Hematopoietic Stem-Cell Transplantation for Solid Tumors of Childhood

Policy Number: MM.07.021  
Original Effective Date: 04/01/2008  
Line(s) of Business: HMO; PPO  
Current Effective Date: 06/22/2012  
Section: Transplants  
Place(s) of Service: Outpatient; Inpatient

Precertification is required for this service.

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

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

Peripheral Neuroblastoma

Neuroblastoma is the most common extracranial solid tumor of childhood, with two thirds of the cases presenting in children younger than 5 years of age. These tumors originate where sympathetic nervous system tissue is present, within the adrenal medulla or paraspinal sympathetic ganglia. They are remarkable for their broad spectrum of clinical behavior, with 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 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

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, 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%. (8)

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. (9) Most children with RMS present with localized disease, and with conventional multimodal therapy, the cure rate in this group is 70–80%. (10) 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. (10,11)

Wilms Tumor

Wilms tumor, the most common primary malignant renal tumor of childhood, is highly sensitive to chemotherapy and radiation, and current cure rates exceed 85%. (12) Ten to 15% of patients with favorable histology and 50% of patients with anaplastic tumors experience tumor progression or relapse. (12) Similar to newly diagnosed Wilms tumor, relapsed Wilms tumor is a heterogeneous disease, and current treatment strategies stratify intensity and scheduling of the treatment modalities based on prognostic features. For newly diagnosed disease, the most important prognostic features are stage and histology. Similar risk-adapted strategies are being attempted for the 15% of patients who experience relapse. Success rates after relapse range from 25–45%. 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), EFS is less than 15%. (13) However, recent trials with high-dose chemotherapy (HDC) and autologous HSCT have reported 3- or 4-year OS rates from 60–73%. (14)

Osteosarcoma

Osteosarcoma is a primary malignant bone tumor that is characterized by formation of bone or osteoid by the tumor cells. Osteosarcoma occurs predominantly in the appendicular skeleton of adolescents. In children and adolescents, more than 50% of these tumors arise from bones around the knee. The prognosis of localized osteosarcoma has greatly improved over the last 30 years, with OS rates increasing from 10% with surgery alone (usually amputation) to 70% with the introduction of neoadjuvant chemotherapy and limb-sparing surgery. (15) However, 30–40% of patients with non-metastatic osteosarcoma of the extremities experience recurrent disease, most commonly in the lungs. (15) 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%. (16)

**Retinoblastoma**
Retinoblastoma is the most common primary tumor of the eye in children. It may occur as a heritable (40%) or nonheritable (60%) tumor. (17) Cases may be unilateral or bilateral, with bilateral tumor almost always occurring in the heritable type. The type of treatment depends on the extent of disease. Retinoblastoma is usually confined to the eye, and with current therapy has at least a 90% cure rate. (17) However, once disease has spread beyond the eye, survival rates drop significantly; 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. (18) Extraocular disease may be localized to the soft tissues surrounding the eye, or to the optic nerve, extending beyond the margin of resection. Further extension may result in involvement of the brain and meninges, with subsequent seeding of the cerebrospinal fluid, as well as distant metastases to the lungs, bone, and bone marrow. Stage 4a disease is defined as distant metastatic disease not involving the central nervous system (CNS), and stage 4b is defined as metastatic disease to the CNS.

II. **Criteria/Guidelines**

A. Autologous hematopoietic stem-cell transplantation is covered (subject to Limitations/Exclusions and Administrative Guidelines) for:
   1. Initial treatment of high-risk neuroblastoma,
   2. Recurrent or refractory neuroblastoma,
   3. Initial treatment of high-risk Ewing’s sarcoma, and
   4. Recurrent or refractory Ewing's sarcoma.

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

C. Autologous hematopoietic stem-cell transplantation is not covered 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:
   1. Rhabdomyosarcoma,
   2. Wilms tumor,
   3. Osteosarcoma,
   4. Retinoblastoma.

D. Tandem autologous hematopoietic stem-cell transplantation is not covered for the treatment of all other types of pediatric solid tumors except high-risk neuroblastoma, as noted above.

E. Allogeneic (myeloablative or nonmyeloablative) hematopoietic stem-cell transplantation is not covered for treatment of pediatric solid tumors.

F. Salvage allogeneic hematopoietic stem-cell transplantation for pediatric solid tumors that relapse after autologous transplant or fail to respond is not covered.
III. Policy Guidelines

A. Hematopoietic stem-cell transplantation refers to any source of stem cells, i.e., autologous, allogeneic, syngeneic, or umbilical cord blood.

