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Original Article

Evaluation of treatment of HER2 positive Breast cancer patients with Trastuzumab combined with cytotoxic chemotherapy – a comparative study.

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Abstract

A prospective and retrospective study had been carried out between January 2013 to December 2015 for evaluation of the overall survival (OS) & disease free survival (DFS) rate of HER2 positive breast cancer patients with Trastuzumab combined with cytotoxic chemotherapy and patients who only takes chemotherapy alone. A randomized control trial was run with the 130 patients having HER2 positive breast cancer in the Rajshahi Medical College and Hospital and different private hospitals and Clinics of Rajshahi city. Among 130 women having HER-2 positive breast cancer 52 women were randomly allocated to the TAC (Taxotere, Doxorubicin and Cyclophosphamide) arm and 61 women were randomly allocated to the TAH (Taxotere, Doxorubicin, Herceptin) arm. TAC arm consists of Taxotere (75mg/m^2), as 1 hour infusion preceded by Doxorubicin (50mg/m^2) and Cyclophosphamide (500mg/m^2), both given as an intravenous bolus. This TAC protocol runs for 6 cycles in every 3 weeks. And TAH arm consists of Taxotere (75mg/m^2), Doxorubicin (50mg/m^2) and Herceptin (8mg/kg for 1st cycle and 6mg/kg from 2nd cycle). In this arm other combined therapy will run till 6 cycles and Herceptin will run up to 12 cycles in every 3 weeks.

TAJ 2013; 26: 30-37

Introduction

Approximately 15% to 20% of invasive breast cancers have amplification of the human epidermal growth factor receptor 2 (HER2) genes or overexpression of the HER2 protein. Before the availability of HER2- directed therapies, women with early-stage HER2-positive breast cancer faced a worse prognosis than those with a diagnosis of HER2-negative disease, with shorter time to disease relapse, an increased incidence of metastases, and higher mortality.[1]

Trastuzumab, a humanized monoclonal antibody that targets the extracellular domain of the HER2 protein, was found to improve survival in the metastatic disease setting when used in combination with chemotherapy.[2]

Breast cancer is the most common cancer in women worldwide[4]. It is also the principle cause of death from cancer among women globally. Despite the high incidence rates, in Western countries, 89% of women diagnosed with breast cancer are still alive 5 years after their diagnosis,

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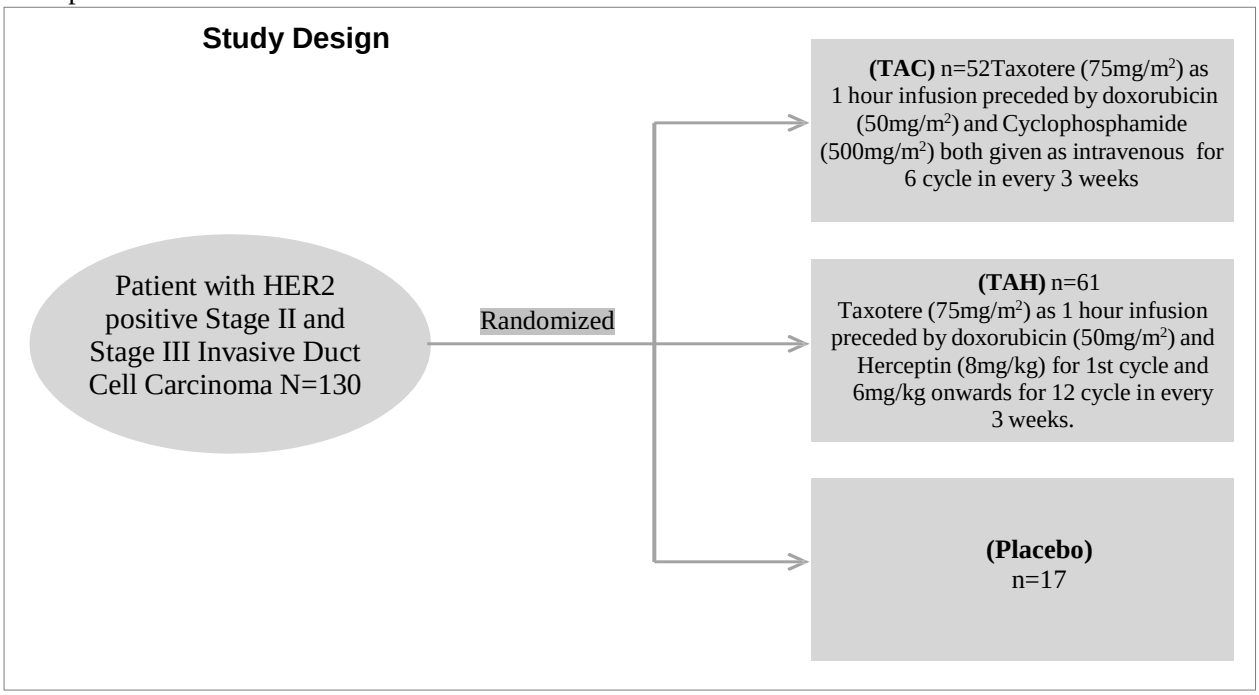
which is due to proper detection and treatment. Mainly there are several types of breast cancer. One of the classes is determined by the expression of proteins or receptor and genes. Cells have receptors on their surface and in their cytoplasm and nucleus. Chemical messengers such as hormones bind to receptors, and this causes changes in the cell. Breast cancer cells may or may not have many different types of receptors, the
three most important in the present classification being: estrogen receptor (ER), progesterone receptor (PR), and HER2/neu. Cells with or without these receptors are called ER positive (ER+), ER negative (ER-), PR positive (PR+), PR negative (PR-), HER2 positive (HER2+), and HER2 negative (HER2-). Cells with none of these receptors are called basal-like or triple negative. HER2/neu (human epidermal growth factor receptor 2), also called ErbB2, is a protein that appears on the surface of some breast cancer cells. This protein is an important part of the pathway for cell growth and survival. **3,17,18**

