Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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Title: BMT - Hematopoietic Cell Transplantation for Solid Tumors of Childhood

Description/Background

Hematopoietic cell transplantation (HCT) is a procedure in which hematopoietic stem cells are infused to restore bone marrow function in cancer patients who receive bone-marrow-toxic doses of drugs, with or without whole body radiotherapy. Stem cells may be obtained from the transplant recipient (autologous HCT) or harvested from a donor (allogeneic HCT). Stem cells may be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates.

SOLID TUMORS OF CHILDHOOD

Solid tumors of childhood arise from mesodermal, ectodermal, and endodermal cells of origin.(1) 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. Pancreatic acinar cell carcinoma is a rare pediatric solid tumor.

General Treatment

The prognosis for pediatric solid tumors has improved over the last two decades, mostly due to the application of multiagent chemotherapy and improvements in local control therapy (including aggressive surgery and advancements in radiotherapy).(2) 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 hematopoietic cell transplantation (HCT), to improve event-free survival and overall survival.

Notes: Other solid tumors of childhood include germ cell tumors, which are considered in the policy, “Bone Marrow Transplant - Hematopoietic Cell Transplantation in the Treatment of Germ-Cell Tumors.” For solid tumors classified as embryonal tumors arising in the central nervous system (CNS), see policy, “Bone Marrow Transplant - Hematopoietic Cell Transplantation for CNS Tumors, Embryonal Tumors and Ependymoma.” and for CNS tumors derived from glial cells (i.e., astrocytoma, oligodendroglioma, or glioblastoma multiforme) see policy, “Bone Marrow Transplantation, Autologous, for Malignant Astrocytomas and Gliomas.”

Descriptions of pediatric-onset solid tumors addressed herein are as follows.

Peripheral Neuroblastoma

Neuroblastoma is the most common extracranial solid tumor of childhood,(1) with approximately 90% of cases presenting in children younger than five years of age.(3) These tumors originate where sympathetic nervous system tissue is present, within the adrenal medulla or paraspinal sympathetic ganglia, but have diverse clinical behavior depending on a variety of risk factors. This policy addresses peripheral neuroblastoma arising from the peripheral nervous system (i.e., neuroblastoma, ganglioneuroblastoma, ganglioneuroma).

Patients with neuroblastoma are stratified into prognostic risk groups (low, intermediate, high) that determine treatment plans. Risk variables include age at diagnosis, clinical stage of disease, tumor histology, and certain molecular characteristics, including the presence of the MYCN oncogene. Tumor histology is categorized as favorable or unfavorable, according to the degree of tumor differentiation, proportion of tumor stromal component, and index of cellular proliferation.(3) It is well-established that MYCN amplification is associated with rapid tumor progression and a poor prognosis,(4) even in the setting of other coexisting favorable factors. Loss of heterozygosity (LOH) at chromosome arms 1p and 11q occurs frequently in neuroblastoma.(5) Although 1p LOH is associated with MYCN amplification, 11q is usually found in tumors without this abnormality.(5) 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.(3) Although the use of these LOH markers in assigning treatment in patients is evolving, they may prove useful to stratify treatment.

In the early 1990s, a uniform clinical staging system based on surgical resectability and distant spread, the International Neuroblastoma Staging System, was adopted by pediatric cooperative groups (see Table 1).

Table 1. International Neuroblastoma Staging System

Stage	Description
1	Localized tumor with complete gross excision, with or without microscopic residual disease; lymph nodes negative for tumor
2A	Localized tumor with incomplete gross excision; lymph nodes negative for tumor
2B	Localized tumor with or without complete gross excision, with ipsilateral lymph nodes positive for tumor
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
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

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.

The International Neuroblastoma Risk Group (2009) proposed a revised staging system, which incorporated pretreatment imaging parameters instead of surgical findings (see Table 2).(6)

Table 2. International Neuroblastoma Risk Group Staging System (6)

Stage	Description
L1	Localized tumor not involving vital structures as defined by the list of Image-Defined Risk Factors and confined to one body compartment
L2	Locoregional tumor with presence of one or more Image-Defined Risk Factors
M	Distant metastatic disease (except stage MS)
MS	Metastatic disease in children younger than 18 months with metastases confined to skin, liver, and/or bone marrow

Treatment

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.(7) Most infants, even with disseminated disease, have favorable outcomes with chemotherapy and surgery.(7)

For intermediate-risk disease, moderately intensive multiagent chemotherapy is the mainstay of therapy.(8) Surgery is needed to obtain a diagnosis, and the extent of resection necessary to obtain an optimal outcome is not clearly established.(9) Patients at high risk have historically had very low (<15%) long-term OS. Current therapy for high-risk disease typically includes an aggressive multimodal approach with chemotherapy, surgical resection, and radiotherapy.(10)

Treatment of recurrent disease is determined by the risk group at diagnosis and the extent of disease and age of the patient at recurrence.

Ewing Sarcoma Family of Tumors

ESFT encompasses a group of tumors that share 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 diagnosis. Included in ESFT are “classic” Ewing sarcoma of bone, extraosseous Ewing, peripheral primitive neuroectodermal tumor, and Askin tumors (chest wall).

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

Treatment

Current therapy for Ewing sarcoma typically includes induction chemotherapy, followed by local control with surgery and/or radiation (dependent on tumor size and location), followed by adjuvant chemotherapy. Multiagent chemotherapy, surgery, and radiotherapy have improved PFS in patients with localized disease to 60% to 70%.(11) The presence of metastatic disease is the most unfavorable prognostic feature, and the outcome for patients presenting with metastatic disease is poor, with 20% to 30% PFS. Other adverse prognostic factors that may categorize a patient as having “high-risk” Ewing are tumor location (e.g., patients with pelvic primaries have worse outcomes), larger tumor size, and older age of the patient. However, “high-risk” Ewing has not always been consistently defined in the literature.

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.(12)

Treatment

Specific treatment is based on tumor location, resection, and node status, and may involve surgery, radiotherapy, and chemotherapy.(13) Five-year survival rates for RMS increased between 1975 and 2017 from 53% to 71% in children younger than 15 years and from 30% to 52% in 15- to 19-years of age.(12)

Approximately 15% of children present with metastatic disease, and despite the introduction of new drugs and intensified treatment, the 5-year survival is 20% to 30% for this “high-risk” group.(14,15) Similarly, post-relapse mortality is very high. The prognosis of metastatic disease is affected by tumor histology, age at diagnosis, the site of metastatic disease, and the number of metastatic sites.(12)

Wilms Tumor

Wilms tumor is the most common primary malignant renal tumor of childhood. In the United States, Wilms tumor is staged using the National Wilms Tumor Study (NWTS) system, which is based on surgical evaluation before chemotherapy (see Table 3).(16)

Table 3. National Wilms Tumor Study Staging

Stage	Description
I	(a) Tumor is limited to the kidney and completely excised; (b) The tumor was not ruptured before or during removal; (c) The vessels of the renal sinus are not involved beyond 2 mm (d) There is no residual tumor apparent beyond the margins of excision
II	(a) Tumor extends beyond the kidney but is completely excised (b) No residual tumor is apparent at or beyond the margins of excision (c) Tumor thrombus in vessels outside the kidney is stage II if the thrombus is removed en bloc with the tumor
III	Residual tumor confined to the abdomen: (a) Lymph nodes in the renal hilum, the periaortic chains, or beyond are found to contain tumor (b) Diffuse peritoneal contamination by the tumor (c) Implants are found on the peritoneal surfaces (d) Tumor extends beyond the surgical margins either microscopically or grossly (e) Tumor is not completely resectable because of local infiltration into vital structures
IV	Presence of hematogenous metastases or metastases to distant lymph nodes
V	Bilateral renal involvement at the time of initial diagnosis

Adapted from Metzger and Dome (2005).(16)

Treatment

In the United States, National Wilms Tumor Study and Children's Oncology Group protocols are based on primary resection for unilateral tumors, followed by escalating levels of chemotherapy and radiotherapy depending on tumor stage and other prognostic factors. Tumor histology, tumor stage, molecular and genetic markers (e.g., loss of heterozygosity at chromosome 16q), and age (>2 years) are all associated with increased risks of recurrence and death. Wilms tumors are highly sensitive to chemotherapy and radiation, and current cure rates exceed 85%.(17) Between 10%and 15% of patients with favorable histology and 50% of patients with anaplastic tumors, experience tumor progression or relapse.(17)

Similar risk-adapted strategies are being tested for the 15% of patients who experience relapse. Success rates after relapse range from 25% to 45%. For patients with adverse prognostic factors (histologically anaplastic tumors, relapse <6 to 12 months after nephrectomy, second or subsequent relapse, relapse within the radiation field, bone or brain metastases), EFS is less than 15%.(18)

Osteosarcoma

Osteosarcoma is a primary malignant bone tumor and the most common bone cancer in children and adolescents; it is characterized by formation of bone or osteoid by the tumor cells. Peak incidence occurs around puberty, most commonly in long bones such as the femur or humerus. Osteosarcomas are characterized by variants in the TP53 tumor suppressor gene.

