



Louisiana

Hematopoietic Cell Transplantation for Central Nervous System Embryonal Tumors and Ependymoma

Policy # 00063

Original Effective Date: 01/28/2002

Current Effective Date: 06/20/2018

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.

Note: Hematopoietic Cell Transplantation for Solid Tumors of Childhood is addressed separately in medical policy 00064.

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.*

Embryonal Tumors of the Central Nervous System

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 HCT to treat recurrent embryonal tumors of the CNS to be **eligible for coverage**.

Note: In general, use of autologous HCT for previously untreated medulloblastoma has shown no survival benefit for those patients 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 [$< 1.5 \text{ cm}^2$ residual tumor]) when compared to conventional therapies.

When 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 tandem autologous HCT to treat embryonal tumors of the CNS to be **investigational**.*

Based on review of available data, the Company considers allogeneic HCT to treat embryonal tumors of the CNS to be **investigational**.*

Ependymoma

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

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Hematopoietic Cell Transplantation for Central Nervous System Embryonal Tumors and Ependymoma

Policy # 00063

Original Effective Date: 01/28/2002

Current Effective Date: 06/20/2018

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. CNS embryonal tumors are more common in children and are the most common brain tumor in childhood. CNS embryonal tumors are primarily composed of undifferentiated round cells, with divergent patterns of differentiation. It has been proposed that these tumors be merged under the term *primitive neuroectodermal tumor* (PNET); however, histologically similar tumors in different locations in the brain demonstrate different molecular genetic variants. Embryonal tumors of the CNS include medulloblastoma, medulloepithelioma, supratentorial PNETs (pineoblastoma, cerebral neuroblastoma, ganglioneuroblastoma), ependymblastoma, atypical teratoid/rhabdoid tumor (AT/RT).

Medulloblastomas account for 20% of all childhood CNS tumors. The other types of embryonal tumors are rare by comparison.

Treatment

Surgical resection is the mainstay of therapy with the goal being gross total resection with adjuvant radiotherapy because medulloblastomas are very radiosensitive. Treatment protocols are based on risk stratification as average or high risk. The average-risk group includes children older than 3 years, without metastatic disease, and with tumors that are totally or near totally resected (<1.5 cm² of residual disease). The high-risk group includes children aged 3 years or younger, or with metastatic disease, and/or subtotal resection (>1.5 cm² of residual disease).

Current standard treatment regimens for average-risk medulloblastoma (postoperative craniospinal irradiation [CSI] with boost to the posterior fossa followed by 12 months of chemotherapy) have resulted in 5-year overall survival (OS) rates of 80% or better. For high-risk medulloblastoma treated with conventional doses of chemotherapy and radiotherapy, the average event-free survival (EFS) at 5 years ranges from 34% to 40% across studies. Fewer than 55% of children with high-risk disease survive longer than 5 years. The treatment of newly diagnosed medulloblastoma continues to evolve, and in children younger than 3 years of age, because of the concern of the deleterious effects of craniospinal radiation on the immature nervous system, therapeutic approaches have attempted to delay and sometimes avoid the use of radiation and have included trials of higher dose chemotherapeutic regimens with autologous HCT.

Supratentorial PNETs are most commonly located in the cerebral cortex and pineal region. The prognosis for these tumors is worse than for medulloblastoma, despite identical therapies. After surgery, children are usually treated similarly to children with high-risk medulloblastoma. Three- to 5-year OS rates of 40% to 50% have been reported and, for patients with disseminated disease, survival rates at 5 years range from 10% to 30%.

Recurrent childhood CNS embryonal tumor is not uncommon and, depending on which type of treatment the patient initially received, autologous HCT may be an option. For patients who receive high-dose chemotherapy (HDC) and autologous HCT for recurrent embryonal tumors, objective response is 50% to

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Hematopoietic Cell Transplantation for Central Nervous System Embryonal Tumors and Ependymoma

Policy # 00063

Original Effective Date: 01/28/2002

Current Effective Date: 06/20/2018

75%; however, long-term disease control is obtained in fewer than 30% of patients and is primarily seen in patients in the first relapse with 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. Initial treatment of ependymoma consists of maximal surgical resection followed by radiotherapy. Chemotherapy usually does not play a role in the initial treatment of ependymoma. However, disease relapse is common, typically occurring at the site of origin.

Treatment

Treatment of recurrence is problematic; further surgical resection or radiotherapy is usually not possible. Given the poor response to conventional-dose chemotherapy, HDC with autologous HCT has been investigated as a possible salvage therapy.

Other CNS tumors include astrocytoma, oligodendroglioma, and glioblastoma multiforme. These tumors arise from glial cells, not neuroepithelial cells. These tumors are considered in medical policy 00058 (archived 9/20/2017).

Due to their neuroepithelial origin, peripheral neuroblastoma and Ewing sarcoma may be considered PNETs. These peripheral tumors are considered in medical policy 00064.

HEMATOPOIETIC CELL TRANSPLANTATION

HCT is a procedure in which hematopoietic cells are infused to restore bone marrow function in cancer patients who receive bone marrow ablative doses of cytotoxic drugs. Bone marrow stem cells may be obtained from the transplant recipient (autologous HCT) or from a donor (allogeneic HCT). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates.

HCT for Brain Tumors

Autologous HCT allows for 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 allogeneic HCT for solid tumors does not rely on escalation of chemotherapy intensity and tumor reduction but rather on a graft-versus-tumor effect. Allogeneic HCT is not commonly used in solid tumors and may be used if an autologous source cannot be cleared of tumor or cannot be harvested.

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Hematopoietic Cell Transplantation for Central Nervous System Embryonal Tumors and Ependymoma

Policy # 00063

Original Effective Date: 01/28/2002

Current Effective Date: 06/20/2018

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

The U.S. 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.

Centers for Medicare and Medicaid Services (CMS)

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.

