Clinical Policy Title: Stem cell transplant for breast cancer

Clinical Policy Number: 05.03.02

Effective Date: April 1, 2016
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Most Recent Review Date: January 20, 2016
Next Review Date: January, 2017

Related policies:

CP# 18.03.02 Stem cell transplant for autoimmune diseases
CP# 14.02.06 Bone marrow transplant

ABOUT THIS POLICY: AmeriHealth Caritas Pennsylvania has developed clinical policies to assist with making coverage determinations. AmeriHealth Caritas Pennsylvania’s clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of “medically necessary,” and the specific facts of the particular situation are considered by AmeriHealth Caritas Pennsylvania when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. AmeriHealth Caritas Pennsylvania’s clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. AmeriHealth Caritas Pennsylvania’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, AmeriHealth Caritas Pennsylvania will update its clinical policies as necessary. AmeriHealth Caritas Pennsylvania’s clinical policies are not guarantees of payment.

Coverage Policy

AmeriHealth Caritas Pennsylvania considers the use of autologous or allogeneic (ablative and non-myeloablative [mini-transplant]) hematopoietic stem cell transplantation (HSCT), (single or planned tandem) for the treatment of any stage of breast cancer to be investigational and, therefore, not medically necessary.

Limitations:

All other uses of autologous or allogeneic (ablative and non-myeloablative [mini-transplant]) HSCT, single or planned tandem for the treatment of any stage of breast cancer are not medically necessary.
Alternative covered services:

Oncologist plan of treatment per plan benefit.

Background

Breast cancer:

Breast cancer is the most common noncutaneous cancer in U.S. women, with an estimated 60,290 cases of in situ disease, 231,840 new cases of invasive disease, and 40,290 deaths expected in 2015. Thus, fewer than one in six women diagnosed with breast cancer die of the disease. By comparison, it is estimated that about 71,660 American women will die of lung cancer in 2015. Men account for 1 percent of breast cancer cases and breast cancer deaths (American Cancer Society 2015).

In 5 to 10 percent of women with breast cancer, a significant family history can be found. For those with a strong family history of breast or ovarian cancer, mutations of the BRCA1 or BRCA2 genes account for the majority of cases. The American College of Obstetricians and Gynecologists (ACOG) estimates between 1 in 300 and 1 in 800 individuals within the general population carry a mutation in the BRCA1 or BRCA2 gene (ACOG 2009).

The BRCA1 and BRCA2 genes in their unmutated states act as suppressors of breast or ovarian cancer. The mutation removes this protective attribute, enhancing the risk of such malignancies. Mutation of BRCA1 or BRCA2 does not guarantee that the individual will develop breast or ovarian cancer, but that they will have a higher risk. A meta-analysis estimated the risk of developing breast cancer and/or ovarian cancer by age 70, in women who are BRCA1 or BRCA2 positive, to be 57 percent and 40 percent, respectively (Chen 2006).

The most common type of breast cancer is ductal carcinoma, which begins in the cells of the ducts. Cancer that begins in the lobes or lobules is called lobular carcinoma and is more often found in both breasts, than are other types of breast cancer. Inflammatory breast cancer is an uncommon type of breast cancer in which the breast looks red, warm, and swollen.

Breast cancer may occur in men. Men at any age may develop breast cancer, but it is usually detected in men between 60 and 70 years of age. Male breast cancer makes up less than 1 percent of all cases of breast cancer.

The following types of breast cancer are found in men:

- Infiltrating ductal carcinoma — Cancer that spreads beyond cells lining the ducts in the breast. Most men with breast cancer have this type of cancer.

- Ductal carcinoma in situ — Abnormal cells found in the lining of a duct, also called intraductal carcinoma.

- Inflammatory breast cancer — Type of cancer in which the breast looks red and swollen and feels warm.
• Paget disease of the nipple — Tumor that grows from ducts beneath the nipple onto the surface of the nipple.

Lobular carcinoma in situ (abnormal cells found in one of the lobes or sections of the breast), which sometimes occurs in women, has not been seen in men.

