Molina Clinical Policy
Hematopoietic Stem Cell Transplantation for Neuroblastoma: Policy No. 193

Last Approval: 10/12/2023
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DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. Policies are not a supplementation or recommendation for treatment; Providers are solely responsible for the diagnosis, treatment, and clinical recommendations for the Member. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (e.g., will be paid for by Molina) for a particular Member. The Member's benefit plan determines coverage – each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their Providers will need to consult the Member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a Member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid Members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this MCP and provide the directive for all Medicare members. References included were accurate at the time of policy approval and publication.

OVERVIEW

Neuroblastoma is a type of cancer that arises in the sympathetic nervous system tissue, mainly in the adrenal medulla. Commonly this type of cancer presents as an abdominal mass. Additional symptoms can be caused by the tumor pressing against other tissues or from metastasis to bone. Signs of neuroblastoma include a mass in the abdomen, neck, or chest, bone pain, abdominal pain, emesis, weight loss, anorexia, fatigue, bulging eyes, dark circles around the eyes, and weakness or paralysis. Infants can present with distended abdomen, difficulty breathing, and blue-colored masses under the skin (Shohet et al. 2023; [1-2]Shohet et al. 2022).

Neuroblastomas largely affect infants and children with approximately 90% of cases being diagnosed before the age of 5 years and it also accounts for approximately 18% of pediatric cancers and 15% of pediatric cancer deaths ([2]Shohet et al. 2022). It is the most common extracranial solid tumor in children, with metastatic disease at diagnosis in half of the cases. The cause is unknown, but because of the early age at onset, factors before conception and during gestation may be considered ([2]Shohet et al. 2022). Children with a localized, resectable neuroblastoma have the best prognosis and chance for long-term, disease-free survival. Infants 12 months or younger with advanced disease also have a good prognosis ([2]Shohet et al. 2022). Some neuroblastoma patients are enrolled in clinical trials for other treatment options. One such therapy being studied in clinical trials is the use of meta-iodobenzylguanidine (MIBG) therapy for the treatment of high-risk neuroblastoma (NIH 2022). MIBG therapy has been available since the 1980s and has had "response rates of approximately 30% following 1-2 treatments (DuBois et al. 2021)." Current studies for MIBG therapy are evaluating combination strategies to determine if MIBG combined with other agents may offer improved outcomes (DuBois et al. 2021).

Prognostic markers 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 mitochondrial copy number (mtTCN) oncogene (Shohet et al. 2023). The risk-based neuroblastoma classification system was developed by the Children's Oncology Group and is used together with the International Neuroblastoma Staging System (INSS) to define risk levels for patients with neuroblastoma (NCI 2023). The classification system was updated in 2021 and the high-risk strata are summarized in the following table (NCI 2023; Irwin et al. 2021):

INSS Stage*	Age	MYCN Status	INPC Classification**	DNA Ploidy***	Other
2A/2B	Any	Amplified	Unfavorable	Any	Any degree of resection
3	Any	Amplified	Any	Any	--
	≥ 18 months	Nonamplified	Unfavorable	Any	--
4	< 12 months	Amplified	Any	Any	--
	12 months to < 18 months	Amplified	Any	Any	--
	12 months to < 18 months	Any	Any	DI = 1	--
	12 months to < 18 months	Any	Unfavorable	Any	--
	≥ 18 months	Any	Any	Any	--
4S	< 12 months	Amplified	Any	Any	Asymptomatic or Symptomatic

* INSS Stage 2A/2B symptomatic patients with spinal cord compression, neurologic deficits, or other symptoms are treated with immediate chemotherapy for four cycles. INSS Stage 3 or Stage 4 patients with clinical symptoms as listed above receive immediate chemotherapy.
** International Neuroblastoma Pathologic Classification (INPC)
*** DNA Ploidy: DNA Index (DI) > 1 is favorable, DI = 1 is unfavorable; hypodiploid tumors (with DI < 1) will be treated as a tumor with a DI > 1 (DI < 1 [hypodiploid] to be considered favorable ploidy).

