Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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***Current Policy Effective Date: 9/1/24**
(See policy history boxes for previous effective dates)

Title: Bone Marrow Transplantation for Malignant Astrocytomas and Gliomas, Autologous

Description/Background

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

BACKGROUND
Hematopoietic stem cells or hemocytoblasts are the stem cells that give rise to all the other blood cells. They are immature cells that divide to form more blood forming stem-cells, or they mature into one of 3 types of blood cells: white blood cells, which fight infection; red blood cells, which carry oxygen; and platelets, which help the blood to clot.

Hematopoietic cell transplantation (HCT) refers to a procedure in which hematopoietic cells are infused to restore bone marrow function. Toxic doses of cytotoxic drugs deplete what is left of the individuals immune system. Hematopoietic stem cells are reintroduced to the body with the intent to reestablish hematopoietic function in individuals whose bone marrow or immune system is damaged or defective.

Bone marrow stem 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 stem cells in it are antigenically “naïve” and thus are associated with a lower incidence of rejection or graft-versus-host disease (GVHD).

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 disease is in complete remission. Individuals who undergo autologous HCT are susceptible to chemotherapy-related toxicities and opportunistic infections prior to engraftment but not graft-versus-host disease.

Astrocytomas and Gliomas
Diffuse fibrillary astrocytomas are the most common type of brain tumor in adults. These tumors are classified histologically into III grades of malignancy: grade II astrocytoma, grade III anaplastic astrocytoma and grade IV glioblastoma multiform. 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 chemo sensitive than other types of astrocytomas. Glioblastoma multiforme is the most malignant stage of astrocytoma, with survival times of less than 2 years for most individuals.

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. Tumors that develop in the midline, basal ganglia, or corpus callosum or those arising in the eloquent speech or motor areas of the cortex, typically cannot be extensively resected and therefore, have a particularly poor outcome. Radiation of the central nervous system (CNS) is avoided whenever possible in young children. Long term-effects of radiation on physical and intellectual function complicate the treatment of children younger than 3 years of age.

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, ependymoblastoma and pinealoblastoma. 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, they are not considered a member of the PNET family.

Regulatory Status

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

Medical Policy Statement

Autologous hematopoietic cell transplantation is experimental/investigational as a treatment of malignant astrocytomas and gliomas. (The latter diagnosis includes both glioblastoma multiforme and oligodendroglioma.)

Inclusionary and Exclusionary Guidelines

N/A

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

N/A

Other codes (investigational, not medically necessary, etc.):

38206	38207	38208	38209	38210	38211
38212	38213	38214	38215	38232	38241
81267	81268	S2150			

Rationale

An updated literature search identified no controlled studies that would change the conclusions of this policy. The published literature consists primarily of single-institution case series.

Bouffet et al reported on a series of 22 children and young adults with high-grade gliomas treated with autologous HCT. The response rate was 29% with one complete and 3 partial responses. However, the authors concluded that survival with this procedure was no better than that reported with conventional treatments.

Heideman et al 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 percent, the authors similarly concluded that overall survival was no better than conventional treatment regimens.

Finlay et al reported on a 1996 case series of 45 children and young adults with a variety of recurrent central nervous system (CNS) tumors, including gliomas, medulloblastomas, ependymomas, and primitive neuroectodermal tumors. Of the 18 individuals 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 et al 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 individuals 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 et al evaluated hematopoietic cell transplantation in 39 patients with newly diagnosed oligodendroglioma. The authors reported the median follow-up of surviving individuals was 80.5 months, with 78 months progression-free survival. The overall survival median had not been reached, and 18 individuals (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.(11) Among the 27 children who received myeloablative chemotherapy and autologous HCT, 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 ± 14% for transplant patients versus 7 ± 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 HCT 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.

Lee et al (2017) evaluated the outcome of tandem high-dose chemotherapy and autologous stem cell transplantation (HDC/auto-SCT) for high-grade gliomas (HGGs), we retrospectively reviewed the medical records of 30 individuals with HGGs (16 glioblastomas, 7 anaplastic astrocytomas, and 7 other HGGs) between 2006 and 2015. Gross or near total resection was possible in 11 individuals. Front-line treatment after surgery was radiotherapy (RT) in 14 individuals and chemotherapy in the remaining 16 individuals including 3 individuals less than 3 years of age. Eight of 12 patients who remained progression free and 5 of the remaining 18 individuals who experienced progression during induction treatment underwent the first HDCT/auto-SCT with carboplatin + thiotepa + etoposide (CTE) regimen and 11 of them proceeded to the second HDCT/auto-SCT with cyclophosphamide + melphalan (CyM) regimen. One person died from hepatic veno-occlusive disease (VOD) during the second HDCT/auto-SCT; otherwise, toxicities were manageable. Four individuals in complete response (CR) and 3 of 7 individuals in partial response (PR) or second PR at the first HDCT/auto-SCT remained event free: however, 2 individuals with progressive tumor experienced progression again. The probabilities of 3-year overall survival (OS) after the first HDCT/auto-SCT in 11 individuals in CR, PR, or second PR was 58.2% ± 16.9%. Tumor status at the first HDCT/auto-SCT was the only significant factor for outcome after HDCT/auto-SCT. There was no difference in survival between glioblastoma and other HGGs. Authors concluded that this study suggests that the outcome of HGGs in children and adolescents after HDCT/auto-SCT is encouraging if the individual could achieve CR or PR before HDCT/auto-SCT. However, this study is a retrospective review, and the size of cohorts is small. Therefore, prospective studies with larger cohorts of individuals are needed to answer the controversy and some debate about the efficacy of HDCT/auto-SCT for HGGs in children.

