Regence Oregon and Utah · Regence Idaho and select counties of Washington

**Medical Policy Manual**

**Topic:** Hematopoietic Stem-Cell Transplantation for Solid Tumors of Childhood

**Date of Origin:** May 2010

**Section:** Transplant

**Last Reviewed Date:** August 2013

**Policy No:** 45.37

**Effective Date**: January 1, 2014

**IMPORTANT REMINDER**

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

## DESCRIPTION

### Hematopoietic Stem Cell Transplantation for Solid Tumors

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. Hematopoietic stem cells may be obtained from the transplant recipient (autologous HSCT) or can be harvested 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 "naïve" and thus are associated with a lower incidence of rejection or graft-versus-host disease (GVHD).

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, Wilms tumor, rhabdomyosarcoma, 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 radiation therapy).[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 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**

Note: Cerebral neuroblastoma is considered separately in Transplant No. 45.33 related to embryonal tumors.

Neuroblastoma is the most common extracranial solid tumor of childhood[2], with two-thirds of the cases presenting in children ages 5 or younger.[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, 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.[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[6], 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 younger 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.[2] Most infants, even with disseminated disease, have favorable outcomes with chemotherapy and surgery.[2] In contrast, most children older than 1 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'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%.[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%–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, or older age of the patient. However, "high-risk" Ewing's has not always been consistently defined in the literature.

**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, pharyngeal), genitourinary tract, and extremities.[8] Most children with RMS present with localized disease, and with conventional multimodal therapy, the cure rate in this group is 70%–80%.[9] However, 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.[9,10]

**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%.[11] Ten to 15% of patients with favorable histology and 50% of patients with anaplastic tumors experience tumor progression or relapse.[11] 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%–45%. For patients with adverse prognostic factors (histologically anaplastic tumors, relapse less than 6–12 months after nephrectomy, second or subsequent relapse, relapse within the radiation field, bone or brain metastases) event-free survival is less than 15%.[12] However, recent trials with HDC and autologous HSCT have reported 3- or 4-year OS rates from 60%–73%.[13]

**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.[14] However, 30%–40% of patients with non-metastatic osteosarcoma of the extremities experience recurrent disease, most commonly in the lungs.[14] Mean 5-year post-relapse 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%–30%.[15]

**Retinoblastoma**

Retinoblastoma is the most common primary tumor of the eye in children. It may occur as a heritable (25% to 30%) or nonheritable (70% to 75%) tumor.[16] 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, however, once disease has spread beyond the eye, survival rates drop significantly.[16] 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.

**MEDICAL POLICY CRITERIA**

*NOTE: This policy addresses only solid tumors of childhood.  Solid tumors in adults are considered separately in Transplant, Policy No. 45.27. This policy also does not address hematopoietic stem cell transplantation (HSCT) as a treatment of embryonal tumors arising in the central nervous system (cerebral neuroblastoma), tumors derived from glial cells (i.e., astrocytoma, oligodendroglioma, or glioblastoma multiforme), or germ cell tumors which are considered separately in Transplant, Policy Nos. 45.33, 45.34, and 45.38, respectively.

I. Autologous HSCT

A. Medically Necessary Indications

Autologous HSCT may be considered **medically necessary** for the following indications:

1. Ewing's sarcoma

a. Initial treatment of high-risk Ewing's sarcoma

Patients may be categorized as "high-risk" if any of the following are present: metastatic disease, unfavorable tumor location (e.g., patients with pelvic primaries have worse outcomes), larger tumor size, or older age of the patient.

b. To consolidate remissions or as a salvage therapy for those with residual, recurrent or refractory Ewing's sarcoma

2. Neuroblastoma

a. Initial treatment of high-risk neuroblastoma

Patients may be characterized as high-risk if any of the following are present: age older than 1 year, disseminated disease, MYCN oncogene amplification, or unfavorable histopathologic findings.

b. Recurrent or refractory neuroblastoma

3. Wilms tumor

Recurrent, high-risk Wilms tumor

B. Investigational Indications

Autologous HSCT is considered **investigational** for the following indications:

1. Initial treatment of low- or intermediate-risk Ewing's sarcoma

2. Initial treatment of low- or intermediate-risk neuroblastoma

3. Other solid tumors of childhood, including but not limited to the following:

   a. Osteosarcoma

   b. Retinoblastoma

   c. Rhabdomyosarcoma

   d. Wilms tumor, other than recurrent, high-risk

II. Tandem Autologous HSCT

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

Patients may be characterized as high-risk if any of the following are present: age older than 1 year, disseminated disease, MYCN oncogene amplification, or unfavorable histopathologic findings.

B. Tandem or multiple HSCT is considered **investigational** for the treatment of all other types of pediatric solid tumors except high-risk neuroblastoma.

III. Allogeneic HSCT

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

B. Salvage allogeneic HSCT is considered **investigational** for all pediatric solid tumors that relapse after autologous transplant or fail to respond.

## POLICY GUIDELINES

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.

## SCIENTIFIC BACKGROUND

The principal outcomes associated with treatment of pediatric solid tumors are typically measured in units of survival past treatment: event-free survival (EFS), a period of time following treatment where the disease is undetectable; progression-free survival (PFS), the duration of time after treatment before the advancement or progression of disease; and overall survival (OS), the period of time the patient remains alive following treatment. Risk of graft-versus-host disease is another primary outcome among patients undergoing allogeneic hematopoietic stem cell transplantation (HSCT). Ideally, in order to understand the impact of HSCT for treatment of peripheral neuroblastoma, Ewing's sarcoma, or any other solid childhood malignancy, comparative clinical trials that compare this therapy with standard medical treatment (chemotherapy, and/or surgical resection with or without radiation), are needed. Further, for treatment of malignant solid tumors, particularly those with a poor prognosis, an understanding of any adverse treatment effects must be carefully weighed against any benefits associated with treatment to understand the net treatment effect.

**Peripheral Neuroblastoma**

Single Autologous Hematopoietic Stem-Cell Transplantation (HSCT)

Three well-designed, randomized trials have been conducted using autologous hematopoietic stem-cell transplantation (HSCT) in the treatment of high-risk neuroblastoma.

- In a study published in 1999, Matthay and colleagues[17] randomly assigned 129 children with high-risk neuroblastoma to a combination of myeloablative chemotherapy, total-body irradiation, and transplantation of autologous bone marrow, and compared their outcomes to those of 150 children randomly assigned to intensive nonmyeloablative chemotherapy; both groups underwent a second randomization to receive subsequent 13-cis-retinoic acid (cis-RA) or no further therapy. The 3-year EFS rate among patients assigned to transplantation was 43 +/- 6% versus 27 +/- 5% among those assigned to continuation chemotherapy (p=0.027). However, OS in the two groups was not significantly different, with 3-year estimates of 43% or 44% for those assigned to transplant or those to continued chemotherapy, respectively (p=0.87).