The prognosis of osteosarcoma has greatly improved, with five-year survival rates increasing between 1975 and 2020 from 40% to 72% in children younger than 15 years and from 56% to 71% in 15- to 19-year-olds. Prognostic factors for patients with localized disease include site and size of the primary tumor, presence of metastases at the time of diagnosis, resection adequacy, and tumor response to neoadjuvant chemotherapy.

Treatment

For patients with recurrent osteosarcoma, the most important prognostic factor is surgical resectability. There is a five-year survival rate of 20% to 45% in patients who had complete resection of metastatic pulmonary tumors and a 20% survival rate for patients with metastatic tumors at other sites.(19)

Retinoblastoma

Retinoblastoma is the most common primary tumor of the eye in children. It may occur as a heritable (25%-30%) or nonheritable (70%-75%) tumor.(20) Cases may be unilateral or bilateral, with bilateral tumors almost always being the heritable type.

Treatment

Treatment options depend on the extent of disease. Retinoblastoma is usually confined to the eye, and with current therapy has a high cure rate. However, once disease spreads beyond the eye, survival rates drop significantly; five-year disease-free survival is reported to be less than 10% in those with extraocular disease, and stage 4B disease (i.e., disease metastatic to the CNS) has been lethal in virtually all cases reported.(21)

The strategy for nonmetastatic disease depends on the disease extent, but may include focal therapies (e.g., laser photocoagulation, cryotherapy, plaque radiotherapy), intravitreal chemotherapy, intra-arterial chemotherapy, systemic chemotherapy, enucleation, or a combination.(22) For metastatic disease, intensive multimodal therapy with high-dose chemotherapy, with or without radiotherapy, is standard care.

Pancreatic Acinar Cell Carcinoma

Malignant tumors of the exocrine pancreas occur mainly in adults. They commonly present in late stages of the disease and associated with poor prognosis. Most exocrine pancreatic tumors are ductal adenocarcinoma. Less frequent histology includes pancreatic acinar cell carcinoma. Population-based cancer databases and epidemiological methods indicated that individuals diagnosed with pancreatic Acinar Cell Carcinoma (ACC) have a median overall survival time of roughly 47 months for patients with localized disease and 14 months for patients with metastatic disease, with a 5-year survival rate ranging from 36.2% to 72.8% for resected cancers.(74)

Pediatric pancreatic tumors arise from embryonic precursor cells of ductal and acinar cells and are termed pancreatoblastoma. Patients with pancreatic tumors often present with weight loss, jaundice, and abdominal symptoms due to tumor mass effects.(75)

Treatment

The treatment chosen for this rare malignancy depends on the type and stage of the pancreatic tumor.(75) An aggressive approach with complete tumor resection whenever possible is the best primary treatment option. Primary systemic combination chemotherapy may be useful to reduce the tumor mass and allow for subsequent secondary tumor resection. As a result of shared genetic alterations, pancreatic acinar cell carcinoma is chemo-sensitive to agents with activity against pancreatic adenocarcinoma and colorectal carcinoma. FOLFIRINOX regimen has been shown to be a highly effective chemotherapy regimen for this cancer. Patients with advanced disease may benefit from multimodality treatment including radiation therapy and high dose chemotherapy followed by autologous stem cell transplant.

Hematopoietic Cell Transplantation

HCT is a procedure in which hematopoietic stem cells are infused to restore bone marrow function in cancer patients who receive bone-marrow-toxic doses of drugs, with or without whole body radiotherapy. Hematopoietic stem cells may be obtained from the transplant recipient (autologous HCT) or a donor (allogeneic HCT). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates. Although cord blood is an allogeneic source, the stem cells in it are antigenically “naive” and thus are associated with a lower incidence of rejection or graft-versus-host disease.

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

Regulatory Status

The U.S. Food and Drug Administration regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research, under Code of Federal Regulation (CFR) title 21, parts 1270 and 1271. Hematopoietic stem cells are included in these regulations.

Medical Policy Statement

The safety and effectiveness of *autologous and tandem* hematopoietic cell transplantation for solid tumors of childhood has been established. It may be considered a useful therapeutic option when criteria are met.

The safety and effectiveness of *autologous* hematopoietic cell transplant is established as a consolidation therapy for children with pancreatic acinar cell carcinoma. It may be considered a useful therapeutic option when criteria are met.

Inclusionary and Exclusionary Guidelines

Inclusions:

- Autologous hematopoietic cell transplantation in the following situations:
  - Initial treatment of high-risk peripheral neuroblastoma,
  - Recurrent or refractory peripheral neuroblastoma,
  - Initial treatment of high-risk Ewing sarcoma,
  - Recurrent or refractory Ewing sarcoma, and
  - Metastatic retinoblastoma
- Tandem autologous hematopoietic cell transplantation for high-risk peripheral neuroblastoma.
- Autologous hematopoietic cell transplantation as a consolidation therapy for children with pancreatic acinar cell carcinoma when **ALL** the following criteria are met:
  - Tumor is not amenable to complete surgical resection.
  - Tumor has been shown to be sensitive to chemotherapy.
  - Residual tumor is widespread and not amenable to radiation therapy with tolerable toxicity.
  - Patient is not eligible to be enrolled in a clinical trial or there is no available clinical trial.

Exclusions:

- Autologous hematopoietic cell transplantation as *initial* treatment of low- or intermediate-risk neuroblastoma, *initial* treatment of low- or intermediate-risk Ewing sarcoma, and for *other* solid tumors of childhood including, but not limited, to the following:
  - Rhabdomyosarcoma
  - Wilms tumor
  - Osteosarcoma
  - Retinoblastoma without metastasis
- Tandem autologous hematopoietic cell transplantation for the treatment of all other types of pediatric solid tumors except high-risk peripheral neuroblastoma, as noted above.

- *Allogeneic* (myeloablative or nonmyeloablative) tandem or single hematopoietic cell transplantation for treatment of pediatric solid tumors.
- Salvage allogeneic hematopoietic cell transplantation for pediatric solid tumors that relapse after autologous transplant or fail to respond.
- All other indications not specified under the inclusions.

*BMT – Hematopoietic Cell Transplantation for Germ-Cell Tumors is a separate policy

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CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

38206	38207	38208	38210	38211	38212
38213	38214	38215	38232	38241	38243
S2150					

Other codes (investigational, not medically necessary, etc.):

Italicized/bolded codes can be used for both auto and allogeneic transplants. If used for allogeneic transplant they would be considered experimental/investigational for a policy that covers autologous transplants only.*

38204	38205	***38207****	38209	***38210****	***38211****
38212*	***38213****	***38214****	***38215****	38230	38240
38242	81267	81268	81370	81371	81372
81373	81374	81375	81376	81377	81378
81379	81380	81381	81382	81383	86812
86813	86816	86817	86821	S2140	S2142
S2150*					

Potential contraindications for transplant

Note: Final patient eligibility for transplant is subject to the judgment and discretion of the requesting transplant center.

The selection process for approved tissue transplants is designed to obtain the best result for each patient. Therefore, relative contraindications to HCT may include, but are not limited to:

- Poor cardiac function: Ejection fraction should be greater than 45% with no overt symptoms of congestive heart failure.
- Poor pulmonary function: Pulmonary function tests must be greater than or equal to 50% of predicted value.
- Poor renal function: There should be no history of severe renal disease.
- Poor liver function: There should be no history of severe chronic liver disease.
- Presence of HIV or an active form of hepatitis B, hepatitis C or human T-cell lymphotropic virus (HTLV-1).

Rationale

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, two domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

PERIPHERAL NEUROBLASTOMA

Single Autologous Hematopoietic Cell Transplantation

Clinical Context and Therapy Purpose

The purpose of single autologous hematopoietic cell transplantation (HCT) is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with high-risk or relapsed peripheral neuroblastoma.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest are individuals with high-risk or relapsed peripheral neuroblastoma.

Interventions

The therapy being considered is single autologous hematopoietic cell transplantation.

Comparators

Comparators of interest include chemotherapy, targeted therapy, surgery, and radiotherapy.

Outcomes

The general outcomes of interest are overall survival, disease-specific survival, treatment-related mortality, and treatment-related morbidity.

