



CIGNA MEDICAL COVERAGE POLICY

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Subject Stem-Cell Transplantation for Solid Tumors in Children

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- Stem-Cell Transplantation for Neuroblastoma

INSTRUCTIONS FOR USE

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Coverage Policy

CIGNA covers high-dose chemotherapy followed by autologous hematopoietic stem-cell transplantation as medically necessary for the treatment of a child with ANY of the following solid tumors:

- relapsed Wilms' tumor
- metastatic non-central nervous system (non-CNS) retinoblastoma
- relapsed or progressive Ewing family of tumors

General Background

Solid tumors in children are a heterogeneous group of cancers that includes Wilms' tumor, retinoblastoma, Ewing family of tumors, rhabdomyosarcoma, germ-cell tumors, and soft tissue sarcomas. Treatment options include surgical resection, radiation and chemotherapy regimens. Stem-cell transplantation has been investigated as a treatment of various solid tumors in children.

Stem-Cell Transplantation

Stem-cell transplantation refers to transplantation of hematopoietic stem cells (HSC) from a donor into a recipient. HSCs are immature cells that can develop into any of the three types of blood cells (red cells, white cells or platelets). HSC transplantation (HSCT) can be either autologous (using the individual's own stem cells) or allogeneic (using stem cells from a donor).

Research has suggested a correlation between dose-intensity of chemotherapy, and response rate and outcome in a variety of solid tumors. The use of high-dose chemotherapy with autologous hematopoietic stem-cell transplantation (HSCT) for solid tumors in children is based on the hypothesis that major dose escalations within the myeloablative range are needed to overcome tumor cell resistance and produce a meaningful clinical improvement. Stem-cell support allows for an increase in the dose well beyond normal bone-marrow tolerance.

Wilms' Tumor

Wilms' tumor, also called nephroblastoma, is the most common cause of kidney cancer in children. Although generally considered curable, with a four-year overall survival rate of 90%, children with stages II, III, and IV anaplastic-histology tumors have a very poor prognosis upon recurrence (National Cancer Institute [NCI], 2011f; Russell, 2008).

Because relapse is rare and individuals in relapse have a poor prognosis, it is unlikely that randomized controlled clinical trials (RCTs) will be conducted in this patient population. Presson et al. (2010) published an individual patient data meta-analysis collected from six studies involving a total of 100 patients with relapsed disease who received chemotherapy and autologous HSCT. These data were compared to outcomes of 118 patients from two studies who received salvage chemotherapy ± radiation therapy (CT). Four-year overall survival (OS) rates of patients treated with autologous HSCT were 54.1%. Patients with lung-only relapse who were treated with autologous HSCT had a four-year OS of 77.7% compared with those who had multiple relapses or relapsed at other sites (41.6%). Four-year survival rates among stage I-II patients were about 30% higher with CT than those treated with HSCT, but outcomes were comparable for stage III-IV patients. The authors note "These findings suggest salvage chemotherapy is typically the better choice for relapsed Wilms' tumor patients, HSCT could be considered for stage III-IV patients with a lung-only relapse."

Several prospective and retrospective studies have suggested a survival benefit with the use of high-dose chemotherapy and autologous HSCT (Spreatico, 2008; Campbell, 2004). Event-free-(EFS) and OS rates range from 56–60%, and 53%–73%, respectively, at variable time intervals.

Although data are not robust, the existing literature suggests that high-dose chemotherapy with autologous HSCT offers improved survival over standard treatment in selected patients. Autologous HSCT is considered an appropriate option for the treatment of relapsed Wilms' tumor.

Retinoblastoma

Retinoblastoma is a relatively uncommon tumor of childhood that arises in the retina. Prognosis is generally poorer in children in whom diagnosis made beyond the age of five. There are several staging systems currently being used in the treatment of retinoblastoma; however, for treatment purposes, the disease is categorized as either intraocular or extraocular. While intraocular retinoblastoma is localized disease and has a five-year disease-free survival rate of over 90%, extraocular retinoblastoma has metastasized beyond the eye, most commonly into the central nervous system (CNS) and has a five-year disease-free survival rate of less than 10% (National Cancer Institute [NCI], 2011e).

