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Hematopoietic Cell Transplantation for Central Nervous System Embryonal Tumors and Ependymoma

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Legislative Mandates

EXCEPTION: For Illinois only: Illinois Public Act 103-0458 [Insurance Code 215 ILCS 5/356z.61] (HB3809 Impaired Children) states all group or individual fully insured PPO, HMO, POS plans amended, delivered, issued, or renewed on or after January 1, 2025 shall provide coverage for therapy, diagnostic testing, and equipment necessary to increase quality of life for children who have been clinically or genetically diagnosed with any disease, syndrome, or disorder that includes low tone neuromuscular impairment, neurological impairment, or cognitive impairment.

Coverage

Central Nervous System Embryonal Tumors

Autologous Hematopoietic Cell Transplantation (HCT)

Autologous HCT **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.

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

Tandem autologous hematopoietic cell transplantation **is considered experimental, investigational and/or unproven** to treat embryonal tumors of the CNS.

Allogeneic Hematopoietic Cell Transplantation

Allogeneic HCT **is considered experimental, investigational and/or unproven** to treat embryonal tumors of the CNS.

Ependymoma

Autologous, tandem autologous, and allogeneic hematopoietic cell transplantation **is considered experimental, investigational and/or unproven** to treat ependymoma.

Policy Guidelines

In general, use of autologous hematopoietic cell transplantation for previously untreated medulloblastoma has shown no survival benefit for those individuals considered to be at average risk (i.e., age >3 years, without metastatic disease, and with total or near-total surgical resection [$<1.5 \text{ cm}^2$ residual tumor]) compared with conventional therapies.

Other CNS tumors include astrocytoma, oligodendroglioma, and glioblastoma multiforme. However, these tumors arise from glial cells and not neuroepithelial cells. These tumors are considered separately in Medical Policy SUR703.042.

Due to their neuroepithelial origin, peripheral neuroblastoma and Ewing sarcoma may be considered primitive neuroectodermal tumors. However, these peripheral tumors are considered separately in Medical Policy SUR703.044.

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. The use of HCT has allowed for a reduction in the dose of radiation needed to treat both average- and high-risk disease with a goal of preserving the quality of life and intellectual functioning.

Central Nervous System Embryonal Tumors

Classification of brain tumors is based on both histopathologic characteristics of the tumor and location in the brain. Central nervous system (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 tumors are 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, the 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 with a first relapse of 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 neuroaxis. Ependymomas are distinct from ependymoblastomas due to their more mature histologic differentiation.

Hematopoietic Cell Transplantation

Hematopoietic cell transplantation is a procedure in which hematopoietic stem cells are intravenously infused to restore bone marrow and immune function in cancer patients who receive bone marrow-toxic doses of cytotoxic drugs with or without whole-body radiotherapy. Hematopoietic stem cells may be obtained from the transplant recipient (autologous HCT) or a donor (allogeneic HCT [allo-HCT]). These cells can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates.

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HCT. In allogeneic stem cell transplantation, immunologic compatibility between donor and patient is a critical factor for achieving a successful outcome. Compatibility is established by typing of human leukocyte antigens (HLA) using cellular, serologic, or molecular techniques. HLA refers to the gene complex expressed at the HLA-A, -B, and -DR (antigen-D related) loci on each arm of chromosome 6. An acceptable donor will match the patient at all or most of the HLA loci.

Conditioning for Hematopoietic Cell Transplantation

Conventional Conditioning

The conventional ("classical") practice of allo-HCT involves administration of cytotoxic agents (e.g., cyclophosphamide, busulfan) with or without total body irradiation at doses sufficient to cause bone marrow ablation in the recipient. The beneficial treatment effect of this procedure is due to a combination of the initial eradication of malignant cells and subsequent graft-versus-malignancy effect mediated by non-self-immunologic effector cells. While the slower graft-versus-malignancy effect is considered the potentially curative component, it may be overwhelmed by existing disease in the absence of pretransplant conditioning. Intense conditioning regimens are limited to patients who are sufficiently medically fit to tolerate substantial adverse effects. These include opportunistic infections secondary to loss of endogenous bone marrow function and organ damage or failure caused by cytotoxic drugs.

