Stem-Cell Transplantation for Central Nervous System Tumors

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Related Coverage Resources

Stem-Cell Transplantation for Neuroblastoma

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Coverage Policy

Autologous hematopoietic stem-cell transplantation (HSCT) following high-dose chemotherapy is considered as medically necessary for the treatment of EITHER of the following central nervous system tumors:

- primitive neuroectodermal tumor (PNET)
- previously untreated or recurrent medulloblastoma

For information on coverage of stem-cell transplantation for neuroblastoma, refer to the Cigna Coverage Policy Stem-Cell Transplantation for Neuroblastoma.

Autologous HSCT is considered experimental, investigational or unproven for the treatment of ANY of the following central nervous system tumors (this list may not be all inclusive):

- astrocytoma
- brainstem glioma
- ependymoma
- oligodendrogloma
Allogeneic HSCT is considered experimental, investigational or unproven for the treatment of central nervous system tumors.

**Overview**

This Coverage Policy addresses hematopoietic stem-cell transplantation (HSCT) for the treatment of central nervous system tumors such as primitive neuroectodermal tumor (PNET), medulloblastoma, astrocytoma, brainstem glioma, ependymoma and oligodendroglioma.

HSCT is a method of replacing immature blood-forming cells in the bone marrow that have been destroyed by drugs, radiation, or disease. It may be autologous (i.e., using a person’s own stem cells) or allogeneic (i.e., using stem cells donated by someone else).

**General Background**

Primary central nervous system (CNS) tumors are a diverse group of tumors originating in the brain or spinal cord. CNS tumors, develop from different cell types, form in different areas of the CNS and may have different prognoses and treatment in children compared with adults. Tumor types include, but are not limited to infratentorial (posterior fossa) tumors, supratentorial tumors and parasellar tumors (National Cancer Institute [NCI], 2017). CNS tumors are more common in children than adults and constitute the most common solid tumors of childhood. For most primary brain tumors in children, the optimal treatment regimens have not been determined. Overall, CNS tumors have a poor prognosis.

In an attempt to eradicate residual neoplastic cells and improve cure rate high-dose chemotherapy with autologous hematopoietic stem-cell transplantation (HSCT) has been investigated as a treatment option for selected individuals with certain high-risk CNS tumors.

**Stem-Cell Transplantation**

HSCT refers to transplantation of hematopoietic stem cells from a donor into a patient. HSCT can be either autologous (i.e., using the patient’s own stem cells) or allogeneic (i.e., using stem cells from a donor).

**Contraindications to Transplantation**

Many factors affect the outcome of tissue transplantation; the selection process is designed to obtain the best result for each individual. The presence of any significant comorbid conditions which would significantly compromise clinical care and chances of survival is a contraindication to transplant. Relative contraindications to HSCT include, but are not limited to:

- poor cardiac function (ejection fraction less than 45%)
- poor liver function (bilirubin greater than 2.0 mg/dL and transaminases greater than two times normal)
- poor renal function (creatinine clearance less than 50 mL/min)
- poor pulmonary function (diffusion capacity [DLCO] less than 60% of predicted)
- presence of human immunodeficiency virus or an active form of hepatitis B, hepatitis C or human T-cell lymphotropic virus
- Karnofsky rating less than 60% and/or Eastern Cooperative Oncology Group (ECOG) performance status greater than two

**Autologous HSCT:** High-dose chemotherapy and autologous HSCT has been used as initial, as well as salvage therapy with a variety of CNS malignancies. Comparison of the effects of HSCT between treatment trials remains challenging given the heterogeneity of these tumors, use of different combinations of chemotherapy as well as radiation therapies, and varied patient selection (Ratko, 2012). Results vary based on the ability of each strategy to allow better penetration of the blood brain barrier and to increase the dose-response effect. Myeloablative therapy may initially delay, and later avoid the use of radiotherapy in infants and toddlers (Kadota, 2008). Due to disease characteristics, overall prognosis and rarity of individual tumor types randomized controlled trials are not feasible; however, several prospective case reports and retrospective analyses demonstrate improvements in disease-free and overall survival in selected patients.
On behalf of the Agency for Healthcare Research and Quality (AHRQ), Ratko et al. (2012) published narrative and systematic reviews evaluating the comparative benefits and harms of HSCT versus standard therapies or disease natural history in children with malignant solid tumors, including central nervous system (CNS) embryonal and glial tumors, inherited metabolic diseases, and autoimmune diseases. The authors noted evidence demonstrating benefit or harm of HSCT versus standard therapies or disease natural history was insufficient for most pediatric indications.

The evidence for narrative review of central nervous system embryonal tumors compiled for this review included seven case series published since 2005. No RCTs, registry reports, or clinical practice guidelines for the treatment of childhood CNS embryonal tumors with HST were identified in the literature search. Published information on outcome for children with CNS embryonal tumors is based on small series and is retrospective in nature. Data suggest there is a favorable risk-benefit for HSCT in young children with high-risk or recurrent medulloblastoma.