- HER2/neu-positive (HER2+) breast cancers have a lot of HER2/neu protein.
- HER2/neu-negative (HER2-)breast cancers have little or no HER2/neu protein.

Material and Methods

A randomized control trial was run with the 130 patients having HER2 positive Stage II and Stage III breast cancer in the Rajshahi Medical College & Hospital, different private hospitals and Clinics of Rajshahi city. Among 130 women having HER-2 positive breast cancer 52 women were randomly allocated to the TAC (Taxotere, Doxorubicin and Cyclophosphamide) arm and 61 women were randomly allocated to the TAH (Taxotere, Doxorubicin, Herceptin) arm. TAC arm consists of Taxotere (75mg/m^2), as 1 hour infusion preceded by Doxorubicin(50mg/m^2) and Cyclophosphamide (500mg/m^2), both given as an intravenous bolus. This TAC protocol runs for 6 cycles in every 3 weeks. And TAH arm consists of Taxotere (75mg/m^2), Doxorubicin (50mg/m^2) and Herceptin (8mg/kg for 1^{st} cycle and 6mg/kg from 2^{nd} cycle). In this arm other combined therapy will run till 6 cycles and Herceptin will run up to 12 cycles in every 3 weeks. and 17 patients were allocated to placebo arm.



Results and Discussion

Breast cancer is the most common cancer in women worldwide[4]. It is also the principle cause of death from cancer among women globally. Despite the high incidence rates, in Western countries, 89% of women diagnosed with breast cancer are still alive 5 years after their diagnosis, which is due to proper detection and treatment. Mainly there are several types of breast cancer. One of the classes is determined by the expression of proteins or receptor and genes[10,11,12]. Cells have receptors on their surface and in their cytoplasm and nucleus. Chemical messengers such as hormones bind to receptors, and this causes changes in the cell. Breast cancer cells may or may not have many different types of receptors, the three most important in the present classification being: estrogen receptor (ER), progesterone receptor (PR), and HER2/neu. Cells with or without these receptors are called ER positive (ER+), ER negative (ER-), PR positive (PR+), PR negative (PR-), HER2 positive (HER2+), and HER2 negative (HER2-). Cells with none of these receptors are called basal-like or triple negative. HER2/neu (human epidermal growth factor receptor 2), also called ErbB2, is a protein that appears on the surface of some breast cancer cells. This protein is an important part of the pathway for

cell growth and survival. [13, 14]

- HER2/neu-positive (HER2+) breast cancers have a lot of HER2/neu protein.
- HER2/neu-negative (HER2-) breast cancers have little or no HER2/neu protein.