  Long-term results from this same trial were reported after a median follow-up time of 7.7 years (range: 130 days to 12.8 years).[18] Five-year EFS for patients who underwent autologous transplant was 30% +/- 4% versus 19% +/- 3% for those who underwent nonmyeloablative chemotherapy (p=0.04). Five-year OS rates from the second randomization of patients who underwent both random assignments were 59% +/- 8% for autologous transplant/cis-RA, 41% +/- 7% for autologous transplant/no cis-RS, and, for nonmyeloablative chemotherapy, 38% +/- 7% and 36% +/- 7% with and without cis-RA. The authors concluded that myeloablative chemotherapy and autologous transplant results in a significantly better 5-year EFS and OS.

- In a study published in 2005, Berthold and colleagues randomly assigned 295 patients with high-risk neuroblastoma to myeloablative therapy (melphalan, etoposide, and carboplatin) with autologous HSCT or to oral maintenance chemotherapy with cyclophosphamide.[19] The primary endpoint was EFS with secondary endpoints of OS and treatment-related deaths. Intention-to-treat analysis showed that the patients who received the myeloablative therapy had an increased 3-year EFS compared with the oral maintenance group (47% [95% confidence interval (CI): 38–55] vs. 31% [95% CI: 23–39]), but did not have significantly increased 3-year OS (62% [95% CI: 54–70] vs. 53% [95% CI: 45–62] p=0.0875). Two patients died from therapy-related complications during induction, no patients who received oral maintenance therapy died from treatment-related toxic effects, and 5 patients who received the myeloablative therapy died from acute complications related to the therapy.

- In a study published in 2005, Pritchard and colleagues reported the results of a randomized, multicenter study that involved 167 children with stage 3 or 4 neuroblastoma who were treated with standard induction chemotherapy and then underwent surgical resection of their tumor.[20] Sixty-nine percent of the patients (n=90) who achieved complete response (CR) or good partial response (PR) to the induction chemotherapy were eligible for randomization to HDC (melphalan) with autologous HSCT or no further treatment (NFT). Seventy-two percent (n=65) of the eligible children were randomly assigned, with 21 surviving at the time of the analysis (median follow-up 14.3 years). A significant difference in the 5-year EFS and OS was seen in children older than 1 year of age with stage 4 disease (n=48 children with stage 4; 5-year EFS 33% versus 17% in the melphalan versus NFT group p=0.01).

Available evidence on the use of autologous HSCT in high-risk neuroblastoma is sufficient to suggest treatment benefit with transplant.

Tandem Hematopoietic Stem-Cell Transplantation (HSCT)

*Systematic Review*

A comparative effectiveness review was conducted on the use of hematopoietic stem-cell transplantation in the pediatric population by the Blue Cross and Blue Shield Association Technology Evaluation Center for the Agency for Healthcare Research and Quality (AHRQ).[21] The review concluded that the body of evidence on overall survival with tandem HSCT compared to single HSCT for the treatment of high-risk neuroblastoma was insufficient to draw conclusions.

*Non-randomized Trials*

- Sung and colleagues retrospectively analyzed the efficacy of single versus tandem autologous HSCT in patients older than 1 year of age newly diagnosed with stage 4 neuroblastoma from 2000 to 2005 who were enrolled in the Korean Society of Pediatric Hematology-Oncology registry.[22] Patients were assigned to receive a single (n=70) or tandem (n=71) autologous HSCT at diagnosis; 57 and 59 patients underwent single and tandem transplantation as scheduled, respectively. Patient characteristics between the 2 groups were similar with the exception of a higher proportion of patients in the tandem group having bone metastases. Median follow-up was 56 months (range 24-88 months) from diagnosis. Transplant-related mortality occurred in 9 patients in the single transplant group and in 8 in the tandem group (2 after the first transplant and 6 after the second). The intent-to treat survival rate was 5-year EFS for single versus tandem 31.3% +/- 11.5% and 51.2% +/- 12.4%, respectively; p=0.03. When the survival analysis was confined to the patients who proceeded to transplant, the probability of relapse-free survival (RFS) after the first transplant was higher in the tandem group than the single group with borderline significance (59.1% +/- 13.5% vs. 41.6% +/- 14.5%; p=0.099). The difference became significant when the analysis was confined to patients who did not achieve a CR prior to the first transplant (55.7% +/-17.0% vs. 0%; p=0.012). The authors concluded that tandem HSCT for high-risk neuroblastoma is superior to single HSCT in terms of survival, particularly in patients not in CR prior to the HSCT.

- Ladenstein and colleagues reported on 28 years of experience for more than 4,000 transplants for primary (89%) and relapsed (11%) neuroblastoma in 27 European countries in the European Group for Blood and Marrow Transplantation registry.[23] Procedures included single autologous (n=2,895), tandem autologous (n=455) and allogeneic HSCT (n=71). The median age at the time of transplantation was 3.9 years (range 0.3-62 years), with 77 patients older than 18 years. The median follow-up time from HSCT was 9 years. Transplant-related mortality (TRM) decreased over time in the registry for the patients who received autologous transplants only. The cumulative incidence of TRM was 4%, 6%, and 8%, respectively, at day 100, 1 year and 5 years for the autologous group, but for the allogeneic group 13%, 16%, and 18%, respectively. Five-year OS for the autologous group (single and tandem) was 37% versus 25% in the allogeneic setting. Five-year OS for single versus tandem autologous HSCT was 38% versus 33%, respectively (p=0.105).

- Kim and colleagues reported a retrospective analysis of 36 patients with high-risk (stage 3 or 4) neuroblastoma who underwent either a single autologous HSCT (n=27) or a tandem autologous HSCT (n=9) at Seoul National University Children's Hospital between 1996 and 2004.[24] EFS of patients who underwent double HSCT was similar to that of patients who underwent a single autologous HSCT (p=0.5).

- George and colleagues reported long-term survival data of high-risk neuroblastoma patients (n=82) treated with tandem autologous HSCT between 1994 and 2002.[25] Median age at diagnosis was 35 months (range 6 months to 18 years). Three- and 5-year OS were 74% (95% CI 62-82%) and 64 % (95% CI 52-74%) respectively.

- von Allmen and colleagues reported outcomes on 76 patients with previously untreated high-risk stage III/IV neuroblastoma treated with aggressive surgical resection with or without local radiation therapy followed by tandem autologous high-dose chemotherapy and stem-cell rescue.[26] Overall EFS for the series at three years was 56%.

