Hematopoietic Stem-Cell Transplantation for CNS Embryonal Tumors and Ependymoma

Precertification is required for this service.

I. Description

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

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

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

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

II. Policy

A. Autologous hematopoietic stem-cell transplantation is covered (subject to Limitations Administrative Guidelines) 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).

B. Autologous hematopoietic stem-cell transplantation is covered (subject to Limitations and Administrative Guidelines) to treat recurrent embryonal tumors of the CNS.

III. Policy Guidelines

In general, use of autologous hematopoietic stem-cell transplantation for previously untreated medulloblastoma has shown no survival benefit for those patients considered to be at average risk (ie, patient age older than 3 years, without metastatic disease, and with total or near total surgical resection [<1.5 cm^2 residual tumor]) when compared to conventional therapies.

IV. Limitations

A. Tandem autologous hematopoietic stem-cell transplant to treat embryonal tumors of the CNS is not covered as it is not known to be effective in improving health outcomes.

B. Allogeneic hematopoietic stem-cell transplantation to treat embryonal tumors of the CNS is not covered as it is not known to be effective in improving health outcomes.

C. Autologous, tandem autologous and allogeneic hematopoietic stem-cell transplant to treat ependymoma is not covered as it is not known to be effective in improving health outcomes.

V. Administrative Guidelines

Precertification is required for a transplant evaluation and for the transplant itself and should be submitted by the proposed treating facility. To precertify, please complete HMSA's Precertification Request and mail or fax the form as indicated along with the required documentation.
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**Hematopoietic Stem-Cell Transplantation for CNS Embryonal Tumors and Ependymoma**

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**VI. Background**

This policy is updated regularly with searches of the MEDLINE database. The most recent literature search was performed through October 8, 2013. Following is the summary of the key literature to date.

**Hematopoietic Stem-Cell Transplantation**

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

**Hematopoietic Stem-Cell Transplantation for Brain Tumors**

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

**CNS Embryonal Tumors**

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

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. For high-risk medulloblastoma treated with conventional doses of chemotherapy and radiotherapy, the average event-free survival (EFS) at 5 years ranges from 34 to 40% across studies. 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 HSCT.

Supratentorial PNETs (sPNET) 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 20 to 30%.

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

**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 radiation therapy is usually not possible. Given the poor response to conventional-dose chemotherapy, high-dose chemotherapy with autologous HSCT has been investigated as a possible salvage therapy.
VII. Rationale

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 (HSCT) for CNS embryonal tumors is whether the use of HSCT allows radiation dose reduction.

Newly diagnosed CNS Embryonal Tumors

The evidence describing outcomes after HSCT 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. 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 HSCT, 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 HSCT, with or without craniospinal irradiation, for CNS embryonal tumors. 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.

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

Supratentorial Primitive Neuroectodermal Tumor
Chintagumpala et al. 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 with autologous hematopoietic stem-cell transplantation (HSCT) 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 cm² or disseminated disease in the neuroaxis). Median age at diagnosis was 7.9 years (range, 3 to 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% (±17%) and 88% (±13%), respectively, and for the high-risk patients 60% (±19%) and 58% (±19%), respectively. No treatment-related toxicity deaths were reported. The authors concluded that high-dose chemotherapy 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. reported outcomes for 43 children with newly diagnosed sPNET treated prospectively in 2 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 HSCT. 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 HSCT (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 radiation therapy.

Massimino et al reported outcomes for 28 consecutive patients with non-cerebellar PNET treated from 2000 to 2011 with a high-dose drug schedule (methotrexate, etoposide, cyclophosphamide, and carboplatin with or without vincristine) with autologous stem cell rescue, followed by one of two radiation treatment options. For the first 15 patients, high-dose chemotherapy and stem cell rescue was followed by hyperfractionated accelerated craniospinal irradiation (CSI) with two 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 PFS rates were 69 ± 9% and 62 ± 10%, respectively; 3- and 5-year event-free survival (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), eight due to their tumor, one due to multi organ failure after the first myeloablative treatment, and two 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. Five-year PFS did not differ for patients with pineal tumors versus those with non-pineal tumors (5-year PFS 83±15% vs 54±12%, respectively; P=nonsignificant).
Lester et al 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); 4-year OS was 67% for pediatric patients and 33% for adult patients (P=0.07). More pediatric patients were treated with high-dose chemotherapy with stem cell transplant than adult patients (82% vs 27%). In unadjusted analysis, compared with standard chemotherapy, treatment with high dose chemotherapy with stem cell transplant was associated with improved OS (HR 0.3; 95% CI 0.1 to 1.0; P=0.05).