Testing:

Three types of tests detect BRCA1 and BRCA2 gene mutations:

• Full nucleotide screening — This comprehensive, full sequencing analytic tool is considered the gold standard, as it can detect single point mutations in either the BRCA1 or BRCA2 gene.

• Allele-specific oligonucleotide hybridization (ASO) — ASO analysis is generally used if there is an already known BRCA mutation within the family. This test detects the carrier potential of the individual being tested. If positive, fuller nucleotide screening would be considered.


In the late 1980s and early 1990s, initial results of phase II trials for breast cancer and autologous HSCT were promising, showing high response rates in patients with metastatic disease who underwent high-dose consolidation, with a subset of up to 30 percent remaining disease-free for prolonged periods. In the early 1990s, larger prospective comparisons of conventional-dose chemotherapy to high-dose therapy with HSCT were initiated but accrued slowly, with up to a decade from initiation to the reporting of results. The first results from randomized controlled trials (RCTs) at a single institution (in early stage and metastatic disease) showed survival benefits, but were ultimately shown to be based on fraudulent data. In the interim, the treatment became almost standard of care (SOC), while many patients received high-dose therapy off protocol, further reducing accrual to ongoing RCTs. The results of the RCTs were first presented in 1999, and showed little survival benefits. Subsequently, the number of HSCT procedures performed for breast cancer decreased from thousands every year to only a few.

Searches

AmeriHealth Caritas Pennsylvania searched PubMed and the databases of:

• UK National Health Services Centre for Reviews and Dissemination.
• Agency for Healthcare Research and Quality’s National Guideline Clearinghouse and other evidence-based practice centers.
• The Centers for Medicare & Medicaid Services (CMS).

We conducted searches on October 28, 2015. Search terms were: "breast cancer, autologous or allogeneic (ablative and non-myeloablative [mini-transplant]) hematopoietic stem cell transplantation, single or planned tandem (MeSH)," and “stem cell transplants (MeSH).”
We included:

- **Systematic reviews**, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.
- **Guidelines based on systematic reviews.**
- **Economic analyses**, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

**Findings**

A Cochrane systematic review and meta-analysis published in July 2005 pooled data from six RCTs on metastatic breast cancer reported through November 2004 (N=438 randomized to autologous HSCT, 412 to conventional dose therapy). The relative risk (RR) for treatment-related mortality was significantly higher in the arm randomized to HSCT (15 vs. 2 deaths; RR=4.07; 95% confidence interval [CI]: 1.39–11.88). Treatment-related morbidity was more severe among those randomized to HSCT. Overall survival 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: 1.40–2.21) and five years (RR=2.84; 95% CI: 1.07–7.50) favored the HSCT arms. Only one of the six RCTs included trials that monitored all patients for at least five years. Reviewers recommended further follow-up for patients randomized in the other five trials. They concluded that, in the interim, patients with metastatic breast cancer should not receive HSCT outside of a clinical trial, since available data showed greater treatment-related mortality and toxicity, without improved overall survival.

A systematic review and meta-analysis published in 2007 included RCTs comparing autologous HSCT to standard dose chemotherapy in women with early, poor prognosis breast cancer, which included 13 trials in September 2006 with 5,064 patients. Major conclusions included that at five years, event-free survival approached statistical significance for the high-dose group, but no overall survival 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 HSCT for treating early, poor prognosis breast cancer.

The 2014 National Comprehensive Cancer Network guidelines do not address the use of HSCT in the treatment of breast cancer.

RCTs of autologous HSCT versus standard dose chemotherapy for patients with high-risk, non-metastatic or metastatic breast cancer show greater treatment-related mortality and toxicity and do not show a survival advantage with HSCT. Therefore, autologous HSCT is considered not medically necessary for this indication. Non-randomized studies using reduced-intensity or myeloablative allogeneic HSCT for metastatic breast cancer suggest a possible graft-versus-tumor effect. However, the data is insufficient to determine whether or not there is a survival benefit. Therefore allogeneic HSCT remains investigational for the treatment of high risk non-metastatic or metastatic breast cancer.