Systematic review addressed single and tandem autologous HSCT as initial therapy compared with conventional therapy and single autologous HSCT, respectively, for CNS embryonal tumors. Evidence included ten observational studies and two RCTs. Fifteen patients received tandem transplant and 132 patients received single HSCT. Based on the evidence it was not possible to clarify the role of single versus tandem procedure. There was also insufficient evidence to draw conclusions on overall survival with single HSCT compared to conventional therapy.

Systematic review also addressed single autologous HSCT as consolidation of high-risk, recurrent/refractory CNS glial tumors compared with conventional therapy. Evidence included one comparative cohort study of HSCT versus conventional therapy, one noncomparative cohort study, four RCTs, three Phase II trials, and 30 case series. Two hundred fifteen patients received hematopoietic stem-cell transplantation (HSCT); 797 received conventional therapy. Evidence was evaluated in five groups: anaplastic astrocytoma and glioblastoma multiforme (astrocytic tumors), choroid plexus tumor, ependymoma, and other glial tumor patients. Low strength evidence on overall survival suggests a benefit with single HSCT compared to conventional therapy for the treatment of high-risk recurrent or progressive anaplastic astrocytoma; however, the authors note the risk of bias is high and data are limited to only 17 patients. Data also suggested a harm of HSCT for overall survival for nonanaplastic mixed or unspecified ependymoma compared to conventional therapy. Evidence was insufficient to determine benefit of HSCT compared to conventional therapy for the treatment of high-risk newly diagnosed glioblastoma multiforme, newly diagnosed anaplastic, non anaplastic, mixed, or unspecified ependymoma, recurrent ependymoma, choroid plexus carcinoma, or other gliomas.

In a retrospective analysis of 18 consecutive children with primary (n=14) and recurrent (n=4) brain tumors Panosyan et al. (2011) reported three-year progression-free and overall survival probabilities of 60.5% and 69.3%, respectively. This data suggest that autologous HSCT may have a definitive role for selected patients with poor prognosis brain tumors.

Gill et al. (2008) performed a retrospective review comparing the results of adult patients (i.e. ≥18 years) with recurrent central nervous system tumors who received HSCT (n=10) or conventional-dose therapy (n=13). Of the patients undergoing transplantation (n=10) eight had a diagnosis of medulloblastoma; two patients were diagnosed with neuroblastoma. Six patients received tandem autologous HSCT; four patients received a single autologous HSCT. Transplantation was associated with increased survival (p=.044) compared with those receiving conventional chemotherapy. There was an improvement in time-to-progression for patients who received tandem versus a single dose of myeloablative chemotherapy (p=0.46); however, no improvement in survival was seen (p=0.132).

The safety and effectiveness of tandem or multiple cycles of high-dose chemotherapy and autologous transplantation for the treatment of CNS tumors is the subject of ongoing research. Peer-reviewed published data are limited to small prospective case series and retrospective reviews. Chemotherapy and radiotherapy regimens are heterogeneous, limiting the ability to draw conclusions regarding impact on health outcomes (Dufour, 2014; Sung, 2013; Giman, 2011; Buturrini, 2009). At this time it is still unknown whether the use of multiple cycles of myeloablative chemotherapy and autologous HSCT improves outcomes compared with a single cycle high-dose chemotherapy regimen in the treatment of individuals with CNS tumors.
Medulloblastoma/Primitive Neuroectodermal Tumor (PNET): CNS embryonal tumors, including medulloblastoma and supratentorial primitive neuroectodermal tumor (sPNET) may be responsive to conventional chemotherapy; however, while 30–50% of patients will have objective response, long-term disease control with conventional therapy is rare.

Treatment options may include combination chemotherapy, systemic and oral chemotherapy plus intrathecal chemotherapy; higher-dose chemotherapy supported by autologous bone marrow rescue or peripheral stem cell rescue, and chemotherapy followed by radiation therapy to the primary tumor site (National Cancer Institute [NCI], 2017e). Especially in young children, high-dose chemotherapy to delay or avoid craniospinal radiotherapy has been recognized as part of a multimodal risk-adapted treatment strategy.

Literature Review
There are limited data from randomized controlled trials regarding the safety and effectiveness of hematopoietic stem-cell transplantation (HSCT) for medulloblastoma or primitive neuroectodermal tumors (PNET). However, outcomes from several prospective trials, case series, and retrospective studies demonstrate improved response rates, and disease-free-, event-free- and/or overall survival with the use of high-dose chemotherapy and autologous HSCT for primary brain tumors, including medulloblastoma and PNET. Five-year overall survival (OS) rates range from 85–39%; event-free survival (EFS) ranged from 83%–49% (Dunkel, 2010; Chintagumpala, 2009; Grodman, 2009; Cheuk, 2008; Fangusaro, 2008a; Ridola, 2008; Sung, 2007; Gajjar, 2006, Chi, 2004).

