Hematopoietic Cell Transplantation for Central Nervous System Embryonal Tumors and Ependymoma

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Policy

Embryonal Tumors of the Central Nervous System (CNS)

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

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

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

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

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

Related Policies

7.01.50 Placental and Umbilical Cord Blood as a Source of Stem Cells
**Policy Guidelines**

In general, use of autologous hematopoietic cell transplantation for previously untreated medulloblastoma has shown no survival benefit for those patients considered to be at average risk (i.e., patient age older than 3 years, without metastatic disease, and with total or near total surgical resection [<1.5 cm² residual tumor]) when compared with conventional therapies.

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**Description**

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

The evidence for autologous HCT in individuals who have newly diagnosed and recurrent/relapsed central nervous system (CNS) embryonal tumors includes prospective and retrospective single-arm studies. Relevant outcomes are overall survival, disease-specific survival, and treatment-related morbidity and mortality. In the case of pediatric CNS embryonal tumors, an important consideration is whether the use of HCT may allow for a reduction in radiation dose. Data from single-arm studies using HDC with autologous HCT to treat newly diagnosed CNS embryonal tumors have shown comparable or improved survival (both event-free survival and overall survival) compared with historical controls treated with conventional therapy, with or without radiotherapy, particularly in patients with disease that is considered high risk. For recurrent/relapsed CNS embryonal tumors, survival outcomes after HCT are more variable, and survival is generally very poor for tumors other than medulloblastoma. Data from some single-arm studies using autologous HCT to treat recurrent CNS embryonal tumors have shown comparable or improved survival compared with historical controls treated with conventional therapy for certain patients. The results of a 2012 systematic review of observational studies in patients with relapsed supratentorial primitive neuroectodermal tumor suggest that a subgroup of infants with chemosensitive disease might benefit from autologous HCT, achieving survival without the use of radiotherapy, whereas the outcome in older children and/or in pineal location is poor with this modality. However, a relatively large prospective multicenter study reported that HCT was not associated with improved survival outcomes in patients who had had a good response to therapy. Overall, data from these single-arm studies suggests HCT may be associated with improved survival outcomes, although data for some tumor types is limited (e.g., atypical teratoid/rhabdoid tumors). 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.

The evidence for tandem autologous HCT in individuals who have CNS embryonal tumors includes prospective and retrospective single-arm studies. Relevant outcomes are overall survival, disease-specific survival, and treatment-related morbidity and mortality. Less evidence specifically addresses the use of tandem autologous HCT for CNS embryonal tumors. The available single-arm studies are very small, but appear to report overall
survival and event-free survival rates comparable to single autologous HCT. Tandem transplants may allow reduced doses of craniospinal irradiation, with the goal of avoiding long-term radiation damage. However, most studies used standard-dose irradiation, making the relative benefit of tandem autologous HCT uncertain. The evidence is insufficient to determine the effects of the technology on health outcomes.

The evidence for allogeneic HCT in individuals who have CNS embryonal tumors includes case reports. Relevant outcomes are overall survival, disease-specific survival, and treatment-related morbidity and mortality. The available evidence is limited. The evidence is insufficient to determine the effects of the technology on health outcomes.

The evidence for autologous HCT in individuals who have ependymoma includes relatively small case series. Relevant outcomes are overall survival, disease-specific survival, and treatment-related morbidity and mortality. The available case series do not report higher survival rates for patients with ependymoma treated with HCT than with standard therapies. The evidence is insufficient to determine the effects of the technology on health outcomes.

Background
Hematopoietic cell transplantation (HCT) refers to a procedure in which hematopoietic cells are infused to restore bone marrow function in cancer patients who receive bone-marrow-toxic doses of cytotoxic drugs. Bone-marrow stem cells may be obtained from the transplant recipient (i.e., autologous HCT) or from a donor (i.e., allogeneic HCT). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood and placenta shortly after delivery of neonates.

