Regence

Medical Policy Manual Transplant, Policy No. 45.33

Hematopoietic Cell Transplantation for Central Nervous System Embryonal Tumors and Ependymoma

Effective: July 1, 2024

Next Review: August 2024
Last Review: May 2024

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Transplantation is performed to restore normal function following chemotherapy treatment.

MEDICAL POLICY CRITERIA

I. Autologous hematopoietic cell transplantation may be considered **medically necessary** in the treatment of embryonal tumors of the central nervous system (CNS).

II. Hematopoietic cell transplantation is considered **investigational** for any of the following:

A. Tandem autologous hematopoietic cell transplantation to treat embryonal tumors of the CNS

B. Allogeneic hematopoietic cell transplantation to treat embryonal tumors of the CNS

C. Autologous hematopoietic cell transplantation to treat ependymoma

D. Tandem autologous hematopoietic cell transplantation to treat ependymoma

E. Allogeneic hematopoietic cell transplantation to treat ependymoma

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

DEFINITIONS

- **Consolidation therapy:** Treatment that is given after cancer has disappeared following the initial therapy. Consolidation therapy is used to kill any cancer cells that may be left in the body. It may include radiation therapy, a stem cell transplant, or treatment with drugs that kill cancer cells. Also called intensification therapy and postremission therapy.
- **Relapse:** The return of a disease or the signs and symptoms of a disease after a period of improvement.
- **Salvage therapy:** Treatment that is given after the cancer has not responded to other treatments.
- **Tandem transplant:** Refers to a planned second course of high-dose therapy and HCT within six months of the first course.

LIST OF INFORMATION NEEDED FOR REVIEW

SUBMISSION OF DOCUMENTATION

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and physical/chart notes
- Diagnosis and indication for transplant
- Documentation of response to induction chemotherapy

CROSS REFERENCES

1. Donor Lymphocyte Infusion for Malignancies Treated with an Allogeneic Hematopoietic Cell Transplant, Transplant, Policy No. 45.03
2. Placental and Umbilical Cord Blood as a Source of Stem Cells, Transplant, Policy No. 45.16
3. Hematopoietic Cell Transplantation for Miscellaneous Solid Tumors in Adults, Transplant, Policy No. 45.27
4. Hematopoietic Cell Transplantation for Solid Tumors of Childhood, Transplant, Policy No. 45.37

BACKGROUND

HEMATOPOIETIC CELL TRANSPLANTATION

Broadly speaking, there are two types of hematopoietic cell transplants (HCT, previously referred to in this policy as a hematopoietic stem cell transplant [HSCT]), autologous and allogeneic. The purpose of an autologous HCT is to treat a disease (e.g. lymphoma) with myeloablative doses of chemotherapy (with or without radiation) that are active against the disease. The recipient's own HCTs (collected previously) are infused after the chemotherapy in order to re-establish normal marrow function. In an allogeneic transplant, the recipient receives HCTs from a donor after myeloablative therapy or non-myeloablative therapy in order to re-establish normal marrow function as well as to use the new blood system as a platform for immunotherapy, a so called "graft versus tumor" effect. Hematopoietic cells can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates.

Although cord blood is an allogeneic source, the cells in it are antigenically “naïve” and thus are associated with a lower incidence of rejection or graft-versus-host disease (GVHD).

HEMATOPOIETIC CELL TRANSPLANTATION 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 uncommonly 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. They 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 the following:

- medulloblastoma
- medulloepithelioma
- supratentorial PNETs (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 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 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).[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] Clinical outcomes are related to molecular characteristics of the tumor.[2] 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 five years ranges from 30% to 70% across studies. Children with medulloblastoma who survive for five years are considered cured of their tumor. Survival rates for other embryonal tumors are generally poorer, ranging from less than five to 50%The treatment of newly diagnosed (i.e., previously untreated) medulloblastoma continues to evolve, and in children under the age of 3, 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.