The INSS stages based on clinical, radiologic, and surgical evaluation are (DynaMed 2023; Shohet et al. 2023; [1]Shohet et al. 2022; Irwin et al. 2021):

- **Stage 1:** Localized tumor with complete gross excision and/or microscopic residual disease, ipsilateral lymph nodes negative for tumor (lymph nodes attached to and removed with tumor may be positive).
- **Stage 2A:** Localized tumor with incomplete gross excision; representative ipsilateral nonadherent lymph nodes negative for tumor microscopically.
- **Stage 2B:** Localized tumor with or without complete gross excision, with ipsilateral nonadherent lymph nodes positive for tumor. Enlarged contralateral lymph nodes must be negative microscopically.
- **Stage 3:** Unresectable unilateral tumor infiltrating across the midline, with or without regional lymph node involvement; or localized unilateral tumor with contralateral regional lymph node involvement; or midline tumor with bilateral extension by infiltration (unresectable) or by lymph node involvement.
- **Stage 4:** Any primary tumor with dissemination to distant lymph nodes, bone, bone marrow, liver, skin, and/or other organ (except as defined by 4S).
- **Stage 4S:** Localized primary tumor (as defined for Stage 1, 2A, or 2B) in infants aged less than one year with dissemination limited to skin, liver, or bone marrow (marrow involvement should be minimal).

The **International Neuroblastoma Risk Group Staging System (INRGSS)** is a preoperative staging system that was developed specifically for the INRG classification system. There are two stages of localized disease (L1 and L2) and two stages of metastatic disease (M and MS). Unlike INSS, the INRGSS is a clinical classification system that is determined prior to any treatment, including surgery. The extent of disease is determined by the presence or absence of image defined risk factors (IDRFs) and/or metastatic tumor at the time of diagnosis before any treatment or surgery. Types of IDRFs include surgical risk factors that are detected by imaging which could potentially make total tumor excision risky or difficult at the time of diagnosis and increase the risk of surgical complications. INRGSS stages are defined below (DynaMed 2023; Shohet et al. 2023; [1]Shohet et al. 2022; Irwin et al. 2021):

- **Stage L1:** Locoregional tumor without IDRFs.
- **Stage L2:** Locoregional tumor with one or more IDRFs.
- **Stage M:** Distant metastatic disease (except MS).
- **Stage MS:** INRG Stage L1 or L2 tumor w/ metastatic disease confined to skin and/or liver and/or bone marrow.

Stem Cell Transplantation

Stem-cell transplantation refers to transplantation of hematopoietic stem cells (HSCs) from a donor into a patient. HSCs are immature cells that can develop into any of the three types of blood cells (red cells, white cells, or platelets). HSCs are created in the bone marrow and are found in the bone marrow and peripheral blood. There is also a high concentration of HSCs in umbilical-cord blood. Hematopoietic stem-cell transplantation (HSCT) can be either autologous (using the person's own stem cells) or allogeneic (using stem cells from a donor). In allogeneic HSCT, it is preferable for donors to have a human leukocyte antigen (HLA) type that is identical to the recipient. Matching is performed on the basis of variability at three of more loci of the HLA gene (e.g., HLA-A, HLA-B, HLA-DRB1). As HLA variability increases, transplant-related morbidity and mortality, including graft rejection and graft-versus-host disease, also increase (Chao 2022; Deeg et al. 2022; Holmberg et al. 2022; Negrin 2022).

COVERAGE POLICY

All transplants require prior authorization from the Corporate Transplant Department. Solid organ transplant requests will be reviewed by the Corporate Senior Medical Director or qualified clinical designee. All other transplants will be reviewed by the Corporate Senior Medical Director or covering Medical Director. If the

criteria are met using appropriate NCD and/or LCD guidelines, State regulations, and/or MCP policies the Corporate Senior Medical Director's designee can approve the requested transplant.

Office visits with participating Providers do NOT require prior authorization. Providers should see the Member in office visits as soon as possible and without delay. Failure to see the Member in office visits may be considered a serious quality of care concern.

Transplant Evaluation

Please see *MCP-323 Pre-Transplant Evaluation* for additional criteria and information.

Components of the transplant evaluation include:

1. History and physical examination; **AND**

2. Psychosocial evaluation and clearance:
   a. Absence of any history of medical treatment non-compliance; **AND**
   b. Member understands surgical risk and post-procedure follow-up required; **AND**
   c. Adequate family and social support; **AND**
   d. No behavioral health disorder by history or psychosocial issues:
      i. If history of behavioral health disorder, no severe psychosis or personality disorder may be present; **AND**
      ii. Mood/anxiety disorder must be excluded or treated, unless actively treated and controlled.

