

## ***Hematopoietic Cell Transplantation for Breast Cancer***

**Effective:** May 1, 2022

**Next Review:** January 2023

**Last Review:** January 2022

### **IMPORTANT REMINDER**

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

### **DESCRIPTION**

Hematopoietic cell transplantation is performed to restore normal function following chemotherapy treatment.

### **MEDICAL POLICY CRITERIA**

- I. Single autologous HCT is considered **not medically necessary** to treat any stage of breast cancer.
- II. Tandem autologous HCT is considered **not medically necessary** to treat any stage of breast cancer.
- III. Allogeneic HCT is considered **investigational** to treat any stage of breast cancer.

*NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.*

### **CROSS REFERENCES**

1. [Donor Lymphocyte Infusion for Malignancies Treated with an Allogeneic Hematopoietic Cell Transplant](#), Transplant, Policy No. 45.03
2. [Placental and Umbilical Cord Blood as a Source of Stem Cells](#), Transplant, Policy No. 45.16
3. [Hematopoietic Cell Transplantation for Miscellaneous Solid Tumors in Adults](#), Transplant, Policy No. 45.27

## POLICY GUIDELINES

### DEFINITIONS

- **Consolidation therapy:** Treatment that is given after cancer has disappeared following the initial therapy. Consolidation therapy is used to kill any cancer cells that may be left in the body. It may include radiation therapy, a stem cell transplant, or treatment with drugs that kill cancer cells. Also called intensification therapy and postremission therapy.
- **Relapse:** The return of a disease or the signs and symptoms of a disease after a period of improvement.
- **Salvage therapy:** Treatment that is given after the cancer has not responded to other treatments.
- **Tandem transplant:** Refers to a planned second course of high-dose therapy and HCT within six months of the first course.

## BACKGROUND

### HEMATOPOIETIC CELL TRANSPLANTATION

Broadly speaking, there are two types of hematopoietic cell transplantation (HCT, previously referred to in this policy as a hematopoietic stem cell transplant [HSCT]), autologous and allogeneic. The purpose of an autologous HCT is to treat a disease high-dose chemotherapy (with or without radiation) that is active against the disease. The recipient's own HCTs (collected previously) are infused after the chemotherapy in order to re-establish normal marrow function. In an allogeneic transplant, the recipient receives HCTs from a donor after myeloablative therapy or non-myeloablative therapy in order to re-establish normal marrow function as well as to use the new blood system as a platform for immunotherapy, a so called "graft versus tumor" effect. Hematopoietic cells 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 cells and the recipient is not an issue in autologous HCT. However, immunologic compatibility between donor and patient is a critical factor for achieving a good outcome of allogeneic HCT. 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 HCT

The conventional ("classical") practice of allogeneic HCT 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 that develop after engraftment of allogeneic 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 HCT, 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 HCT**

Reduced-intensity conditioning (RIC) refers to the conditioning with 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 lymphoablation, with intensity tailored to specific diseases and patient condition. Patients who undergo RIC with allogeneic HCT 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 (conventional) regimens.

## **HCT IN SOLID TUMORS IN ADULTS**

HCT 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 high-dose chemotherapy (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 effect of donor-derived T cells.

## **EVIDENCE SUMMARY**

### **HISTORY OF HEMATOPOIETIC STEM-CELL TRANSPLANT FOR BREAST CANCER**

In the late 1980s/early 1990s, initial results of phase II trials for breast cancer and autologous HCT were promising, showing high response rates in patients with metastatic disease who underwent high-dose consolidation, with a subset of up to 30% remaining disease-free for prolonged periods.<sup>[1]</sup> In the early 1990s, larger prospective comparisons of conventional-dose chemotherapy to high-dose therapy with SCT were initiated but accrued slowly, with up to a decade from initiation to the reporting of results.<sup>[1]</sup> The first results from randomized trials at a single institution in early stage and metastatic disease showed survival benefits, but were ultimately shown to be based on fraudulent data.<sup>[1]</sup> In the interim, though, the treatment became almost standard of care, while many patients received high-dose therapy off protocol, further reducing accrual to ongoing randomized trials.<sup>[1]</sup> The results of the randomized trials were presented beginning in 1999 and showed little survival benefit; subsequently, the number

of HCT procedures performed for breast cancer decreased from thousands every year to only a few.<sup>[1]</sup>

