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Medical Policy

Subject:	**Hematopoietic Stem Cell Transplantation for Pediatric Solid Tumors**		
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Description/Scope

This document addresses hematopoietic stem cell transplantation for pediatric solid tumors including neuroblastoma, primitive neuroectodermal tumors (PNETs) of the central nervous system, ependymoma, pineoblastoma, Ewing sarcoma, Wilms' tumor, osteosarcoma, retinoblastoma, and rhabdomyosarcoma. These types of solid tumors generally develop in children; however, some may also present in adulthood.

Note: For additional information and criteria for umbilical cord transplantation, see:

- **TRANS.00016 Umbilical Cord Blood Progenitor Cell Collection, Storage and Transplantation**

Position Statement

Neuroblastoma

Medically Necessary:

An autologous hematopoietic stem cell transplantation is considered medically necessary as the initial treatment for high-risk neuroblastoma.

A planned autologous tandem* hematopoietic stem cell transplantation is considered medically necessary as the initial treatment for high-risk neuroblastoma.

An autologous hematopoietic stem cell transplantation is considered medically necessary as a treatment for primary refractory or recurrent neuroblastoma in individuals who have not previously undergone treatment with hematopoietic stem cell transplantation.

A repeat autologous hematopoietic stem cell transplantation due to primary graft failure or failure to engraft is considered medically necessary.

Hematopoietic stem cell harvesting* for an anticipated but unscheduled transplant is considered medically necessary in individuals with neuroblastoma who meet the criteria above when the treating physician documents that a future transplant is likely.**

***Tandem transplantation refers to a planned infusion (transplant) of previously harvested hematopoietic stem cells with a repeat hematopoietic stem cell infusion (transplant) that is performed within 6 months of the initial transplant. This is distinguished from a repeat transplantation requested or performed more than 6 months after the first transplant, and is used as salvage therapy after failure of initial transplantation or relapsed disease.**

****~~NOTE:~~ Hematopoietic stem cell harvesting does not include the transplant procedure.**

Investigational and Not Medically Necessary:

An autologous hematopoietic stem cell transplantation is considered investigational and not medically necessary for individuals who do not meet the above criteria.

An allogeneic (ablative or non-myeloablative) hematopoietic stem cell transplantation is considered investigational and not medically necessary as a treatment of neuroblastoma.

A planned tandem allogeneic (ablative or non-myeloablative) hematopoietic stem cell transplantation as a treatment of neuroblastoma is considered investigational and not medically necessary.

A second or repeat autologous hematopoietic stem cell transplantation due to persistent, progressive or relapsed disease is considered investigational and not medically necessary.

Hematopoietic stem cell harvesting for a future but unscheduled transplant is considered investigational and not medically necessary when the criteria above are not met.

Primitive Neuroectodermal Tumors (PNETs) of the Central Nervous System, Ependymoma and Pineoblastoma

Medically Necessary:

An autologous hematopoietic stem cell transplantation with or without associated radiotherapy, is considered medically necessary for the treatment of PNETs (such as medulloblastoma), arising in the central nervous system, ependymoma or pineoblastoma.

A repeat autologous hematopoietic stem cell transplantation due to primary graft failure or failure to engraft is considered medically necessary.

Hematopoietic stem cell harvesting* for an anticipated but unscheduled transplant is considered medically necessary in individuals with PNET, ependymoma or pineoblastoma who meet the criteria above when the treating physician documents that a future transplant is likely.
~~***NOTE: Hematopoietic stem cell harvesting does not include the transplant procedure.***~~

Investigational and Not Medically Necessary:

An allogeneic (ablative or non-myeloablative [mini transplant]) hematopoietic stem cell transplantation is considered investigational and not medically necessary for the treatment of PNETs (such as medulloblastoma), arising in the central nervous system, ependymoma or pineoblastoma.

A planned tandem allogeneic or autologous hematopoietic stem cell transplantation is considered investigational and not medically necessary for the treatment of PNETs (such as medulloblastoma), arising in the central nervous system, ependymoma or pineoblastoma.

A second or repeat autologous hematopoietic stem cell transplantation due to persistent, progressive or relapsed disease is considered investigational and not medically necessary.

Hematopoietic stem cell harvesting for a future but unscheduled transplant is considered investigational and not medically necessary when the criteria above are not met.

Other High-Risk Solid Tumors of Childhood (Ewing Sarcoma, Wilms' Tumor, Osteosarcoma, Retinoblastoma, and Rhabdomyosarcoma)

Medically Necessary:

An autologous hematopoietic stem cell transplantation is considered medically necessary as a treatment for Ewing sarcoma (including extraosseous Ewing, peripheral neuroepithelioma and Askin's tumor).

A syngeneic allogeneic (ablative or non-myeloablative) hematopoietic stem cell transplantation is considered medically necessary as a treatment for Ewing sarcoma (including extraosseous Ewing, peripheral neuroepithelioma and Askin's tumor).

A repeat autologous or allogeneic (ablative or non-myeloablative) hematopoietic stem cell transplantation due to primary graft failure or failure to engraft is considered medically necessary.

Hematopoietic stem cell harvesting* for an anticipated but unscheduled transplant is considered medically necessary in individuals with Ewing sarcoma who meet the criteria above when the treating physician documents that a future transplant is likely.

~~***NOTE: Hematopoietic stem cell harvesting does not include the transplant procedure.**~~

An autologous hematopoietic stem cell transplantation is considered medically necessary as a treatment for stage IVa and stage IVb retinoblastoma.

Investigational and Not Medically Necessary:

An allogeneic (ablative or non-myeloablative [mini transplant]) or autologous hematopoietic stem cell transplantation is considered investigational and not medically necessary for all other pediatric solid tumors, including but not limited to: Wilms' tumor (nephroblastoma), osteosarcoma, ~~retinoblastoma,~~ and rhabdomyosarcoma.

An autologous hematopoietic stem cell transplantation is considered investigational and not medically necessary for retinoblastoma other than stage IVa or stage IVb.

An allogeneic (ablative or non-myeloablative [mini transplant]) is considered investigational and not medically necessary for retinoblastoma.

An allogeneic (ablative or non-myeloablative) hematopoietic stem cell transplantation is considered investigational and not medically necessary as a treatment of all high risk pediatric solid tumors relapsing after prior therapy with high-dose chemotherapy and autologous hematopoietic stem cell transplantation.

A planned tandem allogeneic or autologous hematopoietic stem cell transplantation is considered investigational and not medically necessary as a treatment of all high risk pediatric solid tumors of childhood.

A second or repeat autologous or allogeneic (ablative or non-myeloablative) hematopoietic stem cell transplantation due to persistent, progressive or relapsed disease is considered investigational and not medically necessary.

Hematopoietic stem cell harvesting for a future but unscheduled transplant is considered investigational and not medically necessary when the criteria above are not met.

Rationale

Hematopoietic stem cell transplantation usually utilizes high-dose chemotherapy which involves the administration of cytotoxic agents using doses several times greater than the standard therapeutic dose. In some cases, whole body or localized radiotherapy is also given and is included in the term high-dose chemotherapy when applicable. The rationale for high-dose chemotherapy is that many cytotoxic agents act

according to a steep dose-response curve. Thus, small increments in dosage will result in relatively large increases in tumor cell kill. Increasing the dosage also increases the incidence and severity of adverse effects related primarily to bone marrow ablation (for example, opportunistic infections, hemorrhage, or organ failure). Bone marrow ablation is the most significant side effect of high-dose chemotherapy, thereby necessitating a re-infusion of hematopoietic stem cells (primitive cells capable of replication and formation into mature blood cells) to repopulate the marrow. The potential donors of stem cells include:

1. **Autologous - Stem cells harvested from the individual's own bone marrow prior to the cytotoxic therapy.**
2. **Syngeneic - Stem cells harvested from an identical twin.**
3. **Allogeneic - Stem cells harvested from a histocompatible donor. (Note: this document does not require a specific level of histocompatibility be present as part of the medical necessity evaluation).**

Donor stem cells, either autologous or allogeneic, can be collected from either the bone marrow or the peripheral blood. Stem cells may be harvested from the peripheral blood using a pheresis procedure. To increase the number of stem cells in the peripheral circulation, donors may be pretreated with a course of chemotherapy or hematopoietic growth factors, or both.

Another source of stem cells is from blood harvested from the umbilical cord and placenta shortly after delivery of neonates. Although cord blood is an allogeneic source, these stem cells are antigenically "naïve" and thus, are associated with a lower incidence of rejection or graft versus host disease.

The most appropriate stem cell source for a particular individual depends upon his or her disease, treatment history, and the availability of a compatible donor, balancing the risks of graft failure and re-infusion of malignant cells in autologous procedures against the risks of graft rejection, and graft versus host disease in allogeneic procedures.