Rationale for Study Agents

Docetaxel/Taxotere:

- Prolongs survival in early stage and metastatic breast disease
- Well tolerated in all kind of population

Trastuzumab/Herceptin:

- It attaches to HER2 and can help slow the growth of cancer cells with too much HER2.

It may also stimulate the immune system to more effectively attack the cancer.[10, 11]

Inclusion Criteria

Eligible patients were 25 to 70 years of age. All were female patients with Her2 positive stage II and Stage III invasive duct cell carcinoma. The patients were treated with the cytotoxic chemotherapy with or without Trastuzumab at different private hospitals

and clinics in Rajshahi city during January 2013 to December 2015. The study was followed by all the code and ethics. All the patients were aware about the study.

We have divided our study population in three age groups (25-35 years, 36-50 years and above 50 years.

Age Group	TAC (n=52)	TAH (n=61)	Placebo (n=17)
25-35 years	10	8	3
36-50years	33	31	13
Above 50 years	9	22	1

Table 1: Distribution of patients in three age groups

Statistical methodology

The study retrospectively and prospectively investigated patients with invasive, Stage-II and Stage-III breast cancer who underwent Chemotherapy at different private clinics and hospitals of Rajshahi. The data was collected throughout the study. Collected data was analyzed by the computer applying SPSS software program. The survival analysis was performed using Kaplan-Meier curve. The statistical significance was analyzed using Chi- Squared test. A p value of less than 0.05 was considered statistically significant with a confidence interval of 95%.[7,8,9]

Data Analysis

We have taken both of the stage II and stage III breast disease for the study. Among 130 patients 109 patients had stage II breast disease where 21 patients had stage III disease. We had crosstab the age vs. the disease stage and results are given below. The mean age for stage II was 49.81 and Stage III was 45.47.

Stage	Mean	Number	Std. Deviation
Stage III	49.81	21	15.21
Stage II	45.47	109	9.67
Total	46.17	130	10.81

Table 2: Crosstab results of the age vs. disease stage.

Most of the patients belong to the Middle class family. Because the socio economic condition of the patients who came from Rajshahi, Naogaon, Natore and Chapainawabganj was good. Among 130 patients 68 patients were belong to middle class group. 45 patients belong to upper middle class and 17 patients were from lower middle class.

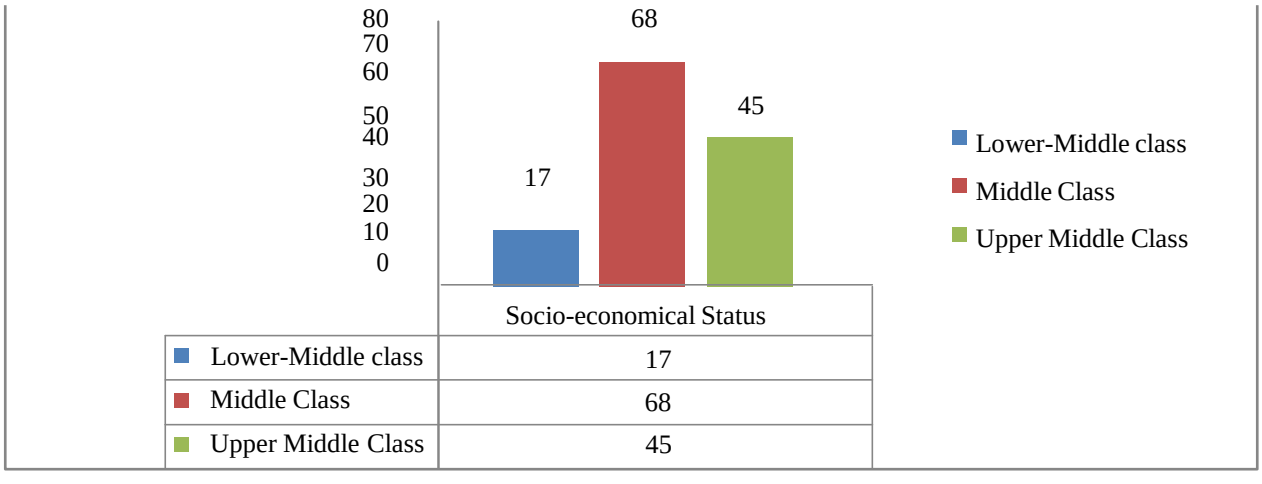


Fig 1: Patients vs. Socio-economical Status

Among 130 patients 79 patients had family history of breast cancer or any other cancers that is 61%. 51 patients (39%) did not have any family history of breast cancer before.