Subsequent to graft infusion in allo-HCT, immunosuppressant drugs are required to minimize graft rejection and graft-versus-host disease (GVHD), which increases susceptibility to opportunistic infections.

The success of autologous HCT is predicated on the potential of cytotoxic chemotherapy, with or without radiotherapy, to eradicate cancerous cells from the blood and bone marrow. This permits subsequent engraftment and repopulation of the bone marrow with presumably normal hematopoietic stem cells obtained from the patient before undergoing bone marrow ablation. Therefore, autologous HCT is typically performed as consolidation therapy when the patient's disease is in complete remission. Patients who undergo autologous HCT are also susceptible to chemotherapy-related toxicities and opportunistic infections before engraftment, but not GVHD.

Reduced-Intensity Conditioning Allogeneic Hematopoietic Cell Transplantation

Reduced-intensity conditioning (RIC) refers to the pretransplant use of lower doses of cytotoxic drugs or less intense regimens of radiotherapy than are used in traditional full-dose myeloablative conditioning treatments. Although the definition of RIC is variable, with numerous versions employed, all regimens seek to balance the competing effects of relapse due to residual disease and non-relapse mortality. The goal of RIC is to reduce disease burden and to minimize associated treatment-related morbidity and non-relapse mortality in the period during which the beneficial graft-versus-malignancy effect of allogeneic transplantation develops. Reduced-intensity conditioning regimens range from nearly total myeloablative to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and patient condition. Patients who undergo RIC with allo-HCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism. In this review, the term reduced-intensity conditioning will refer to all conditioning regimens intended to be nonmyeloablative.

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

Rationale

Medical policies assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the 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 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 technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent 1 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. Randomized controlled trials 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 (CNS) EMBRYONAL TUMORS

Newly Diagnosed CNS Embryonal Tumors

Central nervous system (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.

Treatment protocols for embryonal tumors 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). (2)

Current standard treatment regimens for average-risk medulloblastoma (postoperative craniospinal irradiation [CSI] with a boost to the posterior fossa followed by 12 months of chemotherapy) have resulted in 5-year overall survival (OS) rates of 80% or better. (2) Clinical outcomes are related to molecular characteristics of the tumor. (3) Rates of OS range from 40% to 90%, depending on the molecular subtype of the medulloblastoma, extent of dissemination at time of diagnosis, and degree of resection. For high-risk medulloblastoma in younger children treated with conventional doses of chemotherapy and radiotherapy, event-free survival (EFS) at 5 years ranges from 30% to 70% across studies. Children with medulloblastoma who survive for 5 years are considered cured of their tumor. Survival rates for other embryonal

tumors are generally poorer, ranging from less than 5% to 50%. The treatment of newly diagnosed medulloblastoma continues to evolve.

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.

(3) 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%. (1)

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. Autologous hematopoietic cell transplantation (HCT) allows for the 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.

Clinical Context and Therapy Purpose

The purpose of autologous stem cell transplantation is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals who have newly diagnosed CNS embryonal tumors.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with newly diagnosed CNS embryonal tumors. Embryonal tumors of the CNS include medulloblastoma, medulloepithelioma, supratentorial PNET (pineoblastoma, cerebral neuroblastoma, ganglioneuroblastoma), ependymblastoma, and atypical teratoid/rhabdoid tumor.

Interventions

The therapy being considered is autologous HCT.

Comparators

The following practices are currently being used to treat newly diagnosed CNS embryonal tumors: surgical resection with the goal being gross total resection with adjuvant radiotherapy because medulloblastomas are very radiosensitive.

Outcomes

The general outcomes of interest are OS, disease-specific survival (DSS), change in disease status, and treatment-related mortality. 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.

