Cigna Medical Coverage Policy

Subject **Stem-Cell Transplantation for Breast Cancer**

Effective Date..... 6/15/2014
Next Review Date..... 6/15/2015
Coverage Policy Number.....0100

Table of Contents

Hyperlink to Related Coverage Policies

Emerging Breast Localization/Biopsy Procedures
Circulating Tumor Cells Testing
Cryoablation of Breast Lesions
Genetic Expression Assays for Breast Cancer Prognosis
Mammary Ductoscopy, Aspiration and Lavage
Mammography
Microwave Thermotherapy for Breast Cancer
Prophylactic Mastectomy

INSTRUCTIONS FOR USE
*The following Coverage Policy applies to health benefit plans administered by Cigna companies. Coverage Policies are intended to provide guidance in interpreting certain **standard** Cigna benefit plans. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document **always supersedes** the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations. Proprietary information of Cigna.*

Coverage Policy

Cigna does not cover hematopoietic stem-cell transplantation for the treatment of breast cancer because it is considered experimental, investigational or unproven.

General Background

Breast cancer is a malignant tumor that starts from cells of the breast, usually the ducts or lobules, and may be invasive, or noninvasive. Although breast cancer is more common in females, it does occur rarely in males. Pathology and overall survival in males is similar to that of women with breast cancer (NCI, 2014b). The American Joint Committee on Cancer staging system provides a strategy for grouping patients with respect to prognosis. Therapeutic decisions are formulated in part according to staging categories but primarily according to tumor size, lymph node status, estrogen-receptor and progesterone- receptor levels in the tumor tissue, menopausal status, and the general health of the patient (National Cancer Institute [NCI], 2014a). Breast cancer is commonly treated with various combinations of surgery, radiation therapy, chemotherapy, and hormone therapy. Hematopoietic stem-cell transplantation (HSCT) has been proposed as a treatment option for individuals with breast cancer.

Hematopoietic Stem-Cell Transplantation
Hematopoietic stem-cell transplantation (HSCT) refers to the transplantation of hematopoietic stem cells (HSC) from a donor into a recipient. HSCT can be either autologous (i.e., using the patient's own stem cells) or allogeneic (i.e., using stem cells from a donor).

Autologous Hematopoietic Stem-Cell Transplantation (HSCT)
A correlation between dose-intensity of chemotherapy, response rate and outcomes in high-risk primary and metastatic breast cancer has been suggested by research studies. The use of high-dose chemotherapy (HDC) with autologous HSCT is based on the hypothesis that major dose escalations within the myeloablative range are needed to overcome tumor cell resistance and produce a meaningful clinical improvement. HSCT allows for an increase in the dose well beyond normal bone-marrow tolerance. Myeloablative chemotherapy followed by autologous HSCT has resulted in improved response rates for some individuals; however, an overall survival (OS) benefit has not been demonstrated.

Wang et al. (2012) reported a metaanalysis of fourteen prospective randomized clinical trials (RCT) involving 5747 women (HDC with autologous transplantation [HDCT], n=2987; control, n=2850) with primary breast cancer. The primary outcome was disease-free survival (DFS) and OS. Secondary endpoints included treatment-related mortality (TRM) and second (non-breast) cancers. Patients randomly assigned to HDCT and autologous transplantation (HDCT) had a statistically significantly greater risk of death than those assigned to chemotherapy only (relative risk [RR] = 3.42) as reported in 10 studies. The risk of second (non-breast) cancers was not significantly different in the HDCT group compared with chemotherapy only (RR = 1.28) as reported in 11 studies. A DFS benefit was noted with HDCT (hazard ratio [HR] = 0.89); however, the difference in OS was not statistically significant (HR =0.91, p= 0.062). Data do not suggest a benefit regarding the use of HDCT and autologous transplantation for the treatment of primary breast cancer.

