

RESEARCH ARTICLE

Adjuvant Trastuzumab for 6 Months is Effective in Patients with HER2-positive Stage II or III Breast Cancer

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Abstract

Objective: The optimal duration of adjuvant trastuzumab treatment in patients with HER2-positive breast cancer is not known. The aim of this study was to evaluate the efficacy of 6 months of adjuvant trastuzumab treatment in patients with stage II or III HER2-positive breast cancer. **Methods:** The records of patients with HER2-positive stage II or III breast cancer who were admitted to the Breast Center of Taipei Medical University Hospital and Yuan's General Hospital between 2000 and 2008 were reviewed. All patients received adjuvant trastuzumab at an initial dose of 4 mg/kg followed by a maintenance dose of 2 mg/kg/week for 22 weeks in combination with chemotherapy. **Results:** A total of 51 patients were included with a mean age of 46.9 years. Approximately 55% of the patients had stage III disease. The mean follow-up time from initiation of treatment was 45.2 months (range, 0.9 to 85 months). During follow-up, 46 patients (90.2%) did not experience tumor recurrence. The mean estimated disease free survival was 80.2 months. The estimated 1-, 2-, 5-, and 7-year survival rates were 97.9%, 93.1%, 93.1%, and 93.1%, respectively. The most common adverse effects were gastrointestinal symptoms (21.6%), chills (17.6%), dizziness (9.8%), and bone pain (7.8%). No cardiac or hematologic adverse events occurred. **Conclusion:** Adjuvant therapy with trastuzumab for 6 months resulted in a clinical benefit in patients with HER2-positive breast cancer.

Keywords: Trastuzumab - breast cancer - HER-2 positive - clinical benefit

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Introduction

Amplification of human epidermal growth factor receptor 2 (HER-2) proto-oncogene is found in 20-30% of breast cancer, and is associated with reduced overall survival (Ross and Fletcher, 1998). Trastuzumab, a monoclonal antibody against the extracellular domain of HER-2, is currently the only approved adjuvant treatment specifically for patients with HER-2-positive early stage breast cancer although its mechanism of action is not completely understood (Arteaga et al., 2011). Studies have found that the combination of adjuvant trastuzumab and chemotherapy compared with chemotherapy alone results in significant improvement in overall survival (OS) and disease-free survival (DFS) and decreased rates of locoregional recurrence and distant recurrence (Piccart-Gebhart et al., 2005; Romond et al., 2005; Nahta and Esteva, 2007; Yin et al., 2011).

Although there is extensive clinical data on trastuzumab, the optimal duration of treatment is unknown (Arteaga et al., 2011). The standard treatment duration

with trastuzumab is 1 year, and several ongoing trials are evaluating the efficacy of 9 weeks or 6 months of trastuzumab treatment (Arteaga et al., 2011). In this study, we evaluated the efficacy of adjuvant trastuzumab for 6 months in patients with stage II or stage III breast cancer.

Materials and Methods

Patients and Methods

This was a retrospective study in which the medical records of patients with breast cancer who were admitted to the Taipei Medical University Hospital (Taipei, Taiwan) and Yuan's General Hospital (Kaohsiung, Taiwan) between October 1, 2000 and April 30, 2008 were reviewed. The study was approved by the Institutional Review Board of Taipei Medical University Hospital.

Study Patients and Design

Eligible patients were those who had HER2-positive (with a immunohistochemistry score of 3+, or if the score was 2+ also were positive for HER-2 by fluorescence

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Table 1. Patient Demographic and Clinical Characteristics (N = 51)

Mean age, y	46.9±11.1
Stage	
II	23 (45.1)
III	28 (54.9)
Mean tumor size, cm	3.20±1.82
Lymph node involvement	
0	23 (45.1)
1	8 (15.7)
2	4 (7.8)
3	5 (9.8)
≥ 4	11 (21.6)
Estrogen receptor	
Negative	31 (60.8)
Positive	20 (39.2)
Progesterone receptor	
Negative	38 (74.5)
Positive	13 (25.5)
Treatment	
CEF + docetaxel	27 (52.9)
CEF	22 (43.1)
Docetaxel	1 (2.0)
No chemotherapy	1 (2.0)
Mean follow-up, months	45.2 ± 25.0
Survival status	
Alive	48 (94.1%)
Dead	3 (5.9%)
Tumor recurrence	
Recurrence	5 (9.8%)
No recurrence	46 (90.2%)
Adverse events (≥ 1)	28 (54.9%)