AND

3. EKG; **AND**

4. Chest x-ray; **AND**

5. Cardiac clearance in the presence of any of the following:
   a. Chronic smokers; **OR**
   b. Members > 50 years age; **OR**
   c. Those with a clinical or family history of heart disease or diabetes.

AND

6. Pulmonary clearance if evidence of pulmonary artery hypertension or chronic pulmonary disease; **AND**

7. Neurological exam and clearance for transplant including **ONE** of the following:
   a. Normal neurologic exam; **OR**
   b. Non-life limiting neurological impairment that does not preclude transplant and not caused by hematologic malignancy (e.g., diabetic peripheral neuropathy); **OR**
   c. Abnormal neurological exam with positive findings including **ONE** of the following:
      i. Lumbar puncture normal cytology; **OR**
      ii. Lumbar puncture with cytological exam abnormal, however central nervous system disease treated prior to clearance.

AND

8. A Performance Status that includes **ONE** of the following:
   a. Karnofsky score 70-100%; **OR**
   b. Eastern Cooperative Oncology Group (ECOG) Grade 0-2.

AND

9. Lab studies that include:
   a. Complete blood count; kidney profile (blood urea nitrogen, creatinine); electrolytes; calcium; phosphorous; albumin; liver function tests; and coagulation profile (prothrombin time, and partial thromboplastin time);*

b. Serologic screening for: Human immunodeficiency virus (HIV); Epstein Barr virus; Hepatitis virus B; Hepatitis C; cytomegalovirus; rapid plasma reagin; and/or fluorescent treponemal antibody:*
    i. If HIV positive **ALL** of the following must be met:
        1. CD4 count >200 cells/mm-3 for >6 months; **AND**
        2. Human immunodeficiency virus 1 (HIV-1) ribonucleic acid undetectable; **AND**
        3. On stable anti-retroviral therapy >3 months; **AND**
        4. No other complications from acquired immunodeficiency syndrome (AIDS) (e.g., opportunistic infection, including aspergillus, tuberculosis, coccidioides mycosis, resistant fungal infections, Kaposi's sarcoma, or other neoplasm).
c. Urine drug screen if Member has a history of and/or current drug abuse.

AND

10. Colonoscopy (if indicated or if Member is age ≥ 45) with complete workup and treatment of abnormal results as indicated; an initial screening colonoscopy after initial negative screening requires a follow-up colonoscopy every 10 years).*

AND

11. Gynecological examination with Pap smear for women ages ≥ 21 to ≤ 65 years of age or if indicated (not indicated in women who have had a total abdominal hysterectomy or a total vaginal hysterectomy) within the last three years with complete workup and treatment of abnormal results as indicated.*

AND

12. Dental examination or oral exam showing good dentition and oral care or no abnormality on panorex or plan for treatment of problems pre- or post-transplant within the last 12 months.

AND

13. Mammogram (if indicated or > age 40) with complete workup and treatment of abnormal results as indicated.*

OR

14. Prostate pecific Antigen, if history of prostate cancer or previously elevated PSA with complete workup and treatment of abnormal results as indicated.*

* Participating Centers of Excellence may waive these criteria.

Criteria for Autologous HSCT

Autologous HSCT **may be considered medically necessary** and may be authorized for the treatment of high-risk neuroblastoma when the following criteria are met:

1. All transplant evaluation criteria are met; **AND**

2. Single autologous HSCT **may be considered medically necessary** for initial treatment when **ANY** of the following are present:
    a. INSS Stage 2 or 3 at diagnosis and MYCN amplification (>4x above reference); **OR**
    b. INSS Stage 4 at diagnosis with MYCN amplification (>4x above reference) and **ANY** of the following:
        - Age >18 months at diagnosis; **OR**
        - Age 12-18 months with unfavorable characteristics; **OR**
        - Metastatic disease at diagnosis.

OR

3. Single autologous HSCT **may be considered medically necessary** for recurrent or refractory neuroblastoma when **ANY** of the following are present:

a. Relapse is defined as tumor recurrence after a prior complete response; **OR**
b. Primary refractory disease is defined as a tumor that does not achieve a complete remission after initial standard-dose chemotherapy.

OR

4. A repeat autologous HSCT **may be considered medically necessary** for **ANY** of the following:
   a. Primary graft failure; **OR**
   b. Failure to engraft.