According to breast feeding vs incidences, among 130 patients only 23 patients used to breastfeed their children and remaining 107 patients did not.

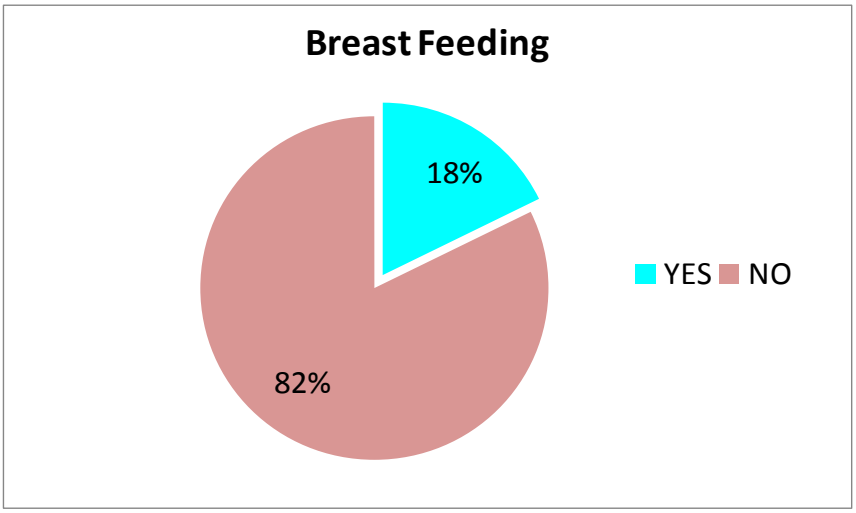


Fig 2: Breast Feeding vs Incidence

A satisfactory explanation for the excess incidence of left breast cancers has not yet been elucidated. However, it has been well established that, on average, the left breast is slightly larger than the right. The finding of increased overall incidence of left breast cancer also extended to males. Data from a pooled analysis of 18 US studies was reported in 1959 and showed a four percent excess in left breast cancers.

- This lends itself to the logic that more breast tissue is present to be at risk for the development of a cancer.
- Left sided disease was more common only after reaching the age of 45.
- For women younger than 45, right handedness, never having been pregnant and late age for beginning to have menstrual periods was associated with a higher incidence of right breast cancer.[14, 15,16]

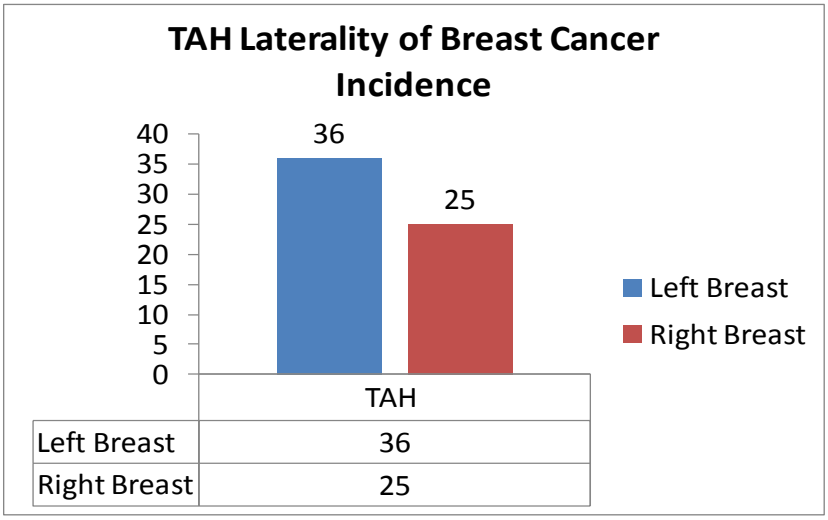
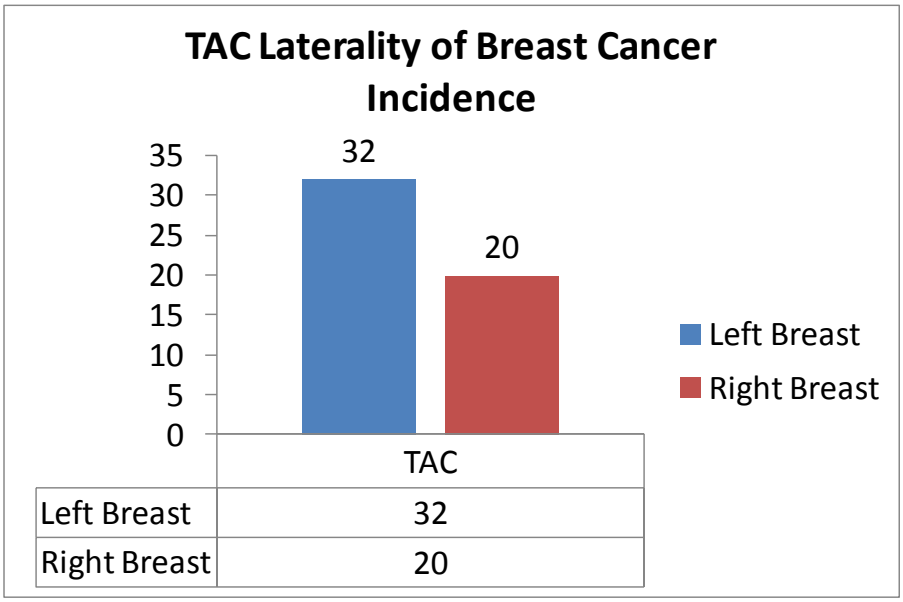


