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Contents

DISCLAIMER 1

Description of Procedure/Service/Pharmaceutical 1

Recommendation 2

Continuation of Therapy 5

Limitations 6

Summary of Medical Evidence [4-16] 6

Coding Information 6

Resource References 7

REVIEW/REVISION HISTORY 9

DISCLAIMER

This Molina Medical Policy (MCP) is intended to facilitate the Utilization Management process. 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 (i.e., 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 Molina Clinical Policy (MCP) document and provide the directive for all Medicare members.[1]

DESCRIPTION OF PROCEDURE/SERVICE/PHARMACEUTICAL

Wilm's Tumor

Wilms' tumor (also known as nephroblastoma) is the most common primary renal cancer of childhood, and accounts for nearly 7% of all pediatric cancers. [27] Several associated abnormalities can occur with this cancer, including aniridia, hemihypertrophy, cryptorchidism, and hypospadias. There are several genetic chromosomal

disorders that carry a high risk for development of Wilms' tumor, the most common ones being WAGR syndrome (Wilms' tumor, aniridia, genitourinary malformation, mental retardation), Denys-Drash syndrome, and Beckwith-Wiedemann syndrome. The tumor usually presents as an abdominal mass with or without pain, fever, and hematuria. Unilateral presentation is more common than bilateral. Cure rates with surgical resection and chemotherapy are now approaching 90% for stages I, II, and III. For stage IV (metastatic) disease, radiation to all sites plus chemotherapy still results in nearly 80% survival for patients with favorable histology. [4] Long-term survival of relapsed Wilms' tumor patients is about 40% to 70%. Second-line treatment consists of either (a) salvage chemotherapy+/-radiation therapy (CT) or (b) chemotherapy followed by high-dose chemotherapy and autologous hematopoietic stem cell rescue (ASCR). [5]

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.

RECOMMENDATION

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 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.

Members must meet UNOS/OPTN policies and guidelines for pretransplantation evaluation and listing criteria and the diagnosis must be made by a Specialist in the Disease and or Transplant Surgeon.

Pre-Transplant Evaluation: [24-31] **Please see MCP-323 Pre-Transplant Evaluation for additional criteria and information.**

Criteria for transplant evaluation include all of the following:

- ❑ History and physical examination
- ❑ Psychosocial evaluation and clearance:
  - o No behavioral health disorder by history or psychosocial issues:
    - ➢ if history of behavioral health disorder, no severe psychosis or personality disorder
    - ➢ mood/anxiety disorder must be excluded or treated
    - ➢ member has understanding of surgical risk and post procedure compliance and follow-up required
  - o Adequate family and social support

- ❑ EKG
- ❑ Chest x-ray
- ❑ Cardiac clearance in the presence of any of the following:
  - chronic smokers
  - > 50 years age
  - those with a clinical or family history of heart disease or diabetes
- ❑ Pulmonary clearance if evidence of pulmonary artery hypertension (PAH) or chronic pulmonary disease
- ❑ Neurological exam and clearance for transplant: [ONE]
  - Normal exam by H&P
  - Abnormal neurological exam with positive findings: [ONE]
    - Lumbar puncture normal cytology
    - Lumbar puncture with cytological exam abnormal: CNS disease treated prior to clearance
- ❑ Performance Status : [ONE]
  - Karnofsky score 70-100%; or
  - Eastern Cooperative Oncology Group (ECOG) grade 0-2
- ❑ Lab studies:
  - *Complete blood count, Kidney profile (blood urea nitrogen, creatinine), electrolytes, calcium, phosphorous, albumin, liver function tests, Coagulation profile (prothrombin time, and partial thromboplastin time)
  - *Serologic screening for HIV, Epstein Barr virus (EBV), Hepatitis virus B (HBV), and Hepatitis C(HCV), cytomegalovirus (CMV), RPR and/or FTA:
    - If HIV positive all of the following are met:
      - CD4 count >200 cells/mm-3 for >6 months
      - HIV-1 RNA undetectable
      - On stable anti-retroviral therapy >3 months
      - No other complications from AIDS (e.g., opportunistic infection, including aspergillus, tuberculosis, coccidioides mycosis, resistant fungal infections, Kaposi's sarcoma, or other neoplasm)
    - If abnormal serology need physician plan to address and/or treatment as indicated
  - UDS (urine drug screen) if patient is current or gives a history of past drug abuse
- ❑ *Colonoscopy (if indicated or if patient is 50 ≥ older should have had an initial screening colonoscopy, after initial negative screening requires follow up colonoscopy every ten years) with complete workup and treatment of abnormal results as indicated
- ❑ *GYN examination with Pap smear for women ≥ 21 to ≤ 65 years of age or indicated (not indicated in women who have had a TAH or TVH) with in the last three year with complete workup and treatment of abnormal results as indicated

