

Protocol

Hematopoietic Cell Transplantation for Central Nervous System Embryonal Tumors and Ependymoma

(80128)

(Formerly Hematopoietic Stem Cell Transplantation for Central Nervous System Embryonal Tumors and Ependymoma)

Medical Benefit		Effective Date: 04/01/13	Next Review Date: 01/19
Preauthorization	Yes	Review Dates: 04/07, 05/08, 01/10, 01/11, 01/12, 01/13, 01/14, 01/15, 01/16, 01/17, 01/18	

Preauthorization is required and must be obtained through Case Management.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

Populations	Interventions	Comparators	Outcomes
Individuals: • With newly diagnosed central nervous system embryonal tumors	Interventions of interest are: • Autologous hematopoietic cell transplant	Comparators of interest are: • Standard therapy (chemotherapy, radiotherapy, and/or surgical resection)	Relevant outcomes include: • Overall survival • Disease-specific survival • Treatment-related mortality • Treatment-related morbidity
Individuals: • With recurrent/relapsed central nervous system embryonal tumors	Interventions of interest are: • Autologous hematopoietic cell transplant	Comparators of interest are: • Standard therapy (chemotherapy, radiotherapy, and/or surgical resection)	Relevant outcomes include: • Overall survival • Disease-specific survival • Treatment-related mortality • Treatment-related morbidity
Individuals: • With central nervous system embryonal tumors	Interventions of interest are: • Tandem autologous hematopoietic cell transplant	Comparators of interest are: • Standard therapy (chemotherapy, radiotherapy, and/or surgical resection)	Relevant outcomes include: • Overall survival • Disease-specific survival • Treatment-related mortality • Treatment-related morbidity
Individuals: • With central nervous system embryonal tumors	Interventions of interest are: • Allogeneic hematopoietic cell transplant	Comparators of interest are: • Standard therapy (chemotherapy, radiotherapy, and/or surgical resection)	Relevant outcomes include: • Overall survival • Disease-specific survival • Treatment-related mortality • Treatment-related morbidity
Individuals: • With ependymoma	Interventions of interest are: • Autologous hematopoietic cell transplant	Comparators of interest are: • Standard therapy (chemotherapy, radiotherapy, and/or surgical resection)	Relevant outcomes include: • Overall survival • Disease-specific survival • Treatment-related mortality • Treatment-related morbidity

Description

High-dose chemotherapy (HDC) with hematopoietic cell transplantation (HCT) has been investigated as a possible therapy in pediatric patients with brain tumors, particularly in those with disease considered high risk. In addition, the use of HCT has allowed for a reduction in the dose of radiation needed to treat both average- and high-risk disease, with preservation of quality of life and intellectual functioning, without compromising survival.

Summary of Evidence

For individuals who have newly diagnosed central nervous system (CNS) embryonal tumors who receive autologous HCT, the evidence includes prospective and retrospective studies. Relevant outcomes are overall survival, disease-specific survival, and treatment-related morbidity and mortality. 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 event-free survival and overall survival) 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 craniospinal irradiation was comparable to survival in those receiving upfront craniospinal irradiation. Overall, data from these observational studies has suggested HCT may allow reduced doses of craniospinal irradiation without worsening survival outcomes. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have recurrent/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 overall survival, disease-specific survival, and treatment-related morbidity and mortality. For recurrent/relapsed CNS embryonal tumors, survival outcomes after HCT are variable, 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 primitive neuroectodermal tumor (SPNET) 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 has suggested HCT may be associated with improved survival outcomes in select patients, although data for some tumor types is limited (e.g., atypical teratoid/rhabdoid tumors). 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 overall survival, disease-specific survival, and treatment-related morbidity and mortality. 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 overall survival and event-free survival rates comparable to single autologous HCT. Tandem transplants may allow reduced doses of craniospinal irradiation, with the goal of avoiding long-term radiation damage. However, most studies used standard-dose irradiation, making the relative benefit of tandem autologous HCT uncertain. The evidence is insufficient to determine 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 overall survival, disease-specific survival, and treatment-related morbidity and

mortality. 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 overall survival, disease-specific survival, and treatment-related morbidity and mortality. 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.

Policy

Embryonal Tumors of the Central Nervous System

Autologous HCT

Autologous hematopoietic cell transplantation may be considered **medically necessary** as consolidation therapy for previously untreated embryonal tumors of the central nervous system (CNS) that show partial or complete response to induction chemotherapy, or stable disease after induction therapy (see Policy Guidelines).