Fig 3: TAH Laterality of Breast Cancer Incidence



Median Survival

Drug	Median
TAC	23.33
TAH	28.51
Placebo	20.407
Overall	25.57

95% Confidence Interval

Fig 4: Median Survival

Kaplan-Meier Survival

Median OS with TAH was 28.51 months compared to 23.33 months with TAC. 30% relative reduction in risk of death with TAH compared to TAC. The evidence of this study is that TAH will 5.181 months probability of more survival over TAC [4,5,6]

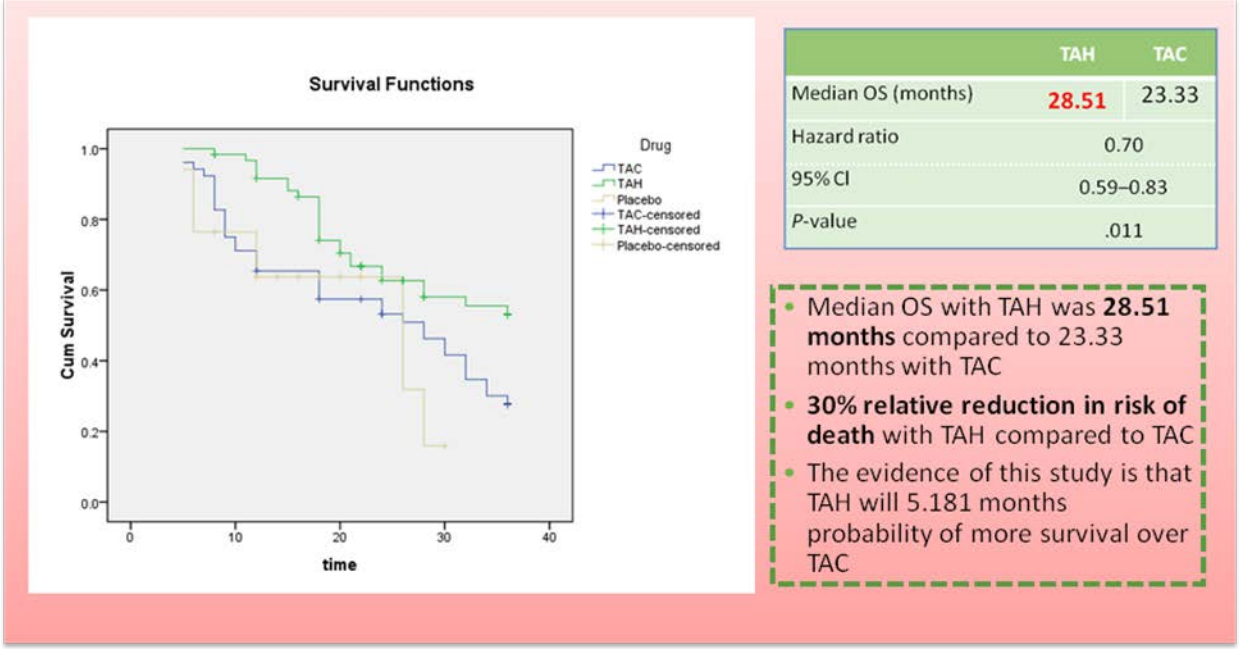


Fig 5: Kaplan-Meier Survival

In the comparison the major outcome between TAC and TAH about the overall survival (OS), the evidence of this study is using TAH will provide (28.511-23.33) = 5.181 months probability of more survival over TAC. The addition of trastuzumab to docetaxel after doxorubicin and cyclophosphamide in early- stage HER2-positive breast cancer results in a substantial and durable improvement in survival as a result of a sustained marked reduction in cancer recurrence.

Conclusion

Trastuzumab + Cytotoxic Chemotherapy significantly improves OS vs Cytotoxic Chemotherapy alone.30% risk reduction of death (HR=0.70, *P* =.011) 28.51 months median OS vs 23.33 months with Cytotoxic Chemotherapy alone. OS benefit was consistent across subgroups. The major outcome between TAC and TAH about the overall survival, TAH will provide (28.511-23.33) = **5.181** months probability of more survival over TAC. Trastuzumab significantly improves quality of life.

References

1. Slamon DJ, Godolphin W, Jones LA, et al: Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer. *Science* 244:707-712, 1989
2. Slamon DJ, Leyland-Jones B, Shak S, et al: Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that over expresses HER2. *N Engl J Med* 344:783-792, 2001
3. "Mastectomy vs. Lumpectomy". Breastcancer.org. 9 June 2013. Retrieved 23 October 2013.
4. McManusic et al. Lancet. 2(8032):297-98, 197
5. Hsieh C et al. European Journal of Cancer. 27(2):131-5,1991
6. Howard J et al. Human Biology. 54(2): 365-71, 1982
7. Bennett, Joseph J. (2006). "Sentinel Lymph Node Biopsy for Breast Cancer and Melanoma". US Oncological Disease 1 (1): 16–19. Retrieved 23 October 2013.
