Hematopoietic Stem Cell Transplantation for Solid Tumors of Childhood

Policy # 00064
Original Effective Date: 01/28/2002
Current Effective Date: 06/18/2014

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the “Company”), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- Benefits are available in the member’s contract/certificate, and
- Medical necessity criteria and guidelines are met.

Based on review of available data, the Company may consider autologous hematopoietic stem cell transplantation (HSCT) for the following conditions to be eligible for coverage:

- Initial treatment of high-risk neuroblastoma,
- Recurrent or refractory neuroblastoma,
- Initial treatment of high-risk Ewing’s sarcoma, and
- Recurrent or refractory Ewing’s sarcoma.

Based on review of available data, the Company may consider tandem autologous hematopoietic stem-cell transplantation (HSCT) for high-risk neuroblastoma to be eligible for coverage.

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers autologous hematopoietic stem cell transplantation (HSCT) 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 to be investigational.*

- Rhabdomyosarcoma (RMS)
- Wilm’s tumor
- Osteosarcoma
- Retinoblastoma.

Based on review of available data, the Company considers tandem autologous hematopoietic stem cell transplantation (HSCT) for the treatment of all other types of pediatric solid tumors except high-risk neuroblastoma, as noted above to be investigational.*

Based on review of available data, the Company considers allogeneic (myeloablative or nonmyeloablative) hematopoietic stem cell transplantation (HSCT) for treatment of pediatric solid tumors to be investigational.*
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Based on review of available data, the Company considers salvage allogeneic hematopoietic stem cell transplantation (HSCT) for pediatric solid tumors that relapse after autologous transplant or fail to respond to be investigational.*

**Background/Overview**

**Hematopoietic Stem-Cell Transplantation for Solid Tumors**

Hematopoietic stem-cell transplantation 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.

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), Wilm’s tumor, 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 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 two thirds of the cases presenting in children younger than five 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 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 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 an 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. 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.
Ewing's Sarcoma and the Ewing 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, 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. Most children with RMS present with localized disease, and with conventional multimodal therapy, the cure rate in this group is 70–80%. 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.

Wilm's Tumor

Wilm's 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 Wilm's tumor, relapsed Wilm's 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
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. However, 30–40% of patients with non-metastatic osteosarcoma of the extremities experience recurrent disease, most commonly in the lungs. 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%.

Retinoblastoma
Retinoblastoma is the most common primary tumor of the eye in children. It may occur as a heritable (40%) or non-heritable (60%) 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 at least a 90% cure rate. However, once disease has spread beyond the eye, survival rates drop significantly; 5-year disease-free survival (DFS) 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.

Rationale/Source
Peripheral Neuroblastoma
Single autologous HSCT
Three well-designed, randomized trials have been conducted using autologous HSCT in the treatment of high-risk neuroblastoma.

In a study published in 1999, Matthay et al 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 2 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). 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 et al randomly assigned 295 patients with high-risk neuroblastoma to myeloablative therapy (melphalan, etoposide, carboplatin) with autologous HSCT or to oral maintenance chemotherapy with cyclophosphamide. The primary end point was EFS with secondary end points of OS and treatment-related deaths. Intention-to-treat (ITT) analysis showed that patients who received the myeloablative therapy had an increased 3-year EFS compared with the oral maintenance group (47%; 95% confidence interval [CI], 38% to 55% vs 31%; 95% CI, 23% to 39%) but did not have significantly increased 3-year OS (62% [95% CI, 54% to 70%] vs 53% [95% CI, 45% to 62%]; p=0.088). 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 et al 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. 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).

A recent Cochrane meta-analysis identified 3 randomized controlled trials (RCTs) that included 739 children with high-risk neuroblastoma. The primary objective was to compare the efficacy of myeloablative therapy with conventional therapy. The included studies all used an age of 1 year as the cut-off point for pretreatment risk stratification. The updated search identified a manuscript reporting additional follow-up data for 1 of these RCTs. There was a statistically significant difference in EFS in favor of myeloablative therapy over conventional chemotherapy or no further treatment (3 studies, 739 patients; hazard ratio [HR], 0.78; 95% CI, 0.67 to 0.90). There was a statistically significant difference in OS in favor of myeloablative therapy over conventional chemotherapy or no further treatment (2 studies, 360 patients; HR=0.74; 95% CI, 0.57 to 0.98). However, when additional follow-up data were included in the analyses, the difference in EFS remained statistically significant (3 studies, 739 patients; HR=0.79; 95% CI, 0.70 to 0.90), but the difference in OS was no longer statistically significant (2 studies, 360 patients; HR=0.86; 95% CI, 0.73 to 1.01). The meta-analysis of secondary malignant disease and treatment-related death did not show any statistically significant differences between the treatment groups. Data from 1 study (379 patients) showed a significantly higher incidence of renal effects, interstitial pneumonitis, and veno-occlusive disease in the
myeloablative group compared with conventional chemotherapy, whereas for serious infections and sepsis, no significant difference between the treatment groups was identified. No information on quality of life was reported.