Berry et al. (2011a) reported results of an analysis of six RCT involving 866 women with metastatic breast cancer (MBC). Women were randomized to the HDCT (n=447) or a control regimen without transplant (n=419). Results were presented as the HR for OS based on the indicated comparison with 95% confidence intervals). The adjusted HR of OS comparing HDCT with control was 0.89 (p=0.13). After adjusting for trial, age, and hormone receptor status, the HR per unit increase of maximum dose intensity (MDI) was 0.94 (p=0.046). As regards progression-free survival (PFS), after adjusting for trial, age, and hormone receptor status, the HR of HDC compared with control per unit increase in MDI was 0.88 (p<.001). Although data suggest a small non-significant OS difference between HDCT and control (p=0.08), the authors concluded that the associations are weak, and interactions are not sufficiently robust to withstand adjustments for multiple comparisons.

Berry et al. (2011b) also merged data from 15 RCTs involving 6210 total patients (HDCT, n=3118; control, n=3092) with high-risk primary breast cancer. Prospectively defined primary end points were relapse-free survival (RFS) and OS. After analysis was adjusted for trial, age, number of positive lymph nodes, and hormone receptor status, HDCT was associated with a non-significant 6% reduction in the risk of death (HR, 0.94; p=.13) and a significant 13% reduction in the risk of recurrence (HR, 0.87; p<.001). After analysis was adjusted for trial, age, number of positive lymph nodes, and hormone receptor status patients in the HDCT arm had a highly significant 16% increase in the risk of death after disease recurrence compared with patients in the control arm (HR, 1.16; p<.001). The authors concluded that HDCT does not have a statistically significant benefit in OS. The authors also note that data from both studies leave open the possibility of a modest reduction in the hazards of OS in the range of 5%to 10%, but neither was able to identify subsets of patients who may benefit from HDC.

Additional RCTs and meta-analyses have examined outcomes related to the effectiveness of autologous HSCT for the treatment of breast cancer. Although response rates and disease-free and/or relapse-free survival rates were noted to be improved in some individuals, no statistically significant survival benefit was noted in the majority of patients (Biron, 2008; Takuda, 2008; Zander, 2008; Crump, 2008; Farquhar, 2007, Moore, 2007; Kroger, 2006; Vredenburgh, 2006; Coombes, 2005; Isaacs, 2005; Nitz, 2006; Peters, 2005; Farquhar, 2004; Leonard, 2004; Tallman, 2003).

Allogeneic Hematopoietic Stem-Cell Transplantation (HSCT)
High quality, randomized control trial data are lacking in the published peer-reviewed scientific literature regarding the safety and effectiveness of allogeneic HSCT for the treatment of breast cancer. To date clinical studies have been limited by small patient populations utilizing allogeneic HSCT. The role of this therapy has not yet been established for this indication.

Professional Societies/Organizations
National Cancer Institute ([NCI], 2014): In discussion of high-dose chemotherapy with bone marrow transplantation (BMT) or stem cell support for women with more than ten positive lymph nodes and in women with four to nine positive lymph nodes, the NCI notes that use of high-dose chemotherapy is not supported outside the context of a randomized clinical trial.

Use Outside of the US
No relevant information.

Summary
A correlation between dose-intensity of chemotherapy, response rate and outcomes has been suggested by several research studies; however, there is insufficient evidence in the published, peer-reviewed scientific literature in the form of to support the safety and effectiveness of hematopoietic stem-cell transplantation (HSCT) for the treatment of breast cancer. Although a subject of ongoing research, at this time the role of HSCT has not been established for this indication.

Coding/Billing Information

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

Experimental/Investigational/Unproven/Not Covered when used to report hematopoietic stem-cell transplantation for the treatment of breast cancer:

CPT* Codes	Description
38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic
38206	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous
38207	Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage
38208	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing, per donor
38209	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing, per donor
38210	Transplant preparation of hematopoietic progenitor cells; specific cell depletion within harvest, T-cell depletion
38211	Transplant preparation of hematopoietic progenitor cells; tumor cell depletion
38212	Transplantation preparation of hematopoietic progenitor cells; red blood cell removal
38213	Transplant preparation of hematopoietic progenitor cells; platelet depletion
38214	Transplantation preparation of hematopoietic progenitor cells; plasma (volume) depletion
38215	Transplant preparation of hematopoietic progenitor cells; cell concentration in plasma, mononuclear, or buffy coat layer
38230	Bone marrow harvesting for transplantation, allogeneic
38232	Bone marrow harvesting for transplantation, autologous
38240	Hematopoietic progenitor cell (HPC);allogeneic transplantation, per donor
38241	Hematopoietic progenitor cell (HPC); autologous transplantation
38242	Allogeneic lymphocyte infusions