HCT for Brain Tumors
Autologous HCT allows for escalation of chemotherapy doses above those limited by myeloablation and has been tried in patients with high-risk brain tumors in an attempt to eradicate residual tumor cells and improve cure rates. The use of allogeneic HCT for solid tumors does not rely on escalation of chemotherapy intensity and tumor reduction but rather on a graft-versus-tumor effect. Allogeneic HCT is not commonly used in solid tumors and may be used if an autologous source cannot be cleared of tumor or cannot be harvested.

CNS Embryonal Tumors
Classification of brain tumors is based on both histopathologic characteristics of the tumor and location in the brain. CNS embryonal tumors are more common in children and are the most common brain tumor in childhood. CNS embryonal tumors are primarily composed of undifferentiated round cells, with divergent patterns of differentiation. It has been proposed that these tumors be merged under the term primitive neuroectodermal tumor (PNET); however, histologically similar tumors in different locations in the brain demonstrate different molecular genetic alterations. Embryonal tumors of the CNS include medulloblastoma, medulloepithelioma, sPNETs (pineoblastoma, cerebral neuroblastoma, ganglioneuroblastoma), ependymoblastoma, atypical teratoid/rhabdoid tumor (AT/RT).

Medulloblastomas account for 20% of all childhood CNS tumors. The other types of embryonal tumors are rare by comparison. Surgical resection is the mainstay of therapy with the goal being gross total resection with adjuvant radiotherapy, as medulloblastomas are very radiosensitive. Treatment protocols are based on risk stratification as average or high risk. The average-risk group includes children older than 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). (1)

Current standard treatment regimens for average-risk medulloblastoma (postoperative craniospinal irradiation with boost to the posterior fossa followed by 12 months of chemotherapy) have resulted in 5-year overall survival (OS) rates of 80% or better. (1) For high-risk medulloblastoma treated with conventional doses of chemotherapy and radiotherapy, the average EFS at 5 years ranges from 34% to 40% across studies. (2) Fewer than 55% of children with high-risk disease survive longer than 5 years. The treatment of newly diagnosed medulloblastoma continues to evolve, and in children younger than age 3 years, because of the concern of the deleterious effects of craniospinal radiation on the immature nervous system, therapeutic approaches have attempted to delay and
sometimes avoid the use of radiation and have included trials of higher-dose chemotherapeutic regimens with autologous HCT.

sPNETs are most commonly located in the cerebral cortex and pineal region. The prognosis for these tumors is worse than for medulloblastoma, despite identical therapies. 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%.

Recurrent childhood CNS embryonal tumor is not uncommon, and depending on which type of treatment the patient initially received, autologous HCT may be an option. For patients who receive HDC and autologous HCT for recurrent embryonal tumors, objective response is 50 to 75%; however, long-term disease control is obtained in fewer than 30% of patients and is primarily seen in patients in first relapse with localized disease at the time of relapse.

**Ependymoma**

Ependymoma is a neuroepithelial tumor that arises from the ependymal lining cell of the ventricles and is, therefore, usually contiguous with the ventricular system. An ependymoma tumor typically arises intracranially in children, while in adults a spinal cord location is more common. Ependymomas have access to the cerebrospinal fluid and may spread throughout the entire neuroaxis. Ependymomas are distinct from ependymoblastomas due to their more mature histologic differentiation. Initial treatment of ependymoma consists of maximal surgical resection followed by radiotherapy. Chemotherapy usually does not play a role in the initial treatment of ependymoma. However, disease relapse is common, typically occurring at the site of origin. Treatment of recurrence is problematic; further surgical resection or radiotherapy is usually not possible. Given the poor response to conventional-dose chemotherapy, HDC with autologous HCT has been investigated as a possible salvage therapy.

**Note:** Other CNS tumors include astrocytoma, oligodendroglioma, and glioblastoma multiforme. However, these tumors arise from glial cells and not neuroepithelial cells. These tumors are considered in a separate policy. (See Related Policies)

**Note:** Due to their neuroepithelial origin, peripheral neuroblastoma and Ewing sarcoma may be considered PNETs. However, these peripheral tumors are considered in a separate policy. (See Related Policies)

**Scope**

Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.

