Section: Medical Oncology

Original Research Article

ADJUVANT TRASTUZUMAB FOR 6 MONTHS VERSUS 12 MONTHS IN HER2-POSITIVE NON-METASTATIC BREAST CANCER – AN ANALYSIS OF OVERALL AND DISEASE-FREE SURVIVAL AT 2 YEARS FOLLOW-UP IN A SOUTH INDIAN REGIONAL CANCER CENTRE

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Abstract

Background: Breast cancer is a systemic disease with disease biology being an important prognostic variable; Luminal A fares better than HER2 positive or Triple negative disease. The availability of targeted agents for HER2 has improved the outcomes in such patients. De-escalation of adjuvant Trastuzumab from 12 to 6 months has provided mixed results. This retrospective study compared OS (Overall Survival) and DFS (disease-free survival) at 1 and 2 years follow-up after completion of Trastuzumab therapy. **Materials and Methods:** This retrospective study was conducted at the Department of Medical Oncology, Tirunelveli Medical College, on 40 eligible HER2-positive breast cancer patients treated in the department. Patients were stratified based on the total duration of Trastuzumab therapy [>6 months to upto 12 months (i.e., 10 to 17 doses) as arm 1 vs. up to 6 months (i.e., up to 9 doses) as arm 2]. The follow-up records were used for OS and DFS calculations. **Result:** Our study included 11 premenopausal and 29 postmenopausal women. Many patients had left-sided cancer (21), with the disease stages distributed as follows: Stage I (4), Stage II (19), and Stage III (17), respectively. Hormone receptor positivity was observed in 24 patients. The overall survival (OS) at one year was 92.5% (arm 1,95%; arm 2,90%), and disease-free survival (DFS) was 87.5% (arm 1:90%, arm 2:85%). **Conclusion:** Both arms were comparable and the duration of adjuvant Trastuzumab alone did not determine the course of the disease. Various other factors such as disease stage, timely treatment completion and patient age may also play a role in patient survival.

INTRODUCTION

Breast cancer is the most common cancer in women worldwide, leading to high morbidity and mortality.[1] Early detection of breast cancer by screening and timely therapy can save the lives of breast cancer patients and improve their quality of life. Surgery, radiation therapy, and chemotherapy are the major treatment modalities used for breast cancer. Current advancements in targeted therapies like Trastuzumab,[2,3] and pertuzumab, have led to better treatment outcomes for HER2-positive breast cancer. Adjuvant Trastuzumab therapy for 12 months is now the standard of care in HER2-positive breast cancer but carries along with it significant cardiotoxicity.[4,5]

Previous trials have produced mixed results on de-escalation of adjuvant Trastuzumab therapy for 6 months in Western populations. Extrapolation of these study results to the Indian population requires caution, and warrants strong evidence in the form of randomised controlled trials to substantiate de-escalation. Hence, the primary aim of this study was to compare OS and DFS at the end of 1- and 2-year follow-up in non-metastatic HER2-positive breast cancer patients who received up to 6 months versus 6-12 months duration of adjuvant Trastuzumab.

MATERIALS AND METHODS

This retrospective study was conducted in the Department of Medical Oncology, Tirunelveli Medical College, on 40 eligible HER2-positive breast cancer patients treated in the department. This study was initiated after obtaining approval from the Institutional Ethics Committee and written informed consent from the enrolled patients.

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Inclusion Criteria

Patients aged 21–80 years, with good performance status (Eastern Cooperative Oncology Group ≤ 2) and IHC (or FISH positive) confirmed HER2-positive (3+) breast cancer, irrespective of Estrogen Receptor (ER) Progesterone receptor (PR) status, were included randomly by census sampling.

Exclusion Criteria

Patients denying informed consent, HER2 IHC Equivocal (2+)/FISH negative or IHC Negative (0, 1+) patients, metastatic breast cancer patients at diagnosis, or poor LV function (Ejection Fraction <45%) by echocardiography were excluded.

