

## Clinical Policy: Tandem Transplant

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### Description

A tandem transplant, (also known as a sequential or double transplant), refers to a planned second course of high-dose therapy and stem cell transplant (SCT) within 6 months.<sup>1</sup> It differs from a repeat SCT as it is planned prospectively rather than performed due to relapse. Tandem transplants are performed to obtain greater and extended response rates. This policy describes the medical necessity requirements for these transplants.

### Policy/Criteria

- I. It is the policy of health plans affiliated with Centene Corporation<sup>®</sup> that a *tandem autologous transplant* is **medically necessary** when meeting all of the following criteria:
  - A. Member/enrollee has any of the following diagnoses:
    1. Newly diagnosed or responsive multiple myeloma (MM);
    2. Testicular germ cell tumors, either of the following:
      - a. Relapsed testicular cancer;
      - b. Tumors that are refractory to a cisplatin-based chemotherapeutic regimen.
    3. High-risk neuroblastoma characterized by any of the following:
      - a. Child with Stage 2A or 2B disease, age 1 year or older with MYCN amplification, and unfavorable histopathology;
      - b. Child with Stage 3 disease and either of the following:
        - i. Any age with MYCN amplification,
        - ii. 18 months or older, no MYCN amplification, and unfavorable histopathology;
      - c. Child with Stage 4 disease and any of the following:
        - i. Any age, with MYCN amplification,
        - ii. Age 18 months or older,
        - iii. Age between 12 months and 18 months old with MYCN amplification, and/or diploidy, and/or unfavorable histology;
      - d. Child who is Stage 4S disease (not yet 1 year old), and MYCN gene amplification.
    - B. Does not have ANY of the following contraindications:
      1. Inadequate cardiac, renal, pulmonary, or hepatic function;
      2. Significant, uncorrectable, life-limiting medical condition;
      3. Chronic infection with highly virulent and/or resistant microbes that are poorly controlled pre-transplant;
      4. Current non-adherence to medical therapy or a history of repeated or prolonged episodes of non-adherence to medical therapy that are perceived to increase the risk of non-adherence after transplantation;
      5. Psychiatric or psychological condition associated with the inability to cooperate or comply with medical therapy;
      6. Absence of an adequate or reliable social support system.

**II.** It is the policy of health plans affiliated with Centene Corporation that a *tandem autologous transplant followed by an allogeneic transplant* from a human leukocyte antigen (HLA)-identical sibling donor with reduced-intensity conditioning is **medically necessary** for untreated, newly diagnosed MM, when none of the contraindications in section I.B. are present.

**III.** It is the policy of health plans affiliated with Centene Corporation that a *tandem autologous transplant followed by an allogeneic transplant* from an HLA-compatible unrelated donor for untreated, newly diagnosed MM, and with none of the contraindications in section I.B., will be considered on a case by case basis.

**IV.** It is the policy of health plans affiliated with Centene Corporation that the current evidence does not support *tandem transplants* for any other indication than what is listed above.

### **Background**

During a tandem transplant, peripheral blood hematopoietic stem cells (HSCs) are collected either during recovery of a cycle of induction chemotherapy or after filgrastim mobilization. The patient receives a second preparative regimen, along with hematopoietic progenitor cells (HPCs) collected during the initial mobilization.<sup>10</sup> The rationale for the second round of therapy is to destroy any residual tumor cells remaining after the initial transplant and thereby reduce the chance of relapse.