Follow-up includes the immediate and 12-month post- transplant period to monitor for engraftment and other relevant outcomes. Follow-up will continue to be life-long depending on the success of single autologous hematopoietic cell transplantation.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess longer term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Systematic Reviews

A 2013 Cochrane review evaluated high-dose chemotherapy (HDC) and autologous hematopoietic cell transplantation (HCT) for high-risk neuroblastomas.(23) Reviewers identified three randomized controlled trials (RCTs) that included 739 children with high-risk neuroblastoma (Matthay et al [1999],(24) Berthold et al [2005],(25) Pritchard et al [2005],(26) detailed in the Randomized Controlled Trial section below). The review was updated in 2015 with no new studies identified, although a manuscript reporting additional follow-up data for one of these RCTs was noted.(27) The primary objective was to compare the efficacy of myeloablative therapy with conventional therapy. Selected studies all used the age of 1 year as the cutoff point for pretreatment risk stratification. A statistically significant difference in event-free survival (EFS) was observed in favor of myeloablative therapy over conventional chemotherapy or no further treatment (3 studies, 739 patients; hazard ratio [HR], 0.78; 95% confidence interval [CI], 0.67 to 0.90). A statistically significant difference in overall survival (OS) was reported 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). When additional follow-up data were included in 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). Meta-analysis of secondary malignant disease and treatment-related death did not show any statistically significant differences between 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 differences between treatment groups were identified. No information on quality of life was reported.

Randomized Controlled Trials

Three well-designed, randomized trials have assessed autologous HCT in the treatment of high-risk neuroblastoma. Matthay et al (1999) randomized 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 randomized to intensive nonmyeloablative chemotherapy; both groups underwent a second randomization to receive subsequent 13-cis-retinoic acid (cis-RA) or no further therapy.(24) The three-year EFS rate among patients assigned to transplantation was 43%

versus 27% among those assigned to continuation chemotherapy (p=.027). However, OS rates for both groups did not differ significantly, with 3-year estimates of 43% or 44% for those assigned to transplant and to continued chemotherapy, respectively (p=.87).

Long-term results from this trial were reported in 2009 after a median follow-up of 7.7 years (range, 130 days to 12.8 years).(28) Five-year EFS for patients who underwent autologous transplant was 30% versus 19% for those who underwent nonmyeloablative chemotherapy (p=.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% for autologous transplant/no cis-RS, and, for nonmyeloablative chemotherapy, 38% and 36% with and without cis-RA. Authors concluded that myeloablative chemotherapy and autologous HCT resulted in a significantly better five-year EFS and OS rates.

Berthold et al (2005) randomized 295 patients with high-risk neuroblastoma to myeloablative therapy (melphalan, etoposide, carboplatin) with autologous HCT or to oral maintenance chemotherapy with cyclophosphamide.(25) 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% 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=.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 myeloablative therapy died from acute complications related to the therapy.

Pritchard et al (2005) reported the results of a randomized, multicenter trial that involved 167 children with stage III or IV neuroblastoma who were treated with standard induction chemotherapy who then underwent surgical resection of their tumor.(26) 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 HCT 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=.01).

Observational Studies

The use of HCT in patients with high-risk neuroblastoma has been supported in clinical practice. For example, in 2016, Proust-Houdemont et al reported on a 30-year single-center series including 215 patients with stage IV, high-risk neuroblastoma treated with HDC (busulfan) with HCT.(29) In this cohort, five-year EFS and OS rates were 35.1% and 40%, respectively, and improved from baseline to the end of reporting period. In addition, Giardino et al (2020) reported results of a retrospective series of 28 patients with relapsed or refractory neuroblastoma who received metaiodobenzylguanidine and high-dose busulfan and melphalan with autologous HCT.(30) After a median follow-up of 15.9 years, OS at 3 and 5 years was 53% and 41%, respectively, and rates of cumulative risk of progression/relapse at 3 and 5 years were 64% and 73%, respectively.

Tandem Autologous HCT

Clinical Context and Therapy Purpose
The purpose of tandem autologous hematopoietic cell transplantation is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with high-risk or relapsed peripheral neuroblastoma.

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest are individuals with high-risk or relapsed peripheral neuroblastoma.

Interventions
The therapy being considered is tandem autologous hematopoietic cell transplantation.

Comparators
Comparators of interest include chemotherapy, single autologous hematopoietic cell transplantation, targeted therapy, surgery, and radiotherapy.

Outcomes
The general outcomes of interest are overall survival, disease-specific survival, treatment-related mortality, and treatment-related morbidity.

Follow-up includes the immediate and 12-month posttransplant period to monitor for engraftment and other relevant outcomes. Follow-up at 24-, 38-, 56-, and 108- months is of interest for tandem autologous HCT to monitor relevant outcomes.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:
- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess longer term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Randomized Controlled Trial
Park et al (2019) conducted an RCT to compare the effects of single versus tandem autologous HCT inpatients with high-risk neuroblastoma.(69) A total of 652 eligible patients were enrolled, of which 355 patients (median age at diagnosis, 36.1 months) were randomized to tandem transplant with thiotepa/cyclophosphamide followed by dose-reduced carboplatin/etoposide/melphalan (n=176) or single transplant with carboplatin/etoposide/melphalan (n=179). Three-year EFS from the time of randomization was 61.6% (95% CI, 54.3% to 68.9%) in the tandem transplant group versus 48.4% (95% CI, 41.0% to 55.7%) in the single transplant group (1-sided log-rank p=.006). The median duration

of follow-up after randomization for181 patients without an event (relapse, progression, secondary malignancy, or death from any cause) was 5.6years (range, 0.6 to 8.9). The most commonly reported grade 3 or higher toxicities following tandem versus single transplant were mucosal (11.7% vs. 15.4%) and infectious (17.9% vs. 18.3%).

Nonrandomized Comparative Studies

Yan et al (2022) retrospectively assessed the efficacy of autologous HCT in 90 patients with high-risk neuroblastoma, and also compared the prognoses of single versus tandem transplant in these patients.(70) The median patient age at diagnosis was 42 months (range, 11 to 97) and the median follow-up time was 29months (range, 5 to 78). Three-year EFS and OS rates for the HCT group (n=59) compared with the non-HCT group (n=31) were 65.5% versus 41.3% (p=.023) and 77.1% versus 57.9% (p=.03), respectively. There were no statistically significant differences between the single transplant group (n=43) and the tandem transplant group (n=16) in the baseline characteristics and treatment response (p>.05). In the tandem versus single transplant group, the 3-year EFS was 51.9% compared with 73.8% (p=.44), respectively, and the 3-year OS was 71.4% compared with 83.4% (p=.73), respectively.

Sung et al (2010) reported on a retrospective analysis of the efficacy of single versus tandem autologous HCT in patients older than one year of age newly diagnosed with stage IV neuroblastoma from 2000 to 2005 who were enrolled in the Korean Society of Pediatric Hematology-Oncology registry.(31) Patients were intended to receive a single (n=70) or tandem (n=71) autologous HCT at diagnosis; 57 and 59 patients underwent single and tandem transplantation as scheduled, respectively. Between groups, patient characteristics were similar with the exception of a higher proportion in the tandem group had bone metastases. Median follow-up was 56 months (range, 24-88 months) from diagnosis. Transplant-related mortality (TRM) occurred in nine patients in the single transplant group and in eight in the tandem group (two after the first transplant and six after the second). The ITT survival rate for five-year EFS for single versus tandem was 31.3% and 51.2%, respectively (p=0.03). When the survival analysis only included patients who proceeded to transplant, the probability of relapse-free survival after the first transplant was higher in the tandem group (59.1%±13.5%) than the single group (41.6%±14.5%; p=.099). The difference was statistically significant when the analysis focused on patients who did not achieve a CR before the first transplant (55.7% vs 0%, p=.012). The authors concluded that tandem HCT for high-risk neuroblastoma is superior to single HCT regarding survival, particularly in patients without CR before HCT.

Ladenstein et al (2008) reported on more than 4000 transplants for primary (89%) and relapsed (11%) neuroblastoma over 28 years in 27 European countries in the European Group for Blood and Marrow Transplantation registry.(32) Procedures included single autologous (n=2895), tandem autologous (n=455), and allogeneic HCT (n=71). Median age at the time of transplantation was 3.9 years (range 0.3-62 years), with 77 patients older than age 18 years. Median follow-up time from HCT was 9 years. TRM decreased over time in registry patients who only received autologous transplants. Five-year OS rates were 37% for the autologous groups (single and tandem) and 25% for the allogeneic group. Five-year OS for single versus tandem autologous HCT was 38% versus 33%, respectively (p=.105).

Single-Arm Studies

George et al (2006) reported on a 4-institution, single-arm clinical trial to evaluate tandem autologous HCT in pediatric patients with high-risk neuroblastoma (n=82) enrolled between 1994 and 2002.(33) 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. Kletzel et al (2002) reported on a single-center pilot study evaluating the outcomes for 25 consecutive newly diagnosed high-risk neuroblastoma patients and 1 with recurrent disease treated with triple-tandem autologous HCT.(34) After stem cell rescue, patients were treated with radiotherapy 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 three cycles of high-dose therapy and stem cell rescue, two patients completed two cycles, and three patients completed one cycle. One toxicity-related death occurred, and one patient died from complications of graft failure. Median follow-up was 38 months, and the one-year EFS and OS rates were 57% and 79%, respectively.

Grupp et al (2000) reported outcomes for a Phase II trial involving 55 children with high-risk neuroblastoma who underwent tandem autologous HCT.(35) Five patients completed the first HCT course but not the second. There were four toxicity-related deaths. With a median follow-up of 24 months from diagnosis, three-year EFS was 59%.