Within the last 12 months:

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

- ❑ *PSA 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 Hematopoietic Autologous Stem Cell transplantation (HSCT) Transplantation: [4-16]

1. ***Hematopoietic Autologous stem-cell transplantation (HSCT)*** may be considered medically necessary and may be authorized for the treatment of Wilm's tumor when the following criteria are met:

- ❑ All pre-transplant criteria are met; and [ONE]
  - o Initially treated with four or more chemotherapeutic agents and disease is recurrent or refractory: Defined as a tumor that does not achieve a complete remission after initial standard-dose chemotherapy; or
  - o Multiple relapses or progression on salvage therapy

AND

- ❑ The requesting transplant recipient should not have any of the following **absolute contraindications**:
  - o Cardiac, pulmonary, and nervous system disease that cannot be corrected and is a prohibitive risk for surgery
  - o Malignant neoplasm with a high risk for reoccurrence, non-curable malignancy (excluding localized skin cancer)
  - o Systemic and/or uncontrolled infection
  - o AIDS (CD4 count < 200cells/mm3)
  - o Unwilling or unable to follow post-transplant regimen
    - ◊ Documented history of non-compliance
    - ◊ Inability to follow through with medication adherence or office follow-up
  - o Chronic illness with one year or less life expectancy
  - o Limited, irreversible rehabilitation potential
  - o Active untreated substance abuse issues, requires documentation supporting free from addiction for minimally 6 months if previous addiction was present
  - o No adequate social/family support

- ❑ The requesting transplant recipient should be evaluated carefully and potentially treated if the following **relative contraindications** are present:
  - o Irreversible lung disease patients require consultation and clearance by a Pulmonologist prior to consideration of transplantation, this includes the following:
  - o Smoking, documentation supporting free from smoking for 6 months
  - o Active peptic ulcer disease
  - o Active gastroesophageal reflux disease
  - o CVA with long term impairment that is not amendable to rehabilitation or a patient with CVA/transient ischemic attack within past 6 months
  - o Obesity with body mass index of >30 kg/m^2 may increase surgical risk
  - o 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

- Gall bladder disease requires ultrasound of the gall bladder with treatment prior to transplantation

Criteria for Subsequent Hematopoietic Stem Cell Transplantation:

2. ***Hematopoietic autologous stem cell transplantation*** may be considered medically necessary and may be authorized after *the first prior stem cell transplantation* has occurred only one time for members with Wilm's tumor who meet all of the above criteria for transplant and have any of the following**:[ONE]**

   ❑ primary graft failure indicated by no signs of engraftment* by 42 days after the transplant;
   OR
   ❑ failure to engraft*;

   ***Note:** Engraftment is defined as the first 3 consecutive days on which the absolute neutrophil count (ANC) exceeds 5 x 10^9/L or > ANC500 at any time after transplantation.*[26]

CONTINUATION OF THERAPY

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

❑ If Molina Healthcare has authorized prior requests for transplantation, the following information is required for medical review: [ALL]
- Presence of no absolute contraindication as listed above;
- History and physical within the last 12 months;
- Kidney profile within the last 12 months;
- Cardiac update if history of cardiac disease within two years (≥ 50 years of age);
- Psychosocial evaluation or update within the last 12 months;
- 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.

❑ If authorized prior requests for transplantation were obtained from another insurer, the following information is required for medical review: [ALL]
- Authorization letter/documentation from previous insurer;
- Presence of no absolute contraindication as listed above;
- History and physical within the last 12 months;
- Cardiac update if history of cardiac disease within two years (≥ 50 years of age);
- Psychosocial evaluation or update within the last 12 months;
- 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

1. Autologous stem cell transplantation when the above criteria are not met
2. Allogeneic hematopoietic stem cell transplantation
3. Hematopoietic stem cell collection, storage and freezing for a future unplanned transplant

SUMMARY OF MEDICAL EVIDENCE [4-16]

The published medical evidence and outcomes for hematopoietic stem cell transplantation Wilm's Tumor is limited to information from international bone marrow transplant registries and case series from individual institutions comparing treatment outcomes that suggest a survival benefit with the use of high dose chemotherapy followed by autologous hematopoietic stem cell transplantation. Several uncontrolled trials demonstrate improved or equivalent survival outcomes with autologous HSCT.

