Chemotherapy in combination with Trastuzumab is better than chemotherapy alone in HER2 positive breast cancer patients

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Abstract

Background: Breast cancer is the most common cancer in women worldwide. It is also the principal cause of death from cancer among women globally. Despite the high incidence rates, majority of the diagnosed breast cancer patients are still alive 5 years after their diagnosis, which is due to proper detection and treatment. **Objective:** To evaluate the survival gains of trastuzumab with standard chemotherapy in patients with HER2+ metastatic breast cancer. **Methods:** This multicenter Randomized Control Trial (RCT) study had conducted in the different hospitals and clinics in Rajshahi city since January 2013 to December 2015. A total of 130 women having HER2 positive breast cancer in the stage II and stage III, 52 in TAC (Taxotere, Doxorubicin and Cyclophosphamide), 61 in TAH (Taxotere, Doxorubicin, Herceptin/ Trastuzumab) and 17 women in placebo arm, were allocated randomly. Data on background characteristics and treatment outcomes including survival status of the intervention groups were collected by a preformed data collection sheet. Kaplan-Meier curves were constructed for the survival distribution of the different intervention groups. The log rank test was applied to compare the survival distribution among the intervention groups. **Results:** The overall median survival of the study subjects was 25.57 months. The median survival for the TAC, TAH and placebo were 23.33, 28.51 and 20.40 months respectively. Using TAH provided 5.18 months more survival over TAC. The survival distributions among the intervention groups was statistically significant ($p = 0.011$). **Conclusion:** Combination of traditional standard chemotherapy and trastuzumab - which is associated with fewer side effects, is an appealing better care for the breast cancer patients of stage II and stage III with HER2 positive than the traditional standard chemotherapy regimens alone.

Key Words: Trastuzumab, Breast Cancer, HER2 Positive.

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Introduction

Breast cancer (BC) is the most common cancer worldwide with an estimated 1.67 million new cases diagnosed in 2012 (25% of all cancers). BC is the fifth cause of death from cancer overall (522,000 deaths) and it is the most frequent cause of cancer death in women in less developed regions. In the developed countries, it is the second cause of cancer death (198,000 deaths 15.4%), after lung cancer. In developed countries 6% to 10% of women will have metastatic disease when diagnosed with BC; in developing countries this percentage can reach 60%. Depending on initial stage, tumor biology, and type of treatment scheme received, 30% to 50% of women with early BC will relapse. The amplification of the human epidermal growth factor receptor 2 (HER2) is observed in 25% to 30% of all BCs. Patients with BC with over expression of HER2 have, originally, a poorer prognosis and shorter overall survival (OS). The development of effective HER2 targeted drugs is considered a major breakthrough in BC therapy. Trastuzumab was the first anti-HER2 drug approved for treatment of HER2 positive (HER2+) metastatic BC, either alone or in combination with chemotherapy. This anti-HER2 monoclonal antibody was associated with a significantly longer time to disease progression, higher response rate, longer response duration, and improved overall survival. During the last decade, HER2 targeted therapeutic approaches continued to evolve with a positive impact on the survival of the women with HER2+ metastatic BC.[1,2]

Trastuzumab is a recombinant humanized monoclonal antibody that selectively targets the extra-cellular domain of the HER2 receptor. It was approved by the FDA in September 1998 as the first targeted therapy for HER2 positive metastatic breast cancer, and has since led to significant improvements in the overall prognosis for patients with HER2 positive metastatic disease.[3,4] Trastuzumab, a monoclonal antibody that targets HER2, has significantly improved disease-free and overall survival when combined with chemotherapy for patients with breast cancers treated in both the adjuvant and metastatic settings.[5,6] The use of trastuzumab with or without chemotherapy is the

backbone of systemic treatment of HER2 positive breast cancer. The incorporation of trastuzumab into the treatment of HER2 positive breast cancer was based on a groundbreaking Phase III trial in which 469 women with HER2 positive metastatic breast cancer (MBC) were randomized to receive standard chemotherapy with or without trastuzumab.[7]

This study aimed to evaluate the combine effect of trastuzumab and low-intensity chemotherapy on patients' survival in comparison with traditional standard chemotherapy regimens in patients with HER2+ metastatic Breast Cancer.

