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Breast Cancer

Efficacy and Safety Profile of Different Schedules of Adjuvant Trastuzumab Therapy among Patients with HER2-Positive Breast Cancer: Real-World Experience from a Tertiary Cancer Center in South India

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Abstract

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One year of adjuvant trastuzumab is the standard of care for HER2-positive breast cancer. In low–middle income countries, delivery of 1-year trastuzumab is challenging due to significant financial burden. Evidence for shorter durations of adjuvant trastuzumab is gaining popularity in this regard. In this study, we compared the effectiveness and safety of 1 year versus shorter durations of adjuvant trastuzumab practiced in our center. In total, 312 patients were included in this analysis. The median age was 52 years. More than two-thirds of patients (67.6%) had stage 2 disease and majority were hormone-receptor-positive (62.5%). The median follow-up duration was 50 months. The 4-year disease-free survival was 97.3%. The 4-year disease-free survival for shorter durations of adjuvant trastuzumab was 98% compared with 96.7% in 1-year trastuzumab therapy group. In univariate analysis, stage at diagnosis was the only factor which had statistically significant association with disease-free survival. In multivariate analysis, none of the variables were found to be predictive of survival. Two patients (0.6%) had significant left ventricular ejection fraction decline.

Shorter durations of adjuvant trastuzumab have comparable 4-year disease-free survival to standard 1-year therapy and is an alternative adjuvant treatment option for HER2-positive breast cancer patients in resource-limited settings.

Keywords

- HER2-positive breast cancer
- adjuvant trastuzumab
- shorter durations of adjuvant trastuzumab

Introduction

One year of adjuvant trastuzumab has been standard of care since its approval in 2006.[1] In India, only 8.6% of eligible patients could afford 1-year adjuvant/neoadjuvant trastuzumab after its approval. After the availability of biosimilars though, this proportion increased to 57%. Still 43% of eligible HER2-positive breast cancer patients could not afford 1-year therapy.[2,3] Meanwhile, evidence for shorter durations of adjuvant trastuzumab therapy, like 9-week FINHER regimen or 6-

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month PERSEPHONE protocol, gained much popularity. Although these individual trials had demonstrated noninferiority for shorter durations, the 2021 metanalysis by Earl et al concluded that 1 year of adjuvant trastuzumab is still the standard.[4–6] In India, a large proportion of patients complete their planned oncological treatment with financial assistance from Government health schemes.[7] So, a shorter duration of adjuvant trastuzumab with comparable benefit to 1-year therapy will help better utilization of our resources without burdening the health care system. A cost-effectiveness analysis study from Iran had favored 6-month duration of adjuvant trastuzumab.[8] Similarly in South Africa, national-level policy change has been done to give 6 months of trastuzumab for HER2-positive early breast cancer.[9] In this study, we audit the effectiveness and safety of shorter durations of adjuvant trastuzumab compared with 1-year therapy in patients with HER2-positive breast cancer treated in our center.

Materials and Methods

This was a retrospective study conducted in a referral tertiary oncology center in South India. The study was approved by the Institutional Review board (1616/IRB-SRC/13/08–07–2023/2). The study conformed to the Declaration of Helsinki. The objective of our study was to assess the effectiveness and safety of shorter durations of adjuvant trastuzumab compared with standard 1-year therapy. *All patients with HER2-positive breast cancer treated at our center between January 01, 2014 to December 31, 2021 who received at least one dose of adjuvant trastuzumab were included*. The details regarding patient demographics, diagnostic and staging work-up, treatment, follow-up, relapse, and observed toxicities were collected from the medical records. Those medical records with incomplete data were excluded. The following operational definitions were used:

