



CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all plans administered by CIGNA Companies including plans administered by Great-West Healthcare, which is now a part of CIGNA.

Subject Stem-Cell Transplantation for Neuroblastoma

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Coverage Policy

CIGNA covers autologous hematopoietic stem-cell transplantation (HSCT) as medically necessary for the treatment of high-risk neuroblastoma.

CIGNA covers allogeneic HSCT from a human leukocyte antigen (HLA)-matched donor (at least five of six HLA-match) following high-dose chemotherapy as medically necessary for the treatment of high-risk neuroblastoma when the individual is not a candidate for autologous HSCT.

CIGNA covers a maximum of three tandem autologous HSCTs as medically necessary for the treatment of high-risk neuroblastoma.

General Background

Neuroblastoma comprises a spectrum of tumors that arise from the primitive sympathetic ganglion cells (Dome, 2008). The location of the tumors appears to vary with age and correlates with the primary disease presentation. Neuroblastoma is predominately a tumor of childhood. Children of any age presenting with localized tumor, and infants with advanced disease and favorable characteristics have a greater likelihood of long-term disease-free survival (DFS); however, older children with advanced disease, older adolescents and adults have a worse long-term prognosis (National Cancer Institute [NCI], 2010). Approximately 70% of patients with neuroblastoma have metastatic disease at diagnosis.

Prognostic variables are used to stratify risk and assign treatment. In addition to age at diagnosis, variables include the clinical stage of disease, regional lymph node involvement, site of primary tumor, tumor histology and the presence of the MTCN oncogene (i.e., v-myc avian myelocytomatosis viral related oncogene, neuroblastoma derived).

Used in conjunction with the International Staging System for neuroblastoma (INSS), the risk-based neuroblastoma treatment plan was developed by the Children’s Oncology Group and assigns each patient to a low-risk, intermediate-risk or high-risk group (National Cancer Institute [NCI], 2010). Risk categories are identified as follows:

Risk category	Description
<p style="text-align: center;">Low risk</p>	<ul style="list-style-type: none"> • stage 1 disease • stages 2A and 2B, except for a child age one or older with MYCN amplification and unfavorable histology • stage 4S with no MYCN amplification, favorable histology, and hyperdiploid
<p style="text-align: center;">Intermediate risk</p>	<ul style="list-style-type: none"> • stage 3, age less than one year and no MYCN amplification • stage 3, age one or older with no MYCN amplification and favorable histology • stage 4, age less than one year with no MYCN amplification • stage 4S with no MYCN amplification, unfavorable histology, and/or diploid
<p style="text-align: center;">High risk</p>	<ul style="list-style-type: none"> • stages 2A and 2B, age one or older, MYCN amplification and unfavorable histology • stage 3 with MYCN amplification • stage 3, age one or older, no MYCN amplification and unfavorable histology • stage 4, age one or older • stage 4, age less than one year with MYCN amplification • stage 4S with MYCN amplification

Stem-Cell Transplantation

Stem-cell transplantation refers to transplantation of hematopoietic stem cells (HSCs) from a donor into a patient. Hematopoietic stem-cell transplantation (HSCT) can be either autologous (using the patient’s own stem cells) or allogeneic (using stem cells from a donor).

The use of high-dose chemotherapy and surgery has been shown to achieve minimal disease states in more than 50% of patients. Consolidation therapy, consisting of myeloablative therapy with autologous hematopoietic stem-cell rescue, results in 30–83% long-term disease-free survival (Luksch, 2005; Laprie, 2004; Kamani, 1999).

Autologous HSCT: According to the NCI (2010), autologous HSCT is listed as a standard treatment option for individuals classified as having high-risk disease. Improved survival has been demonstrated with the use of autologous HSCT compared with chemotherapy in several randomized controlled clinical trials (Berthold, 2005; Matthay, 1999). In a recent meta-analysis of three randomized clinical trials (RCTs) involving 739 children with neuroblastoma Yalcin et al. (2010) noted improved event-free (EFS) (Hazard ratio [HR] 0.78) and overall survival (OS) (HR 0.74) with use of myeloablative therapy compared with conventional therapy, including chemotherapy or no therapy. The authors concluded that myeloablative therapy seems to be a good treatment option for children with high-risk neuroblastoma, resulting in higher survival rates than with conventional therapy. Included in this analysis was an RCT by Berthold et al. (2005) who randomized 295 patients to receive either high-dose chemotherapy with autologous HSCT or conventional chemotherapy. Children who received high-dose therapy with autologous hematopoietic stem-cell transplantation (HSCT) had significantly improved three-