Supratentorial PNETs (sPNET) are most commonly located in the cerebral cortex and pineal region. The prognosis is better than previous estimates, due to improvements in molecular diagnosis. The five-year OS rate is 78.5% with a 5-year event free survival rate of 62.8%.[2]

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 high-dose chemotherapy and autologous HCT for recurrent embryonal tumors, objective response is 50%–75%; however, long-term disease control is obtained in fewer than 30% of patients, and is seen primarily in patients in first relapse with localized disease at the time of relapse.[2]

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. In children, the tumor typically arises intracranially, 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 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 medical policy. See Cross References.
- Due to their neuroepithelial origin, peripheral neuroblastoma and Ewing's sarcoma may be considered PNETs. However, these peripheral tumors are considered in a separate medical policy. See Cross References.

EVIDENCE SUMMARY

The principal outcomes associated with treatment of central nervous system embryonal tumors and ependymoma are typically measured in units of survival past treatment: disease-free survival (DFS), a period of time following treatment where the disease is undetectable; progression-free survival (PFS), the duration of time after treatment before the advancement or progression of disease; and overall survival (OS), the period of time the patient remains alive following treatment. Ideally, in order to understand the impact of HCT for treatment of central nervous system (CNS) embryonal tumors and ependymoma, comparative clinical trials that compare this therapy to standard medical treatment are needed. Further, particularly patients

with a poor prognosis, an understanding of any adverse treatment effects must be carefully weighed against any benefits associated with treatment to understand the net treatment effect.

CENTRAL NERVOUS SYSTEM EMBRYONAL TUMORS

Autologous Transplant for Newly Diagnosed Tumors

Systematic Reviews

Zhang (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.[3] 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).

In 2013, an updated Cochrane Review analyzed randomized controlled trials (RCTs) comparing high-dose chemotherapy with HCT (i.e. myeloablative therapy) with conventional chemotherapy or no further treatment in children with high-risk neuroblastoma.[4] Three RCTs[5-7] with a total of 739 children were included. There was a statistically significant difference in event-free survival (EFS) and OS in favor of the myeloablative therapy group (p<0.0006 and 0.04, respectively). However, analysis of outcomes from the individual studies as well as additional follow-up data from the Matthay trial found no statistically significant between-group difference in OS (p=0.06). No significant between group difference was found for treatment-related death, serious infection, or secondary malignant disease. The myeloablative group has significantly higher incidence of renal effects, interstitial pneumonitis, and veno-occlusive disease. The authors concluded that myeloablative therapy appeared to be effective for EFS, but that there was no current evidence of effect on OS when additional follow-up data were included in the analysis.

Randomized Controlled Trials

No new RCTs have been published since the 2013 Cochrane Review.

Nonrandomized Studies

Gevorgian (2022) conducted tandem autologous HSCT (HSCT) in patients with brain tumors under four years of age.[8] The study included 50 patients with medulloblastoma, EMTR, and other histological types of brain tumors. 42 patients received tandem autologous HSCT and eight received single autologous HSCT. %. Five-year OS was 71% in medulloblastoma, 37% in ETMR and in other tumors - 51% (p=0.07).

Dufour (2021) reported on outcomes for children five 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.[9] 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, eight years; range five to 19 years) were included in the study. All children received postoperative induction chemotherapy (etoposide and carboplatin), followed by two high-dose thiotepa courses with autologous HCT. The median time between diagnosis and onset of radiation therapy was 146 days (range, 117 to 210 days) and in 16 (34%) out of 47 patients, this delay was greater than 150 days. Median follow-up was 7.1 years (range, 3.4 to 9.0 years). At three years, PFS and OS rates were 78% (95% confidence intervals [CI], 65% to 88%) and 84% (95% CI, 72% to 92%), respectively. At five 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. Another study by Granger (2021) performed high dose chemotherapy with autologous stem cell transplant (SCT) for newly diagnosed high risk neuroblastoma.[10] The Children's Oncology Group (COG) conducted a trial (ANBL12P1) to assess the tolerability and feasibility of Busulfan/melphalan ASCT following a COG induction. The patients received busulfan and melphalan followed by autologous SCT. The mean three-year EFS for all the eligible patients was 55.6 ± 4.2% with acceptable pulmonary and hepatic toxicity.