- Marcus and colleagues reported outcomes in 52 children with stage 4 or high-risk stage 3 neuroblastoma treated with induction chemotherapy, surgical resection of the tumor when feasible, local radiotherapy and consolidation with tandem autologous HSCT.[27] Radiotherapy was given if gross or microscopic residual disease was present prior to the myeloablative cycles (n=37). Of the 52 consecutively treated patients analyzed, 44 underwent both transplants, 6 underwent a single transplant, and 2 progressed during induction. The 3-year EFS was 63%, with a median follow-up of 29.5 months.

- Kletzel and colleagues reported on the outcomes of 25 consecutive newly diagnosed high-risk neuroblastoma patients and one with recurrent disease, diagnosed between 1995 and 2000, and treated with triple-tandem autologous HSCT.[28] After stem-cell rescue, patients were treated with radiation to the primary site. Twenty-two of the 26 patients successfully completed induction therapy and were eligible for the triple-tandem consolidation high-dose therapy. Seventeen patients completed all 3 cycles of high-dose therapy and stem-cell rescue, 2 patients completed 2 cycles and 3 patients completed one cycle. There was one toxic death, and one patient died from complications of treatment for graft failure. Median follow-up was 38 months, and the 3-year EFS and survival rates were 57% +/- 11% and 79% +/-10%, respectively.

- Grupp and colleagues reported the outcomes of a Phase II trial that involved 55 children with high-risk neuroblastoma who underwent tandem autologous HSCT.[29] Five patients completed the first HSCT course but did not complete the second. There were 4 toxic deaths. With a median follow-up of 24 months from diagnosis, 3-year EFS was 59%.

Despite the low-quality of existing evidence on the use of tandem autologous HSCT for treatment of high-risk neuroblastoma, there is a suggestion of potentially increased survival with tandem transplant compared with single transplant.

Reduced Intensity Conditioning

- Sung et al. evaluated feasibility and efficacy of reduced-intensity allogeneic stem cell transplantation (RI alloSCT) in six children with neuroblastoma who failed tandem HDCT/autoSCT.[30] Although the regimen-related short-term toxicity was manageable in intensively pretreated patients, graft-versus-tumor effect was not sufficiently strong to control tumor progression in patients who had a significant tumor burden at transplant.

Clinical Practice Guidelines

No evidence-based clinical practice guidelines were identified on the use of autologous or allogeneic HSCT in the treatment of peripheral neuroblastoma.

**Ewing's Sarcoma and the Ewing Family of Tumors (ESFT)**

During the 1980's and 90's, several small series, case reports, and a report from the European Bone Marrow Transplant Registry suggested that autologous HSCT could improve the outcome for patients with high-risk ESFT.[31] The original policy position on Ewing's was based on these studies/reports. Subsequent to the publication of these reports, additional evidence has been reported on the use of autologous HSCT in ESFT, including a systematic review and several non-randomized studies.

Systematic Review

The AHRQ comparative effectiveness review of HSCT in the pediatric population also addressed ESFT, concluding that low-strength evidence on overall survival suggests no benefit with single autologous HSCT compared with conventional therapy for the treatment of high-risk ESFT.[21] The body of evidence on overall survival with tandem autologous HSCT compared with single autologous HSCT for the treatment of high-risk ESFT and overall survival is insufficient to draw conclusions.

Non-randomized Trials

The aforementioned early case series were characterized by small numbers of patients, and comparison of the studies was difficult for several reasons. Within each report, patients often received a variety of chemotherapeutic regimens and many of the studies did not share the same patient eligibility criteria (and in some the definition of high risk included patients with criteria that did not result in inferior prognosis). In addition, some studies used autologous, and others allogeneic HSCT.

- Subsequent to the early wave of publications, in 2001, Meyers and colleagues reported on a prospective study with autologous HSCT in 32 patients with newly diagnosed Ewing's sarcoma metastatic to bone and/or bone marrow.[32] Induction therapy consisted of 5 cycles of cyclophosphamide-doxorubicin-vincristine, alternating with ifosfamide-etoposide. Twenty-three patients proceeded to the consolidation phase with melphalan, etoposide, total body irradiation, and autologous HSCT (of the 9 patients who did not proceed, 2 were secondary to toxicity and 4 to progressive disease). Three patients died during the high-dose phase. Two-year EFS for all eligible patients was 20% and 24% for the 29 patients who received the high-dose consolidation therapy. The study concluded that consolidation with high-dose chemotherapy (HDC), TBI, and autologous stem-cell support failed to improve the probability of EFS for this cohort of patients when compared with a similar group of patients treated with conventional therapy. The authors noted that their findings differed from some previous studies and noted that the previous studies suffered from heterogeneous patient populations. The authors concluded that future trials of autologous HSCT must be conducted prospectively, with identification of a group at high risk for failure, and all patients entering the study at the same point in therapy.

- Gardner and colleagues reported the results of 116 patients with Ewing's sarcoma who underwent autologous HSCT (80 as first-line therapy and 36 for recurrent disease) between 1989 and 2000.[33] Five-year probabilities of PFS in patients who received HSCT as first-line therapy were 49% (95% CI: 30–69%) for those with localized disease at diagnosis and 34% (95% CI: 22–47%) for those with metastatic disease at diagnosis. For the population with localized disease at diagnosis and recurrent disease, 5-year probability of PFS was 14% (95% CI: 3–30%). The authors concluded that PFS rates after autologous HSCT were comparable to rates seen in patients with similar disease characteristics treated with conventional therapy.

- Results from one group of patients in the Euro-EWING 99 trial were reported by Ladenstein and colleagues for patients with primary disseminated multifocal Ewing Sarcoma (PDMES).[34] From 1999 to 2005, 281 patients with PDMES were enrolled in the Euro-EWING 99 R3 study; the Euro-EWING99 Committee agreed to stop enrollment to this group and release the data. Median age was 16.2 years (range: 0.4-49 years). Patients with isolated lung metastases were not part of the analysis. The recommended treatment consisted of induction chemotherapy, HDC and autologous HSCT and local treatment to the primary tumor (surgery and/or radiation or neither). Induction therapy was completed by 250 (89%) of patients. One-hundred sixty-nine (60%) of the patients proceeded to HSCT; reasons for not proceeding to HSCT included disease progression or other or unknown reasons. One patient died during induction therapy from sepsis. High-dose chemotherapy TRM consisted of 3 patients dying within the first 100 days after high-dose therapy- one from acute respiratory distress syndrome and 2 from severe veno-occlusive disease and septicemia; late deaths included 3 patients who died 1-1.5 years after high-dose therapy. After a median follow-up of 3.8 years, score allowed allocation of patients with PDMES at diagnosis to 3 risk groups with the following outcomes: group 1 (score ≤3; n=82) EFS of 50%, group 2 (score >3 but <5; n=102) EFS of 25%, and group 3 (score ≥5; n=70) EFS of 10% ($p<0.0001$). The authors concluded that this scoring system may facilitate risk-adapted treatment strategies. The estimated 3-year EFS and OS for all 281 patients were 27% +/- 3% and 34% +/- 4%, respectively. Individual risk factors were brought into a scoring model to predict outcome at diagnosis. The values of the score points were based on log-hazard ratios, and the factor with the smallest hazard ratio was assigned one point. One score point was attributed to the following risk factors: age older than 14 years, bone marrow metastases, one bone lesion and additional presence of lung metastases; 1.5 points were attributed to the risk factors of primary tumor volume ≥200 mL and more than one bone lesion.

