Medical Policy

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Title: BMT- Hematopoietic Cell Transplantation (HCT) for CNS Tumors, Embryonal Tumors, and Ependymoma

Description/Background

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. They include medulloblastoma, medulloepithelioma, supretentorial PNET's (pineoblastoma, cerebral neuroblastoma, ganglioneuroblastoma), ependymoblastomas, atypical teratoid/rhabdoid tumors and embryonal tumor with multilayered rosettes. 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 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)

Now intensive induction therapy followed by triple tandem cycles of high-dose therapy with peripheral-blood stem cell rescue is proposed for pediatric patients with a CNS brain tumor.

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.

Choroid Plexus Carcinoma
Choroid plexus carcinoma is a rare cancerous primary central nervous system tumor which occur primarily in children. The tumor begins in the brain tissue that makes cerebrospinal fluid (choroid plexus) which is located in the ventricles. Tumors commonly invade nearby tissue and spread widely via the cerebrospinal fluid which surrounds the brain and spinal cord.

Hematopoietic Cell Transplantation
Hematopoietic cell transplantation (HCT) is a procedure in which hematopoietic 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]). They 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 HCT

Myeloablative (Conventional) Conditioning
The myeloablative (conventional) practice of allo-HCT involves administration of cytotoxic agents (e.g., cyclophosphamide, busulfan) with or without total body irradiation. Intense conditioning regimens are limited to individuals whose health status is sufficient to tolerate the administration of cytotoxic agents with 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 initial eradication of malignant cells and subsequent graft-versus-malignancy (GVM) effect mediated by non-self-immunologic effector cells. While the slower GVM effect is considered the potentially curative component, it may be overwhelmed by substantial adverse effects. These include opportunistic infections secondary to loss of endogenous bone marrow function and organ damage and failure caused by the cytotoxic drugs. Subsequent to graft infusion in allo-HCT, immunosuppressant drugs are required to minimize graft rejection and graft-versus-host-disease, which increases susceptibility to opportunistic infections.

The success of autologous HCT is predicated on the ability of cytotoxic chemotherapy with or without radiotherapy, to eradicate cancerous cells from the blood and bone marrow. This permits subsequent engraftment and repopulation of bone marrow with presumably normal

hematopoietic stem cells obtained from the individual before undergoing bone marrow ablation. Therefore, autologous HCT is typically performed as consolidation therapy when the individual's disease is in complete remission. Individuals who undergo autologous HCT are also susceptible to chemotherapy-related toxicities and opportunistic infections before engraftment, but not graft-versus-host disease.

Reduced-Intensity or Non-myeloablative Conditioning for Allo-HCT
Reduced-intensity conditioning (RIC), sometimes referred to as non-myeloablative (NMA) conditioning, refers to the pretransplant use of lower doses of cytotoxic drugs with or without less intense regimens of radiotherapy than are used in myeloablative conditioning treatments. Although the definition of RIC/NMA 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/NMA 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. These RIC/NMA regimens range from nearly totally myeloablative to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and individual condition. Individuals who undergo RIC/NMA with allo-HCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism. 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 allogeneic HCT for solid tumors does not rely on escalation of chemotherapy intensity and tumor reduction but rather on a graft-versus-tumor effect. Allogeneic HCT is not commonly used in solid tumors and may be used if an autologous source cannot be cleared of a tumor or cannot be harvested.

Regulatory Status

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

Medical Policy Statement

Embryonal tumors of the CNS
The safety and effectiveness of specified *autologous* hematopoietic cell transplants for embryonal tumors of the central nervous system have been established. It may be considered a useful therapeutic tool when indicated for individuals who meet specific selection criteria.

Ependymoma
Autologous, tandem autologous and allogeneic hematopoietic cell transplants are experimental/investigational for the treatment of ependymoma. They have not been scientifically demonstrated to improve clinical outcomes better than conventional treatment.

Triple Tandem Transplant
The effectiveness and clinical utility of an *autologous* triple tandem stem cell transplant has been established. It is a useful therapeutic option for individuals with pediatric CNS tumors who meet specific selection criteria.

Inclusionary and Exclusionary Guidelines

The conditioning regimens for the following diseases may include myeloablative conditioning, reduced intensity conditioning, or non-myeloablative conditioning as determined by the treating provider/transplant center.

Embryonal tumors and Choroid Plexus tumors of the CNS
Inclusions:
- *Autologous* hematopoietic cell transplantation for the initial treatment of (newly diagnosed) embryonal[a] tumors of the central nervous system (CNS) that show partial or complete response to induction chemotherapy, or stable disease after induction therapy.
- *Autologous* hematopoietic cell transplantation for the treatment of recurrent embryonal[a] tumors of the CNS.
- *Triple tandem autologous* hematopoietic cell transplant for the treatment of embryonal[a] or choroid plexus tumors when both of the following are met:
  - Procedure may lead to reduced toxicities or less risk to future neurocognition
  - Other established treatments, such as single autologous transplant, have been deemed too risky

[a] Embryonal tumors of the CNS include medulloblastoma, medulloepithelioma, supratentorial PNETs (pineoblastoma, cerebral neuroblastoma, ganglioneuroblastoma), ependymoblastoma, atypical teratoid/rhabdoid tumors and embryonal tumor with multilayered rosettes.

