Hematopoietic Stem-Cell Transplantation for Solid Tumors of Childhood

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 with or without whole body radiation therapy. Stem cells may be obtained from the transplant recipient (autologous HSCT) or can be harvested from a donor (allogeneic HSCT). Stem cells may be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates.

Background

Autologous HSCT takes advantage of the steep dose-response relationship observed with many chemotherapeutic agents and allows for escalation of chemotherapy doses above those limited by myeloablation. The use of allogeneic HSCT for solid tumors relies on a graft-versus-tumor effect. Allogeneic HSCT is uncommonly used in solid tumors, and may be used if an autologous source cannot be cleared of tumor or cannot be harvested.

Solid Tumors of Childhood

Solid tumors of childhood are defined as those not arising from myeloid or lymphoid cells. Some of the most common solid tumors of childhood are neuroblastoma, Ewing’s sarcoma/Ewing’s sarcoma Family of Tumors (ESFT), Wilms tumor, rhabdomyosarcoma (RMS), osteosarcoma, and retinoblastoma.

The prognosis for pediatric solid tumors has improved over the last 2 decades, mostly due to the application of multiagent chemotherapy and improvements in local control therapy (including aggressive surgery and advancements in radiation therapy). However, patients with metastatic, refractory, or recurrent disease continue to have poor prognoses, and these “high-risk” patients are candidates for more aggressive therapy, including autologous HSCT, in an effort to improve event-free survival (EFS) and overall survival (OS).

Descriptions of the solid tumors of childhood that are addressed in this policy are as follows:

Peripheral Neuroblastoma

Neuroblastoma is the most common extracranial solid tumor of childhood with approximately 90% of cases presenting in children younger than 5 years of age. These tumors originate where sympathetic nervous system tissue is present, within the adrenal medulla or paraspinal sympathetic ganglia. They are remarkable for their broad spectrum of clinical behavior, with
Hematopoietic Stem-Cell Transplantation for Solid Tumors of Childhood

...some undergoing spontaneous regression, others differentiating into benign tumors, and still others progressing rapidly and resulting in patient death.

Patients with neuroblastoma are stratified into prognostic risk groups (low, intermediate, and high) that determine treatment plans. Risk variables include age at diagnosis, clinical stage of disease, tumor histology, and certain molecular characteristics, including the presence of the MYCN oncogene. Tumor histology is categorized as favorable or unfavorable, according to the degree of tumor differentiation, proportion of tumor stromal component, and index of cellular proliferation. It is well established that MYCN amplification is associated with rapid tumor progression and a poor prognosis even in the setting of other coexisting favorable factors. Loss of heterozygosity (LOH) at chromosome arms 1p and 11q occurs frequently in neuroblastoma. Although 1p LOH is associated with MYCN amplification, 11q is usually found in tumors without this abnormality. Some recent studies have shown that 1p LOH and unbalanced 11q LOH are strongly associated with outcome in patients with neuroblastoma, and both are independently predictive of worse progression-free survival (PFS) in patients with low- and intermediate-risk disease. Although the use of these LOH markers in assigning treatment in patients is evolving, they may prove useful to stratify treatment.

Clinical stage of disease is based on the International Neuroblastoma Staging System (INSS) as follows:

- **Stage 1**: Localized tumor with complete gross excision, with or without microscopic residual disease; lymph nodes negative for tumor
- **Stage 2A**: Localized tumor with incomplete gross excision; lymph nodes negative for tumor
- **Stage 2B**: Localized tumor with or without complete gross excision, with ipsilateral lymph nodes positive for tumor
- **Stage 3**: Unresectable unilateral tumor infiltrating across the midline, with or without regional lymph node involvement; or localized unilateral tumor with contralateral regional lymph node involvement; or midline tumor with bilateral extension by infiltration or by lymph node involvement
- **Stage 4**: Any primary tumor with dissemination to distant lymph nodes, bone, bone marrow, liver, skin, and/or other organs, except as defined for stage 4S
- **Stage 4S**: Localized primary tumor as defined for stage 1, 2A, or 2B, with dissemination limited to skin, liver, and/or bone marrow (marrow involvement less than 10%), limited to children younger than 1 year of age

The low-risk group includes patients less than 1 year of age with stage 1, 2, or 4S with favorable histopathologic findings and no MYCN oncogene amplification. High-risk neuroblastoma is characterized by an age older than 1 year, disseminated disease, MYCN oncogene amplification, and unfavorable histopathologic findings.

