

Protocol

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

(80128)

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

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 stem 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 stem 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 stem 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 stem 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 stem 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 stem cell transplantation (HSCT) has been investigated as a possible therapy in pediatric patients with brain tumors, particularly in patients with disease that is considered high risk. In addition, the use of HSCT 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

The evidence for autologous HSCT in individuals who have newly diagnosed and recurrent/relapsed central nervous system (CNS) embryonal tumors includes prospective and retrospective single-arm studies. Relevant outcomes are overall survival, disease-specific survival, and treatment-related morbidity and mortality. In the case of pediatric CNS embryonal tumors, an important consideration is whether the use of HSCT may allow for a reduction in radiation dose. Data from single-arm studies using HDC with autologous HSCT 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 that is considered high risk. For recurrent/relapsed CNS embryonal tumors, survival outcomes after HSCT are more variable, and survival is generally very poor for tumors other than medulloblastoma. Data from some single-arm studies using autologous HSCT 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 suggest that a subgroup of infants with chemosensitive disease might benefit from autologous HSCT, achieving survival without the use of radiotherapy, whereas the outcome in older children and/or in pineal location is poor with this modality. However, a relatively large prospective multicenter study reported that HSCT was not associated with improved survival outcomes in patients who had had a good response to therapy. Overall, data from these single-arm studies suggests HSCT may be associated with improved survival outcomes, although data for some tumor types is limited (e.g., atypical teratoid/rhabdoid tumors). HSCT may allow reduced doses of craniospinal irradiation without worsening survival outcomes.

The evidence for tandem autologous HSCT in individuals who have CNS embryonal tumors 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 HSCT for CNS embryonal tumors. The available single-arm studies appear to report overall survival and event-free survival rates comparable to single autologous HSCT. 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 HSCT uncertain.

The evidence for allogeneic HSCT in individuals who have CNS embryonal tumors includes case reports. Relevant outcomes are overall survival, disease-specific survival, and treatment-related morbidity and mortality. The available evidence is limited.

The evidence for autologous HSCT in individuals who have ependymoma 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 HSCT than with standard therapies.

Policy

Embryonal tumors of the CNS

Autologous HSCT

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

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

Allogeneic HSCT

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

Ependymoma

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

Policy Guidelines

In general, the use of autologous hematopoietic stem-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 transplant center review and decide whether the patient is an appropriate candidate for the transplant.

Background

Hematopoietic Stem Cell Transplantation

HSCT refers to a procedure in which hematopoietic stem 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 HSCT) or from a donor (allogeneic HSCT). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood and placenta shortly after delivery of neonates.

HSCT for Brain Tumors

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

CNS 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 alterations. Embryonal tumors of the CNS include medulloblastoma, medulloepithelioma, supratentorial PNETs (sPNETs; pineoblastoma, cerebral neuroblastoma, ganglioneuroblastoma), ependymoblastoma, 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, as 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 HSCT.

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 HSCT may be an option. For patients who receive high-dose chemotherapy and autologous HSCT 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 HSCT has been investigated as a possible salvage therapy.

Note: Other CNS tumors include astrocytoma, oligodendroglioma, and glioblastoma multiforme. However, these tumors arise from glial cells and not neuroepithelial cells.

Note: Due to their neuroepithelial origin, peripheral neuroblastoma and Ewing sarcoma may be considered PNETs. However, these peripheral tumors are considered separately 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 1271.⁴ 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.

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