Exclusions:
- *Allogeneic* hematopoietic cell transplantation for the treatment of embryonal or choroid plexus tumors of the CNS.

Ependymoma
Inclusions:
N/A

Exclusions:
- Autologous, tandem autologous and tandem allogeneic hematopoietic cell transplants are experimental/investigational for the treatment of ependymoma.

CPT/HCPCS Level II Codes ***(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)***

Established codes: *(Note: These codes may be established or investigational based on the diagnosis of embryonal tumor of the CNS or ependymoma. Please refer to medical policy statement)*

38206	38207	38208	38209	38210	38211

38212	38213	38214	38215	38232	38241
S2150					

Other codes (investigational, not medically necessary, etc.): *(Italicized codes can be used for both auto and allogeneic transplants. If used for allogeneic transplant in this policy, they would be considered experimental/investigational.)*

38204	38205	38207	38208	38209	38210
38211	38212	38213	38214	38215	38230
38240	38242	38243	81267	81268	81370
81371	81372	81373	81374	81375	81376
81377	81378	81379	81380	81381	81382
81383	86812	86813	86816	86817	86821
S2140	S2142	S2150			

Potential contraindications for transplant:

Note: Final patient eligibility for transplant is subject to the judgment and discretion of the requesting transplant center.

The selection process for approved tissue transplants is designed to obtain the best result for each patient. Therefore, relative contraindications to HCT may include, but are not limited to:

- Poor cardiac function: Ejection fraction should be greater than 45% with no overt symptoms of congestive heart failure.
- Poor pulmonary function: Pulmonary function tests must be greater than or equal to 50% of predicted value.
- Poor renal function: Renal creatinine clearance should be greater than 40 ml/min or creatinine must be less than or equal to 2mg/dl.
- Poor liver function: There should be no history of severe chronic liver disease
- Presence of HIV or an active form of hepatitis B, hepatitis C or human T-cell lymphotropic virus (HTLV-1).

Clinical documentation supplied to the health plan must demonstrate that attending staff at the transplant center have considered all contraindications as part of their overall evaluation of potential organ transplant recipient and have decided to proceed.

Rationale

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

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

Central Nervous System Embryonal Tumors

Newly Diagnosed Central Nervous System 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 cm^2 of residual disease). The high-risk group includes children aged 3 years or younger, or with metastatic disease, and/or subtotal resection (>1.5 cm^2 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%.

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 central nervous system embryonal tumors.

The following PICOs were used to select literature to inform this review.

Populations
The relevant population of interest is individuals with newly diagnosed central nervous system embryonal tumors. Embryonal tumors of the CNS include medulloblastoma, medulloepithelioma, supratentorial PNETs (pineoblastoma, cerebral neuroblastoma, ganglioneuroblastoma), ependymoblastoma, atypical teratoid/rhabdoid tumor.

Interventions
The therapy being considered is autologous stem cell transplantation.

Comparators
The following practices are currently being used to treat newly diagnosed central nervous system 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 overall survival, disease-specific survival, 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 hematopoietic cell transplant (HCT) for CNS embryonal tumors is whether the use of HCT allows radiation dose reduction.

Patients with newly diagnosed central nervous system 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 lifelong 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 preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with preference for prospective studies.
- To assess longer 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.

Review of Evidence

Observational Studies

The evidence describing outcomes after HCT for newly-diagnosed CNS embryonal tumors consists of relatively small case series, some of which enrolled patients prospectively. While most studies report outcomes for specific tumor types, a number 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, primitive neuroectodermal tumor (PNET), atypical teratoid/rhabdoid tumor, and pineoblastoma. Nine patients were considered average risk based on the presence of all of the following: age three years or older at diagnosis, nonmetastatic disease, and had undergone 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 was at the same doses as for the average-risk group with non-metastatic disease (23.4 gray Gy for those ≥5 years, 18 Gy for those <5 years, with a boost of 54 Gy for all ages), with higher doses for those with metastatic disease (30-36 Gy, with a boost of 54 Gy). In the average-risk group (n = 9), the five-year progression free survival (PFS) and overall survival (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 radiation therapy, along with the patient with atypical teratoid/rhabdoid tumor who received radiotherapy as salvage therapy. The PFS was 50% (95% confidence interval [CI] 18% to 75%) at one year and at two years with a median follow-up of 24 months. All patients with medulloblastoma were alive and without evidence of disease at last follow up, including two with metastatic medulloblastoma who did not received CSI.