Case Series

In a retrospective analysis of prospectively collected data, Pasqualini et al (2016) reported on a series of 26 patients with very high risk neuroblastoma treated with tandem autologous HCT from 2004 to 2011 at a single center.(36) Criteria for “very high risk” included stage IV neuroblastoma at diagnosis or relapse, age over 1 year at diagnosis, less than a PR of metastases, and more than 3 metaiodobenzylguanidine spots after 2 lines of conventional chemotherapy in patients under 10 years old or no CR of metastases after 1 line of conventional chemotherapy in patients over 10 years old. Median age was 4.4 years (range, 1-15.9). Of the 26 patients, 22 were stage IV at diagnosis; 4 patients had a stage III tumor at diagnosis and a metastatic relapse. Three-year EFS and OS rates after diagnosis were 37.3% (95% CI, 21.3% to 56.7%) and 69.0% (95% CI, 49.7% to 83.4%), respectively.

Kim et al (2007) retrospectively analyzed 36 patients with high-risk (stage III or IV) neuroblastoma who underwent a single autologous HCT (n=27) or a tandem autologous HCT (n=9) at a children’s hospital in Seoul, Korea, between 1996 and 2004.(37) Disease-free survival (DFS) of patients who underwent double HCT was similar to that of those who underwent a single autologous HCT (p=.5).

Marcus et al (2003) reported on outcomes for 52 children with stage IV or high-risk stage III neuroblastoma treated with induction chemotherapy, surgical resection of the tumor when feasible, local radiotherapy, and consolidation with tandem autologous HCT.(38) 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 three-year EFS was 63%, with a median follow-up of 29.5 months.

Von Allmen et al (2005) reported on a retrospective series from the same center as Marcus et al, with some overlap in patients.(39) The updated series included 76 patients with previously untreated high-risk stage III or IV neuroblastoma treated with aggressive surgical resection with or without local radiotherapy followed by tandem autologous HDC and stem cell rescue. Overall EFS for the series was 56%.

Section Summary: Single Autologous and Tandem Hematopoietic Cell Transplantation for Peripheral Neuroblastoma
Randomized trials comparing single autologous HCT with conventional chemotherapy have reported EFS rates for the patients who underwent HCT ranging from 43% to 47% at three years and 30% at five years. Case series on the use of tandem autologous for high-risk neuroblastoma have reported three-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 and tandem autologous HCT of 31% and 51%, respectively (p=.03).

EWING SARCOMA FAMILY OF TUMORS

Single Autologous HCT

Clinical Context and Therapy Purpose
The purpose of single autologous hematopoietic cell transplantation is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with high-risk Ewing sarcoma/Ewing sarcoma family of tumors (ESFT).

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest are individuals with high-risk Ewing sarcoma/ESFT.

Interventions
The therapy being considered is single autologous hematopoietic cell transplantation.

Comparators
Comparators of interest include chemotherapy, surgery, and radiotherapy.

Outcomes
The general outcomes of interest are overall survival, disease-specific survival, treatment-related mortality, and treatment-related morbidity.

Follow-up includes the immediate and 12-month post- transplant period to monitor for engraftment and other relevant outcomes. Follow-up will continue to be life-long depending on the success of single autologous hematopoietic cell transplantation.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:
- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with preference for prospective studies.

- To assess longer term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Randomized Controlled Trials

Ladenstein et al (2010) reported on patients with primary disseminated multifocal Ewing sarcoma (PDMES) who were included in the Euro-EWING 99 trial.(40) From 1999 to 2005, 281 patients with PDMES were enrolled in the Euro-EWING 99 R3 study; the Euro-EWING 99 committee stopped 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, autologous HCT, 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 HCT. One patient died during induction therapy from sepsis. HDC TRM consisted of three patients dying within the first 100 days after high-dose therapy - 1 from acute respiratory distress syndrome and two from severe veno-occlusive disease and septicemia; late deaths included three patients who died 1 to 1.5 years after high-dose therapy. After a median follow-up of 3.8 years, the estimated three-year EFS and OS rates for all 281 patients were 27% and 34%, respectively. The international Ewing 2008 trial succeeded the Euro-EWING 99 study in some countries.(41) The Ewing 2008 trial contained an R2Pulm arm for patients with isolated pulmonary metastases (Tables 4 and 5). The primary objective in R2Pulm was to evaluate whether consolidation with HDC plus autologous HCT (n=144) improved EFS compared with consolidation with standard chemotherapy plus whole lung irradiation (n=143). Dirksen et al (2019) reported on the results of this trial, which found no statistically significant difference in EFS between treatment groups. Nine patients died in the HDC plus autologous HCT group (6 of these deaths were treatment-related and 3 were either due to secondary malignancy, another cause, or unknown cause), and 2 died after standard chemotherapy plus whole lung irradiation (1 death was treatment-related and 1 was due to another cause). Severe acute toxicities were also more prevalent in the group who received HDC plus autologous HCT.

Table 4. Summary of Key RCT Characteristics

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Dirksen (2019); R2Pulm[41]	US, EU	144	December 2015 to February 2020	N=267 patients <50 years of age.	n=144; HDC plus autologous HCT	n=143; 7 courses of standard chemotherapy plus whole lung irradiation

HCT: hematopoietic cell transplantation; HDC: high-dose chemotherapy; RCT: randomized controlled trial.

Table 5. Summary of Key RCT Results

Study; Trial	EFS[1] (3 years)	EFS[1] (8 years)	Mortality
Dirksen (2019); R2Pulm[41]			
N	287	287	287
HDC plus autologous HCT	56.6%	52.9%	9/144
Standard chemotherapy plus whole lung irradiation	50.6%	43.1%	2/143
Adjusted HR (95% CI)		0.81 (0.58 to 1.12)	

CI: confidence interval; EFS: event-free survival; HCT: hematopoietic cell transplantation; HDC: high-dose chemotherapy; HR: hazard ratio; RCT: randomized controlled trial.
[1] Intention-to-treat analysis

Tables 6 and 7 summarize study relevance, conduct, and design limitations.

Table 6. Study Relevance Limitations

Study; Trial	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
Dirksen (2019); R2Pulm[41]	4: Only included patients with Ewing sarcoma and lung metastases				

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4, Enrolled populations do not reflect relevant diversity; 5. Other.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5: Other.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

Table 7. Study Design and Conduct Limitations

Study; Trial	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Dirksen (2019); R2Pulm[41]		1,2: Open-label study			4. Recruitment was stopped before the estimated sample size target was reached due of low accrual	

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias; 5. Other.
[b] Blinding key: 1. Participants or study staff not blinded; 2. Outcome assessors not blinded; 3. Outcome assessed by treating physician; 4. Other.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication; 4. Other.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials); 7. Other.
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference; 4. Other.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated; 5. Other.

Single-Arm Studies

Subsequently, Meyers et al (2001) reported on a prospective study with autologous HCT in 32 patients with newly diagnosed Ewing sarcoma metastatic to bone and/or bone marrow. Induction therapy consisted of five cycles of cyclophosphamide-doxorubicin-vincristine, alternating with ifosfamide-etoposide.(42) Twenty-three patients proceeded to the consolidation phase with melphalan, etoposide, total body irradiation (TBI), and autologous HCT (of the nine patients who did not proceed, two were secondary to toxicity and four 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 HCT 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 (2008) reported the results of 116 patients with Ewing sarcoma who underwent autologous HCT (80 as first-line therapy and 36 for recurrent disease) between 1989 and 2000.(43) Five-year rates of progression-free survival (PFS) in patients who received HCT 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, the 5-year probability of PFS was 14% (95% CI, 3% to 30%). The authors concluded that PFS rates after autologous HCT were comparable with rates seen in patients with similar disease characteristics treated with conventional therapy.

Tandem Autologous HCT

Clinical Context and Therapy Purpose
The purpose of tandem autologous hematopoietic cell transplantation is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with high-risk Ewing sarcoma.

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest are individuals with high-risk Ewing sarcoma.

Interventions
The therapy being considered is tandem autologous hematopoietic cell transplantation.

Comparators
Comparators of interest include chemotherapy, single autologous hematopoietic cell transplantation, surgery, and radiotherapy.

Outcomes
The general outcomes of interest are overall survival, disease-specific survival, treatment-related mortality, and treatment-related morbidity.

Follow-up includes the immediate and 12-month post- transplant period to monitor for engraftment and other relevant outcomes. Follow-up will continue to be life-long depending on the success of single autologous hematopoietic cell transplantation.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess longer term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Case Series

Loschi et al (2015) reported on a series of 18 patients with PDMES under age 25 years treated with tandem HCT at a single institution from 2002 to 2009.(44) Of the 18 patients with PDMES planned for tandem HCT, 15 (83%) received the first HCT, and 13 (72%) received the full-tandem HCT program, due to progressive disease before stem cell harvest could be obtained. Eleven patients had no disease progression by the end of the HCT program, but 9 of the 11 had relapsed, at a median delay of 6.2 months (range, 2.5-14.1 months). Median EFS and OS rates were 13.5 and 17.3 months, respectively.