Patients with newly diagnosed CNS embryonal tumors have been considered for stem cell transplantation in the setting of remission after induction therapy. If a transplant were to be performed, follow-up would be intensive weekly to monthly surveillance during the first year after transplant and life-long if there is a successful transplant.

Study Selection

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse effects, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Observational Studies

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.

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. (4) Among all patients included, 16, 4, 3, and 1, respectively, had medulloblastoma, PNET, atypical teratoid/rhabdoid tumor, 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. For the high-risk group, CSI 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 to 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. (5) Of the 10 patients, 5 had medulloblastoma, 3 had atypical teratoid/rhabdoid tumor, 1 had an embryonal tumor with abundant neuropil and true rosettes, and 1 had pineoblastoma; all underwent subtotal resection and induction chemotherapy. Five patients received radiotherapy, along with the atypical teratoid/rhabdoid tumor 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 2 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. (6) All patients underwent surgical resection. Following surgery, 56% of patients received adjuvant CSI followed by chemotherapy (upfront radiotherapy), 32% of patients received high-dose chemotherapy (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 the 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 PNET treated with risk-adapted CSI and subsequent HDC with autologous HCT between 1996 and 2003. (7) Eight patients were considered at average-risk and 8 at high-risk (defined as the presence of residual tumor $>1.5\text{ cm}^2$ or disseminated disease in the neuroaxis). Median age at diagnosis was 7.9 years (range, 3 to 21 years). Seven patients had pineal PNET. After a median follow-up of 5.4 years, 12 patients were alive. Five-year EFS and OS rates for the patients with the 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 supratentorial PNET, without compromising EFS.

Fangusaro et al. (2008) reported on outcomes for 43 children with newly diagnosed supratentorial PNET treated prospectively in 2 serial studies (Head Start 1, Head Start 2) between 1991 and 2002 with intensified induction chemotherapy followed by myeloablative chemotherapy and autologous HCT. (2) There were no statistical differences between Head Start 1 and Head Start 2 patient demographics. After maximal surgical resection, patients underwent induction chemotherapy. If, after induction, the disease remained stable or there was a partial response or complete response, 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 an HDC schedule (methotrexate, etoposide, cyclophosphamide, carboplatin with or without vincristine) with autologous HCT rescue, followed by 1 of 2 radiotherapy options. (8) For the first 15 patients, HDC and stem cell rescue was followed by hyperfractionated accelerated CSI with 2 high-dose thiopeta 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 to 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. (9) Overall, 5-year disease-free survival rates were 78% for pediatric patients and 22% for adult patients ($p=.004$); 5-year OS rates were 67% for pediatric patients and 33% for adult patients ($p=.07$). 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; $p=.05$). However, these results were confounded by higher rates of HCT use in children, who had a 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 subsequent myeloablative chemotherapy and autologous HCT. (10) 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 the 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. (11) After tumor resection, patients were classified as having an 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. (12) Subjects were treated at a single center from 1994 to 2010. On pathology, 14 patients had classic medulloblastoma, while 3 had desmoplastic/nodular medulloblastoma and 1 had medulloblastoma with extensive nodularity. Median follow-up was 40.5 months (range, 14.5 to 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 to 30.7 months) after HCT. The authors concluded that high OS is possible with focal brain irradiation in the setting of HCT for medulloblastoma.

Dufour et al. (2021) reported on outcomes for children 5 years and older with newly diagnosed high-risk medulloblastoma treated with high-dose chemotherapy plus autologous HCT, followed by conventional CSI from an open-label, multicenter, single-arm study. (13) Medulloblastoma was considered high-risk in the presence of metastatic disease, greater than 1.5 cm² residual disease, if unfavorable histopathology was present, or *MYCN* or *MYC* genes were amplified. Fifty-one patients (median age at diagnosis, 8 years; range 5 to 19 years) were included in the study. All children received postoperative induction chemotherapy (etoposide and carboplatin), followed by 2 high-dose thiotepa courses with autologous HCT. The median time between diagnosis and onset of radiation therapy was 146 days (range, 117 to 210 days) and in 16 (34%) out of 47 patients, this delay was greater than 150 days. Median follow-up was 7.1 years (range, 3.4 to 9.0 years). At 3 years, PFS and OS rates were 78% (95% CI, 65% to 88%) and 84% (95% CI, 72% to 92%), respectively. At 5 years, PFS and OS rates were 76% (95% CI, 63% to 86%) and 76% (95% CI, 63% to 86%), respectively. No treatment-related deaths were reported. The authors concluded that the treatment regimen of high-dose chemotherapy plus autologous HCT and conventional CSI resulted in a high survival rate in children with newly diagnosed high-risk medulloblastoma.