Raleigh et al (2017) retrospectively described outcomes of 222 consecutive patients from institutional cancer registries at two 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 craniospinal irradiation 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 the upfront radiotherapy group (4 years vs 6 years) and mean age was younger (2.9 years vs 7.8 years). Time to initiation of radiotherapy was significantly longer in the HDC plus HCT group (median, 198 days) compared to the upfront radiotherapy group (median, 28 days) and 48% of HDC plus HCT patients did not receive radiotherapy. There were no differences in incidence of metastases, PFS or OS between HDC plus HCT and upfront radiotherapy.

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

Supratentorial Primitive Neuroectodermal Tumor

Chintagumpala et al (2009) reviewed event-free survival (EFS) of 16 patients with newly diagnosed supratentorial PNET (sPNET) 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 cm^2 or disseminated disease in the neuroaxis). Median age at diagnosis was 7.9 years (range: 3–21 years). Seven patients had pineal PNET. After a median follow-up of 5.4 years, 12 patients were alive. Five-year EFS and OS rates for the patients with average-risk disease were 75% and 88%, respectively, and for the high-risk patients 60% and 58%, respectively. No treatment-related toxicity deaths were reported. The authors concluded that HDC with HCT support after risk-adapted CSI permitted a reduction in the dose of radiation needed to treat nonmetastatic, average-risk sPNET, without compromising EFS.

Fangusaro et al (2008) reported outcomes for 43 children with newly diagnosed sPNET treated prospectively in two serial studies (Head Start 1 [HS1] and Head Start 2 [HS2]) between 1991 and 2002 with intensified induction chemotherapy followed by myeloablative chemotherapy and autologous HCT.(2) There were no statistical differences between HS1 and HS2 patient demographics. After maximal surgical resection, patients underwent induction chemotherapy. If, after induction, the disease remained stable or there was partial or complete response, patients underwent myeloablative chemotherapy with autologous HCT (n=32). Patients with progressive disease at the end of induction were not eligible 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 non-pineal tumors did significantly better than patients with pineal PNETs (2- and five-year EFS rates of 57% vs. 23% and 48% vs. 15%, respectively and 2- and 5-year OS of 70% vs. 31% and 60% vs. 23%, respectively). Further, 60% of survivors were alive without exposure to radiotherapy.

Massimino et al (2013) reported outcomes for 28 consecutive patients with noncerebellar PNET treated from 2000 to 2011 with a high-dose drug schedule (methotrexate, etoposide, cyclophosphamide, and carboplatin with or without vincristine) with autologous HCT rescue, followed by one of two radiotherapy options.(8) For the first 15 patients, HDC and stem cell rescue was followed by hyper-fractionated accelerated craniospinal irradiation (CSI) with two high-dose thiotepa courses following CSI (for the first 15 patients); for subsequent cases, CSI was replaced with focal radiotherapy for patients whose tumors were nonmetastatic and not progressing during induction chemotherapy. Three- and 5-year PFS rates were 69% and 62% respectively; three- and five-year EFS rates were 59% and 53%, respectively; and three- and five-year OS rates were 73% and 52%, respectively. Eleven children died at a median of 32 months after their diagnosis (range, 5-49 months), eight due to their tumor, one due to multiorgan failure after the first myeloablative treatment, and two due to acute myeloid leukemia and myelodysplastic syndrome. For the 25 patients able to tolerate the entire schedule, including at least one myeloablative course, the five-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, five-year disease-free survival rates were 78% for pediatric patients and 22% for adult patients (p=0.004); five-year OS rates were 67% for pediatric patients and 33% for adult patients (p=0.07). More pediatric patients were treated with HDC plus HCT (82%) than adult patients (27%). In unadjusted analysis, compared with standard chemotherapy, treatment with HDC with HCT was associated with

improved OS (hazard ratio [HR] 0.3; 95% CI 0.1 to 1.0; p=0.05). However, these results were confounded by higher rates of HCT use in children, who had better OS and disease-free survival overall.

Medulloblastoma

Dhall et al (2008) reported outcomes for children younger than three years of age when diagnosed nonmetastatic medulloblastoma, after being treated with five cycles of induction chemotherapy and subsequent myeloablative chemotherapy and autologous HCT.(10) Twenty of 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, five-year EFS and OS were 64% and 79%, respectively, for patients with residual tumor, 29% and 57% respectively. There were four treatment-related deaths. The need for CSI was eliminated in 52% of the patients, and 71% of survivors avoided irradiation completely, with preservation of quality of life and intellectual functioning.

