

(80134)

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Preauthorization is required and must be obtained through Case Management.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

Description

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 radiotherapy. 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.

Summary of Evidence

Neuroblastoma

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

Ewing Sarcoma Family of Tumors

- Evidence on the use of HSCT in the initial treatment of high-risk or recurrent or refractory Ewing sarcoma family of tumors has shown varied results for a survival benefit with the use of HSCT.

Rhabdomyosarcoma

- Use of HSCT for metastatic rhabdomyosarcoma 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).

Osteosarcoma

- 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 in some patients with stage 4 disease treated with HSCT, particularly those with stage 4a disease.
- A recent study of 15 patients showed that some patients with stage 4a retinoblastoma were cured with the use of HSCT.

Allogeneic HSCT

- 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.

Policy

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 sarcoma, and
- recurrent or refractory Ewing sarcoma.

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

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 sarcoma, and for other solid tumors of childhood including, but not limited to, the following:

- rhabdomyosarcoma
- Wilms tumor
- osteosarcoma
- retinoblastoma.

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.

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

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

Policy Guidelines

Individual transplant facilities may have their own additional requirements or protocols that must be met in order for the patient to be eligible for a transplant at their facility.

This protocol 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.

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.

Medicare Advantage

If a transplant is needed, we arrange to have the transplant center review and decide whether the patient is an appropriate candidate for the transplant.

Background

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 radiotherapy. Hematopoietic stem cells may be obtained from the transplant recipient (autologous HSCT) or from a donor (allogeneic HSCT). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates. Although cord blood is an allogeneic source, the stem cells in it are antigenically “naive” and thus are associated with a lower incidence of rejection or graft-versus-host disease. Cord blood is discussed in greater detail in the Placental and Umbilical Cord Blood as a Source of Stem Cells Protocol.

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HSCT. However, immunologic compatibility between donor and patient is a critical factor for achieving a good outcome of allogeneic HSCT. Compatibility is established by typing of human leukocyte antigens using cellular, serologic, or molecular techniques. Human leukocyte antigen (HLA) refers to the tissue type expressed at the class I and class II loci on chromosome 6. Depending on the disease being treated, an acceptable donor will match the patient at all or most of the HLA loci (with the exception of umbilical cord blood).

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 sarcoma/ESFT, Wilms tumor, rhabdomyosarcoma (RMS), osteosarcoma, and retinoblastoma.

The prognosis for pediatric solid tumors has improved over the last two decades, mostly due to the application of multiagent chemotherapy and improvements in local control therapy (including aggressive surgery and advancements in radiotherapy).¹ 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 EFS and OS.

Notes: Other solid tumors of childhood include germ cell tumors, which are considered separately in the Hematopoietic Stem Cell Transplantation in the Treatment of Germ Cell Tumors Protocol. For solid tumors classified as embryonal tumors arising in the central nervous system (CNS) see the Hematopoietic Stem Cell Transplantation for Central Nervous System Embryonal Tumors and Ependymoma Protocol.

Descriptions of the solid tumors of childhood that are addressed in this protocol are as follows.

Peripheral Neuroblastoma

Neuroblastoma is the most common extracranial solid tumor of childhood,² with two-thirds of cases presenting in children younger than five years of age.³ 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 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, 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.⁴ It is well-established that *MYCN* amplification is associated with rapid tumor progression and a poor prognosis,⁵ even in the setting of other coexisting favorable factors. Loss of heterozygosity (LOH) at chromosome arms 1p and 11q occurs frequently in neuroblastoma.⁶ Although 1p LOH is associated with *MYCN* amplification, 11q is usually found in tumors without this abnormality.⁶ 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.⁴ 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 one year of age

The low-risk group includes patients younger than one year of age with stage 1, 2, or 4S with favorable histopathologic findings and no *MYCN* oncogene amplification. High-risk neuroblastoma is characterized by age older than one 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.² Most infants, even with disseminated disease, have favorable outcomes with chemotherapy and surgery.² In contrast, most children older than one year with advanced-stage disease die due to progressive disease, despite intensive multimodality therapy,² 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.

Ewing 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 sarcoma of bone, extrasosseous Ewing, peripheral primitive neuroectodermal tumor, 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 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 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 radiotherapy have improved PFS in patients with localized disease to 60% to 70%.⁷ The presence of metastatic disease is the most unfavorable prognostic feature, and the outcome for patients presenting with metastatic disease is poor, with 20% to 30% PFS. Other adverse prognostic factors that may categorize a patient as having “high-risk” Ewing 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 has not always been consistently defined in the literature. Thirty to 40% of patients with ESFT experience disease recurrence, and patients with recurrent disease have a five-year EFS and OS rate of less than 10%.⁸

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, pharyngeal), genitourinary tract, and extremities.⁹ Most children with RMS present with localized disease, and with conventional multimodal therapy, the cure rate in this group is 70% to 80%.¹⁰ However, approximately 15% of children present with metastatic disease, and despite the introduction of new drugs and intensified treatment, the five-year survival is 20% to 30% for this “high-risk” group.^{10,11}

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%.¹² Ten to 15% of patients with favorable histology and 50% of patients with anaplastic tumors, experience tumor progression or relapse.¹² Similar to newly diagnosed Wilms tumor, 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% to 45%. For patients with adverse prognostic factors (histologically anaplastic tumors, relapse less than six to 12 months after nephrectomy, second or subsequent relapse, relapse within the radiation field, bone or brain metastases),

EFS is less than 15%.¹³ However, recent trials with HDC and autologous HSCT have reported three- or four-year OS rates from 60% to 73%.¹⁴

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. In children and adolescents, more than 50% of these tumors arise from bones around the knee. The prognosis of localized osteosarcoma has greatly improved over the last 30 years, with OS rates increasing from 10% with surgery alone (usually amputation) to 70% with the introduction of neoadjuvant chemotherapy and limb-sparing surgery.¹⁵ However, 30% to 40% of patients with nonmetastatic osteosarcoma of the extremities experience recurrent disease, most commonly in the lungs.¹⁵ Mean five-year postrelapse survival rate is approximately 28%, with some groups having a 0% OS rate. Prognostic factors for recurrence include site and size of the primary tumor, presence of metastases at the time of diagnosis, resection adequacy, and tumor response to preoperative chemotherapy (measured as percent of tumor necrosis in the resection specimen). Overall EFS for patients with metastatic disease at diagnosis is about 20% to 30%.¹⁶

Retinoblastoma

Retinoblastoma is the most common primary tumor of the eye in children. It may occur as a heritable (40%) or nonheritable (60%) tumor.¹⁷ 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 at least a 90% cure rate.¹⁷ However, once disease has spread beyond the eye, survival rates drop significantly; five-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.¹⁸ 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 CNS, and stage 4b is defined as metastatic disease to the CNS.

Related Protocol

Hematopoietic Stem Cell Transplantation for Central Nervous System Embryonal Tumors and Ependymoma

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

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We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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