Effective November 1, 2023, refer to CMS Manual 100-02, Chapter 16-General Exclusions from Coverage for services included in this policy.

BlueCross BlueShield of Alabama

Name of Blue Advantage Policy:

Hematopoietic Stem-Cell Transplantation for Breast Cancer

Policy #: 518
Latest Review Date: October 2023
Category: Surgical
ARCHIVED EFFECTIVE 11/1/2023

BACKGROUND:

Blue Advantage *medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:*

1. *Safe and effective;*
2. *Not experimental or investigational*;*
3. *Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:*
   - *Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;*
   - *Furnished in a setting appropriate to the patient's medical needs and condition;*
   - *Ordered and furnished by qualified personnel;*
   - *One that meets, but does not exceed, the patient's medical need; and*
   - *At least as beneficial as an existing and available medically appropriate alternative.*

Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000 which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill* ***Original Medicare* *for covered services that are related to* ***clinical trials*** *that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).*

POLICY:

Blue Advantage will treat **single or tandem autologous hematopoietic stem-cell transplantation when used to treat any stage of breast cancer** as a **non-covered benefit** and as **investigational**.

Blue Advantage will treat **allogeneic hematopoietic stem-cell transplantation when used to treat any stage of breast cancer** as a **non-covered benefit** and as **investigational**.

Blue Advantage does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Advantage administers benefits based on the members' contract and medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

DESCRIPTION OF PROCEDURE OR SERVICE:

The use of high-dose chemotherapy (HDC) and hematopoietic stem cell transplantation (HSCT), instead of standard dose chemotherapy, has been used in an attempt to prolong survival in women with high-risk non-metastatic and metastatic breast cancer.

Hematopoietic Stem Cell Transplantation

Hematopoietic stem cell transplantation (HSCT) refers to a procedure in which hematopoietic stem cells are infused to restore bone marrow function in cancer patients who receive bone-marrow-toxic doses of cytotoxic drugs with or without whole body radiation therapy. Hematopoietic stem cells may be obtained from the transplant recipient (autologous HSCT) or from a donor (allogeneic HSCT). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates. Although cord blood is an allogeneic source, the stem cells in it are antigenically "naïve" and thus are associated with a lower incidence of rejection or graft-versus-host disease (GVHD).

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HSCT. However, immunologic compatibility between donor and patient is a critical factor for achieving a good outcome of allogeneic HSCT. Compatibility is established by typing of human leukocyte antigens (HLA) using cellular, serologic, or molecular techniques. HLA refers to the tissue type expressed at the Class I and Class II loci on chromosome 6. Depending on the disease being treated, an acceptable donor will match the patient at all or most of the HLA loci (with the exception of umbilical cord blood).

Conventional Preparative Conditioning for HSCT

The success of autologous HSCT is predicated on the ability of cytotoxic chemotherapy with or without radiation to eradicate cancerous cells from the blood and bone marrow. This permits subsequent engraftment and repopulation of bone marrow space with presumably normal

hematopoietic stem cells obtained from the patient prior to undergoing bone marrow ablation. Consequently, autologous HSCT is typically performed as consolidation therapy when the patient's disease is in complete remission. Patients who undergo autologous HSCT are susceptible to chemotherapy-related toxicities and opportunistic infections prior to engraftment, but not GVHD.

The conventional ("classical") practice of allogeneic HSCT involves administration of cytotoxic agents (e.g., cyclophosphamide, busulfan) with or without total body irradiation at doses sufficient to destroy endogenous hematopoietic capability in the recipient. The beneficial treatment effect in this procedure is due to a combination of initial eradication of malignant cells and subsequent graft-versus-malignancy (GVM) effect mediated by non-self-immunologic effector cells that develop after engraftment of allogeneic stem cells within the patient's bone marrow space. While the slower GVM effect is considered to be the potentially curative component, it may be overwhelmed by extant disease without the use of pretransplant conditioning. However, intense conditioning regimens are limited to patients who are sufficiently fit medically to tolerate substantial adverse effects that include pre-engraftment opportunistic infections secondary to loss of endogenous bone marrow function and organ damage and failure caused by the cytotoxic drugs. Furthermore, in any allogeneic HSCT, immune suppressant drugs are required to minimize graft rejection and GVHD, which also increases susceptibility of the patient to opportunistic infections.