**Benefit Application**

The following considerations may supersede this policy:

- State mandates requiring coverage for autologous hematopoietic bone marrow transplantation offered as part of clinical trials of autologous bone marrow transplantation approved by the National Institutes of Health (NIH).
- Some plans may participate in voluntary programs offering coverage for patients participating in NIH-approved clinical trials of cancer chemotherapies, including autologous hematopoietic bone marrow transplantation.
- Some contracts or certificates of coverage (e.g., FEP) may include specific conditions in which
autologous hematopoietic bone marrow transplantation would be considered eligible for coverage.

Rationale

This policy was originally created in December 1999 and was updated regularly with searches of the MEDLINE database. The most recent literature review was performed through November 7, 2016. Following is the summary of the key literature to date.

Central Nervous System Embryonal Tumors

Standard therapy for central nervous system (CNS) embryonal tumors often involves craniospinal irradiation, in addition to surgical resection and chemotherapy. In pediatric patients, craniospinal irradiation is associated with impairments in neurodevelopmental outcomes, with risks increasing in younger age groups, particularly in those under the age of 3. A focus of research in pediatric CNS tumor treatments has been finding methods to reduce radiation exposure to the developing brain without conferring unacceptably high recurrence risks. Therefore, a relevant outcome in evaluating hematopoietic stem cell transplant (HCT) for CNS embryonal tumors is whether the use of HCT allows radiation dose reduction.

Newly Diagnosed Central Nervous System Embryonal Tumors

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 one 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 (AT/RT), 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 had undergone gross total resection; the remaining 16 patients were considered “high risk.” High-risk patients received HCT, in addition to craniospinal irradiation and chemotherapy. Craniospinal irradiation for the high-risk group was in the same doses as for the average-risk group for patients with nonmetastatic disease (23.4 Gy for those aged 5 years and older and 18 Gy for those under 5 years old, 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 5-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 craniospinal irradiation, for CNS embryonal tumors.(5) Of the 10 patients, 5 had medulloblastoma, 3 had AT/RT, 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 AT/RT patient, who received radiotherapy as salvage therapy. The PFS 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 craniospinal irradiation.

Raleigh et al (2016) 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 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 the incidences 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 primitive neuroectodermal tumor (sPNET) treated with risk-adapted craniospinal irradiation and subsequent high-dose chemotherapy (HDC) with autologous hematopoietic stem-cell transplantation (HCT) between 1996 and 2003. Eight patients were considered at average risk, and 8 were at high risk (defined as the presence of residual tumor larger than 1.5 cm³ or disseminated disease in the neuroaxis). Median age at diagnosis was 7.9 years (range, 3-21 years). Seven patients had pineal primitive neuroectodermal tumor (PNET). After a median follow-up of 5.4 years, 12 patients were alive. Five-year EFS and overall survival (OS) for the patients with average-risk disease were 75% and 88%, respectively, and for the high-risk patients 60% (±19%) and 58% (±19%), respectively. No treatment-related toxicity deaths were reported. The authors concluded that HDC with stem-cell support after risk-adapted craniospinal irradiation allows for 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 2 serial studies (Head Start 1 [HS1], Head Start 2 [HS2]) between 1991 and 2002 with intensified induction chemotherapy followed by myeloablative chemotherapy and autologous HCT. 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 response (PR) or complete response (CR), 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 were 39% (95% confidence interval [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-year and 5-year EFS of 57% vs 23% and 48% vs. 15%, respectively, and 2-year and 5-year OS of 70% vs. 31% and 60% vs 23%, respectively). Sixty percent of survivors were alive without exposure to radiotherapy.