Clinical Practice Guidelines

*National Comprehensive Cancer Network (NCCN)*

NCCN guidelines for treatment of ESFT state that the role of high dose chemotherapy and stem-cell rescue in relapsed or progressive Ewing's sarcoma is yet to be determined in prospective randomized studies and makes no recommendations regarding its use in this disease setting.[35]

**Rhabdomyosarcoma (RMS)**

Available evidence on the use of HSCT in RMS consists of several systematic reviews summarizing a body of non-randomized trials.

Systematic Reviews

- A 2010 Cochrane review assessed the effectiveness of HDC with stem cell rescue (SRC) versus standard-dose chemotherapy in improving event-free survival (EFS) and overall survival (OS) of children and young adults with metastatic rhabdomyosarcoma.[36] The review concludes that use of HDC with SCR as a standard therapy for children with metastatic rhabdomyosarcoma is not justified at this time. Overall, the quality and quantity of evidence is limited as no RCTs could be identified, and available non-randomized studies have significant methodological limitations, especially selection bias. The review states that only large, prospective RCTs could answer whether HDC with SCR improves survival in rhabdomyosarcoma.

- The AHRQ comparative effectiveness review addressed above also considered the use of HSCT in RMS.[21] The following conclusions were offered:
  - Moderate-strength evidence on overall survival suggests no benefit with single HSCT compared to conventional therapy for the treatment of high-risk metastatic rhabdomyosarcoma.
  - The body of evidence on overall survival with single HSCT compared to conventional therapy for the treatment of high-risk rhabdomyosarcoma of mixed tumor type is insufficient to draw conclusions.
  - The body of evidence on overall survival with single HSCT compared to conventional therapy for the treatment of congenital alveolar rhabdomyosarcoma, cranial parameningeal rhabdomyosarcoma with metastasis, or the use of allogeneic transplantation for metastatic rhabdomyosarcoma was insufficient to draw conclusions.

- Weigel and colleagues published a systematic review on 2001 on the role of autologous HSCT in the treatment of metastatic or recurrent rhabdomyosarcoma, which involved a total of 389 patients from 22 studies.[37] Based on all of the data analyzing EFS and OS, they concluded that there was no significant advantage to undergoing this type of treatment.

Non-randomized Trials

Autologous HSCT has been evaluated in a limited number of patients with “high-risk” RMS (stage 4 or relapsed) in whom CR is achieved after standard induction therapy. Data are relatively scarce, due in part to the rarity of the condition.

- Carli and colleagues[38] conducted a prospective non-randomized study of 52 patients with metastatic RMS, who were in complete remission after induction therapy and subsequently received HDC (“megatherapy”) and autologous HSCT and compared them to 44 patients who were in remission after induction therapy who subsequently received conventional chemotherapy. No significant differences existed between the two study groups (i.e., no differences in clinical characteristics, induction chemotherapy received, sites of primary tumor, histologic subtype, age, or presence/extent of metastases). Three-year EFS and OS were 29.7% and 40%, respectively, for the autologous HSCT group and 19.2% and 27.7%, respectively, for the group that received standard consolidation chemotherapy. The difference was not statistically significant (p=0.3 and 0.2 for EFS and OS, respectively). The median time after chemotherapy to relapse was 168 days for the autologous

HSCT group, and 104 days for the standard chemotherapy group (p=0.05). Therefore, although there was some delay to relapse, there was no clear survival benefit from using autologous HSCT compared to conventional chemotherapy.

- Klingebiel and colleagues prospectively compared the efficacy of two HDC treatments followed by autologous stem-cell rescue versus an oral maintenance treatment (OMT) in 96 children with stage IV soft tissue sarcoma (88 of whom had rhabdomyosarcoma).[39] Five-year OS probability for the whole group was 0.52 + 0.14 for the patients who received OMT (n=51) and 0.27 + 0.13 for the transplant group (n=45; p=0.03). For the patients with rhabdomyosarcoma, 5-year OS probability was 0.52 + 0.16 with OMT versus 0.15 + 0.12 with transplant (p=0.001). The authors concluded that transplant has failed to improve prognosis in metastatic soft tissue sarcoma, but that OMT could be a promising alternative.

- McDowell and colleagues reported the results of the International Society of Paediatric Oncology (SIOP) study MMT-98, for pediatric patients from 48 centers with metastatic rhabdomyosarcoma, entered into the study from 1998 to 2005.[40] There were a total of 146 patients entered, aged 6 months to 18 years. The patients were risk-stratified and treated accordingly. One hundred and one patients were considered poor risk patients (PRG) if they were older than 10 years of age, or had bone marrow or bone metastases. Planned therapy for the PRG was induction therapy, sequential high-dose chemotherapy and peripheral blood autologous HSCT and finally, maintenance therapy. Seventy-nine of the 101 PRG patients (78.2%) underwent the high-dose therapy, after which 67.1% achieved a partial or complete response. Sixty-seven of the 101 PRG patients received local treatment: 37 radiation alone, 10 surgery alone and 20 both modalities. No treatment-related deaths were reported in the PRG. Three- and 5-year EFS for the PRG group was 16.5% and 14.9%, respectively and 3 and 5-year OS were 23.7% and 17.9%, respectively [HR=2.46; CI: 1.51-4.03; p<0.001).

The most recently published evidence on the use of HSCT for treatment of RMS is not suggestive of treatment benefit.

<u>Clinical Practice Guidelines</u>

*National Comprehensive Cancer Network (NCCN)*

NCCN guidelines regarding soft tissue sarcomas indicate potential treatment benefit for several types of single and multi-drug chemotherapy regimens; however, no recommendation were made regarding HSCT for patients with RMS.[41]

**Wilms Tumor**

Most studies of autologous HSCT for high-risk Wilms tumor have been very small series or case reports.[11,13,42] A systematic review and meta-analysis have also been published and comprise the focus of this review.