## **AUTOLOGOUS STEM-CELL TRANSPLANT**

### **Systematic Reviews**

A meta-analysis by Wang (2012) included aggregate data from 14 trials (n = 5,747) published since March 2010.<sup>[2]</sup> Clinical trials of patients receiving HCT as a first-line treatment for primary breast cancer were eligible for inclusion. A higher treatment-related mortality was found among the patients who received HCT compared to standard chemotherapy (relative risk [RR] 3.42, 95% confidence interval [CI] 1.32 to 8.86). Overall survival did not differ significantly between groups, with a hazard ratio (HR) of 0.91 (95% CI 0.82 to 1.00) for the HCT compared to standard treatment. Risk of secondary, non-breast cancer was higher in the HCT group (RR 1.28, 95% CI 0.82 to 1.98). Disease-free survival was better in the HCT group compared to chemotherapy alone (RR 0.89, 95% CI 0.79 to 0.99). Patients receiving HCT had a greater risk of dying during remission than patients treated with nonmyeloablative chemotherapy due to the toxicity of the regimen. This increase in treatment-related mortality may help explain why there was no observed overall survival benefit for patients receiving HCT when disease-free survival was observed to be superior to standard chemotherapy.

Berry (2011) performed a meta-analysis with individual patient data from 15 randomized trials comparing autologous HCT with HDC (n = 3,118) to standard chemotherapy (n = 3,092) for patients with high-risk primary breast cancer.<sup>[3]</sup> A survival analysis was adjusted for trial, age, number of positive lymph nodes, and hormone receptor status. HCT was associated with a non-significant 6% reduction in risk of death (HR 0.94, 95% CI 0.87 to 1.02, p=0.13) and a significant reduction in the risk of recurrence (HR 0.87, 95% CI 0.81 to 0.93, p<0.001). Toxic death was higher in the HCT group with 72 (6%) of 1,207 deaths in these trial arms compared to 17 (1.4%) of 1,261 deaths in the standard therapy arms. In a subgroup analysis, the authors investigated whether age, number of positive lymph nodes, tumor size, histology, hormone receptor status, or human epidermal growth factor receptor 2 (HER2) status impacted survival when comparing HCT to standard treatment. The authors found that HER2-negative patients receiving HCT had a 21% reduction in the risk of death and HER2-negative and hormone receptor-negative patients receiving HCT had a 33% reduction in the risk of death. In their discussion, the authors state that this relationship could be spurious due to the amount of missing data on HER2 status and suggest that HCT is unlikely to show much benefit in these subgroups of patients.

Another systematic review by Berry (2011) included six randomized trials that compared the use of HDC with autologous HCT to control chemotherapy regimens in metastatic breast cancer.<sup>[4]</sup> Data from a total 866 women were pooled, and overall survival (OS) and progression-free survival (PFS) were assessed in a meta-analysis. While there was a significantly higher PFS in the HDC with HCT group, this did not translate into an OS benefit. A subgroup analysis failed to identify any patient groups that might derive benefit from this treatment.