Zhang et al. (2022) compared the efficacy of HDC and autologous HCT combination (group A) to conventional chemotherapy (group B) after postoperative radiotherapy in patients with newly diagnosed medulloblastoma through a meta-analysis of 22 retrospective, single-arm clinical studies. (14) Of the 22 studies included, 416 patients comprised group A and 2331 patients were in group B. There was no difference in clinical benefit rate between the 2 groups (80% vs. 71.5%; p=.262). The 3- and 5-year PFS rates of HDC and HCT (group A) were significantly better than conventional chemotherapy (group B) (3-year PFS, 79% vs. 69.5%; p=.004; 5-year PFS, 83.6% vs. 75.6%; p=.004). There was no difference between 3- and 5-year OS between the 2 groups. In terms of adverse events, the gastrointestinal toxicity with HDC and HCT was

significantly higher than with conventional chemotherapy ($p=.016$) and the level 3/4 ototoxicity in high-risk group A (HDC and HCT) was higher than in group B ($p=.001$).

Atypical Teratoid/Rhabdoid Tumor

Reddy et al. (2021) studied the impact of high-dose chemotherapy with autologous HCT and early radiation therapy in patients with atypical teratoid or rhabdoid tumors in a nonrandomized cohort study. (15) After surgery, the study regimen consisted of 2 courses of multiagent chemotherapy, followed by 3 courses of high-dose chemotherapy with autologous HCT and radiation therapy. Patients who were younger than 36 months of age ($n=54$) were included in primary analysis and compared with a historical cohort who received a different combination of multiagent chemotherapy followed by radiation therapy but no HCT support. (15, 16) Median follow-up time was 4.7 years (95% CI, 4.2 to 5.3 years). (15) Treatment with the study regimen significantly reduced the risk of EFS events in patients younger than 36 months compared with the historical cohort (HR, 0.43; 95% CI, 0.28 to 0.66; $p<.0005$). Four-year EFS and OS for the entire cohort of patients ($N=65$), including patients older than 36 months, were 37% (95% CI, 25% to 49%) and 43% (95% CI, 31% to 55%), respectively. Treatment-related deaths occurred in 4 patients.

Lee et al. (2012) retrospectively reviewed the medical records of 13 patients diagnosed with atypical teratoid/rhabdoid tumor who were treated at a children's hospital in South Korea. (17) Median age was 12 months (range, 3 to 67 months), with 7 patients being younger than 1 year at diagnosis. Three (23%) patients underwent HDC and autologous HCT. The 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 ($p=.36$); however, median survival was longer in the HCT group (15 months) than in the non-HCT 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 are primarily from single-arm studies and case series. These studies have suggested comparable or improved EFS and OS rates compared with historical controls, particularly in patients with a disease considered high-risk. One retrospective study compared HDC with HCT and delayed CSI to upfront CSI. Rates of metastasis, PFS, and OS were similar in the groups, but patients in the delayed irradiation group were younger than those in the upfront irradiation group. Hematopoietic cell transplantation may permit reduced doses of CSI without worsening survival outcomes.

Recurrent or Relapsed Central Nervous System Embryonal Tumors

Clinical Context and Therapy Purpose

The purpose of autologous stem cell transplantation in individuals who have recurrent or relapsed CNS embryonal tumors is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with recurrent or relapsed CNS embryonal tumors.