HCPCS Codes	Description
S2140	Cord blood harvesting for transplantation, allogeneic

S2142	Cord blood-derived stem-cell transplantation, allogeneic
S2150	Bone marrow or blood-derived stem cells (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation, and related complications; including: pheresis and cell preparation/storage; marrow ablative therapy; drugs, supplies, hospitalization with outpatient follow-up; medical/surgical, diagnostic, emergency, and rehabilitative services; and the number of days of pre-and post-transplant care in the global definition

References

1. American Cancer Society. Breast cancer detailed guide. Updated 2014 Jan 31. Accessed April 30, 2014. Available at URL address: http://documents.cancer.org/104.00/104.00.pdf

2. Berry DA, Ueno NT, Johnson MM, Lei X, Caputo J, Rodenhuis S, et al. High-dose chemotherapy with autologous stem-cell support as adjuvant therapy in breast cancer: overview of 15 randomized trials. J Clin Oncol. 2011(a) Aug 20;29(24):3214-23.

3. Berry DA, Ueno NT, Johnson MM, Lei X, Caputo J, Smith DA, et al. High-dose chemotherapy with autologous hematopoietic stem-cell transplantation in metastatic breast cancer: overview of six randomized trials. J Clin Oncol. 2011(b) Aug 20;29(24):3224-31

4. Biron P, Durand M, Roche H, Delozier T, Battista C, Fargeot P, et al. Pegase 03: a prospective randomized phase III trial of FEC with or without high-dose thiotepa, cyclophosphamide and autologous stem cell transplantation in first-line treatment of metastatic breast cancer. Bone Marrow Transplant. 2008 Mar;41(6):555-62. Epub 2007 Nov 26.

5. Coombes RC, Howell A, Emson M, Peckitt C, Gallagher C, Bengala C, et al. High dose chemotherapy and autologous stem cell transplantation as adjuvant therapy for primary breast cancer patients with four or more lymph nodes involved: long-term results of an international randomised trial. Ann Oncol. 2005;16:726-34.

6. Crump M, Gluck S, Tu D, Stewart D, Levine M, Kirkbride P, et al. Randomized trial of high-dose chemotherapy with autologous peripheral-blood stem-cell support compared with standard-dose chemotherapy in women with metastatic breast cancer: NCIC MA.16. J Clin Oncol. 2008 Jan 1;26(1):37-43. Epub 2007 Nov 19.

7. Farquhar C, Basser R, Marjoribanks J, Lethaby A. High dose chemotherapy and autologous bone marrow or stem cell transplantation versus conventional chemotherapy for women with early poor prognosis breast cancer. In: The Cochrane Library, 2004. ©2005 The Cochrane Collaboration.

8. Farquhar C, Basser R, Hetrick S, Lethaby A, Marjoribanks J. High dose chemotherapy and autologous bone marrow or stem cell transplantation versus conventional chemotherapy for women with metastatic breast cancer. In: The Cochrane Library, 2004. ©2005 The Cochrane Collaboration.

9. Farquhar CM, Marjoribanks J, Lethaby A, Basser R. High dose chemotherapy for poor prognosis breast cancer: systematic review and meta-analysis. Cancer Treat Rev. 2007 Jun;33(4):325-37. Epub 2007 Mar 26.

10. Hanrahan EO, Broglio K, Frye D, Buzdar AU, Theriault RL, Valero V, et al. Randomized trial of high-dose chemotherapy and autologous hematopoietic stem cell support for high-risk primary breast carcinoma: follow-up at 12 years. Cancer. 2006 Jun 1;106(11):2327-36.

11. Hortobagyi GN, Buzdar AU, Theriault RL, Valero V, Frye D, Booser DJ, et al. Randomized trial of high-dose chemotherapy and blood cell autografts for high-risk primary breast carcinoma. J Natl Cancer Inst, 2000 Feb;92(3):225-33.

