Protocol

Hematopoietic Cell Transplantation for Central Nervous System Embryonal Tumors and Ependymoma

(80128)

Medical Benefit		**Effective Date**: 04/01/13	**Next Review Date**: 01/21
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, 01/19, 01/20	

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 or 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 with hematopoietic cell transplantation (HCT) has been investigated as a possible therapy in pediatric patients with brain tumors, particularly in those with high-risk disease. Moreover, the use of

HCT has allowed for a reduction in the dose of radiation needed to treat both average- and high-risk disease, all while preserving the quality of life and intellectual functioning and 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 (OS), disease-specific survival (DSS), and treatment-related mortality (TRM) 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 high-dose chemotherapy with autologous HCT to treat newly diagnosed CNS embryonal tumors have shown comparable or improved survival (both event-free survival and OS) compared with historical controls treated with conventional therapy, with or without radiotherapy, particularly in patients with a disease considered high-risk. In a retrospective comparative study, survival in patients receiving high-dose chemotherapy with HCT and delayed craniospinal irradiation was comparable with survival in those receiving upfront craniospinal irradiation. Overall, data from these observational studies have 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 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, DSS, and TRM 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 primitive neuroectodermal tumor suggested that a subgroup of infants with the 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., 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 OS, DSS, and TRM 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 event-free survival rates comparable with single autologous HCT. Tandem transplants might 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 OS, DSS, and TRM 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, DSS, and TRM 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.

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, 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 cm^2 residual tumor]) compared with 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

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. Medulloblastomas account for 20% of all childhood CNS tumors.

Recurrent childhood CNS embryonal tumor is not uncommon and, depending on which type of treatment the patient initially received, autologous hematopoietic cell transplantation (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 the first relapse with localized disease at the time of the relapse.[1]

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 neuraxis. Ependymomas are distinct from ependymoblastomas due to their more mature histologic differentiation.

Other CNS Tumors

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 primitive neuroectodermal tumors. These peripheral tumors are considered the Hematopoietic Cell Transplantation for Solid Tumors of Childhood Protocol.

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 the 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.

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, title 21, parts 1270 and 1271. Hematopoietic stem cells are included in these regulations.

RELATED PROTOCOL

Hematopoietic Cell Transplantation for Solid Tumors of Childhood

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