OR

5. A planned tandem (or "sequential") autologous HSCT **is considered medically necessary** for the treatment of high-risk neuroblastoma when the criteria above for HSCT is met.

AND

6. The requesting transplant recipient is free from **ALL** of the following absolute contraindications:
   a. Cardiac, pulmonary, and nervous system disease that cannot be corrected and is a prohibitive risk for surgery.
   b. Malignant neoplasm with a high risk for reoccurrence, non-curable malignancy (excluding localized skin cancer).
   c. Systemic and/or uncontrolled infection.
   d. AIDS (CD4 count < 200cells/mm3).
   e. Unwilling or unable to follow post-transplant regimen as documented by history of non-compliance and/or inability to follow through with medication adherence or office follow-up.
   f. Chronic illness, aside from transplant indication, with one year or less life expectancy.
   g. Limited, irreversible rehabilitation potential.
   h. Active, untreated substance abuse or misuse (including daily significant cannabis use) requires documentation of a formal substance use disorder evaluation with clear and unambiguous documentation of:
      i. A reasonable expectation that the Member can adequately comply with a complex, post-transplant plan of care; **AND**
      ii. The Member is free from addiction for at least 6 months.
   i. Inadequate social/family support.

AND

7. The requesting transplant recipient should be evaluated carefully and potentially treated if any of the relative contraindications below are present. (Irreversible lung disease patients require consultation and clearance by a Pulmonologist prior to consideration of transplantation).
   a. Smoking, documentation supporting free from smoking for 6 months; **OR**
   b. Active peptic ulcer disease; **OR**
   c. Active gastroesophageal reflux disease; **OR**
   d. Cerebrovascular accident (CVA) with long term impairment that is not amendable to rehabilitation or a patient with CVA/transient ischemic attack within past 6 months; **OR**
   e. Obesity with body mass index of >30 kg/m^2 may increase surgical risk; **OR**
   f. Chronic liver disease such as Hepatitis B/C/D, or cirrhosis which increases the risk of death from sepsis and hepatic failure requires consultation by a gastroenterologist or hepatologist; **OR**
   g. Gall bladder disease requires ultrasound of the gall bladder with treatment prior to transplantation.

Continuation of Therapy

When extension of a previously approved transplant authorization is requested, review using updated clinical information is appropriate.

1. If Molina Healthcare has authorized prior requests for transplantation **ALL** of the following information is required for medical review:
   a. Presence of no absolute contraindication as listed above; **AND**
   b. History and physical within the last 12 months; **AND**
   c. Kidney profile within the last 12 months; **AND**
   d. Cardiac update if history of cardiac disease within two years (≥ 50 years of age); **AND**
   e. Psychosocial evaluation or update within the last 12 months; **AND**
   f. Per initial and updated history and physical, any other clinically indicated tests and/or scans as determined by transplant center physician or Molina Medical Director.

2. If authorized prior requests for transplantation were obtained from another insurer, **ALL** of the following information is required for medical review:
   a. Authorization letter/documentation from previous insurer; **AND**
   b. Presence of no absolute contraindication as listed above; **AND**
   c. History and physical within the last 12 months; **AND**
   d. Cardiac update if history of cardiac disease within two years (≥ 50 years of age); **AND**
   e. Psychosocial evaluation or update within the last 12 months; **AND**
   f. Per initial and updated history and physical, any other clinically indicated tests and/or scans as determined by transplant center physician or Molina Medical Director.

Limitations and Exclusions

1. Autologous HSCT when the above criteria are not met.
2. Autologous HSCT when used as initial treatment of low or intermediate-risk neuroblastoma.
3. Allogeneic and tandem allogeneic HSCT is considered investigational to treat neuroblastoma as the evidence is insufficient.
4. HSC collection, storage, and freezing for a future unplanned transplant.

DOCUMENTATION REQUIREMENTS. Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational, or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

SUMMARY OF MEDICAL EVIDENCE

The evidence is sufficient and supports the safety and effectiveness of autologous HSCT as a component of the standard of care for the treatment of selected individuals with high-risk neuroblastoma. Currently, some transplant centers use tandem autologous HSCT as the preferred treatment for high-risk neuroblastoma. MIBG therapy combined with additional agents is being researched as a possible treatment for neuroblastoma.

