

Autologous Hematopoietic Cell Transplantation for Malignant Astrocytomas and Gliomas

Policy # 00058

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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.

Investigational or experimental services are not covered. This includes any drug, device, procedure, or service provided under the investigational arm of a clinical trial or clinical study. These services are excluded from coverage under benefits.

Services Are Considered Investigational

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

Based on review of available data, the Company considers autologous hematopoietic cell transplantation (HCT) as a treatment of malignant astrocytomas and gliomas to be **investigational**.* (The latter diagnosis includes both glioblastoma multiforme and oligodendroglioma.)

Background/Overview

Malignant glial tumors are usually resistant to conventional treatment approaches. Autologous HCT has been investigated as a treatment for malignant astrocytomas and gliomas.

Hematopoietic Cell Transplantation

HCT refers to a procedure in which hematopoietic 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. Bone marrow cells may be obtained from the transplant recipient (autologous HCT) and can be harvested from bone marrow, peripheral blood, or umbilical cord blood and placenta shortly after delivery of neonates. Although cord blood is an allogeneic source, the cells in it are antigenically "naïve" and thus are associated with a lower incidence of rejection or graft-versus-host disease.

Preparative Conditioning for Hematopoietic Cell Transplantation

Autologous HCT necessitates myeloablative chemotherapy to eradicate cancerous cells from the blood and bone marrow, thus permitting subsequent engraftment and repopulation of bone marrow space with presumably normal hematopoietic progenitor cells. As a consequence, autologous HCT is typically performed as consolidation therapy when the patient's disease is in complete remission. Patients who undergo autologous HCT are susceptible to chemotherapy-related toxicities and opportunistic infections prior to engraftment but not graft-versus-host disease.

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Astrocytomas and Gliomas

Diffuse fibrillary astrocytomas are the most common type of brain tumor in adults. These tumors are classified histologically into 3 grades of malignancy: grade II astrocytoma, grade III anaplastic astrocytoma, and grade IV glioblastoma multiforme. Oligodendrogliomas are diffuse neoplasms that are clinically and biologically most closely related to diffuse fibrillary astrocytomas. However, these tumors generally have better prognoses than diffuse astrocytomas, with mean survival times of 10 years versus 2–3 years, respectively. In addition, oligodendrogliomas appear to be more chemosensitive than other types of astrocytomas. Glioblastoma multiforme is the most malignant stage of astrocytoma, with survival times of less than 2 years for most patients.

Treatment of primary brain tumors focuses on surgery, either with curative intent or optimal tumor debulking. Surgery may be followed by radiation therapy and/or chemotherapy. Survival after chemoradiotherapy is largely dependent on the extent of residual tumor after surgical debulking. Therefore, tumors arising in the midline, basal ganglia, or corpus callosum or those arising in the eloquent speech or motor areas of the cortex, which typically cannot be extensively resected, have a particularly poor outcome. Treatment of children younger than 3 years is complicated by the long-term effects of radiation therapy on physical and intellectual function. Therefore, in young children, radiation of the central nervous system (CNS) is avoided whenever possible.

Note: Astrocytomas and gliomas arise from the glial cells. Tumors arising from the neuroepithelium constitute a separate category of malignancies that include CNS neuroblastoma, medulloblastoma, ependymoblastomas, and pinealoblastomas. Collectively these tumors may be referred to as primitive neuroectodermal tumors (PNETs). Ependymomas also arise from the neuroepithelium but, because of their more mature histologic appearance, are not considered a member of the PNET family.

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 regulations, other plan medical policies, and accredited national guidelines.

The published literature consists primarily of single-institution case series.

Bouffet and colleagues reported on a series of 22 children and young adults with high-grade gliomas treated with autologous HCT. The response rate was 29% with 1 complete and 3 partial responses. However, the authors concluded that survival with this procedure was no better than that reported with conventional treatments. Heideman and colleagues reported on a case series of 13 pediatric patients with bulky disease or recurrent disease treated with HCT plus radiotherapy. While the overall response rate was 31%, the authors similarly concluded that overall survival was no better

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than conventional treatment regimens. Finlay and colleagues reported on a 1996 case series of 45 children and young adults with a variety of recurrent CNS tumors, including gliomas, medulloblastomas, ependymomas, and primitive neuroectodermal tumors. Of the 18 patients with high-grade gliomas, the response rate was 29%. The median survival of this group was 12.7 months. Of the 5 long-term survivors, all had high-grade glioma with minimal residual disease at the time of transplantation. Based in part on these results, the authors recommended aggressive surgical debulking before this procedure is even considered. Studies focusing on the use of autologous HCT in adults with glioblastoma multiforme reported results similar to those in children, being most successful in those with minimal disease at the time of treatment, with an occasional long-term survivor.