Reddy (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.[11] After surgery, the study regimen consisted of two courses of multiagent chemotherapy, followed by three 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.[11, 12] Median follow-up time was 4.7 years (95% CI, 4.2 to 5.3 years).[11] 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<0.0005). 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 four patients.

Abdelbaki (2020) reported outcomes of patients with pineoblastoma enrolled in the Head Start I, II, and III trials.[13] The treatment plan included resection followed by intensive chemotherapy and myeloablative chemotherapy with autologous hematopoietic cell rescue. Of the 23 enrolled patients (median age 3.12 years; range, 0.44 to 5.72), 10 received the planned hematopoietic cell rescue. Of these, seven additionally received craniospinal irradiation and progressive disease occurred in eight. The five-year PFS and OS were 9.7% (95% CI 2.6% to 36.0%) and 13% (95% CI 4.5% to 37.5%), respectively.

Alsultan (2015) retrospectively reviewed outcomes for 10 children under age 3 years treated with HCT, with or without craniospinal irradiation, for CNS embryonal tumors.[14] Of the 10 patients, five had medulloblastoma, three had AT/RT, one had an embryonal tumor with abundant neuropil and true rosettes, and one 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% 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 receive craniospinal irradiation.

Lester (2014) conducted a retrospective review of 26 patients (11 children and 15 adults) with CNS PNET to evaluate clinical outcomes and prognostic factors.[15] Overall, five-year disease-free survival (DFS) was 78% for pediatric patients and 22% for adult patients (p=0.004). Four-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).

Bergthold (2014) reported outcomes for 19 young (age under five years) children with classical or incompletely-resected medulloblastoma treated with high-dose busulfan-thiotepa with autologous cell transplant, followed by posterior fossa irradiation.[16] 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 1 had medulloblastoma with extensive nodularity. The median follow-up was 40.5 months (range, 14.5 to 191.2 months). At three and five 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 to 30.7 months) after HCT. The authors conclude that high OS is possible with focal brain irradiation in the setting of HCT for medulloblastoma.

Massimino (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, and carboplatin with or without vincristine) with autologous stem cell rescue, followed by one of two radiation treatment options.[17] 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 subsequent cases, CSI was replaced with focal radiotherapy for patients whose tumors were non-metastatic and not progressing during induction chemotherapy. Three- and five-year progression-free survival (PFS) rates were 69±9% and 62±10%, respectively; three- and five-year event-free survival (EFS) rates were 59±10% and 53±10%, respectively; and three- and five-year OS rates were 73±9% and 52±11%, respectively. Eleven children died at a median of 32 months after their diagnosis (range 5 to 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 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 one myeloablative course, the five-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 (five-year PFS 83±15% vs 54±12%, respectively; p=nonsignificant).

Lee (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).[18] The median age was 12 months (range: 3 to 67 months), and seven patients were younger than one-year old at the time of diagnosis. Three patients (23%) underwent high-dose chemotherapy and autologous HCT. The authors assessed the impact on OS in these three patients, as compared to the remaining 10 patients undergoing other chemotherapy regimens. No statistical difference in OS was observed between these two groups (p=0.36); however, the median survival was reported to be higher in the HCT group (15 months) compared to the non-HCT group (nine months).

