Protocol

Placental and Umbilical Cord Blood as a Source of Stem Cells

(70150)

Medical Benefit		**Effective Date**: 04/01/13	**Next Review Date**: 03/21
Preauthorization	Yes	**Review Dates**: 04/07, 05/08, 07/11, 07/12, 07/13, 07/14, 07/15, 11/15, 11/16, 03/17, 03/18, 03/19, 03/20	

Preauthorization is required and must be obtained through Case Management.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

Populations	Interventions	Comparators	Outcomes
Individuals: • With an appropriate indication for allogeneic stem cell transplant	Interventions of interest are: • Cord blood as a source of stem cells	Comparators of interest are: • Stem cells from a source other than cord blood	Relevant outcomes include: • Overall survival • Disease-specific survival • Resource utilization • Treatment-related mortality
Individuals: • With an unspecified potential future need for stem cell transplant	Interventions of interest are: • Prophylactic collection and storage of cord blood	Comparators of interest are: • Usual care without prophylactic storage of cord blood	Relevant outcomes include: • Overall survival • Disease-specific survival • Resource utilization • Treatment-related mortality

DESCRIPTION

This evidence review addresses the collection, storage, and transplantation of placental and umbilical cord blood ("cord blood") as a source of stem cells for allogeneic and autologous stem cell transplantation. Potential indications for the use of cord blood are not addressed herein; they are discussed in the disease-specific evidence reviews.

SUMMARY OF EVIDENCE

For individuals who have an appropriate indication for allogeneic stem cell transplant who receive cord blood as a source of stem cells, the evidence includes a number of observational studies, a meta-analysis of observational studies, and a randomized controlled trial comparing outcomes after single- or double-cord blood units. The relevant outcomes are overall survival, disease-specific survival, resource utilization, and treatment-related mortality. The meta-analysis of observational studies found similar survival outcomes and lower graft-versus-host disease after cord blood transplantation than bone marrow transplantation. In the randomized controlled trial, survival rates were similar after single- and double-unit cord blood transplantation. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have an unspecified potential future need for stem cell transplant who receive prophylactic collection and storage of cord blood, the evidence includes no published studies. The relevant outcomes are overall survival, disease-specific survival, resource utilization, and treatment-related mortality. No evidence was identified on the safety or effectiveness of autologous cord blood transplantation from prophylactically stored cord blood for the treatment of malignant neoplasms. The evidence is insufficient to determine the effects of the technology on health outcomes.

POLICY

Transplantation of cord blood stem cells from related or unrelated donors may be considered **medically necessary** in patients with an appropriate indication for allogeneic stem-cell transplant.

Transplantation of cord blood stem cells from related or unrelated donors is considered **investigational** in all other situations.

Collection and storage of cord blood from a neonate may be considered **medically necessary** when an allogeneic transplant is imminent in an identified recipient with a diagnosis that is consistent with the possible need for allogeneic transplant.

Prophylactic collection and storage of cord blood from a neonate may be considered **not medically necessary** when proposed for some unspecified future use as an autologous stem-cell transplant in the original donor, or for some unspecified future use as an allogeneic stem-cell transplant in a related or unrelated donor.

POLICY GUIDELINES

Refer to the separate protocols for specific conditions and diseases that have patient selection criteria for which allogeneic stem cell transplantation may be considered medically necessary.

Individual transplant facilities may have their own *additional* requirements or protocols that must be met in order for the patient to be eligible for a transplant at **their** facility.

MEDICARE ADVANTAGE

If a transplant is needed, we arrange to have the Medicare–approved transplant center review and decide whether the patient is an appropriate candidate for the transplant.

BACKGROUND

HEMATOPOIETIC CELL TRANSPLANTATION

HCT is a procedure in which hematopoietic stem cells are intravenously infused to restore bone marrow and immune function in cancer patients who receive bone marrow-toxic doses of cytotoxic drugs with or without whole-body radiotherapy. Hematopoietic stem cells may be obtained from the transplant recipient (autologous HCT) or a donor (allogeneic HCT [allo-HCT]). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates. Cord blood transplantation is discussed in detail in the Placental and Umbilical Cord Blood as a Source of Stem Cells Protocol.

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HCT. In allogeneic stem cell transplantation, immunologic compatibility between donor and patient is a critical factor for achieving a successful outcome. Compatibility is established by typing of human leukocyte antigens (HLA) using cellular, serologic, or molecular techniques. HLA refers to the gene complex expressed at the

HLA-A, -B, and -DR (antigen-D related) loci on each arm of chromosome six. An acceptable donor will match the patient at all or most of the HLA loci.