According Dome et al., [9] the value of high-dose therapy with stem-cell transplantation (HDSCT) for the treatment of recurrent WT is one of the unsettled questions in the field. Several groups have reported improved outcomes with HDSCT, with EFS estimates ranging from 36% to 60%, [10-14] yet other groups have reported similar outcomes with conventional doses of chemotherapy. [15] A prospective clinical trial to randomly assign patients to receive or not receive HDSCT was proposed by the COG-RTC and SIOP-RTSG almost a decade ago, but the study was disapproved by regulatory and funding agencies because of concerns about a protracted study duration (estimated at 8 years), scarcity of funding, and anticipation that HDSCT would not yield a major benefit. An international meta-analysis [6] conducted to provide additional insights revealed that the patients most likely to benefit from HDSCT were those initially treated with four or more chemotherapeutic agents and those with multiple relapses or progression on salvage therapy. The meta-analysis provides the best guidance for when HDSCT should be considered. [6]

CODING INFORMATION THE CODES LISTED IN THIS POLICY ARE FOR REFERENCE PURPOSES ONLY. LISTING OF A SERVICE OR DEVICE CODE IN THIS POLICY DOES NOT IMPLY THAT THE SERVICE DESCRIBED BY THIS CODE IS COVERED OR NON-COVERED. COVERAGE IS DETERMINED BY THE BENEFIT DOCUMENT. THIS LIST OF CODES MAY NOT BE ALL INCLUSIVE.

CPT	Description
	Collection Codes
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
	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

38209	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing
38210	Transplant preparation of hematopoietic progenitor cells; specific cell depletion within harvest, T-cell depletion
38211	Transplant preparation of hematopoietic progenitor cells; tumor cell depletion
38212	Transplant preparation of hematopoietic progenitor cells; red blood cell removal
38213	Transplant preparation of hematopoietic progenitor cells; platelet depletion
38214	Transplant preparation of hematopoietic progenitor cells; plasma (volume) depletion
38215	Transplant preparation of hematopoietic progenitor cells; cell concentration in plasma, mononuclear, or buffy coat layer
	Cell infusion codes
38240	Bone marrow or blood-derived peripheral stem cell transplantation; allogeneic
38241	Bone marrow or blood-derived peripheral stem cell transplantation; autologous
38242	Bone marrow or blood-derived peripheral stem cell transplantation; allogeneic donor lymphocyte infusions
38243	Bone marrow or blood-derived peripheral stem cell transplantation; allogeneic hematopoietic cellular transplant boost

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

ICD-10	Description: [For dates of service on or after 10/01/2015]
C64-C64.9	Malignant neoplasm of kidney, except renal pelvis

RESOURCE REFERENCES

Government Agency

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2. National Bone Marrow Donor Program HLA Matching Requirements. Accessed at: http://marrow.org/Patient/Transplant_Process/Search_Process/HLA_Matching__Finding_the_Best_Donor_or_Cord_Blood_Unit.aspx
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Peer Reviewed Publications

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14. Spreafico F, Bisogno G, Collini P, et al. Treatment of high-risk relapsed Wilms tumor with dose-intensive chemotherapy, marrow-ablative chemotherapy, and autologous hematopoietic stem cell support: Experience by the Italian Association of Pediatric Hematology and Oncology. Pediatr Blood Cancer. 2008;51:23–28.
15. Grundy P, Breslow N, Green DM, et al. Prognostic factors for children with recurrent Wilms' tumor: Results from the Second and Third National Wilms' Tumor Study. J Clin Oncol. 1989;7:638–647.
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Professional Society Guidelines

24. National Marrow Donor Program® (NMDP) and the American Society for Blood and Marrow Transplantation (ASBMT) referral guidelines: Recommended Timing for Transplant Consultation. Accessed at: https://bethematchclinical.org/Transplant-Indications-and-Outcomes/Referral-Timing-Guidelines/
25. National Marrow Donor Program® (NMDP). Patient Eligibility for HCT. Accessed at: https://bethematchclinical.org/Transplant-Indications-and-Outcomes/Eligibility/
26. National Bone Marrow Donor Program. Measuring Engraftment. Accessed at: http://marrow.org/Patient/Transplant_Process/Days_0-30/Measuring_Engraftment.aspx

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28. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. Kidney Cancer version 4.2021. Accessed at: https://www.nccn.org/professionals/physician_gls/default.aspx

Other Resources

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30. DynaMed Plus [Internet]. Ipswich (MA): EBSCO Information Services. 1995-2021. Wilm's Tumor.
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REVIEW/REVISION HISTORY

1/5/17: New Policy
7/10/18, 6/19/19, 6/17/20, 6/9/21: Policy reviewed, no changes. Updated references.