Interventions

The therapy being considered is autologous HCT.

Comparators

The following practices are currently being used to treat recurrent and relapsed CNS embryonal tumors: surgical resection. Chemotherapy or radiation therapy alone or chemoradiation are additional treatment options. Some individuals are candidates for palliative therapy.

Outcomes

The general outcomes of interest are OS, DSS, change in disease status, and treatment-related mortality.

If a transplant were to be performed, follow-up would be intensive, weekly to monthly surveillance during the first year after transplant and life-long if there is a successful transplant.

Study Selection

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse effects, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Observational Studies

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 case series, most of which include patients with a single tumor type.

Relapsed Supratentorial Primitive Neuroectodermal Tumor

Raghuram et al. (2012) reported on a systematic review of outcomes for patients with relapsed supratentorial PNET treated with HDC and autologous HCT. (18) Eleven observational studies, including 4 prospective series (N=46 patients) with relapsed supratentorial PNET 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 to 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; $p=.003$). In multivariable

regression, the pineal location was the only independent adverse prognostic factor for survival. Based on these pooled results, CSI may not be associated with survival outcomes in young children treated with HCT. However, OS is poor in older children with relapsed supratentorial PNET, 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. (19) 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 to 35.5 years). Median age at the time of HCT was 13.8 years (range, 7.6 to 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 to 114.7 months). The 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). High-dose chemotherapy before HCT consisted of carboplatin, thiotepa, and etoposide. Total relapse 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 to 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%). The 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. (20) Seven patients had EFS at a median of 54 months, with the OS rate estimated at 46% at 36 months. Hematopoietic cell transplantation was expected to be most effective with minimal disease burden. Thus, Dunkel et al. (1998) suggested increased 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. (21) Mean age was 12.9 years (range, 5 to 27.8 years). Mean survival posttransplant was 4.8 years (range, 8 to 160+ months). Two-year and 5-year OS rates were 75% and 50%, respectively.

Kostaras et al. (2013) conducted a systematic review of therapies for adults with relapsed medulloblastoma, including HDC with HCT. (22) 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; $p=.04$). 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, supratentorial PNET). 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. (23) 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 a 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 historical control group of patients treated with conventional-dose chemotherapy ($n=13$). (24) In the HCT group, 6 patients received tandem autologous transplants. Autologous HCT was associated with increased survival ($p=.044$) and a longer time to progression of the disease ($p=.028$). Median time to progression for the conventional chemotherapy versus 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, 5 of the HCT patients were alive, 4 without disease progression. In a comparison of outcomes between patients who received a single versus tandem transplant, there was an improvement in time to progression favoring tandem transplant ($p=.046$), but no difference in survival was observed ($p=.132$).

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%. (25) 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. (26) Temozolomide was administered, followed by thiotepa and carboplatin and then autologous HCT. The study enrolled 27 patients (age range, 3 to 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 supratentorial PNET 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 the 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.

Central Nervous System Embryonal Tumors Treated with Tandem Transplant

Clinical Context and Therapy Purpose

The purpose of tandem autologous stem cell transplantation in individuals who have CNS embryonal tumors is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this medical policy.

Populations

The relevant population of interest is individuals with CNS embryonal tumors as previously described.

Interventions

The therapy being considered is tandem autologous HCT which has been investigated as a therapy in the setting of remission after induction therapy. The 2 transplants are performed within a 6-month window. A tandem transplant may include a dose escalation of the conditioning chemotherapy regimen.

Comparators

The following practices are currently being used to treat CNS embryonal tumors: chemotherapy, chemoradiation, or post-induction single autologous stem cell transplant.

Outcomes

The general outcomes of interest are OS, DSS, change in disease status, and treatment-related mortality.

Individuals with CNS embryonal tumors have been considered for stem cell transplantation in the setting of remission after induction therapy or relapse after first-line chemotherapy. If a transplant were to be performed, follow-up would be intensive weekly to monthly surveillance during the first year after transplant and life-long if there is a successful transplant.