In general, most patients with low-stage disease have excellent outcomes with minimal therapy, and with INSS stage 1 disease, most patients can be treated by surgery alone. Most infants, even with disseminated disease, have favorable outcomes with chemotherapy and surgery. In contrast, most children older than 1 year with advanced-stage disease die due to progressive disease, despite intensive multimodality therapy and relapse remains common. Treatment of recurrent disease is determined by the risk group at the time of diagnosis, and the extent of disease and age of the patient at recurrence.
Hematopoietic Stem-Cell Transplantation for Solid Tumors of Childhood

**Ewing’s Sarcoma and the Ewing Family of Tumors**

Ewing’s sarcoma family of tumors (ESFT) encompasses a group of tumors that have in common some degree of neuroglial differentiation and a characteristic underlying molecular pathogenesis (chromosomal translocation). The translocation usually involves chromosome 22 and results in fusion of the EWS gene with one of the members of the ETS family of transcription factors, either FLI1 (90–95%) or ERG (5–10%). These fusion products function as oncogenic aberrant transcription factors. Detection of these fusions is considered to be specific for the ESFT, and helps further validate the diagnosis. Included in ESFT are “classic” Ewing’s sarcoma of bone, extraosseous Ewing’s, peripheral primitive neuroectodermal tumor (pPNET), and Askin tumors (chest wall).

Most commonly diagnosed in adolescence, ESFT can be found in bone (most commonly) or soft tissue; however, the spectrum of ESFT has also been described in various organ systems. Ewing’s is the second most common primary malignant bone tumor. The most common primary sites are the pelvic bones, the long bones of the lower extremities, and the bones of the chest wall.

Current therapy for Ewing’s sarcoma favors induction chemotherapy, with local control consisting of surgery and/or radiation (dependent on tumor size and location), followed by adjuvant chemotherapy. Multiagent chemotherapy, surgery, and radiation therapy have improved the PFS in patients with localized disease to 60%–70%. The presence of metastatic disease is the most unfavorable prognostic feature, and the outcome for patients presenting with metastatic disease is poor, with 20%–30% PFS. Other adverse prognostic factors that may categorize a patient as having “high-risk” Ewing’s are tumor location (e.g., patients with pelvic primaries have worse outcomes), larger tumor size, and older age of the patient. However, “high-risk” Ewing’s has not always been consistently defined in the literature. Thirty to forty percent of patients with ESFT experience disease recurrence and patients with recurrent disease have a 5-year EFS and OS rate of less than 10%.

**Rhabdomyosarcoma**

Rhabdomyosarcoma (RMS), the most common soft tissue sarcoma of childhood, shows skeletal muscle differentiation. The most common primary sites are the head and neck (e.g., parameningeal, orbital, and pharyngeal), genitourinary tract, and extremities. Five-year survival rates for rhabdomyosarcoma increased between 1975 and 2010 from 53% to 67% in children younger than 15 years and from 30% to 51% in 15- to 19-year-olds.

Most children with RMS present with localized disease. Approximately 15% of children present with metastatic disease, and despite the introduction of new drugs and intensified treatment, the 5-year survival is 20%–30% for this “high-risk” group. Similarly, post-relapse mortality is very high. The prognosis of metastatic disease is affected by tumor histology, age at diagnosis, the site of metastatic disease, and the number of metastatic sites.

**Wilms Tumor**

Wilms tumor, the most common primary malignant renal tumor of childhood, is highly sensitive to chemotherapy and radiation, and current cure rates exceed 85%. Ten to 15% of patients with favorable histology and 50% of patients with anaplastic tumors experience tumor progression or relapse. Similar to newly diagnosed Wilms, relapsed Wilms tumor is a heterogeneous disease, and current treatment strategies stratify intensity and scheduling of the treatment modalities based on prognostic features. For newly diagnosed disease, the most important prognostic features are stage and histology. Similar risk-adapted strategies are being attempted for the 15% of patients who experience relapse. Success rates after relapse range from 25%–45%. For patients with adverse prognostic factors (histologically anaplastic tumors, relapse less than 6–12 months...
Hematopoietic Stem-Cell Transplantation for Solid Tumors of Childhood

after nephrectomy, second or subsequent relapse, relapse within the radiation field, bone or brain metastases) event-free survival is less than 15%. However, recent trials with HDC and autologous HSCT have reported 3- or 4-year OS rates from 60%–73%.

