Original Article

Efficacy of Trastuzumab in HER2-Positive Early Breast Cancer in Thai Patients: A Single Institution Experience

Pimchanok Patanayindee MD[1], Kamonwan Soonklang MSc[2], Teerapat Ungtrakul MD, MSc[1,3]

[1] Chulabhorn Hospital, HRH Princess Chulabhorn College of Medical Sciences, Chulabhorn Royal Academy, Bangkok, Thailand
[2] Data Management Unit, HRH Princess Chulabhorn College of Medical Science, Chulabhorn Royal Academy, Bangkok, Thailand
[3] Faculty of Medicine and Public Health, HRH Princess Chulabhorn College of Medical Sciences, Chulabhorn Royal Academy, Bangkok, Thailand

Objective: To evaluate the efficacy of 1-year adjuvant trastuzumab in Thai patients with HER2-positive early breast cancer. The primary objective was to determine disease-free survival [DFS] and overall survival [OS] during 1 and 2 years.

Materials and Methods: We retrospectively reviewed the medical records of patients with HER2-positive early breast cancer who received standard adjuvant chemotherapy with trastuzumab at Chulabhorn Hospital between January 2009 and September 2014.

Results: Data of 39 women were available for analysis. Median age was 55 (48 to 60) years. Twenty-seven patients (69.1%) had node-positive disease with median tumor size of 3.0 (0.7 to 12) cm 20 patients also had estrogen receptor-positive disease. Anthracycline-based chemotherapy and taxane were given to 34 and 13 patients, respectively. During median follow-up of 2 years, two patients with recurrence of breast cancer were observed. DFS rate at 1 and 2 years was 97.4% and 93.8%, respectively, whereas OS rate at 2 years was 100%. Unfortunately, congestive heart failure was identified in two patients, with complete recovery after stopping trastuzumab.

Conclusion: Addition of adjuvant trastuzumab in HER2-positive early breast cancer yields a substantial benefit in DFS and OS among the Thai population.

Keywords: HER2-positive early breast cancer, Trastuzumab, Adjuvant therapy, Overall survival

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Breast cancer remains the most common cancer among women in Thailand. Approximately 10 to 25% of breast cancer is caused by human epidermal growth factor 2 [HER2] overexpression[(1)], with particularly poor prognosis, resulting in high recurrence rate after primary therapy of early breast cancer.

Trastuzumab is a selective humanized monoclonal antibody targeting HER2-positive tumors. Several randomized controlled trials and meta-analyses[(2-4)] demonstrated that addition of trastuzumab for 1 year in combination with chemotherapy significantly improved disease-free survival [DFS] and overall survival [OS] among women with HER2-positive early breast cancer. Nonetheless, there are still controversial and limited data in Thailand. The only one study showed no benefits of adjuvant trastuzumab at 4.7 years follow-up in Thai patients[(5)]. Hence, we aimed to evaluate the efficacy of trastuzumab in Thai patients with HER2-positive early breast cancer.

Correspondence to:
Ungtrakul T, Faculty of Medicine and Public Health, HRH Princess Chulabhorn College of Medical Sciences, Chulabhorn Royal Academy, 54 Kamphaengphet 6 Road, Talat Bangkhen, Laksi, Bangkok 10210, Thailand.
Phone: +66-2-5766791, **Fax:** +66-2-5766791
E-mail: teerapat.ung@pccms.ac.th

Materials and Methods

We retrospectively reviewed medical records of 39 women with HER2-positive early breast cancer who received standard adjuvant chemotherapy with trastuzumab at Chulabhorn Hospital, Bangkok, Thailand

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between January 2009 and September 2014. HER2-positive status was identified according to the Joint Consensus Panel of the American Society of Clinical Oncology and the College of American Pathologists[6]. HER2-positive breast cancer is defined as tumor cells with uniform intense membrane staining for HER2 in ≥10% (immunohistochemical stain 3+) of cells or HER2/chromosome probe 17 fluorescence in situ hybridization amplification ratio ≥2.2. Those with a history of breast cancer, bilateral breastcancer, invasive secondary cancer, or treatment with other adjuvant HER2-targeted agents were excluded.

Clinical characteristics, treatment including chemotherapy, radiotherapy or hormonal treatment, and treatment outcome, were obtained from the medical records. DFS was defined from date of primary surgery to date of recurrence, death from any cause, or last follow-up. OS was defined from date of primary surgery to date of death from any cause or last follow-up. The primary objective was DFS and OS at 1 and 2 years.

To evaluate adverse events, especially cardiac dysfunction, all patients were initially screened and cardiac function was monitored at 3-monthly intervals for the duration of treatment. Decline in left ventricular ejection fraction and symptoms of congestive heart failure were also reported.

We used median and range for quantitative variables. DFS and OS at 1 and 2 years were calculated using the Kaplan-Meier method. All data were processed and analyzed by using Stata/SE version 12 software (Stata Corp LP, College Station, TX, USA). The study was approved by the Ethics Committee for Human Research, Chulabhorn Research Institute (EC No. 027/2559).

