical Director review
08/16/2005	Medical Policy Committee review. Coverage eligibility changes: autologous BMT to consolidate a remission after initial therapy in high-risk patients with PNETs, excluding medulloblastoma and ependymoma is considered to be eligible for coverage.
08/24/2005	Managed Care Advisory Council approval
07/12/2006	Medical Director review
07/19/2006	Medical Policy Committee review. Format changes. FDA information added. Additional rationale/source was added.
07/10/2007	Medical Director review
07/18/2007	Medical Policy Committee approval. Statement added to deny investigational when patient selection criteria is not met.
11/07/2007	Medical Director review
11/15/2007	Medical Policy Committee approval. Coverage eligibility unchanged. Investigational policy statement added for tandem transplants.
11/05/2008	Medical Director review
11/18/2008	Medical Policy Committee approval. Coverage eligibility unchanged
11/12/2009	Medical Policy Committee approval

11/18/2009	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
11/04/2010	Medical Policy Committee review
11/16/2010	Medical Policy Implementation Committee approval. Policy title changed to remove "high-dose chemotherapy" and to change PNET to embryonal tumors. Policy statements reworded and separated to address ependymoma and embroyonal CNS tumors specifically; however the intent of the policy remains the same.
11/03/2011	Medical Policy Committee approval
11/16/2011	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
11/01/2012	Medical Policy Committee review
11/28/2012	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
03/04/2013	Coding update
01/09/2014	Medical Policy Committee review
01/15/2014	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/08/2015	Medical Policy Committee review
01/21/2015	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
04/07/2016	Medical Policy Committee review
04/20/2016	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
04/07/2017	Medical Policy Committee review
04/19/2017	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/07/2018	Medical Policy Committee review
06/20/2018	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/06/2019	Medical Policy Committee review

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06/19/2019	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/04/2020	Medical Policy Committee review
06/10/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/03/2021	Medical Policy Committee review
06/09/2021	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/02/2022	Medical Policy Committee review
06/08/2022	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/01/2023	Medical Policy Committee review
06/14/2023	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/06/2024	Medical Policy Committee review
06/12/2024	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 06/2025

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, 38232, 38240, 38241, 38242, 38243
HCPCS	S2140, S2142, S2150
ICD-10 Diagnosis	All related Diagnoses

*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:
    1. Consultation with 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.

‡ Indicated trademarks are the registered trademarks of their respective owners.

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.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

Hematopoietic Cell Transplantation for Central Nervous System Embryonal Tumors and Ependymoma

Policy # 00063
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Current Effective Date: 07/08/2024

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.