A Cochrane systematic review and meta-analysis published in July 2005 pooled data from six randomized controlled trials (RCTs) on metastatic breast cancer reported through November 2004 (n = 438 randomized to autologous HCT, 412 to conventional dose therapy).<sup>[5]</sup> The risk of treatment-related mortality was significantly higher in the arm randomized to HCT (15 vs. 2 deaths, RR 4.07, 95% CI 1.39 to 11.88). Treatment-related morbidity also was more severe

among those randomized to HCT. OS did not differ significantly between groups at one, three, or five years after treatment. Statistically significant differences in event-free survival at one year (RR 1.76, 95% CI 1.40 to 2.21) and five years (RR 2.84, 95% CI 1.07 to 7.50) favored the HCT arms. Only one of the six included trials had followed all patients for at least five years. Reviewers recommended further follow-up for patients randomized in the other five trials. They also concluded that, in the interim, patients with metastatic breast cancer should not receive HCT outside of a clinical trial, since available data showed greater treatment-related mortality and toxicity without improved overall survival.

A second Cochrane systematic review and meta-analysis, also published in July 2005, included data from 13 RCTs on patients with high-risk (poor prognosis) early breast cancer (n = 2,535 randomized to HCT, and 2,529 to conventional dose therapy).<sup>[6]</sup> Treatment-related mortality was significantly greater among those randomized to HDC with HCT (65 vs. 4 deaths, RR=8.58, 95% CI 4.13, 17.80). Treatment-related morbidity also was more common and more severe in the high-dose arms. There were no significant differences between arms in OS at any time after treatment. Event-free survival was significantly greater in the HCT group at three years (RR 1.12, 95% CI 1.06 to 1.19) and four years (RR 1.30, 95% CI 1.16 to 1.45) after treatment. However, the two groups did not differ significantly with respect to event-free survival at five and six years after treatment. Quality of life scores were significantly worse in the HCT arms than in controls soon after treatment, but differences were no longer statistically significant by one year. Reviewers concluded that available data were insufficient to support routine use of HCT for patients with poor-prognosis early breast cancer.

A systematic review and meta-analysis published in 2007 included RCTs comparing autologous HCT to standard dose chemotherapy in women with early, poor prognosis breast cancer, which included 13 trials to September 2006 with 5,064 patients.<sup>[7]</sup> Major conclusions were that at five years, event-free survival approached statistical significance for the high-dose group, but no OS differences were seen. There were more transplant-related deaths in the high-dose group. The end conclusion was that there was insufficient evidence to support routine use of autologous HCT for treating early, poor prognosis breast cancer.

Nieto (2009) performed a meta-analysis of all randomized trials published or updated since 2006 focusing on those that compared HDC with standard-dose chemotherapy for high-risk primary breast cancer.<sup>[8]</sup> The meta-analysis of 15 randomized trials involving patients with high-risk primary breast cancer or metastatic disease (n = 6,102) detected an absolute 13% event-free survival benefit in favor of HDC and autologous HCT (p=0.0001) at a median follow-up of six years. The absolute differences in disease-specific and overall survival did not reach statistical significance (7% and 5%, respectively). Subset analyses suggested that HDC could be particularly effective in patients with triple negative tumors (hormone receptor and HER2-negative). The authors concluded that HDC remains a valid research strategy in certain subpopulations with high-risk primary breast cancer, for example those with triple negative tumors.

### **Randomized Controlled Trials**

Steenbruggen (2020) published a 20-year follow-up analysis of an RCT comparing conventional-dose chemotherapy with high-dose chemotherapy plus autologous HCT.<sup>[9]</sup> The original trial was published in 2003.<sup>[10]</sup> A total of 885 patients were randomized 1:1 with a median follow-up of 20.4 years. The 20-year OS was 45.3% for the HCT group and 41.5% for the conventional-dose chemotherapy group. Patients with 10 or more involved axillary lymph

nodes and those with triple-negative breast cancer experienced a 14.6% (HR 0.72; 95% CI 0.54 to 0.95) and a 15.4% (HR 0.67; 95% CI 0.42 to 1.05) absolute improvement in 20-year OS, respectively. Cumulative incidence risk of a second neoplasm was 12.1% in the HCT group and 16.2% in the conventional-dose chemotherapy group ( $p=0.10$ ). The overall cumulative incidence risk of major cardiovascular events was also not significantly different between groups, though the HCT group had higher incidence of hypertension (21.7% vs 14.3%,  $p=0.02$ ), cholesterol (15.7% vs 10.6%,  $p=0.04$ ), and dysrhythmias (8.6% vs 4.6%,  $p=0.005$ ).