Results

Clinical characteristics

Thirty-nine women were diagnosed with HER2-positive early breast cancer between January 2009 and September 2014. The median age of the patients was 55 years (range, 48 to 60 years). Clinical characteristics are shown in Table 1. Of these, 27 patients (69.1%) had node-positive disease with median tumor size of 3.0 cm (range, 0.7 to 12 cm).

Pathological analysis revealed lymphovas cular invasion and poorly differentiated grade in 13 and 19 patients, respectively. Twenty patients (51.2%) also expressed estrogen receptor [ER] as well as positive progesterone receptor in 26 patients (66.6%).

Most of the patients received mastectomy as primary treatment. All patients with ER-positive breast cancer received adjuvant hormonal treatment with either tamoxifen or aromatase inhibitors. In addition, adjuvant radiotherapy was given to 24 patients. All patients received adjuvant chemotherapy, including anthracycline without taxane (21 patients, 53.8%), antracycline with taxane (13 patients, 33.3%), and other agents (5 patients, 12.9%). The median duration of trastuzumab treatment was 52 weeks (range, 12 to 58 weeks).

Efficacy

At the clinical cutoff date (September 4, 2016), median follow-up was 2 years. Two events were observed with brain metastasis and distant recurrence in lung. DFS rate at 1 and 2 years was 97.4% and 93.8%, respectively, whereas OS rate at 1 and 2 years

Table 1. Clinical characteristics of the patients

Characteristics	Number of patients (percent) (n = 39)
Age <50 year	5 (12.8)
Tumor size	
≤2 cm	7 (17.9)
>2 to 5 cm	24 (61.5)
> 5 cm	5 (12.8)
Unknown	3 (7.8)
No.of positive nodes	
0	11 (28.2)
1 to 3	12 (30.7)
4 to 10	11 (28.2)
>10	4 (10.2)
Unknown	1 (2.7)
Grade	
Well-moderately differentiated	16 (41.0)
Poorly differentiated	19 (48.7)
Unknown	4 (10.3)
Lymphovascular invasion	
Absent	15 (38.4)
Present	13 (33.3)
Unknown	11 (28.3)
Positive for estrogen receptor	20 (51.2)
Positive for progesterone receptor	26 (66.6)
Mastectomy	28 (71.7)
Adjuvant radiotherapy	24 (61.5)
Adjuvant hormonal therapy	20 (51.2)
Type of adjuvant chemotherapy	
Anthracycline, no taxane	21 (53.8)
Anthracycline and taxane	13 (33.3)
Other	5 (12.9)

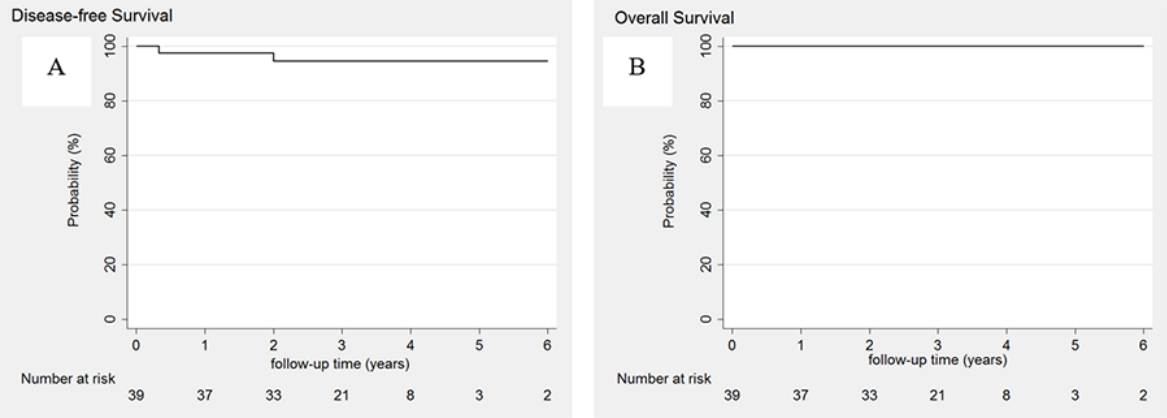

Figure 1. Kaplan-Meier Estimates of Disease Free Survival (Panel A) and Overall Survival (Panel B).

was 100%. Kaplan-Meier curves for DFS and OS are illustrated in Figure 1.

Safety

During treatment, two patients (5%) had congestive heart failure related to trastuzumab. They discontinued trastuzumab at 12 and 32 weeks, respectively, with complete recovery of cardiac function in both patients. Nevertheless, second primary tongue cancer was diagnosed in one patient and trastuzumab was thus discontinued.