Single Autologous HSCT

Berthold et al. (2018) completed an open-label, randomized trial to determine the long-term outcomes of patients with high-risk neuroblastoma following high-dose chemotherapy (HDC) with autologous HSCT or maintenance therapy for consolidation. Patients were eligible for inclusion if they had a "1) newly diagnosed neuroblastoma according to the INSS, 2) high-risk defined as sage 4 disease in patients aged ≥1 to <21 years or MYCN-amplified tumors of patients with stage 1, 2, 3 , or 4S disease aged 6 months to < 21 years or stage 4 disease and age < 1 year with MYCN amplification, and 3) written informed consent from the parents or legal guardian." Exclusion criteria included additional concomitant non-protocol anti-cancer therapies. A total of 295 patients were randomized prior to the end of induction chemotherapy. Maintenance therapy consisted of cyclophosphamide (150 mg/m^2 per day on days 1-8 either orally or infusion) every 3 weeks for 4 cycles. HDC "consisted of melphalan, etoposide, and carboplatinum (MEC: 45 mg/m² melphalan a day [intravenous] over 30 minutes given on days −8 to −5 before stem cell reinfusion, 40 mg/kg etoposide a day [intravenous] over 4 hours given on day −4 before stem cell reinfusion, 500 mg/m² carboplatinum a day [intravenous] over 1 hour on days −4 to−2 before stem cell reinfusion)." Nine patients received

busulfan and melphalan for HDC due to severe auditory impairment. A total of 6 patients either had carboplatinum omitted or substituted with cyclophosphamide. Peripheral stem cells were harvested following 2-4 cycles of induction chemotherapy. Patients were assigned to either the intention-to-treat (ITT), as-treated-group (AT), or treated-as-randomized (TAR) groups as there were minor deviations from the treatment protocol allowed, such as administration of drugs for the treatment of Wilms tumor and changes in the treatment cycle order. The ITT group consisted of all 295 randomized patients with 149 in the autologous HSCT group and 146 in the maintenance therapy group. The AT group consisted of 212 patients (n=110 autologous HSCT; n=102 maintenance therapy) assigned to the group of their treatment, regardless of how they were initially randomized. The TAR group consisted of 145 patients (n=75 autologous HSCT; n=70 maintenance therapy) based on their original randomization. The primary outcome observed was event-free survival (EFS) and the secondary outcome observed was overall survival (OS). Median follow-up was 13.1 years for ITT and TAR and 13.0 years for AT. The 10-year EFS was 34±3% for ITT, 38±3% for AT, and 38±4% for TAR. The 10-year OS was 40±3% for ITT, 41±3% for AT, and 42±4% for TAR. Multivariate analysis showed autologous HSCT had better EFS in the ITT subgroups in patients who had complete or very good partial response before randomization, raised lactate dehydrogenase (LDH) at diagnosis, MYCN amplification, stage 4 and age > 1 year, and ch14.18 treatment as further consolidation. EFS and OS was superior in the AT subgroup for autologous HSCT subgroups with complete or very good partial response before randomization, raised LDH at diagnosis, and MYCN amplification. EFS and OS were significantly better for autologous HSCT in the TAR subgroup in those with complete or very good partial response before randomization, raised LDH at diagnosis, normal MYCN, amplified MYCN, and stage 4 disease and age > 1 year. Antibody ch14.18 treatment showed significant differences in EFS and trends for improved OS, particularly in those receiving autologous HSCT. A higher number of recurrences, defined as relapse or disease progression, was noted in the maintenance therapy group when compared to the autologous HSCT group. However, liver recurrences were more common in the autologous HSCT group. Five patients experienced secondary malignancies (leukemia, myelodysplastic syndrome, low malignant sarcoma, and pheochromocytoma) with 3 of those malignancies occurring in the autologous HSCT group and 2 occurring in the maintenance therapy group. There was a total of 27 late deaths (n=15 autologous HSCT; n=12 maintenance therapy) with the majority of late deaths occurring as a result of a tumor. Overall results of this study showed that HDC with autologous HSCT was superior to maintenance therapy at improving EFS. However, researchers noted limitations of this study included the low compliance with the randomization results and the influence of the treatment of subsequent recurrences on the proportions of OS.

