Hematopoietic Stem-Cell Transplantation for CNS Embryonal Tumors and Ependymoma

Policy Number: 8.01.28  Last Review: 7/2014

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for hematopoietic stem-cell transplantation for CNS embryonal tumors and ependymoma when it is determined to be medically necessary because the criteria shown below are met.

When Policy Topic is covered
Embryonal tumors of the CNS
Autologous hematopoietic stem-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 Considerations).

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

When Policy Topic is not covered
Embryonal tumors of the CNS
Tandem autologous hematopoietic stem-cell transplant is investigational to treat embryonal tumors of the CNS.

Allogeneic hematopoietic stem-cell transplantation is investigational to treat embryonal tumors of the CNS.

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

Considerations
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 (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 to conventional therapies.

Reimbursement for stem cell collection and storage are considered payable under the Transplant Benefit when billed as a one-time, all-inclusive charge.

Transplant Benefit
The date on which the Transplant Benefit starts accumulating is determined by the transplant coordinator. The Transplant Benefit ends when the Transplant Lifetime Maximum benefit (if applicable) has been exhausted.
Benefits include:

- hospitalization of the recipient for medically recognized transplants from a donor to a transplant recipient;
- evaluation tests requiring hospitalization to determine the suitability of both potential (member's benefits must be verified with regard to the potential donor who does not turn out to be the actual donor) and actual donors, when such tests cannot be safely and effectively performed on an outpatient basis (Note: The member's benefits must be verified with regard to the potential donor who does not turn out to be the actual donor.);
- hospital room, board and general nursing in semi-private rooms;
- special care units, such as coronary and intensive care;
- hospital ancillary services;
- physicians' services for surgery, technical assistance, administration of anesthetics, and medical care;
- acquisition, preparation, transportation, and storage of organ / tissue / cells;
- diagnostic services;
- drugs which require a prescription by federal law;
- medical and surgical care of the donor (related to the procurement of the organ / tissue / cells) if coverage is not available to the donor from any other source. (Covered services provided to a donor will be applied against the recipient's transplant maximum benefit, if applicable)

If the donor and recipient are both listed on the same (family) policy, BCBSKC charges only one deductible and one coinsurance, if applicable.

In addition to the specific organ criteria, transplant candidates must also meet the following general criteria, including, but not limited to:

- Since compliance is a major factor in transplant graft survival, the patient (or legal guardian) must have the ability to accept and understand the transplant procedure and to maintain compliance with long-term medical management and immunosuppression.
- If applicable, patients with a history of malignancy must have passed the recommended length of time to be considered cured for that specific cancer. A complete metastatic evaluation must be performed before a patient will be considered an acceptable transplant candidate.
- Patients with a history of alcohol or substance abuse must have a six month history of abstinence as evidenced by negative urine or serum drug screens taken randomly.
- The patient must have adequate cardiopulmonary status.
- The patient must be free from active infection.

A covered person is eligible for retransplantation as deemed medically necessary and appropriate by BCBSKC. Review of a retransplantation request will include review of the covered person’s compliance with relevant transplant selection criteria including, but not limited to, adherence to medication regimens, follow-up examinations and abstinence from the use of alcohol and drugs.

Coverage will not be provided for:

- Transplant services when the cost is covered by government, foundation or charitable grants
- The purchase price of organs which are sold rather than donated to the recipient
- An artificial organ

Clinical trials for conditions other than those allowed in this policy may be available in the research setting. However, these trials are considered investigational and/or experimental and therefore contract exclusions.

Note: There are some state mandates in place that require insurance carriers to cover certain clinical trials under very specific guidelines. Please contact your BCBSKC representative for more information.

Description of Procedure or Service
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.

**Background**

**Hematopoietic Stem-Cell Transplantation (HSCT)**

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).(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 event-free survival (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 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 10 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.

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.

Note: Due to their neuroepithelial origin, peripheral neuroblastoma and Ewing’s sarcoma may be considered PNETs. However, these peripheral tumors are considered in a separate policy.

Rationale
This policy was originally created in December 1998 and was 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.

Literature Review

CNS Embryonal Tumors

Newly Diagnosed

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, 3-21 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.(2) There were no statistical differences between HS1 and HS2 patient demographics. After maximal surgical resection, patients underwent induction chemotherapy. If, after induction, the disease remained stable or there was partial or complete response, patients underwent myeloablative chemotherapy with autologous 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.