Although data are not robust, improved response rates, and improved EFS and OS have been demonstrated in a number of uncontrolled prospective and retrospective studies. Autologous HSCT is considered an acceptable treatment option for this indication. Especially in young children, high-dose chemotherapy to delay or avoid craniospinal radiotherapy has been recognized as part of a multimodal treatment strategy.

Astrocytoma:

High-grade astrocytic tumors (i.e., anaplastic astrocytomas and glioblastoma) are often locally invasive and extensive (NCI, 2017b). Autologous HSCT has been proposed as a treatment for this indication but is not considered standard of care.

Literature Review
Finlay et al. (2008) reported the results of a prospective, nonrandomized trial of 27 children and adolescents with glioblastoma multiforme (n=17), or anaplastic astrocytoma (n=10) who received myeloablative chemotherapy followed by autologous HSCT with one of three chemotherapy regimens following initial tumor progression. Event-free survival (EFS) and mortality rates following myeloablative chemotherapy for these patients was compared with outcomes of a cohort of similar patients who received conventional chemotherapy following initial tumor progression (n=56). Five of 27 children (two with glioblastoma multiforme and three with anaplastic astrocytoma) had an EFS of 8.3 to 13.3 years (median 11.1 years) following myeloablative therapy. No significant differences in overall survival (OS) were noted between the two groups when not stratified according to whether patients were surgically debulked prior to treatment (p=0.39). When patients were stratified according to surgical debulking, differences in survival were statistically significant (p=.017).

Although results are promising, the ability to draw conclusions regarding improved health outcomes with this therapy is limited by study design and small patient population. The role of HSCT for this indication has not yet been established.

Brainstem Glioma:

In brainstem gliomas, the use of more aggressive chemotherapy strategies including high-dose chemotherapy followed by peripheral blood stem-cell reinfusion results in relatively brief-duration responses and few instances of significant tumor reduction lasting 12 months or longer (Dorsey, 2013).

Literature Review
Bay et al. (2007) reported the results of a retrospective study sponsored by the European Group for Blood and Marrow Transplantation. Two-hundred seventeen patients with high-grade supratentorial glioma underwent high-dose chemotherapy followed by autologous HSCT. The median age was 44.8 years. Treatment-related mortality was 4.5%. With a median follow-up of eight years, the median OS was 20 months. The survival probabilities at 6
months, 1, 5 and 10 years were 84%, 62%, 32%, and 17%, respectively. At the time of the study publication, the authors reported that only five patients (8%) were alive.

Data are limited in the published peer-reviewed scientific literature regarding the safety and effectiveness of HSCT for the treatment of glioma. The role of HSCT has not yet been established for this indication.

**Ependymoma:** There are limited data in the published peer-reviewed scientific literature regarding the safety and effectiveness of HSCT for this indication. The role of this therapy has not yet been established for this indication.

**Oligodendroglioma:** There are limited data in the published peer-reviewed scientific literature regarding the safety and effectiveness of HSCT for the treatment of oligodendroglioma. The role of this therapy has not yet been established for this indication.

**Allogeneic HSCT:** There are limited data in the published peer-reviewed scientific literature regarding the safety and effectiveness of allogeneic HSCT for the treatment of central nervous system (CNS) tumors. The role of allogeneic HSCT has not yet been established for this indication.

**Professional Societies/Organizations**

**National Cancer Institute (NCI):** The NCI has published comments regarding the use of high-dose chemotherapy with autologous stem-cell rescue for various central nervous system tumors:

- **Childhood Central Nervous System Embryonal Tumors:** High-dose marrow-ablative chemotherapy with autologous bone marrow rescue or peripheral stem-cell rescue is considered a treatment option for a child ≤ three years with medulloblastoma. Treatment of children aged 3 years and younger with nonmedulloblastoma, nonmedulloepithelioma embryonal tumors is similar to that outlined for children aged 3 years and younger with medulloblastoma (2017e).
- **Ependymomas:** The NCI notes there is no evidence that high-dose chemotherapy with stem cell rescue is of any benefit (2017g)
- **Brain Stem Glioma:** High-dose, marrow-ablative chemotherapy with autologous hematopoietic stem cell rescue has been ineffective in extending survival (2017c).
- **Childhood Astrocytomas:** For children with recurrent childhood high-grade astrocytomas, high-dose chemotherapy followed by autologous HSCT may be a treatment option, but is not considered a standard of care (2017b).

**National Comprehensive Cancer Network Guidelines™ (NCCN Guidelines™):** Regarding medulloblastoma and supratentorial PNET the Guideline (2016) notes that high dose chemotherapy with autologous HSCT is a feasible strategy for individuals who have had a good response to lower doses of chemotherapy.