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

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

D. CPT 38208 and 38209 describe thawing and washing of cryopreserved cells.

E. CPT 38210-38214 describe certain cell types being depleted.

F. CPT 38215 describes plasma cell concentration.

IV. Limitations/Exclusions

The patient must be an appropriate candidate for transplant. This is defined as:

A. Adequate cardiopulmonary status
B. Absence of active infection
C. No history of malignancy within 5 years of transplantation, excluding nonmelanomatous skin cancers
D. Documentation of patient compliance with medical management

V. Administrative Guidelines

A. Precertification is required for this service as well as for any transplant evaluations. To precertify, please complete HMSA's Precertification Request and mail or fax the form as indicated along with the required documentation.

<table>
<thead>
<tr>
<th>CPT Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>38205</td>
<td>Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection, allogeneic</td>
</tr>
<tr>
<td>38206</td>
<td>Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection, autologous</td>
</tr>
<tr>
<td>38208</td>
<td>Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing, per donor</td>
</tr>
<tr>
<td>38209</td>
<td>;thawing of previously frozen harvest with washing, per donor</td>
</tr>
<tr>
<td>38210</td>
<td>;specific cell depletion with harvest, T cell depletion</td>
</tr>
<tr>
<td>38211</td>
<td>;tumor cell depletion</td>
</tr>
<tr>
<td>38212</td>
<td>;red blood cell removal</td>
</tr>
<tr>
<td>38213</td>
<td>;platelet depletion</td>
</tr>
<tr>
<td>38214</td>
<td>;plasma (volume) depletion</td>
</tr>
</tbody>
</table>
VI. Scientific Background

Peripheral Neuroblastoma

Single autologous 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 (19) 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 event-free survival (EFS) rate among patients assigned to transplantation was 43 +/- 6% versus 27 +/- 5% among those assigned to continuation chemotherapy (p=0.027). However, overall survival (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). (20) 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-R, 41% +/- 7% for autologous transplant/no cis-RS, and, for nonmyeloablative chemotherapy, 38% +/- 7% and 36% +/- 7% with and without cis-R. 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. (21) The primary endpoint was EFS with secondary endpoints of OS and treatment-related deaths. Intention-to-treat (ITT) 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 (22) 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 high-dose chemotherapy (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).

**Tandem autologous HSCT**

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. (23) 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 (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 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 complete 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. (24) 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 age 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. (25) Disease-free survival (DFS) 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. (26) 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. (27) Overall event-free survival (EFS) for the series 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. (28) 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. (29) 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. (30) 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%.

Conclusion
No studies directly comparing single autologous to tandem autologous HSCT for high-risk neuroblastoma have been published. Randomized trials comparing single autologous HSCT to 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).

National Cancer Institute (NCI) Clinical Trial Database (PDQ®)
A Phase III randomized, multicenter study of single versus tandem consolidation therapy in young patients with newly diagnosed high-risk neuroblastoma is closed. (NCT00567567) 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 March 2016.

Ewing’s Sarcoma and the Ewing 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 Ewing’s sarcoma family of tumors (ESFT). (31) The original policy position on Ewing’s was based on these studies/reports.

These aforementioned studies 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.
Subsequently, in 2001, Meyers and colleagues (32) reported on a prospective study with autologous HSCT in 32 patients with newly diagnosed Ewing’s 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 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 progression-free survival (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-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. High-dose chemotherapy TRM consisted of 3 patients dying within the first 100 days after high-dose therapy; one from acute respiratory distress syndrome (RDS) 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, 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-hazard ratios (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 equal to or
greater than 200 mL and more than 1 bone lesion. This risk score allowed allocation of patients with PD MES 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.

2012 National Comprehensive Cancer Network (NCCN) Guidelines

NCCN guidelines 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. (v 2.2012)

National Cancer Institute (NCI) Clinical Trial Database (PDQ®)

EURO-EWING 99: A Phase III, randomized, controlled, multicenter (international) study for patients with Ewing’s sarcoma is in progress. Approximately 1,200 patients are expected to enroll. The primary objective is to compare the EFS and OS of patients with tumors of the Ewing's family treated with standard induction chemotherapy comprising vincristine, dactinomycin, ifosfamide, and etoposide (VIDE) followed by consolidation chemotherapy comprising vincristine, dactinomycin, and ifosfamide versus high-dose busulfan and melphalan (Bu-Mel) followed by autologous peripheral blood stem-cell (PBSC) transplantation with or without radiotherapy and/or surgery. The study includes both patients with localized disease and those with metastases, includes three arms for low-, intermediate-, and high-risk patients, and is the first randomized approach of autologous HSCT in high-risk Ewing’s patients. The anticipated end date for this study is December 2011. (NCT00020566).

A Phase III trial is active, which 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’s sarcoma to treatment with either autologous HSCT or standard chemotherapy. Primary outcome measure is EFS. (NCT00987636) Estimated enrollment is 1,383 and estimated trial completion date is March 2018.