#### *Multiple Myeloma*

Multiple myeloma (MM) is a malignant neoplasm of plasma cells that accumulate in bone marrow, leading to bone destruction and marrow failure. MM is a disease of older adults and is classified as either smoldering myeloma (asymptomatic) or MM (symptomatic). Individuals with smoldering disease have no related organ or tissue impairment. These individuals do not need primary therapy, as it may take many months to years before the disease progresses, however, they should be monitored closely.<sup>1</sup> Individuals with symptomatic MM are initially treated with primary therapy, and in selected patients, primary therapy is followed by high-dose chemotherapy with autologous SCT. Although responses are typically durable, relapse is an expected part of the disease course and MM is not considered curable with current approaches.<sup>1</sup>

Following diagnosis and risk stratification, all patients need assessment to determine eligibility for autologous hematopoietic cell transplantation (HCT). Autologous HCT results in high response rates and remains standard of care after primary therapy for eligible patients.<sup>1</sup> However, some controversy currently exists in the era of newer and more effective chemotherapy agents. Eligibility varies across countries and institutions. National Comprehensive Care Network (NCCN) guidelines recommend autologous SCT for transplant-eligible patients as an option after primary induction therapy (category 1) and for treatment of progressive/refractory disease after primary treatment.

Planned tandem transplants have been studied in several randomized trials. Results of a phase III trial (StaMINA) indicate that a tandem autologous SCT followed by lenalidomide maintenance has similar outcomes to a single autologous SCT followed by lenalidomide maintenance in the initial treatment of MM. However, another multicenter phase III trial suggests that tandem

autologous SCT for newly diagnosed MM appear to be superior in extending progression free survival (PFS) compared with a single SCT after induction therapy with a bortezomib-based regimen.<sup>7</sup> A conventional meta-analysis and network meta-analysis of phase 3 RCTs comparing high dose therapy (HDT)/autologous SCT with standard-dose therapy (SDT) using novel agents showed that both tandem HDT/autologous SCT and single HDT/autologous SCT with bortezomib, lenalidomide, and dexamethasone were superior to single HDT/autologous SCT alone and SDT for PFS, but overall survival was similar across the 4 approaches.<sup>11</sup>

The NCCN Multiple Myeloma panel recommends collecting enough stem cells for 2 transplants in all eligible patients. According to the panel, a tandem transplant with or without maintenance therapy can be considered for all patients who are candidates for SCT, and is an option for patients who do not achieve at least a very good partial response (VGPR) after the first autologous SCT.<sup>1</sup>

Per NCCN, patients who have an HLA-identical sibling may be considered candidates for reduced-intensity allogeneic SCT as part of their first line treatment.<sup>1</sup> This recommendation is based on a study that compared outcomes of previously untreated multiple myeloma patients receiving an autologous SCT (auto) followed by reduced-intensity conditioning matched sibling donor allo (auto-allo) to those who received only an autologous transplant. Progression-free survival at 60 months was significantly better with auto-allo than with auto alone (35% v 18%;  $P = .001$ ), as was the risk of death and of relapse in the long term ( $P = .047$  and  $P = .003$ , respectively). Overall survival at 60 months was 65% versus 58%, and relapse incidence was 49% versus 78%. Complete remission rates were 51% and 41%, respectively. Non-relapse mortality at 24 months was 12% after auto-allo compared with 3% in the auto group.<sup>15</sup>

### *Neuroblastoma*

Neuroblastoma is the most common extracranial solid tumor in childhood with more than 650 cases diagnosed each year in North America. Approximately 90% of those diagnosed with neuroblastoma are younger than 5 years of age. The data on age at diagnosis show that this is a disease of infancy, with the highest rate of diagnosis in the first month of life.<sup>18</sup> Neuroblastomas vary in terms of location, histopathologic appearance, and biologic characteristic and can occur anywhere along the sympathetic chains, however, the adrenal gland is the most common primary site followed by abdominal, thoracic, cervical and pelvic sympathetic ganglia. The presenting symptoms reflect the location of the primary tumor and the extent of metastatic disease, if present. Patients with localized disease can be asymptomatic, whereas children with advanced disease appear ill at presentation, usually with systemic symptoms.<sup>14</sup>

Age, stage, and biological features encountered in tumor cells are important prognostic factors and are used for risk stratification and treatment assignment. There are two systems used for neuroblastoma staging today. The International Neuroblastoma Risk Group Staging System (INRGSS) uses results from imaging tests (such as CT or MRI and MIBG scan) prior to surgery to help decide a stage. The INRGSS can be determined before treatment has started. Knowledge regarding the presence or absence of image defined risk factors (IDRF) are required for this staging system. The International Neuroblastoma Staging System (INSS) uses results from the surgery to remove a child's tumor instead of imaging tests. At the present time, most cancer

centers have used the INSS to stage neuroblastoma, however, INRGSS is now being used to determine staging for most Children's Oncology Group studies.