Autologous hematopoietic cell transplantation may be considered **medically necessary** to treat recurrent embryonal tumors of the CNS.

Tandem autologous hematopoietic cell transplantation is **investigational** to treat embryonal tumors of the CNS.

Allogeneic HCT

Allogeneic hematopoietic cell transplantation is **investigational** to treat embryonal tumors of the CNS.

Ependymoma

Autologous, tandem autologous and allogeneic hematopoietic cell transplantation is **investigational** to treat ependymoma.

Policy Guidelines

In general, the use of autologous hematopoietic cell transplantation 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 [less than 1.5 cm² residual tumor]) when compared to conventional therapies.

Individual transplant facilities may have their own additional requirements or protocols that must be met in order for the patient to be eligible for a transplant at their facility.

Medicare Advantage

If a transplant is needed, we arrange to have the Medicare-approved transplant center review and decide whether the patient is an appropriate candidate for the transplant.

Background

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.

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 (sPNETs; pineoblastoma, cerebral neuroblastoma, ganglioneuro-blastoma), ependymblastoma, atypical teratoid/rhabdoid tumor.

Medulloblastomas account for 20% of all childhood CNS tumors. The other types of embryonal tumors are rare by comparison. 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 three 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 three years or younger, or with metastatic disease, and/or subtotal resection (> 1.5 cm² of residual disease).¹

Current standard treatment regimens for average-risk medulloblastoma (postoperative craniospinal irradiation with boost to the posterior fossa followed by 12 months of chemotherapy) have resulted in five-year overall survival (OS) rates of 80% or better.¹ For high-risk medulloblastoma treated with conventional doses of chemotherapy and radiotherapy, the average event-free survival at five years ranges from 34% to 40% across studies.² Fewer than 55% of children with high-risk disease survive longer than five years. The treatment of newly diagnosed medulloblastoma continues to evolve, and in children younger than age three years, 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.

sPNETs are most commonly located in the cerebral cortex and pineal region. The prognosis for these tumors is worse than for medulloblastoma, despite identical therapies.² After surgery, children are usually treated similarly to children with high-risk medulloblastoma. Three- to five-year OS rates of 40% to 50% have been reported and, for patients with disseminated disease, survival rates at five years range from 10% to 30%.³

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

and autologous HCT for recurrent embryonal tumors, objective response is 50% to 75%; however, long-term disease control is obtained in fewer than 30% of patients and is primarily seen in patients in first relapse with localized disease at the time of relapse.³

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 of recurrence is problematic; further surgical resection or radiotherapy is usually not possible. Given the poor response to conventional-dose chemotherapy, high-dose chemotherapy 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.

Due to their neuroepithelial origin, peripheral neuroblastoma and Ewing sarcoma may be considered PNETs. These peripheral tumors are considered in the Hematopoietic Stem Cell Transplantation for Solid Tumors of Childhood Protocol.

Regulatory Status

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

Related Protocol

Hematopoietic Stem Cell Transplantation for Solid Tumors of Childhood

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

References

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

1. Mueller S, Chang S. Pediatric brain tumors: current treatment strategies and future therapeutic approaches. *Neurotherapeutics*. Jul 2009; 6(3):570-586. PMID 19560746
2. 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
3. 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 September 10, 2014.
4. Odagiri K, Omura M, Hata M, et al. Treatment outcomes and late toxicities in patients with embryonal central nervous system tumors. *Radiat Oncol*. 2014; 9:201. PMID 25209395
5. 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
6. 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*. Oct 24 2016. PMID 27778212
7. Chintagumpala M, Hassall T, Palmer S, et al. A pilot study of risk-adapted radiotherapy and chemotherapy in patients with supratentorial PNET. *Neuro Oncol*. Feb 2009; 11(1):33-40. PMID 18796696
8. 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
9. 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
10. 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
11. 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
12. 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
13. 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
14. 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
15. 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
16. 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

17. 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
18. 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
19. 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
20. 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
21. 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
22. Egan G, Cervone KA, Philips 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
23. 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
24. 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
25. 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
26. 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
27. 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
28. 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
29. 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
30. 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
31. 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
32. 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

33. 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
34. 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
35. 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
36. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: central nervous system cancers. Version 1.2016. http://www.nccn.org/professionals/physician_gls/PDF/cns.pdf. Accessed December 7, 2016.