Discussion

Our study demonstrated that the addition of trastuzumab for 1 year to adjuvant chemotherapy yields a favorable prognosis. The 2-year DFS was 93.8% and 2-year OS was 100%. This result is consistent with other previous clinical studies. A meta-analysis of eight clinical trials of chemotherapy plus trastuzumab versus chemotherapy alone in 12,000 patients showed significantly improved DFS hazard ratio [HR] for recurrence 0.60, 95% confidence interval [CI] 0.50 to 0.71 and OS (HR 0.66, 95% CI 0.57 to 0.77) regardless of trastuzumab treatment duration or administration schedule[4].

The clinical characteristics of our patients were not different from those in other studies. Most patients had node-positive disease with tumor size >2 cm. Patient characteristics and outcome from different trastuzumab adjuvant trials are shown in Table 2. Even though trastuzumab is recommended as adjuvant treatment in node-positive disease or high-risk node-negative disease (tumor size >2 cm and positive ER or tumor size >1 cm and negative ER), one patient with node-negative disease in our study received trastuzumab.

Several chemotherapy agents have been evaluated with trastuzumab in prospective studies. Anthracycline-based chemotherapy followed by taxane-based chemotherapy and trastuzumab is a preferred protocol, except in patients with a high risk for cardiotoxicity from anthracyclines. Docetaxel, carboplatin and trastuzumab are alternative agents in patients with pre-existing cardiac conditions, borderline cardiac function, or prior treatment with anthracylines.

Taxane-based chemotherapy was only used in one-third of our patients, and its use differed significantly among previous clinical trials. In the study by Piccart-Gebhart et al[7], taxane-based chemotherapy was used in 26% of patients, which was similar to our study. However, in another previous study in Thailand, there was no use of taxane-based chemotherapy[5].

Although previous studies had heterogeneous populations and different types of chemotherapy, DFS and OS were still similar. Our results for 2-year DFS and OS were similar to those of Piccart-Gebhartet et al[7] and Slamon et al[1]. Chitapanarux et al[5] demonstrated no benefit of adjuvant trastuzumab in Thai patients with early breast cancer, compared with those without adjuvant trastuzumab. Despite the imbalance in the number of patients in both groups, with only 14 cases receiving trastuzumab and 100 cases did not receive trastuzumab, the outcome of trastuzumab treatment was favorable. The 4-year DFS and OS in patients treated with trastuzumab was 92.3% and 100%, respectively. The results were consistent with other studies.

Although we demonstrated the benefit of

Table 2. Summary of patient's characteristics and outcome from different trastuzumab adjuvant trials

Characteristics	Current	Piccart-Gebhart MJ et al[7]	Romond et al[9]	EH Slamon D et al[1]	Chitapanarux I et al[5]
Median age (years)	55	49	50	49	NA
Tumor ≥2 cm (%)	74.3	48.5	59.6	59.0	78.5
ER positive (%)	51.2	54.5	52.2	54.0	35.0
Node positive (%)	69.1	68.0	94.3	71.0	64.0
Poorly differentiated grade (%)	48.7	60.0	69.0	NA	57.0
Endocrine therapy (%)	51.2	46.0	52.0	54.0	NA
Taxane based chemotherapy (%)	33.3	26.0	100	100	0
DFS rate (%)	93.8 (2-year)	85.8 (2-year)	87.1 (3-year)	93.0 (2-year)	92.3 (4-year)
OS rate (%)	100 (2-year)	96.0 (2-year)	91.4 (3-year)	99.0 (2-year)	100 (4-year)

NA = not available; ER = estrogen receptor; DFS = disease free survival; OS = overall survival

adjuvant trastuzumab in HER2-positive breast cancer, trastuzumab significantly increases the risk of congestive heart failure and decline in left ventricular ejection fraction.Previous studies have shown a 4-6-fold increase in the incidence of symptomatic myocardial dysfunction among patients receiving trastuzumab as a single agent or incombination therapy[4,8]. Approximately 2% of patients reported evidence of congestive heart failure.This adverse effect was higher in our study (5%).

There were a few limitations to our study, including small number of patients and short period of follow-up with a small number of events. These should be considered when interpreting the results. However, in other trials, one quarter of patients with HER2-positive early breast cancer had a high chance of recurrence at 2years if they did not receive trastuzumab[1].

Conclusion

Our study shows that adjuvant trastuzumab in patients with HER2-positive early breast cancer yields substantial benefit in DFS and OS among Thai women.

What is already known on this topic?

Most of HER2-positive early breast cancer patients had node-positive disease and tumor size more than 2 cm. The addition of one-year of adjuvant trastuzumab in HER2 positive early breast cancer demonstrated similar efficacy as western countries. Despite the benefit of adjuvant trastuzumab, cardiotoxicity needs to be monitored.

What this study adds?

This study confirmed benefit of addition of 1-year of adjuvant trastuzumab among HER2-positive early breast cancer in Thai patients.

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Potential conflicts of interest

The authors declare no conflict of interest.

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