## Nonrandomized Studies

In 2013, the Italian Group of Bone Marrow and Hematopoietic Stem-Cell Transplantation and Cellular Therapy (GITMO) published registry data on 415 patients with metastatic breast cancer who received HDC and autologous HCT between 1990 and 2005.<sup>[11]</sup> More than 95% of the transplants performed used peripheral blood stem cells. Sixteen percent of patients received a tandem transplant. Estrogen-receptor (ER) status was known in 328 patients, 65% of whom were ER-positive. HER2 expression data were insufficient for subset analysis. After a median follow-up of 27 months (range 0 to 172 months), PFS at 5 and 10 years was 23% and 14%, and OS was 47% and 32%, respectively. The authors reported statistically significant survival benefit in patient subgroups including those with ER-positive tumors and those without visceral metastases; however, these are established positive prognostic factors. In addition, the authors did not report which patients received hormonal therapy, nor was it known if/which patients received targeted HER2 therapy, and it is unclear what impact on survival therapies other than HCT may have had.

In 2013, GITMO published registry data on the use of adjuvant HDC with autologous HCT in 1,183 patients with high-risk primary breast cancer (three or more involved lymph nodes), treated between 1990 and 2005.<sup>[12]</sup> Data on ER and HER2 status were available in 85% and 48% of patients, respectively. The majority of patients with hormone receptor-positive tumors received tamoxifen after HCT. The median lymph node involvement at surgery was 15 (range 4 to 63). Greater than 95% of the patients received peripheral blood-mobilized stem cells. After a median follow-up of 7.1 years, disease-free survival was 9.6 years, with 65% of patients free of disease at five years. Median OS was not reached, with 75% of patients alive at five years post-transplantation. Subgroup analysis showed significantly better OS in endocrine-responsive tumors and in patients who received multiple transplant procedures. Transplant-related mortality was 0.8% and late cardiac and secondary tumor-related mortality were approximately 1% overall.

Cheng (2017) compared long-term outcomes for inflammatory and non-inflammatory breast cancer (IBC, non-IBC) treated with HDC and autologous HCT, using data from the Center for International Blood & Marrow Transplant Research (CIBMTR).<sup>[13]</sup> A total of 3,387 patients from 91 centers, who underwent treatment between 1990 and 2002 and had sufficient follow-up data, were included in the study. There were 2,423 patients excluded due to lack of follow-up data. The majority of patients had non-IBC ( $n=2,860$ , 84.4%). At initial presentation, 84% of the 527 patients with IBC had stage III disease, and 80% of the non-IBC patients had high-risk, stage II/III disease. No differences were seen in transplant-related mortality, 1- and 10-year PFS, or OS between the those with stage III IBC and those with stage II/III non-IBC.

Additional retrospective and registry studies have reported outcomes in high-risk or metastatic breast cancer patients treated with HDC and autologous HCT.<sup>[14-17]</sup> As with other studies of

breast cancer treatment, most of these have reported improved survival in patients with endocrine-responsive tumors relative to those with triple-negative.

## **TANDEM AUTOLOGOUS STEM-CELL TRANSPLANT**

Kroger (2006) reported on the comparison of single vs. tandem autologous HCT in 187 patients with chemotherapy-sensitive metastatic breast cancer.<sup>[18]</sup> Only 52 of 85 patients completed the second HDC cycle in the tandem arm, mostly due to withdrawal of consent (most common reason), adverse effects, progressive disease, or death. The rate of complete remission was 33% in the single-dose arm versus 37% in the tandem arm ( $p=0.48$ ). Although there was a trend toward improved PFS after tandem HCT, median overall survival tended to be greater after single versus tandem HDC (29 vs. 23.5 months, respectively,  $p=0.4$ ). The authors concluded that tandem HCT cannot be recommended for patients with chemotherapy-sensitive metastatic breast cancer because of a trend for shorter overall survival and higher toxicity compared with single HCT.

