RESEARCH ARTICLE

Taxane-Based Regimens as Adjuvant Treatment for Breast Cancer: a Retrospective Study in Egyptian Cancer Patients

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Abstract

Background: To evaluate the impact of adding taxanes to anthracycline-based regimens in the adjuvant setting in localized young female breast cancer patients on the overall survival (OS) and the disease free survival (DFS).

Materials and Methods: This retrospective study included all female breast cancer patients who were candidates for adjuvant chemotherapy presenting to Kasr Al Ainy centre of clinical oncology and Cairo oncology centre (Cairo Cure) in the period from January 2005 till December 2010.

Results: Our study included 865 patients, 732 of whom received anthracycline based regimens and 133 taxane based regimens. The mean age of patients was 39 years. After a median follow up of 50 months the median DFS was 48.4 months. Survival analysis indicated that the tumor size (>5cm vs. <5cm) p=0.001), nodal involvement (Yes vs. No) p=0.0001) and pathology (invasive lobular vs. ductal) p=0.048) affected DFS. As regards hormonal status, ER, PR and HER 2neu positive patients had longer DFS (p=0.001, 0.003, 0.106). On multivariate analysis DFS was affected by tumor size and lymph node involvement (p=0.014, 0.007). Subgroup analysis showed improvement in arms treated with taxanes in terms of DFS with positive Her2neu, ER and PR, but this was not statistically significant. Conclusions: Adding adjuvant taxanes to anthracyclines is beneficial for treatment of localized breast cancer among all subgroups, especially higher risk groups. The type of adjuvant chemotherapy regimens and tumor characteristics have direct effects on DFS.

Keywords: Breast cancer - Egypt - adjuvant chemotherapy - taxanes - her2neu - hormonal status

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Introduction

In Egypt, breast cancer (BC) is the most common cancer among women, representing 18.9% of total cancer cases and 35.1% of cancer in women (Elatar, 2002). Invasive duct carcinoma is the most common pathology constituting 83.4% with high incidence of grade II and III, 66% and 28.6% respectively (El-Bolkainy, 2000).

Breast cancer in Egypt occurs ten years earlier than in developing countries and most of them are premenopausal (Omar et al., 2003). The age-adjusted rate is 49.6 per 100,000 populations (Ibrahim, 2002). The incidence is steadily increasing with a tendency for breast cancer to occur in younger age groups and with advanced stages (Ahmed, 2010). An Australian study found that the Egyptian women had the highest breast cancer rates of all Middle Eastern immigrants to Australia (McCredie, 1994). Egyptian publications conducted in Egypt in the adjuvant breast cancer setting are scarce (Abd-El-Moneim et al., 2011; Hamza et al., 2011; Sakr et al., 2013)

Over three decades Montemurro and Aglietta (Montemurro & Aglietta, 2009) summarized adjuvant chemotherapy for BC patients into three eras: first, the era of CMF regimen; then, that of anthracyclines; and more recently taxanes (Montemurro and Aglietta, 2009).

The feasibility of six cycles of either docetaxel plus cyclophosphamide (TC6) or sequential taxane and anthracyline regimen (T-FEC) in Japanese patients with HER2-negative early breast cancer, was assessed (Abe et al., 2014). The study suggested that TC6 is tolerable in Japanese and can be performed in outpatient clinics with slightly lower compliance and appropriate supportive treatment. Another Indian study also showed better tolerance to neoadjuvant sequential docetaxol than concurrent anthracycline and taxane regimen with a similar pathological remission in locally advanced breast cancer patients (Gogia et al., 2014).

In the adjuvant setting taxane-based were more effective than the anthracycline-based regimens in terms of DFS and OS in lymph node positive patients. Its relation to endocrine responsive tumors and Her2neu was limited (Mamounas et al., 2005, Hayes et al., 2007) with
controversial results (Montemurro and Aglietta, 2009).

The aim of our study is to evaluate the impact of the addition of Taxanes to Anthracycline-based regimens in the adjuvant setting for Egyptian female patients with localized breast cancer in a younger population. The overall survival (OS) and the disease free survival (DFS) were assessed and correlated with the type of adjuvant chemotherapy and the tumor characteristics.