CONDITIONING FOR HEMATOPOIETIC CELL TRANSPLANTATION

Conventional Conditioning

The conventional ("classical") practice of allo-HCT involves administration of cytotoxic agents (e.g., cyclophosphamide, busulfan) with or without total body irradiation at doses sufficient to cause bone marrow ablation in the recipient. The beneficial treatment effect of this procedure is due to a combination of the initial eradication of malignant cells and subsequent graft-versus-malignancy effect mediated by non-self-immunologic effector cells. While the slower graft-versus-malignancy effect is considered the potentially curative component, it may be overwhelmed by existing disease in the absence of pretransplant conditioning. Intense conditioning regimens are limited to patients who are sufficiently medically fit to tolerate substantial adverse effects. These include opportunistic infections secondary to loss of endogenous bone marrow function and organ damage or failure caused by cytotoxic drugs. Subsequent to graft infusion in allo-HCT, immunosuppressant drugs are required to minimize graft rejection and graft-versus-host disease, which increases susceptibility to opportunistic infections.

The success of autologous HCT is predicated on the potential of cytotoxic chemotherapy, with or without radiotherapy, to eradicate cancerous cells from the blood and bone marrow. This permits subsequent engraftment and repopulation of the bone marrow with presumably normal hematopoietic stem cells obtained from the patient before undergoing bone marrow ablation. Therefore, autologous HCT is typically performed as consolidation therapy when the patient's disease is in complete remission. Patients who undergo autologous HCT are also susceptible to chemotherapy-related toxicities and opportunistic infections before engraftment, but not graft-versus-host disease.

Reduced-Intensity Conditioning Allogeneic Hematopoietic Cell Transplantation

RIC refers to the pretransplant use of lower doses of cytotoxic drugs or less intense regimens of radiotherapy than are used in traditional full-dose myeloablative conditioning treatments. Although the definition of RIC is variable, with numerous versions employed, all regimens seek to balance the competing effects of relapse due to residual disease and non-relapse mortality. The goal of RIC is to reduce disease burden and to minimize associated treatment-related morbidity and non-relapse mortality in the period during which the beneficial graft-versus-malignancy effect of allogeneic transplantation develops. RIC regimens range from nearly total myeloablative to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and patient condition. Patients who undergo RIC with allo-HCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism. In this review, the term reduced-intensity conditioning will refer to all conditioning regimens intended to be nonmyeloablative.

REGULATORY STATUS

According to the U.S. Food and Drug Administration, cord blood stored for potential use by a patient unrelated to the donor meets the definitions of "drug" and "biological products." As such, products must be licensed under a biologics license application or an investigational new drug application before use. Facilities that prepare cord blood units only for autologous and/or first- or second-degree relatives are required to register and list their products, adhere to Good Tissue Practices issued by the Food and Drug Administration, and use applicable processes for donor suitability determination.[1]

RELATED PROTOCOLS

Allogeneic Hematopoietic Stem Cell Transplantation for Genetic Diseases and Acquired Anemias

Allogeneic Hematopoietic Cell Transplantation for Myelodysplastic Syndromes and Myeloproliferative Neoplasms

Hematopoietic Cell Transplantation for Acute Lymphoblastic Leukemia

Hematopoietic Cell Transplantation for Acute Myeloid Leukemia

Hematopoietic Cell Transplantation for Autoimmune Diseases

Hematopoietic Cell Transplantation for Central Nervous System Embryonal Tumors and Ependymoma

Hematopoietic Cell Transplantation for Chronic Myeloid Leukemia

Hematopoietic Cell Transplantation for Epithelial Ovarian Cancer

Hematopoietic Cell Transplantation for Hodgkin Lymphoma

Hematopoietic Cell Transplantation for Miscellaneous Solid Tumors in Adults

Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas

Hematopoietic Cell Transplantation for Waldenström Macroglobulinemia

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Services that are the subject of a clinical trial do not meet our Technology Assessment and Medically Necessary Services Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment and Medically Necessary Services Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

REFERENCES

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

1. Food and Drug Administration (FDA). Cord Blood Banking: Information for Consumers. 2012 July 23; http://www.fda.gov/biologicsbloodvaccines/resourcesforyou/consumers/ucm236044.htm. Accessed November 21, 2019.
2. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Placental and Umbilical Cord Blood as a Source of Stem Cells for Hematopoietic Support. TEC Assessments. 1996;Volume 11:Tab 17.
3. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Transplanting Adult Patients with Hematopoietic Stem Cells from Placental and Umbilical Cord Blood TEC Assessments. 2001;Volume 16:Tab 17.
4. Wall DA. Regulatory issues in cord blood banking and transplantation. Best Pract Res Clin Haematol. Jun 2010;23(2):171-177. PMID 20837328
5. NetCord-FACT. International standards for cord blood collection banking and release of information accreditation manual. Sixth Edition Draft. 2015 September; http://www.factwebsite.org/uploadedFiles/Standards/NetCord%20FACT%206th%20Ed%20Manual%20Draft.09.01.15.pdf. Accessed November 21, 2019.