Rationale/Source

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

CENTRAL NERVOUS SYSTEM EMBRYONAL TUMORS

Standard therapy for CNS embryonal tumors often involves CSI, in addition to surgical resection and chemotherapy. In pediatric patients, CSI is associated with impairments in neurodevelopmental outcomes, with risks increasing in younger age groups, particularly in those under the age of 3. Research into pediatric CNS tumor treatments has yielded methods to reduce radiation exposure to the developing brain without conferring unacceptably high recurrence risks. Therefore, a relevant outcome in evaluating HCT for CNS embryonal tumors is whether the use of HCT allows radiation dose reduction.

Newly Diagnosed Central Nervous System Embryonal Tumors

The evidence describing outcomes after HCT for newly diagnosed CNS embryonal tumors consists of relatively small case series, some of which have enrolled patients prospectively. While most studies have reported outcomes for specific tumor types, several studies include multiple tumor types.

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Hematopoietic Cell Transplantation for Central Nervous System Embryonal Tumors and Ependymoma

Policy # 00063

Original Effective Date: 01/28/2002

Current Effective Date: 06/20/2018

In a study that grouped CNS embryonal tumors, Odagiri et al (2014) reported outcomes for 24 patients treated for various CNS embryonal tumors on the basis of high- or average-risk prognosis. Among all patients included, 16, 4, 3, and 1, respectively, had medulloblastoma, PNET, AT/RT, and pineoblastoma. Nine patients were considered average risk based on the presence of all of the following: age 3 years or older at diagnosis, nonmetastatic disease, and gross total resection; the remaining 16 patients were considered high risk. High-risk patients received HCT in addition to CSI and chemotherapy. CSI for the high-risk group was at the same doses as for the average-risk group with nonmetastatic disease (23.4 gray [Gy] for those ≥ 5 years, 18 Gy for those < 5 years old, with a boost of 54 Gy for all ages), with higher doses for those with metastatic disease (30-36 Gy, with a boost of 54 Gy). In the average-risk group (n=9), the 5-year progression-free survival (PFS) and OS rates were 71.1% and 88.9%, respectively. In the high-risk group (n=15), the 5-year PFS and OS rates were 66.7% and 71.1%, respectively. Survival rates did not differ significantly between the average- and high-risk groups.

Alsultan et al (2015) retrospectively reviewed outcomes for 10 children under age 3 years treated with HCT, with or without CSI, for CNS embryonal tumors. Of the 10 patients, five had medulloblastoma, three had AT/RT, one had an embryonal tumor with abundant neuropil and true rosettes, and one had pineoblastoma; all underwent subtotal resection and induction chemotherapy. Five patients received radiotherapy, along with the AT/RT patient, who received radiotherapy as salvage therapy. The PFS rate was 50% (95% confidence interval [CI], 18% to 75%) at 1 year and at 2 years, with a median follow-up of 24 months. All patients with medulloblastoma were alive and without evidence of disease at last follow-up, including two with metastatic medulloblastoma who did not receive CSI.

Raleigh et al (2017) retrospectively described outcomes of 222 consecutive patients from institutional cancer registries at 2 California hospitals who had newly diagnosed embryonal brain tumors from 1988 to 2014. All patients underwent surgical resection. Following surgery, 56% of patients received adjuvant CSI followed by chemotherapy (upfront radiotherapy), 32% of patients received HDC with HCT to delay radiotherapy, and 16% received neither upfront radiotherapy nor HDC plus HCT due to death or poor clinical condition. Median follow-up was shorter in the HDC plus HCT group than in the upfront radiotherapy group (4 years vs 6 years) and mean age was younger (2.9 years vs 7.8 years). Time to initiation of radiotherapy was significantly longer in the HDC plus HCT group (median, 198 days) than in the upfront radiotherapy group (median, 28 days); moreover, 48% of HDC plus HCT patients did not receive radiotherapy. There were no differences in the incidence rates of metastases, PFS, or OS between HDC plus HCT and upfront radiotherapy.

Studies that describe HCT for specific tumor types are discussed next.

Supratentorial Primitive Neuroectodermal Tumor

Chintagumpala et al (2009) reviewed EFS for 16 patients with newly diagnosed supratentorial *primitive neuroectodermal tumor* (sPNET) treated with risk-adapted CSI and subsequent HDC with autologous HCT between 1996 and 2003. Eight patients were considered at average risk and 8 at high risk (defined as the presence of residual tumor > 1.5 cm² or disseminated disease in the neuroaxis). Median age at diagnosis was 7.9 years (range, 3-21 years). Seven patients had pineal PNET. After a median follow-up of 5.4 years,

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Hematopoietic Cell Transplantation for Central Nervous System Embryonal Tumors and Ependymoma

Policy # 00063

Original Effective Date: 01/28/2002

Current Effective Date: 06/20/2018

12 patients were alive. Five-year EFS and OS rates for the patients with average-risk disease were 75% and 88%, respectively, and for the high-risk patients 60% and 58%, respectively. No treatment-related toxicity deaths were reported. The authors concluded that HDC with HCT support after risk-adapted CSI permitted a reduction in the dose of radiation needed to treat nonmetastatic, average-risk sPNET, without compromising EFS.

Fangusaro et al (2008) reported on outcomes for 43 children with newly diagnosed sPNET treated prospectively in 2 serial studies (Head Start 1 [HS1], Head Start 2 [HS2]) between 1991 and 2002 with intensified induction chemotherapy followed by myeloablative chemotherapy and autologous HCT. There were no statistical differences between HS1 and HS2 patient demographics. After maximal surgical resection, patients underwent induction chemotherapy. If, after induction, the disease remained stable or there was PR or CR, patients underwent myeloablative chemotherapy with autologous HCT (n=32). Patients with progressive disease at the end of induction were ineligible for consolidation. Five-year EFS and OS rates were 39% (95% CI, 24% to 53%) and 49% (95% CI, 33% to 62%), respectively. Patients with nonpineal tumors did significantly better than patients with pineal PNETs (2- and 5-year EFS rates of 57% vs 23% and 48% vs 15%, respectively, and 2- and 5-year OS rates of 70% vs 31% and 60% vs 23%, respectively). Further, 60% of survivors were not exposed to radiotherapy.