Materials and Methods

Our study was a retrospective analysis that included Egyptian Female patients with localized breast cancer presented to 2 Egyptian Centers namely: Kasr Al-Ainy Center of Clinical Oncology, Cairo University and Cairo Oncology Center in the period from January 2005 till December 2010. The study had the institutional ethical review board approval. Inclusion criteria included all female patients with proven pathological diagnosis of breast cancer with localized disease who underwent surgery and were candidate for adjuvant chemotherapy with at least six months follow up.

Metastatic breast cancer cases (proven by chest X-ray, bone scan or abdominal ultrasound) at presentation was excluded from the study. Patients receiving neoadjuvant or non-anthracycline-based chemotherapy and followed up for less than six months were also not included.

Surgery consisted of modified radical mastectomy with axillary dissection of level I and II lymph nodes or conservative breast surgery in the form of lumpectomy and axillary evacuation.

The adjuvant chemotherapy regimens for patients in the study were Anthracycline-based regimen or Taxane + anthracycline-based regimen. The most common Anthracycline-based regimen used was FAC (5-Flurouracil 500mg/m², Doxorubicin 50mg/m², Cyclophosphamide 500mg/m²) given every 3 weeks for 6 cycles. Taxanes used in combined Taxane-Anthracycline-based regimens were either weekly Paclitaxel or 3-weekly Docetaxel for 3 cycles proceeded by Anthracycline-based regimen in the first 3 cycles.

Patients who underwent lumpectomy and axillary evacuation received local radiation to the breast after completion of chemotherapy. Patients who underwent mastectomy received radiation to the chest wall in case of positive or close margins, tumors 4 cm or more in maximum dimension or node positive disease. Patients with positive axillary lymph nodes (LN) received radiotherapy to the supraclavicular LN.

Hormone receptor assays were performed in the histopathology department by immunohistochemistry (IHC). Estrogen and progesterone receptors were considered positive if >1% of tumor cells showed expression by IHC. HER 2neu positive patients had either scored 3+ by IHC or are positive by fluorescence in situ hybridization FISH or Silver in situ hybrization (SISH). Premenopausal women with ER or PR positive tumors received 5 years of adjuvant tamoxifen 20 mg/day. Postmenopausal women with ER or PR positive tumors were assigned to 5 years of sequential aromatase inhibitor

| Table 1. Clinico-Pathological Characteristics in Both Groups |
|---------------------------------------------------------------|
| Variables | Anthracycline No=477 |  | Taxane No=133 |  |
| Age <35 years | 43 | 9% | 12 | 9% | 0.984 |
| 35-50 | 250 | 52.4% | 68 | 51.1% |
| >50 | 184 | 38.5% | 53 | 39.9% |
| Menopausal status |  |  |  |  |
| Premenopausal | 253 | 55.1% | 76 | 58.9% | 0.443 |
| Postmenopausal | 206 | 44.9% | 53 | 41.1% |
| Type of surgery |  |  |  |  |
| MRM | 346 | 72.5% | 89 | 66.9% | 0.205 |
| BSC | 131 | 27.5% | 44 | 33.1% |
| Tumor size (T) |  |  |  |  |
| T1-2 | 343 | 80.9% | 102 | 81.0% | 0.989 |
| T3-4 | 81 | 19.1% | 24 | 19% |
| Nodal status (N) |  |  |  |  |
| N0 | 38 | 8.5% | 10 | 7.5% | 0.757 |
| N+ | 410 | 91.5% | 121 | 92.4% |
| Pathology |  |  |  |  |
| IDC | 389 | 81.7% | 108 | 81.8% | 0.98 |
| ILC | 87 | 18.3% | 24 | 18.2% |
| Grade |  |  |  |  |
| I | 10 | 2.6% | 4 | 3.6% | 0.833 |
| II | 305 | 79.2% | 87 | 79.1% |
| III | 70 | 18.2% | 19 | 17.3% |
| ER |  |  |  |  |
| Negative | 149 | 32.6% | 42 | 32.6% | 0.874 |
| Positive | 308 | 67.4% | 87 | 67.4% |
| PgR |  |  |  |  |
| Negative | 191 | 43.1% | 56 | 43.8% | 0.898 |
| Positive | 252 | 56.9% | 72 | 56.2% |
| Her2 |  |  |  |  |
| Negative | 231 | 73.6% | 76 | 66.1% | 0.128 |
| Positive | 83 | 26.4% | 39 | 33.9% |
| Relapse |  |  |  |  |
| No | 212 | 44.4% | 97 | 73.0% | <0.001 |
| Yes | 265 | 55.6% | 36 | 27.0% |

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and tamoxifen. Herceptin was not offered to HER 2 neu positive patients due to its unavailability in our centre at that time.