While the intensity of the regimens used for conditioning in conventional high-dose chemotherapy varies, collectively they have been termed "myeloablative." Several less intense conditioning regimens have been developed recently and rely on immunosuppression rather than cytotoxic effects to permit engraftment of donor cells. These regimens, collectively termed "non-myeloablative" also vary in intensity with substantial overlap between the ranges for "myeloablative" and "non-myeloablative" regimens. Studies have shown that donor allogeneic stem cells can engraft in recipients using less-intensive conditioning regimens that are sufficiently immunosuppressive to permit graft-host tolerance. This results in a stable mixed donor-host hematopoietic chimerism. Once chimerism has developed, a further infusion of donor leukocytes may be given to eradicate malignant cells by inducing a graft vs. tumor effect. Non-myeloablative allogeneic transplants, also referred to as "mini-transplant" or "reduced intensity conditioning (RIC)", are thought to be potentially as effective as conventional high-dose chemotherapy followed by an allogeneic stem cell transplantation, but with decreased morbidity and mortality related to the less intense non-myeloablative chemotherapy conditioning regimen. Consequently, for individuals with malignancies who are eligible for

conventional high-dose chemotherapy/allogeneic stem cell transplantation, conditioning with milder, non-myeloablative regimens represents a technical modification of an established procedure.

Tandem high-dose or non-myeloablative chemotherapy with autologous or allogeneic stem cell support is the planned administration of two cycles of high-dose chemotherapy, alone or with total body irradiation, each of which is followed by re-infusion of stem cells. Despite treatment with high-dose chemotherapy, many individuals with advanced malignancies eventually relapse, indicating the presence of residual neoplastic cells. The hypothesis is that eradication of residual tumor cells can be achieved using multiple cycles of myeloablative or non-myeloablative chemotherapy with stem cell support.

Neuroblastoma

Autologous hematopoietic stem cell or bone marrow transplantation for the treatment of neuroblastoma has been used since the early 1980s in a variety of settings. The first randomized trial by the European Neuroblastoma Study Group showed better progression-free survival (PFS) for children with transplantation. However, the study was small and the controls received no continuing therapy. Subsequent phase I/II trials indicated that increased disease-free survival (DFS) and PFS were achieved with autologous transplant compared with historical controls or groups that had received more standard chemotherapy regimens. Interpretation and comparison of the studies is difficult due to the variety of regimens tested and whether time to progression was calculated from the start of induction therapy or from the date of transplant. Comparison with historical controls is also complicated by the addition of platinum regimens in 1982, which improved PFS and overall survival (OS) results for standard chemotherapy.

A Phase II Study (protocol number CCG-3891) by the Children's Cancer Group (CCG) investigated tandem autologous stem cell transplantation in children with high-risk neuroblastoma (Grupp, 2000). The study enrolled 39 participants but only 37 completed the first autologous stem cell transplant and 33 (89%) completed the second autologous stem cell transplant. With a median follow-up of 22 months, 26 (67%) children remained event free, with a 3-year estimated event-free survival (EFS) of 58%. The rate of death due to toxicity 8% was comparable to the mortality rate of a single-cycle autologous stem cell transplant.

Kletzel and colleagues (2002), in a pilot study, reported on the outcomes of 25 consecutive individuals with newly diagnosed high-risk neuroblastoma and 1 with recurrent disease, diagnosed between 1995 and 2000, and treated with triple-tandem autologous hematopoietic stem cell transplantation. After stem cell rescue, individuals were treated with radiation to the primary site. Twenty-two of the 26 participants successfully completed induction therapy and were eligible for the triple-tandem consolidation high-dose therapy. Seventeen participants completed all 3 cycles of high-dose therapy and stem cell rescue, 2 participants completed two cycles and 3 participants completed one cycle. There was one toxic death and one death from complications of treatment for graft failure. Median follow-up was 38 months, and the 3-year EFS and survival rates were 57% ± 11% and 79% ± 10%, respectively.

In an update of 97 individuals treated between 1994 and 2002, George and colleagues (2006) reported encouraging long-term survival with tandem autologous stem cell transplants for those with high risk neuroblastoma. Individuals with high-risk neuroblastoma who had received no prior therapy or one course of chemotherapy (for intermediate-risk disease that was later reclassified) underwent induction therapy with five cycles of standard agents, resection of the primary tumor and local radiation followed by two consecutive courses of myeloablative therapy along with total-body irradiation and peripheral blood stem cell rescue. The study reported PFS at 5 and 7 years of 47% and 45%, and an OS rate at 5 and 7 years was 60% and 53%, respectively.

In a randomized trial of 295 children with high-risk neuroblastoma, Berthold and colleagues (2005) reported an improved EFS with autologous stem cell transplant 47% (95% confidence interval [CI], 38-55) compared with those assigned to the maintenance therapy cohort 31% (95% CI, 23-39); p=0.0221. However the 3-year OS 62% (95% CI, 54-70) was not significantly increased versus the control group 53% (95% CI, 45-62); p=0.0875. There were two treatment-related deaths reported in the transplant group.

Matthay and colleagues (2009) reported long-term results for treatment of high-risk neuroblastoma. The first randomization of the trial compared autologous stem cell transplant to chemotherapy. After completion of treatment, individuals without progressive disease were randomized to a second assignment of 13-cisretinoic acid (cis-RA) versus observation. Significantly higher 5-year EFS of 30% versus 19% (p=0.04) was noted in those treated with transplant compared with chemotherapy alone.

A Cochrane Review by Yalcin and colleagues (2015) evaluated three randomized controlled trials consisting of 739 children. The efficacy of myeloablative therapy was compared to conventional therapy for treatment of high-risk neuroblastoma. Initially, there was a statistically significant difference in EFS in favor of myeloablative therapy over conventional chemotherapy or no further treatment (three studies, 739 subjects; HR 0.78; 95% CI, 0.67 to 0.90). Also, there was a statistically significant difference in OS in favor of myeloablative therapy over conventional chemotherapy or no further treatment (two studies, 360 subjects; HR 0.74; 95% CI, 0.57 to 0.98). When additional follow-up data were subsequently obtained, the difference in EFS remained statistically significant (three studies, 739 subjects; HR 0.79; 95% CI, 0.70 to 0.90), but the difference in OS was no longer statistically significant (two studies, 360 subjects; HR 0.86; 95% CI, 0.73 to 1.01). The authors concluded that based on the currently available evidence, myeloablative therapy seemed to work in terms of EFS. However, there was no evidence of effect for OS with the inclusion of additional follow-up data.

In a large case series, Ladenstein and colleagues (2008) reported on 28 years of high-dose therapy and stem cell transplantation for primary (89%) and relapsed (11%) neuroblastoma in Europe which included a total of 4098 procedures (3974 autologous/124 allogeneic) performed between 1978 and 2006. This case series indicates that allogeneic hematopoietic stem cell transplantation is rarely used for the treatment of neuroblastoma and mortality is higher for allogeneic versus autologous hematopoietic stem cell transplantation. The 5-year OS was 37% in the autologous setting as compared to only 25% in the allogeneic

setting. Currently, there is a lack of clinical trials evaluating allogeneic hematopoietic stem cell transplantation for the treatment of neuroblastoma.

Multiple studies have analyzed the use of ^{131}I-Metaiodobenzylguanidine (MIBG) for treatment of relapsed/refractory neuroblastoma and required the use of hematopoietic stem cell support to limit hematologic toxicity. Johnson and colleagues (2011) described using hematopoietic stem cell support to decrease the median hematologic toxicity to 15 days. Matthay and colleagues (2012) described the need for hematopoietic stem cell rescue 14 days after the ^{131}I-MIBG treatment. Polishchuk (2011) performed a retrospective analysis of 39 persons with recurrent or refractory neuroblastoma treated with ^{131}I-MIBG and subsequently hematopoietic stem cell infusions for prolonged myelosuppression. The authors concluded that ^{131}I-MIBG it is a highly effective salvage agent for adolescents and adults with neuroblastoma. The use of an infusion of autologous stem cells following treatment with ^{131}I-MIBG is supported in the current medical literature as a method to help overcome the toxicities of this therapy.

In a 2019 randomized clinical trial by Park and colleagues, the authors investigated whether a tandem autologous transplant improves EFS compared to a single transplant. Eligible participants had newly diagnosed high-risk neuroblastoma. Primary outcome was EFS from the time of randomization to when a first event occurred (that is; relapse, progressive disease, second malignancy, or death). Additional outcomes included the assessment of response at the end of the induction therapy and local recurrence (which is to be reported separately). There were 652 participants enrolled in the study. A total of 207 participants chose not to be randomized, 62 participants were ineligible for randomization, and 1 participant did not receive protocol therapy. This left 355 participants randomized to either tandem transplant (n=176) or single transplant (n=179). The protocol therapy included 3 phases: induction, consolidation, and post consolidation. For the 652 eligible participants, the 3-year EFS from enrollment or initiation of treatment was 51.1%. From the 355 randomized participants, the 3-year EFS from the time of randomization was 54.9%. Three years after randomization, the EFS for participants in the tandem transplant group was 61.6% and 48.4% for participants in the single transplant group. The study has limitations including the large number of participants who were not randomized leading to a potential selection bias. The EFS rates associated with tandem transplant are only relevant within the context of the total therapy delivered. Other delivered therapies may suggest differing EFS. There were 10% of participants who did not continue beyond the induction phase. While this study showed a better EFS in the participants who received tandem transplant, the findings may not be representative of all subjects with high-risk neuroblastoma.