12. Isaacs C, Slack R, Gehan E, Ballen K, Boccia R, Areman E, et al. A multicenter randomized clinical trial evaluating interleukin-2 activated hematopoietic stem cell transplantation and post-transplant IL-2 for high risk breast cancer patients. Breast Cancer Res Treat. 2005 ep;93(2):125-34.

13. Kroger N, Frick M, Gluz O, Mohrmann S, Metzner B, Jackish C, et al. Randomized trial of single compared with tandem high-dose chemotherapy followed by autologous stem-cell transplantation in patients with chemotherapy-sensitive metastatic breast cancer. J Clin Oncol. 2006 Aug 20;24(24):3919-26

14. Kurian S, Qazilbash M, Fay J, Wolff S, Herzig R, Hobbs G, et al. Complete response after high-dose chemotherapy and autologous hematopoietic stem cell transplantation in metastatic breast cancer results in survival benefit. Breast J. 2006 Nov-Dec;12(6):531-5.

15. Leonard RC, Lind M, Twelves C, Coleman R, van Belle S, Wilson C, et al. Conventional adjuvant chemotherapy versus single-cycle, autograft-supported, high-dose, late-intensification chemotherapy in high-risk breast cancer patients: a randomized trial. J Natl Cancer Inst. 2004 Jul 21;96(14):1076-83.

16. Moore HC, Green SJ, Gralow JR, Bearman SI, Lew D, Barlow WE, et al. Intensive dose-dense compared with high-dose adjuvant chemotherapy for high-risk operable breast cancer: Southwest Oncology Group/Intergroup study 9623. J Clin Oncol. 2007 May 1;25(13):1677-82.

17. National Cancer Institute. Breast cancer treatment (PDQ®): health professional. [a] Updated 2014 Apr 11. Accessed Apr 30, 2014. Available at URL address: http://www.cancer.gov/cancertopics/pdq/treatment/breast/healthprofessional/allpages

18. National Cancer Institute. Male breast cancer treatment (PDQ®): health professional. [b] Updated 2014 Apr 11. Accessed Apr 30, 2014. Available at URL address: http://www.cancer.gov/cancertopics/pdq/treatment/malebreast/HealthProfessional

19. National Comprehensive Cancer Network® (NCCN) [a]. NCCN GUIDELINES™ Clinical Guidelines in Oncology ™. Breast cancer. V3.2014. © National Comprehensive Cancer Network, Inc. 2014, All Rights Reserved. Accessed April 30, 2014. Available at URL address: http://www.nccn.org/professionals/physician_gls/PDF/breast.pdf

20. Nitz UA, Mohrmann S, Fischer J, Lindemann W, Berdel WE, Jackish C, et al. Comparison of rapidly cycled tandem high-dose chemotherapy plus peripheral-blood stem-cell support versus dose-dense conventional chemotherapy for adjuvant treatment of high-risk breast cancer: results of a multicentre phase III trial. Lancet. 2005 Dec 3;366(9501):1935-44. Erratum in: Lancet. 2006 Mar 4;367(9512):730.

21. Peters WP, Rosner GL, Vredenburgh JJ, Shpall EJ, Crump M, Richardson PG, et al. Prospective, randomized comparison of high-dose chemotherapy with stem-cell support versus intermediate-dose chemotherapy after surgery and adjuvant chemotherapy in women with high-risk primary breast cancer: a report of CALGB 9082, SWOG 9114 and NCIC MA-13. J Clin Oncol. 2005 Apr 1;23(10):2191-200.

22. Rodenhuis S, Bontenbal M, Beex L, Wagstaff J, Richel DJ, Nooij MA, et al. High-dose chemotherapy with hematopoietic stem-cell rescue for high-risk breast cancer. N Engl J Med. 2003 Jul 3;349(1):7-16.

23. Schmid P, Schippinger W, Nitsch T, Huebner G, Heilmann V, Schultze W, et al. Up-front tandem high-dose chemotherapy compared with standard chemotherapy with doxorubicin and paclitaxel in metastatic breast cancer: results of a randomized trial. J Clin Oncol. 2005 Jan 20;23(3):432-440.