Tandem Autologous HSCT

Park et al. (2019) completed a RCT to determine if patients with high-risk neuroblastoma had improved EFS with tandem autologous HSCT compared to single autologous HSCT. The RCT included a total of 652 eligible patients with a median age of 37.2 months. However, only 355 patients were randomized due to being excluded from randomization for either physician/parent preference (n=207), being ineligible for randomization (n=62), being nonrandomly assigned (n=27), or not undergoing therapy (n=1). Of the 355 patients that were randomized, 176 were randomized to the tandem transplant group and 179 were randomized to the single transplant group. Inclusion criteria included “newly diagnosed high-risk neuroblastoma as defined by Children’s Oncology Group criteria…and patients initially diagnosed with non-high-risk neuroblastoma (including stage 1) who had not received chemotherapy and progressed to high-risk neuroblastoma.” Patients were randomized on a 1:1 basis before receiving consolidation therapy. The protocol for therapy consisted of induction, consolidation, and post-consolidation phases. The induction phase consisted of two cycles of topotecan/cyclophosphamide followed by peripheral blood stem cell collection and finally four alternating cycles of cisplatin/etoposide and doxorubicin/cyclophosphamide/vincristine. Patients were eligible for consolidation therapy if there was “no disease progression, no uncontrolled infection, recovery from induction therapy toxicity, sufficient peripheral blood stem cell level, and adequate kidney, cardiac, and liver function.” Those with more favorable prognoses were assigned to receive a single transplant and their data was not included in the analyses. To receive a tandem transplant, patients had to have “no clinical evidence of neuroblastoma progression, available peripheral blood stem cell product, resolution of acute toxicity from the first transplant, adequate cardiac, kidney, hematopoietic, and hepatic function, no uncontrolled infection, and no history of moderate or severe sinusoidal obstruction syndrome during the first transplant.” All patients received radiotherapy following transplant recovery at the primary, residual, and/or metaiodobenzylguanidine-positive metastatic sites. The primary outcome of the RCT was to observe EFS from the time of randomization to relapse, progression, secondary malignancy, or death from any cause. Overall, 3-year EFS for all eligible patients (n=652) was 51.1% and 3-year EFS for the randomized patients (n=355) was 54.9%. The 3-year EFS for patients randomized to the tandem transplant group was 61.6% compared to 48.4% for those randomized to the single transplant group. EFS from time of randomization to the first

event was noted to be higher in the tandem transplant group. The 3-year OS for all randomized patients was 71.6%. The 3-year OS for patients in the tandem transplant group was 74.1% compared to 69.1% for the single transplant group. After consolidation therapy, 250 of the randomized patients (n=121 tandem transplant; n=129 single transplant) received immunotherapy in the form of isotretinoin plus anti-GD2 chimeric antibody and cytokines. The 3-year EFS and OS following immunotherapy was higher in the tandem transplant group (EFS=73.3%; OS=84.0%) compared to the single transplant group (EFS=54.7%; OS=73.5%). In terms of treatment-related morbidity and mortality, tandem transplants were associated with less complications, such as infection, organ injury, and death compared to single transplants. Researchers noted that limitations of this study included a lack of randomization for a large proportion of included patients, tandem transplants are associated with longer hospital stays, newer therapies are available for relapsed neuroblastoma that have the potential to improve survival, and "the higher EFS rate associated with tandem transplant is relevant only within the context of the total therapy delivered." Researchers note that approximately 10% of patients in the study did not progress beyond the induction phase due to disease progression or death.

In a multicenter study completed by Park et al. (2016), 355 patients with high-risk neuroblastoma were randomly assigned after induction therapy to either single transplant with carboplatin-etoposide-melphalan (CEM) or tandem transplant with thiotepa-cyclophosphamide, followed by a modified CEM (TC:CEM). High-risk disease was defined as a tumor with amplification of the MYCN oncogene occurring in children of any age or as metastatic disease occurring in children who were older than 18 months at diagnosis. While the tandem transplant group experienced improved three-year EFS compared with those receiving single transplants (61 versus 48 percent), the difference in OS at three years did not reach statistical significance (74 versus 69 percent). For the subset of patients receiving immunotherapy, tandem transplants were associated with improvements in both EFS (74 versus 56 percent) and OS (84 versus 76 percent); however, longer-term follow-up will be needed to confirm these results. Cumulative rates of severe mucosal, infectious, or liver toxicities and regimen-related mortality were similar between arms. In addition, as dose intensity of treatment increases, the need to monitor for late effects including secondary cancers becomes even more important.

