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Original Article

Trastuzumab in Combination with Traditional Chemotherapy is better than Chemotherapy Alone in HER2 Positive Breast Cancer Patients

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Abstract

Breast cancer is one of the most common types of cancer, making up about 25% of all cancer. 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. 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/neuHER2/neu (human epidermal growth factor receptor 2) receptors. 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 negative receptors are called triple negative. Around 25% to 30% of breast cancers show amplification of the HER2 gene. Trastuzumab is a humanized monoclonal antibody targeting the extracellular domain of HER2 receptor. In the metastatic breast cancer setting, Trastuzumab significantly improves overall survival, and is responsible for a change in the natural course of this disease. In this study we have gone to assess the outcome of HER2 positive breast cancer patients with trastuzumab along with cytotoxic chemotherapy in comparison to the conventional chemotherapy. All tumours were tested for HER2/neu status. A randomized control trial was run with 130 patients having HER2 positive breast cancer in Rajshahi Medical College Hospital and different private hospitals and clinics of Rajshahi city in this study.

Key Words: Breast Cancer, HER2 Positive, Trastuzumab.

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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.

Patients with BC with over expression of HER2 have, originally, a poorer prognosis and shorter overall survival (OS). Trastuzumab was the first anti-HER2 drug approved for treatment of 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. This study aimed at evaluating the survival gains associated with HER2 targeted

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therapies in patients withHER2+ metastatic BC.HER2/neu-positive breast cancer has changed from being an aggressive disease with a poor prognosis to a disease that is highly treatable, with prolonged survival possible even in patients with metastatic disease.[1,2]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.[3, 4] The purpose of this study was to determine Trastuzumab has proven to improve the prognosis of HER2 positive breast cancer

Materials and Methods

This experimental study–a Randomized Control Clinical Trial was conducted in the Department of Radiation Oncology, Rajshahi Medical College Hospital and other private hospitals and clinics in Rajshahi city. Patients with HER2 positive breast cancer attended at these hospitals and clinics during the study period had included in the study according to inclusion and exclusion criteria. Clinical trial was run with the 130 patients having HER2 positive stage II and stage III breast cancer. 130 women having HER2 positive BC was enrolled in this study. The study was conducted from January 2013 to December 2015.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. 17 patients were allocated to placebo arm. Data analysis was done by using SPSS (Statistical Package for Social Science) software program. Then data were analyzed by applying relevant statistical tests (parametric and non –parametric) with appropriate probability level (p=0.05).

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. 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 patients belong to that group. 45 patients belong to upper-middle class.17 patients belong to the Lower-Middle class. Most of the patients were found to have the tobacco addiction along with betel leaf. Some patients were the victim of passive smoking of tobacco. Among 130 patients 89 patients took tobacco and 41 patients did not have any addiction to tobacco.97 (75%) patients did not experience any radiation therapy in their lifetime. 33 (25%) 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%) did not get any Hormone Replacement Therapy (HRT). 52 (40%) patients experienced HRT in their lifetime. Among 130 patients 74 patients were used to take oral contraceptive as their contraception. 56 patients took other contraception method not oral contraceptive. Among 130 patients 51 patients had ER-/PR-, 19 patients had ER+/PR-, 45 patients had ER+/PR+, 15 patients had ER-/PR+ receptor status. Most of the cancer incidences were found in the 36-50 years age group. Among 130 patients 77 patients belonged to that group. Among 130 patients only 23 patients used to breastfeed their children and remaining 107 patients did not. Among 130 patients 75 patients maintained their conjugal life and remaining 55 patients did not have normal conjugal life. 54 patients had menopause and rest of the patients did not experience it. Hypertension was mostly found in the patients that is 55 among 130 patients.

Diabetes Mellitus (DM) with or without hypertension was also found in many patients.33 patients 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. Women randomly 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. From the Kaplan-Meier we can see that the placebo given group has overall survival of 20.407 months and we can see that the control group has the survival month only. On the other hand, the TAC group, the overall survival is 23.33 month and among 52 patients the percent of incidence is 62.3% (35). There are a significant number of death incidents between 4-12 month and a highly significant number of death incident occurred between 22-34 month and most of the incident had occurred between in this time.

