

ORIGINAL ARTICLE

The short-term safety of adjuvant paclitaxel plus trastuzumab – A single centre experience

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Summary

Purpose: HER2-amplified breast cancer (BC) has a poor prognosis. The combination of trastuzumab with chemotherapy in the adjuvant setting decreases recurrence and improves overall survival in HER2-positive BC. However, the role of adjuvant treatment in patients with HER2-amplified small BC without lymph node involvement is still under debate. The purpose of this study was to investigate the safety of adjuvant paclitaxel and trastuzumab (APT) in this group of patients.

Methods: A total of 87 operated early BC patients without lymph node involvement (NO) were treated with APT for 12 weeks followed by trastuzumab alone for a total of 9 months. Clinicopathological features and adverse events were analyzed.

Results: The median patient age was 50 years (range 28-82), and 51% of them were postmenopausal. The median

tumor diameter was 2.4 cm (range 0.5-6), with 51% of the patients having tumor size between 2 and 3 cm. Eighty-one percent of patients had invasive ductal carcinoma (IDC), and 64% had grade 3 tumors. Adjuvant hormone therapy and adjuvant radiotherapy were administered to 65 and 54% of patients, respectively. At a median follow up of 13 months (range 6-38), one patient (1.1%, 95% CI 0-3.4) experienced an asymptomatic decrease in left ventricular ejection fraction (LVEF) and 3 patients (3.4%, 95% CI 0-6.9) experienced grade 3 neuropathy.

Conclusions: APT appears to be a safe combination in early-stage, HER2-amplified and node-negative BC.

Key words: breast cancer, HER2 positive, node negative, safety, trastuzumab

Introduction

HER2-amplified BC accounts for 20-25% of all cases and is accompanied with poorer prognosis leading to high risk for regional recurrence and distant metastasis [1]. So far, a study has shown that adjuvant trastuzumab improved disease-free survival (DFS) and overall survival (OS), independent of histological grade, hormone status, lymph node involvement, and age [2]. The combination of trastuzumab with chemotherapy improves outcome in these patients compared with chemotherapy alone [3].

Adjuvant trastuzumab following chemotherapy is accepted as the standard treatment in early

BC since 2006 due to its favorable impact on the clinical outcomes. The role of adjuvant treatment in patients with HER2-amplified small breast tumors without lymph node involvement has been debated. Patients with small, low grade, early HER2-amplified BC (particularly ER-positive tumors) have a relatively better prognosis, and hence, adjuvant therapy should be planned considering the risk/benefit ratio. Due to the risk of cardiotoxicity of anthracyclines, other chemotherapy regimens were administered in this group of patients. Favorable results with weekly paclitaxel and trastuzumab have been reported [4].

In the present study we evaluated the short-term safety of weekly APT in HER2-positive BC patients without lymph node involvement. This is a single center experience that may reflect features of the Turkish population.

Methods

This was a retrospective study of early BC patients followed at Hacettepe University Institute of Oncology between 2013 and 2016. Patients with histopathologically proven early HER2-positive BC without nodal involvement were enrolled. HER2 status was determined by immunohistochemical (IHC) staining. Tumors having a score of 3 (+) were considered as HER2-positive. Tumors scoring 2 (+) for HER2 expression were subsequently analyzed by fluorescence in situ hybridization (FISH) test and were considered as HER2-positive if HER2 amplification was present in FISH. Estrogen (ER) and progesterone receptors (PR) nuclear staining $\geq 1\%$ was accepted as ER and/or PR-positive by IHC evaluation according to the ASCO/CAP- guidelines [5].

A total of 87 patients were treated with APT combination at the following dose schedule: paclitaxel 80 mg/m² weekly for 12 weeks, and trastuzumab 2 mg/kg weekly for 11 weeks after a 4mg/kg loading dose. At the end of 12 weeks, trastuzumab was extended to one year at a dose of 6 mg/kg every 3 weeks. Demographic data, histopathological features, ER and PR status, type of surgery, adjuvant chemotherapy, radiotherapy, and recurrence were evaluated. BC staging was performed according to American Joint Committee on Cancer (AJCC) [6]. Cardiac function was assessed by transthoracic echocardiography (ECHO) prior to treatment and was repeated every 3 months during treatment. Primary cardiac endpoints were defined as follows: class III/IV heart failure (New York Heart Association/NYHA/Functional Classification/NYHA [7]) 10-15% decrease in LVEF, or LVEF<50%.

