Subject: Haploidentical Allogeneic Hematopoietic Cell Transplantation in Blood Cancers	Original Effective Date: 4/23/20
Policy Number:MCP-362	Revision Date(s):
MCPC Approval Date: 4/23/20, 4/5/21	Review Date: 4/5/21

Contents

DISCLAIMER

This Molina clinical policy 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 document and provide the directive for all Medicare members. [1]

DESCRIPTION OF PROCEDURE/SERVICE/PHARMACEUTICAL [22]

Allogeneic hematopoietic cell transplantation (HCT) is a potentially curative therapy for a wide variety of malignant and non-malignant hematologic disorders. The hematopoietic stem cells required for this procedure are usually obtained from the bone marrow or peripheral blood of a related or unrelated donor. Historically, the best results of allogeneic HCT have been obtained when the stem cell donor is a human leukocyte antigen (HLA)-matched sibling. Given the small family sizes

in developed nations and the 25 percent likelihood that any sibling is fully HLA-matched to the patient, an HLA-matched sibling can be found for only approximately 30 percent of patients. For patients who lack an HLA-matched sibling, alternative sources of donor grafts include suitably HLA-matched adult unrelated donors, umbilical cord blood stem cells, and partially HLA-mismatched, or HLA-haploidentical, related donors.

The major challenge of HLA-haploidentical HCT is intense bi-directional alloreactivity leading to high incidences of graft rejection and graft-versus-host disease (GVHD). Advances in graft engineering and in pharmacologic prophylaxis of GVHD have reduced the risks of graft failure and GVHD after HLA-haploidentical HCT, and have made this stem cell source a viable alternative for patients lacking an HLA-matched sibling.

Definitions: An HLA-haploidentical donor is one who shares, by common inheritance, exactly one HLA haplotype with the recipient and is mismatched for a variable number of HLA genes, ranging from zero to six, on the unshared haplotype. Potential HLA-haploidentical donors include biological parents; biological children; full or half siblings; and even extended family donors such as aunts, uncles, nieces, nephews, cousins, or grandchildren.

RECOMMENDATION CLINICAL CRITERIA

1. Haploidentical allogeneic hematopoietic cell transplantation may be considered a medically necessary option when there are no matched sibling or unrelated donors for the following blood cancers*: [ALL]
    - ❑ Acute Myelogenous Leukemia (AML); or
    - ❑ Aplastic Anemia and other Bone Marrow Failure Disorders; or
    - ❑ Hodgkin's Lymphoma

2. HLA-haploidentical donor selection criteria incudes all of the following: [22]
    - ❑ Donor must be medically, socially, and psychologically fit to donate
    - ❑ Donor age <40 years preferred over donor age ≥40 years
    - ❑ No major ABO incompatibility between donor and recipient. Major ABO incompatibilities include:
        - Recipient blood type O: Donor type A, B, or AB
        - Recipient blood type A: Donor blood type B or AB
        - Recipient blood type B: Donor blood type A or AB
        - Recipient blood type AB: No major ABO incompatibilities
    - ❑ Matched CMV IgG serologic status between donor and recipient include:
        - For a recipient who is CMV IgG negative, use a CMV IgG negative donor
        - For a recipient who is CMV IgG positive, use a CMV IgG positive donor
    - ❑ Use an ABO compatible donor over a minor ABO incompatible donor:
        - ABO compatible transplants are O→O, A→A, B→B, or AB→AB

***Note: Please see the specific MCP for clinical criteria for each of the above diagnoses**

LIMITATIONS [22]

Absolute contraindications to the use of a specific HLA-haploidentical donor are:

- ❑ Donor is medically or psychologically unfit; or
- ❑ Recipient has anti-donor HLA antibodies of sufficient strength to result in a positive crossmatch result by flow cytometry or by complement-dependent cytotoxicity assay.

SUMMARY OF MEDICAL EVIDENCE [2-27]

At the current time, there are no published randomized controlled trials of haploidentical HCT that compare either umbilical cord blood HCT or mismatched unrelated donor HCT. For patients with acute leukemia in complete remission or with lymphoma, the United States Blood and Marrow Transplant Clinical Trials Network conducted a phase III, randomized trial of reduced intensity conditioning and transplantation of either double unrelated donor umbilical cord blood or HLA-haploidentical bone marrow (BMT CTN 1101; NCT01597778).[2] The results of this trial have not yet been published. Data regarding outcomes are mostly from retrospective analyses and large multi-institutional studies comparing post-transplant graft vs. host disease (GVHD), transplant related mortality, disease-free survival, or relapse.

