



Cigna Medical Coverage Policy

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 an appropriately-matched human leukocyte antigen (HLA) donor 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 primarily occurs in childhood and comprises a spectrum of tumors with primitive sympathetic ganglion cell origin (Dome, 2008). About 37% of cases are diagnosed as infants, and 90% are younger than five years at diagnosis, with a median age at diagnosis of 19 months. Approximately 70% of patients with neuroblastoma have metastatic disease at diagnosis. 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], 2013).

Prognostic variables are used to stratify risk and assign treatment. In addition to age at diagnosis, these 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 Neuroblastoma Staging System (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], 2013). According to the NCI (2013), treatment is based on whether the tumor is low, intermediate, or high risk:

- “For low-risk tumors the approach is either observation or resection, and survival is greater than 98%.
- For intermediate-risk tumors, chemotherapy is usually given before resection, with the amount and duration based on clinical and tumor biological risk factors. The survival rate for intermediate-risk patients in recent trials is close to 95%, and thus, the current trend is to decrease chemotherapy to diminish side effects.
- For high-risk patients, treatment has intensified to include chemotherapy, surgery, radiation therapy, hematopoietic stem cell transplantation, and immunotherapy, resulting in survival rates of 40% to 50%.”

The idea that further increasing dose intensity may overcome the resistance to drugs has provided a rationale for aggressive high-dose chemotherapy consolidation protocols (Yalcin, 2013). High-dose chemotherapy with stem-cell rescue has been proposed as a treatment option for individuals with high-risk neuroblastoma.

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).

In neuroblastoma, a boost of hematopoietic progenitor or stem cells, also referred to as a hematopoietic stem-cell infusion (HSCI) is used to facilitate more rapid hematopoietic recovery, graft loss, or loss of chimerism following HSCT. The cell product used for a boost may be a previously cryopreserved cell product that contains stem cells or may alternatively require the donor to undergo additional evaluation, mobilization, and harvest. A boost is not preceded by a preparative regimen, and may be required when additional conventional chemotherapy is given to treat relapse and reestablish remission after transplantation. Prolonged cytopenias and immunosuppression may result, requiring additional HSCI which is typically given days to weeks after reinduction chemotherapy (LeMaistre, 2013).

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 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

Autologous HSCT: According to the NCI (2013), autologous HSCT is 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). Yalcin et al. (2013) updated a 2010 Cochrane systematic review and meta-analysis of three randomized clinical trials (RCTs) involving 739 children with neuroblastoma. The update noted a continuing statistically significant difference in event-free survival in favor of myeloablative therapy over conventional therapy or no further treatment (hazard ratio 0.79%). However, with updated data from Matthay (1999), the difference in overall survival was no longer statically significant (HR 0.86.95%). The authors noted no definitive

conclusions can be made regarding adverse effects, quality of life, or the best treatment strategy and suggest that a randomized clinical trial is needed to answer outstanding questions.

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 overall survival (OS) rates of 29%-37% (Ladenstein, 2008; Zage, 2008; Trahair, 2007; Vedeguer, 2004; Phillip, 1997). High-dose chemotherapy and surgery have been shown to achieve minimal disease states in more than 50% of patients. Consolidation therapy, consisting of myeloablative therapy with autologous hematopoietic stem-cell transplantation (HSCT) rescue, results in 30–83% long-term disease-free survival (Luksch, 2005; Laprie, 2004).

Data in the published, peer-viewed scientific literature suggest that autologous HSCT is a safe and effective treatment option for individuals with high-risk neuroblastoma.

Tandem Autologous HSCT: In tandem HSCT, the patient receives multiple cycles of high-dose chemotherapy and/or radiation therapy, each followed by HSCT. According to the NCI (2013), tandem transplantation has been shown to be feasible for patients with high-risk neuroblastoma. Although improved outcomes have been demonstrated they are limited by the toxicity of the chemotherapy.

Several case series demonstrated significantly better outcomes for individuals with high-risk disease who received tandem autologous transplantation compared with single autologous transplantation. Three-year 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. Progression-free survival (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.

Allogeneic HSCT: The superiority of allogeneic HSCT compared with autologous HSCT in children with neuroblastoma has not been established; treatment-related morbidity and mortality of HSCT and subsequent graft-versus-host disease (GVHD) are higher than results seen with autologous HSCT. However, although this therapy has not been investigated in large numbers of patients, it may play a role in treatment of 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; Gratwohl, 2004; Evans, 1994; Ladenstein, 1994; Matthey, 1994). Unlike autologous HSCT, high-dose chemotherapy with allogeneic HSCT does not entail the possibility of tumor re-infusion with the graft.

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 PFS rates at four years after HSCT were 25% and 49% ($p=.051$) for patients receiving allogeneic and autologous HSCT, respectively. 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). In a more recent analysis of registry data, Ladenstein et al. (2008) analyzed outcomes for >4000 individuals who received HSCT for consolidation of primary treatment (i.e., autologous HSCT, n=3974; allogeneic HSCT, n=124). Five-year overall survival was 37% and 25%, for autologous and allogeneic HSCT, respectively.

Although these initial results do not show any clear benefit of allogeneic hematopoietic stem-cell transplantation (HSCT) over 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 is an accepted treatment option for selected individuals with high-risk neuroblastoma who are not candidates for autologous HSCT.

Professional Societies/Organizations

National Cancer Institute (NCI): The NCI (2014) notes that myeloablative chemotherapy with autologous HSCT is a standard treatment option for patients with high-risk neuroblastoma. Two or more sequential cycles of myeloablative chemotherapy and stem cell rescue given in a tandem fashion has been shown to be feasible for patients with high-risk neuroblastoma. Autologous HSCT may also benefit patients initially diagnosed with low-, intermediate- or high-risk disease and who have recurrence of the disease.

Use Outside of the US: No relevant information.

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) as a component of the standard of care for the treatment of selected individuals with high-risk neuroblastoma. 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: 1) This list of codes may not be all-inclusive.

2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

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, per donor
38209	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing, per donor
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, allogeneic
38232	Bone marrow harvesting for transplantation; autologous
38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation, per donor
38241	Hematopoietic progenitor cell (HPC); autologous transplantation
38242	Allogeneic lymphocyte infusions

HCPCS 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

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