Tandem autologous HSCT
Sung et al 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. 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 (TRM) 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 ITT 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 before 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 complete CR before the HSCT.

Ladenstein et al reported on 28 years of experience for more than 4000 transplants for primary (89%) and relapsed (11%) neuroblastoma in 27 European countries in the European Group for Blood and Marrow Transplantation registry. Procedures included single autologous (n=2895), 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 age 18 years. The median follow-up time from HSCT was 9 years. 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 et al 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. DFS of patients who underwent double HSCT was similar to that of patients who underwent a single autologous HSCT (p=0.5).

George et al reported OS of high-risk neuroblastoma patients (n=82) treated with tandem autologous HSCT between 1994 and 2002. Median age at diagnosis was 35 months (range, 6 months to 18 years). Three- and 5-year OS were 74% (95% CI, 62% to 82%) and 64% (95% CI, 52% to 74%) respectively.
von Allmen et al 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 HDC and stem-cell rescue. Overall EFS for the series was 56%.

Marcus et al 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. Radiotherapy was given if gross or microscopic residual disease was present before 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 et al reported on the outcomes of 25 consecutive newly diagnosed high-risk neuroblastoma patients and 1 with recurrent disease, diagnosed between 1995 and 2000, and treated with triple-tandem autologous HSCT. 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 1 cycle. There was 1 toxic death, and 1 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 et al reported the outcomes of a phase 2 trial that involved 55 children with high-risk neuroblastoma who underwent tandem autologous HSCT. 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%.

Section Summary
No studies that directly compared single autologous to tandem autologous HSCT for high-risk neuroblastoma have been published. Randomized trials that compared single autologous HSCT with conventional chemotherapy have reported EFS rates for the patients who underwent HSCT ranging from 43% to 47% at 3 years and 30% at 5 years. Case series on the use of tandem autologous for high-risk neuroblastoma have reported 3-year EFS rates ranging from 57% to 63%. A retrospective analysis of a registry of patients with newly diagnosed high-risk neuroblastoma reported 5-year EFS rates for single versus tandem autologous HSCT of 31% versus 51%, respectively (p=0.03).

2014 National Comprehensive Cancer Network (NCCN) Guidelines

NCCN guidelines do not offer recommendations on neuroblastoma.

National Cancer Institute (NCI) Clinical Trial Database (PDQ®)‡
A Phase III randomized, multicenter study (NCT00567567) of single versus tandem consolidation therapy in young patients with newly diagnosed high-risk neuroblastoma is closed. Primary outcomes are EFS, response after induction therapy, and incidence rate of local recurrence. Expected enrollment is 664 with an estimated trial completion date of December 2015.
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Ewing Sarcoma Family of Tumors

During the 1980s and 1990s, 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. The original policy position on Ewing was based on these reports. Subsequently, in 2001, Meyers et al reported on a prospective study with autologous HSCT in 32 patients with newly diagnosed Ewing sarcoma metastatic to bone and/or bone marrow. 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 (TBI), 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 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 et al reported the results of 116 patients with Ewing sarcoma who underwent autologous HSCT (80 as first-line therapy, 36 for recurrent disease) between 1989 and 2000. Five-year probabilities of PFS in patients who received HSCT as first-line therapy were 49% (95% CI, 30% to 69%) for those with localized disease at diagnosis and 34% (95% CI, 22% to 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% to 30%). The authors concluded that PFS rates after autologous HSCT were comparable with rates seen in patients with similar disease characteristics treated with conventional therapy.

Results from 1 group of patients in the Euro-EWING 99 trial were reported by Ladenstein et al for patients with primary disseminated multifocal Ewing Sarcoma (PDMES). From 1999 to 2005, 281 patients with PDMES were enrolled in the Euro-EWING 99 R3 study; the Euro-EWING 99 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. HDC TRM consisted of 3 patients dying within the first 100 days after high-dose therapy; 1 from acute respiratory distress syndrome and 2 from severe veno-occlusive disease and septicemia; late deaths included 3 patients who died 1 to 1.5 years after high-dose therapy. After a median follow-up of 3.8 years, the estimated 3-year EFS and OS for all 281 patients was 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-HRs, and the factor with the smallest HR was assigned 1 point. One score point was attributed to the following risk factors: age older than 14 years, bone marrow metastases, 1 bone lesion and additional presence of lung metastases; 1.5 points were attributed to the risk factors of primary tumor
volume of 200 mL or more and more than 1 bone lesion. This risk 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<0.001). The authors concluded that this scoring system may facilitate risk-adapted treatment strategies.