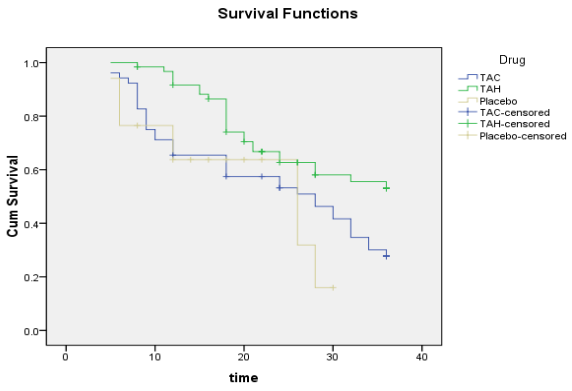

Fig-1: Time vs. Survival Curve

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 it gave an eye evident that though there is a couple of incidence between 8-16 and 18-23 but it had a steadier period from 24-36 months with an interval of only 3 incidences. 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 study was significant. The study showed the P value of 0.011 in all the Log Rank (Mantel-Cox), Breslow (Generalized Wilcoxon), and Tarone-Ware test.

Discussion

HER2 positive breast cancer is characterized by an aggressive disease progression and poor prognosis. The lifetime probability of developing invasive breast cancer is one in eight. 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.[5]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.[6] 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 5.181 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. In this study a total of 130 patients with HER2 positive stage II and stage III invasive duct cell carcinoma was observed & divided into three arm naming respectively as TAC (n=52), TAH (61) and Placebo (n=17) arm. Patients had HER2 positive breast cancer were randomly chosen to include in the study. Chemotherapy was often given as a combination of drugs. In the TAC arm patients were given 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 IV for 6 cycles in every three weeks. In the TAH arm patients were given taxotere (75mg/m^2, day 1) as 1 hour infusion preceded by doxorubicin (50 mg/m^2, day 1) and Herceptin (8 mg/kg for 1stcycle and 6mg/kg onwards, day 1) for 12 cycles in every 3 weeks. Detection of HER2 protein over expression is necessary for selection of patients appropriate for Herceptin therapy because these are the only patients studied and for whom benefit has been shown. Placebos are used in studies in order to find out whether or not the pharmacological effect of a drug actually includes pain relief or whether the effects produced by the drug might be related to psychological processes that are generically called the placebo effect.[7]In Placebo arm 17 patients were included and patients were chosen randomly. We took stage II and stage III breast cancer patients, because most of the patients came in these stages. 109 patients had stage II breast disease where 21 patients had stage III disease. The mean age for stage II was 49.81 and Stage III was 45.47. The mean age of Stage II patients were slightly higher than the mean age of stage III patients. Standard deviation of stage II patients were 9.67 and stage III patients were 15.21.Patients who were enrolled had both the left and right sided HER2 positive breast cancer. Among 61 TAH arm patients, 36 patients had left sided breast cancer and 25 patients had right sided breast cancer. On the other hand among 52 patients in TAC arm, 32 patients had left sided breast cancer and 20 patients had right sided breast cancer. Slightly more breast tumours were diagnosed in the left breast than the right. Several facts about the asymmetric laterality of breast cancer are known. Different quadrants of the breast have different laterality ratios. The laterality ratio may vary with age. Asymmetric laterality is present in both invasive and in situ tumours. About 5% -10% of breast cancer cases are thought to be hereditary, meaning that they result directly from gene defects inherited from a parent. The most common cause of hereditary breast cancer is an inherited mutation in the BRCA1 and BRCA2 genes.[8,9] Women who eat more foods containing fiber both before and after diagnosis may have a lower risk of dying from breast cancer. Breast cancer survivors who eat more foods containing soy after diagnosis may have a lower risk of dying from the disease. In our study we found that 17% patients do regular physical exercise and maintain healthy diet that is helpful in preventing breast cancer. The relationship between obesity and breast cancer may be affected by the stage of life in which a woman gains weight and becomes obese. Weight gain during adult life, most often from about age 18 to between the ages of 50 and 60 years, has been consistently associated with risk of breast cancer after menopause. 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, 89 patients took tobacco and 41 patients did not have any addiction to tobacco[10].In our study we found that 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, we assume that at any time patients who are censored have the same survival prospects as those who continue to be followed. Secondly, we assume that the survival probabilities are the same for subjects recruited early and late in the study. Thirdly, we assume that the event happens at the time specified.[11] 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. In our study we wanted to prove that treatment of HER2 Positive Breast cancer patients with Trastuzumab combined with cytotoxic chemotherapy will have a better overall survival rate than the patients who only take chemotherapy. The median survival for the TAC and TAH was 23.33 and 28.51 respectively. So, in the comparison the major outcome between TAC and TAH about the overall survival, the evidence of this study is using TAH will provide (28.511-23.33) = 5.181 months probability of more 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.

Conclusion

The combination of trastuzumab with chemotherapy is now standard for the first-line treatment of women with HER2 positive MBC. The use of trastuzumab in the metastatic setting has changed HER2 positive status from a marker of poor prognosis to one of better overall outcome. 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. Trastuzumab has become the foundation of care in HER2 positive disease. 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 (DFS) was better in women who got trastuzumab plus chemotherapy compared to women who got only chemotherapy.

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