Gajjar et al (2006) reported 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 average-risk disease (n=86), defined as 1.5 cm^2 or less residual tumor and no metastatic disease, or high-risk disease (n=48), defined as greater than 1.5 cm^2 residual disease or metastatic disease localized to the neuroaxis. A total of 119 children completed the planned protocol. Five-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 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 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 three had desmoplastic/nodular medulloblastoma and one had medulloblastoma with extensive nodularity. The median follow-up was 40.5 months (range, 14.5–191.2 months). At 3 and 5 years, EFS and OS were 68% (95% CI 45% to 84%) and 84% (95% CI 61% to 94%), respectively. Treatment failures occurred in 6 children at a median of 13 months (range, 5.8–30.7 months) after HCT. Authors concluded that high OS is possible with focal brain irradiation in the setting of HCT for medulloblastoma.

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 cm^2 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 to19 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 7.1years (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).(14) 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 diagnose with atypical teratoid/rhabdoid tumor who were treated at their children's hospital in Seoul, Korea.(17) Median age was 12 months (range: 3–67 months), with 7 patients being younger than 1 year at diagnosis. Three (23%) patients underwent HDC and autologous HCT. Authors assessed the impact on OS in these 3 patients, as compared with the remaining 10 patients undergoing other chemotherapy regimens. No statistical difference in OS was observed between these two groups (p=0.36); however, median survival was longer in the HCT group (15 months) than in the non-HCTs group (9 months).

Section Summary: Newly Diagnosed Central Nervous System Embryonal Tumors

Data evaluating HDC with autologous HCT, in the setting of newly diagnosed CNS embryonal tumors, is primarily from single-arm studies and case series. These studies have suggested comparable or improved EFS and OS compared with historical controls, particularly in patients with disease considered high risk. One retrospective study compared HDC with HCT and delayed CSI to upfront craniospinal irradiation. 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. HCT may permit reduced doses of craniospinal irradiation 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 central nervous system embryonal tumors is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICOs were used to select literature to inform this review.

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

Interventions
The therapy being considered is autologous stem cell transplantation.

Comparators
The following practices are currently being used to treat recurrent and relapsed central nervous system 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 overall survival (OS), disease-specific survival (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 preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with preference for prospective studies.
- To assess longer 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.

Review of Evidence

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 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 sPNET treated with HDC and autologous HCT.(18) Eleven observational studies, including 4 prospective series (n=46 patients) with relapsed sPNET or pineoblastoma, published before 2010, met reviewers' inclusion criteria. Of the 46 patients, 15 were children younger than 3 years of age. After a median follow-up of 40 months (range, 3- to 123 months), 15 patients were reported alive. Of the 15 survivors, 13 did not receive CSI. OS for the entire cohort was 44.2 months; OS was longer for children younger than 36 months (66.7 months) than for those over 36 months (27.8 months; p=0.003). In multivariable regression, 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 sPNET, particularly with pineal tumors, even when treated with HCT.

Relapsed Medulloblastoma
Dunkel et al (2010) reported on an expanded series with longer follow-up using autologous HCT for previously irradiated recurrent medulloblastoma.(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: 4.2-35.5 years). Median age at the time of HCT was 13.8 years (range: 7.6-44.7 years). All patients had previously received postoperative external beam radiation with (n=15) or without (n=10) chemotherapy. Median time from diagnosis to disease relapse or progression was 29.8 months (range 5.3-114.7 months). Stage at relapse was M0 n=6, M1 n=1, M2 n=8, M3 n=10 (M0=no evidence of subarachnoid or hematogenous metastasis, M1=tumor cells found in cerebrospinal fluid, M2=intracranial tumor beyond primary site, M3=gross nodular seeding in spinal subarachnoid space). HDC before HCT consisted of carboplatin, thiotepa and etoposide. Treatment-related mortality was 12% within 30 days of transplant. Tumors recurred in 16 patients at a median of 8.5 months after HCT (range: 2.3-58.5 months). Median OS was 26.8 months (95% CI: 11.9-51.1 months) and EFS and OS 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 the outcomes of 23 patients with recurrent medulloblastoma treated with high-dose carboplatin, thiotepa and etoposide.(20) Seven patients had event-free survival at a median of 54 months, with OS rate estimated at 46% at 36 months. HCT was expected to be most effective with minimal disease burden. Thus, Dunkel et al suggested increased surveillance for recurrence or aggressive surgical debulking at the time of recurrence. The authors also acknowledged the potential for effects of patient selection bias on their results, since not all patients eligible for the protocol were enrolled.

Grodman et al (2009) reported outcomes of 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: 5–27.8 years). Mean survival post-transplant was 4.8 years (range: 8–160+ 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/relapsed medulloblastoma. Limitations of the selected studies included the fact that all are 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 (two years; p=0.04). Reviewers concluded: "Although the data are limited, the collective published evidence for this treatment modality suggests a role for HDCT [high-dose chemotherapy] plus stem cell transplantation in the management of well-selected adult patients with recurrent medulloblastoma."