Section Summary: Single Autologous and Tandem HCT for Ewing Sarcoma Family of Tumors

Studies of HCT in patients with ESFT are characterized by small numbers of patients, and comparisons across studies were difficult for several reasons. Within each report, patients could have received a variety of chemotherapeutic regimens, and many 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 allogeneic HCT. The risk-adjusted system used in Euro-EWING 99 may allow best selection of patients appropriate for treatment. The international Ewing 2008 trial succeeded the Euro-EWING 99 study in some countries. The Ewing 2008 trial contained an R2Pulm arm for patients with Ewing sarcoma and pulmonary and/or pleural metastases. The R2PulmRCT compared consolidation with HDC plus autologous HCT to standard chemotherapy plus whole lung irradiation and did not find a significant EFS advantage with either treatment.

RHABDOMYOSARCOMA

Clinical Context and Therapy Purpose

The purpose of single autologous hematopoietic cell transplantation is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with rhabdomyosarcoma (RMS).

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest are individuals with rhabdomyosarcoma.

Interventions

The therapy being considered is single autologous hematopoietic cell transplantation.

Comparators
Comparators of interest include chemotherapy, surgery, and radiotherapy.

Outcomes
The general outcomes of interest are overall survival, disease-specific survival, treatment-related mortality, and treatment-related morbidity.
Follow-up includes the immediate and 12-month post- transplant period to monitor for engraftment and other relevant outcomes. Follow-up will continue to be life-long depending on the success of single autologous hematopoietic cell transplantation.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess longer term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Systematic Review
Weigel et al (2001) reviewed and summarized published evidence on the role of autologous HCT in the treatment of metastatic or recurrent RMS from 22 studies (total N=389 patients).(46) Based on all of the evidence analyzing EFS and OS rates, they concluded that there was no significant advantage to undergoing this type of treatment.

Nonrandomized Comparative Studies
McDowell et al (2010) reported the results of the International Society of Paediatric Oncology study MMT-98, pediatric patients from 48 centers with metastatic rhabdomyosarcoma (RMS) entered into the study from 1998 to 2005.(47) A total of 146 patients enrolled (age range, 6 months to 18 years). Patients were risk-stratified and treated accordingly. One hundred one patients were stratified as poor risk (poor-risk group [PRG]) defined as being older than 10 years of age or had bone marrow or bone metastases. Planned therapy for the PRG was induction therapy, sequential HDC, peripheral blood autologous HCT, and maintenance therapy. Seventy-nine (78.2%) of the 101 PRG patients 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 rates for the PRG group were 16.5% and 14.9%, respectively, with 3- and 5-year OS rates of 23.7% and 17.9%, respectively (HR=2.46; 95% CI, 1.51 to 4.03; p<.001).

Klingebiel et al (2008) 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).(48) 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 (standard deviation [SD], 0.14) for the patients who received OMT (n=51) and 0.27 (SD, 0.13)

for the transplant group (n=45; p=.03). For the patients with RMS, 5-year OS probability was 0.52 (SD, 0.16) with OMT and 0.15 (SD, 0.12) with transplant (p=.001). The authors concluded that transplant failed to improve prognosis in metastatic soft tissue sarcoma but that OMT could be a promising alternative.

Carli et al (1999) 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 HCT and compared them to 44 patients who were in remission after induction therapy who subsequently received conventional chemotherapy.(49) No significant differences existed between the 2 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 HCT group and 19.2% and 27.7%, respectively, for the group that received standard consolidation chemotherapy. Differences were not statistically significant for EFS (p=.3) or OS (p=.2). Median time to relapse after chemotherapy was 168 days for the autologous HCT group and 104 days for the standard chemotherapy group (p=.05). Although the use of autologous HCT delayed time to relapse, there was no clear survival benefit compared with conventional chemotherapy.

Section Summary: Rhabdomyosarcoma
Autologous HCT has been evaluated in a limited number of patients with high-risk RMS (stage IV 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.

WILMS TUMOR

Clinical Context and Therapy Purpose
The purpose of single autologous hematopoietic cell transplantation is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with Wilms tumor.

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest are individuals with Wilms tumor.

Interventions
The therapy being considered is single autologous hematopoietic cell transplantation.

Comparators
Comparators of interest include chemotherapy, surgery, and radiotherapy.

Outcomes
The general outcomes of interest are overall survival, disease-specific survival, treatment-related mortality, and treatment-related morbidity.

Follow-up includes the immediate and 12-month post- transplant period to monitor for engraftment and other relevant outcomes. Follow-up will continue to be life-long depending on the success of single autologous hematopoietic cell transplantation.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess longer term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Meta-analysis
A 2010 individual patient data meta-analysis reported on the efficacy of autologous HCT in recurrent Wilms tumor for studies published between 1984 and 2008 that reported survival data.(50) Six studies were included (total N=100 patient).(17,51-55) 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. The 4-year OS rate among the 100 patients was 54.1% (95% CI, 42.8%-64.1%), and the four-year EFS rate (based on 79 patients) was 50.0% (95% CI, 37.9%-60.9%). In multivariate analysis, site of relapse and histology were important predictors for survival; patients who did not have a lung-only relapse were at approximately 3 times higher risk of death or recurrence (HR=3.5) than patients who relapsed in the lungs only (HR=2.4), and the patients with unfavorable histology had approximately twice the risk of death compared with those with favorable histology. For all six studies, reviewers compared the survival rates for patients treated with autologous HCT to patients treated with conventional chemotherapy. In general, the chemotherapy-treated patients had similar or improved 4-year survival rates compared with the HCT group; however, there was a suggestion that patients with lung-only stage III and IV relapse could benefit from autologous HCT; they had a 21.7% survival advantage over chemotherapy (however, the confidence interval ranges were very wide): four-year OS rates for the stage III and IV patients with lung only relapse treated with HCT were 74.5% (95% CI, 51.7% to 87.7%) and 52.8% (95% CI, 29.7% to 71.5%) for chemotherapy.

Retrospective Studies
Delafoy et al (2021) published a retrospective analysis describing the outcomes of 54 patients with Wilms tumor in France who received HDC plus autologous HCT as first-line treatment or following disease recurrence between 2000 and 2016.(56) The 5-year estimates for EFS and OS in patients receiving first-line treatment were 54% (95% CI, 32% to 76%) and 62% (95% CI, 31% to 82%), respectively. The 5-year estimates for EFS and OS in patients receiving treatment following disease recurrence were 57% (95% CI, 39% to 71%) and 69% (95% CI, 52% to 81%), respectively. Treatment-related death occurred in 3 patients.

Malogolowkin et al (2017) published a retrospective analysis describing the outcomes of 253 patients with relapsed Wilms tumor (WT) who received high-dose chemotherapy (HDT) followed by autologous hematopoietic stem cell transplant (HCT) between 1990 and 2013 that were reported to Center for International Blood and Marrow Transplant Research.(57) The five-year estimates for event-free survival (EFS) and overall survival (OS) were 36% (95% confidence interval (CI); 29–43%) and 45% (95 CI; 38–51%), respectively. Relapse of primary

disease was the cause of death in 81% of the population. EFS, OS, relapse, and transplant-related mortality showed no significant differences when broken down by disease status at transplant, time from diagnosis to transplant, year of transplant, or conditioning regimen. The data suggest that high-dose chemotherapy (HDT) followed by autologous hematopoietic stem cell transplant (HCT) for relapsed WT is well tolerated and outcomes are similar to those reported in the literature. The greatest limitation of the study is its retrospective, registry-based analyses and that the data originate from basic forms, and thus, did not include histology, site of metastases, stage of disease, genetic syndrome, tumor spillage, and radiation.

Section Summary: Wilms Tumor
The evidence on the use of autologous HCT for high-risk Wilms tumor consists of retrospective studies and an individual patient data meta-analysis. For some subgroups—particularly patients with lung-only stage III and IV relapse—some analyses suggested that HCT could be associated with a survival benefit.

OSTEOSARCOMA

Clinical Context and Therapy Purpose
The purpose of single autologous hematopoietic cell transplantation is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with osteosarcoma.

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest are individuals with osteosarcoma.

Interventions
The therapy being considered is single autologous hematopoietic cell transplantation.

Comparators
Comparators of interest include chemotherapy, surgery, and radiotherapy.

Outcomes
The general outcomes of interest are overall survival, disease-specific survival, treatment-related mortality, and treatment-related morbidity.

