Hematopoietic Cell Transplantation for Miscellaneous Solid Tumors in Adults

Policy # 00059
Original Effective Date: 01/28/2002
Current Effective Date: 06/14/2021

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Hematopoietic Cell Transplantation for Epithelial Ovarian Cancer is addressed separately in medical policy 00054.

Note: Hematopoietic Cell Transplantation in the Treatment of Germ Cell Tumors is addressed separately in medical policy 00056.

Note: Hematopoietic Cell Transplantation for Central Nervous System Embryonal Tumors and Ependymoma is addressed separately in medical policy 00063.

Note: Hematopoietic Cell Transplantation for Solid Tumors of Childhood is addressed separately in medical policy 00064.

Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers autologous or allogeneic hematopoietic cell transplant (HCT) for miscellaneous solid tumors in adults including, but not limited to, the following malignancies to be **investigational.***

- Lung cancer, any histology
- Colon cancer
- Rectal cancer
- Pancreas cancer
- Stomach cancer
- Esophageal cancer
- Gall bladder cancer

- Cancer of the bile duct
- Renal cell cancer
- Cervical cancer
- Uterine cancer
- Cancer of the fallopian tubes
- Prostate cancer
- Nasopharyngeal cancer
- Paranasal sinus cancer
- Neuroendocrine tumors
- Soft tissue sarcomas
- Thyroid tumors
- Tumors of the thymus
- Tumors of unknown primary origin
- Malignant melanoma

Background/Overview

Hematopoietic Cell Transplantation

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.

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 6. 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 the 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 (GVHD), 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 GVHD.

Reduced-Intensity Conditioning Allogeneic Hematopoietic Cell Transplantation

Reduced-intensity conditioning (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 RIC will refer to all conditioning regimens intended to be nonmyeloablative.

Hematopoietic Cell Transplantation in Solid Tumors in Adults
HCT is an established treatment for certain hematologic malignancies. Its use in solid tumors is less well established, although it has been investigated for a variety of solid tumors. With the advent of nonmyeloablative allogeneic transplant, interest has shifted to exploring the generation of alloreactivity to metastatic solid tumors via a graft-versus-tumor effect of donor-derived T cells.

HCT as a treatment for ovarian cancer, germ cell tumors, ependymoma, or malignant glioma is addressed separately (evidence reviews 8.01.23, 8.01.35, and 8.01.28, respectively). HCT as a treatment for breast cancer is not addressed. This evidence review collectively addresses other solid tumors of adults for which HCT has been investigated, including lung cancer, malignant melanoma, tumors of the gastrointestinal tract (affecting the colon, rectum, pancreas, stomach, esophagus, gallbladder, or bile duct), male and female genitourinary systems (eg, renal cell carcinoma, prostate cancer, cervical cancer, uterine cancer, fallopian tube cancer), tumors of the head and neck, soft tissue sarcoma, thyroid tumors, tumors of the thymus, and tumors of unknown primary origin.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
The U.S. Food and Drug Administration regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research, under Code of Federal Regulation, Title 21, parts 1270 and 1271. Hematopoietic stem cells are included in these regulations.

Rationale/Source

Description
Hematopoietic cell transplantation (HCT) is an established treatment for certain hematologic malignancies and has been investigated for a variety of adult solid tumors. Interest continues in exploring nonmyeloablative allogeneic HCT (allo-HCT) for a graft-versus-tumor effect of donor-derived T-cells in metastatic solid tumors.

Summary of Evidence

Autologous Hematopoietic Cell Transplantation
For individuals who have adult soft tissue sarcomas who receive autologous HCT, the evidence includes a RCT, a number of phase 2 single-arm studies (some of which have been summarized in a systematic review), and a retrospective registry study. Relevant outcomes are overall survival (OS), disease-specific survival, and treatment-related mortality and morbidity. Although a small phase 2 RCT reported longer survival for patients treated with autologous HCT than with standard chemotherapy, this trial did not show a survival benefit with HCT. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have small cell lung cancer who receive autologous HCT, the evidence includes several RCTs, and systematic reviews of these studies. Relevant outcomes are OS, disease-specific survival, and treatment-related mortality and morbidity. Studies have not reported increased OS for patients with small-cell lung cancer treated with autologous HCT. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Allogeneic Hematopoietic Cell Transplantation
For individuals who have renal cell carcinoma, colorectal cancer , pancreatic cancer, or nasopharyngeal cancer who receive allo-HCT, the evidence includes small single-arm series. Relevant outcomes are OS, disease-specific survival, and treatment-related mortality and morbidity. The evidence for allo-HCT to treat renal cell carcinoma, colorectal cancer, pancreatic cancer, and nasopharyngeal cancer has been limited to small case series. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Supplemental Information

Practice Guidelines and Position Statements

National Comprehensive Cancer Network
Current National Comprehensive Cancer Network guidelines (2020) on the tumors addressed in this evidence review do not discuss hematopoietic cell transplantation (HCT) as a treatment option.