8. Effect of neoadjuvant anthracycline-taxane-based chemotherapy in different biological breast cancer phenotypes: overall results from the GeparTrio study. Breast Cancer Res Treat 2010;124:133-140.
9. "Causes, incidence, and risk factors". Lymphatic obstruction. U.S. National Library of Medicine. 3 September 2012. Retrieved 23 October 2013.
10. "Lifting Weights Reduces Lymphedema Symptoms Following Breast Cancer Surgery". Medical News

Today. 13 August 2009. Retrieved 23 October 2013.
11. Nelson, J. C.; Beitsch, P. D.; Vicini, F. A.; Quiet, C. A.; Garcia, D.; Snider, H. C.; Gittleman, M. A.; Zannis, V. J.; Whitworth, P. W.; Fine, R. E.; Keleher, A. J.; Kuerer, H. M. (2009). "Four-year clinical update from the American Society of Breast Surgeons MammoSite brachytherapy trial". The American Journal of Surgery 198 (1): 83–91. doi:10.1016/j.amjsurg.2008.09.016. PMID 19268900.
12. Keisch; et al. (February 2007). "American Brachytherapy Society breast brachytherapy task group" (PDF). American Brachytherapy Society. Retrieved 25 September 2009.
13. Polgár, C.; Major, T. (2009). "Current status and perspectives of brachytherapy for breast cancer". International Journal of Clinical Oncology 14 (1): 7–0. Doi: 10.1007/s10147-008-0867-y. PMID 19225919.
14. Management of triple negative breast cancer. Breast 2010;19:312-321.
15. Minckwitz, G (March 2007). "Docetaxel/anthracycline combinations for breast cancer treatment". Expert Opinion on Pharmacotherapy 8 (4): 485–495. doi:10.1517/14656566.8.4.485. PMID 17309343.
16. Goss PE, Ingle JN, Martino S, et al. A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. N Engl J Med 2003; 349:1793.
17. "Women With Metastatic Breast Cancer Can Benefit From Estrogen Pills". Medical News Today. 12 December 2008. Retrieved 23 October 2013.
18. Berry DA, Cirrincione C, Henderson IC, et al. Estrogen-receptor status and outcomes of modern chemotherapy for patients with node-positive breast cancer. JAMA 2006; 295:1658.

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