Chintagumpala (2009) reviewed event-free survival (EFS) of 16 patients with newly diagnosed (i.e., previously untreated) supratentorial primitive neuroectodermal tumor (sPNET) treated with risk-adapted craniospinal irradiation and subsequent high-dose chemotherapy with autologous hematopoietic cell transplantation (HCT) between 1996 and 2003.[19] Eight patients were considered at average risk and eight were at high risk (defined as the presence of residual tumor larger than 1.5 cm^2 or disseminated disease in the neuroaxis). Median age at diagnosis was 7.9 years (range: three to 21 years). Seven patients had pineal PNET. After a median follow-up of 5.4 years, 12 patients were alive. Five-year EFS and overall survival (OS) for the patients with average risk disease was 75% (+/- 17%) and 88% (+/- 13%), respectively. For the high-risk patients, these outcomes were 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 PNETs, without compromising EFS.

Fangusaro (2008) reported outcomes for 43 children with newly diagnosed (i.e., previously untreated) PNETs treated prospectively on 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.[20] 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 were 39% (95% CI: 24–53) and 49% [95% confidence interval (CI): 33 to 62], respectively. Patients with nonpineal tumors did significantly better than patients with pineal PNETs (two-year and five-year EFS of 57% vs. 23% and 48% vs. 15%, respectively and two-year and five-year OS of 70% vs. 31% and 60% vs. 23%, respectively). Sixty percent of survivors were alive without exposure to radiation therapy.

Dhall (2008) reported outcomes for children younger than three years of age at diagnosis of nonmetastatic medulloblastoma, after being treated with five cycles of induction chemotherapy and subsequent myeloablative chemotherapy and autologous HCT.[21] Twenty of 21 children enrolled completed induction chemotherapy, of which 14 had a gross total surgical resection and 13 remained free of disease at the completion of induction chemotherapy. Of seven 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, five-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 four 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 (2006) reported the results of risk-adapted craniospinal radiotherapy followed by high-dose chemotherapy and autologous HCT in 134 children with newly diagnosed (i.e., previously untreated) medulloblastoma.[22] After tumor resection, patients were classified as having average-risk disease (n=86), defined as ≤1.5 cm^2 residual tumor and no metastatic disease or high-risk disease (n=48), defined as >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: 75–94) 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.

Autologous Transplant for Recurrent Tumors

Systematic Reviews

Kato (2020) performed a retrospective analysis of tandem high dose chemotherapy comprising the MEC and Busulfan/melphalan regimens in four patients with high risk neuroblastoma.[23] Gastrointestinal mucosal injuries was observed in all four patients and one patient experienced renal dysfunction after the first high dose chemotherapy. These regimens did not result in any life-threatening adversities. This regimen is potentially effective regimen for patients with high-risk neuroblastoma, including for those who respond poorly to induction chemotherapy. Retrospective analysis of 54 patients with high risk neuroblastoma who received a single autologous SCT between 2006 and 2016 was reported by Hillier (2020).[24] Patients receiving busulfan/melphalan had a delay in induction chemotherapy, were significant for delayed engraftment of neutrophils, platelets, and hemoglobin in high risk neuroblastoma undergoing autologous SCT.

In 2013 Kostaras and Easaw published a systematic review of studies of HDCT with HCT for recurrent medulloblastoma in adults included 13 articles[25-34] with a total of 66 adult patients.[35] The analysis found a small population of adult patients for which HDCT with HCT may be a treatment option, including those with recurrent disease confined to the CNS, are unlikely to benefit from conventional chemotherapy, and are otherwise healthy enough to tolerate the treatment. The authors recommended that cases of recurrent adult medulloblastoma in which HCT is being considered should be discussed by a multidisciplinary tumor board including a hematologic oncologist and transplant specialists.

Raghuram (2012) performed a systematic review of the literature regarding the outcome of patients with relapsed sPNET treated with high-dose chemotherapy and autologous HCT.[36] 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 HCT for treatment of relapse. Of those, 15 patients were children younger than three 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 HCT 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.

Randomized Controlled Trials

No new RCTs have been published since the 2013 systematic review.