Reduced-Intensity Conditioning for Allogeneic HSCT

Reduced-intensity conditioning (RIC) refers to the pretransplant use of lower doses or less intense regimens of cytotoxic drugs or radiation than are used in traditional full-dose myeloablative conditioning treatments. The goal of RIC is to reduce disease burden but also to minimize as much as possible associated treatment-related morbidity and non-relapse mortality (NRM) in the period during which the beneficial GVM effect of allogeneic transplantation develops. Although the definition of RIC remains arbitrary, with numerous versions employed, all seek to balance the competing effects of NRM and relapse due to residual disease. RIC regimens can be viewed as a continuum in effects, from nearly totally myeloablative to minimally myeloablative with lympho-ablation, with intensity tailored to specific diseases and patient condition. Patients who undergo RIC with allogeneic HSCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism, which may be supplemented with donor lymphocyte infusions to eradicate residual malignant cells.

For the purposes of this policy, the term reduced-intensity conditioning will refer to all conditioning regimens intended to be non-myeloablative, as opposed to fully myeloablative (traditional) regimens.

HSCT in Solid Tumors in Adults

HSCT is an established treatment for certain hematologic malignancies; however, its use in solid tumors in adults continues to be largely experimental. Initial enthusiasm for the use of autologous transplant with the use of HDC and stem cells for solid tumors has waned with the realization that dose intensification often fails to improve survival, even in tumors with a linear-dose response to chemotherapy. With the advent of reduced-intensity allogeneic transplant,

interest has shifted to exploring the generation of alloreactivity to metastatic solid tumors via a graft-versus-tumor (GVT) effect of donor-derived T cells.

KEY POINTS:

The most recent literature review was performed through October 16, 2023. The following is a summary of key literature to date.

Summary of Evidence

Randomized trials of autologous hematopoietic stem cell transplantation (HSCT) versus standard dose chemotherapy for patients with high-risk non-metastatic or metastatic breast cancer have not shown a survival advantage with HSCT, with greater treatment-related mortality and toxicity. Therefore, autologous HSCT is considered not medically necessary for this indication.

Nonrandomized studies using reduced-intensity or myeloablative allogeneic HSCT for metastatic breast cancer have suggested a possible graft-versus-tumor effect, but remains investigational for this indication.

Practice Guidelines and Position Statements

National Comprehensive Cancer Network (NCCN)

NCCN guidelines (V4.2022) do not address the use of HSCT in the treatment of breast cancer.

Table 1. American Society for Transplantation and Cellular Therapy (2020)

Adults	Allogeneic HCT	Autologous HCT
Breast cancer, adjuvant high risk	N	N
Breast cancer, metastatic	D	N

(N: Not generally recommended; C: standard of care, clinical evidence available; S: standard of care; R: standard of care, rare indication; D: developmental.)

National Cancer Institute (NCI)

The National Cancer Institute does not mention the use of stem cell transplant in Breast Cancer Treatment (Adult) (PDQ®)–Health Professional Version (Updated: September 2, 2020).

U.S. Preventive Services Task Force Recommendations

Not applicable.

KEY WORDS:

Hematopoietic stem cell transplantation for breast cancer, stem cell transplant, breast cancer, HSCT, autologous SCT, allogeneic SCT

APPROVED BY GOVERNING BODIES:

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 the Code of Federal Regulation title 21, parts 1270 and 1271. Hematopoietic stem cells are included in these regulations.

BENEFIT APPLICATION:

Coverage is subject to member's specific benefits. Group-specific policy will supersede this policy when applicable.

CURRENT CODING:

CPT Codes:

38204	Management of recipient hematopoietic cell donor search and cell acquisition
38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection, allogeneic
38206	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection, autologous
38208	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing, per donor
38209	; thawing of previously frozen harvest, with washing, per donor
38210	; specific cell depletion with harvest, T cell depletion
38211	; tumor cell depletion
38212	; red blood cell removal
38213	; platelet depletion
38214	; plasma (volume) depletion
38215	; cell concentration in plasma, mononuclear, or buffy coat layer
38220	Diagnostic bone marrow; aspiration(s)

38221	Diagnostic bone marrow; biopsy(ies)
38222	Diagnostic bone marrow; biopsy(ies) and aspiration(s)
38230	Bone marrow harvesting for transplantation; allogeneic
38232	; autologous
38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor
38241	; autologous transplantation
38242	Allogeneic lymphocyte infusions

HCPCS:

S2140	Cord blood harvesting for transplantation, allogeneic
S2142	Cord blood derived stem-cell transplantation, allogeneic
S2150	Bone marrow or blood-derived peripheral stem-cell harvesting and transplantation, allogeneic or autologous, including pheresis, high-dose chemotherapy, and the number of days of posttransplant care in the global definition (including drugs; hospitalization; medical surgical, diagnostic, and emergency services)

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POLICY HISTORY:

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Medical Policy Group, October 2021
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Medical Policy Group, October 2023: No new published peer-reviewed literature available that would alter the coverage statement in this policy.
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