**International Neuroblastoma Staging System (INSS)<sup>16</sup>**

Stage	Description
Stage 1	Localized tumor with complete gross excision, with or without microscopic residual disease; representative ipsilateral lymph nodes negative for tumor microscopically (i.e., nodes attached to and removed with the primary 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. The midline is defined as the vertebral column. Tumors originating on one side and crossing the midline must infiltrate to or beyond the opposite side of the vertebral column.
Stage 4	Any primary tumor with dissemination to distant lymph nodes, bone, bone marrow, liver, skin, and/or other organs, except as defined for stage 4S.
Stage 4S	Localized primary tumor, as defined for stage 1, 2A, or 2B, with dissemination limited to skin, liver, and/or bone marrow (by definition limited to infants younger than 12 months). Marrow involvement should be minimal (i.e., <10% of total nucleated cells identified as malignant by bone biopsy or by bone marrow aspirate). More extensive bone marrow involvement would be considered stage 4 disease. The results of the metaiodobenzylguanidine (MIBG) scan, if performed, should be negative for disease in the bone marrow.

**International Neuroblastoma Risk Group Staging System (INRGSS)<sup>16</sup>**

Stage	Description
L1	Localized tumor not involving vital structures as defined by the list of image-defined risk factors and confined to one body compartment
L2	Locoregional tumor with presence of one or more image-defined risk factors
M	Distant metastatic disease (except stage MS)
MS	Metastatic disease in children younger than 18 months with metastases confined to skin, liver, and/or bone marrow

Treatment of neuroblastoma is determined based on risk categories. Risk categories are expected to evolve as newer staging systems are adopted and further knowledge is acquired about molecular and genetic determinants of tumor behavior and prognosis.<sup>14</sup> Patients are classified into low, intermediate, and high-risk categories based on the following characteristics at the time of diagnosis:

- Stage of the disease
- Patient age
- Histologic appearance of the tumor

- Presence or absence of amplification of the MYCN oncogene
- Quantitative DNA content of the tumor (DNA index or ploidy).

Patients with low-risk and intermediate-risk neuroblastoma have excellent prognosis and outcome. However, those with high-risk disease continue to have very poor outcomes despite intensive therapy. Patients at the highest risk for disease progression and mortality are those who are older than 18 months of age and have disseminated disease, or localized disease with unfavorable markers such as MYCN amplification (high-risk neuroblastoma).<sup>14</sup>

Historically, the long-term survival probability for children with high-risk disease was less than 15 percent. Better results have been achieved using an aggressive multimodality approach that includes chemotherapy, surgical resection, high-dose chemotherapy with hematopoietic stem-cell rescue, and radiation therapy. Results from randomized trials have consistently demonstrated improved progression-free survival in patients who received myeloablative chemotherapy with stem cell rescue, and some of these studies demonstrated an improvement in overall survival in certain groups of patients.<sup>14</sup>

Two 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.<sup>18</sup> A recent multicenter RCT comparing tandem vs. single consolidation in patients with high risk neuroblastoma reported that in children with high-risk neuroblastoma, tandem autologous stem cell transplant (ASCT) improved event-free survival rates. While the tandem transplant group experienced improved three-year event-free survival (EFS) compared with those receiving single transplants (61 versus 48 percent), the difference in overall survival 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 overall survival (84 versus 76 percent). Cumulative rates of severe mucosal, infectious, or liver toxicities and regimen-related mortality were similar between arms.<sup>19</sup>