- The AHRQ review discussed above also addressed HSCT in pediatric patients with Wilms tumor, concluding: Low-strength evidence on overall survival suggests no benefit with single HSCT compared to conventional therapy for the treatment of high-risk relapsed Wilms tumor.[21]

- A meta-analysis reported on the efficacy of autologous HSCT in recurrent Wilms' tumor for articles published between 1984 and 2008 that reported survival data.[43] Six studies were included for a total of 100 patients, and patient characteristics and treatment methods were similar across studies, although there was variation in the preparative regimens used.[11,13,42,44-46] Patients were between the ages of 11 months and 16 years, and had similar primary tumor stage, relapse location and time to relapse across studies. The 4-year OS among the 100 patients was 54.1% (42.8-64.1%) and 4-year EFS based on 79 patients was 50.0% (37.9-60.9%). A multivariate analysis found that site of relapse and histology were important predictors for survival, in that patients who did not have a lung-only relapse had more than 3 times the risk of death or recurrence than patients who relapsed in the lungs only, and the patients with unfavorable histology had more than twice the risk of death compared to those with favorable histology (hazard ratios 3.5 and 2.4, respectively). The authors compared the survival rates from these 6 studies in which the patients were treated with autologous HSCT to patients treated with conventional chemotherapy between 1995 and 2002. The authors found that, in general, the chemotherapy treated patients had comparable or improved 4-year survival compared to the HSCT group, however, there was a suggestion that patients with lung-only stage 3 and 4 relapse may benefit from autologous HSCT with a 21.7% survival advantage over the chemotherapy patients (however the ranges were very wide): 4-year OS for the stage 3 and 4 patients with lung only relapse treated with HSCT versus chemotherapy was 74.5% (51.7-87.7%) and 52.8% (29.7-71.5%), respectively.

Evidence on the use of HSCT in treatment of Wilms tumor has not firmly established the effectiveness of transplant over standard care. Although comparative clinical trials are needed to describe the treatment effect of HSCT across all patients, the current evidence appears to suggest some survival benefit of HSCT in patients with certain types of Wilms tumor relapse.

Clinical Practice Guidelines

No evidence-based clinical practice guidelines were identified on the use of autologous or allogeneic HSCT in the treatment of Wilms' tumor.

**Osteosarcoma**

Rare small series and case reports are available examining the use of autologous HSCT in osteosarcoma.[47] Autologous HSCT has been successful in inducing short-lasting remissions but has not shown an increase in survival.[14]

Clinical Practice Guidelines

*National Comprehensive Cancer Network (NCCN)*

NCCN guidelines for osteosarcoma state that the safety and efficacy of HSCT in high-risk osteosarcoma patients has yet to be determined in prospective randomized studies and makes no recommendations regarding its use in this disease setting.[35]

**Retinoblastoma**

Most studies of autologous HSCT for high-risk retinoblastoma have been very small series or case reports.[48-53] However, a recently published systematic review also addresses the use of autologous HSCT in retinoblastoma.

Systematic Review

The AHRQ review considered above addressed the use of HSCT in pediatric patients with retinoblastoma, concluding that available evidence on overall survival suggests no benefit with single HSCT compared to conventional therapy for the treatment of extraocular retinoblastoma with central nervous system involvement.[21] The body of evidence on overall survival with single HSCT compared with conventional therapy for the treatment of extraocular retinoblastoma without CNS involvement was insufficient to draw conclusions. Likewise, the body of evidence on overall survival with single HSCT compared with conventional therapy for the treatment of trilateral retinoblastoma without CNS involvement was also insufficient to draw conclusions.

Non-randomized Trials

- Dunkel and colleagues reported the outcomes of 15 consecutive patients with stage 4a metastatic retinoblastoma who presented between 1993 and 2006 and were treated with HDC and autologous HSCT.[54] Twelve patients had unilateral retinoblastoma and 3 had bilateral disease. Metastatic disease was not detected at the time of diagnosis, but became clinically evident at a median of 6 months (range: 1-82 months) post-enucleation. The patients had metastatic disease to bone marrow (n=14), bone (n=10), the orbit (n=9) and/or the liver (n=4). Two patients progressed prior to HSCT and died. Thirteen patients underwent HSCT, and 10 are retinoblastoma-free in first remission at a median follow-up of 103 months (range: 34-202 months). Three patients recurred 14-20 months post-diagnosis of metastatic disease, (2 in the CNS and one in the mandible), and all died of their disease. Five-year retinoblastoma-free and event-free survival were 67% (95% CI 38-85%) and 59% (31-79%), respectively. Six of the 10 patients who survived received radiation therapy. Three patients developed secondary osteosarcoma at 4, 9 and 14 years after diagnosis of metastatic disease, 2 in previously irradiated fields and one in a non-irradiated field. The authors concluded that HSCT was curative for the majority of patients treated in their study with stage 4a retinoblastoma.

- Dunkel and colleagues reported the outcomes of 8 patients diagnosed with stage 4b retinoblastoma between 2000 and 2006 treated with autologous HSCT.[55] Seven of the patients had leptomeningeal disease and one had only direct extension to the CNS via the optic nerve. At the time of diagnosis of intra-ocular retinoblastoma, 3 patients already had stage 4b disease; the other 5 patients developed metastatic disease at a median of 12 months (range 3-69 months). Two patients progressed prior to HSCT and one patient died of toxicity during induction chemotherapy. Of the 5 patients that underwent HSCT, 2 are event-free at 40 and 101 months. One of the event-free survivors received radiation therapy (external beam plus intrathecal radioimmunotherapy) and the other did not receive any form of radiation. Three patients had tumor recurrence at 3, 7, and 10 months post-HSCT. The authors concluded that HSCT may be beneficial for some patients with stage 4b retinoblastoma, but that longer follow-up is necessary to determine whether it is curative in this population.

Available evidence, from small case series with short follow-up, is insufficient to indicate whether treatment with autologous or allogeneic HSCT is superior to conventional therapy.

Clinical Practice Guidelines

No evidence-based clinical practice guidelines were identified on the use of autologous or allogeneic HSCT in the treatment of retinoblastoma.

## Summary

Neuroblastoma

*Single Autologous Hematopoietic Stem-Cell Transplantation (HSCT)*

Evidence from available literature has shown improved event-free survival (EFS) and overall survival (OS) with use of single autologous hematopoietic stem cell transplantation (HSCT) for treatment of children with high-risk neuroblastoma. Use of single autologous HSCT may therefore be considered medically necessary for first-line treatment of high-risk neuroblastoma, or as treatment of recurrent or refractory neuroblastoma.

*Tandem Autologous HSCT*

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). Therefore, among pediatric patients with high-risk neuroblastoma, treatment with tandem HSCT may be considered medically necessary.

*Allogeneic 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. Pending the publication of evidence which demonstrates clear treatment benefit with allogeneic HSCT, the use of this intervention is considered investigational.