Regarding retinoblastoma with central nervous system disease the NCI (2011e) notes that "therapeutic intensification with high-dose marrow-ablative chemotherapy and autologous hematopoietic progenitor cell rescue has been explored, but its role is not yet clear." According to the NCI (2011e), there is no clearly proven effective or standard therapy for the treatment of extraocular retinoblastoma. "Studies of small series of patients have shown that metastatic retinoblastoma can be cured using high-dose marrow-ablative chemotherapy and autologous hematopoietic stem cell rescue." Because metastatic retinoblastoma is rare and prognosis is usually poor, it is unlikely that RCTs will be conducted for this population.

Although the data are not robust, several prospective case series and retrospective studies have suggested the safety and effectiveness of autologous HSCT for the treatment of metastatic non-CNS retinoblastoma (Lee, 2008; Kremens, 2005; Rodriguez-Galindo, 2003; Dunkel, 2000). Treatment-related mortality was zero for all studies. In the study by Lee involving 14 children with bilateral disease, vision was preserved in one eye for nine patients and in both eyes in two patients; without the use of external beam radiation. Disease-free survival (DFS) ranged from 42–107 months.

The evidence from these case series suggests that high-dose chemotherapy and autologous hematopoietic stem-cell transplantation (HSCT) offers improved outcomes for selected children with non-central nervous system (CNS) metastatic retinoblastoma. Although data are limited, autologous HSCT appears to be an acceptable treatment option for this indication.

Ewing Family of Tumors

Ewing family of tumors (EFTs) are found in the bone (e.g., Ewing tumor of bone, ETB, or Ewing sarcoma of bone), or in soft tissue. EFTs belong to the group of neoplasms commonly referred to as small, round, blue-cell tumors of childhood. Children and adolescents with localized disease may have occult metastasis.

Children with relapsed Ewing tumors have poor prognosis with standard therapy with 10-year survival of 10%. Patients with metastasis have a four-year overall survival of 39% (Barrett, 2010). High-dose chemotherapy and autologous HSCT has been studied in relapsed or metastatic Ewing tumors in an effort to increase survival rates. These tumors are very sensitive to alkylators, a group of agents with a very steep dose-response curve, which provides the basis for the use of consolidation with myeloablative therapy and autologous HSCT (Dome, 2008). Dome (2008) also notes "The results of treatment with megatherapy and HSCT for patients with high-risk Ewing family of tumors must be analyzed with caution because of the lack of randomized studies and the heterogeneity of patients and treatments. Results of most retrospective European and American studies do not seem to support the use of this approach. In more recent results reported by the European Bone Marrow Transplant Registry; however, conditioning regimens that incorporate high doses of alkylating agents, generally busulfan and melphalan, confer an apparent survival advantage."

Several uncontrolled trials demonstrate improved or equivalent survival outcomes with autologous HSCT (Ladenstein, 2010; Gardener, 2008; Rosenthal, 2008; McTierman, 2006; Barker, 2005; Burdach, 2003; Kushner, 2001). Ladenstein et al. (2010) published results from the Euro-EWING-99 Trial which analyzed outcomes of 281 patients with primary disseminated multifocal Ewing sarcoma treated with multiple cycles of chemotherapy, local treatment consisting of surgery or radiation, and high-dose chemotherapy followed by autologous HSCT. Of 281 total patients, 169 received HSCT. After a median follow-up of 3.8 years, three-year event-free- and overall survival for all patients were 27% and 34%, respectively. Estimated three-year survival from the start of HSCT for 46 children <14 years was 46%. At analysis, 93 of 281 were still alive; 64 of these patients had received HSCT. Eighty-two percent of patients without HSCT died after a median of one year, with another seven deaths beyond the second year.

Gardner et al. (2008) reported results of 116 patients with Ewing sarcoma who underwent autologous HSCT. One hundred-day and one-year probabilities of treatment-related mortality were 4% and 9%, respectively. Five-year probabilities of relapse or progression-free survival (PFS) with localized and metastatic disease at diagnosis were 49% and 34%, respectively, compared with 51% and 60%, respectively for patients with localized or metastatic disease who received HSCT as first-line therapy. The authors note that these results are comparable to those seen in patients receiving standard treatment with surgery, radiation, and standard dose chemotherapy.