A review by Brandes and colleagues concluded that the high drug doses used in this treatment caused excessive toxicity that was not balanced by a significant improvement in survival. Additional reports on small, uncontrolled series of patients with pontine gliomas, recurrent oligodendrogliomas, or those undergoing radiation therapy for high-grade gliomas also did not suggest that this treatment improves survival. In a Phase II study, Abrey and colleagues evaluated hematopoietic cell transplantation in 39 patients with newly diagnosed oligodendroglioma. The authors reported the median follow-up of surviving patients was 80.5 months, with 78 months progression-free survival. The overall survival median had not been reached, and 18 patients (46%) had relapsed.

A nonrandomized study compared survival outcomes of 27 children (age, 0.4–22 years) with recurrent malignant astrocytomas who underwent myeloablative chemotherapy and autologous HCT with outcomes in a matched historical cohort (n=56) that received standard chemotherapy regimens following tumor recurrence. Among the 27 children who received myeloablative chemotherapy and autologous HSCT, 5 (18%) succumbed to treatment-related toxicities within approximately 2 months of transplantation, 17 (63%) had disease progression, while 5 survived and were alive a median of 11 years (range: 8–13 years) after transplantation. Overall survival rates at 4 years were $40 \pm 14\%$ for transplant patients versus $7 \pm 4\%$ with conventional chemotherapy ($p=0.018$, hazard ratio [HR]: 1.9; 95% confidence interval [CI]: 1.1–3.2). The results of this study suggest myeloablative chemotherapy with autologous HSCT can produce long-term survival among children with recurrent malignant astrocytoma. However, lack of a contemporaneous treatment comparison group precludes conclusions as to the relative efficacy of this approach.

A comprehensive review article identified in the search did not report any evidence for the role of HCT in this disease.

Summary

The data on the use of autologous hematopoietic cell transplantation for malignant astrocytomas and gliomas, consisting of case series, has, in general, shown no survival benefit compared to conventional therapy with increased treatment-related toxicity. Therefore, this is considered investigational for this indication.

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National Cancer Institute Physician Data Query (PDQ) Clinical Trials Database

Ongoing and Unpublished Clinical Trials

Some currently ongoing trials that might influence this review is listed in Table below.

Summary of Key Trials

NCT Number	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT00669669	O6-Benzylguanine-Mediated Tumor Sensitization with Chemo protected Autologous Stem Cell in Treating Patients with Malignant Gliomas	24	Dec 2017
NCT01505569	Auto Transplant for High-Risk or Relapsed Solid or CNS Tumors	20	Jan 2019
NCT00638898	Busulfan, Melphalan, Topotecan Hydrochloride, and Stem-Cell Transplant in Treating Newly Diagnosed or Relapsed Solid Tumor	25	Apr 2019

Table Key:

NCT: National Clinical Trial.

National Comprehensive Cancer Network (NCCN) Guidelines on Central Nervous System Cancers

The 2019 NCCN Guidelines on Central Nervous System Tumors (v.2.2018) do not list hematopoietic HSCT as a treatment option for patients with astrocytomas or gliomas.

References

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2. Heideman RL, Douglass EC, Krance RA et al. High-dose chemotherapy and autologous bone marrow rescue followed by interstitial and external-beam radiotherapy in newly diagnosed pediatric malignant gliomas. J Clin Oncol 1993; 11(8):1458-65.
3. Finlay JL, Goldman S, Wong MC et al. Pilot study of high-dose thiopeta and etoposide with autologous bone marrow rescue in children and young adults with recurrent CNS tumors. The Children's Cancer Group. J Clin Oncol 1996; 14(9):2495-503.