Massimino et al (2013) reported on outcomes for 28 consecutive patients with noncerebellar PNET treated from 2000 to 2011 with a HDC schedule (methotrexate, etoposide, cyclophosphamide, carboplatin with or without vincristine) with autologous HCT rescue, followed by 1 of 2 radiotherapy options. For the first 15 patients, HDC and stem cell rescue was followed by hyperfractionated accelerated CSI with 2 high-dose thiotepa courses following CSI (for the first 15 patients); for subsequent cases, CSI was replaced with focal radiotherapy for patients whose tumors were nonmetastatic and not progressing during induction chemotherapy. Three- and 5-year PFS rates were 69% and 62%, respectively; 3- and 5-year EFS rates were 59% and 53%, respectively; and 3- and 5-year OS rates were 73% and 52%, respectively. Eleven children died at a median of 32 months after their diagnosis (range, 5-49 months), 8 due to their tumor, 1 due to multiorgan failure after the first myeloablative treatment, and 2 due to acute myeloid leukemia and myelodysplastic syndrome. For the 25 patients able to tolerate the entire schedule, including at least 1 myeloablative course, the 5-year PFS and OS rates were 67% and 61%, respectively.

Lester et al (2014) retrospectively evaluated the clinical outcomes and prognostic factors for 26 patients (11 children, 15 adults) with CNS PNET. Overall, 5-year disease-free survival rates were 78% for pediatric patients and 22% for adult patients (p=0.004); 5-year OS rates were 67% for pediatric patients and 33% for adult patients (p=0.07). More pediatric patients were treated with HDC plus HCT (82%) than adult patients (27%). In unadjusted analysis, compared with standard chemotherapy, treatment with HDC with HCT was associated with improved OS (hazard ratio [HR], 0.3; 95% CI, 0.1 to 1.0; p=0.05). However, these results were confounded by higher rates of HCT use in children, who had better OS and disease-free survival.

Medulloblastoma

Dhall et al (2008) reported on outcomes for children younger than 3 years of age when diagnosed with nonmetastatic medulloblastoma, after being treated with 5 cycles of induction chemotherapy and

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Hematopoietic Cell Transplantation for Central Nervous System Embryonal Tumors and Ependymoma

Policy # 00063

Original Effective Date: 01/28/2002

Current Effective Date: 06/20/2018

subsequent myeloablative chemotherapy and autologous HCT. Twenty of the 21 children enrolled completed induction chemotherapy, of whom 14 had a gross total surgical resection and 13 remained free of disease at the completion of induction chemotherapy. Of 7 patients with residual disease at the beginning of induction, all achieved a complete radiographic response to induction chemotherapy. Of the 20 patients who received consolidation chemotherapy, 18 remained disease-free at the end of consolidation. In patients with gross total tumor resection, 5-year EFS and OS rates were 64% and 79%, respectively; for patients with residual tumor, 29% and 57%, respectively. There were 4 treatment-related deaths. The need for CSI was eliminated in 52% of the patients, and 71% of survivors avoided irradiation completely while managing to preserve quality of life and intellectual functioning.

Gajjar et al (2006) reported on the results of risk-adapted craniospinal radiotherapy followed by HDC and autologous HCT in 134 children with newly diagnosed medulloblastoma. After tumor resection, patients were classified as having average-risk disease (n=86), defined as 1.5 cm² or less residual tumor and no metastatic disease, or high-risk disease (n=48), defined as greater than 1.5 cm² residual disease or metastatic disease localized to the neuroaxis. A total of 119 children completed the planned protocol. The 5-year OS rate was 85% (95% CI, 75% to 94%) among the average-risk cases and 70% (95% CI, 54% to 84%) among the high-risk patients. The 5-year EFS rate was 83% (95% CI, 73% to 93%) and 70% (95% CI, 55% to 85%) for average- and high-risk patients, respectively. No treatment-related deaths were reported.

Bergthold et al (2014) reported on outcomes for 19 young children (age, <5 years) with classical or incompletely resected medulloblastoma treated with high-dose busulfan-thiotepa plus autologous HCT, followed by posterior fossa irradiation. Subjects were treated at a single center from 1994 to 2010. On pathology, 14 patients had classic medulloblastoma, while three had desmoplastic/nodular medulloblastoma and one had medulloblastoma with extensive nodularity. Median follow-up was 40.5 months (range, 14.5-191.2 months). At 3 and 5 years, EFS and OS rates were 68% (95% CI, 45% to 84%) and 84% (95% CI, 61% to 94%), respectively. Treatment failures occurred in 6 children at a median of 13 months (range, 5.8-30.7 months) after HCT. Authors concluded that high OS is possible with focal brain irradiation in the setting of HCT for medulloblastoma.

Atypical Teratoid/Rhabdoid Tumor

Lee et al (2012) retrospectively reviewed the medical records of 13 patients diagnosed with AT/RT who were treated at a children's hospital in South Korea. Median age was 12 months (range, 3-67 months), with 7 patients were younger than 1 year at diagnosis. Three (23%) patients underwent HDC and autologous HCT. Authors assessed the impact on OS in these 3 patients, as compared with the remaining 10 patients who had other chemotherapy regimens. No statistical difference in OS was observed between these groups (p=0.36); however, median survival was longer in the HCT group (15 months) than in the non-HCTs group (9 months).