Section Summary
The aforementioned studies were characterized by small numbers of patients, and comparison of the studies was difficult for several reasons. Within each report, patients could have 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. However, given the need for multiple courses of chemotherapy in the high-risk patients versus a single treatment in HDC with autologous stem cell support, the similarity in outcomes supports use of the latter in high-risk patients.

2014 NCCN Guidelines
NCCN guidelines state that the role of HDC and stem-cell rescue in relapsed or progressive Ewing sarcoma is yet to be determined in prospective randomized studies and makes no recommendations regarding its use in this disease setting (v 1.2014).

NCI Clinical Trial Database (PDQ)
An active phase 3 trial (NCT00987636) and will randomly assign patients with high-risk (localized disease and unfavorable tumor response or tumor volume >200 mL) or very high-risk (primary disseminated disease) Ewing sarcoma to treatment with either autologous HSCT or standard chemotherapy. Primary outcome measure is EFS. Estimated enrollment is 1383 and estimated trial completion date is March 2018.

Rhabdomyosarcoma
McDowell et al reported the results of the International Society of Paediatric Oncology study MMT-98, for pediatric patients from 48 centers with metastatic RMS entered into the study from 1998 to 2005. There were a total of 146 patients entered, aged 6 months to 18 years. The patients were risk-stratified and treated accordingly. One hundred one patients were considered poor risk patients (poor risk group [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 HDC, 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 PR or CR. 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; 95% CI, 1.51 to 4.03; p<0.001).

Klingebiel et al prospectively compared the efficacy of 2 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 RMS). 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 RMS, 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.

Weigel et al reviewed and summarized published evidence on the role of autologous HSCT in the treatment of metastatic or recurrent RMS, which involved a total of 389 patients from 22 studies. Based on all of the evidence analyzing EFS and OS, they concluded that there was no significant advantage to undergoing this type of treatment.

Carli et al conducted a prospective nonrandomized study of 52 patients with metastatic RMS, who were in CR after induction therapy and subsequently received HDC ("megatherapy") and autologous HSCT and compared them with 44 patients who were in remission after induction therapy who subsequently received conventional chemotherapy. No significant differences existed between the 2 study groups (ie, 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 with conventional chemotherapy.

Section Summary
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. Evidence is relatively scarce, due in part to the rarity of the condition. The role of stem cell transplantation of any type for this cancer is not established.

2014 NCCN Guidelines
NCCN guidelines on soft tissue sarcomas do not discuss HDC and stem-cell rescue in relapsed or progressive RMS and make no recommendations regarding its use in this disease setting (v.1.2014).

NCI Clinical Trial Database (PDQ)
No phase 3 trials using HSCT for the treatment of RMS and assessing survival outcomes were identified.

Wilms Tumor
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. 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. 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 were at approximately 3 times the risk of death.
or recurrence than patients who relapsed in the lungs only (HR=3.5 and 2.4, respectively), and the patients with unfavorable histology had approximately twice the risk of death compared with those with favorable histology. The authors compared the survival rates from these 6 studies in which the patients were treated with autologous HSCT with patients treated with conventional chemotherapy between 1995 and 2002. In general, the chemotherapy-treated patients had comparable or improved 4-year survival compared with 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.

Section Summary
The evidence on the use of autologous HSCT for high-risk Wilms tumor consists of small series or case reports. The use of stem-cell transplantation of any type is not established for this cancer.

2014 NCCN Guidelines
NCCN does not offer guidelines on Wilms tumor therapy (v.1.2014).

NCI Clinical Trial Database (PDQ)
A phase 2 trial (NCT00025103) was launched to evaluate chemotherapy followed by surgery and radiation, with or without HSCT in patients with relapsed or refractory Wilms tumor or clear cell sarcoma of the kidney. The study design is interventional and uses 1 of 3 regimens (1 of which includes HSCT) depending on patient risk stratification. Primary outcome measures include unified treatment strategy, improvement of current survival rates, efficacy and toxicity and prognostic variables. Estimated enrollment is 75 (50 for HSCT, 25 for each of the non-HSCT regimens). Estimated final data collection date was November 2008, but the status is unknown, as no updates have been published since June 2009.