Methods

This multicenter Experimental – Randomized Control Clinical Trial study had conducted in the department of Radiation Oncology, Rajshahi Medical College Hospital (RMCH) and other private hospitals and clinics in Rajshahi city since January 2013 to December 2015. Patients with HER2 positive breast cancer having stage II and stage III attended at these hospitals and clinics during the study period were the study population. Total 130 women, 52 in TAC, 61 in TAH and 17 women in placebo arm were enrolled randomly in this study. In TAC arm: 52 women were randomly allocated to the TAC (Taxotere, Doxorubicin and Cyclophosphamide) arm. TAC arm consists of Taxotere (75 mg/m^2, day 1), as 1 hour infusion preceded by Doxorubicin (50 mg/m^2, day 1) and Cyclophosphamide (500 mg/m^2, day 1), both given as an intravenous bolus. This TAC protocol runs for 6 cycles in every 3 weeks. In TAH arm: 61 women were randomly allocated to the TAH (Taxotere, Doxorubicin, Herceptin/ Trastuzumab) arm. TAH arm consists of Taxotere (75 mg/m^2, day 1), Doxorubicin (50 mg/m^2, day 1) and Herceptin/ Trastuzumab (8mg/kg for 1st cycle and 6mg/kg from 2nd cycle, day 1), In this arm other combined therapy will run till 6 cycles and Herceptin will run up to 12 cycles in every 3 weeks. In Placebo arm: 17 patients were allocated to placebo arm. The patients having cardiovascular disease were excluded from the study. After selection, every patient was followed at the interval of 3 months up to 36 months (3 years), if survived. Before selection the women, informed written consent was taken from each of them. Data on back ground characteristics and treatment outcomes of the intervention groups were collected by a pre formed data collection sheet.

Data were computed and processed using SPSS for window. Descriptive analytic techniques involving frequency distribution, computation of percentage etc. were done. Kaplan-Meier curves were constructed for the survival distribution of the different intervention groups. The log rank test was applied to compare the survival distribution among the intervention groups.

Results

TAC arm had a total of 52 patients, TAH arm had a total of 61 patients and Placebo arm had a total of 17 patients. A total of 130 patients, 77 (59.2%) patients belonged to the 36-50 years age group, 21 (16.2%) patients were in the age group of 25-35 years and the rest 32 (24.6%) were above 50 years. In between age 25-35 years, 10 patients received TAC, 8 patients received TAH and 3 patients received placebo. In between age 36-50 years, 33 patients received TAC, 31 patients received TAH and 13 patients received placebo. Age above 50 years, 9 patients received TAC, 22 patients received TAH and 1 patient received placebo.

In this study, most of patients belong to the middle class family. Among 130 patients, 68 (52.3%) patients belong to that group, 45 (34.6%) patients belong to upper- middle class and 17 (13.1%) patients belong to the Lower-Middle class. Most of the patients were found to have the tobacco addiction along with betel leaf. Among 130 patients 89 (68.5%) patients took tobacco and 41(31.5%) patients did not have any addiction to tobacco. Most of the study subjects, 97 (75.0%) patients did not experience any radiation therapy in their lifetime and the rest 33 (25.0%) patients had the history of getting radiation therapy in their early age for any kind of cancers or other diseases. Among 130 patients 78 (60.0%) did not get any Hormone Replacement Therapy (HRT). 52 (40.0%) patients experienced HRT in their lifetime. Among 130 patients 74 (57.0%) patients were used to take oral contraceptive as their contraception. 56 (43.0%) patients took other contraception method not oral contraceptive. Among 130 patients 51(39.3%) patients had ER-/PR-, 19 (14.6%) patients had ER+/PR-, 45 (34.6%) patients had ER+/PR+, 15 (11.5%) patients had ER-/PR+ receptor status.

Among 130 patients only 23(17.7%) patients used to breastfeed their children and remaining 107 (82.3%) patients did not. Among 130 patients 75 (57.7%)

patients maintained their conjugal life and remaining 55(42.3%) patients did not have normal conjugal life. More than forty one percent (54, 41.5%) of the patients had menopause and rest (76, 58.5%) of the patients did not experience it. Hypertension was found among the 42.3% (55) of the patients and the rest 75(57.3%) were normotensive. Diabetes Mellitus (DM) with or without hypertension was also found in many patients. A total of 130 patients, 97(74.6%) patients had comorbidity and the rest 33(25.4%) did not have any comorbidity. If the circumstances surrounding a patient's death were not available, the cause of death was classified as unknown, even if the patient had developed recurrent breast cancer or a second malignancy. The other efficacy end point examined was disease free survival (DFS), defined as the time from enrollment to documentation of the first of any of these events: local, regional, or distant recurrence of breast cancer; a contra lateral breast cancer; a second primary cancer; or death as a result of any cause.

