Hematopoietic Stem-Cell Transplantation for CNS Embryonal Tumors and Ependymoma

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Line(s) of Business: HMO; PPO
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Section: Transplants
Place(s) of Service: Outpatient; Inpatient

Precertification is required for this service.

I. Description

Hematopoietic Stem-Cell Transplantation

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 (i.e., autologous HSCT) or from a donor (i.e., 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. They are primarily composed of
undiifferentiated 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 34–40% 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 under the age of 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. (2) After surgery, children are usually treated similarly to children with high-risk medulloblastoma. Three- to 5-year OS rates of 40–50% have been reported, and for patients with disseminated disease, survival rates at 5 years range from 20–30%. (3)

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 50–75%; 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. (3)

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 HSCT has been investigated as a possible salvage therapy.

II. Policy

A. Embryonal tumors of the CNS
   1. Autologous hematopoietic stem-cell transplantation is covered (subject to Limitations/Exclusions and 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).
   2. Autologous hematopoietic stem-cell transplantation is covered (subject to Limitations/Exclusions and Administrative Guidelines) to treat recurrent embryonal tumors of the CNS.
   3. Tandem autologous hematopoietic stem-cell transplant to treat embryonal tumors of the CNS does not meet payment determination criteria.
   4. Allogeneic hematopoietic stem-cell transplantation to treat embryonal tumors of the CNS does not meet payment determination criteria.

B. Ependymoma
   1. Autologous, tandem autologous and allogeneic hematopoietic stem-cell transplant to treat ependymoma does not meet payment determination criteria.

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 (i.e., 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/Exclusions

The patient must be an appropriate candidate for transplant. This is defined as:

A. Adequate cardiopulmonary status
B. Absence of active infection
C. No history of malignancy within 5 years of transplantation, excluding nonmelanomatous skin cancers
D. Documentation of patient compliance with medical management
V. Scientific Background

CNS Embryonal Tumors

Newly diagnosed

Chintagumpala and colleagues 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. (4) 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 and colleagues reported outcomes for 43 children with newly diagnosed sPNET 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 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]: 24–53%) and 49% (95% CI: 33–62%), 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 and colleagues 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 and colleagues 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: 75–94%) among the average-risk cases and 70% (95% CI: 54–84%) in the high-risk patients. Five-year EFS was 83% (95% CI: 73–93%) and 70% (95% CI: 55–85%) for average- and high-risk patients, respectively. No treatment-related deaths were reported.

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

- 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 two different regimens of radiation therapy when given together with chemotherapy and autologous stem-cell transplant. Projected accrual is 342 patients, and estimated date of study completion is April 2016.
- 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 two alternative induction regimens prior to myeloablative chemotherapy and stem-cell rescue. Accrual will be 120 patients, with an estimated trial completion date in December 2010.
- 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 was 96 patients, with an estimated trial completion date of August 2011.

Recurrent

Dunkel and colleagues report an expanded series with longer follow-up using autologous HSCT for previously irradiated recurrent medulloblastoma. (7,8) Twenty-five patients were treated between 1990 and 1999 and consisted of 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, 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: 2.3–58.5 months). Median OS was 26.8 months (95% CI: 11.9–51.1 months) and EFS and OS at 10 years post-HSCT was 24% for both (95% CI: 9.8–41.7%). The authors concluded that this retrieval strategy provides long-term EFS for some patients with previously irradiated recurrent medulloblastoma.

In the earlier publication, Dunkel and colleagues reported the outcomes of 23 patients with recurrent medulloblastoma treated with high-dose carboplatin, thiotepa, and etoposide. (8) 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 and colleagues 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. (9) 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.

Gill and colleagues reported outcomes for 23 adult patients (18 years or older) treated for recurrent embryonal 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). (10) 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**

Tandem and colleagues 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. (11) 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.
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Allogeneic Transplant

The use of allogeneic HSCT for CNS embryonal tumors consists of rare case reports with mixed results. (12-14)

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. Mason and colleagues reported on a case series of 15 patients with recurrent ependymoma. (15) 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 and colleagues similarly reported a disappointing experience in 16 children treated with a thiotepa-based high-dose regimen. (16)

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. (17) 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. Accrual will be 120 patients, with an estimated trial completion date in December 2010.

National Comprehensive Cancer Network (NCCN) Practice Guidelines 2010

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. (18)

Summary

Data from single-arm studies using autologous HSCT to treat newly diagnosed 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.

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.

VI. Administrative Guidelines

Precertification is required for this service as well as for any transplant evaluations. 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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<td>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)</td>
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VII. 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.

VIII. References