Rosenthal et al. (2008) analyzed outcomes of 20 patients with high-risk Ewing family of tumors who underwent high-dose chemotherapy and autologous HSCT, and a cohort of thirteen who received a second cycle of chemotherapy and HSCT. For the entire group the probabilities of overall survival (OS) at one- and three-years were 60% and 45%, respectively. The estimated probabilities for event-free survival (EFS) at one-, and three-years were 45% and 47%, respectively. In patients who completed only one cycle of high-dose chemotherapy and HSCT the probability of OS was 43% compared with 69% for patients who received both cycles of high-dose chemotherapy and HSCT.

Other retrospective trials reflect no statistically significant survival benefit with the use of HSCT (Al-Faris, 2007; Shanker, 2003; Burdach, 2000). Al-Faris et al. (2007) retrospectively analyzed the outcomes of 45 children with high-risk Ewing sarcoma (defined as metastatic at diagnosis or relapsed). Twenty patients received autologous HSCT and 25 received conventional chemotherapy. The three-year OS rate for the transplanted group was 59% compared to 34% for those who received conventional chemotherapy ($p=0.06$). The three-year EFS was 39% for the transplanted group and 32% for the children who received conventional chemotherapy ($p=0.08$). Fifty percent ($n=10$) of the children who underwent autologous hematopoietic stem-cell transplantation (HSCT) were alive at six years, with eight or ten children remaining in remission greater than five years after transplantation. There were no treatment-related deaths. Low patient numbers prevented reliable analysis of these subgroups.

According to the authors, "While there was no statistically significant benefit with autologous hematopoietic stem-cell transplantation (HSCT) for this population of patients, it is feasible and may improve the prognosis of children with very high-risk features such as bone or bone marrow dissemination." The authors also noted that in the absence of other targeted therapies, this may be a reasonable option to consider.

In view of the universally poor prognosis, high-dose chemotherapy and autologous HSCT would appear to be an appropriate treatment goal for individuals with minimal, responsive disease following conventional second-line therapy for progression or relapse (McTiernan, 2006). Although data are not robust, the published peer-reviewed scientific literature suggests that high-dose chemotherapy with autologous HSCT may result in improved outcomes for a selected group of children with Ewing family of tumors and it is considered an acceptable therapy for this indication.

Extracranial Germ-Cell Tumors

Germ-cell tumors, which are relatively rare in childhood, develop from primordial germ cells that may migrate to locations outside of the yolk sac and subsequently develop into cancerous tumors. Prognosis and appropriate treatment depend upon factors such as histology, age, stage of disease, and primary site. Conventional treatment for extracranial germ-cell tumors is based on risk level in order to minimize treatment-related morbidity.

According to the National Cancer Institute ([NCI], 2011a), only a small number of children and adolescents with extracranial germ-cell tumors experience relapse of disease after treatment with surgery and chemotherapy. There is no standard treatment for this type of tumor, and prognosis is poor.

Trials of high-dose chemotherapy with autologous HSCT have been conducted in adults with good results in individuals with certain types of recurrent testicular cancer, which is of germ cell type. However, the NCI notes "The role of high-dose chemotherapy and hematopoietic stem cell rescue for recurrent pediatric germ-cell tumors is not established, despite anecdotal reports (NCI, 2011a)."

There is insufficient evidence to support the similarity between pediatric and adult extracranial germ-cell tumor such that the evaluation of treatment in adults can be applied to children. The differences between children and adults regarding the location of the primary germ cell tumor site, pattern of relapse, and the biology of childhood germ cell tumors may limit the applicability of adult salvage approaches to children. At this time the role of high-dose chemotherapy with autologous HSCT for the treatment of extracranial germ-cell tumors in children has not been established.

Childhood Soft Tissue Sarcoma

Soft tissue sarcomas are a group of malignant tumors that originate from primitive mesenchymal tissue. These sarcomas account for seven percent of all childhood tumors, and include rhabdomyosarcoma, and non-rhabdomyosarcomatous soft tissue sarcomas. Treatment options include surgery, radiation therapy and chemotherapy.

Rhabdomyosarcoma: This is a malignant soft tissue tumor of skeletal muscle origin which is most commonly found in the head and neck, genitourinary tract, and the extremities (NCI, 2011b). Prognosis is related to the age of the child, site of origin, resectability, extent of any metastasis and tissues involvement, histopathology of the tumor, and unique biological characteristics of rhabdomyosarcoma cells. Standard systemic therapy for children with metastatic disease is combination chemotherapy with five-year survival rates of >70%; infants may not be able to tolerate full doses of radiation and chemotherapy and may therefore have decreased survival (NCI, 2011b).