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5. Fernandez-Hidalgo OA, Vanaclocha V, Vieitez JM et al. High-dose BCNU and autologous progenitor cell transplantation given with intra-arterial cisplatinum and simultaneous radiotherapy in the treatment of high-grade gliomas: benefit for selected patients. Bone Marrow Transplant 1996; 18(1):143-9.
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8. Cairncross G, Swinnen L, Bayer R et al. Myeloablative chemotherapy for recurrent aggressive oligodendroglioma. Neuro Oncol 2000; 2(2):114-9.
9. Jakacki RI, Siffert J, Jamison C et al. Dose-intensive, time-compressed procarbazine, CCNU, vincristine (PCV) with peripheral blood stem cell support and concurrent radiation in patients with newly diagnosed high-grade gliomas. J Neurooncol 1999; 44(1):77-83.
10. Abrey LE, Childs BH, Paleologos N et al. High-dose chemotherapy with stem cell rescue as initial therapy for anaplastic oligodendroglioma: long-term follow-up. Neuro Oncol 2006; 8(2):183-8.
11. Finlay JL, Dhall G, Boyett JM et al. Myeloablative chemotherapy with autologous bone marrow rescue in children and adolescents with recurrent malignant astrocytoma: outcome compared with conventional chemotherapy: a report from the Children's Oncology Group. Pediatr Blood Cancer 2008; 51(6):806-11.
12. Ricard D, Idbaih A, Ducray F et al. Primary brain tumours in adults. Lancet 2012; 379(9830):1984-96.

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. Coverage eligibility unchanged.

03/31/2004 Medical Director review

04/20/2004 Medical Policy Committee review. High-dose chemotherapy and hematopoietic stem cell support for treatment of malignant astrocytomas and gliomas policy developed separately from current HDC with Hematopoietic Stem cell Support policy. Coverage eligibility unchanged.

04/26/2004 Managed Care Advisory Council approval

04/05/2006 Medical Director review

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04/19/2006	Medical Policy Committee review. Format revision, including addition of FDA and or other governmental regulatory approval and rationale/ source.
04/04/2007	Medical Director review
04/18/2007	Medical Policy Committee approval. No change to coverage eligibility.
04/02/2009	Medical Director review
04/15/2009	Medical Policy Committee approval. Changed title to "Autologous Hematopoietic Stem Cell Transplantation for Malignant Astrocytomas and Gliomas". Clarified investigational coverage statement by adding the phrase, "including glioblastoma multiforme and oligodendroglioma". No change to coverage eligibility.
04/08/2010	Medical Policy Committee approval
04/21/2010	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
04/07/2011	Medical Policy Committee review
04/13/2011	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
04/12/2012	Medical Policy Committee review
04/25/2012	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
02/19/2013	coding updated
04/04/2013	Medical Policy Committee review
04/24/2013	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
04/03/2014	Medical Policy Committee review
04/23/2014	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
09/03/2015	Medical Policy Committee review
09/23/2015	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
09/08/2016	Medical Policy Committee review
09/21/2016	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
09/07/2017	Medical Policy Committee review. Recommend archiving policy.
09/20/2017	Medical Policy Implementation Committee approval. Archived
03/07/2019	Medical Policy Committee review.
03/20/2019	Medical Policy Implementation Committee approval. Brought back to active status.
03/05/2020	Medical Policy Committee review.
03/11/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
03/04/2021	Medical Policy Committee review.

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03/10/2021	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
03/03/2022	Medical Policy Committee review.
03/09/2022	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
03/02/2023	Medical Policy Committee review.
03/08/2023	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
03/07/2024	Medical Policy Committee review.
03/13/2024	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
03/06/2025	Medical Policy Committee review.
03/12/2025	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
03/05/2026	Medical Policy Committee review.
03/11/2026	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 03/2027

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, 38206, 38207, 38208, 38209, 38210, 38211, 38212, 38213, 38214, 38215, 38232, 38241 Delete codes effective 04/01/2025: 38242, 38243
HCPCS	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.

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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.

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.

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.

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NOTICE: If an authorization for an ongoing course of treatment has been provided to a member and the member changes from one health plan to another health plan (e.g., a member moves from carrier A to Louisiana Blue), Louisiana Blue may honor the previous health plan's authorization for the same service under the same type of in-network benefit for a 90-day transition period. Documentation of the authorization for the ongoing course of treatment from the previous health plan must be provided to us by the member or their provider and the services provided for the course of treatment must otherwise be a covered service under the Louisiana Blue health plan. This provision does not apply to medications covered under the plan's pharmacy benefit.