Follow-up includes the immediate and 12-month post- transplant period to monitor for engraftment and other relevant outcomes. Follow-up will continue to be life-long depending on the success of single autologous hematopoietic cell transplantation.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:
- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess longer term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Prospective and Retrospective Studies

Hong et al (2022) retrospectively evaluated 113 patients with nonmetastatic osteosarcoma.(71) The median patient age at diagnosis was 12.6 years (range, 5.0 to 20.3). All patients received neoadjuvant chemotherapy, which was continued when the postoperative necrosis rate was more than 90% (good response), whereas most cases with less than 90% (poor response) were changed to chemotherapy (either adjuvant conventional chemotherapy, or HDC [melphalan/etoposide/carboplatin] with autologous HCT). In patients with poor response (n=44), the 5-year EFS rates of the HDC plus HCT group (n=24) compared with conventional chemotherapy (n=20) were 78.6% (95% CI, 61.9% to 95.3%) and 53.6% (95% CI, 31.1% to 76.1%; p=.065),respectively, and the 5-year OS rates were 100% and 76.9% (95% CI, 56.7% to 97.1%; p=.024), respectively. A limitation of the study is that it was a retrospective analysis that included patients who received heterogeneous chemotherapies. The study authors also acknowledged that previous studies, including the Venkatramani et al (2016) prospective study summarized below, (58) did not find improved outcomes with HDC with HCT. However, this study is different from previous studies in the regimen used (melphalan/etoposide/carboplatin) and in analyzing only patients with nonmetastatic osteosarcoma who showed low-degree necrosis following neoadjuvant chemotherapy.

Venkatramani et al (2016) reported on outcomes from a protocol in which patients with newly diagnosed, biopsy-proven high-grade osteosarcoma with less than 90% tumor necrosis after preoperative chemotherapy were treated with three courses of HDC with autologous HCT.(58) The study enrolled 52 patients with localized osteosarcoma, most commonly of the femur (52%) from 1999 to 2006 who underwent definitive surgery; 6 patients withdrew prior to surgery, and six after surgery. Under the study's initial protocol, those with less than 90% tumor necrosis were intended for HCT following HDC with melphalan and cyclophosphamide, and those with good tumor response were allocated to standard chemotherapy. However, after the first 18 patients received HCT, interim analysis showed a two-year EFS rate of 41%, which was less than the objective of 75% EFS compared with historical data of 55% by treating 48 patients with nonmetastatic disease who showed less than 90% necrosis following preoperative chemotherapy. Subsequently, all patients were enrolled to the standard therapy arm. Forty patients were evaluable after a median follow-up of 39 months. The five-year EFS and OS rates were 62% (95% CI, 36% to 80%) and 74% (95% CI, 44% to 90%), respectively, for patients treated on the standard chemotherapy arm. The 5-year EFS and OS rates were 28% (95% CI, 10% to 49%) and 48% (95% CI, 23% to 69%), respectively, for patients treated on the HCT arm.

Case Series

Hong et al (2015) reported on a retrospective series of 19 patients with high-risk osteosarcoma treated with autologous HCT at a single center from 2006 to 2013.(57) Median age at diagnosis was 11.8 years (range, 5.4-15.7 years). The indications for HCT were tumor necrosis less than 90% (n=8), initial metastasis (n=2), relapse (n=2), or a combination of tumor necrosis less than 90%, initial metastasis, and/or progression (n=6). At a mean follow-up of 31 months (range, 1-91 months), OS was 78.3% and EFS was 67.4%.

Additional small case series and case reports have examined the use of autologous HCT in osteosarcoma.(60,61) Autologous HCT has been successful in inducing short-lasting remissions but has not shown an increase in survival.

Section Summary: Osteosarcoma
The evidence on the use of autologous HCT for treatment of osteosarcoma is limited to case series and a prospective single-arm study. An interim analysis of the single-arm study showed that patients receiving autologous HCT were experiencing lower event-free survival rates than historical controls, resulting in all patients enrolling in the standard of care chemotherapy arm for the remainder of the study.

RETINOBLASTOMA

Localized Retinoblastoma

Clinical Context and Therapy Purpose
The purpose of single autologous hematopoietic cell transplantation is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with localized retinoblastoma.

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest are individuals with localized retinoblastoma.

Interventions
The therapy being considered is single autologous hematopoietic cell transplantation.

Comparators
Comparators of interest include laser photocoagulation, cryotherapy, chemotherapy (local or systemic), surgery, and radiotherapy.

Outcomes
The general outcomes of interest are overall survival, disease-specific survival, treatment-related mortality, and treatment-related morbidity.

Follow-up includes the immediate and 12-month post- transplant period to monitor for engraftment and other relevant outcomes. Follow-up will continue to be life-long depending on the success of single autologous hematopoietic cell transplantation.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:
- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess longer term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence
No studies focusing on autologous HCT for patients with localized retinoblastoma were identified in literature searches.

Metastatic Retinoblastoma

Clinical Context and Therapy Purpose
The purpose of single autologous hematopoietic cell transplantation is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with metastatic retinoblastoma.

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest are individuals with metastatic retinoblastoma.

Interventions
The therapy being considered is single autologous hematopoietic cell transplantation.

Comparators
Comparators of interest include chemotherapy, surgery, and radiotherapy.

Outcomes
The general outcomes of interest are overall survival, disease-specific survival, treatment-related mortality, and treatment-related morbidity.

Follow-up includes the immediate and 12-month post- transplant period to monitor for engraftment and other relevant outcomes. Follow-up will continue to be life-long depending on the success of single autologous hematopoietic cell transplantation.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess longer term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Prospective and Retrospective Studies
A prospective, international trial assessed the effectiveness of intensive multimodality therapy in patients aged 10 years and younger with extraocular retinoblastoma.(72) Patients with stage 2 or 3 (locoregional) disease received 4 cycles of chemotherapy and radiation therapy. Patients with stage 4A or 4B (metastatic or trilateral) disease received 4 cycles of chemotherapy; those with at least a PR then received 1 cycle of HDC with autologous HCT. The median follow-up was 7.3 years. One-year EFS was 88.1% (90% CI, 66.6% to 96.2%) for stage 2 or 3 disease (n=19), 82.6% (90% CI, 61.0% to 92.9%) for stage 4A disease (n=18),and 28.3% (90% CI, 12.7% to 46.2%) for stage 4B disease (n=20). Recurrences occurred in 2 patients with stage 4A disease at5 and 9 months, and 10 patients with stage 4B disease at a median of 6 months; all recurrences were in the central nervous system (CNS). The authors

concluded that more effective therapy is needed for stage 4B disease (patients with CNS involvement).

Farouk et al (2022) performed a retrospective analysis of 24 patients with stage 4A metastatic retinoblastoma who underwent HDC plus autologous HCT.(73) All patients experienced hematopoietic recovery post HCT. The median age at diagnosis of stage4A retinoblastoma and HCT was 2 years (range, 0.1 to 7.4) and 3.7 years (range, 2.3 to 9.8), respectively. The median follow-uptime from HCT was 6.3 years (range, 0.4 to 27.7). Kaplan-Meier estimates of 5-year and 10-year OS were 81% ± 8.6% and 59.3% ± 12.4%, respectively, with early deaths due to recurrent retinoblastoma (n=4) and late deaths due to subsequent malignant neoplasms. The authors concluded that intensive multimodality therapy including HDC plus autologous HCT is curative in most patients with stage 4A retinoblastoma.

Case Series

Most studies of autologous HCT for metastatic retinoblastoma have been very small series or case reports.(62-65) More recently, Dunkel et al (2010) reported on outcomes for 15 consecutive patients with stage 4A metastatic retinoblastoma who presented between 1993 and 2006 and were treated with HDC and autologous HCT.(66) 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 six 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 HCT and died. Thirteen patients underwent HCT, and 10 are retinoblastoma-free in first remission at a median follow-up of 103 months (range: 34-202 months). Three patients recurred 14-20 months post diagnosis of metastatic disease, (2 in the CNS and 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, two in previously irradiated fields and 1 in a non-irradiated field. The authors concluded that HCT was curative for the majority of patients treated in their study with stage 4a retinoblastoma.

Dunkel et al (2010) also reported the outcomes of 8 patients diagnosed with stage 4B retinoblastoma between 2000 and 2006 treated with the intention of autologous HCT.(21) Seven 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 HCT, and 1 patient died due to toxicity during induction chemotherapy. Of the 5 patients that underwent HCT, 2 were 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-HCT. The authors concluded that HCT 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: Localized and Metastatic Retinoblastoma
There is a lack of evidence evaluating use of autologous HCT for localized retinoblastoma.

The results have been promising in terms of prolonging DFS in patients with metastatic disease, particularly those without CNS involvement (stage 4a). Given that clinical prognosis is very poor for patients with metastases, results showing survival of some patients for three or more years after HCT may provide evidence to demonstrate a benefit in survival.