High-dose chemotherapy with autologous HSCT for the treatment of rhabdomyosarcoma is under clinical evaluation in children. Available data indicate that this is of no benefit in poor-risk rhabdomyosarcoma and should be only used in the context of a clinical trial. According to the NCI (2011b), "High-dose chemotherapy with stem cell rescue has been evaluated in a limited number of patients with rhabdomyosarcoma but has failed to improve the outcome of patients with high-risk metastatic rhabdomyosarcoma. Children with recurrent disease who underwent very intensive doses of chemotherapy followed by autologous HSCT did not realize a significant benefit from use of this therapy." The NCI also notes, "Very intensive chemotherapy followed by autologous bone marrow reinfusion is also under investigation for patients with recurrent rhabdomyosarcoma. A review of the published data did not determine a significant benefit for patients who underwent this salvage

treatment approach. “End-intensification with high-dose chemotherapy, dose intensification of alkylating agents, and integration of novel agents have failed to improve survival in these patients (Wang, 2011)

Carli et al. (2004) presented data on the final results from two European intergroup studies designed to identify prognostic variables and determine the value of high-dose chemotherapy and hematopoietic stem-cell transplantation (HSCT) for patients with rhabdomyosarcoma in complete remission. The two studies were run consecutively. The first study treated 62 patients with four cycles of standard chemotherapy. The second study treated 53 patients with three cycles of standard chemotherapy and one cycle of high-dose chemotherapy and HSCT. The estimated five-year overall survival (OS) rate for patients undergoing HSCT was not statistically improved over that for patients receiving standard chemotherapy (36% vs. 27%, respectively).

Matsubara et al. (2003) documented a series of 22 patients with intermediate-risk or high-risk rhabdomyosarcoma treated with high-dose chemotherapy and HSCT. All of the patients survived the treatment; however, eight of the patients who had high-risk disease at the time of HSCT died of recurrent or progressive disease. The five-year OS for all patients was 45%. The five-year OS rate for the 14 patients who underwent HSCT in complete remission was 70%, whereas the five-year OS rate for the eight patients who underwent HSCT in partial remission or with progressive disease was 0%.

Weigel et al. (2001) conducted a meta-analysis of 22 articles documenting outcomes of 389 patients who were treated with HSCT for high-risk rhabdomyosarcoma. Patients treated in first complete or partial remission had an overall survival rate of 20–40% at two–six years after diagnosis. Patients treated during subsequent remissions or with residual disease had worse outcomes, with three-year OS estimated at 12%. This does not demonstrate a survival advantage for patients with high-risk rhabdomyosarcoma treated with high-dose chemotherapy and HSCT.

At this time, there is insufficient evidence in the published peer-reviewed scientific literature to support the effectiveness of high-dose chemotherapy and HSCT in children with high-risk rhabdomyosarcoma. The role of HSCT for this indication has not yet been established.

Non-Rhabdomyosarcomatous Soft Tissue Sarcomas (NRSTS): NTSTS are a heterogeneous group of tumors that include neoplasms of the smooth muscle, connective and vascular tissue, and the peripheral nervous system. Subtypes include alveolar soft part sarcoma (ASPS), desmoplastic small round cell tumor, clear cell sarcoma of soft parts, hemangioendotheliomas, and angiosarcomas. Prognosis for children with metastatic, progressive or recurrent disease is poor, four-year survival is <33% (NCI, 2010c). Standard treatment options include surgical resection, radiation therapy, and chemotherapy, although use of adjuvant chemotherapy is controversial for some subtypes of childhood sarcoma.

There are scarce data regarding the safety or effectiveness of high-dose chemotherapy and HSCT for this indication. In a study of individuals with ASPS, Ogose et al. (2003) documented outcomes in a multicenter case series of 57 adult and pediatric patients with ASPS treated over the course of 20 years. Chemotherapy was performed in 47 patients with different regimens. Two patients who were treated with intra-arterial chemotherapy regimens experienced a partial response. There was no response in patients treated with high-dose ifosfamide or cisplatin. None of the patients with metastatic disease responded to chemotherapy of any type. The results suggest that high doses of chemotherapy are not beneficial in the treatment of ASPS.