Nonrandomized Studies

Egan (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.[37] Temozolomide was administered, followed by thiotepa and carboplatin and then autologous HCT. The study enrolled 27 patients (age range, 3 to 46 years) with high-grade glioma (n=12), medulloblastoma/PNET (n=9), CNS germ cell tumor (n=4), ependymoma (n=1), and spinal cord PNET (n=1). Fourteen (52%) patients survived longer than 24 months. After 10 years, three patients were alive.

Bode (2014) reported results 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.[38] The intensive-chemotherapy arm included 72 patients, 59 who had disseminated disease. Patients received two courses of carboplatin and etoposide; those who had complete or partial remission on MRI received two more cycles of carboplatin and etoposide followed by high-dose chemotherapy with carboplatin, etoposide, and thiotepa, with stem cell rescue. For the cohort of 72 patients, median PFS and OS were 11.6 months (95% CI 10.1 to 13.1 months) and 21.1 months (95% CI 15.7 to 26.5 months) months, respectively. Compared with patients with non-medulloblastoma PNETS, patients with medulloblastoma had longer PFS (12.6 months vs 3.1 months; P=0.004), but not significantly different OS (22.6 months vs 12.3 months; p=0.1). Twenty-four patients received high-dose chemotherapy following complete/partial remission on induction therapy, along with 3 patients with stable disease; for those patients, the median PFS and OS were 8.4 months (95% CI 7.7 to 9.1 months) and 20.2 months (95% CI 11.7 to 28.8 months), respectively. Twenty-two patients who had good response to standard chemotherapy and received high-dose chemotherapy with stem cell support were compared with 12 patients who had good response to standard chemotherapy but did not receive subsequent high-dose chemotherapy. Median PFS and OS did not significantly differ between those who did and did not receive high-dose chemotherapy.

Allogeneic Transplant

The use of allogeneic HCT for CNS embryonal tumors consists of rare case reports with mixed results.[29, 39-41] More data on the use of allogeneic HCT for treatment of these tumors is needed.

Tandem Transplant

In 2016, Sung reported prospective follow-up for 13 children with AT/RT who received tandem HDC and autologous HCT.[42] Five of the children were less than three years old; the remaining eight were three years or older. Tandem HDC and autologous HCT was administered after six cycles of induction chemotherapy with deferred radiotherapy until age three unless the tumor showed relapse or progression in the younger children. Reduced-dose radiotherapy was administered either after two cycles of induction chemotherapy or after surgery with tandem HDC and autologous HCT after six cycles of induction chemotherapy in the older children. All five younger children died from disease progression. Four of the eight older children remained progression-free, with median follow-up of 64 months.

In 2014, Dufour reported outcomes for patients with newly-diagnosed high-risk medulloblastoma and supratentorial PNET treated with tandem high-dose chemotherapy with autologous stem cell support followed by conventional craniospinal radiotherapy.[43] Twenty-four children over the age of 5 were treated from 2001 to 2010, 21 with newly-diagnosed high-risk medulloblastoma (disseminated medulloblastoma or medulloblastoma with residual tumor

volume >1.5 cm2 or MYCN amplification) and three with sPNET. Patients received two courses of conventional chemotherapy with carboplatin/etoposide, followed by two courses of high-dose thiotepa followed by stem cell rescue and craniospinal radiotherapy. Twenty-three patients received two courses of high-dose chemotherapy, while one patient received only one 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 five-year EFS and OS were 65% (95% CI 45 to 81%) and 74% (95% CI 51 to 89%), respectively.

Park (2012) reported the results of tandem double high-dose chemotherapy with autologous HCT in six children younger than three years of age with newly diagnosed AT/RT.[44] No treatment-related death occurred during the tandem procedure, and five of six patients were alive at a median follow-up of 13 months (range 7 to 64) from first HCT. Although three patients remained progression-free after tandem HCT, the effectiveness of this modality is unclear, because all survivors received radiotherapy, as well as tandem HCT.