Pasqualini et al. (2016) reported on another study of 26 patients with high-risk neuroblastoma reported the results of an intensified HDC strategy to improve the prognosis of VHR patients. The strategy was based on tandem HDC with thiotepa and busulfan-melphalan (Bu-Mel) followed by autologous HSCT. All patients were eligible for tandem HDC. The median age at diagnosis was 4.4 years (1-15.9). All patients had metastatic disease. MYCN was amplified in 5/26 tumors. Despite the cumulative toxicity of alkylating agents, the toxicity of the intensified HDC strategy was manageable. Thiotepa-related toxicity was mainly digestive, whereas sinusoidal obstruction syndrome was the main toxicity observed after Bu-Mel. The 3-year EFS of this cohort was 37.3% (21.3-56.7%).

MIBG Therapy

DuBois et al. (2021) completed a randomized phase II trial to compare the response rates of three MIBG regimens. The regimens consisted of only MIBG (arm A), intravenous vincristine on day 0 and irinotecan daily for days 0-4 (arm B), and vorinostat 180 mg/m^2/dose oral once daily from day 1 to 12 (arm C). All patients "received MIBG 18 mCi/kg on day 1 and autologous stem cell on day 15." Patients were initially allowed to receive a second course of therapy if there was no disease progression. However, the study protocol was later amended to allow only one course of therapy due to financial constraints. Inclusion criteria included "age 1-30 years with MIBG-avid high-risk neuroblastoma…with one of the following responses to frontline therapy: relapsed disease, refractory disease (persistent disease after best overall response of stable disease after a minimum of four induction cycles), or persistent disease (persistent disease after best overall response of partial response after a minimum of four induction cycles)." Other inclusion criteria included a Lansky or Karnofsky score ≥ 50, adequate hematologic, hepatic, renal, pulmonary, cardiac, and coagulation function, and a minimum of $1.5x10^6$ CD34+ autologous peripheral blood stem cells available. Exclusion criteria included previous total body irradiation or allogeneic transplant, currently pregnant or breastfeeding, active or uncontrolled infection, previous non-catheter-associated deep venous thrombosis, or active diarrhea. A total of 105 eligible and evaluable patients were included in analysis with 36 patients in arm A, 35 in arm B, and 34 in arm C. Patients were stratified within each arm based on age (< or > 18 years), response to frontline therapy, bone marrow involvement at enrollment, and previous MIBG therapy. Researchers noted that MYCN status was not used for stratification due to "the lack of association with response to MIBG." The primary end point of the study was response to one course of therapy using the New Approaches to Neuroblastoma Therapy (NANT) Response Criteria v1.2. The secondary outcome observed was toxicity based on the National Cancer Institute Common Terminology Criteria for Adverse Events version 4. Other outcomes observed included overall response, whole-body radiation dose,

progression-free survival (PFS), and OS. Overall response rates following one course of therapy were 14% (n=5) for arm A, 14% (n=5) for arm B, and 32% (n=11) for arm C. Approximately 27 patients received a second course of therapy and overall response rates for those patients were 17% (n=1/6) for arm A, 36% (n=4/11) for arm B, and 60% (n=6/10) for arm C. Rates of any grade 3 or higher nonhematologic toxicity were 19% for arm A, 49% for arm B, and 35% for arm C. Approximately 66% of patients in arm B developed diarrhea while no patients in arms A or C developed grade 3 or higher diarrhea. Gastrointestinal-related adverse events, anorexia, and dehydration were more common in arm B compared to arms A and C. Patients in arm C had nominally lower PFS and OS compared to those in arms A and B. The median overall whole-body radiation dose was 238.0 cGy (range 104.0-471.2 cGy) and was similar across each arm of the study (arm A=258.7 cGy; arm B=232.0 cGy; arm C= 230.1 cGy). Researchers determined that MIBG combined with vorinostat (arm C) demonstrated the highest response rate following one or two courses of therapy. MIBG combined with vincristine and irinotecan (arm B) resulted in increased toxicity and no improvement in response rate. Researchers reported that the response rate for MIBG therapy alone in this study was much lower in comparison to other studies investigating the use of MIBG therapy alone.