In a 2021 retrospective review by Khan and colleagues the authors reported on the survival and toxicity of high-risk subjects with neuroblastoma following treatment with single autologous stem cell transplant. There were 99 subjects analyzed. With a median follow-up of 50.2 months, there were 20 subjects who died due to disease progression, 4 subjects died due to septicemia, 1 death related to renal failure, and 1 death due to viral pneumonia. There were no transplant-related mortalities. Median time of relapse from diagnosis was 15 months with the majority (n=37) relapsing within 2 years of diagnosis. OS for 3 years was 68.5% with 3-

year EFS of 48.3%. There were no significant differences in survival rates for those who received total body radiation compared to those who did not (54.4% and 44.9% respectively).

A 2022 retrospective review by Suwannaying and colleagues reported on the outcomes of participants with high-risk neuroblastoma who received conventional chemotherapy (n=116) or hematopoietic stem cell transplant (n=53). For those who received conventional chemotherapy, 5five-year OS~~overall survival~~ was 39.8%, 5five-year EFS was 17.1%. For those who received hematopoietic stem cell transplant, 5five-year OS~~overall survival~~ was 48.7%, 5five-year EFS was 36%.

Primitive Neuroectodermal Tumors (PNETs) of the Central Nervous System, Ependymoma and Pineoblastoma

Hematopoietic stem cell transplants have also been studied for PNETs of the central nervous system. In 2008, Dhall and colleagues reported outcomes for children younger than 3 years of age at diagnosis of nonmetastatic medulloblastoma, after being treated with five cycles of induction chemotherapy, subsequent myeloablative chemotherapy and autologous hematopoietic stem cell transplantation. Twenty of 21 participants completed induction chemotherapy, of which 14 had a gross total surgical resection and 13 remained free of disease at the completion of induction chemotherapy. Of 7 children with residual disease at the beginning of induction, all achieved a complete radiographic response to induction chemotherapy. Of the 20 children who received consolidation chemotherapy, 18 remained free of disease at the end of consolidation. In those with gross total tumor resection, 5-year EFS and OS were 64% (± 13) and 79% (± 11), respectively, and for children with residual tumor, 29% (± 17) and 57% (± 19), respectively. There were four treatment-related deaths. The need for craniospinal irradiation was eliminated in 52% of the children and 71% of survivors avoided irradiation completely, with preservation of quality of life and intellectual functioning.

Dunkel and colleagues (2010b) reported on 25 individuals with previously irradiated recurrent medulloblastoma treated with high-dose chemotherapy consisting of carboplatin, thiotepan, and etoposide with autologous stem cell transplant. The median age at the time of diagnosis was 11.5 years with a range from 4.2 to 35.5 years. Although 3 persons died of treatment-related toxicities within 30 days post transplantation, there were 6 event-free survivors at a median of 151.2 months post transplantation.

Chintagumpala and colleagues (2009) reviewed EFS of 16 children and adolescents (3.8 to 12.9 years of age) with newly diagnosed supratentorial PNET (sPNET) treated with risk-adapted craniospinal irradiation and subsequent high-dose chemotherapy with autologous hematopoietic stem cell transplantation between 1996 and 2003. Eight subjects were considered at average-risk and 8 were at high-risk (defined as the presence of residual tumor larger than 1.5 cm^2 or disseminated disease in the neuroaxis). Median age at diagnosis was 7.9 years (range: 3-21 years). Seven subjects had pineoblastoma. After a median follow-up of 5.4 years, 12 subjects were alive. Five-year EFS and OS for those with average-risk disease were 75% (± 17%) and 88% (± 13%) and for the high-risk group 60% (± 19%) and 58% (± 19%). No treatment-related toxicity deaths

were reported. The authors concluded that high-dose chemotherapy with stem cell transplantation after risk-adapted craniospinal irradiation allows for a reduction in the dose of radiation needed to treat nonmetastatic, average-risk sPNET, without compromising EFS.

A 2017 retrospective study by Raleigh and colleagues reported on the outcomes of 222 children with newly diagnosed embryonal brain tumors treated with adjuvant craniospinal irradiation versus treatment with high-dose chemotherapy, stem cell transplant and delayed craniospinal irradiation. There were 105 children who received adjuvant craniospinal irradiation followed by chemotherapy. High-dose chemotherapy regimens incorporating stem cell transplant was given to 64 children and the remainder of the children (n=32) received neither upfront radiation therapy nor high-dose chemotherapy/stem cell transplants. OS~~verall survival~~ for those who received adjuvant craniospinal irradiation was 66% and PFS~~progression-free survival~~ was 67%. For those who received high-dose chemotherapy/stem cell transplants, OS~~overall survival~~ was 61% and PFS~~progression free survival~~ was 62%. At the last follow-up, 31 children from the high-dose chemotherapy/stem cell transplant group had not received definitive or salvage radiotherapy. In this study, delaying irradiation in very young children resulted in similar outcomes compared to upfront craniospinal irradiation. The authors note prospective studies are necessary before eliminating irradiation from treatment.

Dufour and colleagues (2014) evaluated tandem high-dose chemotherapy (HDCT) with autologous stem cell support followed by conventional craniospinal radiotherapy (RT) for the treatment of children with newly diagnosed high-risk medulloblastoma (MB) or supratentorial PNET(sPNET). At a single European center, between May 2001 and April 2010, 24 children older than 5 years of age were treated with conventional chemotherapy, followed by two courses of high-dose thiotepa followed after each course by autologous stem cell transplantation. Irradiation was started at least 45 days after the last course of HDCT. The median follow-up was 4.4 years (range, 0.8-11.3 years). For children with metastatic MB, the 5-year EFS and OS were 72%and 83%, respectively. No toxic death occurred and side effects were reported as manageable. The authors concluded that the study suggests that tandem HDCT with autologous stem cell support followed by conventional craniospinal RT proved feasible and successful in treating children with metastatic MB. However, they further noted that a prospective study with a larger cohort of subjects is needed to confirm the results of the present study.

Survival with conventional chemotherapy has been generally disappointing. Additionally, younger children tend to have a poorer prognosis (Zacharoulis, 2007). Given the poor response to conventional-dose chemotherapy, high-dose chemotherapy with autologous hematopoietic stem cell transplant has been investigated as a possible therapy. The published literature addressing ependymomas consists mainly of case series and includes heterogeneous groups of brain tumors. Zacharoulis and colleagues (2007) investigated the efficacy of an intensive chemotherapy induction regimen followed by myeloablative chemotherapy and autologous hematopoietic stem cell transplantation in children with newly diagnosed ependymoma. Twenty-nine children less than 10 years of age at diagnosis of ependymoma were enrolled on the "Head Start" protocols. The location of the primary tumor was the posterior fossa in 22 children. Five children had

evidence of metastatic disease at the time of diagnosis and were treated with methotrexate during induction. Twenty-four children with localized disease received an induction regimen including five cycles of chemotherapy. Following induction, the 24 participants without evidence of disease were treated with marrow-ablative chemotherapy (thiotepa, carboplatin, and etoposide) and autologous hematopoietic stem cell transplantation. The estimated 5-year EFS and OS in this study were 12% (± 6%) and 38% (± 10%), respectively. Clinical trials continue to study the long-term safety and efficacy of high-dose chemotherapy with autologous stem cell transplantation for this heterogeneous group of tumors that do not occur frequently.

In addition, specialty consensus opinion suggests autologous hematopoietic stem cell transplant may be useful under specific circumstances to treat childhood ependymomas or pineoblastomas.

Ewing Sarcoma

A case series of 33 individuals with recurrent or progressive Ewing sarcoma studied treatment outcomes of hematopoietic stem cell transplants with different preparatory regimens. Two of the individuals received autologous bone marrow, 1 received autologous bone marrow and stem cells, 29 received autologous peripheral blood stem cells, and 1 received an allogeneic bone marrow transplant due to an unsuccessful autologous harvest. EFS was 42.5% (95% CI, 26-59%) at 2 years and 38.2% at 5 years (95% CI, 21-55%). Although this treatment demonstrated the potential for long-term survival with high-dose therapy ~~(HDT)~~ for recurrent or refractory Ewing sarcoma, it was associated with significant toxicity. One treatment-related death was reported and 2 participants experienced grade IV infections. The authors concluded that a prospective randomized clinical trial of high-dose therapy~~HDT~~ in this group of individuals is needed (McTiernan, 2006).