Starting from 2008, the human epidermal growth factor receptor (HER2) was assayed by immunohistochemistry. It was considered positive if score 3+, and considered negative for score 0, 1+ while score 2+ was considered equivocal. No patients with amplified HER2, in either groups received adjuvant trastuzumab.

After completion of adjuvant chemotherapy and radiotherapy, patients were planned for follow up visits every 3 months during the first year, every 4 months in the second year, then every 6 months until the end of the fifth year and yearly thereafter. Patients underwent a history and physical examination at each follow-up, a mammogram and echocardiography were performed yearly. Chest X ray, Abdomino-pelvic ultrasonography, bone scan and labs were requested as clinically indicated.

Patients were divided into 2 groups according to the type of adjuvant chemotherapy regimen received: anthracycline based regimen and taxane based regimen. The primary end point of this study was disease-free survival (DFS), which was defined as the time from surgery to disease progression in the form of local breast (including ductal carcinoma in situ) or nodal recurrence and metastatic disease. Patients who had contralateral breast cancer after 2 years, a second malignancy, or non-disease-related death were not considered relapsing.

Statistical analysis

All data were tabulated and statistically studied by descriptive analysis as well as survival analysis in relation to different prognostic factors. Comparison between groups was done using Student t test for continuous data and Chi square test for categorical data. Survival analysis was done according to Kaplan-Meier method and both groups were compared by log-rank test for significance. Multivariate analysis using Cox regression module was performed to test the power of relation between the independent variables and survival. Differences were considered significant if p value is less than 0.05. All statistical calculations, data management and analysis were performed using computer programs Microsoft Excel version 7 (Microsoft Corporation, NY, USA) and SPSS version 17 (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA).

Results

During the period from January 2005 till December 2010, 865 patients fulfilling the inclusion criteria were included in this study.

The median age of the whole group was 49 years (21 - 73 years). Regarding the type of surgery, 70% underwent MRM. Less than 20% of patients were presenting with T3-4 tumors while lymph nodes were positive in more than 90% of patients, two thirds of them had 4 or more positive nodes. As expected, IDC was the main pathological subtype (81.7%); with 80% of them Grade II. Among those with available immunohistochemistry, ER was positive in more than two thirds of patients, while Her2 was positive

Table 2. Multivariate Analysis Among Group Study Patients

| Variable | HR  | 95.0%CI Lower | 95.0%CI Upper | P value |
|----------|-----|---------------|---------------|---------|
| Tumor stage |      |               |               |         |
| T3-4 vs T1-2 | 1.707 | 1.112          | 2.621          | 0.014   |
| Nodal stage |      |               |               |         |
| N+ vs N0 | 1.937 | 1.198          | 3.132          | 0.007   |
| Regimen |      |               |               |         |
| Taxane vs Anthra | 0.716 | 0.439          | 1.168          | 0.181   |
| Age |      |               |               |         |
| >35 yrs vs <35 yrs | 1.042 | 0.602          | 1.804          | 0.882   |
| Pathology |      |               |               |         |
| IDC vs ILC | 1.011 | 0.126          | 8.116          | 0.992   |
| Grade |      |               |               |         |
| II vs I, III | 1.326 | 0.929          | 1.893          | 0.12    |
| ER |      |               |               |         |
| +ve vs -ve | 0.821 | 0.515          | 1.311          | 0.409   |
| PgR |      |               |               |         |
| +ve vs -ve | 0.774 | 0.484          | 1.236          | 0.283   |
| Her2 |      |               |               |         |
| +ve vs -ve | 1.187 | 0.815          | 1.728          | 0.371   |