Relapsed Embryonal Tumors – Multiple Types

The largest study identified an HCT in relapsed CNS embryonal tumors included patients with multiple PNET tumor types (medulloblastoma, sPNET). Bode et al (2014) reported 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, 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 three 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 two-, three-, and five-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 two-, three-, and five-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 two-, three-, and five-year rates PFS of 20%, 10%, and 0.1%, respectively. HCT-treated patients had median OS of 20.2 months (95% CI, 11.7 to 28.8 months), with two-, three-, and five-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 outcomes for 23 adult patients (≥18 years of age) treated for recurrent embryonal CNS tumors between 1976 and 2004, comparing HDC plus autologous HCT (n=10) with a historic control group of patients treated with conventional-dose chemotherapy (n=13).(24) In the HCT group, patients received tandem autologous transplants. Autologous HCT was associated with increased survival (p=0.044) and a longer time to progression of the disease (p=0.028). 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 the patients who received a single versus tandem transplant, there was improvement in time to progression favoring tandem transplant (p=0.046), but no difference in survival was observed (p=0.132).

Kim et al (2013) reported 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 note that patients could concurrently receive radiotherapy, surgery, and/or HDC and stem cell rescue, it is not specified how many patients received stem cell support, making it difficult to determine the benefit from specific intervention components.

Egan et al (2016) reported outcomes from a Phase I study of temozolomide in combination with thiotepa and carboplatin with 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 3-46 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 Central Nervous System Embryonal Tumors
The prognosis is generally poor for recurrent CNS tumors and there are few treatment options. Data from some single-arm studies using autologous HCT compared with conventional therapy to treat recurrent CNS embryonal tumors have shown comparable or improved survival for certain patients. A 2012 systematic review of observational studies in patients with relapsed sPNET suggested that infants with chemo sensitive disease might benefit from autologous HCT because survival outcomes are similar without radiotherapy. However, reviewers found that outcomes in older children and/or in those with pineal location were poor with this modality. A relatively large prospective multicenter study reported that HCT was not associated with improved survival outcomes in patients who had a good response to therapy.

CNS Embryonal Tumors Treated with Tandem Transplant

Clinical Context and Therapy Purpose
The purpose of tandem autologous stem cell transplantation in individuals who have central nervous system embryonal tumors is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICOs were used to select literature to inform this review.

Populations
The relevant population of interest is individuals with central nervous system embryonal tumors as previously described.

Interventions
The therapy being considered is tandem autologous hematopoietic stem cell transplant 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 central nervous system embryonal tumors: chemotherapy, chemoradiation or post-induction single autologous stem cell transplant.

Outcomes
The general outcomes of interest are overall survival, disease-specific survival, 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 preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with preference for prospective studies.
- To assess longer 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.

Review of Evidence

Observational Studies

Sung et al (2016) reported prospective follow-up of 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 was administered after 6 cycles of induction chemotherapy with deferred radiotherapy until age 6 unless the tumor showed relapse or progression in the younger children. Reduced-dose radiotherapy was administered either after 2 cycles of induction chemotherapy or after surgery with tandem HDC, and autologous HCT was performed after 6 cycles of induction chemotherapy in the older children. All 5 younger children died from disease progression. Four of the 8 older children remained progression-free with median follow-up of 64 months.

Cohen et al (2015) assessed the toxicity, feasibility and tolerability of, as well as the response rate to an intensive chemotherapy regimen. Induction chemotherapy followed by Consolidation chemotherapy with the administration of repetitive cycles of marrow-ablative chemotherapy supported by peripheral blood hematopoietic cells in young children with various malignant brain tumors was studied. Between May 1998 and April 2004, children (n=92) between the age of 6 and 36 months with malignant brain or spinal cord tumors (medulloblastoma, other CNS primitive neuroectodermal tumors [PNET], ependymoma, CNS atypical teratoid/rhabdoid tumors [AT/RT] and choroid plexus carcinoma [CPC] were enrolled into the CCG-99703 study. Patients were ineligible if they had received any prior treatment for the malignant brain tumor other than surgery and corticosteroids. Adequate renal, hepatic and hematopoietic functions and an anticipated life expectancy of greater than eight weeks were required for eligibility. Participants received 3 identical cycles of Induction chemotherapy (vincristine, cyclophosphamide, etoposide and cisplatin) administered every 21–28 days. Post Induction, patients without tumor progression received three Consolidation cycles of marrow-ablative chemotherapy (thiotepa and carboplatin) followed by autologous hematopoietic cell rescue. The Maximum Tolerated Dose (MTD) of thiotepa was 10mg/kg/day x 2 days per cycle. The toxic mortality rate was zero during Induction and 2.6% during Consolidation. Centrally evaluated response rates to Induction and Consolidation in evaluable patients with residual tumor were 73.3% and 66.7% respectively. Disease progression rates on Induction and Consolidation were 4%. Five-year event-free survival (EFS) and overall survival (OS) were 43.9±5.2% and 63.6±5% respectively. Gross total resection (GTR) versus <GTR were the only