6. Gluckman E, Broxmeyer HA, Auerbach AD, et al. Hematopoietic reconstitution in a patient with Fanconi's anemia by means of umbilical-cord blood from an HLA-identical sibling. N Engl J Med. Oct 26 1989;321(17): 1174-1178. PMID 2571931
7. Wagner JE, Rosenthal J, Sweetman R, et al. Successful transplantation of HLA-matched and HLA-mismatched umbilical cord blood from unrelated donors: analysis of engraftment and acute graft-versus-host disease. Blood. Aug 1 1996;88(3):795-802. PMID 8704232
8. Broxmeyer HE, Douglas GW, Hangoc G, et al. Human umbilical cord blood as a potential source of transplantable hematopoietic stem/progenitor cells. Proc Natl Acad Sci U S A. May 1989;86(10):3828-3832. PMID 2566997
9. Kurtzberg J, Cairo MS, Fraser JK, et al. Results of the Cord Blood Transplantation (COBLT) study unrelated donor banking program. Transfusion. Jun 2005;45(6):842-855. PMID 15934981
10. Martin PL, Carter SL, Kernan NA, et al. Results of the Cord Blood Transplantation Study (COBLT): outcomes of unrelated donor umbilical cord blood transplantation in pediatric patients with lysosomal and peroxisomal storage diseases. Biol Blood Marrow Transplant. Feb 2006;12(2):184-194. PMID 16443516
11. Kurtzberg J. Update on umbilical cord blood transplantation. Curr Opin Pediatr. Feb 2009;21(1):22-29. PMID 19253461
12. Zhang H, Chen J, Que W. Meta-analysis of unrelated donor umbilical cord blood transplantation versus unrelated donor bone marrow transplantation in acute leukemia patients. Biol Blood Marrow Transplant. Aug 2012;18(8):1164-1173. PMID 22289799
13. Rocha V, Cornish J, Sievers EL, et al. Comparison of outcomes of unrelated bone marrow and umbilical cord blood transplants in children with acute leukemia. Blood. May 15 2001;97(10):2962-2971. PMID 11342418
14. Kato K, Choi I, Wake A, et al. Treatment of patients with adult T cell leukemia/lymphoma with cord blood transplantation: a Japanese nationwide retrospective survey. Biol Blood Marrow Transplant. Dec 2014; 20(12):1968-1974. PMID 25172635
15. Liu HL, Sun ZM, Geng LQ, et al. Similar survival, but better quality of life after myeloablative transplantation using unrelated cord blood vs. matched sibling donors in adults with hematologic malignancies. Bone Marrow Transplant. Aug 2014;49(8):1063-1069. PMID 24842525
16. Mo XD, Tang BL, Zhang XH, et al. Comparison of outcomes after umbilical cord blood and unmanipulated haploidentical hematopoietic stem cell transplantation in children with high-risk acute lymphoblastic leukemia. Int J Cancer. Nov 1 2016;139(9):2106-2115. PMID 27356906
17. 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. Feb 2018;24(2):359-365. PMID 29128555
18. Barker JN, Weisdorf DJ, DeFor TE, et al. Transplantation of 2 partially HLA-matched umbilical cord blood units to enhance engraftment in adults with hematologic malignancy. Blood. Feb 1 2005;105(3):1343-1347. PMID 15466923
19. Wagner JE, Jr., Eapen M, Carter S, et al. One-unit versus two-unit cord-blood transplantation for hematologic cancers. N Engl J Med. Oct 30 2014;371(18):1685-1694. PMID 25354103
20. Scaradavou A, Brunstein CG, Eapen M, et al. Double unit grafts successfully extend the application of umbilical cord blood transplantation in adults with acute leukemia. Blood. Jan 31 2013;121(5):752-758. PMID 23223509
21. Baron F, Ruggeri A, Beohou E, et al. Single- or double-unit UCBT following RIC in adults with AL: a report from Eurocord, the ALWP and the CTIWP of the EBMT. J Hematol Oncol. Jun 21 2017;10(1):128. PMID 28637512
22. Shearer WT, Lubin BH, Cairo MS, et al. Cord Blood Banking for Potential Future Transplantation. Pediatrics. Nov 2017;140(5). PMID 29084832
23. Thornley I, Eapen M, Sung L, et al. Private cord blood banking: experiences and views of pediatric hematopoietic cell transplantation physicians. Pediatrics. Mar 2009;123(3):1011-1017. PMID 19255033

24. ACOG committee opinion no. 771: umbilical cord banking. Obstet Gynecol. 2019 Mar;133(3):e249e253. PMID: 30801478.
25. Ballen KK, Barker JN, Stewart SK, et al. Collection and preservation of cord blood for personal use. Biol Blood Marrow Transplant. Mar 2008;14(3):356-363. PMID 18275904