Rhabdomyosarcoma

Autologous HSCT has been evaluated in a limited number of patients with “high-risk” rhabdomyosarcoma (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.

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 RMS entered into the study from 1998 to 2005. (35) 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 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 [hazard ratio [HR]: 2.46; 95% CI: 1.51-4.03; p<0.001).

Klingebiel and colleagues 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). (36) 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 and colleagues (37) reviewed and summarized published data 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 data analyzing EFS and OS, they concluded that there was no significant advantage to undergoing this type of treatment.

Carli and colleagues (38) 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 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.

National Cancer Institute (NCI) Clinical Trial Database (PDQ®)

No Phase III trials using HSCT for the treatment of RMS and assessing survival outcomes were identified.

Wilms Tumor

The data on the use of autologous HSCT for high-risk Wilms tumor consist of small series or case reports.

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. (39) Six studies were included (12,14,40-43) 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 to those with favorable histology. 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.

National Cancer Institute (NCI) Clinical Trial Database (PDQ®)

A Phase II trial, status unknown, is studying 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 (one of which includes HSCT) depending upon 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 and 25 for each of the non-HSCT regimens). Estimated final data collection date is November 2008 (NCT00025103).

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

Osteosarcoma

Rare small series and case reports are available that examine the use of autologous HSCT in osteosarcoma. (44) Autologous HSCT has been successful in inducing short-lasting remissions but has not shown an increase in survival. (15)

2012 National Comprehensive Cancer Network (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 2.2012)
No Phase 3 trials on the use of HSCT for osteosarcoma were identified.

**Retinoblastoma**

Most studies of autologous HSCT for high-risk retinoblastoma have been very small series or case reports (45-50); however, the results have been promising in terms of prolonging DFS in these patients, particularly those without central nervous system (CNS) involvement (stage 4a).

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. (51) 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 postdiagnosis of metastatic disease, (2 in the CNS and 1 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 1 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 the intention of autologous HSCT. (18) 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 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 1 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.

**National Cancer Institute (NCI) Clinical Trial Database (PDQ®)**

A single-arm, Phase III 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 to historical controls. Expected enrollment is 60 patients. The estimated date of completion of the trial is February 2014.
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 (AHRQ). (52) The following conclusions were offered:

- **Neuroblastoma:** 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.
- **ESFT:** Low-strength evidence on overall survival suggests no benefit with single HSCT compared to conventional therapy for the treatment of high-risk ESFT. The body of evidence on overall survival with tandem HSCT compared to single HSCT for the treatment of high-risk ESFT and overall survival is insufficient to draw conclusions.
- **Rhabdomyosarcoma:** 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.
- **Wilms tumor:** 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.
- **Osteosarcoma** was not addressed.
- **Retinoblastoma:** Low-strength 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. The body of evidence on overall survival with single HSCT compared to conventional therapy for the treatment of extraocular retinoblastoma without CNS involvement was insufficient to draw conclusions. The body of evidence on overall survival with single HSCT compared to conventional therapy for the treatment of trilateral retinoblastoma without CNS involvement was insufficient to draw conclusions.

Comparative Effectiveness Review

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 considers autologous HSCT medically necessary for advanced stage retinoblastoma. One of the reviewers did not consider autologous HSCT for low- to intermediate-risk Ewing’s sarcoma investigational but did state that the results of the Euro-Ewing’s Phase III trial are awaited. Two reviewers agree with the policy statement that tandem autologous HSCT for pediatric solid tumors is investigational, two consider
it medically necessary for high-risk neuroblastoma, and the fifth reviewer agrees 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 OS.
- No studies directly comparing single autologous to tandem autologous HSCT for high-risk neuroblastoma have been published; however, case series on the use of tandem autologous for high-risk neuroblastoma have reported EFS rates superior to those reported with the use of single autologous HSCT (reported in randomized trials comparing single autologous HSCT to conventional chemotherapy).

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

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

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

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

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

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

**Retinoblastoma**
Small case series and case reports have shown prolonged DFS in some patients with stage 4 disease treated with HSCT, particularly those with stage 4a disease.

A recent study (47) 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**

Studies using allogeneic HSCT for pediatric solid tumors, either upfront or as salvage therapy after a failed autologous HSCT, are lacking. A large retrospective review of the use of allogeneic HSCT for high-risk neuroblastoma (24) failed to show a survival benefit over autologous HSCT and was associated with a higher risk of transplant-related mortality.

**VII. Important Reminder**

The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii’s Patients’ Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4), generally accepted standards of medical practice and review of medical literature and government approval status. HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA’s determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

**VIII. References**