In a study including 26 adult and pediatric patients with sPNET treated with a variety of modalities, Lester et al (2014) evaluated factors prognostic for OS and DFS, including treatment with HSCT. Compared with treatment with standard chemotherapy, HSCT was associated with a nonsignificant tendency toward improved DFS (HR=0.4; 95% CI, 0.1 to 1.0; p=0.07) and improved OS (HR=0.3; 95% CI, 0.1 to 1.0; p=0.05). However, these results are confounded by higher rates of HSCT use in children, who had better OS and DFS overall.

**Medulloblastoma**

Dhall et al. 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 HSCT. 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. reported the results of risk-adapted craniospinal radiotherapy followed by high-dose chemotherapy and autologous HSCT in 134 children with newly diagnosed medulloblastoma. After tumor resection, patients were classified as having average-risk disease (n=86), defined as equal to or less than 1.5 cm$^2$ 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 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 stem cell transplant, followed by posterior fossa irradiation. 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 six children at a median time of 13 months (range, 5.8–30.7 months) after HSCT. The authors conclude that high OS is possible with focal brain irradiation in the setting of HSCT for medulloblastoma.

**Atypical Teratoid/Rhabdoid Tumor**

Lee et al. 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). The median age was 12 months (range, 3 to 67 months), and 7 patients were younger than 1-year old at the time of diagnosis. Three patients (23%) underwent high-dose chemotherapy and autologous HSCT. The authors assessed the impact on OS in these 3 patients, as compared to 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 HSCT group (15 months) compared to the non-HSCT group (9 months).

**Recurrent/Relapsed Central Nervous System Embryonal Tumors**

Similar to the literature for HSCT for newly diagnosed CNS embryonal tumors, the evidence for HSCT 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**

Raghuram et al. performed a systematic review of the literature regarding the outcome of patients with relapsed sPNET treated with high-dose chemotherapy and autologous HSCT. (8) Eleven observational studies published before 2010 met their inclusion criteria; 4 of these were prospective case-series. The 11 studies consisted of 46 patients diagnosed with relapsed sPNET or pineoblastoma who received autologous HSCT for treatment of relapse. Of those, 15 patients were children younger than 3 years of age, and 15 were pineoblastomas. With a median follow-up of 40 months (range 3 to 123 months) 15 patients were reported alive. Thirteen patients (of 15 survivors) did not receive craniospinal irradiation. The 12-month OS rate of the cohort was 44.2 ±7.5 months. Twelve-month OS for children younger than 36 months was 66.7 ±12.2 months, while for older children, 12-month OS was 27.8 ± 10.6 (p=0.003). Twelve-month OS was 20.0 ± 10.3 for those patients with pineoblastoma versus 54.6 ±9.0 for those with non-pineal sPNETs (p<0.001). Cox regression analysis revealed pineal location as the only independent adverse prognostic factor. Based on these pooled results, high-dose chemotherapy with HSCT might lead to survival primarily in younger children with relapsed sPNET, even in the absence of concomitant use of radiotherapy, whereas the outcome in older children and/or in a pineal location is poor with this modality.