Additional research in the form of large and otherwise well-designed RCTs is needed to determine the role of HDC/autograft in patients with breast cancer. This may be difficult to achieve since RCTs to date, generally have not shown a benefit for HDC/autograft (Hayes 2010).
Summary of clinical evidence:

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- Of 10 men receiving autotransplants as adjuvant therapy, three relapsed 3, 5 and 50 months post-transplant, and died 16, 19, and 67 months post-transplant.  
- Seven of 10 are disease-free with median follow-up of 23 months (range 6 – 50 months). Of three men treated for metastatic breast cancer, one had progressive disease and two recurrent disease at 6, 7 and 16 months post-transplant.  
- In conclusion, results of autotransplants for male breast cancer appear similar to those reported for women receiving autotransplants for breast cancer. |
| Moore, HC, (1999) Autologous stem-cell transplant after conventional dose adjuvant chemotherapy for high-risk breast cancer: impact on the delivery of local-regional radiation therapy | **Key points:**  
- Patients with high-risk primary breast cancer were treated with high-dose cyclophosphamide and thiopeta and stem-cell transplant, following surgery and conventional-dose adjuvant chemotherapy. Outcome, including sites of failure and delivery of local radiation therapy, was assessed for 103 patients.  
- Overall and disease-free survival rates at 18 months were 83% (+/- 4%) and 77% (+/- 4%), respectively. Twenty patients (19.4%) received radiation therapy prior to transplant. Of the remaining 83 patients, 77 received radiation therapy after transplant. Overall, five (19.2%) of 26 first sites of recurrence were local alone. For patients receiving radiation prior to transplant, three of seven (43%, 95% CI: 6%-80%) sites of first recurrence were local, while two of 19 (10.5%, 95% CI: 0%-24.5%) sites of first recurrence were local alone, in patients receiving post-transplant radiation or no radiation. |
| Coombes RC, et al. (2005) on autologous HSCT as adjuvant therapy for primary breast cancer in women free of metastatic disease, with a median follow-up of 68 months | **Key points:**  
- A total of 281 patients were randomized to receive standard chemotherapy or high-dose chemotherapy with HSCT.  
- They found no significant difference in relapse-free survival or overall survival (overall survival hazard ratio 1.18, 95% CI: 0.80-1.75, p=0.40). |
| Crump M, et al. (2008) A randomized trial of women who had not previously been treated with chemotherapy, and had metastatic breast cancer or locoregional recurrence after mastectomy | **Key points:**  
- After initial response to induction therapy, 112 women were allocated to standard chemotherapy and 112 to autologous HSCT.  
- After a median follow-up of 48 months, 79 deaths were observed in the high-dose group, and 77 in the standard. No difference in overall survival was observed between the two groups after a median follow-up of 48 months, with median overall survival being 24 months in the HSCT group (95% CI: 21–35 months).  
- Twenty-eight months for the standard chemotherapy group (95% CI: 22–33 months; hazard ratio: 0.9; 95% CI: 0.6–1.2; p=0.43). |
### Key points:
- **Biron P, et al. (2008)**  
  Prospective trial of women with metastatic breast cancer  
  - The results of a phase III, open, multicenter, prospective trial of women with metastatic breast cancer (and/or local or regional relapse beyond curative treatment by surgery or radiation).  
  - After a complete or at least 50% partial response to induction therapy, 88 women were randomized to HSCT, and 91 to no further treatment.  
  - No overall survival difference was seen between the two groups, with a 3-year survival of 33.6% in the high-dose group, and 27.3% in the observation group (p=0.8).

### Key points:
- **Zander AR et al. (2008)**  
  Women with surgically resected breast cancer and axillary lymph node dissection with 10 or more positive axillary lymph nodes but no evidence of metastatic disease  
  - Reported survival data after six years of follow-up on a trial that was previously reported, after 3.8 years of follow-up.  
  - Women with surgically resected breast cancer and axillary lymph node dissection, with 10 or more positive axillary lymph nodes, but no evidence of metastatic disease were randomized to standard chemotherapy (n=152) or HSCT (n=150).  
  - No difference in overall survival was observed.  
  - The estimated five year overall survival rate in the standard arm was 62% (95% CI: 54-70%) and 64% (95% CI: 56-72%) in the high-dose transplant group.