Gardner and colleagues (2008) reported on 116 individuals with Ewing sarcoma who underwent autologous hematopoietic stem cell transplantation (80 [69%] as first-line therapy and 36 [31%] for recurrent disease) between 1989 and 2000. Five-year probabilities of PFS in individuals who received hematopoietic stem cell transplantation 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 those with localized disease at diagnosis and recurrent disease, 5-year probability of PFS was 14% (95% CI, 3-30%). The authors concluded that PFS rates after autologous hematopoietic stem cell transplantation were comparable to rates seen in those with similar disease characteristics treated with conventional therapy.

Wilms' Tumor

The majority of Wilms' tumor cases respond to standard therapies. However, individuals with adverse prognostic factors and relapsed disease often have poor outcomes and EFS of less than 15% (Dallorso, 2008). Various case series and reviews note the lack the prospective randomized trials for this small number of high-risk individuals who experience relapse.

There have been reports of autologous stem cell transplantation use in the reinduction and consolidation treatment for high-risk recurrent Wilms' tumors. In a study by Spreafico and colleagues (2008), 20 consecutive children were treated with various reinduction regimens and autologous stem cell transplant. At a median of 25 months, 3-year DFS was 56 ± 12%; OS 55 ± 13% and EFS 53 ± 12%. There were 8 treatment failures with re-relapse in 5 children, and progressive disease while on reinduction in 3 children. One child died as a result of treatment-related toxicities.

In a series reported by Campbell (2004), 13 individuals with relapsed Wilms' tumor were treated with a single or double cycle of autologous stem cell transplant. At a median follow-up of 30 months, 7 individuals were alive with no evidence of disease, and the 4-year estimated EFS was 60% (95% CI, 0.40 to 6.88) while the OS estimated rate at 4 years was 73% (95% CI, 0.40 to 6.86).

A 2008 report from the National Wilms' Tumor Study Group (Malogolowkin, 2008) assessed the outcome of alternating cycles of cyclophosphamide/etoposide and carboplatin/etoposide to treat children with relapsed disease. Four-year EFS was 42.3% and OS was 48% in all participants. For individuals who relapsed in the lungs only, EFS and OS was 48.9% and 52.8% respectively. The authors concluded "approximately one-half of children with unilateral Wilms' tumor who relapse after initial treatment with vincristine, actinomycin-D and doxorubicin (VAD) and radiation therapy can be successfully retreated." In addition, the authors noted that development of a prospective international cooperative trial for the treatment of individuals with high-risk relapsed Wilms' tumor is necessary to determine if treatment with conventional intensive chemotherapy or high-dose chemotherapy followed by autologous stem cell transplantation will be associated with a better outcome.

Presson and colleagues (2010) performed a meta-analysis of 100 subjects from six studies to determine characteristics that predict survival in relapsed Wilms' tumors treated with autologous hematopoietic stem cell rescue. These results were then compared to survival data on 118 subjects treated with chemotherapy. Four-year OS in the combined autologous hematopoietic stem cell rescue treated group was 54.1% (95% CI: 42.8-64.1%). The subjects who only relapsed in the lungs had higher 4-year survival rates of 77.7% (58.6% to 88.8%) than those who relapsed in other sites and/or suffered multiple relapses 41.6% (24.8% to 57.6%). Lung-only relapse was considered a favorable prognostic factor; however, there was no absolute advantage for those treated with salvage chemotherapy. Four-year survival rates among stage I-II disease were about 30% higher with chemotherapy than transplantation, but both were comparable for stage III-IV disease. The authors concluded that salvage chemotherapy is typically the better choice for relapsed Wilms' tumors; however, autologous hematopoietic stem cell rescue could be considered for stage III-IV cases with a lung-only relapse.

In 2013, Ha and colleagues studied EFS and OS from published cases describing relapsed Wilms' tumor outcomes. A total of 19 articles (5 with high dose chemotherapy with autologous stem cell rescue, 6 without, 8 both) were identified. Study results suggested an advantage to high dose chemotherapy with autologous stem

cell rescue with a hazard ratio (HR) for EFS of 0.87 (95% CI, 0.67-1.12) and 0.94 (0.71-1.24) for OS. The authors concluded that evidence is suggestive of the value of a high dose option and proposed a worldwide randomized trial which should lead to an improved level of certainty in the evidence base.

Osteosarcoma

Small case series and reports (Fagioli, 2002; Fagioli, 2003; Lee, 2008; Sauerbrey, 2001) have evaluated the use of autologous hematopoietic stem cell transplantation for treatment of osteosarcoma. Overall, outcomes generally indicated that autologous hematopoietic stem cell transplantation induced short remissions of the disease; however, long-term survival benefits appeared to be lacking.

A small phase II study by Arpaci and colleagues (2005) evaluated 22 subjects with stage IIB high-grade osteosarcoma. Treatment consisted of two cycles of induction chemotherapy that included cisplatin, doxorubicin, and ifosfamide followed by high dose chemotherapy and autologous peripheral blood stem cell transplantation. Post engraftment, subjects underwent limb-sparing surgery (LSS) followed by three to six cycles of chemotherapy. The median follow-up, total duration of treatment, and the time to surgery were 23.7 months, 5.96 months, and 3.03 months, respectively. At time of last follow-up, metastasis had occurred in 5 of 22 subjects (23%) post therapy. During follow-up, 3 subjects developed lung metastases, 1 subject developed local disease recurrence with lung metastasis, and 1 other developed lung metastases and multiple bone metastases. A total of 17 subjects remained alive and free of disease at time of last follow-up and 3 subjects had died of disease progression. OS~~verall survival~~ rates were reported as 100% in the first year, 92% in the second year, 83% in the third year and 75% in the fourth year and after. DFS~~isease free survival~~ rates were 94% and 70% in the first and second years, respectively. The authors indicated that based on their study results a phase III randomized study was needed.

Boye and colleagues (2014) evaluated high-dose chemotherapy and stem cell rescue for the primary treatment of metastatic and pelvic osteosarcoma. Between May 1996 and August 2004, 71 individuals participated in a single arm phase II study. A total of 29 subjects (43%) received two courses of high dose chemotherapy and 10 (15%) received one course. Fourteen subjects (20%) had progression of disease before study protocol completion, and only 29 received the full planned treatment course. Median EFS was 18 months, and estimated 5-year EFS was 27%. Median OS was 34 months, and estimated 5-year OS was 31%. When subjects who did not receive HDCT due to disease progression were excluded, there was no difference in EFS (P=0.72) or OS (P=0.49) between those who did or did not receive HDCT. The authors concluded that high dose chemotherapy with carboplatin and etoposide with stem cell rescue is not a treatment option for high-risk osteosarcoma.

A 2023 retrospective review by Kang and colleagues reported on the effectiveness of HDCT with ASCT in children with relapsed osteosarcoma. Records were reviewed for 40 children. With a median follow-up of 67.5 months, the 5-year OS was 51%. There were 25 participants who achieved CR with salvage therapy; 15 of whom received HDCT/ASCT. The 5-year OS was 82.4% for those who achieved OS. For the participants

who achieved OS and had HDCT/ASCT, the 5-year OS was 83.9% and was 80.0% for those who did not receive HDCT/ASCT. The authors noted that receipt of HDCT/ASCT did not significantly improve outcomes. Outcomes were more affected by achieving CR.

Retinoblastoma

Retinoblastoma is a rare intraocular malignancy of childhood that can be deadly if left untreated. ~~AA~~ variety of treatment options have been evaluated~~investigated~~ for individuals with retinoblastoma including autologous hematopoietic stem cell transplantation. Dunkel and colleagues (2010a) described a multi-center retrospective case series of 8 children diagnosed with stage IV4b retinoblastoma. A single protocol was not used and induction chemotherapy included cyclophosphamide, carboplatin or both with a topoisomerase inhibitor in all cases. Five of the 8 children were treated with high-dose chemotherapy and autologous hematopoietic stem cell rescue after attaining either a major or complete response to induction chemotherapy. Four of the 5 subsequently were also treated with external beam radiation therapy and 1 also received intrathecal radioimmunotherapy. Two children survived event-free at 40 and 101 months and the remaining 3 died of their disease. The child surviving event-free at 40 months had been irradiated post high-dose chemotherapy and the child surviving at 101 months had not received radiation therapy.

Dunkel and colleagues (2010c) performed a multi-center retrospective review of 13 individuals with trilateral retinoblastoma. Trilateral retinoblastoma refers to the development of a primary intra-cranial primitive neuro-ectodermal tumor in an individual with intra-ocular retinoblastoma (Dunkel, 2010b). Nine children were treated with high-dose chemotherapy with autologous hematopoietic stem cell transplantation. Seven children received a high-dose thiotepa based chemotherapy regimen, 2 received high-dose cyclophosphamide and melphalan, and 1 child received both regimens (tandem transplant). Five of these children survived event-free with a median follow-up time of 77 months from diagnosis of the disease and the remaining 4 died of the disease.