Ewing's Sarcoma Family of Tumors (ESFT)

Evidence on the initial treatment of high-risk or recurrent or refractory ESFT have not consistently shown a survival benefit with the use of autologous HSCT. Additional clinical trials are needed to establish the safety and efficacy of either transplant for treatment of ESFT. Until then, use of this type of transplant is considered investigational.

Based upon early evidence of potential treatment benefit, use of allogeneic HSCT may be considered medically necessary to consolidate remissions or treat residual, recurrent or refractory Ewing's sarcoma.

Rhabdomyosarcoma

Evidence on the use of HSCT for metastatic rhabdomyosarcoma (RMS) has failed to show a survival benefit; therefore use of autologous or allogeneic transplant in RMS is considered investigational.

Wilms tumor

The use of HSCT has not consistently shown a survival benefit in all patients with high-risk relapsed Wilms tumors, although a few reports have suggested some benefit in certain subpopulations (e.g., patients with advanced-stage disease with lung-only metastases). Additional trials are needed to establish patient selection criteria. However based upon early evidence of potential benefit in some high-risk relapsed Wilm's tumor patients, use of allogeneic HSCT may be considered medically necessary.

Osteosarcoma

The use of autologous or allogeneic HSCT for osteosarcoma has failed to show a survival benefit. Therefore the use of HSCT in osteosarcoma is considered investigational. Additional comparative clinical trials are needed to establish the safety and effectiveness of this treatment compared with standard chemotherapy.

Retinoblastoma

Although small case series and case reports have shown indications of prolonged disease-free survival in some patients with stage 4 disease treated with autologous or allogeneic HSCT, evidence from a prospective multicenter trial is needed to better determine the role of HSCT in patients with retinoblastoma. Currently, the use of autologous or allogeneic HSCT in retinoblastoma is considered investigational.

## REFERENCES


1. Hale, GA. Autologous hematopoietic stem cell transplantation for pediatric solid tumors. *Expert Rev Anticancer Ther*. 2005 Oct;5(5):835-46. PMID: 16221053
2. Weinstein, JL, Katzenstein, HM, Cohn, SL. Advances in the diagnosis and treatment of neuroblastoma. *Oncologist*. 2003;8(3):278-92. PMID: 12773750
3. Physician Data Query (PDQ®). Neuroblastoma treatment: health professional version. National Cancer Institute; last updated 05/07/2012. [cited 08/23/2012]; Available from: http://www.cancer.gov/cancertopics/pdq/treatment/neuroblastoma/healthprofessional
4. Shimada, H, Ambros, IM, Dehner, LP, Hata, J, Joshi, VV, Roald, B. Terminology and morphologic criteria of neuroblastic tumors: recommendations by the International Neuroblastoma Pathology Committee. *Cancer*. 1999 Jul 15;86(2):349-63. PMID: 10421272
5. Tang, XX, Zhao, H, Kung, B, et al. The MYCN enigma: significance of MYCN expression in neuroblastoma. *Cancer Res*. 2006 Mar 1;66(5):2826-33. PMID: 16510605
6. Attiyeh, EF, London, WB, Mosse, YP, et al. Chromosome 1p and 11q deletions and outcome in neuroblastoma. *N Engl J Med*. 2005 Nov 24;353(21):2243-53. PMID: 16306521
7. Barker, LM, Pendergrass, TW, Sanders, JE, Hawkins, DS. Survival after recurrence of Ewing's sarcoma family of tumors. *J Clin Oncol*. 2005 Jul 1;23(19):4354-62. PMID: 15781881
8. Physician Data Query (PDQ®). Childhood rhabdomyosarcoma treatment: health professional version. National Cancer Institute; last updated 08/17/2012. [cited 08/23/2012]; Available from: http://www.cancer.gov/cancertopics/pdq/treatment/childrhabdomyosarcoma/healthprofessional
9. Admiraal, R, Van der Paardt, M, Kobes, J. High dose chemotherapy for children with stage IV rhabdomyosarcoma (protocol). *Cochrane Database of Systematic Reviews*. 2007(Issue 3). PMID:
10. Koscielniak, E, Klingebiel, TH, Peters, C, et al. Do patients with metastatic and recurrent rhabdomyosarcoma benefit from high-dose therapy with hematopoietic rescue? Report of the German/Austrian Pediatric Bone Marrow Transplantation Group. *Bone Marrow Transplant*. 1997 Feb;19(3):227-31. PMID: 9028550

11. Campbell, AD, Cohn, SL, Reynolds, M, et al. Treatment of relapsed Wilms' tumor with high-dose therapy and autologous hematopoietic stem-cell rescue: the experience at Children's Memorial Hospital. *J Clin Oncol*. 2004 Jul 15;22(14):2885-90. PMID: 15254057
12. Dallorso, S, Dini, G, Faraci, M, Spreafico, F. SCT for Wilms' tumour. *Bone Marrow Transplant*. 2008 Jun;41 Suppl 2:S128-30. PMID: 18545233
13. Spreafico, F, Bisogno, G, Collini, P, et al. Treatment of high-risk relapsed Wilms tumor with dose-intensive chemotherapy, marrow-ablative chemotherapy, and autologous hematopoietic stem cell support: experience by the Italian Association of Pediatric Hematology and Oncology. *Pediatr Blood Cancer*. 2008 Jul;51(1):23-8. PMID: 18293386
14. Fagioli, F, Biasin, E, Mereuta, OM, et al. Poor prognosis osteosarcoma: new therapeutic approach. *Bone Marrow Transplant*. 2008 Jun;41 Suppl 2:S131-4. PMID: 18545234
15. Physician Data Query (PDQ®). Osteosarcoma/Malignant fibrous histiocytoma of bone treatment: health professional version. National Cancer Institute; last updated 08/09/2012. [cited 08/23/2012]; Available from: http://www.cancer.gov/cancertopics/pdq/treatment/osteosarcoma/healthprofessional
16. Physician Data Query (PDQ®). Retinoblastoma treatment: health professional version. National Cancer Institute; last updated 03/08/2012. [cited 08/23/2012]; Available from: http://www.cancer.gov/cancertopics/pdq/treatment/retinoblastoma/healthprofessional
17. Matthay, KK, Villablanca, JG, Seeger, RC, et al. Treatment of high-risk neuroblastoma with intensive chemotherapy, radiotherapy, autologous bone marrow transplantation, and 13-cis-retinoic acid. Children's Cancer Group. *N Engl J Med*. 1999 Oct 14;341(16):1165-73. PMID: 10519894
18. Matthay, KK, Reynolds, CP, Seeger, RC, et al. Long-term results for children with high-risk neuroblastoma treated on a randomized trial of myeloablative therapy followed by 13-cis-retinoic acid: a children's oncology group study. *J Clin Oncol*. 2009 Mar 1;27(7):1007-13. PMID: 19171716
19. Berthold, F, Boos, J, Burdach, S, et al. Myeloablative megatherapy with autologous stem-cell rescue versus oral maintenance chemotherapy as consolidation treatment in patients with high-risk neuroblastoma: a randomised controlled trial. *Lancet Oncol*. 2005 Sep;6(9):649-58. PMID: 16129365
20. Pritchard, J, Cotterill, SJ, Germond, SM, Imeson, J, de Kraker, J, Jones, DR. High dose melphalan in the treatment of advanced neuroblastoma: results of a randomised trial (ENSG-1) by the European Neuroblastoma Study Group. *Pediatr Blood Cancer*. 2005 Apr;44(4):348-57. PMID: 15546135
21. Ratko TA, Belinson SE, Brown HM et al. Hematopoietic stem-cell transplantation in the pediatric population. Comparative Effectiveness Review No 48. (Prepared by the Blue Cross and Blue Shield Association Technology Evaluation Center Evidence-based Practice Center under Contract No. HHSA 290-2007-10058.) AHRQ Publication No. 12-EHC018-EF. Rockville, MD: Agency for Healthcare Research and Quality. February 2012. www.effectivehealthcare.ahrq.gov/reports/final.cfm.
22. Sung, KW, Ahn, HS, Cho, B, et al. Efficacy of tandem high-dose chemotherapy and autologous stem cell rescue in patients over 1 year of age with stage 4 neuroblastoma: the Korean Society of Pediatric Hematology-Oncology experience over 6 years (2000-2005). *J Korean Med Sci*. 2010 May;25(5):691-7. PMID: 20436703
23. Ladenstein, R, Potschger, U, Hartman, O, et al. 28 years of high-dose therapy and SCT for neuroblastoma in Europe: lessons from more than 4000 procedures. *Bone Marrow Transplant*. 2008 Jun;41 Suppl 2:S118-27. PMID: 18545256