Study Selection

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse effects, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Observational Studies

Sung et al. (2016) reported on prospective follow-up for 13 children with atypical teratoid/rhabdoid tumor who received tandem HDC and autologous HCT. (27) Five of the children were younger than 3 years old; the remaining 8 were 3 years or older. Tandem HDC and autologous HCT were 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 a median follow-up of 64 months.

Dufour et al. (2014) reported on outcomes for patients with newly diagnosed high-risk medulloblastoma and supratentorial PNET treated with tandem HDC and autologous HCT support followed by conventional craniospinal radiotherapy. (28) Twenty-four children older than 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 3 with supratentorial PNET. 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 to 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.

Sung et al. (2013) 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 cm² without metastasis). (29) The tumor relapsed or progressed in 4 patients, and 2 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 to 82 months) from diagnosis. Late adverse events, evaluated at a median of 36 months (range, 12 to 68 months) after tandem HCT included hypothyroidism, growth hormone deficiency, sex hormone deficiency, hearing loss, and renal tubulopathy.

Friedrich et al. (2013) reported on the results of double-tandem HDC with autologous HCT in 3 children younger than 4 years of age with metastatic supratentorial PNET. (30) These patients also received preventive craniospinal radiotherapy; they had the residual disease before HCT but no evidence of disease after transplant (survival range, 2 to 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 atypical teratoid/rhabdoid tumors. (31) 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 to 64 months) from the 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.

Sung et al. (2007) 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. (32) Three-year EFS rates for patients in complete or partial response and less than partial response at first HDC were 67% and 16.7%, respectively. For 19 cases in complete or partial response 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 but appear to report OS and EFS rates comparable with single autologous HCT. Tandem transplants may allow reduced doses of craniospinal irradiation, but most studies used standard-dose irradiation, making the relative benefit of tandem autologous HCT uncertain.

Central Nervous System Embryonal Tumors Treated with Allogeneic Transplant

Clinical Context and Therapy Purpose

The purpose of allogeneic stem cell transplantation in individuals who have CNS embryonal tumors is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with CNS embryonal tumors, as previously described.

Interventions

The therapy being considered is allogeneic HCT.

Comparators

The following practices are currently being used to treat CNS embryonal tumors: chemotherapy, chemoradiation, or post-induction single autologous stem-cell transplant.

Outcomes

The general outcomes of interest are OS, DSS, change in disease status, and treatment-related mortality. Follow-up would be intensive weekly to monthly surveillance during the first year after transplant and life-long if there is a successful transplant.

Study Selection

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse effects, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Observational Studies

Use of allogeneic HCT for CNS embryonal tumors consists of rare case reports with mixed results. (33-35)

Section Summary: Central Nervous System Embryonal Tumors Treated with Allogeneic Transplant

For individuals who have CNS embryonal tumors who receive allogeneic HCT, the evidence includes case reports. Relevant outcomes are OS, DDS, and treatment-related mortality and morbidity. The available evidence is limited.

Central Nervous System Ependymoma Tumors Treated with Autologous Transplant

The 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, HDC with autologous HCT has been investigated as possible salvage therapy.

Clinical Context and Therapy Purpose

The purpose of autologous stem cell transplantation in individuals who have CNS ependymomas is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with CNS ependymomas.

Interventions

The therapy being considered is autologous HCT.

Comparators

The following practices are currently being for the treatment of ependymomas: maximal surgical resection followed by radiotherapy.

Outcomes

The general outcomes of interest are OS, DSS, change in disease status, and treatment-related mortality. Follow-up would be intensive weekly to monthly surveillance during the first year after transplant and life-long if there is a successful transplant.

Study Selection

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse effects, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Observational Studies

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. (36) All patients were alive at a median follow-up of 45 months (range, 31 to 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. (37) Five patients died of treatment-related toxicities, 8 died from a progressive disease, and 1 died of unrelated causes. After 25 months, 1 patient remained alive but with tumor recurrence. The authors concluded that their high-dose regimen of thiotepa and etoposide was not an effective treatment of ependymoma. Grill et al. (1996) similarly reported a disappointing experience in 16 children treated with a thiotepa-based high-dose regimen. (38)

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. (39) 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.