Massimino et al (2013) reported outcomes for 28 consecutive patients with non-cerebellar PNET treated from 2000 to 2011 with a high-dose drug schedule (methotrexate, etoposide, cyclophosphamide, carboplatin with or without vincristine) with autologous stem-cell rescue, followed by 1 of 2 radiation treatment options. For the first 15 patients, HDC and stem-cell rescue was followed by hyperfractionated accelerated craniospinal irradiation (CSI) with 2 high-dose thiotepa courses following CSI (for the 1st 15 patients); for subsequent cases, CSI was replaced with focal radiotherapy for patients whose tumors were non-metastatic and not progressing during induction chemotherapy. Three- and 5-year progression-free survival (PFS) rates were 69±9% and 62±10%, respectively; 3- and 5-year EFS rates were 59±10% and 53±10%, respectively; and 3- and 5-year OS rates were 73±9% and 52±11%, respectively. Eleven children died at a median of 32 months after their diagnosis (range, 5-49 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, which developed 23 and 34 months after their primary diagnosis. For the 25 patients who were able to tolerate the entire schedule, including at least 1 myeloablative course, the 5-year PFS and OS rates were 67±11% and 61±11%, respectively.

Lester et al. (2014) conducted a retrospective review of 26 patients (11 children and 15 adults) with CNS PNET to evaluate clinical outcomes and prognostic factors. Overall, 5-year disease-free survival (DFS) was 78% for pediatric patients and 22% for adult patients (p=0.004); 5-year OS was 67% for pediatric patients and 33% for adult patients (p=0.07). More pediatric patients were treated with HDC plus HCT than adult patients (82% vs 27%). In an 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 DFS overall. Medulloblastoma.

Dhall et al (2008) reported outcomes for children younger than 3 years of age at diagnosis of nonmetastatic medulloblastoma, after being treated with 5 cycles of induction chemotherapy and subsequent myeloablative chemotherapy and autologous HCT. 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 free of disease at the end of consolidation. In patients with gross total tumor resection, 5-year EFS and OS were 64% (±13%) and 79% (±11%), respectively, and for patients with residual tumor, 29% (±17%) and 57% (±19%), respectively. There were 4 treatment-related deaths. The need for craniospinal irradiation 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 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. Five-year OS was 85% (95% CI: 75% to 94%) among the average-risk cases and 70% (95% CI: 54% to 84%) in the high-risk patients. Five-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. reported outcomes for 19 young (age, <5 years) children with classical or incompletely-resected medulloblastoma treated with high-dose busulfan-thiotepa with 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. 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 time of 13 months (range, 5.8–30.7 months) after HCT. The authors conclude that high OS is possible with focal brain irradiation in the setting of HCT for medulloblastoma.

Atypical Teratoid/Rhabdoid Tumor
Lee et al (2012) retrospectively reviewed the medical records of 13 patients diagnosed with atypical teratoid/rhabdoid tumor (AT/RT) who were treated at their institute at Seoul National Children’s University Hospital (Korea). (13) The median age was 12 months (range, 3-67 months), and 7 patients were younger than 1-year-old at the time of diagnosis. Three patients (23%) underwent HDC and autologous HCT. The 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 2 groups (p=0.36); however, the median survival was reported to be higher in the HCT group (15 months) compared with the non-HCT group (9 months). (13)

Section Summary
Data evaluating HDC with autologous HCT in the setting of newly diagnosed CNS embryonal tumors is primarily from single-arm studies. These studies have suggested comparable or improved EFS and OS rates compared with historical controls, particularly in patients with disease considered high risk. One retrospective study compared HDC with HCT and delayed craniospinal irradiation to upfront craniospinal irradiation. Rates of metastasis, PFS, and OS were similar in the 2 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/Relapsed Central Nervous System Embryonal Tumors
Similar to the literature for HCT for newly diagnosed CNS embryonal tumors, the evidence for HCT for recurrent/relapsed CNS embryonal tumors consists of small series, most of which include patients with a single tumor type.