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

In a discussion regarding diffuse intrinsic pontine glioma, Marcus et al (2022) indicate that evidence remains unclear regarding the benefit of high-dose therapy with stem cell rescue in both adults and children.

Summary
The data on the use of autologous hematopoietic cell transplantation for malignant astrocytomas and gliomas, consisting of case series and small sample sizes, have, in general, shown no survival benefit compared to conventional therapy with increased treatment-related toxicity. No clinical guidelines were noted that recommend HCT for people with malignant astrocytomas and gliomas. Therefore, autologous HCT is considered investigational for the treatment of malignant astrocytomas and gliomas..

Supplemental Information

Ongoing and Unpublished Clinical Trials
Currently unpublished trial(s) that might influence this review are listed in Table 1.

Table 1.

Clinical Trial Identifier	Purpose	N	Completion Date
NCT00638898	This clinical trial is studying how well giving busulfan, melphalan, and topotecan hydrochloride together with a stem cell transplant works in treating patients with newly diagnosed or relapsed solid tumor.	25	December 2023

National Comprehensive Cancer Network Guidelines
The National Comprehensive Cancer Network Guidelines on Central Nervous System Tumors do not list hematopoietic cell transplantation as a treatment option for individuals with astrocytomas or gliomas.

American Association of Neurological Surgeons and Congress of Neurological Surgeons
The American Association of Neurological Surgeons and Congress of Neurological Surgeons (2015) partnered and released guidelines regarding the role of emerging therapy in the management of patients with diffuse low-grade gliomas: There is no evidence to support a recommendation in regard to the efficacy of immunotherapy or tumor vaccines for the treatment of low-grade that gliomas. It is recommended that patients be enrolled in properly designed clinical trials to assess immunotherapies and tumor vaccines for low grade gliomas.

Other Associations
The following Associations guidelines on clinical management of CNS tumors do not include the use of hematopoietic cell transplantation as a treatment option.
- American Brain Tumor Association (Astrocytoma - 2020)
- National Cancer Institute (Adult CNS Tumors - 2021)

Government Regulations
National:

Medicare National Coverage Determinations Manual, Chapter 1, Part 2, Section 110.23, "Stem Cell Transplantation." Effective date: 1/27/16; Implementation Date: 10/3/16

Does not address astrocytomas or gliomas under the covered indications.

A. General

Stem cell transplantation is a process in which stem cells are harvested from either a patient's (autologous) or donor's (allogeneic) bone marrow or peripheral blood for intravenous infusion. Autologous stem cell transplantation (AuSCT) is a technique for restoring stem cells using the patient's own previously stored cells. AuSCT must be used to effect hematopoietic reconstitution following severely myelotoxic doses of chemotherapy (HDCT) and/or radiotherapy used to treat various malignancies. Allogeneic hematopoietic stem cell transplantation (HSCT) is a procedure in which a portion of a healthy donor's stem cell or bone marrow is obtained and prepared for intravenous infusion. Allogeneic HSCT may be used to restore function in recipients having an inherited or acquired deficiency or defect. Hematopoietic stem cells are multi-potent stem cells that give rise to all the blood cell types; these stem cells form blood and immune cells. A hematopoietic stem cell is a cell isolated from blood or bone marrow that can renew itself, differentiate to a variety of specialized cells, can mobilize out of the bone marrow into circulating blood, and can undergo programmed cell death, called apoptosis - a process by which cells that are unneeded or detrimental will self-destruct.

The Centers for Medicare & Medicaid Services (CMS) is clarifying that bone marrow and peripheral blood stem cell transplantation is a process which includes mobilization, harvesting, and transplant of bone marrow or peripheral blood stem cells and the administration of high dose chemotherapy or radiotherapy prior to the actual transplant. When bone marrow or peripheral blood stem cell transplantation is covered, all necessary steps are included in coverage. When bone marrow or peripheral blood stem cell transplantation is non-covered, none of the steps are covered.