Pancreatic Acinar Cell Carcinoma
Pancreatic acinar cell carcinoma (ACC) is a rare pancreatic malignancy. Currently, there is no definitive course of treatment for ACC; however, surgery is regarded as the optimal treatment modality for ACCs that are regionally circumscribed and resectable. Surgical resection with negative margins has been linked to improved long-term survival. There is no reported patient series on this malignancy and the understanding of the disease and management are based on case reports. There are no standard treatment protocols available for patients in which total surgical resection of the tumor is not possible.(76)

Successful treatment with high dose chemotherapy and autologous stem cell transplant have been reported in children with pancreatoblastoma and pancreatic acinar cell carcinoma.(75) This may be the only viable option in cases that are not amenable to gross surgical resection. Using the American Society of Blood and Marrow Transplantation (ASBMT) definitions of autologous hematopoietic cell transplantation (AHCT) indications, this will fall under the category, “standard of care, rare indications” for rare diseases where AHCT has demonstrated effectiveness but large clinical trials and observational studies are not feasible.

COMPARATIVE EFFECTIVENESS REVIEW
The Blue Cross and Blue Shield Association Technology Evaluation Center (2012) prepared a comparative effectiveness review on the use of HCT in the pediatric population for the Agency for Healthcare Research and Quality.(67) The following conclusions were offered:

- Neuroblastoma: The body of evidence on overall survival with tandem HCT compared to single HCT for the treatment of high-risk neuroblastoma was insufficient to draw conclusions.
- Ewing sarcoma family of tumors (ESFT): The low-strength evidence on overall survival (OS) suggests no benefit with single HCT compared to conventional therapy for the treatment of high-risk ESFT.
  - The body of evidence on OS with tandem HCT compared to single HCT for the treatment of high-risk ESFT and overall survival is insufficient to draw conclusions.
- Rhabdomyosarcoma: The moderate-strength evidence on OS suggests no benefit with single HCT compared to conventional therapy for the treatment of high-risk metastatic rhabdomyosarcoma.
  - The body of evidence on OS with single HCT 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 OS with single HCT 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: The low-strength evidence on OS suggested no benefit with single HCT compared to conventional therapy for the treatment of high-risk relapsed Wilms tumor.
- Osteosarcoma was not addressed.
- Retinoblastoma: The low-strength evidence on OS suggested no benefit with single HCT compared to conventional therapy for the treatment of extraocular retinoblastoma with central nervous system involvement.
  - The body of evidence on OS with single HCT compared to conventional therapy for the treatment of extraocular retinoblastoma without CNS involvement was insufficient to draw conclusions.
  - The body of evidence on OS with single HCT compared to conventional therapy for the treatment of trilateral retinoblastoma without CNS involvement was insufficient to draw conclusions.

SUMMARY OF EVIDENCE

For individuals who have high-risk or relapsed peripheral neuroblastoma who receive single or tandem autologous HCT, the evidence includes randomized controlled trials (RCTs) and systematic reviews with meta-analyses of those trials, and observational studies. Relevant outcomes are overall survival (OS), disease-specific survival (DSS), and treatment-related mortality (TRM) and morbidity. In the pooled analysis, patients with high-risk neuroblastoma treated with first-line therapy with single autologous HCT with myeloablative conditioning had significantly improved event-free survival (EFS) compared with standard therapy. Similarly, nonrandomized comparative studies, single-arm studies, and case series evaluating tandem autologous HCT showed improvements in event-free survival for children with high-risk neuroblastoma. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have high-risk Ewing sarcoma who receive single or tandem autologous HCT, the evidence includes an RCT, single-arm studies, and case series. Relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. Although early nonrandomized studies were promising, more recent prospective nonrandomized study results have been inconsistent regarding whether HCT extends survival compared with typical conventional therapy. An RCT comparing consolidation with high-dose chemotherapy (HDC) plus autologous HCT to standard chemotherapy plus whole lung irradiation in patients with Ewing sarcoma with pulmonary and/or pleural metastases did not find a significant improvement in EFS in the group that received HCT. The evidence is insufficient to determine that the technology results in an improvement in the health outcome.

For individuals who have rhabdomyosarcoma (RMS) who receive single autologous HCT, the evidence includes a systematic review and nonrandomized comparative studies. Relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. Available studies have not demonstrated improvements in overall survival or event-free survival with autologous HCT. Additional research is needed to demonstrate a benefit with autologous HCT for pediatric rhabdomyosarcoma. The evidence is insufficient to determine that technology results in an improvement in the net health outcome.

For individuals who have Wilms tumor who receive single autologous HCT, the evidence includes retrospective studies and a meta-analysis. Relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. Overall, 4-year survival rates were similar between patients receiving HCT and receiving chemotherapy. There was a trend suggesting that patients with lung-only stage 3 or 4 relapse might benefit from autologous HCT. However, the overall body of evidence is limited. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have osteosarcoma who receive single autologous HCT, the evidence includes case series and a prospective single-arm study. Relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. An interim analysis of the prospective single-arm study showed that patients receiving autologous HCT were experiencing lower event-free survival rates than historical controls, resulting in all patients being enrolled in standard of care chemotherapy. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have localized retinoblastoma who receive single autologous HCT, there are no studies. Relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have metastatic retinoblastoma who receive single autologous HCT, the evidence includes small case series, case reports and prospective and retrospective studies. Relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. Results from the limited data have suggested that autologous HCT may prolong disease-free survival, particularly in patients without central nervous system involvement (stage 4A). Given the poor prognosis for this indication with conventional therapies, the incremental improvement with autologous HCT might be considered a significant benefit. However, the overall body of evidence is limited. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have pancreatic acinar cell carcinoma, there is no reported patient series on this malignancy and the understanding of the disease and management are based on case reports. There are no standard treatment protocols available for patients in which total surgical resection of the tumor is not possible. Successful treatment with high dose chemotherapy and autologous stem cell transplant have been reported in children with pancreatoblastoma and pancreatic acinar cell carcinoma. This may be the only viable option in cases that are not amenable to gross surgical resection.

Supplemental Information

CLINICAL INPUT FROM PHYSICIAN SPECIALTY SOCIETIES AND ACADEMIC MEDICAL CENTERS

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.

2017 Input

In response to requests, clinical input on autologous hematopoietic cell transplantation for individuals with advanced-stage Wilms tumor, osteosarcoma and retinoblastoma was received from 2 respondents, including 2 physicians with academic medical center affiliation.

For individuals who have advanced-stage Wilms tumor who receive autologous HCT, clinical input does not support a clinically meaningful improvement in net health outcome and does not indicate this use is consistent with generally accepted medical practice.

For individuals who have osteosarcoma who receive autologous HCT, clinical input does not support a clinically meaningful improvement in net health outcome and does not indicate this use is consistent with generally accepted medical practice.

For individuals who have metastatic retinoblastoma who receive autologous HCT, clinical input supports this use provides a clinically meaningful improvement in net health outcome and indicates this use is consistent with generally accepted medical practice.

2011 Input

In response to requests, input was received from 3 academic medical centers and 2 Blue Distinction Centers for Transplants regarding the use of single autologous HCT for individuals with high-risk Ewing sarcoma.

For individuals who have high-risk Ewing sarcoma who receive single autologous HCT, clinical input supports this use provides a clinically meaningful improvement in net health outcome and indicates this use is consistent with generally accepted medical practice. One reviewer did not consider autologous HCT for low- to intermediate-risk Ewing sarcoma investigational but did state that the results of the Euro-EWING's phase III trial were awaited.

PRACTICE GUIDELINES AND POSITION STATEMENTS

The American Society for Transplantation and Cellular Therapy (2020) published consensus guidelines for clinically appropriate indications for hematopoietic cell transplantation based on best prevailing evidence. The following was excerpted from original publication.(68) Indications for HCT in pediatric patients with the solid tumors types addressed in this review are outlined in Table 8.

Table 8. Indications for HCT in Pediatric Patients with Solid Tumors

Indication and Disease Status	Allogeneic HCT[a]	Autologous HCT[a]
Ewing sarcoma, high risk or relapse	D	S
Soft tissue sarcoma, high risk or relapse	D	D
Neuroblastoma, high risk or relapse	D	S
Wilms Tumor, relapse	N	C
Osteosarcoma, high risk	N	C

Adapted from Kanate et al (2020).(68)
HCT: hematopoietic cell transplantation.
[a] "Standard of care (S): This category includes indications that are well defined and are generally supported by evidence in the form of high-quality clinical trials and/or observational studies (e.g., through CIBMTR or EBMT)." "Standard of care, clinical evidence available (C): This category includes indications for which large clinical trials and observational studies are not available. However, HCT has been shown to be an effective therapy with acceptable risk of morbidity and mortality in sufficiently large single- or multi-center cohort studies. HCT can be considered as a treatment option for individual patients after careful evaluation of risks and benefits. As more evidence becomes available, some indications may be reclassified as 'Standard of Care'." "Developmental; (D): Developmental indications include diseases where pre-clinical and/or early phase clinical studies show HCT to be a promising treatment option. HCT is best pursued for these indications as part of a clinical trial. As more evidence becomes available, some indications may be reclassified as 'Standard of Care, Clinical Evidence Available' or 'Standard of Care'." "Not generally recommended (N): Transplantation is not currently recommended for these

indications where evidence do not support the routine use of HCT. The effectiveness of non-transplant therapies for an earlier phase of a disease does not justify the risks of HCT. Alternatively, a meaningful benefit is not expected from the procedure in patients with an advanced phase of a disease. However, this recommendation does not preclude investigation of HCT/IECT as a potential treatment and may be pursued for these indications within the context of a clinical trial."
[b]Tandem autologous HCT recommended.