Relapsed Supratentorial Primitive Neuroectodermal Tumor
In 2012, Raghuram et al. performed a systematic review of the literature regarding the outcome of patients with relapsed sPNET treated with HDC and autologous HCT. (14) Eleven observational studies, including 4 prospective series (total 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, 3-123 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, pineal location was the only independent adverse prognostic factor for survival. Based on these pooled results, CSI may be not 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) report an expanded series with longer follow-up using autologous HCT for previously irradiated recurrent medulloblastoma. (15) 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. The median time from diagnosis to disease relapse or progression was 29.8 months (range, 5.3-114.7 months). Stage at the time of 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). HDC before HCT consisted of carboplatin, thiotepa, and etoposide. Treatment-related mortality was 12% within 30 days of transplant. Tumor 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 to 51.1 months) and EFS and OS at 10 years post-HCT was 24% for both (95% CI: 9.8 to 41.7%). The authors concluded that this retrieval strategy provides 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.(16) Seven patients were event-free survivors at a median of 54 months, with OS 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, because 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.(17) Mean age was 12.9 years (range, 5-27.8 years). Mean survival post-transplant was 4.8 years (range, 8-160+ months). The 2-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.(18) The authors identified 13 publications including 66 adult patients treated with HCT for recurrent/relapsed medulloblastoma. Limitations to the available studies include the fact that all are small case series, case reports, or retrospective reviews. The single study with a comparison group identified in the review, which included 10 patients treated with HCT, reported that patients with medulloblastoma treated with HDC with HCT at recurrence had improved OS compared with historical controls treated with conventional chemotherapy at recurrence (OS, 3.47 years vs 2 years; p=0.04). The authors conclude, “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 of HCT in relapsed CNS embryonal tumors included patients with multiple primitive neuroectodermal 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.(19) 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 chemotherapy, 34 patients (48%) 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 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 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 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 2-, 3-, and 5-year OS 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 with autologous HCT (n=10) with a historic control group of patients treated with conventional-dose chemotherapy (n=13). (20) In the HCT group, 6 patients received tandem autologous transplants. Autologous HCT was associated with increased survival (p=0.044) and a longer time to progression (TTP) of disease (p=0.028). Median TTP for the conventional versus HCT group 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 those who received a single versus tandem transplant, there was improvement in TTP 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 (irinotecan, vincristine, cisplatin, cyclophosphamide, etoposide), with an objective tumor response rate of 38.5%.(21) 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 1 study of temozolomide in combination with thiotepa and carboplatin with autologous HCT in patients with recurrent malignant brain tumors. (22) 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
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 chemosensitive disease might benefit from autologous HCT because survival outcomes are similar without radiotherapy. However, reviewers found that outcomes in older children and/or 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.

Tandem Transplant for CNS Embryonal Tumors
In 2016, Sung et al reported prospective follow-up for 13 children with AT/RT who received tandem HDC and autologous HCT. (23) Five of the children were less 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 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 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.

In 2014, Dufour et al. reported outcomes for patients with newly-diagnosed high-risk medulloblastoma and supratentorial PNET treated with tandem HDC with autologous stem-cell support followed by conventional craniospinal radiotherapy. (24) Twenty-four children older than age 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 cm³ or MYCN amplification) and 3 with sPNET. Patients received 2 courses of conventional chemotherapy with carboplatin/etoposide, 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 were 65% (95% CI: 45% to 81%) and 74% (95% CI: 51% to 89%), respectively.
In 2013, Sung et al. reported the results of reduced-dose craniospinal radiotherapy followed by tandem double 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). (25) The tumor relapsed/progressed in 4 patients, and 2 patients 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.

In 2013, Friedrich et al. reported the results of double tandem high-dose chemotherapy with autologous HCT in 3 children younger than 4 years of age with metastatic sPNET. (26) These patients also received preventive craniospinal radiotherapy; they had residual disease before HCT, but no evidence of disease after transplant (survival range, 2-10 years). (26)

Park et al. (2012) reported the results of tandem double HDC with autologous HCT in 6 children younger than 3 years of age with newly diagnosed AT/RT. (27) 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 HCT. Although 3 patients remained progression-free after tandem HCT, the effectiveness of this modality is unclear because all survivors received radiotherapy, as well as tandem HCT. (27)

In 2007, Sung et al. reported the results of a single or tandem double HDC with autologous HCT in 25 children with newly diagnosed high-risk or relapsed medulloblastoma or PNET following surgical resection. (28) Three-year EFS for patients in CR or PR and less than PR at first HDC was 67% or 16.7%, respectively. For 19 cases in CR or PR at first HDC, 3-year EFS was 89% in the tandem double group and 44% in the single high-dose chemotherapy group, respectively. Four treatment-related deaths occurred, and in 4 of 8 young children, craniospinal radiotherapy was successfully withheld without relapse.