Section Summary: CNS Ependymomas Treated with Autologous Stem-Cell Transplant

For individuals who have ependymoma who receive autologous HCT, the evidence includes relatively small case series. The available case series do not report higher survival rates for patients with ependymoma treated with HCT compared with standard therapies.

Summary of Evidence

For individuals who have newly diagnosed central nervous system (CNS) embryonal tumors who receive autologous hematopoietic cell transplantation (HCT), the evidence includes prospective and retrospective studies. Relevant outcomes are overall survival (OS), disease-specific survival (DSS), 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 high-dose chemotherapy with autologous HCT to treat newly diagnosed CNS embryonal tumors have shown comparable or improved survival (both event-free survival [EFS] 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 (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 an 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 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 primitive neuroectodermal tumor (PNET) 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 the 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 an 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 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 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 that the technology results in an improvement in the net health outcome.

For individuals who have CNS embryonal tumors who receive allogeneic HCT, the evidence includes case reports. Relevant outcomes are OS, DSS, and treatment-related mortality and morbidity. The available evidence is limited. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have ependymoma who receive autologous HCT, the evidence includes relatively small case series. Relevant outcomes are OS, DSS, 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 that the technology results in an improvement in the net health outcome.

Practice Guidelines and Position Statements

American Society for Blood and Marrow Transplantation

In 2015, the American Society for Blood and Marrow Transplantation (now referred to as the American Society for Transplantation and Cellular Therapy) published consensus guidelines on the use of hematopoietic cell transplantation (HCT) to treat specific conditions, in both clinical trial and clinical practice settings. (40) These guidelines were updated in 2020. (41) Neither the 2015 nor the 2020 guidelines address HCT in treatment of ependymomas. The tumors addressed in this review for which the Society has provided recommendations are listed in Table 1.

Table 1. Recommendations for Use of Autologous and Allogeneic Hematopoietic Cell Transplantation in Pediatric Patients (<18 years)

Condition	Treatment Option	2015 Recommendation	2020 Recommendation
Neuroblastoma, high-risk or relapse	Allogeneic HCT	Developmental	Developmental
	Autologous HCT	Standard of care	Standard of care; tandem autologous HCT recommended over single transplant
Medulloblastoma, high-risk	Allogeneic HCT	Not generally recommended	Not generally recommended
	Autologous HCT	Standard of care, clinical evidence available	Standard of care, clinical evidence available
Other malignant brain tumors	Allogeneic HCT	Not generally recommended	Not generally recommended
	Autologous HCT	Standard of care, clinical evidence available	Standard of care, clinical evidence available

HCT: hematopoietic cell transplantation.

National Comprehensive Cancer Network

Current National Comprehensive Cancer Network (NCCN; v.3.2024) guidelines on treating central nervous system tumors make the following recommendations about HCT (42):

- For medulloblastoma and supratentorial primitive neuroectodermal tumor, high-dose chemotherapy with autologous HCT for localized recurrent disease with maximum safe resection is a category 2A recommendation (based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate).

Ongoing and Unpublished Clinical Trials

A currently ongoing and unpublished trial that might influence this policy is listed in Table 2.

Table 2. Summary of Key Trials

NCT Number	Trial Name	Planned Enrollment	Completion Date
<i>Ongoing</i>			
NCT00336024	A Phase III Randomized Trial for the Treatment of Newly Diagnosed Supratentorial PNET and High Risk Medulloblastoma in Children < 36 Months Old With Intensive Induction Chemotherapy With Methotrexate Followed by Consolidation With Stem Cell Rescue Versus the Same Therapy Without Methotrexate	91	Dec 2028