Methods

Patients in the early stages underwent breast-conserving surgery (BCS) or modified radical mastectomy (MRM) followed by adjuvant radiation therapy in eligible patients. Most of the eligible patients received adjuvant chemotherapy. A few patients with stage III cancer underwent neoadjuvant chemotherapy before local therapy. Common chemotherapy regimens used were Adriamycin(A)+Cyclophosphamide(C)+/- 5Fluoro Uracil(F) followed by Paclitaxel(T) or Epirubicin(E)+C+/-F followed by T or Docetaxel+ Carboplatin+ Trastuzumab for 6 to 8 cycles, totally spanning about 6 months.

Trastuzumab was started along with Paclitaxel chemotherapy at doses of 8 mg/kg iv at cycle 1 and 6 mg/kg iv at subsequent doses in 3-weekly cycles for a total duration of up to 6 months (9 doses) or 6-12 months (10-17 doses). Owing to toxicity, logistical, or other issues, a few patients defaulted to a few doses of Trastuzumab.

OS was defined as the time from the completion of adjuvant Trastuzumab therapy to death from any cause. DFS was defined as the time from treatment completion to the first documented disease recurrence or death from any cause, whichever occurred first. Eligible patient records were retrieved from departmental records and patients on follow-up visits to the department's OPD.

Data analysis

The retrieved data were tabulated, organised, and analysed for various patient, treatment, and outcome characteristics. OS and DFS were measured 1 and 2 years after the completion of treatment. KM (Kaplan-Meier) survival curves for OS and DFS (in months) were obtained using SPSS software version 23.

RESULTS

The total number of participants included in the study was 40 age-matched female patients [20 patients received adjuvant Trastuzumab for a duration of up to 6 months (up to 9 doses) in arm 1 and 20 patients received up to 6-12 months (10-17 doses) in arm 2].

The menopausal status of the patients was premenopausal in 11 and postmenopausal in 29 patients, respectively. The laterality of the breast cancer was left-sided in 21 and right-sided in 19 patients, respectively. The disease stage at presentation was stage I in 4, stage II in 19 patients, and stage III in 17 patients, respectively. The hormone receptor status (ER and/or PR) of breast cancer was positive in 24 patients and negative in 16 patients, respectively. The type of surgery performed was MRM in 38 patients and BCS in 2 patients, respectively. Neo-adjuvant chemotherapy was administered to 8 patients and adjuvant radiation therapy was administered to 29 out of the total 40 patients.

The measured OS was 92.5% at 1 year (Arm 1, 95%; Arm 2, 90%) and 90% at 2 years (Arm 1: 90% and Arm 2: 90%) follow-up among the study population (p=0.999) and illustrated (in months) as a KM curve in [Figure 1].

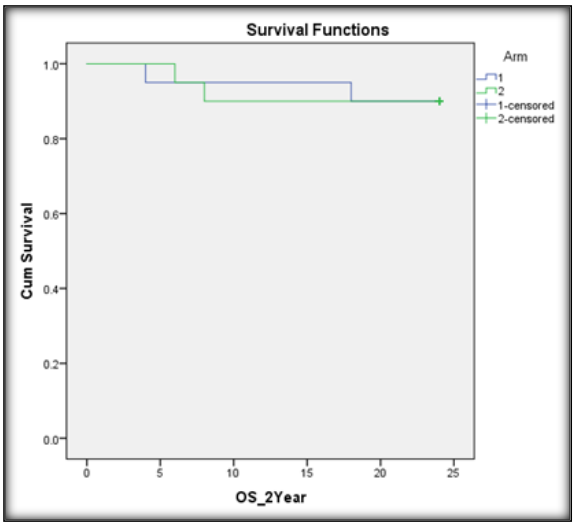

Figure 1: Measured OS at 2 years

The measured DFS was 87.5% at 1 year (Arm 1, 90%; Arm 2, 85%) and 82.5% at 2 years (Arm 1, 85%; Arm 2, 80%) follow-up among the study population (p=0.698) and illustrated (in months) as a KM curve in [Figure 2].