Statistics

All statistical analyses were performed using the Statistical Package for Social Sciences software, version 21.0 for Windows (SPSS, Inc., Chicago, ILL, USA). Fisher's and chi-square tests were used for nominal variables and numeric data analyses. A p value ≤ 0.05 was accepted as statistically significant in all analyses.

Results

The median age at diagnosis was 50 years (range 28-82) (Table 1). Among 87 patients, 51% were postmenopausal and 45% premenopausal. Eighty-one percent of the patients had IDC, and 64% had grade 3 tumors. Of the 87 patients, 48% had modified radical mastectomy (MRM), and

Table 1. Patient and disease features

Features	n	%
T stage		
T1a	2	2
T1b	1	1
T1c	22	25
T2 (2-3 cm)	44	51
T2 (3-4 cm)	11	13
T2 (4-5 cm)	3	3
T3	4	5
Age at diagnosis, years		
<40	14	16
40-49	28	32
50-59	27	31
60-69	13	15
>70	5	6
Menopause		
Premenopausal	37	45
Postmenopausal	44	51
Perimenopausal	4	4
Operation		
Simple mastectomy	3	3
Modified radical mastectomy	42	48
Breast-conserving surgery	41	47
Pathology		
Invasive ductal cancer (IDC)	71	81
Mix (IDC+ILC)	6	7
Invasive lobular cancer (ILC)	3	3
Invasive mucinous	2	2.2
Invasive micropapillary	2	2.2
Apocrine cancer	2	2.2
Metaplastic cancer	1	1.1
HER2		
IHC 3+	80	92
FISH	6	7
SISH	1	1
Grade		
1	2	2
2	29	33
3	56	64
Invasion status		
Lymphovascular invasion (LVI)	26	30
LVI+PNI	3	3
Perineural invasion (PNI)	3	3
Hormone status		
ER positive	54	62
PR positive	45	51
Hormone receptor		
Positive	57	65
Negative	30	35
Radiotherapy		
RT applied	47	54

47% breast-conserving surgery (BCS). The median tumor diameter was 2.4 cm (range 0.5-6), with 51% of the patients having tumor size between 2 and 3 cm, and 21% greater than 3cm.

ER and PR were positive in 62 and 51% of the patients, respectively. Adjuvant hormone therapy and adjuvant radiotherapy were given to 65 and 54% of the patients, respectively. At a median follow up time of 13 months (range 6-38), no toxicity-related death was noted. One patient (1.1%, 95% CI 0-3.4) developed distant metastasis in the liver after 10 months of treatment. One patient (1.1%, 95% CI 0-3.4) experienced an asymptomatic decrease in LVEF, and 13 (14.9%) patients experienced neuropathy, with 3 of them (3.4%, 95% CI 0-6.9) having grade 3 neuropathy. The treatment was stopped until LVEF recovered in the patients with decreased LVEF. Other adverse effects were as follows: hyperglycemia, diarrhea in one patient, nails changes in 3 patients, and allergic reaction in 3 patients (Table 2).

Table 2. Toxicity

Parameters	Grade 1-2	Grade 3	Total
	n	n	n
Neuropathy	10	3	13
Decrease in LVEF	1	-	1
Diarrhea	1	-	1
Hyperglycemia	1	-	1
Nail change	3	-	3
Denial toxicity	1	-	1

LVEF: left ventricular ejection fraction

Discussion

HER2 amplification is a poor prognostic factor with an increased risk of recurrence. Adjuvant treatment in small HER2-amplified BC without node involvement is still a therapeutic challenge. Before trastuzumab, results on adjuvant chemotherapy concerning whether the prognosis is better [8] or not [9-11] in this group of patients are conflicting. In patients with T1 stage, and HER2-overexpressing tumors, the clinical adverse factors are as follows: ER negativity, lymphovascular invasion, higher histological grade, younger than 50 years, and T1b tumors. Adjuvant trastuzumab based chemotherapy has improved outcomes for patients with HER2 overexpressing tumors [12]. The National Comprehensive Cancer Network (NCCN) guideline recommends trastuzumab in small, node-negative BC patients with T1b tumors.