Section Summary: Newly Diagnosed Central Nervous System Embryonal Tumors

Data evaluating HDC with autologous HCT in the setting of newly diagnosed CNS embryonal tumors is primarily from single-arm studies. These studies have suggested comparable or improved EFS and OS rates compared with historical controls, particularly in patients with disease considered high risk. One

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Hematopoietic Cell Transplantation for Central Nervous System Embryonal Tumors and Ependymoma

Policy # 00063

Original Effective Date: 01/28/2002

Current Effective Date: 06/20/2018

retrospective study compared HDC with HCT and delayed CSI to upfront CSI. Rates of metastasis, PFS, and OS were similar in the two groups but patients in the delayed irradiation group were younger than those in the upfront irradiation group. HCT may permit reduced doses of CSI without worsening survival outcomes.

Recurrent or Relapsed CNS Embryonal Tumors

Similar to the literature on HCT for newly diagnosed CNS embryonal tumors, the evidence on HCT for recurrent or relapsed CNS embryonal tumors consists of small series, most of which include patients with a single tumor type.

Relapsed sPNET

In 2012, Raghuram et al reported on a systematic review of outcomes for patients with relapsed sPNET treated with HDC and autologous HCT. Eleven observational studies, including 4 prospective series (total N=46 patients) with relapsed sPNET or pineoblastoma, published before 2010, met reviewers' inclusion criteria. Of the 46 patients, 15 were children younger than 3 years of age. After a median follow-up of 40 months (range, 3-123 months), 15 patients were reported alive. Of the 15 survivors, 13 did not receive CSI. For the entire cohort, OS was 44.2 months; OS was longer for children younger than 36 months (66.7 months) than for those over 36 months (27.8 months; $p=0.003$). In multivariable regression, pineal location was the only independent adverse prognostic factor for survival. Based on these pooled results, CSI may be not associated with survival outcomes in young children treated with HCT. However, OS is poor in older children with relapsed sPNET, particularly with pineal tumors, even when treated with HCT.

Relapsed Medulloblastoma

Dunkel et al (2010) reported on an expanded series with longer follow-up using autologous HCT for previously irradiated recurrent medulloblastoma. Twenty-five patients (18 males, 7 females) were treated between 1990 and 1999 and had a median age at diagnosis of 11.5 years (range, 4.2-35.5 years). Median age at the time of HCT was 13.8 years (range, 7.6-44.7 years). All patients had previously received postoperative external-beam radiotherapy with (n=15) or without (n=10) chemotherapy. Median time from diagnosis to disease relapse or progression was 29.8 months (range, 5.3-114.7 months). Stage at relapse was M0 (n=6), M1 (n=1), M2 (n=8), and M3 (n=10) (M0=no evidence of subarachnoid or hematogenous metastasis, M1=tumor cells found in cerebrospinal fluid, M2=intracranial tumor beyond primary site, M3=gross nodular seeding in spinal subarachnoid space). HDC before HCT consisted of carboplatin, thiotepa, and etoposide. Treatment-related mortality was 12% within 30 days of transplant. Tumors recurred in 16 patients at a median of 8.5 months after HCT (range, 2.3-58.5 months). Median OS was 26.8 months (95% CI, 11.9 to 51.1 months) and EFS and OS rates at 10 years post-HCT were 24% for both (95% CI, 9.8% to 41.7%). Authors concluded that this retrieval strategy provided "long-term EFS for some patients with previously irradiated recurrent medulloblastoma."

In the earlier publication, Dunkel et al (1998) reported on outcomes for 23 patients with recurrent medulloblastoma treated with high-dose carboplatin, thiotepa, and etoposide. Seven patients were event-free survivors at a median of 54 months, with the OS rate estimated at 46% at 36 months. HCT was expected to be most effective with minimal disease burden. Thus, Dunkel et al suggested increased

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Hematopoietic Cell Transplantation for Central Nervous System Embryonal Tumors and Ependymoma

Policy # 00063

Original Effective Date: 01/28/2002

Current Effective Date: 06/20/2018

surveillance for recurrence or aggressive surgical debulking at the time of recurrence. They also acknowledged the potential for selection bias to influence their results, because not all patients eligible for the protocol were enrolled.

Grodman et al (2009) reported on outcomes for 8 patients with relapsed medulloblastoma with metastasis (n=7) and relapsed germinoma (n=1) who received dose-intensive chemotherapy with autologous HCT. Mean age was 12.9 years (range, 5-27.8 years). Mean survival posttransplant was 4.8 years (range, 8-160+ months). Two-year and 5-year OS rates were 75% and 50%, respectively.

Kostas et al (2013) conducted a systematic review of therapies for adults with relapsed medulloblastoma, including HDC with HCT. Reviewers identified 13 publications including 66 adults treated with HCT for recurrent or relapsed medulloblastoma. Limitations of the selected studies included the fact that all were small case series, case reports, or retrospective reviews. The single study with a comparator group identified in the review, which included 10 patients treated with HCT, reported that patients with medulloblastoma treated with HDC plus HCT at recurrence had improved OS (3.47 years) compared with historical controls treated with conventional chemotherapy at recurrence (2 years; p=0.04). Reviewers concluded: "Although the data are limited, the collective published evidence for this treatment modality suggests a role for HDCT [high-dose chemotherapy] plus stem cell transplantation in the management of well-selected adult patients with recurrent medulloblastoma."