**The American Board of Internal Medicine’s (ABIM) Foundation Choosing Wisely® Initiative (2014):** No relevant statements.

**Use Outside of the US:** No relevant information.

**Coding/Billing Information**

**Note:** 1) This list of codes may not be all-inclusive.

2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered medically necessary when criteria in the applicable policy statements listed above are met for the treatment of medulloblastoma/primitive neuroectodermal tumors (PNET):

<table>
<thead>
<tr>
<th>CPT® Codes</th>
<th>Description</th>
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Medical Coverage Policy: 0369
<table>
<thead>
<tr>
<th>HCPCS Codes</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>S2150</td>
<td>Bone marrow or blood-derived stem cells (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation, and related complications; including: pheresis and cell preparation/storage; marrow ablative therapy; drugs, supplies, hospitalization with outpatient follow-up; medical/surgical, diagnostic, emergency, and rehabilitative services; and the number of days of pre-and post-transplant care in the global definition</td>
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**Considered Experimental/Investigational/Unproven when used to report autologous hematopoietic stem-cell transplantation (HSCT) for any other CNS tumors including astrocytoma, brainstem glioma, ependymoma, and oligodendroglioma:**

<table>
<thead>
<tr>
<th>CPT® Codes</th>
<th>Description</th>
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<tr>
<td>38206</td>
<td>Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous</td>
</tr>
<tr>
<td>38207</td>
<td>Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage</td>
</tr>
<tr>
<td>38208</td>
<td>Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing, per donor</td>
</tr>
<tr>
<td>38209</td>
<td>Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing, per donor</td>
</tr>
<tr>
<td>38211</td>
<td>Transplant preparation of hematopoietic progenitor cells; tumor cell depletion</td>
</tr>
<tr>
<td>38212</td>
<td>Transplant preparation of hematopoietic progenitor cells; red blood cell removal</td>
</tr>
<tr>
<td>38213</td>
<td>Transplant preparation of hematopoietic progenitor cells; platelet depletion</td>
</tr>
<tr>
<td>38214</td>
<td>Transplant preparation of hematopoietic progenitor cells; plasma (volume) depletion</td>
</tr>
<tr>
<td>38215</td>
<td>Transplant preparation of hematopoietic progenitor cells; cell concentration in plasma, mononuclear or buffy coat layer</td>
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<tr>
<td>38232</td>
<td>Bone marrow harvesting for transplantation; autologous</td>
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<tr>
<td>38241</td>
<td>Hematopoietic progenitor cell (HPC); autologous transplantation</td>
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<table>
<thead>
<tr>
<th>HCPCS Codes</th>
<th>Description</th>
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| S2150       | Bone marrow or blood-derived stem cells (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation, and related complications; including:
Considered Experimental/Investigational/Unproven when used to report allogeneic hematopoietic stem-cell transplantation (HSCT) for the treatment of central nervous system tumors:

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<tr>
<td>38205</td>
<td>Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogenic</td>
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<td>38207</td>
<td>Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage</td>
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<tr>
<td>38208</td>
<td>Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing, per donor</td>
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<tr>
<td>38209</td>
<td>Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing, per donor</td>
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<tr>
<td>38210</td>
<td>Transplant preparation of hematopoietic progenitor cells; specific cell depletion within harvest, T-cell depletion</td>
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<tr>
<td>38212</td>
<td>Transplant preparation of hematopoietic progenitor cells; red blood cell removal</td>
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<tr>
<td>38213</td>
<td>Transplant preparation of hematopoietic progenitor cells; platelet depletion</td>
</tr>
<tr>
<td>38214</td>
<td>Transplant preparation of hematopoietic progenitor cells; plasma (volume) depletion</td>
</tr>
<tr>
<td>38215</td>
<td>Transplant preparation of hematopoietic progenitor cells; cell concentration in plasma, mononuclear or buffy coat layer</td>
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<tr>
<td>38230</td>
<td>Bone marrow harvesting for transplantation; allogeneic</td>
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<td>38240</td>
<td>Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor</td>
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<tr>
<td>38242</td>
<td>Allogeneic lymphocyte infusions</td>
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<th>Description</th>
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<td>S2140</td>
<td>Cord blood harvesting for transplantation, allogeneic</td>
</tr>
<tr>
<td>S2142</td>
<td>Cord blood-derived stem cell transplantation, allogeneic</td>
</tr>
<tr>
<td>S2150</td>
<td>Bone marrow or blood-derived stem cells (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation, and related complications; including: pheresis and cell preparation/storage; marrow ablative therapy; drugs, supplies, hospitalization with outpatient follow-up; medical/surgical, diagnostic, emergency, and rehabilitative services; and the number of days of pre-and post-transplant care in the global definition</td>
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References