Table 3. Median DFS (in months) According to Regimen Received Among Different Subgroups

| Subgroup | Anthracycline | Taxane | P value |
|----------|---------------|--------|---------|
| Age < 35 yrs | 28.6 | 59.7 | 0.241   |
| Age > 35 yrs | 41.9 | 68.7 | 0.465   |
| T1-2 | 48.4 | 59.7 | 0.467   |
| T3-4 | 29.4 | 71.4 | 0.449   |
| N+ | 43.5 | 68.7 | 0.62    |
| N1 | 61.7 | 59.7 | 0.973   |
| N2-3 | 40 | 68.7 | 0.402   |
| ER-ve | 32.2 | Not reached | 0.206  |
| ER+ | 50 | 68.7 | 0.248   |
| Her2–ve | 43.5 | 71.4 | 0.068   |
| Her2+ve | 38.3 | 68.7 | 0.038   |
Patients were divided into 2 groups according to adjuvant chemotherapy regimen received. Among 610 patients, 477 patients received anthracycline-based regimen (Group 1) while 133 patients received taxane-based regimen (Group 2). Both groups were balanced regarding their clinicopathological characteristics with no statistical significant difference Table 1.

At a median follow up period of 40 months (6-180 months), the relapse rate was 55.6% for Group 1 compared to 27.1% for Group 2 (p<0.001). The median DFS for the whole population was 42.5 months (95%CI 37.7-47.3 months). Comparing the 2 groups, the median DFS for Group 1 was 41.7 months versus 59.7 months for Group 2 but this difference did not reach statistical significance (p=0.231) Figure 1.

Multivariate analysis was done for different risk factors affecting disease free survival. The only independent variable affecting DFS in our group study was tumor size and lymph node status Table 2.

Subgroup analysis was done to identify subgroups benefiting from adding Taxanes. The only subgroup that showed a statistically significant benefit from the addition of Taxanes were Her2 positive patients with median DFS of 68.7 months compared to 38.3 months for those received anthracycline-based regimens (p=0.038). Although there was a benefit of adding taxanes in other subgroups but it did not reach a statistical significance Table 3.

### Discussion

This study supports the use of a Taxane drug as part of the adjuvant chemotherapy regimen following surgery for early stage breast cancer patients as it provides a statistically significant improvement in relapse rate.

Our findings revealed that tumor size of 5 cm and above and positive lymph node status was significantly associated with a higher risk of relapse and decreased survival in breast cancer patients. This results was consistent with (Cihan, 2014) that showed that stage including tumor size and nodal status remained the strongest prognostic factors in long term survival. This was confirmed by an Iranian study done by (Faradmal et al., 2010) and an Egyptian study by (Sedhom et al., 2011).

Our study reported that positive axillary lymph nodes decreased the median survival of breast cancer patients. This coincides with (Kim et al., 2005) that found that the most important prognostic factor affecting local control, disease-free survival, and overall survival was axillary lymph node metastasis.

The results of this study showed an improvement of DFS in favor of taxane-based regimens, but the difference compared to anthracycline-based regimens was not significant (59.7 vs 41.7 months, HR=0.716, 95% CI: 0.439-1.168, p=0.181). The 5 years DFS was 50% and 37% for the taxanes and the anthracycline regimen respectively with 28.5% reduction in the risk of relapse which was statistically significant (p=0.001).

A meta-analysis in 100,000 women in 123 randomized trials was conducted by (Peto et al., 2012) to compare between different polychemotherapy regimens for breast cancer. In trials adding 4 separate cycles of a taxane to a fixed anthracycline based control regimen, the extension of treatment duration reduced breast cancer mortality (RR 0.86, SE 0.04, two sided significance [2p]=0.0005). Eight years follow up of the French trial PACS01 trial demonstrated a benefit for DFS and OS rates with the sequential administration of docetaxel after FEC100 (Fluorouracil 500mg/m², Epirubicin 100mg/m², and Cyclophosphamide 500mg/m²) for patients with node-positive, operable breast cancer. Eight-year DFS rates were 65.8% with FEC alone and 70.2% with FEC-D. OS rates at 8 years were 78% with FEC alone and 83.2% with FEC-D. Cox regression analysis adjusted for age and number of positive nodes showed a 15% reduction in the relative risk of relapse and a 25% reduction in the relative risk of death in favor of FEC-D. Significant relative risk reductions were observed in the hormone positive, HER2-positive, and Ki67 ≥20% (Coudert et al., 2012). This is consistent with an Egyptian study done by (Sakr et al., 2013) using the same regimen as the French trial. Five-year DFS rates were 74 % with FEC and 78 % with FEC-D (p=0.013). Multivariate analysis adjusted for prognostic factors showed a 17 % reduction in the relative risk of relapse with FEC-D. Five-year overall survival rates were 85 % with FEC and 89.4 % with FEC-D, demonstrating a 27 % reduction in the relative risk of death (p=0.014). Another Malaysian study showed similar but earlier response to FEC as regard tumor size reduction in all stages of breast cancer when compared to docetaxol (Hassan, 2013).