Sung (2007) reported the results of a single or tandem double high-dose chemotherapy with autologous HCT in 25 children with newly diagnosed (i.e., previously untreated) high-risk or relapsed medulloblastoma or PNET following surgical resection.[45] 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, three-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 four of eight young children craniospinal radiotherapy was successfully withheld without relapse.

In 2013 Sung reported on 20 consecutive children with high-risk medulloblastoma who received two cycles of chemotherapy combined with radiotherapy and four cycles of post-RT chemotherapy followed by tandem high-dose chemotherapy (HDCT) with autologous SCT.[46] It is unclear whether these patients overlap with the prior study. The tumor relapsed/progressed in four patients, and there were two treatment-related deaths during the second HDCT/autoSCT. Therefore, 14 patients remained event-free at a median follow-up of 46 months (range, 23 to 82) from diagnosis. The probability of five-year event-free survival was 70.0% ± 10.3% for all patients and 70.6% ± 11.1% for patients with metastases. Late adverse effects evaluated at a median of 36 months (range, 12-68) after tandem HDCT/autoSCT were acceptable.

Sung (2013) also reported on 50 consecutive patients with high-risk neuroblastoma who received tandem HDCT with autologous SCT.[47] Of the 50 patients, 49 underwent a first HDCT/auto-SCT and 47 underwent a second HDCT/auto-SCT. The tumor relapsed or progressed in 14 patients who had either tumor relapse or progression; one patient developed secondary malignancy, one patient died from chronic lung disease, and 34 patients remained event free with a median follow-up of 54.5 months (range, 14-94 months) from diagnosis. Five-year probabilities of OS and EFS were 77% and 71.4%, respectively. However, all patients remained event free for three years or more after tandem HDCT/auto-SCT experienced late adverse effects. The authors concluded that, while outcomes were encouraging for survival, further studies are needed with newer treatment modalities to reduce late adverse effects.

Another study (2010) of tandem high dose chemotherapy with HCT included 19 patients, 12 of which had CNS embryonal tumors.[48] The initial regimen consisted of three days each of

carboplatin, etoposide, and thiotepa. Patients without disease progression or excessive toxicity (n=11) received a second regimen of melphalan for three days and cyclophosphamide for four days. Projected overall survival for the 19 patients was 37% and 28% at one and five years, respectively. However, toxicity was significant, including six treatment related deaths. The authors concluded that this regimen was not feasible due to toxicity.

A feasibility study (2012) reported the outcomes of tandem HDC with stem cell rescue (HDC/SCR) for high risk neuroblastoma.[49] Of the 33 patients enrolled, 22 completed one HDC/SCR and 17 patients completed both rounds. There was one transplant-related death. Five-year PFS and OS for all 33 patients was 24.2% and 36.4%, respectively. For patients who received at least one transplant, PFS and OS at five years was 36.4% and 45.5%, respectively. These investigators determined that tandem HDC/SCR is feasible and will be designing a phase III study testing the efficacy of this treatment regimen.

In 2013 Friedrich reported the results of double tandem high-dose chemotherapy with autologous HCT in three children younger than four years of age with metastatic sPNET.[50] These patients also received preventive craniospinal radiotherapy; they had residual disease before HCT, but no evidence of disease after transplant (survival ranging from 2 to 10 years).

EPENDYMOMA

Literature regarding autologous HCT for the treatment of ependymoma consists primarily of small case series.

Sung (2012) reported the results of tandem double high-dose chemotherapy with autologous HCT in five children younger than three years of age with newly diagnosed anaplastic ependymoma.[51] All patients were alive at median follow-up of 45 months (range 31 to 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 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 (1998) reported on a case series of 15 patients with recurrent ependymoma.[52] Five patients died of treatment-related toxicities, eight died from progressive disease, and one died of unrelated causes. After 25 months, one 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 similarly reported a disappointing experience in 16 children treated with a thiotepa-based high-dose regimen.[53]

A small series (2007) reported five-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 (i.e., previously untreated) ependymoma.[54] 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.