### Key points:
- **Kroger, et al. (2006)**  
  The comparison of single versus tandem autologous HSCT in 187 patients with chemotherapy-sensitive metastatic breast cancer  
  - Only 52 of 85 patients completed the second, high-dose chemotherapy 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=.48). Although there was a trend toward improved progression-free survival (PFS) after tandem HSCT, median overall survival tended to be greater after single versus tandem high-dose chemotherapy (29 vs. 23.5 months, respectively; p=0.4).  
  - The authors concluded that tandem HSCT 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 HSCT.

### Key points:
- **Fleskens AJ, et al. (2010)**  
  Phase II study of 15 patients with metastatic breast cancer treated with HLA-matched reduced-intensity allogeneic HSCT  
  - Phase II study of 15 patients with metastatic breast cancer, treated with HLA-matched reduced-intensity allogeneic HSCT. Median patient age was 49.5 years (range: 39.7-60.8 years) and all patients had been extensively pretreated and undergone at least one palliative chemotherapy regimen for metastatic disease.  
  - Treatment-related mortality was 2/15 (13%). One-year PFS was 20% and 1- and 2-year overall survival (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.

### Glossary

**Ablative**— Very high dose of a treatment, calculated to kill a tumor.

**Allogeneic** — Stem cells harvested from a histocompatible donor.

**Autologous** — Stem cells can be harvested from an individual's own bone marrow or peripheral blood.
Bone marrow — A spongy tissue located within flat bones, including the hip and breast bones and the skull. This tissue contains hematopoietic stem cells, the precursors of platelets, red blood cells, and white cells.

Bone marrow stromal cells—A population of cells found in bone marrow that are different from blood cells.

Chemotherapy — Medical treatment of a disease, particularly cancer, with drugs or other chemicals.

Chimerism — Cell populations derived from different individuals; may be mixed or complete.

Cord blood stem cells/Umbilical cord blood stem cells — Stem cells collected from the umbilical cord at birth that can produce all of the blood cells in the body. Cord blood is currently used to treat patients who have undergone chemotherapy, to destroy their bone marrow, due to cancer, or other blood-related disorders.

Cytotoxic — Destructive to cells.

Graft-versus-host disease (GVHD) — A life-threatening complication of bone marrow transplants in which the donated marrow causes an immune reaction against the recipient's body.

Hematopoietic stem cells (HSC) — Unique cells that mature into a number of blood cell types found in the body. Also referred to as stem cells, they are primarily located in bone marrow and give rise to all red and white blood cells and platelets.

High-dose or myeloablative chemotherapy (HDC) — The administration of cytotoxic agents using doses several times greater than the standard therapeutic dose.

Human leukocyte antigen (HLA) — A group of protein molecules located on bone marrow cells that can provoke an immune response.

Myelodysplastic syndromes (MDS) — A group of cancers in which immature blood cells in the bone marrow do not mature, or become healthy blood cells.

Non-myeloablative chemotherapy — Less intense chemotherapy conditioning regimens, which rely more on immunosuppression than cytotoxic effects, to permit engraftment of donor cells.

Somatic cell — Any body cell other than gametes (egg or sperm); sometimes referred to as "adult" cells.

Stromal cells — Connective tissue cells found in virtually every organ. In bone marrow, stromal cells support blood formation.

Tandem transplant — Planned administration of more than one cycle of high-dose or non-myeloablative chemotherapy, alone or with total body irradiation. Each infusion is followed by re-infusion of stem cells.
References

Professional society guidelines/other:


Peer-reviewed references:


**Clinical trials:**

Searched clinicaltrials.gov on October 28, 2015 using terms breast cancer and stem cell transplant | Open Studies. 11 studies found, 2 relevant.


**CMS National Coverage Determinations (NCDs):**

CMS has established national coverage policies for autologous stem cell transplantation (ASCT) for a variety of indications. While these policies do not specifically address the use of ASCT for treating breast cancer, coverage for ASCT is not approved for treating any type of solid tumor except neuroblastoma


**Local Coverage Determinations (LCDs):**

No LCDs identified as of the writing of this policy.
**Commonly submitted codes**

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.

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