Osteosarcoma

Osteosarcoma is a primary malignant bone tumor that is characterized by formation of bone or osteoid by the tumor cells. Osteosarcoma occurs predominantly in the appendicular skeleton of adolescents. The prognosis of osteosarcoma has greatly improved, with 5-year survival rates increasing between 1975 and 2010 from 40% to 76% in children younger than 15 years and from 56% to 66% in 15- to 19-year olds.

Prognostic factors for patients with localized disease include site and size of the primary tumor, presence of metastases at the time of diagnosis, resection adequacy, and tumor response to neoadjuvant chemotherapy. For patients with recurrent osteosarcoma, the most important prognostic factor is surgical resectability. There is a 5-year survival rate of 20% to 45% in patients who had complete resection of metastatic pulmonary tumors and a 20% survival rate for patients with metastatic tumors at other sites.

Retinoblastoma

Retinoblastoma is the most common primary tumor of the eye in children. It may occur as a heritable (25%-30%) or nonheritable (70%-75%) tumor. Cases may be unilateral or bilateral, with bilateral tumor almost always occurring in the heritable type. The type of treatment depends on the extent of disease. Retinoblastoma is usually confined to the eye, and with current therapy has a high cure rate. However, once disease has spread beyond the eye, survival rates drop significantly; 5-year disease-free survival is reported to be less than 10% in those with extraocular disease, and stage 4b disease has been lethal in virtually all cases reported. Extraocular disease may be localized to the soft tissues surrounding the eye, or to the optic nerve, extending beyond the margin of resection. Further extension may result in involvement of the brain and meninges, with subsequent seeding of the cerebrospinal fluid, as well as distant metastases to the lungs, bone, and bone marrow. Stage 4a disease is defined as distant metastatic disease not involving the central nervous system (CNS), and stage 4b is defined as metastatic disease to the CNS.

Related Policies:
Cord Blood As a Source of Stem Cells.
Hematopoietic Stem-Cell Transplantation for CNS Embryonal Tumors and Ependymoma
Hematopoietic Stem-Cell Transplantation for Germ Cell Tumors

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.

Policy

BCBSNC will provide coverage for hematopoietic stem-cell transplantation for solid tumors of childhood when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.

If the medical criteria and guidelines are not met, some patients may be eligible for coverage under clinical trials. Refer to the policy, Clinical Trial Services.

Benefits Application
Hematopoietic Stem-Cell Transplantation for Solid Tumors of Childhood

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

Some health benefit plans may exclude benefits for transplantation.

When Hematopoietic Stem-Cell Transplantation for Solid Tumors of Childhood is covered

Autologous hematopoietic stem-cell transplantation may be considered medically necessary for:

- initial treatment of high-risk neuroblastoma,
- recurrent or refractory neuroblastoma,
- initial treatment of high-risk Ewing’s sarcoma,
- recurrent or refractory Ewing’s sarcoma, and
- metastatic retinoblastoma.

Tandem autologous hematopoietic stem-cell transplantation may be considered medically necessary for high-risk neuroblastoma.

When Hematopoietic Stem-Cell Transplantation for Solid Tumors of Childhood is not covered

Autologous hematopoietic stem-cell transplantation is considered investigational as initial treatment of low- or intermediate-risk neuroblastoma, initial treatment of low- or intermediate-risk Ewing’s sarcoma, and for other solid tumors of childhood including, but not limited, to the following:

- rhabdomyosarcoma
- Wilms tumor
- osteosarcoma
- retinoblastoma without metastasis

Tandem autologous hematopoietic stem-cell transplantation is considered investigational for the treatment of all other types of pediatric solid tumors except high-risk neuroblastoma, as noted above.

Salvage allogeneic hematopoietic stem-cell transplantation pediatric solid tumors that relapse after autologous transplant or fail to respond is considered investigational.

Allogeneic (myeloablative or nonmyeloablative) hematopoietic stem-cell transplantation is considered investigational for treatment of pediatric solid tumors.

Policy Guidelines

Refer to the individual member’s benefit booklet for prior review requirements.

This policy addresses peripheral neuroblastoma; those arising from the peripheral nervous system.