Section Summary
Little evidence is available on the use of tandem autologous HCT for CNS embryonal tumors. The single-arm studies are very small report OS and EFS rates comparable to 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.

Allogeneic Transplant for CNS Embryonal Tumors
The use of allogeneic HCT for CNS embryonal tumors consists of rare case reports with mixed results. (29-31)

Ependymoma
Literature regarding autologous HCT for the treatment of ependymoma primarily consists of small case series. Sung et al. (2012) reported the results of tandem double HDC with autologous HCT in 5 children younger than 3 years of age with newly diagnosed anaplastic ependymoma. (32) All patients were alive at median follow-up of 45 months (range, 31-62) from diagnosis, although tumor progressed at the primary site in one patient. No significant endocrine dysfunction occurred except for hypothyroidism in one patient, and one patient had significant neurologic injury from primary surgical treatment. (32) 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 a possible option to improve survival in these patients without unacceptable long-term toxicity. Further studies with larger patient cohorts are needed to confirm these results.

Mason et al. (1998) reported on a case series of 15 patients with recurrent ependymoma. (33) Five patients died of treatment-related toxicities, 8 died from progressive disease, and 1 died of unrelated causes. After 25 months, 1 patient remains 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. similarly reported a disappointing experience in 16 children treated with a thiotepa-based high-dose regimen. (324)

A small 2007 series reported 5-year EFS of 12% (±6%) and OS of 38% (±10%) among 29 children younger than 10 years of age who received autologous HCT following intensive induction chemotherapy to treat newly diagnosed ependymoma. (35) Importantly, radiation-free survival was only 8% (±5%) in these cases. The results
of these series, although limited in size, further suggest HCT is not superior to other previously reported chemotherapeutic approaches.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 1.

Table 1. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
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<tr>
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<td></td>
<td></td>
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<tr>
<td>NCT00653068</td>
<td>Treatment of Atypical Teratoid/Rhabdoid Tumors (AT/RT) of the Central Nervous System With Surgery, Intensive Chemotherapy, and 3-D Conformal Radiation</td>
<td>70</td>
<td>Apr 2015 (ongoing)</td>
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<td>NCT00336024</td>
<td>A Phase III Randomized Trial for the Treatment of Newly Diagnosed Supratentorial PNET and High Risk Medulloblastoma in Children &lt; 36 Months Old With Intensive Induction Chemotherapy With Methotrexate Followed by Consolidation With Stem Cell Rescue Versus the Same Therapy Without Methotrexate</td>
<td>96</td>
<td>Dec 2016 (ongoing)</td>
</tr>
<tr>
<td>NCT00085202</td>
<td>Treatment of Patients With Newly Diagnosed Medulloblastoma, Supratentorial Primitive Neuroectodermal Tumor, or Atypical Teratoid Rhabdoid Tumor</td>
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<td>Sep 2018</td>
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<tr>
<td>NCT02653196</td>
<td>A Multi-Institutional Phase II Feasibility Study of Allogeneic Hematopoietic Stem Cell Transplantation for Patients With Malignant Neuro-Epithelial and Other Solid Tumors</td>
<td>30</td>
<td>Jul 2019</td>
</tr>
<tr>
<td>Unpublished</td>
<td></td>
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<tr>
<td>NCT01342237</td>
<td>Tandem High Dose Chemotherapy and Autologous Stem Cell Rescue for High Risk Pediatric Brain Tumors</td>
<td>33</td>
<td>Feb 2014 (unknown)</td>
</tr>
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</table>

NCT: national clinical trial.