Relapsed Embryonal Tumors: Multiple Types

The largest study identified an HCT in relapsed CNS embryonal tumors included patients with multiple PNET types (medulloblastoma, sPNET). Bode et al (2014) reported on the results of the intensive chemotherapy treatment arm of a nonrandomized stratified protocol for the treatment of relapsed cerebral PNET, in which patients could receive intensive chemotherapy, which could be potentially high-dose or oral chemotherapy. The intensive chemotherapy arm included 72 patients, 59 of whom had disseminated disease. Patients in the intensive treatment arm received conventional chemotherapy with carboplatin and etoposide; those considered to have a good response underwent HCT. At the end of conventional intravenous and/or intrathecal chemotherapy, 34 (48%) patients were considered to be good responders, of whom 24 were selected for HCT, along with 3 patients with stable disease. Among the 72 patients who received intensive chemotherapy, median PFS was 11.6 months (95% CI, 10.1 to 13.1 months), with 2-, 3-, and 5-year PFS rates of 44%, 18%, and 0.5%, respectively. Among all patients, median OS was 21.9 months (95% CI, 15.7 to 26.5 months), with 2-, 3-, and 5-year OS rates of 45%, 31%, and 16%, respectively. Among those treated with HCT, median PFS was 8.4 months (95% CI, 7.7 to 9.1 months), with 2-, 3-, and 5-year PFS rates of 20%, 10%, and 0.1%, respectively. HCT-treated patients had median OS of 20.2 months (95% CI, 11.7 to 28.8 months), with 2-, 3-, and 5-year OS rates of 35%, 30%, and 17%, respectively. Among the 34 good responders, there was no difference in OS or PFS between those treated with and without HCT.

Gill et al (2008) reported on outcomes for 23 adults (≥ 18 years of age) treated for recurrent embryonal CNS tumors between 1976 and 2004, comparing HDC plus autologous HCT (n=10) with a historic control group of patients treated with conventional-dose chemotherapy (n=13). In the HCT group, 6 patients received

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Hematopoietic Cell Transplantation for Central Nervous System Embryonal Tumors and Ependymoma

Policy # 00063

Original Effective Date: 01/28/2002

Current Effective Date: 06/20/2018

tandem autologous transplants. Autologous HCT was associated with increased survival ($p=0.044$) and a longer time to progression of disease ($p=0.028$). Median time to progression for the conventional chemotherapy vs HCT was 0.58 years and 1.25 years, respectively. Median survival was 2.00 years and 3.47 years, respectively. There were no long-term survivors in the conventional chemotherapy group. With a median follow-up of 2.9 years, five of the HCT patients were alive, four without disease progression. In a comparison of outcomes between patients who received a single vs tandem transplant, there was improvement in time to progression favoring tandem transplant ($p=0.046$), but no difference in survival was observed ($p=0.132$).

Kim et al (2013) reported on outcomes for 13 patients with refractory or relapsed medulloblastoma or PNET treated with combination HDC, with an objective tumor response rate of 38.5%. However, while the authors noted that patients could concurrently receive radiotherapy, surgery, and/or HDC and stem cell rescue, they did not specify how many patients received stem cell support, making it difficult to determine the benefit from specific intervention components.

Egan et al (2016) reported on outcomes from a phase 1 study of temozolomide in combination with thiotepa and carboplatin plus autologous HCT in patients with recurrent malignant brain tumors. Temozolomide was administered, followed by thiotepa and carboplatin and then autologous HCT. The study enrolled 27 patients (age range, 3-46 years) with high-grade glioma ($n=12$), medulloblastoma/PNET ($n=9$), CNS germ cell tumor ($n=4$), ependymoma ($n=1$), and spinal cord PNET ($n=1$). Fourteen (52%) patients survived longer than 24 months. After 10 years, 3 patients were alive.

Section Summary: Recurrent or Relapsed CNS Embryonal Tumors

The prognosis is generally poor for recurrent CNS tumors, and there are few treatment options. Data from some single-arm studies using autologous HCT compared with conventional therapy to treat recurrent CNS embryonal tumors have shown comparable or improved survival for certain patients. A 2012 systematic review of observational studies in patients with relapsed sPNET suggested that infants with chemosensitive disease might benefit from autologous HCT because survival outcomes are similar without radiotherapy. However, reviewers found that outcomes in older children and/or in those with pineal location were poor with this modality. A relatively large prospective multicenter study reported that HCT was not associated with improved survival outcomes in patients who had a good response to therapy.

CNS Embryonal Tumors Treated With Tandem Transplant

In 2016, Sung et al reported on prospective follow-up for 13 children with AT/RT who received tandem HDC and autologous HCT. Five of the children were less than 3 years old; the remaining eight were 3 years or older. Tandem HDC and autologous HCT was administered after 6 cycles of induction chemotherapy with radiotherapy deferred until age 3 unless the tumor showed relapse or progression in the younger children. Reduced-dose radiotherapy was administered either after 2 cycles of induction chemotherapy or after surgery with tandem HDC, and autologous HCT was performed after 6 cycles of induction chemotherapy in the older children. All 5 younger children died from disease progression. Four of the 8 older children remained progression-free, with median follow-up of 64 months.

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Hematopoietic Cell Transplantation for Central Nervous System Embryonal Tumors and Ependymoma

Policy # 00063

Original Effective Date: 01/28/2002

Current Effective Date: 06/20/2018

In 2014, Dufour et al reported on outcomes for patients with newly diagnosed high-risk medulloblastoma and sPNET treated with tandem HDC and autologous HCT support followed by conventional craniospinal radiotherapy. Twenty-four children older than age 5 years were treated from 2001 to 2010, 21 with newly diagnosed high-risk medulloblastoma (disseminated medulloblastoma or medulloblastoma with residual tumor volume $>1.5 \text{ cm}^2$ or *MYCN* amplification) and three with sPNET. Patients received 2 courses of conventional chemotherapy, followed by 2 courses of high-dose thiotepa followed by stem cell rescue and craniospinal radiotherapy. Twenty-three patients received 2 courses of HDC, while 1 patient received only 1 course of high-dose thiotepa due to seizures. Median follow-up was 4.4 years (range, 0.8-11.3 years). Three-year EFS and OS rates were 79% (95% CI, 59% to 91%) and 82% (95% CI, 62% to 93%), respectively, while 5-year EFS and OS rates were 65% (95% CI, 45% to 81%) and 74% (95% CI, 51% to 89%), respectively.