In a systematic literature review, Jaradat and colleagues (2012) investigated the role of high-dose chemotherapy followed by stem cell transplantation in the treatment of metastatic or relapsed, trilateral or bilateral advanced retinoblastoma, and in those with tumor at the surgical margin of the optic nerve and/or extrascleral extension. The authors located 15 studies (101 individuals) that met the inclusion criteria. Following treatment for metastatic and relapsed disease, 44 of 77 individuals (57.1%) were alive with no evidence of disease at the time of follow-up. A higher rate of local relapse occurred with CNS metastases (73.1%), which dropped to 47.1% in those who received thiotepa. In individuals with trilateral or bilateral advanced retinoblastoma, 5of 7 (71.4%) with reported outcome data were alive with no evidence of disease at the time of follow-up. In individuals with tumor at the surgical margin of the optic nerve with or without extrascleral extension, 6 of 7 (85.7%) were alive with no evidence of disease at the time of follow-up. The authors concluded that durable tumor control is possible in individuals with non-CNS metastases, trilateral or bilateral advanced retinoblastoma, and in those with tumor at the surgical margin of the optic nerve and/or extrascleral extension.

Friedman and colleagues (2013) retrospectively analyzed long-term medical outcomes in 19 survivors of extra-ocular retinoblastoma treated between 1992 and 2009. All survivors had received intensive multimodality therapy for their extra-ocular disease after management of their primary intra-ocular disease, including conventional chemotherapy (n=19, 100%), radiotherapy (n=15, 69%), and/or high-dose chemotherapy and autologous stem cell transplant (n=17, 89%). From the onset of diagnosis of extra-ocular retinoblastoma, the median follow-up was 7.8 years. The most common long-term non-visual outcomes were hearing loss (n=15, 79%), short stature (n=7, 37%), and secondary malignancies [SMN] (n=6, 31%). Sixty-eight percent developed two or more non-visual long-term outcomes of any grade. With the exception of short stature, which was not graded for severity, Grade 3-4 outcomes were limited to: ototoxicity (n=8; n=4 require hearing aids), SMNs (n=6), and unequal limb length (n=1). Five survivors who developed SMNs carried a known RB1 mutation. SMNs developed at a median of 11.1 years after initial diagnosis and 2 individuals died of their SMN. Long-term cardiac, pulmonary, hepatobiliary, or renal conditions were not observed. The authors concluded that longer comprehensive follow-up is needed to fully assess treatment-related health conditions in this population.

In 2022 Dunkel and colleagues published the results from a prospective, international trial in which 57 participants with metastatic retinoblastoma were treated with intensified therapy. The study included 19 participants with locoregional disease (stage II or III), 18 with stage IVa disease (hematogenous metastasis), and 20 with stage IVb disease (CNS extension). All participants received induction chemotherapy. ~~and t~~Those with stage II or III retinoblastoma also received radiation therapy. ~~Those with partial response also~~ All participants with stage IVa or IVb disease received high-dose chemotherapy and autologous HSCT after induction. Stage IVa or IVb participants with residual disease after chemotherapy also received radiation therapy. While the authors note limitations regarding missing data and lack of information regarding previously administered treatment, ~~F~~for stage II and stage III retinoblastoma, 1~~one~~-year EFS was 88.1%. One-year EFS was 82.6% for stage IVa and 28.3% for stage IVb. There were 2 treatment-related deaths. The authors concluded that intensive multimodality treatment is highly effective for stage II, stage III, and stage IVa retinoblastoma. ~~The authors note limitations regarding missing data. There was no information provided regarding previously administered treatment and sites of previously administered radiation. An alternative chemotherapy regimen may have had an impact on clinical outcomes.~~

Another 2022 study reported on the outcomes of autologous HSCT for participants with stage IVa metastatic retinoblastoma. In this retrospective review, Sait and colleagues discussed 24 participants (some who had been reported before from the Dunkel 2010a study discussed above) who received high-dose chemotherapy and autologous HSCT. Four participants had recurrences and died from the disease. With a median follow-up of 7.1 years, 16 participants remained in remission and free of retinoblastoma~~. concluding that intensive multimodality therapy supported by autologous HSCT can be curative for retinoblastoma.

Given the rarity of certain stages of retinoblastoma, there may not be many randomized clinical trials of autologous hematopoietic stem cell transplantation conducted for this condition. Several case series

(Tsuruta, 2011; Uppuluri, 2019) show complete remission following autologous hematopoietic stem cell transplantation for retinoblastoma and improvement in net health outcomes. Current literature ~~indicates potential promise~~ has shown promising results from ~~surrounding~~ the use of autologous stem cell transplantation for stage IVa or IVb retinoblastoma. Expert opinion encourages the use of this treatment. ~~but there is a need for further investigation and longer follow-up. Of note, given the rarity of stage 4a and 4b retinoblastoma it is unlikely that randomized clinical trials of autologous hematopoietic stem cell transplantation will be conducted for this condition and individual consideration may be needed.~~

Rhabdomyosarcoma

Weigel and colleagues (2001) reviewed and summarized published data on the role of autologous hematopoietic stem cell transplantation in the treatment of metastatic or recurrent rhabdomyosarcoma (RMS), which involved a total of 389 participants from 22 studies. Based on all of the data analyzing EFS and OS, they concluded that there was no significant advantage to undergoing this type of treatment.

Klingebiel and colleagues (2008) prospectively compared the efficacy of two high-dose chemotherapy (HDC) treatments followed by autologous stem cell rescue versus an oral maintenance treatment (OMT) in 96 children with stage IV soft tissue sarcoma (88 of whom had RMS). Five-year OS probability for the whole group was 0.52 ± 0.14, for the children who received OMT (n=51), and 0.27 ± 0.13 for the transplant group (n=45, p=0.03). For those with RMS, 5-year OS probability was 0.52 ± 0.16 with OMT versus 0.15 ± 0.12 with transplant (p=0.001). The authors concluded that transplant has failed to improve prognosis in metastatic soft tissue sarcoma but that OMT could be a promising alternative.

In a 2022 retrospective review by Schober and colleagues, the authors reported the role of allogeneic HSCT for participants with rhabdomyosarcoma compared to standard-of-care regimens. There were 50 total participants (15 HLA-matched and 35 not HLA-matched). There were no significant differences in median EFS, OS, and transplant-related mortality. The authors noted no survival benefits of those who received HSCT compared to matched controls.

Other Solid Tumors

No randomized controlled trials of autologous bone marrow transplantation have been published to date for other high-risk pediatric solid tumors except neuroblastoma. Several small phase I/II or case control studies have been performed. Most of these studies include different tumor types, multiple prior treatments, and even different bone marrow transplant regimens, making conclusions and comparisons quite difficult. While some studies may indicate a benefit for transplant, other trials have found no difference.

A 2020 single-arm, single-center study by Ma and colleagues evaluated the feasibility and effectiveness of tandem high-dose chemotherapy and autologous stem cell transplant to minimize the use of radiotherapy in very young children with non-metastatic malignant brain tumors. This was an extension of a previous trial

to allow for a larger cohort of participants and a longer follow-up time. There were 20 study participants under the age of 3 years enrolled. All participants had a diagnosis of malignant brain tumor (4 had anaplastic ependymoma, 4 had medulloblastoma, 4 had PNET, 3 had choroid plexus carcinoma, 2 had high-grade glioma, 1 had immature teratoma, 1 had malignant fibrous histiocytoma, and 1 had atypical teratoid/rhabdoid tumor). Following six cycles of induction chemotherapy, participants received tandem high-dose chemotherapy and autologous stem cell transplantation. Only those individuals with post-operative gross residual tumor at older than 3 years received radiotherapy. After the first session of high-dose chemotherapy and autologous stem cell transplantation, 18 participants went on to phase two and received the second high-dose chemotherapy and autologous stem cell transplantation. Of those 18 who received the second transplant, 2 died from toxicity, 4 participants had relapse or disease progression with 3 of those who survived after salvage treatment including radiotherapy. There were 17 participants who remained alive at a median of 7.8 years from diagnosis. Of the survivors, 9 did not receive radiotherapy, 6 received radiotherapy alone, and 2 had relapse following tandem high-dose chemotherapy and autologous stem cell transplant. The 5-year OS was 85%, EFS rate was 70%, and radiotherapy-free survival rate was 75%. EFS rate was 37.5% in those with gross residual tumor compared to 91.7% in those without gross residual tumor. While clinicians try to minimize the use of radiotherapy, particularly craniospinal radiotherapy due to the risk of functional impairment of the developing brain and late adverse effects, tandem high-dose chemotherapy and autologous stem cell transplant has greater issues with toxicity and higher treatment-related mortality, particularly during the second transplant. The single-arm and single-center design, along with treatment of a diverse set of CNS tumors makes it difficult to make generalizations about tandem high-dose chemotherapy and autologous stem cell transplant in very young subjects with malignant brain tumors. Multi-center, prospective, randomized controlled trials are needed to compare toxicity and efficacy of treatment strategies.