### *Testicular Cancer*

Testicular cancer is the most common solid malignancy affecting males between the ages of 15 and 35, although it accounts for only 1 percent of all cancers in men. Germ cell tumors (GCTs) account for 95 percent of testicular cancers.<sup>27</sup> Testicular cancers are among the most curable solid neoplasms with the current five-year survival rate at over 95 percent. Initial therapy of early stage testicular GCTs is based upon histology and tumor extent.<sup>28</sup> NCCN guidelines recommend radical inguinal orchiectomy as the primary treatment for most patients with a testicular mass that is concerning for malignancy on ultrasound. Additionally, cisplatin-based combination chemotherapy can cure patients with disseminated GCTs, even in the context of widespread visceral metastases, highly elevated serum tumor markers, and other adverse prognostic features.

Men with GCTs in second or subsequent relapse and those who progress during or immediately after their initial platinum-based chemotherapy regimen are considered to have platinum-refractory disease. These patients have a poorer prognosis than those treated with chemotherapy for their initial relapse.<sup>29</sup> Men who are diagnosed with relapsed or refractory testicular GCTs should be referred to a cancer center with multidisciplinary expertise, and patients should be

offered the opportunity to participate in clinical studies whenever possible.<sup>29</sup> High-dose chemotherapy followed by autologous stem cell transplant, either single or tandem, is an accepted treatment option for these patients. A observational study that compared results of patients intended to undergo tandem autotransplant versus those in whom a second autotransplant was not planned reported that tandem autotransplants are associated with less treatment-related mortality than a planned single transplant, with no differences in disease-related outcomes or overall survival at 3 years.<sup>30</sup> It is important to note that a significant percent of patients undergoing planned tandem HSCT in this study had poorer risk features including more advanced disease at diagnosis and greater likelihood of exhibiting cisplatin resistance when compared to subjects where 2 autotransplants were not planned.

**Coding Implications**

This clinical policy references Current Procedural Terminology (CPT®). CPT® is a registered trademark of the American Medical Association. All CPT codes and descriptions are copyrighted 2020, American Medical Association. All rights reserved. CPT codes and CPT descriptions are from the current manuals and those included herein are not intended to be all-inclusive and are included for informational purposes only. Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

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
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

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 of pre and post-transplant care in the global definition

**ICD-10-CM Diagnosis Codes that Support Coverage Criteria**

+ Indicates a code requiring an additional character

ICD-10-CM Code	Description
C62.00-C62.92	Malignant neoplasm of testis
C74.00-C74.92	Malignant neoplasm of adrenal gland

ICD-10-CM Code	Description
C90.00-C90.02	Multiple myeloma
D07.69	Carcinoma in situ of other male genital organs

Reviews, Revisions, and Approvals	Revision Date	Approval Date
Policy developed and specialist reviewed	07/18	07/18
In section I.A., changed “candidate for tandem transplant for any of the following” to “patient has any of the following.” Specified that contraindications in section I.B. also apply to types of tandem transplants listed in sections II and III.	12/18	
References reviewed and updated. Specialist review.	06/19	07/19
Changed contraindication of significant systemic or multisystem disease to “significant, uncorrectable, life-limiting medical condition. Removed substance abuse or dependence contraindication. Background updated with no impact on criteria. References reviewed and updated.	07/20	07/20
Annual review. References updated. Minor wording changes with no clinical significance. Coding reviewed. Replaced all instance of “member” with “member/enrollee.” Changed “review date” in the header to “date of last revision” and “date” in the revision log header to “revision date.” Sent for specialist review.	07/21	07/21

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**Important Reminder**

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. “Health Plan” means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan’s affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members/enrollees. This clinical policy is not intended to recommend treatment for members/enrollees. Members/enrollees should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

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**Note: For Medicaid members/enrollees**, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

**Note: For Medicare members/enrollees**, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs, LCDs, and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Refer to the CMS website at <http://www.cms.gov> for additional information.

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