PROFESSIONAL SOCIETY GUIDELINES

The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology for Acute Myeloid Leukemia mention that haploididentical transplantation may be considered a treatment option if no appropriated matched sibling donor is found and the patient is a candidate for HCT. (Category 2A recommendation) [28]

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
	N/A There are no specific codes for haploididentical transplantation

HCPCS	Description
	N/A There are no specific codes for haploididentical transplantation

ICD-10	Description: [For dates of service on or after 10/01/2015]
	Any/All

REFERENCES

Government Agency

1. Centers for Medicare & Medicaid Services (CMS). Medicare Coverage Database. National coverage determination (NCD) Search. Accessed at: https://www.cms.gov/medicare-coverage-database/new-search/search.aspx
2. NIH U.S. National Library of Medicine. Clinical Trials. Double Cord versus Haploidentical (BMT CTN 1101). Accessed at: https://clinicaltrials.gov/ct2/show/NCT01597778

Peer Reviewed Publications

3. Ahmed S, Kanakry JA et al. Lower Graft-versus-Host Disease and Relapse Risk in Post-Transplant Cyclophosphamide-Based Haploidentical versus Matched Sibling Donor Reduced-Intensity Conditioning Transplant for Hodgkin Lymphoma. Biol Blood Marrow Transplant. 2019 Sep;25(9):1859-1868.

4. Bazarbachi A, Labopin M et al. Haploidentical transplant with post-transplant cyclophosphamide for T-cell acute lymphoblastic leukemia: a report from the EBMT acute leukemia working party. Biol Blood Marrow Transplant. 2020 Jan 8. pii: S1083-8791(20)30013-6.
5. Bashey A, Zhang X, Sizemore CA, et al. T-cell-replete HLA-haploidentical hematopoietic transplantation for hematologic malignancies using post-transplantation cyclophosphamide results in outcomes equivalent to those of contemporaneous HLA-matched related and unrelated donor transplantation. J Clin Oncol 2013; 31:1310.
6. Bazarbachi A, Boumendil A, et al. Influence of donor type, stem cell source and conditioning on outcomes after haploidentical transplant for lymphoma - a LWP-EBMT study. Br J Haematol. 2019 Sep 9.
7. Bonini C, Peccatori J et al. Haploidentical HSCT: a 15-year experience at San Raffaele. Bone Marrow Transplant. 2015 Jun;50 Suppl 2:S67-71
8. Brissot E, Labopin L et al. Haploidentical versus unrelated allogeneic stem cell transplantation for relapsed/refractory acute myeloid leukemia: a report on 1578 patients from the Acute Leukemia Working Party of the EBMT. Haematologica. 2019 Mar; 104(3): 524–532. Accessed at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6395335/
9. Burroughs LM, O'Donnell PV, Sandmaier BM, et al. Comparison of outcomes of HLA-matched related, unrelated, or HLA-haploidentical related hematopoietic cell transplantation following nonmyeloablative conditioning for relapsed or refractory Hodgkin lymphoma. Biology of blood and marrow transplantation: Journal of the American Society for Blood and Marrow Transplantation. 2008;14(11):1279–1287.
10. Chen D, Zhou D et al. Comparison of Outcomes in Hematological Malignancies Treated With Haploidentical or HLA-identical Sibling Hematopoietic Stem Cell Transplantation Following Myeloablative Conditioning: A Meta-Analysis. PLoS One. 2018 Jan 30;13(1):e0191955.
11. Dezern A, Brodsky R. Haploidentical Donor Bone Marrow Transplantation for Severe Aplastic Anemia. Hematol Oncol Clin North Am. 2018 Aug; 32(4): 629–642.
12. Eapen M, O'Donnell P, Brunstein CG, et al. Mismatched related and unrelated donors for allogeneic hematopoietic cell transplantation for adults with hematologic malignancies. Biol Blood Marrow Transplant. 2014;20(10):1485–1492. doi:10.1016/j.bbmt.2014.05.015
13. Gauthier J, Poiré X, Gac AC, et al. Better outcome with haploidentical over HLA-matched related donors in patients with Hodgkin's lymphoma undergoing allogeneic haematopoietic cell transplantation-a study by the Francophone Society of Bone Marrow Transplantation and Cellular Therapy. Bone Marrow Transplant. 2018;53(4):400-409.
14. Hsu J, Artz A, Mayer SA, et al. Combined haploidentical and umbilical cord blood allogeneic stem cell transplantation for high-risk lymphoma and chronic lymphoblastic leukemia. Biol Blood Marrow Transplant. 2018;24(2):359-365
15. Huo MR, Xu LP, Li D, et al. The effect of HLA disparity on clinical outcome after HLA-haploidentical blood and marrow transplantation. Clin Transplant 2012; 26:284.
16. Jaiswal SR, Chakrabarti S. Haploidentical Transplantation in Children with Acute Leukemia: The Unresolved Issues. Adv Hematol. 2016;2016:3467672. doi:10.1155/2016/3467672
17. Kasamon YL, Luznik L, Leffell MS, et al. Nonmyeloablative HLA-haploidentical bone marrow transplantation with high-dose posttransplantation cyclophosphamide: effect of HLA disparity on outcome. Biol Blood Marrow Transplant 2010; 16:482.
18. Lorentino F, Labopin M, Fleischhauer K, et al. The impact of HLA matching on outcomes of unmanipulated haploidentical HSCT is modulated by GVHD prophylaxis. Blood Adv 2017; 1:669.
19. Lu DP, Dong L, Wu T, et al. Conditioning including antithymocyte globulin followed by unmanipulated HLA-mismatched/haploidentical blood and marrow transplantation can achieve comparable outcomes with HLA-identical sibling transplantation. Blood 2006; 107:3065.