Data are presented as mean ± standard or number (percentage). CEF, cyclophosphamide plus epirubicin plus fluorouracil

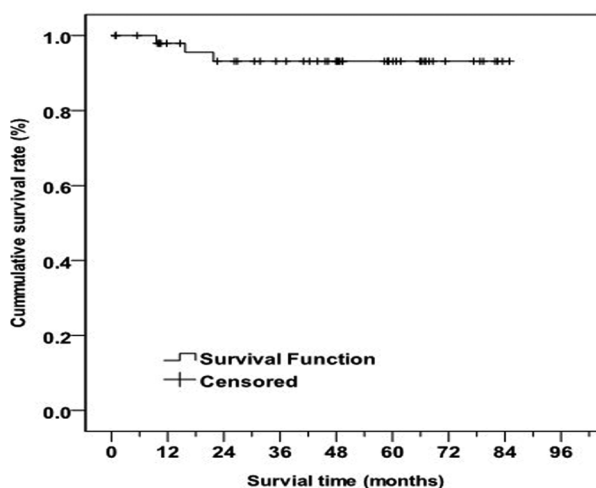
in situ hybridization) stage II or III breast cancer who received adjuvant trastuzumab. All patients received adjuvant trastuzumab at an initial dose of 4 mg/kg followed by a maintenance dose of 2 mg/kg/week for 22 weeks in combination with chemotherapy following curative resection. For patients with stage II cancer, the chemotherapy regimen was cyclophosphamide, epirubicin, and fluorouracil (CEF), and for stage III patients was CEF plus docetaxel. Patients with stage IIb breast cancer who were estrogen receptor (ER) or progesterone receptor (PR) positive, or whose lymph nodes were positive for metastasis, received CEF plus docetaxel. Patients with hormone-receptor positive disease received endocrine therapy administered according to standard guidelines. Recurrences were identified by standard imaging methods including chest radiographs, computed tomography (CT) scans, bone scans, and sonography. Patients were followed-up according to standard clinical practice guidelines and data was gathered until a patient died or the end of the study period. Efficacy was defined as absence of tumor recurrence.

Statistical analysis

Demographic and clinical characteristics were summarized as mean ± standard deviations (SD) with range (minimum to maximum) for age, tumor size, and follow-up duration; categorical values were summarized as number (percentage). A Kaplan-Meier analysis was

Table 2. Summary of Adverse Events

Any	28 (54.9)
Gastrointestinal symptoms	11 (21.6)
Nausea/vomiting	3 (5.9)
Diarrhea	3 (5.9)
Oral ulcer	2 (3.9)
Acid regurgitation	1 (2.0)
Gastritis	1 (2.0)
Gastric ulcer	1 (2.0)
Chills	9 (17.6)
Dizziness	5 (9.8)
Bone pain	4 (7.8)
Malaise	2 (3.9)
Headache	2 (3.9)
Chest tightness	2 (3.9)
Sweating	1 (2.0)
Rhinorrhea	1 (2.0)
Hot flush	1 (2.0)
Fever	1 (2.0)
Cough	1 (2.0)
Backache	1 (2.0)

**Figure 1. Kaplan-Meier Survival Analysis (N = 51)**

conducted to determine estimated survival rates. Statistical analyses were performed using SPSS 18.0 statistics software (SPSS Inc, Chicago, IL, USA).

Results

A total of 51 female patients with HER-2-positive breast cancer who received adjuvant trastuzumab were included in the study (Table 1). The mean age of the patients was 46.9 years, and more patients had stage III disease (54.9%). Twenty (39.2%) and 13 (25.5%) patients were ER and PR positive, respectively.

The mean follow-up time from initiation of treatment was 45.2 months (range, 0.9 to 85 months). During follow-up, 46 patients (90.2%) had no disease progression. The mean estimated disease free survival was 80.2 months (95% confidence interval [CI]: 75.1 to 85.4). The 1-, 2-, 5-, and 7-year estimated survival rates were 97.9%, 93.1%, 93.1%, and 93.1%, respectively (Figure 1). Three patients died during the study and all deaths were due to disease recurrence and progression; none were treatment-related.

Approximately half of the patients (54.9%) experienced adverse effects. The most common adverse effects were

gastrointestinal symptoms (21.6%), chills (17.6%), dizziness (9.8%), and bone pain (7.8%) (Table 2). No patient experienced a cardiac or hematologic adverse event.