National Comprehensive Cancer Network

Current National Comprehensive Cancer Network (NCCN) guidelines or comments on HCT related to the cancers addressed in this review are summarized in Table 9. Other tumor types are not addressed in Network guidelines.

Table 9 NCCN Guidelines

Guideline	Tumor Type	Year	NCCN Comments
Bone cancer[77]	Osteosarcoma	v.2.2024	"The safety and efficacy of HDT/HCT in patients with locally advanced, metastatic, or relapsed osteosarcoma have also been evaluated. In the Italian Sarcoma Group study, treatment with carboplatin and etoposide was followed by stem cell rescue, combined with surgery-induced complete response in chemo sensitive disease. Transplant-related mortality was 3.1%. The 3-year OS and DFS rates were 20% and 12%, respectively. The efficacy of this approach in patients with high-risk disease is yet to be determined in prospective randomized studies."
Bone cancer[77]	Ewing sarcoma	v.2.2024	"High dose chemotherapy followed by hematopoietic cell transplant (HDT/HCT) has been evaluated in patients with localized as well as metastatic disease. HDT/HCT has been associated with potential survival benefit in patients with non-metastatic disease. However, studies that have evaluated HDT/HCT in patients with primary metastatic disease have shown conflicting results…. HDT/HCT has been associated with improved long-term survival in patients with relapsed or progressive Ewing sarcoma in small, single-institution studies. The role of this approach is yet to be determined in prospective randomized studies."
Soft tissue sarcoma[78]	Rhabdomyosarcoma	v.1.2024	HCT not addressed
Wilms tumor (nephroblastoma)[79]	Wilms tumor	v.1.2023	HCT not addressed

DFS: disease-free survival; HCT: hematopoietic cell transplantation; HDT: high-dose therapy; NCCN: National Comprehensive Cancer Network; OS: overall survival

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

Not applicable.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this policy are listed in Table 6.

Table 10. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Combined solid tumor			
NCT00638898	Pilot Study of High-Dose Chemotherapy With Busulfan, Melphalan, and Topotecan Followed by Autologous Hematopoietic Stem Cell Transplant in Advanced Stage and Recurrent Tumors	25	Dec 2023 (ongoing)
NCT01505569	Alkylator-Intense Conditioning Followed by Autologous Transplantation for Patients With High Risk or Relapsed Solid or CNS Tumors	20	Mar 2025 (recruiting)
NCT04530487	A Pilot Study of Allogeneic Hematopoietic Stem Cell Transplantation for Pediatric and Adolescent-Young Adults Patients With High Risk Solid Tumors	40	May 2025 (recruiting)
Peripheral neuroblastoma			
NCT01526603	High Dose Chemotherapy and Autologous Peripheral Blood Stem Cell (PBSC) Rescue for Neuroblastoma: Standard of Care Considerations	20	Feb 2024 (recruiting)
NCT02605421	Tandem Myeloablative Consolidation Therapy and Autologous Stem Cell Rescue for High-Risk Neuroblastoma	12	Jul 2025 (recruiting)
NCT01704716	High Risk Neuroblastoma Study 1 of SIOP-Europe (SIOPEN)	3300	Sep 2026 (recruiting)
Ewing sarcoma			
NCT03011528	CombinaiR3 - First-line Treatment of Ewing Tumours with Primary Extrapulmonary Dissemination in Patients from 2 to 50 Years	45	Feb 2024 (ongoing)

NCT: national clinical trial.

Government Regulations

Medicare National Coverage Determinations Manual, Chapter 1, Part 2, Section 110.23, "Stem Cell Transplantation." Effective date: 3/06/24; Implementation Date: 10/07/24

There are numerous autoimmune diseases and the Centers for Medicare and Medicaid Services have not issued a national coverage determination (NCD) for stem cell transplantation for each disease. CMS has a general NCD for stem cell transplantation which does not address solid tumors of childhood.

Local:

There is no local coverage determination specifically addressing hematopoietic stem cell transplantation for solid tumors of childhood.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- BMT – Hematopoietic Cell Transplantation for Acute Lymphoblastic Leukemia
- BMT – Hematopoietic Cell Transplantation for Acute Myeloid Leukemia and Blastic plasmacytoid dendritic cell neoplasm (BPDCN)
- BMT – Hematopoietic Cell Transplantation for Autoimmune Diseases
- BMT – Hematopoietic Cell Transplantation for Chronic Lymphocytic Leukemia/Small Cell Lymphocytic Lymphoma – Autologous and Allogeneic
- BMT – Hematopoietic Cell Transplantation for Chronic Myeloid Leukemia
- BMT – Hematopoietic Cell Transplantation (HCT) for CNS Tumors, Embryonal Tumors and Ependymoma
- BMT – Hematopoietic Cell Transplantation for Epithelial Ovarian Cancer
- BMT – Hematopoietic Cell Transplantation for Genetic Diseases and Acquired Anemias, Allogeneic
- BMT – Hematopoietic Cell Transplantation for Germ-Cell Tumors
- BMT – Hematopoietic Cell Transplantation for Hodgkin Lymphoma
- BMT – Hematopoietic Cell Transplantation for Miscellaneous Solid Tumors in Adults
- BMT – Hematopoietic Cell Transplantation for Myelodysplastic Syndromes and Myeloproliferative Neoplasms, Allogeneic
- BMT – Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas
- BMT – Hematopoietic Cell Transplantation for Plasma Cell Dyscrasias, Including Multiple Myeloma and POEMS Syndrome
- BMT – Hematopoietic Cell Transplantation for Primary Amyloidosis
- BMT – Hematopoietic Cell Transplantation for Waldenström's Macroglobulinemia
- BMT – Malignant Astrocytomas and Gliomas (Autologous)
- Donor Lymphocyte Infusion for Malignancies Treated with an Allogeneic Hematopoietic Cell Transplant
- Orthopedic Applications of Stem-Cell Therapy (Including Allografts and Bone Substitutes used with Autologous Bone Marrow)

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through May 30, 2024, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
1/1/13	10/16/12	10/16/12	• Topic split out from former combined JUMP policies on autologous, allogeneic and tandem bone marrow transplants. • Policy formatted to mirror BCBSA. • Added “relative contraindications” to inclusionary/exclusionary section.
3/1/14	12/10/13	1/6/14	Routine maintenance. CPT codes checked for accuracy; added lab CPT codes applicable for transplants,
11/1/15	8/24/15	9/14/15	Routine maintenance. References and rationale updated.
11/1/16	8/16/16	8/16/16	Routine review
11/1/17	8/15/17	8/15/17	Routine maintenance • References and rationale updated • Changed “hematopoietic stem cell transplantation” to “hematopoietic cell transplantation” per NCCN terminology change. • Clinical input added. • “Metastatic retinoblastoma” added to inclusions. • Under exclusions, ‘retinoblastoma” changed to “retinoblastoma without metastases.”
11/1/18	8/21/18	8/21/18	• Routine maintenance • Removed procedure codes 38220 and 38221
11/1/19	8/20/19		• Routine maintenance
11/1/20	8/18/20		• Routine maintenance
11/1/21	8/17/21		• Routine maintenance
11/1/22	8/16/22		• Routine maintenance
11/1/23	8/15/23		• Routine maintenance • Clarified dual-use codes (both autologous and allogeneic) and

			updated cover sheet and internal coding section of policy to align. ○ Removed code 38242 from internal coding section from EST and added to Investigational in the internal section and cover page as this code is for allogeneic. ○ Code 38207 is listed on cover sheet under Investigational but not on internal coding page. Added 38207 to Investigational internal coding section. ○ Removed this language (Italicized codes/bolded* can be used for both auto and allogeneic transplants. If used for allogeneic transplant they would be considered experimental/investigational for a policy that covers autologous transplants only) from EST to Investigational section in internal code section. ○ Added italicized/bolded* codes from the cover page under E/I section to E/I internal section to align. • Vendor: N/A (ky)
11/1/24	8/20/24		• Routine maintenance • Added IMP “Autologous Hematopoietic Stem Cell Transplant for Pancreatic Acinar Cell Carcinoma in Children” 6/6/24 to JUMP policy. • Updated MPS and Inclusions section with Pancreatic Acinar Cell Carcinoma. • Moved code 38208 from E/I to EST as this procedure is used for both autologous/allogeneic. • Code 86822 deleted from policy – per encoder, code was deleted effective 1/1/18.

			• Vendor: N/A (ky)

Next Review Date: 3rd Qtr, 2025

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: BMT - HEMATOPOIETIC CELL TRANSPLANTATION FOR SOLID TUMORS OF CHILDHOOD

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered; criteria apply
BCNA (Medicare Advantage)	Refer to Medicare information under the Government Regulations section of this policy.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.