20. Ma YR, Wang WJ, Cheng YF et al. Impact of ABO incompatibility on outcomes after haploidentical hematopoietic stem cell transplantation for severe aplastic anemia. Bone Marrow Transplant. 2020 Jan 13. doi: 10.1038/s41409-020-0779-7.
21. Marani C, Raiola AM et al. Haploidentical Transplants with Post-Transplant Cyclophosphamide for Relapsed or Refractory Hodgkin Lymphoma: The Role of Comorbidity Index and Pretransplant Positron Emission Tomography. Biol Blood Marrow Transplant. 2018 Dec;24(12):2501-2508.
22. Martínez C, Gayoso J et al. Post-Transplantation Cyclophosphamide-Based Haploidentical Transplantation as Alternative to Matched Sibling or Unrelated Donor Transplantation for Hodgkin Lymphoma: A Registry Study of the Lymphoma Working Party of the European Society for Blood and Marrow Transplantation. J Clin Oncol. 2017 Oct 20;35(30):3425-3432.
23. Raiola AM, Dominietto A, di Grazia C, et al. Unmanipulated haploidentical transplants compared with other alternative donors and matched sibling grafts. Biol Blood Marrow Transplant 2014; 20:1573.
24. Wang Y, Liu QF et al. Haploidentical versus Matched-Sibling Transplant in Adults with Philadelphia-Negative High-Risk Acute Lymphoblastic Leukemia: A Biologically Phase III Randomized Study. Clin Cancer Res. 2016 Jul 15;22(14):3467-76.
25. Xu LP, Jin S et al. Upfront haploidentical transplant for acquired severe aplastic anemia: registry-based comparison with matched related transplant. J Hematol Oncol. 2017 Jan 21;10(1):25.
26. XZhang Y, Guo Z et al. Comparison of haploidentical hematopoietic stem cell transplantation and immunosuppressive therapy for the treatment of acquired severe aplastic anemia in pediatric patients. American Journal of Therapeutics. 2017;24(2):e196-e201.
27. Yang B, Yu R et al. Haploidentical versus Matched Donor Stem Cell Transplantation for Patients With Hematological Malignancies: A Systemic Review and Meta-Analysis. Bone Marrow Transplant. 2019 Jan;54(1):99-122.

Professional Society Guidelines

28. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. Accessed at: https://www.nccn.org/professionals/physician_gls/default.aspx
    - Acute Myeloid Leukemia. Version 3.2021
    - Hodgkin lymphoma. V2.2021.
29. National Cancer Institute:
    - Adult Acute Myeloid Leukemia PDQ 2021. Accessed at: http://www.cancer.gov/types/leukemia/patient/adult-aml-treatment-pdq
    - Childhood Acute Myeloid Leukemia PDQ 2021. Accessed at: http://www.cancer.gov/types/leukemia/patient/adult-aml-treatment-pdq
    - Adult Hodgkin's Lymphoma Treatment. Accessed at: http://www.cancer.gov/types/lymphoma/hp/adult-hodgkin-treatment-pdq
    - Childhood Hodgkin's lymphoma Treatment. Accessed at: http://www.cancer.gov/types/lymphoma/hp/child-hodgkin-treatment-pdq

Other Resources

22. UpToDate: [website]. Waltham, MA: Walters Kluwer Health; 2021.
    - Fuchs E, Luznik L. HLA-haploidentical hematopoietic cell transplantation.
23. IRO Peer Review: Advanced Medical Review: Policy reviewed by practicing MD board certified Oncology, Hematology. 2/25/20.

REVIEW REVISION HISTORY

4/23/20: New Policy
4/5/21: Policy reviewed, no changes to criteria. Updated references.