Dunkel et al. report an expanded series with longer follow-up using autologous HSCT for previously irradiated recurrent medulloblastoma. (Twenty-five patients were treated between 1990 and 1999 and included 18 males and 7 females with a median age at diagnosis of 11.5 years (range, 4.2 to 35.5 years). Median age at the time of HSCT was 13.8 years (range, 7.6 to 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 to 114.7 months). Stage at the time of 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). High-dose chemotherapy prior to HSCT 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 HSCT (range, 2.3 to 58.5 months). Median OS was 26.8 months (95% CI, 11.9 to 51.1 months) and EFS and OS at 10 years post-HSCT 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. reported the outcomes of 23 patients with recurrent medulloblastoma treated with high-dose carboplatin, thiotepa, and etoposide. Seven patients were event-free survivors at a median of 54 months, with OS estimated at 46% at 36 months. HSCT 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. reported outcomes of 8 patients with relapsed medulloblastoma with metastasis (n=7) and relapsed germinoma (n=1) who received dose-intensive chemotherapy with autologous HSCT. 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. conducted a systematic review of therapies for adults with relapsed medulloblastoma, including HDC with HSCT. The authors identified 13 publications including 66 adult patients treated with HSCT 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 HSCT, reported that patients with medulloblastoma treated with HDC 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 HSCT in relapsed CNS embryonal tumors included patients with multiple primitive neuroectodermal tumor types (medulloblastoma, sPNET). Bode et al. 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. 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 HSCT. At the end of conventional chemotherapy, 34 patients (48%) were considered to be good responders, of whom 24 were selected for HSCT, 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 HSCT, 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. HSCT-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 HSCT.

Gill et al. reported outcomes for 23 adult patients (18 years or older) treated for recurrent embryonal central nervous system (CNS) tumors between 1976 and 2004, comparing high-dose chemotherapy with autologous HSCT (n=10) with a historic control group of patients treated with conventional-dose chemotherapy (n=13). In the HSCT group, 6 patients received tandem autologous transplants. Autologous HSCT was associated with increased survival (p=0.044) and a longer time to disease progression (TTP) (p=0.028). Median TTP for the conventional versus HSCT 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. In a comparison of outcomes between the patients 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. 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%. 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.

CNS Embryonal Tumors Treated With Tandem Transplant

In 2014, Dufour et al. reported outcomes for patients with newly diagnosed high-risk medulloblastoma and sPNET treated with tandem HDC with autologous stem cell support followed by conventional craniospinal radiotherapy. 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 cm$^2$ 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, 0.8-11.3 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 high-dose chemotherapy with autologous HSCT in 20 children older than 3 years of age with high-risk medulloblastoma with metastatic disease and 3 having a postoperative residual tumor >1.5 cm$^2$ without metastasis. 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 HSCT 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 HSCT in 3 children younger than 4 years of age with metastatic sPNET. These patients also received preventive craniospinal radiotherapy; they had residual disease before HSCT, but no evidence of disease after transplant (survival ranging from 2 to 10 years).

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

Sung et al. reported the results of a single or tandem double high-dose chemotherapy with autologous HSCT in 25 children with newly diagnosed high-risk or relapsed medulloblastoma or PNET following surgical resection. Three-year EFS for patients in complete remission (CR) or partial remission (PR) and less than PR at first high-dose chemotherapy was 67% or 16.7%, respectively. For 19 cases in CR or PR at first high-dose chemotherapy, 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.

**CNS Embryonal Tumors Treated With Allogeneic Transplant**

The use of allogeneic HSCT for CNS embryonal tumors consists of rare case reports with mixed results.

**Ependymoma**

Literature regarding autologous HSCT for the treatment of ependymoma primarily consists of small case series. Sung et al. reported the results of tandem double high-dose chemotherapy with autologous HSCT in 5 children younger than 3 years of age with newly diagnosed anaplastic ependymoma. (20) 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. The results of this very small case series indicate that treatment with tandem HSCT 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. reported on a case series of 15 patients with recurrent ependymoma. 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.

A small 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 HSCT following intensive induction chemotherapy to treat newly diagnosed ependymoma. Importantly, radiation-free survival was only 8% (± 5%) in these cases. The results of these series, although limited in size, further suggest HSCT is not superior to other previously reported chemotherapeutic approaches.

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Practice Guidelines and Position Statements

National Comprehensive Cancer Network guidelines on treating central nervous system (CNS) tumors (v.1.2015) make the following recommendations about HSCT:

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

VIII. Important Reminder

The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii’s Patients’ Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4), generally accepted standards of medical practice and review of medical literature and government approval status. HMSA has determined that services not covered under this Medical Policy will not
be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA’s determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

IX. References