Node-negative small BC patients with HER2 amplification were investigated in few studies, like Herceptin Adjuvant treatment (HERA), the Finland Herceptin (FINHER), North American trials-North Central Cancer Treatment Group (NCCTG) N9831, and Breast Cancer International Research Group (BCIRG 006). However, stage I patients comprised the minority of these study populations. BCIRG 006 included high-risk node-negative patients, and defined the high-risk with the following criteria: tumor >2 cm, age <35 years, HR negative, and tumor grade II-III [13]. Trastuzumab efficacy benefit observed with anthracycline and non anthracycline-containing regimens and in patients with low and high-risk disease [13]. Anthracycline-free regimens are associated with fewer critical adverse effects. In a study, non-hematological toxicities such as arthralgia, myalgia, stomatitis, hand-foot syndrome, vomiting, nail changes and neuropathies were significantly less in the TCH arm (docetaxel / carboplatin / trastuzumab) than in the AC-TH arm (doxorubicin plus cyclophosphamide [AC] / docetaxel / trastuzumab) [14]. In addition hematological toxicities such as neutropenia and leukopenia favored the TCH arm. In the HERA study, although 32% of the patients were node-negative, and 40% had tumor size 0-2 cm, only 6% of the patients received anthracycline-free chemotherapy protocols. The most common grade 3 or 4 adverse events were congestive heart failure, hypertension, arthralgia, back pain, hot flush, headache, and diarrhea, each seen in less than 1% of the patients [15].

NCCTG N9831, National Surgical Adjuvant Breast, and Bowel Project (NSABP) B-31 trials assessed the efficacy and safety of adding 52 weeks of trastuzumab to standard anthracycline/taxane-based chemotherapy (AC, followed by paclitaxel) [16].

A recent trial has assessed the effectiveness of Adjuvant Paclitaxel and Trastuzumab Trial (APT), and published favorable results. Tolaney et al. administered weekly adjuvant paclitaxel and trastuzumab in 406 node-negative patients with smaller than 3 cm tumor size, and HER2 overexpression [4]. Of the patients, 67% were hormone responsive, and 49% had tumor size smaller than 1 cm. Thirteen (3.2%) patients had grade 3 neuropathy, and 13 patients (3.2%, 95% CI 1.7-5.4) experienced asymptomatic decrease in LVEF, with 11 of them showing a recovery in ejection fraction. Two patients developed symptomatic heart failure. In our study, the rate of high-grade tumors was greater compared to the Tolaney et al. trial (64 vs 56%).

The rate of patients having tumor size of 2-3 cm was 51% in our study and 9% in the aforementioned study. Moreover, only one patient (1.1%) had asymptomatic decrease in LVEF in our study (1.1 vs 3.2%).

Trastuzumab-related cardiotoxicity is idiosyncratic and dose-independent. However, while cardiotoxicity is generally reversible, some cases persist. In a meta-analysis, decrease in LVEF and the risk of other cardiac events was reported to be 2.2-14% [17,18]. In the NSABP-B31 trial, the rate of cardiac events was 3.9% in the sequential anthracyclines and trastuzumab arm, and 1.5% in the anthracyclines without trastuzumab [19]. In the BCIRG 006 trial the rate of cardiac events was 2% in the sequential, 0.7% in anthracycline and trastuzumab combination and 0.4% in trastuzumab alone patients [13]. Recent data have shown that trastuzumab-based adjuvant protocols without anthracycline may be more cardiotoxic than anthracyclines-based protocols without trastuzumab.

A meta-analysis has revealed that cardiac event risk was higher (hazard ratio/HR, 3.96; 95% CI, 3.01 to 5.22) in the sequential anthracyclines and trastuzumab arm compared to the trastuzumab without anthracycline arm (HR, 1.76; 95% CI, 1.19 to 2.60) and patients receiving anthracyclines without trastuzumab arm (HR 0.97; 95% CI 0.73 to 1.27) [20]. In our study, lower rate of cardiotoxicity was observed.

In the present study evaluating 87 patients, we showed that APT was safe and well-tolerated in our patients. Limitations of the present study are the study design, low number of patients, and the short follow up period. However, we consider that our findings are substantial since they reflect a low rate of toxicity and a higher safety profile of APT in Turkish population.

Conflict of interests

The authors declare no conflict of interests.

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