In 2013, Sung et al reported on the results of reduced-dose craniospinal radiotherapy followed by double-tandem HDC with autologous HCT in 20 children older than 3 years of age with high-risk medulloblastoma (17 with metastatic disease, 3 with postoperative residual tumor $>1.5 \text{ cm}^2$ without metastasis). The tumor relapsed or progressed in 4 patients, and two died of treatment-related toxicity during the second transplant. Fourteen (70%) patients remained event-free at a median follow-up of 46 months (range, 23-82 months) from diagnosis. Late adverse events, evaluated at a median of 36 months (range, 12-68 months) after tandem HCT included hypothyroidism, growth hormone deficiency, sex hormone deficiency, hearing loss, and renal tubulopathy.

In 2013, Friedrich et al reported on the results of double-tandem HDC with autologous HCT in 3 children younger than 4 years of age with metastatic sPNET. These patients also received preventive craniospinal radiotherapy; they had residual disease before HCT, but no evidence of disease after transplant (survival range, 2-10 years).

Park et al (2012) reported on the results of double-tandem HDC with autologous HCT in 6 children younger than 3 years of age with newly diagnosed AT/RT. No treatment-related death occurred during the tandem procedure, and 5 (of 6) patients were alive at a median follow-up of 13 months (range, 7-64 months) from first transplant. Although 3 patients remained progression-free after tandem HCT, the effectiveness of this modality is unclear because all survivors received radiotherapy and tandem HCT.

In 2007, Sung et al reported on the results of a single- or double-tandem HDC with autologous HCT in 25 children with newly diagnosed high-risk or relapsed medulloblastoma or PNET following surgical resection. Three-year EFS rates for patients in complete or PR and less than PR at first HDC were 67% and 16.7%, respectively. For 19 cases in complete or PR at first HDC, 3-year EFS rates were 89% in the double-tandem group and 44% in the single HDC group, respectively. Four treatment-related deaths occurred, and in 4 of 8 young children, craniospinal radiotherapy was successfully withheld without relapse.

Section Summary: CNS Embryonal Tumors Treated With Tandem Transplant

Little evidence is available on the use of tandem autologous HCT for CNS embryonal tumors. The single-arm studies are very small report OS and EFS rates comparable with single autologous HCT. Tandem

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Hematopoietic Cell Transplantation for Central Nervous System Embryonal Tumors and Ependymoma

Policy # 00063

Original Effective Date: 01/28/2002

Current Effective Date: 06/20/2018

transplants may allow reduced doses of CSI, but most studies used standard-dose irradiation, making the relative benefit of tandem autologous HCT uncertain.

CNS Embryonal Tumors Treated With Allogeneic Transplant

Use of allogeneic HCT for CNS embryonal tumors consists of rare case reports with mixed results.

EPENDYMOMA

The literature on autologous HCT for the treatment of ependymoma primarily consists of small case series. Sung et al (2012) reported the results of double-tandem HDC with autologous HCT in 5 children younger than 3 years of age with newly diagnosed anaplastic ependymoma. All patients were alive at median follow-up of 45 months (range, 31-62 months) from diagnosis, although the tumor progressed at the primary site in 1 patient. No significant endocrine dysfunction occurred except for hypothyroidism in 1 patient, and significant neurologic injury from primary surgical treatment in another patient. The results of this very small case series indicate that treatment with tandem HCT is feasible in very young children with anaplastic ependymoma and that this strategy might also be an option to improve survival in these patients without unacceptable long-term toxicity.

Mason et al (1998) reported on a case series of 15 patients with recurrent ependymoma. Five patients died of treatment-related toxicities, 8 died from progressive disease, and 1 died of unrelated causes. After 25 months, 1 patient remained alive but with tumor recurrence. Authors concluded that their high-dose regimen of thiopeta and etoposide was not an effective treatment of ependymoma. Grill et al (1996) similarly reported a disappointing experience in 16 children treated with a thiopeta-based high-dose regimen.

A small 2007 series reported 5-year EFS and OS rates of 12% and 38%, respectively, among 29 children younger than 10 years of age who received autologous HCT after intensive induction chemotherapy to treat newly diagnosed ependymoma. Importantly, the radiation-free survival rate was only 8% in these cases. The results of these series, although limited in size, would suggest HCT is not superior to other previously reported chemotherapeutic approaches.

SUMMARY OF EVIDENCE

For individuals who have newly diagnosed CNS embryonal tumors who receive autologous HCT, the evidence includes prospective and retrospective studies. Relevant outcomes are OS, disease-specific survival, 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 HDC 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 disease considered high risk. In a retrospective comparative study, survival in patients receiving HDC with HCT and delayed 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 a meaningful improvement in the net health outcome.

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Hematopoietic Cell Transplantation for Central Nervous System Embryonal Tumors and Ependymoma

Policy # 00063

Original Effective Date: 01/28/2002

Current Effective Date: 06/20/2018

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, disease-specific survival, 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 chemosensitive disease might benefit from autologous HCT, achieving survival without the use of radiotherapy, whereas outcomes in older children and/or in 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 (e.g., AT/RTs). The evidence is sufficient to determine that the technology results in a meaningful 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, disease-specific survival, 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 CSI, 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 the effects of the technology on health outcomes.

For individuals who have CNS embryonal tumors who receive allogeneic HCT, the evidence includes case reports. Relevant outcomes are OS, disease-specific survival, and treatment-related mortality and morbidity. The available evidence is limited. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have ependymoma who receive autologous HCT, the evidence includes relatively small case series. Relevant outcomes are OS, disease-specific survival, 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 the effects of the technology on health outcomes.