- Disease-free survival (DFS) was calculated as the time period from the date of surgery to the date of recurrence or date of last follow-up.
- Overall survival (OS) was calculated as the time period from the date of diagnosis to the date of death or last follow-up.
- HER2-positive breast cancer was confirmed either by 3+ score in immunohistochemical testing OR 2+ score (equivocal) in immunohistochemical testing with positive FISH (fluorescence in situ hybridization) test.
- Standard 1-year schedule of trastuzumab: loading dose 8 mg/kg followed by 6 mg/kg every 3 weeks for 17 cycles.
- 6-month schedule trastuzumab: loading dose 8 mg/kg followed by 6 mg/kg every 3 weeks for 9 cycles.
- 9-week schedule trastuzumab: loading dose 4 mg /kg followed by 2 mg/kg weekly for 9 weeks.
- Shorter durations of adjuvant trastuzumab: either 9-week schedule or 6-month schedule as described above.

During their treatment period, all patients with HER2-positive breast cancer eligible for adjuvant trastuzumab therapy were counselled regarding the standard 1-year treatment option. If they could not afford this, then the 9-week treatment option was discussed. Once the evidence for 6-month adjuvant trastuzumab was published in 2019 by Earl et al, we started counselling the option of 6-month therapy. Adjuvant chemotherapy, radiation therapy, and endocrine therapy were given as per standard guidelines.

Statistical Methods

Since this was a retrospective study, sample size calculation was not done. Statistical analysis was done using the Statistical Package for the Social Sciences (SPSS) version 24 (IBM Corp., Armonk, New York, United States). Categorical variables were expressed in median, range, or percentage. Continuous variables were summarized using mean with standard deviation or median with range based on normality. Survival outcomes were calculated by the Kaplan–Meier method. A log-rank test was used to compare the survival outcomes between the three groups. Cox regression analysis was used for determining the association between variables and survival outcome. A p-value <0.05 was considered significant.

Results

Between 2017 and 2021, 710 patients (12%) had HER2-positive breast cancer. The consort diagram is given in ►Fig. 1. For the final analysis, 312 patients were eligible. Baseline characteristics are shown in ►Table 1. There were two cases of male breast cancer. Two-thirds ($n = 211$, 67.6%) had stage 2 breast cancer. More than half of the patients

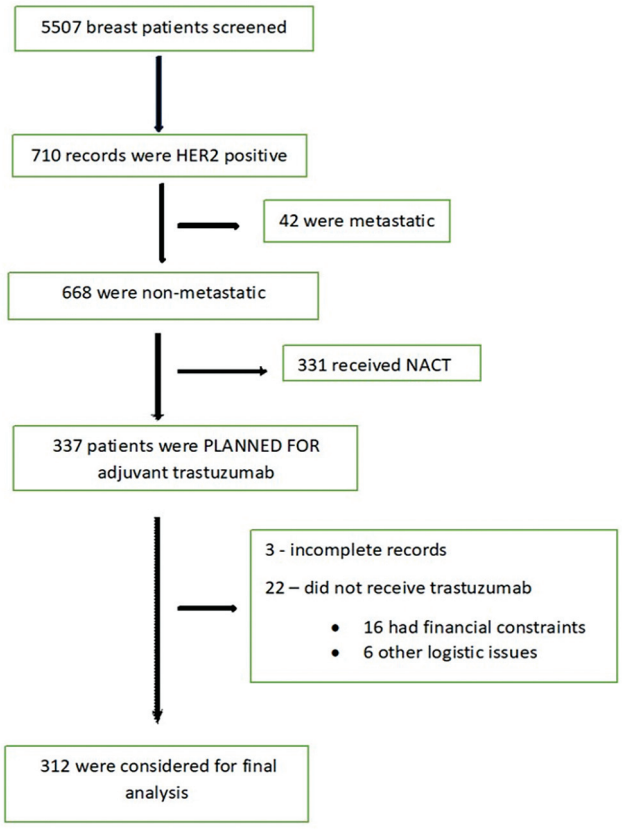

Fig. 1 Consort diagram.