National and Specialty Organizations

According to the **National Cancer Institute (NCI)** *Neuroblastoma Treatment PDQ,* treatment is stratified according to the following tumor risks (NCI 2023):

- **For low-risk tumors,** the approach is surgery followed by observation, or chemotherapy with or without surgery (for symptomatic disease or unresectable progressive disease after surgery), observation without biopsy (for perinatal neuroblastoma with small adrenal tumors) and radiation therapy (only for emergency therapy). Five-year OS was 97% in a large COG study.
- **For intermediate-risk tumors,** treatment options include chemotherapy with or without surgery, surgery and observation in infants, and radiation therapy (if needed). In recent studies, select patients have been observed without undergoing chemotherapy or attempted resection. The three-year OS rate for intermediate-risk patients was about 96% in a large COG study; thus, the current trend is to decrease chemotherapy to diminish side effects.
- **For high-risk tumors,** treatment has intensified to include chemotherapy, surgery, tandem cycles of myeloablative therapy and HSCT, radiation therapy, and dinutuximab, with IL-2/GM-CSF and isotretinoin.

The **American Society for Transplantation and Cellular Therapy (ASTCT)** published guidelines for the indications for HSCT and immune effector cell therapy (Kanate et al. 2020). The guidelines recommend autologous HSCT for high-risk or relapse neuroblastoma as the standard of care. The guidelines state that allogeneic HSCT is "developmental," indicating that "preclinical and/or early-phase studies show [HSCT and immune effector cell therapy] to be a promising treatment option."

The **National Institute for Health and Care Excellence (NICE)** published guidelines for treating neuroblastoma using dinutuximab beta (NICE 2018). The guidelines state "treatments for high-risk neuroblastoma include chemotherapy, radiotherapy, stem cell transplant, surgery, and isotretinoin." The guidelines recommend dinutuximab beta as a "potentially curative option for maintenance treatment of [neuroblastoma]" in patients aged 12 months and over.

The **National Marrow Donor Program (NMDP)** has published the following guidance: *Disease-Specific HCT Indications and Outcomes Data; Engraftment; HLA Matching; Patient Eligibility for HCT; Transplant Consultation Timing; and Treatment Before Transplant* ([1-6] NMDP date unknown).

CODING & BILLING INFORMATION

CPT (Current Procedural Terminology) Codes

CPT	Description
	Collection Codes
38206	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous
38232	Bone marrow harvesting for transplantation; autologous

	Cell Processing Services
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
	Cell infusion codes
38241	Hematopoietic progenitor cell (HPC); autologous transplantation
38243	Hematopoietic progenitor cell (HPC); HPC boost

HCPCS (Healthcare Common Procedure Coding System) Codes

HCPCS	**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 of pre-and post-transplant care in the global definition

CODING DISCLAIMER. Codes listed in this policy are for reference purposes only and may not be all-inclusive. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry standard coding practices for all submissions. When improper billing and coding is not followed, Molina has the right to reject/deny the claim and recover claim payment(s). Due to changing industry practices, Molina reserves the right to revise this policy as needed.

APPROVAL HISTORY

10/12/2023	Policy reviewed, changes to criteria include age for colonoscopy reduced to 45 years, addition of non-life limiting neurological impairment criteria and substance use to absolute contraindications, and removal of abnormal serology criteria and cannabis use section. Updated Overview, Summary of Medical Evidence, and References. IRO Peer Review on September 11, 2023, by a practicing, board-certified physician with specialties in Oncology and Hematology.
10/12/2022	Policy reviewed, no changes to criteria, included section on marijuana use.
10/13/2021	Policy reviewed, no update to criteria, updated references.
9/16/2020	Policy reviewed, updated criteria for single autologous HSCT for initial treatment of INSS Stage 2,3,4 based on NMDP guidelines. Added INRGSS information (recommended by AMR peer reviewer). Updated professional guidelines, references. IRO Peer Review on June 1, 2020, by a practicing, board-certified physician with specialties in Pediatrics and Pediatric Hematology/Oncology.
6/19/2019	Policy reviewed, no changes.
7/10/2018	Policy reviewed, no changes.
6/12/2017	Policy reviewed; criteria added for tandem transplants as medically necessary.
6/15/2016	Policy reviewed, no changes.
6/2/2015	Policy reviewed, updated pre-transplant criteria, continuation of therapy, absolute and relative contraindications, and coding.
7/17/2014	New policy.

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