Data are lacking regarding the safety and effectiveness of high-dose chemotherapy and HSCT for the treatment of children with NRSTS, including alveolar soft part sarcoma. The role of this therapy has not yet been established for this indication.

Contraindications

Many factors affect the outcome of tissue transplantation. The selection process is designed to obtain the best result for each individual. Relative contraindications to HSC transplantation include but are not limited to:

- poor cardiac function (ejection fraction less than 45%)
- poor liver function (bilirubin greater than 2.0 mg/dl and transaminases greater than two times normal), unless related to disease
- poor renal function (creatinine clearance less than 50 ml/min)

- poor pulmonary function (diffusion capacity less than 60% of predicted)
- presence of human immunodeficiency virus or of an active form of hepatitis B, hepatitis C or HTLV-1

Professional Societies/Organizations

National Cancer Institute (NCI): For retinoblastoma, the NCI (2011e) notes “Patients presenting with extensive non-central nervous system (CNS) metastases have been treated successfully with myeloablative chemotherapy with stem cell rescue.” “Two reports suggest that there may be a role for intensive multimodality therapy with autologous stem cell rescue for patients with metastatic retinoblastoma. A few responses were noted in both CNS (including trilateral) and systemic metastases. However, these strategies remain under clinical investigation.”

For Ewing family of tumors (EFT), the NCI (2011d) notes “Multiple small studies that report benefit for hematopoietic stem-cell transplantation (HSCT) have been published but are difficult to interpret because only patients who have a good initial response to standard chemotherapy are considered for HSCT. The role of high-dose therapy followed by stem cell rescue is being investigated in a Euro-Ewing clinical trial for patients that present with pulmonary metastases.”

For metastatic disease, the NCI (2011d) notes “More intensive therapies, many of which incorporate high-dose chemotherapy with or without total-body irradiation in conjunction with stem cell support, have not shown improvement in event-free survival (EFS) rates for patients with bone and/or bone marrow metastases. The impact of high-dose chemotherapy with peripheral blood stem cell support for patients with lung metastases is unknown.”

Regarding recurrent EFT, the NCI notes, “Aggressive attempts to control the disease, including myeloablative regimens, have been used but there is no evidence at this time to conclude that myeloablative therapy is superior to standard chemotherapy. Surveys of patients undergoing allogeneic stem cell transplantation for recurrent ETB did not show improved event-free survival when compared with autologous stem cell transplantation and was associated with a higher complication rate.”

For extracranial germ cell tumors (GCT), the NCI (2011a) notes “The role of high-dose chemotherapy and hematopoietic stem cell rescue for recurrent pediatric GCT is not established, despite anecdotal reports.”

Summary

Although the data are not robust, the published peer-reviewed scientific literature suggests the effectiveness of autologous hematopoietic stem-cell transplantation (HSCT) for the treatment of a child with relapsed Wilms’ tumor, metastatic non-central nervous system retinoblastoma, and relapsed or progressive Ewing family of tumors.

Coding/Billing Information

Note: This list of codes may not be all-inclusive.

Covered when medically necessary when used to report autologous bone-marrow or blood-derived stem-cell procedures:

CPT®* Codes	Description
38206	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous
38207	Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage
38208	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing
38209	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing
38211	Transplant preparation of hematopoietic progenitor cells; tumor cell depletion

38212	Transplant preparation of hematopoietic progenitor cells; red blood cell removal
38213	Transplant preparation of hematopoietic progenitor cells; platelet depletion
38214	Transplant preparation of hematopoietic progenitor cells; plasma (volume) depletion
38215	Transplant preparation of hematopoietic progenitor cells; cell concentration in plasma, mononuclear, or buffy coat layer
38230	Bone marrow harvesting for transplantation
38241	Bone marrow or blood-derived peripheral stem cell transplantation; autologous

HCPCS Codes	Description
S2150	Bone marrow or blood-derived 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 or pre-and post-transplant care in the global definition

ICD-9-CM Diagnosis Codes	Description
170.0-170.9	Malignant neoplasm of bone and articular cartilage
171.0-171.9	Malignant neoplasm of connective tissue and other soft tissue
189.0	Malignant neoplasm of kidney, except pelvis
190.5	Malignant neoplasm of retina

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Policy History

Pre-Merger Organizations	Last Review Date	Policy Number	Title
CIGNA HealthCare	8/15/2008	0385	Stem-Cell Transplant for Solid Tumors In Children

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