Clinical Policy: Tandem Transplant

Reference Number: LA.CP.MP.162 Coding Implications
Date of Last Revision: 4/23 Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

A tandem transplant, (also known as a sequential or double transplant), refers to a planned second course of high-dose therapy and hematopoietic cell transplant (HCT) within six months of the first course.[1] It differs from a repeat HCT 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 Louisiana Healthcare Connections that a *tandem autologous transplant* is **medically necessary** when meeting all 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, any age, with MYCN amplification;
      b. Child with Stage 3 disease and either of the following:
         i. Any age with MYCN amplification,
         ii. ≥ 547 days old, no MYCN amplification, and unfavorable histopathology;
      c. Child with Stage 4 disease and any of the following:
         i. <365 days old, with MYCN amplification,
         ii. ≥ 547 days old ,
         iii. 365 to <547 days old with MYCN amplification, and/or diploidy, and/or unfavorable histology;
      d. Child who is Stage 4S disease <365 days old, and MYCN gene amplification.

B. Does not have ANY of the following contraindications:
   1. Glomerular filtration rate < 40 mL/min/1.73m2 unless being considered for multi-organ transplant;
   2. Acute renal failure with rising creatinine or on dialysis and low likelihood of recovery;
   3. Acute liver failure, or cirrhosis with portal hypertension or synthetic dysfunction unless being considered for multi-organ transplant;
   4. Stroke, acute coronary syndrome, or myocardial infarction (excluding demand ischemia) within 30 days;
   5. Inadequate cardiac, renal, pulmonary, or hepatic function;
   6. Significant, uncorrectable, life-limiting medical condition;
   7. Septic shock;
   8. Active extrapulmonary or disseminated infection;
   9. Active tuberculosis infection;

10. HIV infection with detectable viral load;
11. Progressive cognitive impairment;
12. Inability to adhere to the regimen necessary to preserve the transplant, even with caregiver support;
13. Absence of an adequate or reliable social support system;
14. Other severe uncontrolled medical condition expected to limit survival after transplant.
15. Active substance use or dependence including current tobacco use, vaping, marijuana use (unless prescribed by a licenced practitioner), or IV drug use without convincing evidence of risk reduction behaviors (unless urgent transplant timelines are present, in which case a commitment to reducing behaviors is acceptable). Serial blood and urine testing may be used to verify abstinence from substances that are of concern.

II. It is the policy of Louisiana Healthcare Connections 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 Louisiana Healthcare Connections 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.

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.[10] 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. All patients with smoldering myeloma have a risk of progression to MM. However, the rate of progression varies from months to several years based on certain risk features. The historic approach for management of smoldering myeloma has been close observation. However, recently there has been mounting evidence that those with high-risk features may benefit for early intervention.[1] Individuals with symptomatic MM are initially treated with primary therapy, and primary therapy is followed by high-dose chemotherapy with autologous HCT in transplant-eligible patients. Although responses are typically durable, relapse is an expected part of the disease course and MM is not considered curable with current approaches.[1]

Following diagnosis and risk stratification, all patients need assessment to determine eligibility for HCT. National Comprehensive Care Network (NCCN) guidelines indicate that all types of HCT are appropriate in different clinical settings, i.e., single autologous HCT, a tandem HCT or an allogeneic HCT. Allogeneic HCT should preferentially be done in the context of a trial when possible. Autologous HCT results in high response rates and remains standard of care after primary therapy for eligible patients.[1] However, some controversy currently exists in the era of newer and more effective chemotherapy agents. Eligibility varies across countries and institutions. NCCN guidelines recommend autologous HCT for transplant-eligible patients as an option after primary induction therapy while a delayed HCT after early stem cell collection and storage is appropriate as well (category 1). A repeat HCT can be considered for treatment of progressive/refractory disease after primary treatment in patients with prolonged response to initial HCT.

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.[7] A conventional meta-analysis and network meta-analysis of phase three 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 four approaches.[11]

The NCCN Multiple Myeloma panel recommends collecting enough hematopoietic cells for two transplants in all eligible patients (depending on the intended number of transplants and age). According to the panel, a tandem transplant with or without maintenance therapy can be considered for all patients who are candidates for HCT, and is an option for patients who do not achieve at least a very good partial response (VGPR) after the first autologous HCT and those with high-risk features.[1]

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 five 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.[17] 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.[13]

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) [15]

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)[15]

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.[14] 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
- Extent of INRGSS L1 disease resection
- Presence or absence of amplification of the MYCN oncogene
- Quantitative DNA content of the tumor (DNA index or ploidy).
- Histologic appearance of the tumor
- Segmental chromosomal aberrations (eg, loss of heterozygosity)

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).[13]

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.[13]

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.[17] 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.[18]

Testicular Cancer

Testicular cancer is the most common solid malignancy affecting males between the ages of 15 and 35, although it accounts for only one percent of all cancers in men. Germ cell tumors (GCTs) account for 95 percent of testicular cancers.[26] 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.[27] 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.[28] 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.[27] High-dose chemotherapy followed by autologous stem cell transplant, either single or tandem, is an accepted treatment option for these patients. An 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 three years.[28] 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 two autotransplants were not planned.

Coding Implications

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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
38243	Hematopoietic progenitor cell (HPC); HPC boost

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

* All non-covered codes are reviewed for medical necessity for members under 21 years old

Reviews, Revisions, and Approvals	Revision Date	Approval Date
Converted corporate to local policy.	08/15/2020	
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." Added "may not support medical necessity" to coding implications. Replaced contraindications regarding past or current nonadherence to medical therapy, and psychological condition associated with the inability to comply with medical therapy with "Inability to adhere to the regimen necessary to preserve the transplant, even with caregiver support."	2/22	2/22
Replaced contraindications "Inadequate cardiac, renal, pulmonary, or hepatic function and significant, uncorrectable, life-limiting medical condition" with those concerning GFR, acute liver failure…, acute renal failure…, septic shock, active extrapulmonary or disseminated infection, active tuberculosis infection, HIV infection with detectable viral load, progressive cognitive impairment, other severe uncontrolled medical condition…Updated references. Added and may not support medical necessity to Coding Implications section	5/22	8/13/22
Updated verbiage I.3.b.ii., I.3.c.i. through iii., and I.A.3.d. Added substance use contraindication I.B.15. Removed criteria IV. stating, current evidence does not support tandem transplants for any other indication than what is listed above. Added CPT code 38243. Updated references.	4/23	7/24/23

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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. LHCC 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.

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