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.(5) 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.(6) After tumor resection, patients were classified as having average-risk disease (n=86), defined as equal to or less than 1.5 cm² 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.

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).(7) 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 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).(7)

National Cancer Institute (NCI) Clinical Trial Database (PDQ®)

- A Phase III study of combination chemotherapy, radiation therapy, and an autologous peripheral bloodstem-cell transplantin treating young patients with AT/RT (NCT00653068, COG-ACNS0333) is active. The primary purpose of this multicenter study (being undertaken in 88 trial sites across the U.S., Australia, and Canada) is to determine the EFS and OS of children (birth to 21 years of age)
with AT/RT treated with surgery, high-dose chemotherapy combined with HSCT, and radiation therapy. Expected enrollment is 70 patients, with an estimated trial completion date of April 2014.

- A Phase III study of radiation therapy and combination chemotherapy followed by autologous stem-cell transplant in patients with newly diagnosed medulloblastoma, supratentorial primitive neuroectodermal tumor, or atypical teratoid rhabdoid tumor (NCT00085202, SJCRH-SJMB03) is active. The purpose of the study is to compare 2 different regimens of radiation therapy when given together with chemotherapy and autologous stem-cell transplant. Projected accrual is 413 patients, and estimated date of study completion is September 2018.

- A Phase III pilot study of induction chemotherapy followed by consolidation myeloablative chemotherapy comprising thiopeta and carboplatin with or without etoposide followed by autologous hematopoietic stem-cell rescue in pediatric patients with previously untreated malignant brain tumors (NCT00392886; CHLA-HEAD-START-III) is closed. The study compares 2 alternative induction regimens prior to myeloablative chemotherapy and stem-cell rescue. Expected enrollment was 120 patients, with an estimated trial completion date in December 2010. The publication date of this study is presently unknown.

- A Phase III randomized study of intensive induction chemotherapy comprising vincristine, etoposide, cyclophosphamide, and cisplatin with or without high-dose methotrexate and leucovorin followed by consolidation chemotherapy comprising carboplatin and thiopeta and peripheral blood stem-cell rescue in pediatric patients with newly diagnosed supratentorial primitive neuroectodermal tumors or high-risk medulloblastoma (NCT00336024, COG-ACNS0334) is active. The study was intended to compare the response rate of induction therapy with or without methotrexate and leucovorin. Expected enrollment is 96 patients, with an estimated trial completion date of September 2018.

Recurrent

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 3-123 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 nonpineal sPNETs (p<0.001). Cox regression analysis revealed pineal location as the only independent adverse prognostic factor.(8) 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.(9,10) 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: 4.2-35.5 years). Median age at the time of HSCT 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, 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, thiopeta, 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, 2.3-58.5 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. (10) 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. (11) Mean age was 12.9 years (range, 5-27.8 years). Mean survival posttransplant was 4.8 years (range, 8–160+ months). The 2-year and 5-year OS rates were 75% and 50%, respectively.

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). (12) 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. With a median follow-up of 2.9 years, 5 of the HSCT patients were alive, 4 without disease progression. In a comparison of outcomes between the patients who received a single versus tandem transplant, there was improvement in TTP favoring tandem transplant (p=0.046), but no difference in survival was observed (p=0.132).

Tandem Transplant

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 (17 with metastatic disease and 3 having a postoperative residual tumor >1.5 cm² without metastasis). (13) 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. (13)

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. (14) 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). (14)

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. (15) 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. (15)

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. (16) 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.

Allogeneic Transplant

The use of allogeneic HSCT for CNS embryonal tumors consists of rare case reports with mixed results.(17-19)

National Cancer Institute (NCI) Clinical Trial Database (PDQ®)

No Phase III randomized trials using HSCT for recurrent embryonal CNS tumors are identified.

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.(20) 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.(21) 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.(22)

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.(23) 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.

National Cancer Institute (NCI) Clinical Trial Database (PDQ®)

- A Phase III pilot study of induction chemotherapy followed by consolidation myeloablative chemotherapy comprising thiotepa and carboplatin with or without etoposide followed by autologous hematopoietic stem-cell rescue in pediatric patients with previously untreated malignant brain tumors, including ependymomas (NCT00392886; CHLA-HEAD-START-III) is closed. The study compares 2 alternative induction regimens prior to myeloablative chemotherapy and stem-cell rescue. Expected enrollment was 120 patients, with an estimated trial completion date in December 2010. The publication date of this study is presently unknown.