year overall survival (OS) compared with those who received conventional therapy (66% versus 52%, respectively), as well as a significant improvement in three-year event-free survival (EFS) (53% versus 30%, respectively). Additionally, several large prospective series and retrospective analyses suggest improved outcomes with OS rates of 29%-37% (Ladenstein, 2008; Zage, 2008; Trahair, 2007; Vedeguer, 2004; Phillip, 1997). Data suggest that autologous hematopoietic stem-cell transplantation (HSCT) is a safe and effective therapy for the treatment of selected individuals with high-risk neuroblastoma.

Allogeneic Transplant: The superiority of allogeneic HSCT compared with autologous HSCT in children with neuroblastoma has not been established; however, it can play a role in treatment for those patients who are not candidates for autologous HSCT when a human leukocyte antigen (HLA)-matched donor is available (at least 5 of 6 HLA-match) (Ladenstein, 2008; Evans, 1994; Ladenstein, 1994; Matthey, 1994). Unlike autologous HSCT, high-dose chemotherapy with allogeneic HSCT does not entail the possibility of tumor reinfusion with the graft. Treatment-related morbidity and mortality of HSCT and subsequent graft-versus-host disease (GVHD) are higher than results seen with autologous HSCT; however, and the procedure has not been investigated in large numbers of patients (National Cancer Institute [NCI], 2010; Gratwohl, 2004).

Matthey et al. (1994) compared the toxicity, relapse rate and progression-free survival rates of high-risk neuroblastoma patients receiving identical induction therapy and myeloablative chemotherapy plus total-body irradiation followed by allogeneic or autologous HSCT. Twenty-six patients with sibling HLA-matched donors received allogeneic HSCT, and 34 patients received autologous HSCT. The relapse rate for patients receiving allogeneic HSCT was 69%, compared with 49% for patients receiving autologous HSCT ($p=0.14$). The estimated progression-free survival (PFS) rates at four years after HSCT were 25% and 49% ($p=.051$) for patients receiving allogeneic and autologous HSCT, respectively. The authors concluded that overall outcome was similar with patients receiving autologous transplant with purged marrow or allogeneic marrow, although selection bias cannot be excluded in this nonrandomized population. A case-controlled study by Ladenstein (1994) compared 61 children with advanced or poorly responding neuroblastoma receiving allogeneic ($n=17$) or autologous ($n=34$) HSCT. No difference in PFS between the two treatment groups was found (35% and 41% at 2 years, respectively). Although these initial results do not show any clear benefit of allogeneic versus autologous HSCT for high-risk neuroblastoma, the advent of reduced intensity conditioning regimens has provided the possibility that reduction of treatment-related mortality allows for the detection of a therapeutic benefit (Barrett, 2010). Data are not robust; however, allogeneic HSCT may be considered an appropriate treatment option for selected individuals with high-risk neuroblastoma who are not candidates for autologous HSCT.

Tandem Autologous HSCT: In tandem HSCT, the patient receives multiple cycles of high-dose chemotherapy and/or radiation therapy, each followed by HSCT. In neuroblastoma, outcomes improve with more intense therapy although this improvement is limited by the toxicity of the regimens.

According to the NCI (2010), tandem myeloablation with stem-cell rescue may be used for individuals with high-risk, recurrent neuroblastoma. Sequential, tandem high-dose therapy has been developed in view of the frequency of early relapse following HSCT (Ladenstein, 2008).

Several case series demonstrated significantly better outcomes for individuals with high-risk disease who received tandem autologous transplantation compared with single autologous HSCT. Three-year overall survival (OS) rates ranged from 57–79% (Grupp, 2000a; Kletzel, 2002; von Allmen, 2005). Sung et al. (2007) evaluated 52 patients > one year with newly diagnosed stage IV neuroblastoma who were assigned to receive tandem high-dose chemotherapy and autologous HSCT. Fifty patients received the first HSCT and 44 patients underwent a second HSCT with high-dose chemotherapy. Five-year OS and event-free survival (EFS) rates for the entire cohort were 64.3% and 62.1%, respectively.