NCT: national clinical trial.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	36511, 38204, 38205, 38206, 38207, 38208, 38209, 38210, 38211, 38212, 38213, 38214, 38215, 38220, 38221, 38222, 38230, 38232, 38240, 38241, 38242, 38243, 81265, 81266, 81267, 81268, 81370, 81371, 81372, 81373, 81374, 81375, 81376, 81377, 81378, 81379, 81380, 81381, 81382, 81383, 86805, 86806, 86807, 86808, 86812, 86813, 86816, 86817, 86821, 86822, 86825, 86826, 86828, 86829, 86830, 86831, 86832, 86833, 86834, 86835, 86849, 86950, 86985, 88240, 88241
HCPCS Codes	S2140, S2142, S2150

*Current Procedural Terminology (CPT®) ©2024 American Medical Association: Chicago, IL.

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <<https://www.cms.hhs.gov>>.

Policy History/Revision	
Date	Description of Change
04/01/2025	Reviewed. No changes.
02/01/2025	Document updated with literature review. Coverage unchanged. No new references added; some updated.
01/01/2024	Document updated with literature review. Coverage unchanged. Reference 14 added.
06/15/2022	Document updated with literature review. Coverage unchanged. References 13-15 and 41 added; some updated and others removed.
08/01/2021	Reviewed. No changes.
08/15/2020	Document updated with literature review. Coverage unchanged. No new references added; other references updated. Title changed from: Hematopoietic Stem-Cell Transplantation for Central Nervous System Embryonal Tumors and Ependymoma.
06/15/2019	Reviewed. No changes.
07/01/2018	Document updated with literature review. Coverage unchanged. References 7, 23-24, and 38 added.
06/01/2017	Reviewed. No changes.
07/01/2016	Document updated with literature review. Coverage unchanged.
02/15/2015	Document updated with literature review. Coverage language modified, without change to coverage position. CPT/HCPCS code(s) updated. Title changed from: Stem-Cell Transplant for Central Nervous System (CNS) Embryonal Tumors and Ependymoma.
10/15/2013	Document updated with literature review. The following was added: 1) Autologous stem-cell support may be considered medically necessary for the treatment of CNS embryonal tumors as consolidation therapy for previously untreated embryonal CNS tumors that show partial or complete response to induction chemotherapy; or stable disease after induction therapy; 2) Autologous stem-cell support is considered experimental, investigational and unproved for the treatment of previously untreated medulloblastoma; 3) Hematopoietic progenitor cell (HPC) boost is considered experimental, investigational and unproven; and 4) Any related services, other than autologous SCS determined to be medically necessary, for the treatment of embryonal tumors of the CNS or ependymoma, such as short tandem repeat (STR) markers, are considered experimental, investigational and unproven. Rationale significantly revised. Title changed from Stem-Cell Transplant for Primitive Neuroectodermal Tumors (PNET) of the CNS and Ependymoma.
04/01/2010	New medical document originating from: SUR703.017, Peripheral/Bone Marrow Stem Cell Transplantation (PSCT/BMT) for Non-Malignancies; SUR703.018, Peripheral/Bone Marrow Stem Cell Transplantation

	(PSCT/BMT) for Malignancies; SUR703.022, Cord Blood as a Source of Stem Cells (CBSC); SUR703.023, Donor Leukocyte Infusion (DLI); and SUR703.024, Tandem/Triple High-Dose Chemoradiotherapy with Stem Cell Support for Malignancies. Stem cell transplant continues to be medically necessary when stated criteria are met. NOTE: A link to the medical policies with the following titles can be found at the end of the medical policy SUR703.002, Stem-Cell Reinfusion or Transplantation Following Chemotherapy (General Donor and Recipient Information): • Peripheral/Bone Marrow Stem Cell Transplantation (PSCT/BMT) for Non-Malignancies; • Peripheral/Bone Marrow Stem Cell Transplantation (PSCT/BMT) for Malignancies; • Cord Blood as a Source of Stem Cells; • Donor Leukocyte Infusion (DLI); and • Tandem/Triple High-Dose Chemoradiotherapy
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