An ongoing phase 2 study (NCT00141765) is assessing HDC with bone marrow or stem-cell therapy for rare, poor-prognosis cancers, including Wilms. Primary outcome measure is DFS. Estimated enrollment is 30 with anticipated study completion date of January 2014.

Osteosarcoma
Small series and case reports are available that examine the use of autologous HSCT in osteosarcoma. Autologous HSCT has been successful in inducing short-lasting remissions but has not shown an increase in survival.

2014 NCCN Guidelines
NCCN states that the 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 (v.1.2014).

National Cancer Institute (NCI) Clinical Trial Database (PDQ)
No Phase 3 trials on the use of HSCT for osteosarcoma were identified.
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Retinoblastoma
Most studies of autologous HSCT for high-risk retinoblastoma have been very small series or case reports.

Dunkel et al 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. 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) postenucleation. 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 before 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 to 20 months postdiagnosis of metastatic disease, (2 in the CNS and 1 in the mandible), and all died of their disease. Five-year retinoblastoma-free and EFS were 67% (95% CI, 38% to 85%) and 59% (31% to 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 1 in a nonirradiated field. The authors concluded that HSCT was curative for most patients treated in their study with stage 4a retinoblastoma.

Dunkel et al reported the outcomes of 8 patients diagnosed with stage 4b retinoblastoma between 2000 and 2006 treated with the intention of autologous HSCT. Seven of the patients had leptomeningeal disease, and 1 had only direct extension to the CNS via the optic nerve. At the time of diagnosis of intraocular 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 before HSCT, and 1 patient died of toxicity during induction chemotherapy. Of the 5 patients who 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.

Section Summary
Although the results have been promising in terms of prolonging DFS in some patients, particularly those without CNS involvement (stage 4a), the role of stem cell transplantation has not been established in this disease.

2014 NCCN Guidelines
NCCN does not offer guidelines on retinoblastoma therapy.

NCI Clinical Trial Database (PDQ)
A single-arm, phase 3 trial (COG ARET 0321, NCT00554788) is underway to estimate the proportion of children with extraocular retinoblastoma who achieve long-term EFS after autologous HSCT compared with historical controls. Expected enrollment is 60 patients. The estimated date of completion of the trial is February 2017.
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Comparative Effectiveness 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. The following conclusions were offered:

- Neuroblastoma: The body of evidence on OS with tandem HSCT compared with single HSCT for the treatment of high-risk neuroblastoma was insufficient to draw conclusions.
- Ewing sarcoma family of tumors: Low-strength evidence on OS suggests no benefit with single HSCT compared with conventional therapy for the treatment of high-risk ESFT.
  - The body of evidence on OS with tandem HSCT compared with single HSCT for the treatment of high-risk ESFT and OS is insufficient to draw conclusions.
- Rhabdomyosarcoma: Moderate-strength evidence on OS suggests no benefit with single HSCT compared with conventional therapy for the treatment of high-risk metastatic RMS.
  - The body of evidence on OS with single HSCT compared with conventional therapy for the treatment of high-risk RMS of mixed tumor type is insufficient to draw conclusions.
  - The body of evidence on OS with single HSCT compared with conventional therapy for the treatment of congenital alveolar RMS, cranial parameningeal RMS with metastasis, or the use of allogeneic transplantation for metastatic RMS was insufficient to draw conclusions.
- Wilms tumor: Low-strength evidence on OS suggests no benefit with single HSCT compared with conventional therapy for the treatment of high-risk relapsed Wilms tumor.
- Osteosarcoma was not addressed.
- Retinoblastoma: Low-strength evidence on OS suggests no benefit with single HSCT compared with conventional therapy for the treatment of extraocular retinoblastoma with central nervous system involvement.
  - The body of evidence on OS with single HSCT compared with conventional therapy for the treatment of extraocular retinoblastoma without CNS involvement was insufficient to draw conclusions.
  - The body of evidence on OS with single HSCT compared with conventional therapy for the treatment of trilateral retinoblastoma without CNS involvement was insufficient to draw conclusions.

Clinical Input Received Through Physician Specialty Society and Academic Medical Centers
In response to requests, input was received from 3 academic medical centers and 2 Blue Distinction Centers for Transplants for review in April 2011. While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

There was general agreement from all of the reviewers for most of the policy statements with the following exceptions. One of the reviewers considered autologous HSCT medically necessary for advanced stage retinoblastoma. One of the reviewers did not consider autologous HSCT for low- to intermediate-risk Ewing sarcoma investigational but did state that the results of the Euro-Ewing’s phase 3 trial are awaited. Two reviewers agreed with the policy statement that tandem autologous HSCT for pediatric solid tumors is...
investigational, 2 considered it medically necessary for high-risk neuroblastoma, and the fifth reviewer agreed that tandem autologous HSCT is considered investigational for pediatric solid tumors but also stated that it is considered standard for high-risk neuroblastoma at some centers.