The results of subgroup analysis of this work indicated also that there were favorable gains in DFS in the taxane-based treatment arm but no statistical difference between the 2 treatment arms except for Her2 positive patients taking into consideration that none of them received adjuvant Trastuzumab. The DFS was 68.7 months compared to 38.3 months for those receiving anthracycline-based regimens (p=0.038).

Eleven trials reported subgroup results of ER status. For ER-positive subgroup the pooled HR of 0.83 (95% CI 0.76-0.90) for DFS indicated a 17% reduction in the risk of recurrence presented in the taxanes-based treatment arm, and for the ER-negative subgroup the pooled HR of 0.80 (95%CI 0.73-0.88) for DFS indicated a 20% reduction in the risk of recurrence presented among patients receiving taxanes (Berry et al., 2004; Citron et al., 2013). However M.D. Anderson Cancer Center (MDACC) trial In the MDACC trial (Madarnas et al., 2011), a subgroup analysis found no significant difference in Disease-free survival (DFS) by estrogen receptor (ER) status (p=0.07 for ER negative, p=0.39 for ER positive).

The benefit of addition of Taxanes in Her2 positive disease shown in our study was also demonstrated by (Hayes et al., 2007) that found that the addition of Paclitaxel to doxorubicin plus cyclophosphamide improved DFS compared to doxorubicin plus cyclophosphamide in HER2 positive patients. Five year DFS rate was approximately 75% in taxane arm vs 55% in the anthracycline arm. These results were inferior to Tai et al., (2013) showing a mean estimated disease free survival of 80.2 months when adjuvant trastuzumab was added with a mean DFS of 68.7 months.
of 93.1% at 7 years.

The DFS in this Egyptian study was lower than that in developed countries. This may be due to the young age, high percent of Her2+ not receiving trastuzumab and high lymph node involvement.

This study is limited by the relative small number of patients, lack of number of events and shorter follow up among the group receiving taxanes. Also the unavailability of trastuzumab at that time in our Centre affected the results. We conclude from this study that the type of adjuvant chemotherapy regimens and tumor characteristics have direct effects on DFS. Adding taxanes to anthracyclines is beneficial for treatment of localized breast cancer after surgery among all subgroups especially higher risk groups. If Trastuzumab is not affordable for Her2 positive patients, use of Taxane-based regimen in adjuvant setting significantly improve DFS.

In Egypt, raising awareness about early detection of breast cancer by breast self-examination and screening programs should be accentuated to improve treatment results and survival.

References

Abd-El-Moneim NA, Abdelmoneim S, ElAify E (2011). Impact of comorbidity, hormonal receptor status and adjuvant chemotherapy plus tamoxifen versus tamoxifen alone on survival of senior breast cancer patients: retrospective study. J Geriatric Oncol, 2, 57.

Abe H, Mori T, Kawai Y, Tomida K, Kubota Y et al (2014). Feasibility study of docetaxel and cyclophosphamide six-cycle therapy as adjuvant chemotherapy for Japanese human epidermal growth factor receptor 2-negative breast cancer patients. Asian Pac J Cancer Prev, 14, 4835-38.

Salem AAS, Salem MAE, Abbass H (2010). Breast cancer: surgery at the South Egypt Cancer Institute. Cancers, 2, 1771-8.

Berry DA, Cirrincione C, Henderson IC, et al (2004). Effects of improvements in chemotherapy on disease-free and overall survival of estrogen-receptor-negative, node-positive breast cancer: 20-Year experience of the CALGB & U.S. Breast Intergroup. Breast Cancer Res Treat, 88, 17.

Cihan YB (2014). Relationship of body mass index with prognosis in breast cancer patients treated with adjuvant radiotherapy and chemotherapy. Asian Pac J Cancer Prev, 15, 4233-38.