Hematopoietic stem-cell transplantation refers to any source of stem cells, i.e., autologous, allogeneic, syngeneic, or umbilical cord blood.
Hematopoietic Stem-Cell Transplantation for Solid Tumors of Childhood

**Relapse** is defined as tumor recurrence after a prior complete response.

**Primary refractory** disease is defined as a tumor that does not achieve a complete remission after initial standard-dose chemotherapy.

**Neuroblastoma**
- The use of single autologous HSCT has become a widely accepted treatment option for children with “high-risk” neuroblastoma, after randomized studies have shown improved event-free survival (EFS) and overall survival (OS).
- No studies directly comparing single autologous to tandem autologous HSCT for high-risk neuroblastoma have been published; however, case series on the use of tandem autologous for high-risk neuroblastoma have reported EFS rates superior to those reported with the use of single autologous HSCT (reported in randomized trials comparing single autologous HSCT to conventional chemotherapy).

Some transplant centers use tandem autologous HSCT as the preferred approach to the treatment of high-risk neuroblastoma.

A Phase III, randomized trial of single versus tandem autologous HSCT for high-risk neuroblastoma is currently underway.

**Ewing’s sarcoma family of tumors (ESFT)**
- Evidence on the use of HSCT in the initial treatment of high-risk or recurrent or refractory Ewing’s sarcoma family of tumors (ESFT) has shown varied results for a survival benefit with the use of HSCT. Two Phase III trials are currently underway using risk-stratified approaches which will likely serve to guide future treatment options for ESFT.

**Rhabdomyosarcoma**
- The use of HSCT for metastatic rhabdomyosarcoma (RMS) has failed to show a survival benefit.

**Wilms tumor**
- The use of HSCT for high-risk relapsed Wilms tumor, in general, has failed to show a survival benefit, although a few reports have suggested some benefit in certain subpopulations (e.g., patients with advanced-stage disease with lung-only metastases). A Phase II trial is currently underway using a risk-stratified approach to treatment and includes high-risk patients who will be treated with HSCT.

**Osteosarcoma**
- The use of HSCT for osteosarcoma has failed to show a survival benefit.

**Retinoblastoma**
- Small case series and case reports have shown prolonged disease-free survival (DFS) in some patients with stage 4 retinoblastoma, particularly those with stage 4a disease.
- A recent study of 15 patients showed that some patients with stage 4a disease were cured with the use of HSCT. A prospective multicenter trial (COG ARET 0321) is underway to better determine the role of HSCT in patients with retinoblastoma.

**Allogeneic HSCT**
Hematopoietic Stem-Cell Transplantation for Solid Tumors of Childhood

Very little evidence is available on the use of allogeneic HSCT for pediatric solid tumors, either upfront or as salvage therapy after a failed autologous HSCT. A large retrospective review of the use of allogeneic HSCT for high-risk neuroblastoma failed to show a survival benefit over autologous HSCT and was associated with a higher risk of transplant-related mortality.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 38205, 38206, 38230, 38232, 38240, 38241, 38242, 38243, S2150

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

Bone Marrow Transplant for Solid Tumors In Childhood

TEC Assessment, July 1999; Volume 14, No. 11


Hematopoietic Stem-Cell Transplantation for Solid Tumors In Childhood

Hematopoietic Stem-Cell Transplantation for Solid Tumors of Childhood

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Policy Implementation/Update Information

**Bone Marrow Transplant for Solid Tumors In Childhood**

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<thead>
<tr>
<th>Date</th>
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<tbody>
<tr>
<td>2/01</td>
<td>Original policy issued.</td>
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<tr>
<td>2/03</td>
<td>Specialty Matched Consultant Advisory Panel review 11/2002. Revised the policy statement to include, &quot;Please refer to the Neuroectodermal Tumors and Ependymoma policy.&quot; Codes 86812-86822 removed; codes 38231 and 86915 deleted and codes 38242, 38205 and 38206 added to the Billing/Coding section. System coding changes.</td>
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<td>1/04</td>
<td>Benefits Application and Billing/Coding sections updated for consistency.</td>
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<td>2/04</td>
<td>Individual CPT codes listed for CPT code ranges 38240-38242 under Billing/Coding section.</td>
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<tr>
<td>7/29/04</td>
<td>HCPCS code S2150 added to Billing/Coding section.</td>
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Hematopoietic Stem-Cell Transplantation for Solid Tumors of Childhood