References

1. Blue Cross and Blue Shield Association, *Medical Policy Reference Manual*, "Hematopoietic Cell Transplantation for Central Nervous System Embryonal Tumors and Ependymoma", 8.01.28. 1:2018.
2. Mueller S, Chang S. Pediatric brain tumors: current treatment strategies and future therapeutic approaches. *Neurotherapeutics*. Jul 2009;6(3):570-586. PMID 19560746

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Hematopoietic Cell Transplantation for Central Nervous System Embryonal Tumors and Ependymoma

Policy # 00063

Original Effective Date: 01/28/2002

Current Effective Date: 06/20/2018

3. Fangusaro J, Finlay J, Sposto R, et al. Intensive chemotherapy followed by consolidative myeloablative chemotherapy with autologous hematopoietic cell rescue (AuHCR) in young children with newly diagnosed supratentorial primitive neuroectodermal tumors (sPNETs): report of the Head Start I and II experience. *Pediatr Blood Cancer*. Feb 2008;50(2):312-318. PMID 17668858
4. National Cancer Institute Physician Data Query (PDQ®). Childhood Central Nervous System Embryonal Tumors (last modified August 1, 2013). <http://www.cancer.gov/cancertopics/pdq/treatment/childCNSembryonal/healthprofessional>. Accessed November 21, 2017.
5. Odagiri K, Omura M, Hata M, et al. Treatment outcomes and late toxicities in patients with embryonal central nervous system tumors. *Radiat Oncol*. Sep 11 2014;9:201. PMID 25209395
6. Alsultan A, Alharbi M, Al-Dandan S, et al. High-dose chemotherapy with autologous stem cell rescue in Saudi children less than 3 years of age with embryonal brain tumors. *J Pediatr Hematol Oncol*. Apr 2015;37(3):204-208. PMID 25551668
7. Raleigh DR, Tomlin B, Buono BD, et al. Survival after chemotherapy and stem cell transplant followed by delayed craniospinal irradiation is comparable to upfront craniospinal irradiation in pediatric embryonal brain tumor patients. *J Neurooncol*. Jan 2017;131(2):359-368. PMID 27778212
8. Chintagumpala M, Hassall T, Palmer S, et al. A pilot study of risk-adapted radiotherapy and chemotherapy in patients with supratentorial PNET. *Neuro Oncol*. Sep 2009;11(1):33-40. PMID 18796696
9. Massimino M, Gandola L, Biassoni V, et al. Evolving of therapeutic strategies for CNS-PNET. *Pediatr Blood Cancer*. Dec 2013;60(12):2031-2035. PMID 23852767
10. Lester RA, Brown LC, Eckel LJ, et al. Clinical outcomes of children and adults with central nervous system primitive neuroectodermal tumor. *J Neurooncol*. Nov 2014;120(2):371-379. PMID 25115737
11. Dhall G, Grodman H, Ji L, et al. Outcome of children less than three years old at diagnosis with non-metastatic medulloblastoma treated with chemotherapy on the "Head Start" I and II protocols. *Pediatr Blood Cancer*. Jun 2008;50(6):1169-1175. PMID 18293379
12. Gajjar A, Chintagumpala M, Ashley D, et al. Risk-adapted craniospinal radiotherapy followed by high-dose chemotherapy and stem-cell rescue in children with newly diagnosed medulloblastoma (St Jude Medulloblastoma-96): long-term results from a prospective, multicentre trial. *Lancet Oncol*. Oct 2006;7(10):813-820. PMID 17012043
13. Bergthold G, El Kababri M, Varlet P, et al. High-dose busulfan-thiotepa with autologous stem cell transplantation followed by posterior fossa irradiation in young children with classical or incompletely resected medulloblastoma. *Pediatr Blood Cancer*. May 2014;61(5):907-912. PMID 24470384
14. Lee JY, Kim IK, Phi JH, et al. Atypical teratoid/rhabdoid tumors: the need for more active therapeutic measures in younger patients. *J Neurooncol*. Apr 2012;107(2):413-419. PMID 22134767
15. Raghuram CP, Moreno L, Zacharoulis S. Is there a role for high dose chemotherapy with hematopoietic stem cell rescue in patients with relapsed supratentorial PNET? *J Neurooncol*. Feb 2012;106(3):441-447. PMID 21850536
16. Dunkel IJ, Gardner SL, Garvin JH, Jr., et al. High-dose carboplatin, thiotepa, and etoposide with autologous stem cell rescue for patients with previously irradiated recurrent medulloblastoma. *Neuro Oncol*. Mar 2010;12(3):297-303. PMID 20167818
17. Dunkel IJ, Boyett JM, Yates A, et al. High-dose carboplatin, thiotepa, and etoposide with autologous stem-cell rescue for patients with recurrent medulloblastoma. Children's Cancer Group. *J Clin Oncol*. Jan 1998;16(1):222-228. PMID 9440746
18. Grodman H, Wolfe L, Kretschmar C. Outcome of patients with recurrent medulloblastoma or central nervous system germinoma treated with low dose continuous intravenous etoposide along with dose-intensive chemotherapy followed by autologous hematopoietic stem cell rescue. *Pediatr Blood Cancer*. Jul 2009;53(1):33-36. PMID 19326417
19. Kostaras X, Easaw JC. Management of recurrent medulloblastoma in adult patients: a systematic review and recommendations. *J Neurooncol*. Oct 2013;115(1):1-8. PMID 23877361
20. Bode U, Zimmermann M, Moser O, et al. Treatment of recurrent primitive neuroectodermal tumors (PNET) in children and adolescents with high-dose chemotherapy (HDC) and stem cell support: results of the HITREZ 97 multicentre trial. *J Neurooncol*. Dec 2014;120(3):635-642. PMID 25179451
21. Gill P, Litzow M, Buckner J, et al. High-dose chemotherapy with autologous stem cell transplantation in adults with recurrent embryonal tumors of the central nervous system. *Cancer*. Apr 15 2008;112(8):1805-1811. PMID 18300237
22. Kim H, Kang HJ, Lee JW, et al. Irinotecan, vincristine, cisplatin, cyclophosphamide, and etoposide for refractory or relapsed medulloblastoma/PNET in pediatric patients. *Childs Nerv Syst*. Oct 2013;29(10):1851-1858. PMID 23748464
23. Egan G, Cervone KA, Phillips PC, et al. Phase I study of temozolomide in combination with thiotepa and carboplatin with autologous hematopoietic cell rescue in patients with malignant brain tumors with minimal residual disease. *Bone Marrow Transplant*. Apr 2016;51(4):542-545. PMID 26726947