24. Kim, EK, Kang, HJ, Park, JA, Choi, HS, Shin, HY, Ahn, HS. Retrospective analysis of peripheral blood stem cell transplantation for the treatment of high-risk neuroblastoma. *J Korean Med Sci*. 2007 Sep;22 Suppl:S66-72. PMID: 17923758
25. George, RE, Li, S, Medeiros-Nancarrow, C, et al. High-risk neuroblastoma treated with tandem autologous peripheral-blood stem cell-supported transplantation: long-term survival update. *J Clin Oncol*. 2006 Jun 20;24(18):2891-6. PMID: 16782928
26. von Allmen, D, Grupp, S, Diller, L, et al. Aggressive surgical therapy and radiotherapy for patients with high-risk neuroblastoma treated with rapid sequence tandem transplant. *J Pediatr Surg*. 2005 Jun;40(6):936-41; discussion 41. PMID: 15991174
27. Marcus, KJ, Shamberger, R, Litman, H, et al. Primary tumor control in patients with stage 3/4 unfavorable neuroblastoma treated with tandem double autologous stem cell transplants. *J Pediatr Hematol Oncol*. 2003 Dec;25(12):934-40. PMID: 14663275
28. Kletzel, M, Katzenstein, HM, Haut, PR, et al. Treatment of high-risk neuroblastoma with triple-tandem high-dose therapy and stem-cell rescue: results of the Chicago Pilot II Study. *J Clin Oncol*. 2002 May 1;20(9):2284-92. PMID: 11980999
29. Grupp, SA, Stern, JW, Bunin, N, et al. Rapid-sequence tandem transplant for children with high-risk neuroblastoma. *Med Pediatr Oncol*. 2000 Dec;35(6):696-700. PMID: 11107149
30. Sung, KW, Park, JE, Chueh, HW, et al. Reduced-intensity allogeneic stem cell transplantation for children with neuroblastoma who failed tandem autologous stem cell transplantation. *Pediatr Blood Cancer*. 2011 Oct;57(4):660-5. PMID: 21681924
31. Meyers, PA. High-dose therapy with autologous stem cell rescue for pediatric sarcomas. *Curr Opin Oncol*. 2004 Mar;16(2):120-5. PMID: 15075902
32. Meyers, PA, Krailo, MD, Ladanyi, M, et al. High-dose melphalan, etoposide, total-body irradiation, and autologous stem-cell reconstitution as consolidation therapy for high-risk Ewing's sarcoma does not improve prognosis. *J Clin Oncol*. 2001 Jun 1;19(11):2812-20. PMID: 11387352
33. Gardner, SL, Carreras, J, Boudreau, C, et al. Myeloablative therapy with autologous stem cell rescue for patients with Ewing sarcoma. *Bone Marrow Transplant*. 2008 May;41(10):867-72. PMID: 18246113
34. Ladenstein, R, Potschger, U, Le Deley, MC, et al. Primary disseminated multifocal Ewing sarcoma: results of the Euro-EWING 99 trial. *J Clin Oncol*. 2010 Jul 10;28(20):3284-91. PMID: 20547982
35. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in OncologyTM. Bone Cancer. v2.2013. [cited 07/30/2013]; Available from: http://www.nccn.org/professionals/physician_gls/pdf/bone.pdf
36. Admiraal, R, van der Paardt, M, Kobes, J, Kremer, LC, Bisogno, G, Merks, JH. High-dose chemotherapy for children and young adults with stage IV rhabdomyosarcoma. *Cochrane Database Syst Rev*. 2010(12):CD006669. PMID: 21154373
37. Weigel, BJ, Breitfeld, PP, Hawkins, D, Crist, WM, Baker, KS. Role of high-dose chemotherapy with hematopoietic stem cell rescue in the treatment of metastatic or recurrent rhabdomyosarcoma. *J Pediatr Hematol Oncol*. 2001 Jun-Jul;23(5):272-6. PMID: 11464981
38. Carli, M, Colombatti, R, Oberlin, O, et al. High-dose melphalan with autologous stem-cell rescue in metastatic rhabdomyosarcoma. *J Clin Oncol*. 1999 Sep;17(9):2796-803. PMID: 10561355
39. Klingebiel, T, Boos, J, Beske, F, et al. Treatment of children with metastatic soft tissue sarcoma with oral maintenance compared to high dose chemotherapy: report of the HD CWS-96 trial. *Pediatr Blood Cancer*. 2008 Apr;50(4):739-45. PMID: 18286501
40. McDowell, HP, Foot, AB, Ellershaw, C, Machin, D, Giraud, C, Bergeron, C. Outcomes in paediatric metastatic rhabdomyosarcoma: results of The International Society of Paediatric Oncology (SIOP) study MMT-98. *Eur J Cancer*. 2010 Jun;46(9):1588-95. PMID: 20338746

41. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Soft Tissue Sarcoma v.1.2013. [cited 07/30/2013]; Available from: http://www.nccn.org/professionals/physician_gls/pdf/sarcoma.pdf
42. Kremens, B, Gruhn, B, Klingebiel, T, et al. High-dose chemotherapy with autologous stem cell rescue in children with nephroblastoma. *Bone Marrow Transplant*. 2002 Dec;30(12):893-8. PMID: 12476282
43. Presson, A, Moore, TB, Kempert, P. Efficacy of high-dose chemotherapy and autologous stem cell transplant for recurrent Wilms' tumor: a meta-analysis. *J Pediatr Hematol Oncol*. 2010 Aug;32(6):454-61. PMID: 20505538
44. Garaventa, A, Hartmann, O, Bernard, JL, et al. Autologous bone marrow transplantation for pediatric Wilms' tumor: the experience of the European Bone Marrow Transplantation Solid Tumor Registry. *Med Pediatr Oncol*. 1994;22(1):11-4. PMID: 8232074
45. Pein, F, Michon, J, Valteau-Couanet, D, et al. High-dose melphalan, etoposide, and carboplatin followed by autologous stem-cell rescue in pediatric high-risk recurrent Wilms' tumor: a French Society of Pediatric Oncology study. *J Clin Oncol*. 1998 Oct;16(10):3295-301. PMID: 9779704
46. Kullendorff, CM, Bekassy, AN. Salvage treatment of relapsing Wilms' tumour by autologous bone marrow transplantation. *Eur J Pediatr Surg*. 1997 Jun;7(3):177-9. PMID: 9241510
47. Fagioli, F, Aglietta, M, Tienghi, A, et al. High-dose chemotherapy in the treatment of relapsed osteosarcoma: an Italian sarcoma group study. *J Clin Oncol*. 2002 Apr 15;20(8):2150-6. PMID: 11956277
48. Dunkel, IJ, Aledo, A, Kernan, NA, et al. Successful treatment of metastatic retinoblastoma. *Cancer*. 2000 Nov 15;89(10):2117-21. PMID: 11066053
49. Jubran, RF, Erdreich-Epstein, A, Butturini, A, Murphree, AL, Villablanca, JG. Approaches to treatment for extraocular retinoblastoma: Children's Hospital Los Angeles experience. *J Pediatr Hematol Oncol*. 2004 Jan;26(1):31-4. PMID: 14707710
50. Kremens, B, Wieland, R, Reinhard, H, et al. High-dose chemotherapy with autologous stem cell rescue in children with retinoblastoma. *Bone Marrow Transplant*. 2003 Feb;31(4):281-4. PMID: 12621463
51. Matsubara, H, Makimoto, A, Higa, T, et al. A multidisciplinary treatment strategy that includes high-dose chemotherapy for metastatic retinoblastoma without CNS involvement. *Bone Marrow Transplant*. 2005 Apr;35(8):763-6. PMID: 15750608
52. Namouni, F, Doz, F, Tanguy, ML, et al. High-dose chemotherapy with carboplatin, etoposide and cyclophosphamide followed by a haematopoietic stem cell rescue in patients with high-risk retinoblastoma: a SFOP and SFGM study. *Eur J Cancer*. 1997 Dec;33(14):2368-75. PMID: 9616283
53. Rodriguez-Galindo, C, Wilson, MW, Haik, BG, et al. Treatment of metastatic retinoblastoma. *Ophthalmology*. 2003 Jun;110(6):1237-40. PMID: 12799253
54. Dunkel, IJ, Khakoo, Y, Kernan, NA, et al. Intensive multimodality therapy for patients with stage 4a metastatic retinoblastoma. *Pediatr Blood Cancer*. 2010 Jul 15;55(1):55-9. PMID: 20486171
55. Dunkel, IJ, Chan, HS, Jubran, R, et al. High-dose chemotherapy with autologous hematopoietic stem cell rescue for stage 4B retinoblastoma. *Pediatr Blood Cancer*. 2010 Jul 15;55(1):149-52. PMID: 20486181
56. BlueCross BlueShield Association Medical Policy Reference Manual "Hematopoietic Stem-Cell Transplantation for Solid Tumors of Childhood." Policy No. 8.01.34

## CROSS REFERENCES

Donor Lymphocyte Infusion for Malignancies Treated with an Allogeneic Hematopoietic Stem-Cell Transplant, Transplant, Policy No. 45.03

Placental and Umbilical Cord Blood as a Source of Stem Cells, Transplant, Policy No. 45.16

Hematopoietic Stem-Cell Transplantation for Miscellaneous Solid Tumors in Adults, Transplant, Policy No. 45.27

Hematopoietic Stem Cell Transplantation for CNS Embryonal Tumors and Ependymoma, Transplant, Policy No. 45.33

Autologous Hematopoietic Stem Cell Transplantation for Malignant Astrocytomas and Gliomas, Transplant, Policy No. 45.34

Hematopoietic Stem Cell Transplantation in the Treatment of Germ-Cell Tumors, Transplant, Policy No. 45.38

| CODES | NUMBER | DESCRIPTION |
|---|---|---|
| CPT | 38204 | Management of recipient hematopoietic cell donor search and cell acquisition |
| | 38205 | Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection, allogeneic |
| | 38206 | ;autologous |
| | 38207 | Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage |
| | 38208 | ;thawing of previously frozen harvest, without washing, per donor |
| | 38209 | ;thawing of previously frozen harvest with washing, per donor |
| | 38210 | ;specific cell depletion with harvest, T cell depletion |
| | 38211 | ;tumor cell depletion |
| | 38212 | ;red blood cell removal |
| | 38213 | ;platelet depletion |
| | 38214 | ;plasma (volume) depletion |
| | 38215 | ;cell concentration in plasma, mononuclear, or buffy coat layer |
| | 38220 | Bone marrow; aspiration only |
| | 38221 | Bone marrow; biopsy, needle or trocar |

| CODES | NUMBER | DESCRIPTION |
|---|---|---|
| | 38230 | Bone marrow harvesting for transplantation; allogeneic |
| | 38232 | Bone marrow harvesting for transplantation; autologous |
| | 38240 | Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor |
| | 38241 | ;autologous transplantation |
| | 38243 | ;HPC boost |
| | 38242 | Allogeneic lymphocyte infusions |
| HCPCS | J9000–J9999 | Chemotherapy drugs code range |
| | Q0083–Q0085 | Chemotherapy administration code range |
| | S2140 | Cord blood harvesting for transplantation; allogeneic |
| | S2142 | Cord blood derived stem-cell transplantation, allogeneic |
| | S2150 | 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) |