American Society for Blood and Marrow Transplantation
In 2015, the American Society for Blood and Marrow Transplantation (now referred to as the American Society for Transplantation and Cellular Therapy) issued guidelines related to indications for autologous and allogeneic HCT. The tumors addressed herein for which the Society has provided recommendations are listed in Table 1.

Table 1. Recommendations for Use of Autologous and Allogeneic Hematopoietic Cell Transplantation

Condition	Treatment Option	Recommendation
Ewing sarcoma, high-risk	Allogeneic HCT	Not generally recommended
	Autologous HCT	Standard of care, clinical evidence available
Renal cancer, metastatic	Allogeneic HCT	Developmental
	Autologous HCT	Not generally recommended

HCT: hematopoietic cell transplantation.

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
The Centers for Medicare & Medicaid Services currently have the following national noncoverage decision on autologous stem cell transplantation: "Insufficient data exist to establish definite conclusions regarding the efficacy of AuSCT [autologous stem cell transplantation] for the following condition[s]: Solid tumors (other than neuroblastoma)."

Ongoing and Unpublished Clinical Trials
Some currently ongoing and unpublished trials that might influence this review are listed in Table 2.

Table 2. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT04530487	Donor Stem Cell Transplant After Chemotherapy for the Treatment of Recurrent or Refractory High-Risk Solid Tumors in Pediatric and Adolescent-Young Adults	40	May 2025

NCT: national clinical trial.

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Policy History

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12/06/2001	Medical Policy Committee review
01/28/2002	Managed Care Advisory Council approval
03/31/2004	Medical Director review
05/07/2004	Medical Director review
05/18/2004	Medical Policy Committee review. Format revision. High-Dose Chemotherapy and Hematopoietic Stem Cell Support for Miscellaneous Solid Tumors in Adults policy developed separately from current HDC with Hematopoietic Stem Cell Support policy. No substance change to policy.
06/28/2004	Managed Care Advisory Council approval
07/12/2006	Medical Director review
07/19/2006	Medical Policy Committee approval. Format revision including addition of FDA and or other governmental regulatory approval and rationale/source. Coverage eligibility is unchanged.
06/04/2008	Medical Director review

06/18/2008	Medical Policy Committee approval. Coverage eligibility is unchanged.
06/04/2009	Medical Director review
06/17/2009	Medical Policy Committee approval. Changed title from "High-Dose Chemotherapy and Hematopoietic Stem Cell Support for Miscellaneous Solid Tumors in Adults" to "High-Dose Chemotherapy and Hematopoietic Stem Cell Transplantation for Miscellaneous Solid Tumors in Adults." Coverage eligibility is unchanged.
06/03/2010	Medical Policy Committee review
06/16/2010	Medical Policy Implementation Committee approval. Changed title from "High-Dose Chemotherapy and Hematopoietic Stem Cell Transplantation for Miscellaneous Solid Tumors in Adults." to "Hematopoietic Stem Cell Transplantation for Miscellaneous Solid Tumors in Adults." Changed the wording of the investigational statement from, "high-dose chemotherapy (HDC) with autologous or allogeneic stem cell support (SCS) for miscellaneous solid tumors" to "autologous or allogeneic stem cell transplant (SCT) for miscellaneous solid tumors." Coverage eligibility unchanged.
06/02/2011	Medical Policy Committee review
06/15/2011	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/14/2012	Medical Policy Committee review
06/20/2012	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
03/04/2013	Coding updated
08/01/2013	Medical Policy Committee review
08/21/2013	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/04/2014	Medical Policy Committee review
12/17/2014	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
12/03/2015	Medical Policy Committee review
12/16/2015	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

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12/01/2016	Medical Policy Committee review
12/21/2016	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
12/07/2017	Medical Policy Committee review
12/20/2017	Medical Policy Implementation Committee approval. "Stem" removed from title and policy. HSCT changed to HCT in policy text. Coverage eligibility unchanged.
12/06/2018	Medical Policy Committee review
12/19/2018	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/05/2019	Medical Policy Committee review
12/11/2019	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/07/2020	Medical Policy Committee review
05/13/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/06/2021	Medical Policy Committee review
05/12/2021	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 05/2022

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HCPCS	S2140, S2142, S2150
ICD-10 Diagnosis	All related diagnosis

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
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2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
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