Table 1 Median survival among different intervention groups

Drug	Median Survival (months)
TAC	23.33
TAH	28.51
Placebo	20.40
Overall	25.57

Women assigned to the Trastuzumab had a significantly increased Overall Survival (OS) relative to those randomly assigned to the control group when the stratification factors are taken into account (stratified HR, 0.70; 95% CI, 0.59–0.83; *P*=.011). The median survival for the TAC and TAH was 23.33 and 28.51 months respectively (Table 1).

From the Kaplan-Meier curves we can see that the median survival of placebo group was 20.40 months. On the other hand, the TAC group, the overall survival is 23.33 months (Table 1) and among 52 patients the percent of incidence is 62.3% (35). There were a significant number of death incidents between 4-12 months and a highly significant number of death incident occurred between 22-34 months and most of the incident had occurred between in this time.

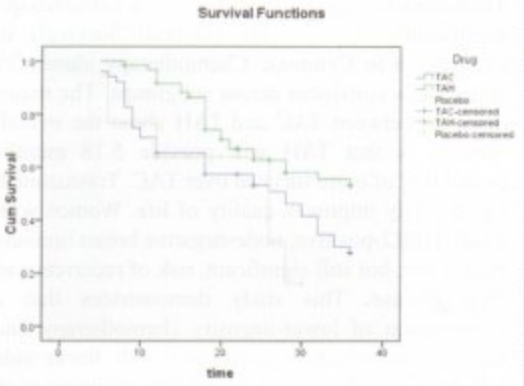

Figure-1 Kaplan Meier curves for different groups associated with patient survival

On the contrary, for TAH, the overall survival is 28.51 months and among 61 patients the percent of incidence is 41% (25) which showed better efficacy of using this combination. Moreover, from the Kaplan-Meier curve it gave an eye evident that though there is a couple of incidence between 8-16 and 18-23 but it had a more steady period from 24-36 months with an interval of only 3 incidence. So, in the comparison, the major outcome between TAC and TAH about the overall survival, the evidence of this study was using TAH would provide (28.511-23.33) = 5.181 months, probability of more survival over TAC.

The log rank test was applied to compare the survival distribution among the intervention groups. The survival distributions among the intervention groups was statistically significant (p = 0.011).

Discussion

Globally, breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death in females. In developing countries like Bangladesh and in India, the breast cancer is also becoming the most common Cancer among women for the last few years.[8] The drug trastuzumab is a monoclonal antibody and works by targeting breast cancer cells that over express the HER2 protein. By binding to the protein receptors on these cells, trastuzumab interrupts the growth signal, thereby slowing and stopping the growth and helps not to spread the tumours. Approximately 20% to 25% of breast cancers over express the HER2 protein[9]

Trastuzumab and Cytotoxic Chemotherapy significantly improve OS (Overall Survival) in comparison to Cytotoxic Chemotherapy alone. OS benefit was consistent across subgroups. The major outcome between TAC and TAH about the overall survival is that TAH will provide 5.18 months probability of more survival over TAC. Trastuzumab significantly improves quality of life. Women with small, HER2-positive, node-negative breast tumours have a low, but still significant, risk of recurrence of their disease. This study demonstrates that a combination of lower-intensity chemotherapy and trastuzumab which is associated with fewer side effects than traditional chemotherapy regimens is an appealing standard of care for this group of patients.

In the study, we wanted to know if a combination of Herceptin and just chemotherapy with doxorubicin and taxane, would offer benefits to women diagnosed with small HER2 positive breast cancers that hadn't spread to the lymph nodes and had a low risk of recurrence. It was evident that overall survival was better in women who got Trastuzumab plus chemotherapy compared to women who got only chemotherapy. Disease-free survival was better in women who got Trastuzumab plus chemotherapy compared to women who got only chemotherapy.

We found only 17% patients who are obese in our study. Carcinogens found in tobacco smoke pass through the alveolar membrane and into the blood stream, by means of which they may be transported to the breast via plasma lipoproteins. Those potential breast carcinogens in tobacco smoke can be taken up and metabolized in humans. In our study, among 130 patients 89 patients took tobacco and 41 patients did not have any addiction to tobacco.[10]

A review of 54 studies in 1996 found that women have a slightly higher risk of breast cancer while they are taking birth control pills that contain both estrogen and progestin and during the 10 years after they stop taking the pills.[11] The present study findings goes in favour of it.