Poor Graft Function

Poor graft function or graft failure is one of the major causes of morbidity and mortality after hematopoietic stem cell transplantation. Poor graft function is defined as slow or incomplete recovery of blood cell counts following a stem cell transplant or decreasing blood counts after initially successful hematopoietic engraftment following a stem cell transplant. There are various options for the management of poor graft function. Stem cell "boost" is a non-standardized term that is used to describe an infusion of additional hematopoietic stem cells to an individual who has undergone a recent hematopoietic stem cell transplantation and has poor graft function (Larocca, 2006). The infusion of additional hematopoietic stem cells is to mitigate either graft failure or rejection with or without immunosuppression. This process may include the collection of additional hematopoietic stem cells from a donor and infusion into the transplant recipient. Note that a "boost" is distinct from a repeat transplant and that there may be separate medical necessity criteria for a repeat transplant.

Allogeneic Hematopoietic Stem Cell Transplantation

Studies using allogeneic of hematopoietic stem cell transplantation for pediatric solid tumors are either lacking or associated with a higher risk of transplant-related mortality.

Summary

In 2020, the American Society for Transplantation and Cellular Therapy (Kanate, 2020) published guidelines on indications for hematopoietic cell transplant and immune effector cell therapy. Definitions used for classifying indications for hematopoietic cell transplant were: standard of care (S); standard of care, clinical evidence available (C); standard of care, rare indication (R); Developmental (D); and not generally recommended (N). Indications for hematopoietic cell transplantation in "pediatric patients" (generally age below 18 years of age) include the following classifications for solid tumors:

- **Ewing's sarcoma, high risk or relapse (D for allogeneic and S for autologous)**
- **Soft tissue sarcoma, high risk or relapse (D for allogeneic and D for autologous**
- **Neuroblastoma, high risk or relapse (D for allogeneic and S for autologous)**
- **Wilms' tumor, relapse (N for allogeneic and C for autologous)**
- **Osteosarcoma, high risk (N for allogeneic and C for autologous)**
- **Medulloblastoma, high risk (N for allogeneic and C for autologous)**
- **Other malignant brain tumors (N for allogeneic and C for autologous)**

Neuroblastoma

The use of single autologous hematopoietic stem cell transplantation has become widely accepted as a treatment option for children with high-risk neuroblastoma. Encouraging results have been reported on the use of tandem autologous hematopoietic stem cell transplantation for the initial treatment of high-risk neuroblastoma. Currently, some transplant centers use tandem autologous hematopoietic stem cell as the preferred treatment for high-risk neuroblastoma. There is insufficient evidence to support the use of three or more autologous hematopoietic stem cell transplantations for neuroblastoma. A large retrospective review that included allogeneic hematopoietic stem cell transplantations for high-risk neuroblastoma (Ladenstein, 2008) indicated that allogeneic HSCTs failed to produce a survival benefit over autologous hematopoietic stem cell transplantation and was associated with a higher risk of transplant related mortality.

PNETs of the Central Nervous System, Ependymoma and Pineoblastoma

The use of single autologous HSCT is supported by case series demonstrating EFS. In addition, specialty consensus opinion suggests autologous hematopoietic stem cell transplant may be useful under specific circumstances to treat childhood ependymomas or pineoblastomas.

Ewing Sarcoma

Case series demonstrate a survival benefit with the use of a single autologous hematopoietic stem cell transplantation for Ewing Sarcoma.

Wilms' Tumor

The use of hematopoietic stem cell transplant for Wilms' tumor failed to show a survival benefit.

Osteosarcoma

The use of hematopoietic stem cell transplant for osteosarcoma has failed to show a survival benefit.

Retinoblastoma

~~**There is potential promise for the use of autologous hematopoietic stem cell transplantation for retinoblastoma, but there is a need for further investigation and longer follow-up.**~~ **Given the rarity of stage IV4a and IV4b retinoblastoma it is unlikely that randomized clinical trials of autologous hematopoietic stem cell transplantation will be conducted for this condition**~~**. and individual consideration may be needed.**~~

Rhabdomyosarcoma

The use of hematopoietic stem cell transplant for rhabdomyosarcoma has failed to show a survival benefit.

Background/Overview

Neuroblastoma

Neuroblastoma is a rare solid cancerous tumor that forms in nerve cells of infants and young children. There are approximately 650 cases diagnosed each year in the United States. Neuroblastomas can originate in nerve tissues of the neck, chest, abdomen, or pelvis, but they most often originate in the tissues of the adrenal gland.

Peripheral neuroblastomas arise within the sympathetic nervous system and can present as a neck, mediastinal, abdominal, or pelvic mass. Peripheral neuroblastomas may be categorized as low, intermediate and high-risk based on patient age, the stage of the tumor and the amplification of the MYCN gene. Treatment typically consists of initial induction chemotherapy to reduce tumor burden, followed by surgery and local irradiation, followed by consideration of high-dose chemotherapy.

Central Nervous System Embryonal Tumors

CNS embryonal tumors are the most common malignant brain tumors in children. They account for 20% to 25% of primary CNS tumors in children. Embryonal tumors include supratentorial primitive neuroectodermal tumor (PNETs), medulloblastoma, neuroblastoma arising in the CNS, ependymoblastoma,

medulloepithelioma, ganglioneuroblastoma, and atypical teratoid/rhabdoid tumor. Classification is based on both histopathologic characteristics of the tumor and location in the brain. Medulloblastoma is the most common type of CNS embryonal tumor.

Ependymoma

Ependymoma is a neuroepithelial tumor that may arise throughout the central nervous system, but is typically contiguous with the ventricular system. In children the tumor typically arises intracranially, while in adults a spinal cord location is more common. Ependymomas are distinct from ependymoblastomas due to their more mature histological differentiation. For this reason, ependymomas are not formally considered a member of the PNET family. Ependymomas comprise about 9% of all brain and spinal cord tumors in children which represents about 200 cases per year in the United States.

Pineoblastoma

A pineoblastoma is a fast growing type of brain tumor that occurs in or around the pineal gland, near the center of the brain. This type of tumor closely resembles a PNET, except for location and is considered by some to be a variant of a PNET. These types of tumors are rare and comprise 0.2% of all brain tumors.

Ewing Sarcoma

Ewing sarcoma is a cancer that occurs primarily in the bone or soft tissue. Ewing sarcoma can occur in any bone, but is most often found in the extremities and can involve muscle and the soft tissues around the tumor site. Ewing sarcoma cells can also spread (metastasize) to other areas of the body including the bone marrow, lungs, kidneys, heart, adrenal gland, and other soft tissues. This type of bone tumor accounts for about 30% of pediatric bone cancers. Ewing sarcoma most often occurs in children between the ages of 5 and 20.

Wilms' Tumor

Wilms' tumor is the most frequent tumor of the kidney in children and infants. There are approximately 650 cases diagnosed each year in the United States. Most incidences of Wilms tumor develop in healthy children, but approximately 10% of those children have been reported to have a congenital anomaly. Treatment may include surgery, chemotherapy and radiation therapy.

Osteosarcoma

Osteosarcoma is a cancer of the bone that destroys tissue and weakens the bone. It starts in immature bone cells that normally form new bone tissue. There are approximately 450 cases of osteosarcoma diagnosed in the United States each year.

Retinoblastoma

Retinoblastoma is an uncommon childhood tumor. It arises in the retina and is the most common primary tumor of the eye in children with approximately 200-300 cases diagnosed each year. If left untreated, mortality is 100% but with current therapy has at least a 90% cure rate. Once disease has spread beyond the eye, survival rates drop significantly (5-year DFS~~disease free survival~~ is less than 10% in those with extraocular disease).

Rhabdomyosarcoma

Rhabdomyosarcoma is a cancerous tumor that originates in the soft tissues of the body, including the muscles, tendons, and connective tissues. The most common sites for this tumor include the head, neck, bladder, vagina, arms, legs, and trunk. Embryonal rhabdomyosarcoma, the most common type, usually occurs in children under 6 years of age. Alveolar rhabdomyosarcoma occurs in older children and accounts for about 20 percent of all cases. Rhabdomyosarcoma is the most common soft tissue sarcoma in childhood. In the United States, about 250 children are diagnosed with rhabdomyosarcoma each year.

Definitions

Ablative: A very high dose of a treatment, calculated to kill a tumor.

Bone marrow: A spongy tissue located within flat bones, including the hip and breast bones and the skull. This tissue contains stem cells, the precursors of platelets, red blood cells, and white cells.

Chemotherapy: Medical treatment of a disease, particularly cancer, with drugs or other chemicals.

Chimerism: Cell populations derived from different individuals and may be mixed or complete.

Complete response/remission (CR): The disappearance of all signs of cancer in response to treatment. This does not always mean the cancer has been cured; also called a complete response.

Cytotoxic: Destructive to cells.

Event-free survival: Refers to the length of time after primary treatment for a cancer that an individual is free of complications or events that treatment was intended to prevent or delay. This may include return of the cancer or the onset of other symptoms. EFS is used in clinical trials as a way to measure how well a new treatment works.

Failure to engraft: When the hematopoietic stem cells infused during a stem cell transplant do not grow and function adequately in the bone marrow.

Graft versus host disease: A life-threatening complication of bone marrow transplants in which the donated marrow causes an immune reaction against the recipient's body.

