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Medical Policy

Title: HDC & Allogeneic Stem &/or Progenitor Cell Support for Primitive Neuroectodermal Tumors (PNET) & Ependymoma

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Code(s):
38230, Bone marrow harvesting for transplantation
38240, Bone marrow or blood-derived peripheral stem cell transplantation; allogenic
38241, Bone marrow or blood-derived peripheral stem cell transplantation; autologous
38242, Bone marrow or blood-derived peripheral stem cell transplantation; allogeneic donor lymphocyte infusions

Public Statement:

Allogeneic stem cell transplants have not been shown to improve health outcomes in patients with primitive neuroectodermal tumors or ependymomas, and are not covered for these indications.

Medical Policy Statement:

High dose chemotherapy with allogeneic bone marrow, stem cell or progenitor cell support is considered investigational and is not covered for the treatment of primitive neuroectodermal tumors (pineoblastoma, cerebral neuroblastoma, ganglioneuroblastoma), ependymoblastoma, atypical teratoid/rhabdoid tumors or ependymoma.

Limits:

High dose chemotherapy with allogeneic stem and/or progenitor cell support is not covered following autologous stem and/or progenitor cell transplantation.
Tandem high dose chemotherapy with autologous stem and/or progenitor cell support is not covered for any diseases other than multiple myeloma and Waldenstrom’s macroglobulinemia.

A second or subsequent course of high dose chemotherapy with allogeneic or autologous stem cell and/or progenitor cell support for treatment of relapsed disease is covered only for patients who have shown a complete response to the initial high dose chemotherapy/transplant regimen.

Coverage of high dose chemotherapy with allogeneic or autologous stem and/or progenitor cell support for a patient with two active malignant diseases is covered only if both diseases have a specific coverage policy and the patient meets all criteria for both high dose chemotherapy with stem and/or progenitor cell treatment regimens.

**Background:**

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 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) (Mueller, 2009).

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 (Mueller, 2009). 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 (Fangusaro, 2008). 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 (Fangusaro, 2008). 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% (National Cancer Institute).

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 (National Cancer Institute).

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.

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

Treatment of neuroblastoma using HDC was addressed in 2 Blue Cross Blue Shield Association Technology Evaluation Center Evaluations in 1987 and 1988. At that time, the importance of N-myc oncogene amplification as a risk factor was not appreciated. Since that time, many studies have been published on HDC for neuroblastoma, particularly in patients with high-risk, primarily Stage IV, disease. Two clinical settings have been investigated: one, for initial treatment of patients presenting with high-risk, typically Stage IV, disease, and second, for salvage therapy in patients with primary refractory or recurrent disease. Although there have been no randomized studies of
HDC in patients with Stage IV disease, case series data suggest that HDC with either autologous or allogeneic stem-cell support yields 25%–50% 2-year progression-free survival (PFS) in those treated before disease progression, and 7%–25% PFS in those treated after disease progression. Due to the challenges of promptly finding a compatible allogeneic stem-cell donor, autologous stem cells may be used more commonly.

Most recently, the Children's Cancer Group (CCG) compared health outcomes of 379 patients randomized to HDC plus total body irradiation or to conventional-dose chemotherapy for initial treatment of high-risk neuroblastoma (defined as stages II-III with N-myc amplification). With a median follow-up of 43 months, event-free survival was significantly better among patients treated with HDC compared to conventional-dose chemotherapy (39% versus 22% at 3 years, respectively; p<0.034). Overall survival of the 2 treatment arms did not differ in this study. Adverse prognostic factors included stage IV disease; amplification of the N-myc oncogene; elevated serum ferritin; and poor response to induction therapy. [Note: In this study, 258 of the patients were further randomized to either receive or not receive 13-cis-retinoic acid maintenance therapy. Event free survival was reportedly significantly improved in the cis-retinoic acid treatment in this study; a subsequent randomized study in similar patients did not report a similar survival benefit.]

Several alternative treatment strategies are being studied in attempts to increase event-free and overall survival, especially in the high-risk patient population. One approach is administration of tandem or triple cycles of high-dose regimens, each followed by stem-cell infusion. Another is the use of targeted radiotherapy or radio-immunotherapy using I131-metaiodobenzylguanidine (I131MIBG) or a similar agent shortly before administration of myeloablative chemotherapy. Yet a third strategy is to reduce tumor-cell contamination of bone marrow and peripheral blood stem-cell harvests by in vivo cytoablation or positive cell-collection techniques. The evidence on these methods is limited to a few small clinical series, so the true effects of these alternatives on health outcomes currently cannot be assessed.

References:

1987 Blue Cross Blue Shield Association Technology Evaluation Center Assessment; p 51.

1988 Blue Cross Blue Shield Association Technology Evaluation Center Assessment; p 398.

1999 Blue Cross Blue Shield Association Technology Evaluation Center Assessment; Tab 11.


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Application to Products

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This policy applies to ARBenefits. Consult ARBenefits Summary Plan Description (SPD) for additional information.

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