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Hematopoietic Cell Transplantation for Central Nervous System Embryonal Tumors and Ependymoma

Policy # 00063

Original Effective Date: 01/28/2002

Current Effective Date: 06/20/2018

24. Sung KW, Lim DH, Yi ES, et al. Tandem high-dose chemotherapy and autologous stem cell transplantation for atypical teratoid/rhabdoid tumor. *Cancer Res Treat.* Oct 2016;48(4):1408-1419. PMID 27034140
25. Dufour C, Kieffer V, Varlet P, et al. Tandem high-dose chemotherapy and autologous stem cell rescue in children with newly diagnosed high-risk medulloblastoma or supratentorial primitive neuro-ectodermic tumors. *Pediatr Blood Cancer.* Aug 2014;61(8):1398-1402. PMID 24664937
26. Sung KW, Lim do H, Son MH, et al. Reduced-dose craniospinal radiotherapy followed by tandem high-dose chemotherapy and autologous stem cell transplantation in patients with high-risk medulloblastoma. *Neuro Oncol.* Mar 2013;15(3):352-359. PMID 23258845
27. Friedrich C, von Bueren AO, von Hoff K, et al. Treatment of young children with CNS-primitive neuroectodermal tumors/pineoblastomas in the prospective multicenter trial HIT 2000 using different chemotherapy regimens and radiotherapy. *Neuro Oncol.* Feb 2013;15(2):224-234. PMID 23223339
28. Park ES, Sung KW, Baek HJ, et al. Tandem high-dose chemotherapy and autologous stem cell transplantation in young children with atypical teratoid/rhabdoid tumor of the central nervous system. *J Korean Med Sci.* Feb 2012;27(2):135-140. PMID 22323859
29. Sung KW, Yoo KH, Cho EJ, et al. High-dose chemotherapy and autologous stem cell rescue in children with newly diagnosed high-risk or relapsed medulloblastoma or supratentorial primitive neuroectodermal tumor. *Pediatr Blood Cancer.* Apr 2007;48(4):408-415. PMID 17066462
30. Lundberg JH, Weissman DE, Beatty PA, et al. Treatment of recurrent metastatic medulloblastoma with intensive chemotherapy and allogeneic bone marrow transplantation. *J Neurooncol.* Jun 1992;13(2):151-155. PMID 1432032
31. Matsuda Y, Hara J, Osugi Y, et al. Allogeneic peripheral stem cell transplantation using positively selected CD34+ cells from HLA-mismatched donors. *Bone Marrow Transplant.* Feb 1998;21(4):355-360. PMID 9509968
32. Secondino S, Pedrazzoli P, Schiavetto I, et al. Antitumor effect of allogeneic hematopoietic SCT in metastatic medulloblastoma. *Bone Marrow Transplant.* Jul 2008;42(2):131-133. PMID 18372908
33. Sung KW, Lim do H, Lee SH, et al. Tandem high-dose chemotherapy and autologous stem cell transplantation for anaplastic ependymoma in children younger than 3 years of age. *J Neurooncol.* Apr 2012;107(2):335-342. PMID 22081297
34. Mason WP, Goldman S, Yates AJ, et al. Survival following intensive chemotherapy with bone marrow reconstitution for children with recurrent intracranial ependymoma--a report of the Children's Cancer Group. *J Neurooncol.* Apr 1998;37(2):135-143. PMID 9524092
35. Grill J, Kalifa C, Doz F, et al. A high-dose busulfan-thiotepa combination followed by autologous bone marrow transplantation in childhood recurrent ependymoma. A phase-II study. *Pediatr Neurosurg.* Jul 1996;25(1):7-12. PMID 9055328
36. Zacharoulis S, Levy A, Chi SN, et al. Outcome for young children newly diagnosed with ependymoma, treated with intensive induction chemotherapy followed by myeloablative chemotherapy and autologous stem cell rescue. *Pediatr Blood Cancer.* Jul 2007;49(1):34-40. PMID 16874765
37. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: central nervous system cancers. Version 1.2017. http://www.nccn.org/professionals/physician_gls/PDF/cns.pdf. Accessed November 21, 2017.
38. Majhail NS, Farnia SH, Carpenter PA, et al. Indications for Autologous and Allogeneic Hematopoietic Cell Transplantation: Guidelines from the American Society for Blood and Marrow Transplantation. *Biol Blood Marrow Transplant.* Nov 2015;21(11):1863-1869. PMID 26256941

Policy History

Original Effective Date: 01/28/2002

Current Effective Date: 06/20/2018

- | | |
|------------|--|
| 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. |

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Hematopoietic Cell Transplantation for Central Nervous System Embryonal Tumors and Ependymoma

Policy # 00063

Original Effective Date: 01/28/2002

Current Effective Date: 06/20/2018

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 embryonal 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.
Next Scheduled Review Date: 06/2019

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT)[®]†, copyright 2017 by the American Medical Association (AMA).

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Hematopoietic Cell Transplantation for Central Nervous System Embryonal Tumors and Ependymoma

Policy # 00063
Original Effective Date: 01/28/2002
Current Effective Date: 06/20/2018

CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

The responsibility for the content of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines is with Blue Cross and Blue Shield of Louisiana and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

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	C71.0-C71.9

*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 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.

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Hematopoietic Cell Transplantation for Central Nervous System Embryonal Tumors and Ependymoma

Policy # 00063

Original Effective Date: 01/28/2002

Current Effective Date: 06/20/2018

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: 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.

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.