In another study, George et al. (2006) reported the outcomes of 97 patients with high-risk neuroblastoma who were treated with two consecutive courses of myeloablative therapy and autologous HSCT. PFS at five and seven years from diagnosis was 47% and 45%, respectively. OS at five and seven years was 60% and 53%, respectively. Relapse occurred in 42% of patients, mainly within three years of transplantation and in primarily diffuse osseous sites. The published peer-reviewed scientific literature supports the safety and effectiveness of up to three tandem autologous HSCTs for the treatment of selected individuals with high-risk neuroblastoma.

Contraindications

Many factors affect the outcome of a tissue transplant. The presence of any significant comorbid conditions which would significantly compromise clinical care and chances of survival is a contraindication to transplant. Relative contraindications to hematopoietic stem-cell transplantation (HSCT) include, but are not limited to:

- poor cardiac function (ejection fraction < 45%)
- poor liver function (bilirubin > 2.0mg/dl and transaminases greater than two times normal), unless related to disease
- poor renal function (creatinine clearance < 50ml/min)
- poor pulmonary function [diffusion capacity (DLCO) < 60% of predicted]
- presence of human immunodeficiency virus (HIV) OR the active form of ANY of the following:
 - hepatitis B virus (HBV)
 - hepatitis C virus (HCV)
 - human T cell lymphotropic virus (HTLV-1)
- Karnofsky rating < 60% and/or Eastern Cooperative Oncology Group (ECOG) performance status > 2

Professional Societies/Organizations

National Cancer Institute (NCI): The NCI (2010) supports myeloablative chemotherapy with HSCT as a treatment option for patients with high-risk neuroblastoma. This includes patients initially diagnosed with low-, intermediate- or high-risk disease who have recurrence of the disease. The NCI lists tandem myeloablation and stem-cell transplantation as a treatment option currently under clinical evaluation for patients with high-risk or recurrent disease.

Summary

The published peer-literature evidence supports the safety and effectiveness of single and tandem (i.e., up to three cycles) autologous hematopoietic stem-cell transplantation (HSCT) for the treatment of high-risk neuroblastoma in selected individuals. Although data are not robust, allogeneic HSCT may be an appropriate treatment option for selected individuals with high-risk neuroblastoma who are not candidates for autologous HSCT.

Coding/Billing Information

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

Covered when medically necessary:

CPT®* Codes	Description
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	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
38210	Transplant preparation of hematopoietic progenitor cells; specific cell depletion within harvest, T-cell depletion
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
38240	Bone marrow or blood-derived peripheral stem cell transplantation; allogeneic
38241	Bone marrow or blood-derived peripheral stem cell transplantation; autologous
38242	Bone marrow or blood-derived peripheral stem cell transplantation; allogeneic donor infusions

HCCPS Codes	Description
S2140	Cord blood harvesting for transplantation, allogeneic
S2142	Cord blood-derived stem-cell transplantation, allogeneic
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
160.0	Malignant neoplasm of nasal cavities
164.2	Malignant neoplasm of anterior mediastinum
164.3	Malignant neoplasm of posterior mediastinum
164.8	Malignant neoplasm of other parts of mediastinum
164.9	Malignant neoplasm of mediastinum, part unspecified
171.4	Malignant neoplasm of connective and other soft tissue of thorax
171.5	Malignant neoplasm of connective and other soft tissue of abdomen
171.7	Malignant neoplasm of connective and other soft tissue of trunk, unspecified site
171.8	Malignant neoplasm of other specified sites of connective and other soft tissue
171.9	Malignant neoplasm of connective and other soft tissue, site unspecified
192.8	Malignant neoplasm of other specified sites of nervous system
192.9	Malignant neoplasm of nervous system, part unspecified
194.0	Malignant neoplasm of adrenal gland
195.1	Malignant neoplasm of thorax
195.2	Malignant neoplasm of abdomen

*Current Procedural Terminology (CPT®) © 2010 American Medical Association: Chicago, IL.

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2. American Society of Clinical Oncology. Cancer.net guide to neuroblastoma. Update 2009 Oct. Accessed Sep 7, 2010. Available at URL address: <http://www.cancer.net/portal/site/patient/menuitem.00a3259e57e760d90d0bde106e37a01d/?vgnnextoid=7384ea97a56d9010VgnVCM100000f2730ad1RCRD&vgnnextfmt=default>
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Policy History

<u>Pre-Merger Organizations</u>	<u>Last Review Date</u>	<u>Policy Number</u>	<u>Title</u>
CIGNA HealthCare	10/15/2008	0189	Stem-Cell Transplant for Neuroblastoma

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