24. Schrama JG, Faneyte IF, Schornagel JH, Baars JW, Peterse JL, van de Vijver MJ, et al. Randomized trial of high-dose chemotherapy and hematopoietic progenitor-cell support in operable breast cancer

with extensive lymph node involvement: final analysis with 7 years of follow-up. Ann Oncol. 2002 May;13(5):689-98.

25. Stadtmauer EA, O'Neill A, Goldstein LJ, Crilley PA, Mangan KF, Ingle JN, et al. Conventional-dose chemotherapy compared with high-dose chemotherapy plus autologous hematopoietic stem-cell transplantation for metastatic breast cancer. N Engl J Med. 2000 Apr 13;342(15):1069-76.

26. Tallman MS, Gray R, Robert NJ, LeMaistre CF, Osborne CK, Vaughan WP, et al. Conventional adjuvant chemotherapy with or without high-dose chemotherapy and autologous stem-cell transplantation in high-risk breast cancer. N Engl J Med. 2003 Jul 3;349(1):17-26.

27. Tokuda Y, Tajima T, Narabayashi M, Takeyama K, Watanabe T, Fukutomi T, et al. Phase III study to evaluate the use of high-dose chemotherapy as consolidation of treatment for high-risk postoperative breast cancer: Japan Clinical Oncology Group study, JCOG 9208. Cancer Sci. 2008 Jan;99(1):145-51. Epub 2007 Oct 25.

28. Ueno NT, Konoplev, S Buchholz TA, Smith T, Rondon G, Anderlini P, et al. High-dose chemotherapy and autologous peripheral blood stem cell transplantation for primary breast cancer refractory to neoadjuvant chemotherapy. Bone Marrow Transplant. 2006 May;37(10):929-35.

29. Ueno NT, Rizzo JD, Demirer T, Cheng YC, Hegenbart U, Zhang MJ, et al. Allogeneic hematopoietic cell transplantation for metastatic breast cancer. Bone Marrow Transplant. 2008 Mar;41(6):537-45.

30. VanderWalde A, Ye W, Frankel P, Asuncion D, Leong L, Luu T, Morgan R, et al. Long-term survival after high-dose chemotherapy followed by peripheral stem cell rescue for high-risk, locally advanced/inflammatory, and metastatic breast cancer. Biol Blood Marrow Transplant. 2012 Aug;18(8):1273-80. Epub 2012 Feb 2

31. Vose JM. Hematopoietic stem cell transplantation. In: Goldman L, Shafer AI, editors. Cecil medicine. 24th ed. Philadelphia, PA: Saunders Elsevier; 2011.

32. Vredenburgh JJ, Madden B, Coniglio D, Ross M, Broadwater G, Niedzweicki D, et al. A randomized phase III comparative trial of immediate consolidation with high-dose chemotherapy and autologous peripheral blood progenitor cell support compared to observation with delayed consolidation in women with metastatic breast cancer and only bone metastases following intensive induction chemotherapy. Bone Marrow Transplant. 2006 Apr 24;[Epub ahead of print].

33. Wang J, Zhang Q, Zhou R, Chen B, Ouyang J. High-dose chemotherapy followed by autologous stem cell transplantation as a first-line therapy for high-risk primary breast cancer: a meta-analysis. PLoS One. 2012;7(3):e33388.

34. Zander AR, Kroger N, Schmoor C, Kruger W, Mobus V, Frickhofen N, et al. High-dose chemotherapy with autologous hematopoietic stem-cell support compared with standard-dose chemotherapy in breast cancer patients with 10 or more positive lymph nodes: first results of a randomized trial. J Clin Oncol. 2004 Jun 15;22(12):1-11

35. Zander AR, Schmoor C, Kroger N, Kruger W, Mobus V, Frickhofen N, et al. Randomized trial of high-dose adjuvant chemotherapy with autologous hematopoietic stem-cell support versus standard-dose chemotherapy in breast cancer patients with 10 or more positive lymph nodes: overall survival after 6 years of follow-up. Ann Oncol. 2008 Feb 27. [Epub ahead of print]