significant outcome comparisons: 5-year EFS and OS of 54.4±7% versus 28.9±7% (p= .0065) and 75.9±8% versus 48.7±8% (p= .0034) respectively. The 5-year EFS for localized (M0) versus metastatic (M1+) medulloblastoma was 67.5+/−9.5% versus 30+/−14.5% (p= .007). The 5-year EFS and OS for desmoplastic medulloblastoma patients versus other medulloblastoma were 78.6+/−11% versus 50.5+/−12% (p= .038) and 85.7±9.4% versus 60.6±11.6% (p= .046) respectively. The 1- and 5-year EFS rates for ependymoma were 86% ±8% and 38% ±11%; supratentorial PNET were 35% ± 12% and 29% ±11%; AT/RT were 37.5% ± 17% and 37.5% ± 17%; and “other eligible” were 60% ± 15% and 30% ± 15%,respectively. The use of high-dose, marrow-ablative chemotherapy with autologous bone marrow or hematopoietic cell rescue was shown to have some efficacy at treating children with recurrent malignant brain tumors and young children with newly-diagnosed malignant brain tumors. Authors concluded that the brief Induction regimen followed by the innovative sequential tandem marrow-ablative chemotherapy cycles, each with autologous hematopoietic cell rescue, resulted in acceptable morbidity and mortality and is feasible for the majority of patients in the cooperative group setting.

Dufour et al (2014) reported on outcomes for patients with newly diagnosed high-risk medulloblastoma and sPNET treated with tandem HDC and autologous HCT support followed by conventional craniospinal radiotherapy.(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 cm^2 or MYCN amplification) and 3 with sPNET. Patients received 2 courses of conventional chemotherapy, followed by 2 courses of high-dose thiotepa followed by stem cell rescue and craniospinal radiotherapy. Twenty-three patients received 2 courses of HDC, while 1 patient received only 1 course of high-dose thiotepa due to seizures. Median follow up was 4.4 years (range 0.8 to 11.3 years). Three-year EFS and OS 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 the results of reduced-dose craniospinal radiotherapy followed by double-tandem HDC with autologous HCT in 20 children older than three years of age with high-risk medulloblastoma (17 with metastatic disease and having a postoperative residual tumor >1.5 cm^2 without metastasis).(29) The tumor relapsed or progressed in 4 patients, and 2 died of toxicity during the second transplant. Fourteen (70%) patients remained event-free at a median follow-up of 46 months (range, 23-82 months) from diagnosis. Late adverse effects evaluated at a median of 36 months (range, 12-68 months) after tandem HCT included hypothyroidism, growth hormone deficiency, sex hormone deficiency, hearing loss, and renal tubulopathy.

Friedrich et al (2013) reported the results of double tandem HDC with autologous HCT in 3 children younger than 4 years of age with metastatic sPNET.(30) These patients also received preventive craniospinal radiotherapy; they had residual disease before HCT, but no evidence of disease after transplant (survival range from 2 to 10 years).(30)

Park et al (2012) reported 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 7-64) from first transplant. Three patients remained progression-free after tandem HCT.

Sung et al (2007) reported 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 for patients in complete or partial response and less than partial response at first HDC were 67% or 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
The evidence includes prospective and retrospective single-arm studies. The available single-arm studies are very small but appear to report overall survival and event-free survival rates comparable with single autologous HCT. Tandem transplants may allow reduced doses of craniospinal irradiation, with the goal of avoiding long-term radiation damage.

CNS 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 review.

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

Interventions
The therapy being considered is allogeneic stem cell transplantation.

Comparators
The following practices are currently being used to treat CNS embryonal tumors: chemotherapy, chemoradiation, or postinduction 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.

Review of Evidence

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, disease-specific survival, and treatment-related mortality and morbidity. The available evidence is limited.

CNS 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 central nervous system ependymomas is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICOs were used to select literature to inform this review.

Populations
The relevant population of interest is individuals with central nervous system ependymomas.

Interventions
The therapy being considered is autologous stem cell transplantation.

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

Outcomes
The general outcomes of interest are overall survival, disease-specific survival, 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 preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with

preference for prospective studies.
- To assess longer 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.