Summary of Evidence
The evidence for autologous hematopoietic stem cell transplantation (HCT) in individuals who have newly diagnosed central nervous system (CNS) embryonal tumors includes prospective and retrospective single-arm studies. Relevant outcomes are overall survival, disease-specific survival, and treatment-related morbidity and mortality. In the case of pediatric CNS embryonal tumors, an important consideration is whether the use of HCT may allow for a reduction in radiation dose. Data from single-arm studies using high-dose chemotherapy (HDC) with autologous HCT to treat newly diagnosed CNS embryonal tumors have shown comparable or improved survival (both event-free survival and overall survival) compared with historical controls treated with conventional therapy, with or without radiotherapy, particularly in patients with disease that is considered high risk. In a retrospective comparative study, survival in patients receiving HDC with HCT and delayed craniospinal irradiation was comparable to survival in those receiving upfront craniospinal irradiation. Overall, data from these observational studies has suggested HCT may allow reduced doses of craniospinal irradiation without worsening survival outcomes. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have recurrent/relapsed CNS embryonal tumors who receive autologous HCT, the evidence includes prospective and retrospective single-arm studies and a systematic review of these studies. Relevant outcomes are overall survival, disease-specific survival, and treatment-related morbidity and mortality. For recurrent/relapsed CNS embryonal tumors, survival outcomes after HCT are more variable, and survival is generally very poor for tumors other than medulloblastoma. Data from some single-arm studies using autologous HCT to treat recurrent CNS embryonal tumors have shown comparable or improved survival compared with historical controls treated with conventional therapy for certain patients. The results of a 2012 systematic review of observational studies in patients with relapsed supratentorial primitive neuroectodermal tumor suggest that a subgroup of infants with chemosensitive disease might benefit from autologous HCT, achieving survival without the use of radiotherapy, whereas the outcome in older children and/or in pineal location is poor with this modality. However, a relatively large prospective multicenter study reported that HCT was not associated with improved survival outcomes in patients who had had a good response to therapy. Overall, data from these single-arm studies suggests HCT may be associated with improved survival outcomes, although data for some tumor types is limited (eg, atypical teratoid/rhabdoid tumors). HCT may allow reduced doses of craniospinal irradiation without
worsening survival outcomes.

The evidence for tandem autologous HCT in individuals who have CNS embryonal tumors includes prospective and retrospective single-arm studies. Relevant outcomes are overall survival, disease-specific survival, and treatment-related morbidity and mortality. Less evidence specifically addresses the use of tandem autologous HCT for CNS embryonal tumors. The available single-arm studies appear to report overall survival and event-free survival rates comparable to single autologous HCT. Tandem transplants may allow reduced doses of craniospinal irradiation, with the goal of avoiding long-term radiation damage. However, most studies used standard-dose irradiation, making the relative benefit of tandem autologous HCT uncertain. The evidence is insufficient to determine the effects of the technology on health outcomes.

The evidence for allogeneic HCT in individuals who have CNS embryonal tumors includes case reports. Relevant outcomes are overall survival, disease-specific survival, and treatment-related morbidity and mortality. The available evidence is limited. The evidence is insufficient to determine the effects of the technology on health outcomes.

The evidence for autologous HCT in individuals who have ependymoma includes relatively small case series. Relevant outcomes are overall survival, disease-specific survival, and treatment-related morbidity and mortality. The available case series do not report higher survival rates for patients with ependymoma treated with HCT than with standard therapies. The evidence is insufficient to determine the effects of the technology on health outcomes.

Practice Guidelines and Position Statements

National Comprehensive Cancer Network Practice Guidelines 2014

Current National Comprehensive Cancer Network guidelines on treating central nervous system (CNS) tumors (v.1.2016) make the following recommendations about hematopoietic cell transplant (HCT)(36):

- The guidelines do not address the use of autologous HCT in treating ependymomas.
- For medulloblastoma and supratentorial primitive neuroectodermal tumor, autologous HCT for localized recurrent disease with maximum safe resection is a category 2A recommendation.

U.S. Preventive Services Task Force Recommendations

Hematopoietic stem-cell transplant is not a preventive service.

Medicare National Coverage

There is no national coverage determination (NCD) for hematopoietic stem-cell transplant. In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Regulatory Status

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

References


Appendix

N/A

History

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<td>12/11/01</td>
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<td>03/11/03</td>
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<td>01/10/06</td>
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U.S. Department of Health and Human Services
200 Independence Avenue SW, Room 509F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)

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