Summary

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 EFS and overall survival.
- 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.
  - A phase 3, randomized trial of single versus tandem autologous HSCT for high-risk neuroblastoma is currently underway.

Ewing sarcoma family of tumors
- Evidence on the use of HSCT in the initial treatment of high-risk or recurrent or refractory ESFT has shown varied results for a survival benefit with the use of HSCT. Two phase 3 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 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 (eg, patients with advanced-stage disease with lung-only metastases). A phase 2 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 in some patients with stage 4 disease treated with HSCT, particularly those with stage 4a disease.
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- A recent study of 15 patients showed that some patients with stage 4a retinoblastoma 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

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.

References

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Policy History

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12/06/2001 Medical Policy Committee review
01/28/2002 Managed Care Advisory Council approval
05/07/2004 Medical Director review
05/18/2004 Medical Policy Committee review. Format revision. High-Dose Chemotherapy and Hematopoietic Stem Cell Support for Pediatric Solid Tumors policy separated from current HDC with Hematopoietic Stem Cell Support policy. No substance change to policy.
06/28/2004 Managed Care Advisory Council approval
05/03/2005 Medical Director review. Format revision. No substance change to policy.
05/17/2005 Medical Policy Committee review. Policy statement language changed from, “may consider HDC and autologous or syngeneic SCS to treat recurrent or refractory Ewing’s sarcoma to be eligible for coverage” to; “Based on review of available data, the Company may consider HDC and autologous or syngeneic SCS to consolidate remissions of poor-risk Ewing’s sarcoma, or as salvage therapy for those with residual, recurrent or refractory disease to be eligible for coverage.” Patient selection criteria added.
05/23/2005 Managed Care Advisory Council approval
08/02/2006 Medical Director review
06/13/2007 Medical Director review
06/20/2007 Medical Policy Committee approval. Policy updated with literature review. Policy statement added to indicate that multiple cycle high-dose chemotherapy and hematopoietic stem-cell support is considered to be investigational for the treatment of neuroblastoma.
07/02/2008 Medical Director review
07/16/2008 Medical Policy Committee approval
06/04/2009 Medical Director review
06/17/2009 Medical Policy Committee approval. Changed title from “High-Dose Chemotherapy with Stem Cell Support for Solid Tumors of Childhood” to “High-Dose Chemotherapy with Hematopoietic Stem Cell Support for Solid Tumors of Childhood”. Changed “poor-risk Ewing’s sarcoma” to “high-risk Ewing’s sarcoma” in the “When Services May Be Eligible for Coverage” section and under the “Patient Selection Criteria.” Extensive changes made to “Background/Overview, FDA, Rationale and References” sections of the policy. No change to coverage eligibility.
06/03/2010 Medical Policy Committee review
06/16/2010 Medical Policy Implementation Committee approval. Changed title from “High-Dose Chemotherapy with Hematopoietic Stem Cell Support for Solid Tumors of Childhood” to “Hematopoietic Stem Cell Transplantation for Solid Tumors of Childhood”. Changed all “high-dose chemotherapy with stem cell support” verbiage to “hematopoietic stem cell transplantation” throughout the coverage section of the policy. Coverage eligibility unchanged.
06/02/2011 Medical Policy Committee review
06/15/2011 Medical Policy Implementation Committee approval. Investigational statement modified to specify that “tandem autologous-autologous hematopoietic stem cell transplantation for treatment of pediatric solid tumors” is investigational. Added that allogeneic (myeloablative or nonmyeloablative) hematopoietic stem cell transplantation for treatment of pediatric solid tumors is investigational.
06/14/2012 Medical Policy Committee review
06/20/2012 Medical Policy Implementation Committee approval. Policy updated and reformatted.
03/04/2013 Coding updated

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06/06/2013  Medical Policy Committee review
06/25/2013  Medical Policy Implementation Committee approval. The coverage statements were modified to state specifically that tandem autologous HSCT for high-risk neuroblastoma is considered to be eligible for coverage, but is investigational for all other indications.
06/05/2014  Medical Policy Committee review
06/18/2014  Medical Policy Implementation Committee approval. No change to coverage.
Next Scheduled Review Date:  06/2015

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
   1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
   2. credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
   3. reference to federal regulations.

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A. in accordance with nationally accepted standards of medical practice;
B. clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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