Hematopoietic stem cells: Primitive cells capable of replication and formation into mature blood cells in order to repopulate the bone marrow.

High-dose or myeloablative chemotherapy (HDC): The administration of cytotoxic agents using doses several times greater than the standard therapeutic dose.

HLA (human leukocyte antigen): A group of protein molecules located on bone marrow cells that can provoke an immune response.

International Neuroblastoma Staging System (INSS) High Risk Neuroblastoma:

- **INSS Stage 2A/2B tumors in children older than 1 year, and in whom the tumor has both unfavorable Shimada classification and MYCN gene amplification**
- **INSS Stage 3 tumors in infants younger than 1 year, and in whom the tumor has MYCN gene amplification**
- **INSS Stage 3 tumors in children older than 1 year and in whom the tumor demonstrates either MYCN gene amplification or unfavorable Shimada classification**
- **INSS Stage 4 tumors in infants younger than 18 months at diagnosis and in whom the tumor demonstrates MYCN gene amplification**
- **INSS Stage 4 tumors in children older than 18 months with or without MYCN gene amplification**
- **INSS Stage 4S tumor in infants younger than 1 year of age at diagnosis and in whom the tumor demonstrates MYCN gene amplification**

Non-myeloablative chemotherapy: Less intense chemotherapy conditioning regimens, which rely more on immunosuppression than cytotoxic effects to permit engraftment of donor cells.

Partial response: A decrease in the size of a tumor, or in the extent of cancer in the body, in response to treatment. Also called partial remission.

Primary graft failure: When the hematopoietic stem cells infused during a stem cell transplant do not grow and function adequately in the bone marrow.

Primary refractory disease: Cancer that does not respond at the beginning of treatment; also called resistant disease.

Relapse: After a period of improvement, the return of signs and symptoms of cancer.

Tandem: Planned infusion (transplant) of previously harvested hematopoietic stem cells with a repeat hematopoietic stem cell infusion (transplant) that is performed within six months of the initial transplant. This is distinguished from a repeat transplantation requested or performed more than six months after the first transplant, and is used as salvage therapy after failure of initial transplantation or relapsed disease.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services may be Medically Necessary when criteria are met for autologous transplants:

CPT	
38206	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous
38207-38215	Transplant preparation of hematopoietic progenitor cells [includes codes 38207, 38208, 38209, 38210, 38211, 38212, 38213, 38214, 38215; when specified for autologous transplant]
38232	Bone marrow harvesting for transplantation; autologous
38241	Hematopoietic progenitor cell (HPC); autologous transplantation
HCPCS	
S2150	Bone marrow or blood-derived peripheral stem cells (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation, and related complications; including pheresis and cell preparation/storage, marrow ablative therapy, drugs, supplies, hospitalization with outpatient follow-up, medical/surgical, diagnostic, emergency, and rehabilitative services, and the number of days of pre- and post-transplant care in the global definition [when specified as autologous]
ICD-10 Procedure	
	Autologous transplantation
30233G0-30243G0	Transfusion of autologous bone marrow into peripheral or central vein, percutaneous approach [includes codes 30233G0, 30243G0]
30233Y0-30243Y0	Transfusion of autologous hematopoietic stem cells into peripheral or central vein, percutaneous approach [includes codes 30233Y0, 30243Y0]
	Pheresis [when specified as autologous]
6A550ZV	Pheresis of hematopoietic stem cells, single [when specified as autologous]
6A551ZV	Pheresis of hematopoietic stem cells, multiple [when specified as autologous]
ICD-10 Diagnosis	
C40.00-C40.92	Malignant neoplasm of bone and articular cartilage or limbs [specified as Ewing's sarcoma]

C41.0-C41.9	Malignant neoplasm of bone and articular cartilage of other and unspecified sites [specified as Ewing's sarcoma]
C47.0-C47.9	Malignant neoplasm of peripheral nerves and autonomic nervous system [neuroepithelioma]
C69.20-C69.22	Malignant neoplasm of retina (retinoblastoma)
C71.0-C71.9	Malignant neoplasm of brain
C74.00-C74.92	Malignant neoplasm of adrenal gland (neuroblastoma)
C75.3	Malignant neoplasm of pineal gland

When services are Investigational and Not Medically Necessary for autologous transplants:
For the procedure and diagnosis codes listed above when criteria are not met, for the following diagnosis codes, or when the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

ICD-10 Diagnosis	
	Other pediatric solid tumors, including, but not limited to, the following:
C64.1-C64.9	Malignant neoplasm of kidney, except renal pelvis (Wilm's tumor)
C65.1-C65.9	Malignant neoplasm of renal pelvis (Wilm's tumor)

When services may be Medically Necessary when criteria are met for allogeneic transplants:

CPT	
38204	Management of recipient hematopoietic progenitor cell donor search and cell acquisition
38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic
~~38206~~	~~Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous~~
38207-38215	Transplant preparation of hematopoietic progenitor cells [includes codes 38207, 38208, 38209, 38210, 38211, 38212, 38213, 38214, 38215; when specified for allogeneic transplant]
38230	Bone marrow harvesting for transplantation; allogeneic
~~38232~~	~~Bone marrow harvesting for transplantation; autologous~~
38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor
~~38241~~	~~Hematopoietic progenitor cell (HPC); autologous transplantation~~
38243	Hematopoietic progenitor cell (HPC); HPC boost

HCPCS	
S2142	Cord blood-derived stem cell transplantation, allogeneic

S2150	Bone marrow or blood-derived peripheral stem cells (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation, and related complications; including pheresis and cell preparation/storage, marrow ablative therapy, drugs, supplies, hospitalization with outpatient follow-up, medical/surgical, diagnostic, emergency, and rehabilitative services, and the number of days of pre- and post-transplant care in the global definition [when specified as allogeneic]
ICD-10 Procedure	
	~~Autologous transplantation~~
~~30233G0-30243G0~~	~~Transfusion of autologous bone marrow into peripheral or central vein, percutaneous approach [includes codes 30233G0, 30243G0]~~
~~30233Y0-30243Y0~~	~~Transfusion of autologous hematopoietic stem cells into peripheral or central vein, percutaneous approach [includes codes 30233Y0, 30243Y0]~~
	Allogeneic transplantation
30233G2-30243G4	Transfusion of allogeneic bone marrow, related, unrelated or unspecified into peripheral or central vein, percutaneous approach [includes codes 30233G2, 30233G3, 30233G4, 30243G2, 30243G3, 30243G4]
30233U2-30243U4	Transfusion of allogeneic T-cell depleted hematopoietic stem cells, related, unrelated or unspecified into peripheral or central vein, percutaneous approach [includes codes 30233U2, 30233U3, 30233U4, 30243U2, 30243U3, 30243U4]
30233X2-30243X4	Transfusion of allogeneic cord blood stem cells, related, unrelated or unspecified into peripheral or central vein, percutaneous approach [includes codes 30233X2, 30233X3, 30233X4, 30243X2, 30243X3, 30243X4]
30233Y2-30243Y4	Transfusion of allogeneic hematopoietic stem cells, related, unrelated or unspecified into peripheral or central vein, percutaneous approach [includes codes 30233Y2, 30233Y3, 30233Y4, 30243Y2, 30243Y3, 30243Y4]
	Pheresis [when specified as allogeneic]
6A550ZV	Pheresis of hematopoietic stem cells, single [when specified as allogeneic]
6A551ZV	Pheresis of hematopoietic stem cells, multiple [when specified as allogeneic]
ICD-10 Diagnosis	
C40.00-C40.92	Malignant neoplasm of bone and articular cartilage or limbs [specified as Ewing's sarcoma]
C41.0-C41.9	Malignant neoplasm of bone and articular cartilage of other and unspecified sites [specified as Ewing's sarcoma]
C47.0-C47.9	Malignant neoplasm of peripheral nerves and autonomic nervous system [neuroepithelioma]
~~C71.0-C71.9~~	~~Malignant neoplasm of brain [autologous only]~~
~~C74.00-C74.92~~	~~Malignant neoplasm of adrenal gland (neuroblastoma) [autologous only]~~
~~C75.3~~	~~Malignant neoplasm of pineal gland [autologous only]~~

~~**When services are Investigational and Not Medically Necessary:**~~
~~**For the procedure and diagnosis codes listed above when criteria are not met; or when the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.**~~

When services are ~~also~~ Investigational and Not Medically Necessary for allogeneic transplants:
For the procedure and diagnosis codes listed above when criteria are not met, for the following diagnoses, or when the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

ICD-10 Diagnosis	
	Other pediatric solid tumors, including, but not limited to, the following:
C64.1-C64.9	Malignant neoplasm of kidney, except renal pelvis (Wilm's tumor)
C65.1-C65.9	Malignant neoplasm of renal pelvis (Wilm's tumor)
C69.20-C69.22	Malignant neoplasm of retina (retinoblastoma)
C71.0-C71.9	Malignant neoplasm of brain
C74.00-C74.92	Malignant neoplasm of adrenal gland (neuroblastoma)
C75.3	Malignant neoplasm of pineal gland