Review of Evidence

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 median follow-up of 45 months (range 31–62 months) from diagnosis, although the tumor progressed at the primary site in one patient. No significant endocrine dysfunction occurred except for hypothyroidism in 1 patient, and 1 patient had 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 following intensive induction chemotherapy to treat newly diagnosed ependymoma.(39) Importantly, radiation-free survival was only 8% in these cases. The results of these series, although limited in size, 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 embryonal tumors who receive autologous HCT, the evidence includes prospective and retrospective studies. Relevant outcomes are overall survival, disease-specific survival, and treatment-related morbidity and mortality. For pediatric CNS embryonal tumors, an important consideration is whether the use of HCT may allow for a reduction in radiation dose. Data from single-arm studies using high-dose chemotherapy with autologous HCT to treat newly diagnosed CNS embryonal tumors have shown comparable or improved survival (both event-free survival and overall survival) compared with historical controls treated with conventional therapy, with or without radiotherapy, particularly in patients with disease that is considered high risk. In a retrospective comparative study, survival in patients receiving HDC 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 overall survival, disease-specific survival, and treatment-related mortality and morbidity. For recurrent/relapsed CNS embryonal tumors, survival outcomes after HCT vary, and survival is generally very poor for tumors other than medulloblastoma. Data from some single-arm studies using autologous HCT to treat recurrent CNS embryonal tumors have shown comparable or improved survival compared with historical controls treated with conventional therapy for certain patients. The results of a 2012 systematic review of observational studies in patients with relapsed supratentorial primitive neuroectodermal tumor (sPNET) suggested that a subgroup of infants with chemo sensitive disease might benefit from autologous HCT, achieving survival without the use of radiotherapy, whereas outcomes in older children and/or in pineal location are poor with this modality. However, a relatively large prospective multicenter study has reported that HCT was not associated with improved survival outcomes in patients who had a good response to therapy. Overall, data from these single-arm studies has suggested HCT may be associated with improved survival outcomes in select patients, although data for some tumor types 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 overall survival, disease-specific survival, and treatment-related mortality and morbidity. Less evidence specifically addresses the use of tandem autologous HCT for CNS embryonal tumors. The available single-arm studies are small but appear to report overall survival 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. 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 allogeneic HCT, the evidence includes case reports. Relevant outcomes are overall survival, disease-specific survival, 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 overall survival, disease-specific survival, and treatment-related morbidity and mortality. The available case series do not report higher survival rates for patients with ependymoma treated with HCT compared with standard therapies. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Supplemental Information

PRACTICE GUIDELINES AND POSITION STATEMENTS

American Society for Blood and Marrow Transplantation

The American Society for Blood and Marrow Transplantation (2015; now referred to as the American Society for Transplantation and Cellular Therapy) published consensus guidelines on the use of 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 HCT 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 guidelines on treating central nervous system tumors make the following recommendations about hematopoietic cell transplant (HCT):(42)

- For medulloblastoma and sPNET, 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).

National Cancer Institute

The National Cancer Institute's health professional version, which addresses childhood medulloblastoma and other central nervous system embryonal tumor treatment, list high-dose chemotherapy supported by stem cell rescue as an effective treatment for most infants and very young children in the following tumor types:

- Desmoplastic/MBEN medulloblastoma and/or tumors with SHH signaling
- Pineoblastoma in children aged 3 years and younger
- Recurrent childhood medulloblastoma and other CNS embryonal tumors

American Society of Clinical Oncology

The American Society of Clinical Oncology indicates the use of high-dose chemotherapy may be used before or instead of radiation therapy for children younger than 3 to 4 years old with Medullobastomas. An autologous bone marrow transplant may be used for children with

recurrent medulloblastoma. The goal is to destroy all of the tumor cells in the bone marrow, blood, and other parts of the body using high doses of chemotherapy and/or radiation therapy and then allow replacement blood stem cells to create healthy bone marrow.

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

Not applicable.

ONGOING AND UNPUBLISHED CLINICAL TRIALS

Some currently unpublished trials that might influence this review are listed in Table 2.

Table 2. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
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

Government Regulations

National:

National Coverage Determination (NCD) for Stem Cell Transplantation Formerly 110.8.1 (110.23), Effective Date of this Version 1/27/2016, Implementation Date 10/3/2016

A. General

Stem cell transplantation is a process in which stem cells are harvested from either a patient's (autologous) or donor's (allogeneic) bone marrow or peripheral blood for intravenous infusion. Autologous stem cell transplantation (AuSCT) is a technique for restoring stem cells using the patient's own previously stored cells. AuSCT must be used to effect hematopoietic reconstitution following severely myelotoxic doses of chemotherapy (HDCT) and/or radiotherapy used to treat various malignancies. Allogeneic hematopoietic stem cell transplantation (HSCT) is a procedure in which a portion of a healthy donor's stem cell or bone marrow is obtained and prepared for intravenous infusion. Allogeneic HSCT may be used to restore function in recipients having an inherited or acquired deficiency or defect. Hematopoietic stem cells are multi-potent stem cells that give rise to all the blood cell types; these stem cells form blood and immune cells. A hematopoietic stem cell is a cell isolated from blood or bone marrow that can renew itself, differentiate to a variety of specialized cells, can mobilize out of the bone marrow into circulating blood, and can undergo programmed cell death, called apoptosis - a process by which cells that are unneeded or detrimental will self-destruct.