Citron ML, Berry DA, Cirrincione C et al (2013). Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-negative primary breast cancer: First report of Intergroup trial CALGB 9741. J Clin Oncol, 21, 4311-39.

Coudert B, Asselin B, Campone M et al (2012). UNICANCER Breast Group. Extended benefit from sequential administration of docetaxel after standard fluorouracil, epirubicin, and cyclophosphamide regimen for node-positive breast cancer: the 8-year follow-up results of the UNICANCER-PACS01 trial. Oncologist, 17, 900-9.

Dignam JJ, Dukic V, Anderson SJ et al (2009). Hazard of recurrence and adjuvant treatment effects over time in lymph node-negative breast cancer. Breast Cancer Res Treat, 116, 595-602.

El-Bolkainy MN (2000). Topographic pathology of cancer, 2nded. Cairo, National Cancer Institute, Cairo University:87. Elatar I (2001). Cancer registration, NCI Egypt(2001). Cairo, Egypt, National Cancer Institute, 2002 (http://www.nci.edu/ eg/Journal/nci2001%20.pdf, accessed 1 April 2004).

Faradmal J, Kazemnejad A, Khodabakhshi R, Gohary MR, Hajizadeh E (2010). Comparison of three adjuvant chemotherapy regimes using an extended log-logistic model in women with operable breast cancer. Asian Pac J Cancer Prev, 11, 353-58.

Gogia A, Raina V, Deo SV et al (2014). Taxane and anthracycline based neoadjuvant chemotherapy for locally advanced breast cancer: Institutional experience. Asian Pacific J Cancer Prev, 15, 1989-92.

Hamza Abbas, Ashraf Elryanamy, Mohamed Salem et al (2011). The optimal sequence of radiotherapy and chemotherapy in adjuvant treatment of breast cancer. Int Arch Med, 4, 35.

Hassan BA, Yusoff ZB, Hassali MA, Othman SB, Weiderpass E (2012). Impact of chemotherapy on hypercalcaemia in breast and lung cancer patients. Asian Pacific J Cancer Prev, 13, 4373-78.

Hayes DF, Thor AD, Dressler LG et al (2007). HER2 and response to Paclitaxel in node-positive breast cancer. New Engl J Med, 357, 1496-506.

Ibrahim AS, Komodiki C, Najjar K, Rahamimoff R, Tuncer M (2002). Cancer Profile in Gharbiah, Egypt. Methodology and Results; Ministry of Health and Population Egypt and Middle East Cancer Consortium: Cairo, Egypt.

Kim KJ, Huh SJ, Yang JH et al (2005). Treatment results and prognostic factors of early breast cancer treated with a breast conserving operation and radiotherapy. Jpn J Clin Oncol, 35, 126-33.

Madamouss EP, Bryant J, Lembersky B et al (2005). Paclitaxel after doxorubicin plus cyclophosphamide as adjuvant chemotherapy for node-negative breast cancer: results from NSABP B-28. J Clin Oncol, 23, 3686-96.

McCredie, M, Coates M, Gruilich A (1994). Cancer incidence in migrants to New South Wales (Australia) from the Middle East, 1972-1991. Cancer Causes Contr, 5, 414-21.

Montemurro F, Aglietta M (2009). Hormone receptor-positive early breast cancer: Controversies in the use of adjuvant chemotherapy. Endocr Relat Cancer, 16, 1091-102.

Omar S, Khaled H, Gaafar R et al (2003). Breast cancer in Egypt: a review of disease presentation and detection strategies. East Mediterr Health J, 9, 448-63.

Peto R, Davies C, Godurin J et al (2012). Early breast cancer trialist’s collaborative group (EBCTCG). Lancet, 379, 432-44.

Sakr H, Hamed RH, Anter AH, Youssef T (2013). Sequential docetaxel as adjuvant chemotherapy for node-positive or/ and T3 or T4 breast cancer: clinical outcome. Med Oncol, 30, 457.

Seedorhorn AE, Kamal NN (2011). Factors affecting survival of women diagnosed with breast cancer in El-Minia Governorate, Egypt. Int J Prev Med, 2, 131-38.

Tai C, Pan CK, Chen CS et al (2014). Adjuvant trastuzumab for 6 months is effective in patients with HER2 positive stage II or III breast cancer. Asian Pac J Cancer Prev, 14, 1981-84.