PRACTICE GUIDELINE SUMMARY

NATIONAL COMPREHENSIVE CANCER NETWORK

The National Comprehensive Cancer Network (NCCN) guidelines for Central Nervous System Cancers (v.1.2023) offer the following on the use of HCT in CNS tumors:[55]

All recommendations are category 2A unless otherwise indicated. Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

For adult medulloblastoma treatment for localized brain recurrence with high-dose chemotherapy followed by autologous stem cell rescue may be considered for patients showing no evidence of disease following resection or conventional systemic chemotherapy.

The NCCN guidelines for Pediatric Central Nervous System Cancers (v1.2024) do not address the use of HCT.[56]

AMERICAN SOCIETY FOR TRANSPLANTATION AND CELLULAR THERAPY

In 2015, the American Society for Blood and Marrow Transplantation (now referred to as the American Society for Transplantation and Cellular Therapy) published consensus guidelines on the use of HCT to treat specific conditions, in both clinical trial and clinical practice settings.[57] These guidelines were updated in 2020.[58] For people younger than 18 years, autologous HCT is the standard of care, but a rare indication for high risk medulloblastoma and other malignant brain tumors. The guidelines do not address HCT in the treatment of CNS tumors in people aged 18 years and older.

SUMMARY

CENTRAL NERVOUS SYSTEM EMBRYONAL TUMORS

Newly Diagnosed Tumors

There is enough research to show that autologous hematopoietic cell transplantation (HCT) has a survival benefit (both event-free and overall) when used to treat central nervous system (CNS) embryonal tumors in patients with disease that is considered high-risk. In addition, the use of autologous 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. Therefore, autologous HCT may be considered medically necessary for CNS embryonal tumors.

Recurrent Tumors

It appears that autologous hematopoietic cell transplantation (HCT) may improve survival in patients with recurrent central nervous system (CNS) embryonal tumors, and therefore may be considered medically necessary for these patients.

Allogeneic and Tandem HCT

There is not enough research to show whether tandem autologous hematopoietic cell transplantation (HCT) or allogeneic HCT improves overall health outcomes for people with

central nervous system (CNS) embryonal tumors, and therefore both treatments are considered investigational for these tumors.

EPENDYMOMAS

There is not enough research to know if or how well hematopoietic cell transplantation (HCT) works to improve overall health outcomes for people with ependymoma, and therefore HCT is considered investigational for this indication.

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CODES

Codes	Number	Description
CPT	38204	Management of recipient hematopoietic cell donor search and cell acquisition
	38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection, allogeneic
	38206	;autologous
	38207	Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage
	38208	;thawing of previously frozen harvest, without washing, per donor
	38209	;thawing of previously frozen harvest with washing, per donor
	38210	;specific cell depletion with harvest, T cell depletion
	38211	;tumor cell depletion
	38212	;red blood cell removal
	38213	;platelet depletion
	38214	;plasma (volume) depletion
	38215	;cell concentration in plasma, mononuclear, or buffy coat layer
	38230	Bone marrow harvesting for transplantation; allogeneic
	38232	Bone marrow harvesting for transplantation; autologous
	38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor
	38241	;autologous transplantation
	38242	Allogeneic lymphocyte infusions
HCPCS	S2140	Cord blood harvesting for transplantation; allogeneic
	S2142	Cord blood derived stem-cell transplantation, allogeneic
	S2150	Bone marrow or blood-derived peripheral stem-cell harvesting and transplantation, allogeneic or autologous, including pheresis, high-dose chemotherapy, and the number of days of post-transplant care in the global

	definition (including drugs; hospitalization; medical surgical, diagnostic and emergency services)

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