Summary

Data from single-arm studies using high-dose chemotherapy with autologous hematopoietic stem-cell transplantation (HSCT) to treat newly diagnosed central nervous system (CNS) embryonal tumors have shown an improved survival benefit (both event-free and overall), particularly in patients with disease that is considered high risk. In addition, the use of autologous 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.

Data from single-arm studies using autologous HSCT to treat recurrent CNS embryonal tumors have shown improved survival benefit for some patients. The results from a 2012 systematic review of observational studies in patients with relapsed supratentorial primitive neuroectodermal tumor (sPNET) suggest that a subgroup of infants with chemo-sensitive disease might benefit from autologous HSCT, achieving survival without the use of radiation therapy, whereas the outcome in older children and/or in pineal location is poor with this modality.

More data on the use of tandem and allogeneic transplants for CNS embryonal tumors are needed. The use of HSCT for ependymoma has not shown a survival benefit compared to the use of conventional approaches, and the policy statement regarding ependymoma remains investigational.

Practice Guidelines and Position Statements

National Comprehensive Cancer Network (NCCN) Practice Guidelines 2013

NCCN guidelines on treating CNS tumors do not address the use of autologous HSCT in treating ependymomas. For medulloblastoma and supratentorial PNET, autologous HSCT for recurrent disease with maximum safe resection is a category 2A recommendation.(24)

References

11. Grodman H, Wolfe L, Kretschmar C. Outcome of patients with recurrent medulloblastoma or central nervous system germinoma treated with low dose continuous intravenous etoposide

**Billing Coding/Physician Documentation Information**

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38213 Transplant preparation of hematopoietic progenitor cells; platelet depletion
38214 Transplant preparation of hematopoietic progenitor cells; plasma (volume) depletion
38215 Transplant preparation of hematopoietic progenitor cells; cell concentration in plasma, mononuclear, or buffy coat layer
38220 Bone marrow; aspiration only
38221 Bone marrow; biopsy, needle or trocar
38230 Bone marrow harvesting for transplantation; allogeneic
38232 Bone marrow harvesting for transplantation; autologous
38240 Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor
38241 Hematopoietic progenitor cell (HPC); autologous transplantation
38242 Allogeneic lymphocyte infusions
38243 Hematopoietic progenitor cell (HPC); HPC boost
Q0083 Chemotherapy administration by other than infusion technique only (e.g., subcutaneous, intramuscular, push), per visit
Q0084 Chemotherapy administration by infusion technique only, per visit
Q0085 Chemotherapy administration by both infusion technique and other technique(s) (e.g., subcutaneous, intramuscular, push), per visit
S2150 Bone marrow or blood-derived peripheral stem cell harvesting and transplantation, allogeneic or autologous, including pheresis, high-dose chemotherapy, and 28 days of post-transplant care (including drugs; hospitalization; medical surgical, diagnosis and emergency services)

Additional Policy Key Words
N/A

Policy Implementation/Update Information
7/1/02 New policy added to Medical Section.
8/1/03 No policy statement changes. Changed from Medical section to Surgery and Transplant sections.
7/1/04 Policy statement revised to include high dose chemotherapy (with or without associated radiotherapy) and autologous stem cell support to consolidate a complete remission after initial therapy for medulloblastoma and other PNETs of the CNS as investigational.
7/1/05 No policy statement changes.
4/1/06 Considerations section revised to include general criteria.
7/1/06 No policy statement changes.
7/1/07 Policy statement added to indicate that multiple-cycle high-dose chemotherapy (with or without associated radiotherapy) and autologous stem-cell support (i.e., tandem transplants) is investigational.
7/1/08 No policy statement changes.
7/1/09 No policy statement changes.
7/1/10 Policy statement changed regarding autologous consolidation therapy in patients with previously untreated embryonal tumors showing complete or partial response to, or stable disease after, induction therapy; now considered medically necessary. Other policy statements reworded and separated to address ependymoma and embryonal CNS tumors specifically; however, the intent of the statements remains the same.
7/1/11 No policy statement changes.
1/1/12 Coding updated.
7/1/12 No policy statement changes.
7/1/13 No policy statement changes.
7/1/14 Updated description on CPT 38240, 38241, 38242 and added CPT 38243.

State and Federal mandates and health plan contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining
eligibility for coverage. The medical policies contained herein are for informational purposes. The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents Blue KC and are solely responsible for diagnosis, treatment and medical advice. No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, photocopying, or otherwise, without permission from Blue KC.