Table 1 Baseline characteristics

Baseline variable	$N = 312$ (%)
Median age at diagnosis in years (range)	52 (29–75)
ECOG Performance Status	
1	309 (99%)
2	3 (0.009%)
Composite stage at diagnosis	
1	40 (12.8%)
2	211 (67.6%)
3	61 (19.5%)
Nodal involvement	
Node negative (N0)	169 (54.1%)
Node positive (N+)	143 (45.8%)
N1	83 (58%)
N2	42 (29.3%)
N3	18 (12.5%)
HER2 positivity confirmed by	
Immunohistochemistry (IHC)	289 (92.6%)
IHC equivocal with FISH positive	23 (7.3%)
Molecular subtype	
HER2 enriched	124 (39.7%)
Luminal B HER2 positive	188 (60.25%)
Surgical management	
Breast conservative surgery	75 (24.03%)
Mastectomy	237 (75.9%)
Axillary dissection	269 (86.2%)
Axillary sampling or SLNB	43 (13.7%)
Chemotherapy regimen used	
Anthracycline–Taxane combination	199 (63.7%)
Anthracycline-free regimens[a]	107 (34.2%)
Others[b]	5 (1.6%)
Not given	1 (0.3%)
Schedule of trastuzumab therapy	
1 year	73 (23.3%)
6 months	107 (34.2%)
9 weeks	130 (41.6%)
Others (less than 9 weeks)	2 (0.6%)
Completion rate of planned trastuzumab therapy	
Completed	282 (90.3%)
Not completed	30 (9.6%)
Reasons for trastuzumab discontinuation ($n = 30$)	
Financial constraints	16 (53.3%)
Cardiac toxicity	2 (6.6%)
Other logistics issues	12 (40%)

Abbreviation: FISH, fluorescence in situ hybridization.
[a]Include regimens like docetaxel/carboplatin, docetaxel/cyclophosphamide.
[b]Include regimens like 5-FU/epirubicin/cyclophosphamide, epirubicin/cyclophosphamide.

($n = 169$, 54.1%) had node-negative disease. Majority were hormone-receptor-positive ($n = 188$, 60.2%). Majority of our patients ($n = 237$, 75.9%) received shorter durations of adjuvant trastuzumab. Ninety percent of the patients ($n = 282$, 90.3%) completed the planned trastuzumab treatment. The most common reason for treatment discontinuation was financial constraints.

Survival Outcomes

The median duration of follow-up was 50 months. Median OS and median DFS were not reached. The 4-year OS was 100%. The 4-year DFS was 97.3%. The 4-year DFS of patients receiving 1-year, 6-month, and 9-week trastuzumab therapy are 96.7, 98, and 98.4%, respectively ($p = 0.6$). In patients with node-negative disease, the 4-year DFS was 100, 98.6, and 98.5% for 1-year, 6-month, and 9-week trastuzumab treatment groups, respectively ($p = 0.627$). For patients with node-positive disease, the 4-year DFS was 95.1, 96.4, and 98.2% for 1-year, 6-month, and 9-week trastuzumab treatment groups, respectively ($p = 0.871$). In univariate analysis, only stage at diagnosis was found to have statistically significant association with DFS (►Table 2). In multivariate analysis, none of the variables were found to be predictors of DFS.

Safety Outcomes

Two patients (0.64%) had significant left ventricular ejection fraction decline and required medical management. In both of them, further trastuzumab therapy was permanently discontinued. All other patients tolerated trastuzumab therapy very well.

Discussion

Majority of our patients received shorter durations of adjuvant trastuzumab and had comparable 4-year DFS to the standard 1-year therapy. Even in node-positive patients, shorter durations of adjuvant trastuzumab had acceptable 4-year DFS. Only two patients had significant left ventricular ejection fraction decline; all others tolerated trastuzumab therapy very well.