Exposure to ionizing radiation is the longest-established and most firmly established environmental cause of human breast cancer in both women and men. Ionizing radiation can increase the risk for breast cancer through a number of different mechanisms, including direct mutagenesis (causing changes in the structure of DNA), genomic instability (increasing the rate of changes in chromosomes, therefore increasing the likelihood of future mutations).[12] In this study among 130 patients 51 patients had ER-/PR-, 19 patients had ER+/PR-, 45 patients had ER+/PR+, 15 patients had ER-/PR+.

The Kaplan-Meier survival curve is defined as the probability of surviving in a given length of time while considering time in many small intervals. There are three assumptions used in this analysis. Firstly, at any time patients who are censored have the same survival prospects as those who continue to be followed. Secondly, the survival probabilities are the same for subjects recruited early and late in the study. Thirdly, the event happens at the time specified.[13] Patients randomly assigned to the Trastuzumab had a significantly increased OS relative to those randomly assigned to the control group when the stratification factors are taken into account (stratified HR, 0.70; 95% CI, 0.59–0.83; *P*=.011). The median survival for the TAC and TAH was 23.33 and 28.51 respectively. The absolute decreases in distant recurrence were 7.2 percentage points after two years and 14.9 percentage points after three years, although the latter value had a wide confidence interval (10.1 to 19.5 percentage points). Among eligible patients who continued treatment after doxorubicin and cyclophosphamide and who were HER2 positive on central testing, the relative reduction in the mortality rate associated with trastuzumab was 38 percent (P=0.01). The primary concern regarding the safety of trastuzumab is the increased risk of cardiac dysfunction. In the study, the cumulative three-year incidence of congestive heart failure increased by about 3 percentage points with the addition of trastuzumab. Most episodes occurred during trastuzumab treatment, but additional follow-up will be needed to define the long-term cardiotoxicity of trastuzumab. Clearly, appropriate selection and careful cardiac monitoring of patients are essential. Trastuzumab did not increase the overall frequency or severity of non-cardiac adverse effects associated with the chemotherapy regimens, but we did see rare cases of interstitial pneumonitis in patients receiving trastuzumab during or shortly after the docetaxel phase of treatment. Two cases were fatal. Possible explanations have included the left breast is slightly larger than the right, breast feeding preferentially on the right breast protects from cancer, and that right handed women check the left breast for lumps more often. However, these explanations have been countered by findings that different quadrants of the

breast have different laterality ratios, men also have asymmetric occurrence of breast tumours, and this asymmetry is present in both invasive and in situ tumours. Left breast is slightly larger than right breast so it naturally contains more breast tissue. More breast tissue is present to be at risk for the development of a cancer more frequently than the smaller breast.

The comparison of the overall survival between TAC and TAH intervention group in this study suggests that TAH will provide more than 5 months probability of additional survival over TAC. So, the addition of Trastuzumab with cytotoxic chemotherapy to HER2 breast cancer patient gives better result in comparison to traditional chemotherapy alone considering both response rate and overall survival.

This study demonstrates that a combination of low-intensity chemotherapy and trastuzumab - which is associated with fewer side effects than traditional chemotherapy regimens, is an appealing standard of care for the breast cancer patients of stage II and stage III with HER2 positive. Trastuzumab combined with cytotoxic agents such as taxanes, vinorelbine, gemcitabine, and capecitabine has been shown to produce superior response rates, TTP, and overall survival times in patients with MBC, and triplet combinations have the potential to offer additional benefit. Trials of trastuzumab treatment beyond disease progression and retreatment after neoadjuvant relapse are also under way, and it is hope that data from those trials will provide further guidance for clinical practice. The number of trastuzumab-based treatment options in clinical practice is steadily increasing with each new clinical trial. Trastuzumab has become the foundation of care in HER2 positive disease, and ongoing studies seek to provide further improvements in outcomes, broaden potential treatment approaches, and provide further information about the optimal use in clinical practice. Moreover, trastuzumab can be combined with a wide range of chemotherapy regimens while adding little to the toxicity profile of chemotherapy. Cardiac events can occur during trastuzumab treatment but are generally reversible and manageable. It is evident that overall survival was better in women who got trastuzumab plus chemotherapy compared to women who got only chemotherapy. Disease-free survival was better in women who got trastuzumab plus chemotherapy compared to women who got only chemotherapy.

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