Insufficient data exist to establish definite conclusions regarding the efficacy of Autologous SCT for the following conditions:

- Solid Tumors (other than neuroblastoma)

…AuSCT is not considered reasonable and necessary within the meaning of §l862(a)(1)(A) of the Act and is not covered under Medicare.

All other indications for STEM CELL TRANSPLANTATION not otherwise noted above as covered or non-covered remain at local Medicare Administrative Contractor discretion.

(This NCD last reviewed January 2016.)

Local:

No Local coverage position statement found.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- BMT – Hematopoietic Cell Transplantation for Acute Lymphoblastic Leukemia
- BMT – Hematopoietic Cell Transplantation for Acute Myeloid Leukemia
- BMT – Hematopoietic Cell Transplantation for Autoimmune Diseases
- BMT – Hematopoietic Cell Transplantation for Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma - Autologous or Allogeneic
- BMT – Hematopoietic Cell Transplantation for Chronic Myeloid Leukemia
- BMT – Hematopoietic Cell Transplantation for CNS Embryonal Tumors and Ependymoma
- BMT – Hematopoietic Cell Transplantation for Epithelial Ovarian Cancer
- BMT – Hematopoietic Cell Transplantation for Genetic Diseases and Acquired Anemias
- BMT – Hematopoietic Cell Transplantation for Germ-Cell Tumors
- BMT – Hematopoietic Cell Transplantation for Hodgkin Lymphoma
- BMT – Hematopoietic Cell Transplantation for Miscellaneous Solid Tumors in Adults
- BMT – Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas
- BMT – Hematopoietic Cell Transplantation for Primary Amyloidosis
- BMT – Hematopoietic Cell Transplantation for Solid Tumors of Childhood
- BMT – Hematopoietic Cell Transplantation for Treatment of Multiple Myeloma
- BMT – Hematopoietic Cell Transplantation for Waldenström's Macroglobulinemia
- BMT – Hematopoietic Cell Transplantation in the Treatment of Germ-Cell Tumors
- Donor Lymphocyte Infusion for Malignancies Treated with an Allogeneic Hematopoietic Cell Transplant
- Orthopedic Applications of Stem-Cell Therapy (Including Allografts and Bone Substitutes used with Autologous Bone Marrow)

References

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2. American Brain Tumor Association. "Astrocytoma". 2022. https://www.abta.org/tumor_types/astrocytoma/. Accessed April 5, 2024.
3. Blue Cross and Blue Shield Association. Autologous Hematopoietic Stem-Cell Transplantation for Malignant Astrocytomas and Gliomas. Medical Policy Reference Manual, Policy #8.01.31, Issue 7:2013, original policy date 12/1/99, last review date 7/11/13, policy archived 7/11/13.
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10. 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.
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12. Food and Drug Administration (FDA). Tissue and Tissue Products. https://www.fda.gov/vaccines-blood-biologics/tissue-tissue-products. Accessed April 5, 2024.
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16. Linassier C, Benboubker L, Velut S et al. High-dose BCNU with ABMT followed by radiation therapy in the treatment of supratentorial glioblastoma multiforme. Bone Marrow Transplant 1996; 18 Suppl 1:S69-72.
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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through April 5, 2024, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
3/1/12	12/13/11	1/31/12	Joint policy established. Note: This policy was generated from former combined policies on investigational bone marrow transplants
3/1/13	12/11/12	12/31/12	Routine maintenance. No change in policy status. References updated.
7/1/14	4/10/14	4/15/14	Routine maintenance. No change in policy status.
9/1/15	6/19/15	7/16/15	Routine maintenance. No change in policy status.
9/1/16	6/21/16	6/21/16	• Routine policy maintenance. No change in policy status. • Recommendation for retirement denied
9/1/17	6/20/17	6/20/17	Routine maintenance
9/1/18	6/19/18	6/19/18	• Routine maintenance • NCD updated
9/1/19	6/18/19		Routine maintenance
9/1/20	6/16/20		• Routine maintenance
9/1/21	6/15/21		• Routine maintenance
9/1/22	6/21/22		• Routine maintenance
9/1/23	6/13/23		• Routine maintenance (slp) • Vendor Managed: N/A
9/1/24	6/11/24		• Routine maintenance (slp) • Vendor Managed: N/A • No new literature

Next Review Date: 2nd Qtr, 2025

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: BONE MARROW TRANSPLANTATION FOR MALIGNANT ASTROCYTOMAS AND GLIOMAS, AUTOLOGOUS

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Not covered.
BCNA (Medicare Advantage)	Refer to the Medicare information under the Government Regulations section of this policy.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.