The overall 4-year DFS in our study was 97.3%. The 4-year DFS for shorter durations of adjuvant trastuzumab therapy was 98% compared with 96.7% for 1-year therapy ($p = 0.6$, 95% confidence interval: 122.832–127.305). Although the differences were not statistically significant, the 4-year DFS values are higher than other adjuvant trastuzumab studies in which 5-year DFS varied between 66 and 82%.[10–15] The presence of early stage disease and hormone-receptor-positive subtype in majority of the patients, along with our high treatment completion rate of 90%, might be the reason for better 4-year DFS in our study.[15] These results are also consistent with our previous publication in 2020 that reported 3-year DFS of 97.4% among patients who received 9 weeks of adjuvant trastuzumab.[16]

In our study, among node-positive patients, shorter durations of adjuvant trastuzumab delivered better 4-year DFS compared with standard 1-year therapy, though it was not

Table 2 Univariate analysis of known prognostic factors of breast cancer

Variables	4-year DFS (mo)	*p*-Value (confidence interval)
Age at diagnosis (less than 40 years vs. 40–60 years vs. more than 60 years)	100% vs. 97.3% vs. 96%	0.125
Composite stage (stage 1 vs. stage 2 vs. stage 3)	94.8% vs. 99.2% vs. 92.6%	0.003 (122.832–127.305)
Hormone receptor status (HR-positive vs. HR-negative)	96.5% vs. 98.3% vs.	0.175
Nodal involvement Node negative vs. node positive	98.8% vs. 95.8%	0.243
Duration of adjuvant trastuzumab therapy (1 year vs. 6 months vs. 9 weeks)	96.7% vs. 98% vs. 98.4%	0.600

Abbreviation: DFS, disease-free survival.

statistically significant. This included 26 patients with bulky nodal metastases (more than four positive lymph nodes) who had received 9-week adjuvant trastuzumab. This observation may suggest that the one-size-fits-all approach might not be appropriate even for all node-positive patients. There might be a subset of patients with favorable molecular characteristics among node-positive patients, who may not need standard 1-year trastuzumab therapy. But how to identify these patients needs further exploration in well-designed molecular studies.

The incidence of trastuzumab-induced cardiac dysfunction in our study was very low (0.64%). This is consistent with the existing literature and further emphasizes the fact that adjuvant trastuzumab therapy is safe.[17,18]

One of the major obstacles for delivering 1 year of trastuzumab therapy in our country is affordability.[19] In our study, 16 patients (4.7%) did not receive any trastuzumab therapy and around 9.6% patients could not complete the planned trastuzumab schedule. Financial constraints constituted the prime reason here. In our setting, cost of 1-year trastuzumab therapy is ~2.5 lakhs INR; for 6-month trastuzumab it is ~1.3 lakhs INR, and for 9-week trastuzumab therapy it is ~50,000 INR. The use of 9-week trastuzumab reduces the cost of treatment by ~60% for each patient. So, using shorter durations of trastuzumab therapy can reduce the burden on government health care financing schemes and facilitate wider delivery of these lifesaving medicines.

Limitations of the Study

Our study had a few limitations apart from its retrospective nature. Since majority of our patient population had early-stage and hormone-positive disease, the median follow-up duration of 50 months may be short for recurrence events. The confounding effects of adjuvant chemotherapy and hormonal therapy, both of which contribute to survival outcome, cannot be assessed due to the retrospective nature of our study.

Conclusion

Shorter durations of adjuvant trastuzumab had comparable 4-year DFS to standard 1 year therapy and can be considered as an effective and safe alternative adjuvant treatment option for HER2-positive breast cancer in resource-limited settings.

Author's Contribution

N.D.R, P.K.S, and M.A contributed to the project through conceptualization, data curation, formal analysis, investigation, methodology, and both the original draft and review & editing of the writing. A.M and S.S were involved in data curation, formal analysis, investigation, methodology, and writing the original draft, while S.S also participated in writing. B.T contributed by focusing on formal analysis, investigation, methodology, and both the original draft and review & editing of the writing.

Previous Presentation

Part of this study was presented as POSTER at the 21st Annual Conference of Women Cancer Initiative-Tata Memorial Centre at Mumbai on 01–03–2024.

Financial Disclosures

All the authors declare that none of them have any relevant or material financial interests that relate to the research described in this article.

Conflict of Interest

None declared.

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