In a study that was included in the systematic reviews above, Schmid (2005) randomized 93 patients without prior chemotherapy for metastatic breast cancer to standard-dose chemotherapy or double HDC with autologous HCT.<sup>[19]</sup> The primary study objective was to compare complete response rates. Objective response rates for the patients in the HDC group were 66.7% versus 64.4% for the standard group ( $p=0.82$ ). There were no significant differences between the two treatments in median time to disease progression, duration of response, or OS (OS 26.9 months vs. 23.4 months for the double high-dose arm versus the standard arm, respectively,  $p=0.60$ ).

## **ALLOGENEIC STEM-CELL TRANSPLANT**

To date, allogeneic HCT for breast cancer has mostly been used in patients who have failed multiple lines of conventional chemotherapy.<sup>[20]</sup>

Ueno (2008) reported the results of allogeneic HCT in 66 women with high-risk metastatic breast cancer from 15 centers who underwent transplantation between 1992 and 2000.<sup>[21]</sup> Thirty-nine (59%) received myeloablative and 27 (41%) reduced-intensity conditioning (RIC) regimens. A total of 17 (26%) patients had received a prior autologous HCT. Median follow-up time for survivors was 40 months (range 3 to 64 months). Treatment-related mortality was lower in the RIC group (7% vs. 29% at 100 days,  $p=0.03$ ). PFS at one year was 23% in the myeloablative group versus 8% in the RIC group ( $p=0.09$ ). Overall survival rates after myeloablative conditioning versus the RIC group were 51% (95% CI 36 to 67%) versus 26% (95% CI 11 to 45%,  $p=0.04$ ) at one year, 25% (95% CI 13% to 40%) versus 15% (95% CI 3% to 34%,  $p=0.33$ ) at two years, and 19% (95% CI 8% to 33%) versus 7% (95% CI <1% to 25%,  $p=0.21$ ) at three years, respectively.

Fleskens reported the results of a Phase II study of 15 patients with metastatic breast cancer treated with HLA-matched reduced-intensity allogeneic HCT.<sup>[22]</sup> Median patient age was 49.5 years (range 39.7 to 60.8 years) and all patients had been extensively pretreated and had undergone at least one palliative chemotherapy regimen for metastatic disease. Treatment-related mortality was 2/15 (13%). One-year PFS was 20% and one- and two-year OS was 40% and 20%, respectively. The authors noted no objective tumor responses, but concluded that the relatively long PFS suggests a graft-versus-tumor effect.

The National Comprehensive Cancer Network guidelines do not address the use of HCT in the treatment of breast cancer.<sup>[23]</sup>

## SUMMARY

The research does not show that autologous hematopoietic cell transplantation (HCT) improves survival in people with breast cancer. No clinical guidelines based on research recommend autologous HCT for people with breast cancer. Therefore, autologous HCT is considered not medically necessary for this indication.

There is not enough research to show that allogeneic HCT can improve health outcomes for people with breast cancer. No clinical guidelines based on research recommend allogeneic HCT for people with breast cancer. Therefore, allogeneic HCT is considered investigational for the treatment of any breast cancer.

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## CODES

Codes	Number	Description
CPT	38204	Management of recipient hematopoietic cell donor search and cell acquisition
	38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection, allogeneic
	38206	;autologous
	38207	Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage
	38208	;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	Bone marrow harvesting for transplantation; autologous
	38240	Bone marrow or blood-derived peripheral stem-cell transplantation; allogeneic
	38241	;autologous
	38242	Allogeneic donor lymphocyte infusions
38243	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor, HPC boost	
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 post-transplant care in the global definition (including drugs; hospitalization; medical surgical, diagnostic and emergency services)

**Date of Origin:** May 2010