The Centers for Medicare & Medicaid Services (CMS) is clarifying that bone marrow and peripheral blood stem cell transplantation is a process which includes mobilization, harvesting, and transplant of bone marrow or peripheral blood stem cells and the administration of high dose chemotherapy or radiotherapy prior to the actual transplant. When bone marrow or peripheral blood stem cell transplantation is covered, all necessary steps are included in

coverage. When bone marrow or peripheral blood stem cell transplantation is non-covered, none of the steps are covered.

Nationally Non-Covered Indications

Autologous STEM CELL transplantation (AuSCT)

Insufficient data exist to establish definite conclusions regarding the efficacy of AuSCT for the following conditions:

- Solid tumors (other than neuroblastoma)

(This NCD last reviewed January 2016.)

Local:

There is no current WPS LCD on this topic; refer to NCD.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- BMT – Hematopoietic Cell Transplantation for Acute Lymphoblastic Leukemia
- BMT – Hematopoietic Cell Transplantation for Acute Myeloid Leukemia
- BMT – Hematopoietic Cell Transplantation for Autoimmune Diseases
- BMT – Hematopoietic Cell Transplantation for Chronic Lymphocytic Leukemia and Small Cell Lymphocytic Lymphoma – Autologous or Allogeneic
- BMT – Hematopoietic Cell Transplantation for Chronic Myeloid Leukemia
- BMT – Hematopoietic Cell Transplantation for Epithelial Ovarian Cancer
- BMT – Hematopoietic Cell Transplantation for Genetic Diseases and Acquired Anemias (Allogeneic)
- BMT – Hematopoietic Cell Transplantation for Germ-Cell Tumors
- BMT – Hematopoietic Cell Transplantation for Hodgkin Lymphoma
- BMT – Hematopoietic Cell Transplantation for Miscellaneous Solid Tumors in Adults
- BMT – Hematopoietic Cell Transplantation for Myelodysplastic Syndromes and Myeloproliferative Neoplasms
- BMT – Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas
- BMT – Hematopoietic Cell Transplantation for Plasma Cell Dyscrasias, Including Multiple Myeloma and POEMS Syndrome
- BMT – Hematopoietic Cell Transplantation for Primary Amyloidosis
- BMT – Hematopoietic Cell Transplantation for Solid Tumors of Childhood
- BMT – Hematopoietic Cell Transplantation for Waldenström's Macroglobulinemia
- BMT – Malignant Astrocytomas and Gliomas (Autologous)
- Donor Lymphocyte Infusion for Malignancies Treated with an Allogeneic Hematopoietic Stem-Cell Transplant
- Orthopedic Applications of Stem-Cell Therapy (Including Allografts and Bone Substitutes used with Autologous Bone Marrow)

References

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through March 22, 2024, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
3/1/12	12/13/11	1/31/12	Joint policy established; topic pulled out from combined joint policies on autologous and allogeneic bone marrow/stem cell transplants
3/1/13	12/11/12	12/31/12	Routine update. References added. No change in policy status.
3/1/14	12/10/13	1/16/14	Routine update. References added. No change in policy status.
3/1/15	12/12/14	12/29/14	Routine update. References added. No change in policy status.
5/1/16	2/16/16	2/16/16	Routine update. References added. No change in policy status.
5/1/17	2/21/17	2/21/17	Routine update. References updated. Changed Hematopoietic Stem Cell Transplantation to Hematopoietic Cell Transplantation per NCCN terminology change. Policy statement unchanged.
5/1/18	2/20/18	2/20/18	Routine maintenance
5/1/19	2/19/19		Routine maintenance
9/1/19	6/18/19		Routine maintenance
9/1/20	6/16/20		Routine maintenance
9/1/21	6/15/21		• Triple tandem criteria added • Choroid plexus tumors added to both inclusions and exclusions • 86822 deleted per AMA • Title changed from: BMT – HCT for CNS Embryonal Tumors and Ependymoma
9/1/22	6/21/22		• Routine maintenance
9/1/23	6/13/23		• Routine maintenance (slp) • Vendor Managed: N/A
9/1/24	6/11/24		• Routine maintenance (slp) • Vendor Managed: N/A

Next Review Date: 2nd Qtr, 2025

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: BMT- HEMATOPOIETIC CELL TRANSPLANTATION (HCT) FOR CNS TUMORS, EMBRYONAL TUMORS, AND EPENDYMOMA

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered; criteria apply. For an approved, preauthorized transplant, BCN will cover the necessary hospital, surgical, lab and X-ray services for a non-member donor, including charges for donating the bone marrow, under the BCN member's certificate, unless the non-member donor has coverage for such services. This also includes solid organ donor procurement fees. Donor travel, meals and lodging expenses are *not* covered unless the BCN member has a rider that covers such services. BCN does NOT cover expenses incurred by a BCN member for donating bone marrow, stem cells or a solid organ (e.g., kidney, liver lobe, lung lobe) to a non-BCN member. The donor services would be considered not medically necessary for the BCN member.
BCNA (Medicare Advantage)	Refer to the Medicare information under the Government Regulations section of this policy.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.