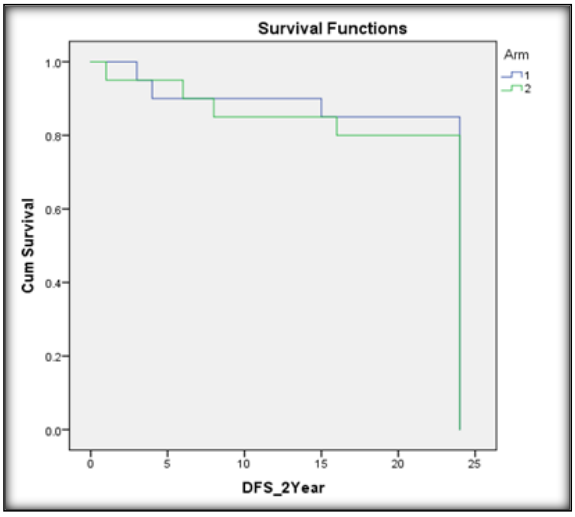

Figure 2: Measured DFS at 2 years

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DISCUSSION

The OS of HER2-positive non-metastatic patients was significantly good without affecting the quality of life in the majority of patients and was 92.5% at 1 year and 90% at 2 years follow-up, respectively. The DFS was reasonably good at 87.5% at 1 year and 82.5% at 2 years follow-up, respectively.

The results of this retrospective study demonstrate that adjuvant Trastuzumab is beneficial in HER2-positive breast cancer patients to mitigate disease progression and survival. The duration of adjuvant targeted therapy or the number of doses received had little impact on patient survival, as there was no statistically significant difference in overall survival ($p = 0.999$) and disease-free survival ($p = 0.698$) across the arms, that is, in patients who received Trastuzumab therapy for 6 months versus 6-12 months.

The PERSEPHONE trial showed that 6 months of adjuvant Trastuzumab therapy was non-inferior to 12 months of therapy in patients with early breast cancer.[6] This was an open-label, phase 3 randomized non-inferiority trial that recruited 4089 patients from 152 centres in the UK. The primary objective was 4-year DFS with a margin of 3% and at a median follow-up of 5.4 years, and non-inferiority was proven with a hazard ratio of 1.07 and a p-value of 0.011.

In contrast, the PHARE trial,[7] an open-label, phase 3, non-inferiority trial, enrolled 3384 non-metastatic HER2-positive breast cancer patients in 156 centres in France and randomized them to 6 months versus 12 months of adjuvant Trastuzumab therapy. The primary objective of DFS was a pre-specified hazard ratio margin of 1.15 pre-specified. At a median follow-up of 7.5 years, the hazard ratio for DFS was 1.08, and the study did not show non-inferiority.

Studies by Deng et al,[8] and Goldvaser et al,[9] showed that 12 months of adjuvant Trastuzumab was superior to 6 months of therapy but at the cost of increased cardiotoxicity. A cost-effectiveness analysis by Clarke et al,[10] showed that a shorter duration of Trastuzumab therapy is patient-friendly, cost-wise, and clinically effective. The recent addition of generic versions of Trastuzumab drug may decrease the economic burden of the patients, without affecting drug efficacy,

The limitations of the present study were as follows: it was conducted in patients diagnosed at various time points spread over many years and the retrospective nature of the study.

CONCLUSION

Adjuvant Trastuzumab is beneficial for non-metastatic breast cancer patients. The duration of adjuvant-targeted therapy with Trastuzumab does not affect survival outcomes after primary therapies such as surgery, chemotherapy, and radiotherapy. Further randomised controlled prospective trials in the Indian population are needed to investigate whether 6 months of Trastuzumab is non-inferior to the current standard of 12 months of therapy.

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