12/23/04 Specialty Matched Consultant Advisory Panel review 11/29/2004. Revised Description of Procedure or Service section. Added additional information to "When covered" to indicate: “3. High-dose chemotherapy (with or without associated radiotherapy) and autologous or syngeneic (harvested from an identical twin) stem cell support may be considered medically necessary to consolidate remissions of poor-risk Ewing’s sarcoma, or as salvage therapy for those with residual, recurrent or refractory Ewing’s sarcoma.” “When not covered” revised to indicate; “1. High-dose chemotherapy (with or without associated radiotherapy) and hematopoietic stem cell support is considered investigational as initial treatment or to consolidate remission of low or intermediate risk Ewing’s sarcoma. 2. Salvage allogeneic transplant for neuroblastoma or other solid tumors of childhood that relapse after autologous transplant or fail to respond is considered investigational. 3. High-dose chemotherapy (with or without associated radiotherapy) and hematopoietic stem-cell support is considered investigational as initial treatment of low or intermediate risk neuroblastoma. 4. High-dose chemotherapy for other solid tumors of childhood is considered investigational, including but not limited to, Wilms’ tumor, retinoblastoma, osteosarcoma, rhabdomyosarcoma, hepatoblastoma, and undifferentiated tumors.” Rationale added to Policy Guidelines section. Policy number added to Key Words. "Hematopoietic" and "Opportunistic" added to Definitions. References added. Notice given 12/23/2004. Effective date of policy 3/3/2005.

12/11/06 Specialty Matched Consultant Advisory Panel review 11/6/2006. Added the following statement to the "Policy" section; "If the medical criteria and guidelines are not met, some patients may be eligible for coverage under Clinical Trials. Refer to the policy, Clinical Trial Services for Life-Threatening Conditions." Updated rationale in “Policy Guidelines” section. References added.

12/22/08 Specialty Matched Consultant Advisory Panel review 11/13/2008. Changed wording in #3 in the "When Covered" section from "poor" risk to "high" risk. Added #5 to the "When Not Covered" section to indicate: "Multiple cycle high-dose chemotherapy and hematopoietic stem cell support (i.e., tandem or multiple transplants) is considered investigational for the treatment of neuroblastoma." Updated "Policy Guideline" section. References added. Notice given 12/22/08. Effective date 3/30/09. (btw)

6/22/10 Policy Number(s) removed (amw)

Hematopoietic Stem-Cell Transplantation for Solid Tumors In Childhood


3/15/11 Revised the Retinoblastoma information in the “Description” section. Updated the “When Not Covered” section to indicate that “tandem autologous-autologous” HSCT is considered investigational and that “allogeneic (myeloablative or
Hematopoietic Stem-Cell Transplantation for Solid Tumors of Childhood

nonmyeloablative)" HSCT is considered investigational in treatment of pediatric solid tumors.” Reviewed with Medical Director 2/17/2011. References added. (btw)

6/21/11 Reference added. (btw)

1/10/12 Specialty Matched Consultant Advisory Panel review 11/30/2011. No change to policy intent. “Policy Guidelines” updated. (btw)

2/21/12 Added new 2012 CPT code 38232 to Billing/Coding section. (btw)

6/29/12 Added the following statement to the When Covered section; “Tandem autologous hematopoietic stem-cell transplantation may be considered medically necessary for high-risk neuroblastoma.” Removed the following statement from the When Not Covered section; “Tandem autologous-autologous hematopoietic stem-cell transplantations are considered investigational for treatment of pediatric solid tumors.” And added: “Tandem autologous hematopoietic stem-cell transplantation is considered investigational for the treatment of all other types of pediatric solid tumors except high-risk neuroblastoma, as noted above.” Policy Guidelines updated. Reference added. Medical Director review 6/10/2012. (btw)


5/28/13 Reference added. (btw)

12/10/13 Specialty Matched Consultant Advisory Panel review. 11/20/2013. No change to policy intent. (btw)

5/27/14 References updated. Re-titled reference policy in Policy Statement section from “Clinical Trial Services for Life-Threatening Conditions” to “Clinical Trial Services.” No other changes to Policy Statements. (mco)

12/9/14 Specialty Matched Consultant Advisory Panel review 11/24/2014. No change to policy intent. (lpr)

7/1/15 Reference added. No changes to policy statement. (lpr)

12/30/15 Specialty Matched Consultant Advisory Panel review 11/18/2015. No change to policy statement. (lpr)

12/30/16 Specialty Matched Consultant Advisory Panel review 11/30/2016. No change to policy intent. (lpr)


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