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   - **Childhood Soft Tissue Sarcoma Treatment (PDQ). Updated December 7, 2022.**
   - **Ewing Sarcoma Treatment (PDQ). Updated February 13, 2023.**
   - **Neuroblastoma (PDQ): Treatment. Updated April 7, 2023.**
   - **Osteosarcoma and Malignant Fibrous Histiocytoma of Bone Treatment (PDQ). Updated April 5, 2023.**
   - **Retinoblastoma Treatment (PDQ). Updated August 9, 2022.**
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Index

Document History

Status	Date	Action
Revised	11/09/2023	Medical Policy & Technology Assessment Committee (MPTAC) review. Added definition of tandem to Position Statement. Revised MN criteria for autologous hematopoietic stem cell transplantation for stage IVa and stage IVb retinoblastoma Revised INV/NMN statement for allogeneic (ablative or non-myeloablative [mini transplant]) for retinoblastoma. ~~Position Statement to include for~~ Updated Rationale, Coding and References sections.
Reviewed	05/11/2023	~~Medical Policy & Technology Assessment Committee (~~MPTAC~~)~~ review. Updated Rationale and References sections.
Reviewed	11/10/2022	MPTAC review. Updated Rationale, Background/Overview, Definitions, and References sections.
Reviewed	11/11/2021	MPTAC review. Updated Rationale, Background/Overview, and References sections.
	10/01/2021	Updated Coding section with 10/01/2021 ICD-10-PCS changes; removed open approach codes deleted 09/30/2021.
Reviewed	11/05/2020	MPTAC review. Updated Rationale, Background/Overview, and References sections.
Reviewed	11/07/2019	MPTAC review. Updated Rationale and References sections.

	10/01/2019	**Updated Coding section with 10/01/2019 ICD-10-PCS changes; added 30230U2-30243U4; removed 30250G0-30263G1, 30250X1-30263Y1 deleted 09/30/2019.**
Reviewed	**11/08/2018**	**MPTAC review.**
Reviewed	**10/31/2018**	**Hematology/Oncology Subcommittee review. Updated References section.**
Revised	**11/02/2017**	**MPTAC review.**
Revised	**11/01/2017**	**Hematology/Oncology Subcommittee review. The document header wording updated from "Current Effective Date" to "Publish Date." In the Position Statement, removed the requirement that individuals must meet the "Individual Selection Criteria for all diagnoses." Updated Rationale, Definitions, and References sections.**
Reviewed	**11/03/2016**	**MPTAC review.**
Reviewed	**11/02/2016**	**Hematology/Oncology Subcommittee review. Formatting updated in Position Statement section. Rationale and References sections updated.**
	10/01/2016	**Updated Coding section with 10/01/2016 ICD-10-PCS procedure code changes.**
Reviewed	**11/05/2015**	**MPTAC review.**
Reviewed	**11/04/2015**	**Hematology/Oncology Subcommittee review. Rationale, Background and Reference sections updated. Removed ICD-9 codes from Coding section.**
Reviewed	**11/13/2014**	**MPTAC review.**
Reviewed	**11/12/2014**	**Hematology/Oncology Subcommittee review. Rationale and Reference sections updated.**
Reviewed	**11/14/2013**	**MPTAC review.**
Reviewed	**11/13/2013**	**Hematology/Oncology Subcommittee review. Description, Rationale, Background, and Reference sections updated.**
Revised	**11/08/2012**	**MPTAC review.**
Revised	**11/07/2012**	**Hematology/Oncology Subcommittee review. Position statements clarified by replacing the term "stem cell support" with hematopoietic stem cell transplantation. Clarified that a planned autologous tandem hematopoietic stem cell transplantation is medical necessary for the initial treatment of high-risk neuroblastoma. Rationale, Definition, Coding and Reference sections updated.**
Revised	**05/10/2012**	**MPTAC review.**
Revised	**05/09/2012**	**Hematology/Oncology Subcommittee review. Removed "future" from all medically necessary stem cell harvesting criteria. Added "but unscheduled" to all stem cell harvesting investigational and not medically necessary criteria. Clarified hepatic insufficiency Individual Selection Criterion. Removed redundant investigational and not medically necessary statements for "PNETs of the Central Nervous System, Ependymoma and**

		Pineoblastoma" and "Other High-Risk Solid Tumors of Childhood". Rationale, Reference and Discussion sections updated.
	01/01/2012	**Updated Coding section with 01/01/2012 CPT changes.**
Revised	**05/19/2011**	**MPTAC review.**
Revised	**05/18/2011**	**Hematology/Oncology Subcommittee review. Removed allogeneic transplant (ablative or non myeloablative) as medically necessary for neuroblastoma. Clarified that allogeneic (ablative or non myeloablative) transplant for neuroblastoma is investigational and not medically necessary. Added language in Rationale section addressing stage 4a and 4b retinoblastoma and the possibility of randomized clinical trials. Rationale, Background, Coding, and Reference sections updated.**
Revised	**11/18/2010**	**MPTAC review.**
Revised	**11/17/2010**	**Hematology/Oncology Subcommittee review. Updated position statement heading for PNETs and Ependymomas to include pineoblastoma and also added the wording "of the Central Nervous System" after PNETs. Clarified criteria for PNET and ependymoma by separating ependymoma from PNETs with a comma in the medically necessary statements and by adding parenthesis around "such as medulloblastoma" in the medically necessary and investigational and not medically necessary statements. Clarified investigational and not medically necessary statements by adding pineoblastoma and also added the wording "arising in the central nervous system" after PNETs. Added investigational and not medically necessary indication for stem cell harvesting for PNETs, Ependymoma and Pineoblastoma. Updated Rationale, Background, Definitions, Coding, References, Websites, and Index.**
Revised	**11/19/2009**	**MPTAC review.**
Revised	**11/18/2009**	**Hematology/Oncology Subcommittee review. Added criteria for stem cell harvesting for future but unscheduled transplant as medically necessary for neuroblastoma. Combined autologous and allogeneic transplant criteria to reduce redundant statements. Clarified stem cell harvest language for anticipated but unscheduled transplant. Updated rationale, references and websites.**
	05/21/2009	**Updated rationale to include information about stem cell "boosts".**
Revised	**11/20/2008**	**MPTAC review.**
Revised	**11/19/2008**	**Hematology/Oncology Subcommittee review. Clarified Individual Selection Criteria. Updated websites.**
Reviewed	**05/15/2008**	**MPTAC review.**
Reviewed	**05/14/2008**	**Hematology/Oncology Subcommittee review. Updated rationale, references and websites.**

	01/01/2008	**Updated Coding section with 01/01/2008 HCPCS changes; removed HCPCS G0267 deleted 12/31/2007.**
Revised	**11/29/2007**	**MPTAC review.**
Revised	**11/28/2007**	**Hematology/Oncology Subcommittee review. Clarified a planned autologous tandem stem cell transplant is medically necessary for "high risk" neuroblastoma Updated rationale, references and websites. The phrase "investigational/not medically necessary" was clarified to read "investigational and not medically necessary."**
	05/17/2007	**Added note to cross reference TRANS.00016 Umbilical Cord Blood Progenitor Cell Collection, Storage and Transplantation.**
Revised	**12/07/2006**	**MPTAC review.**
Revised	**12/06/2006**	**Hematology/Oncology Subcommittee review. Addition of graft failure indication.**
Revised	**06/08/2006**	**MPTAC review.**
Revised	**06/07/2006**	**Hematology/Oncology Subcommittee review. Revision to general patient selection criteria.**
Revised	**12/01/2005**	**MPTAC review.**
Revised	**11/30/2005**	**Hematology/Oncology Subcommittee. Eliminated age requirements and revised general individual selection criteria.**
	11/22/2005	**Added reference for Centers for Medicare and Medicaid Services (CMS) – National Coverage Determination (NCD).**
Reviewed	**07/14/2005**	**MPTAC review.**
Revised	**04/28/2005**	**MPTAC review. Revision based on Pre-merger Anthem and Pre-merger WellPoint Harmonization.**

Pre-Merger Organizations	**Last Review Date**	**Document Number**	**Title**
Anthem, Inc.	**10/28/2004**	**TRANS.00002**	**Stem Cell Transplant following Chemotherapy for Malignant Diseases**
WellPoint Health Networks, Inc.	**12/02/2004**	**7.11.02**	**Autologous Bone Marrow Transplantation or Peripheral Blood Stem Cell Support (PBSCS) for Malignancies**
	12/02/2004	**7.11.03**	**Allogeneic Bone Marrow or Stem Cell Transplantation**
	12/02/2004	**7.11.05**	**Mini-Transplants**
	12/02/2004	**Clinical Guideline**	**Bone Marrow Transplant for Neuroblastoma**

12/02/2004	**Clinical Guideline**	**Bone Marrow Transplant for Ewing Sarcoma/PNET**