Discussion

Trastuzumab is currently the only approved adjuvant therapy specifically for patients with HER-2 positive early stage breast cancer (Artega et al., 2011). In the adjuvant setting, the National Comprehensive Cancer Network (NCCN) in the United States and the Saint Gallen European guidelines recommend its use as monotherapy following the completion of chemotherapy, in combination with paclitaxel or docetaxel after completion of doxorubicin plus cyclophosphamide, or given concurrently with carboplatin and docetaxel (Goldhirsch et al., 2011; NCCN, 2012). These recommendations are based on the findings of 4 large randomized studies (Artega et al., 2011). Although, there is a large amount of clinical data available for this therapy, the optimal duration of trastuzumab treatment is still an open question (Artega et al., 2011). In this study, we found that adjuvant therapy with trastuzumab for 6 months resulted in clinical benefit as assessed by non-recurrence of disease, estimated survival, and minimal side effects.

Several ongoing studies are investigating the efficacy of adjuvant trastuzumab treatment for periods less than 1 year (Joensuu et al., 2006; Guarneri V, et al., 2008; Joensuu et al., 2009; Arteaga et al., 2011). Our findings are similar to those of the FinHer study which found that 9 weeks of trastuzumab given concurrently with chemotherapy improved the distant relapse-free survival rate as compared with chemotherapy alone (Joensuu et al., 2006; 2009). Patients who were HER-2 positive treated with trastuzumab for 9 weeks tended to have better distant DFS (defined as the time period from the date of study randomization to date of first cancer recurrence outside of the ipsilateral locoregional regions or to death if that occurred first) than those treated with chemotherapy alone (hazard ratio [HR] = 0.65; 95% CI 0.38 to 1.12; P=0.12) (Joensuu et al., 2009). Another ongoing study (Short-HER Trial [NCT00629278]) is also investigating the efficacy of 9 weeks of trastuzumab, and its primary endpoint is DFS (Artega et al., 2011). One limitation of the FinHer study, as well as the current study, is that findings were not compared with the standard 1-year duration of trastuzumab treatment.

In contrast to prior studies, this study found no evidence of hematologic or cardiac adverse events. A retrospective study of patients enrolled in 7 Phase II and III trastuzumab clinical trials found that trastuzumab was associated with an increased risk of cardiac dysfunction, which was greatest in patients who received concurrent anthracyclines (Seidman et al., 2002). In a Phase II study of women with HER2 expressing breast cancer (N=40), Sato et al. (2006) reported that treatment with trastuzumab and docetaxel for 6 cycles resulted in greater than half of the patients experiencing grade 3 or 4 leukopenia (88%) or neutropenia 83%, and 10% of patients developed a > 10% decrease in the left ventricular ejection from baseline.

The authors also reported an overall non-recurrence rate of 65% (95% CI, 48% to 79%), consistent with our results that suggest that a shorter course of adjunctive trastuzumab is clinically efficacious. In another Phase II study in which HER2 positive breast cancer patients (N=62) received docetaxel and cisplatin or carboplatin for 6 cycles and trastuzumab for 1 year, hematologic events were more common in patients who received carboplatin than in those who received cisplatin (Pegram et al., 2004). These findings may indicate that the increased hematologic and cardiac adverse events associated with trastuzumab may be at least in part dependent upon the chemotherapy administered.

Trastuzumab-related cardiac events may result from the fact that cardiomyocytes are constantly active, and require large amounts of ATP generated by mitochondria. Mitochondria produce reactive oxygen species (ROS) which have negative pleiotropic effects on the cells. Antioxidants normally scavenge the ROS; however, blocking HER2 signaling results in the inability of cardiomyocytes to cope with the excess ROS leading cardiac dysfunction (Zeglinski et al., 2011).

A shorter course of trastuzumab has the potential to reduce the costs of treatment associated with the drug. Our data suggest that it is possible to treat patients for only 6 months with trastuzumab without losing clinical benefit. In this study, the total cost of trastuzumab for each patient per therapeutic cycle was about \$390,000 New Taiwan Dollars (\$139,000 US dollars [USD]). This cost is based on a patient using 6 vials of trastuzumab (440 mg/vial) over 22 weeks. Even this shorter course of treatment is a large financial burden to patients in Taiwan where the gross domestic product (GDP) per capita is \$20,139 (USD). The idea of a shorter course of trastuzumab having a cost benefit is supported by a cost-effectiveness analysis of the FinHer study (Purmonen et al., 2011) which found that 9-week adjuvant trastuzumab therapy compared with standard treatment without trastuzumab in a cost-effectiveness ratio of €12,000 per quality adjusted life year and €9,300 per life year gained (Purmonen et al., 2011).

There are some limitations to this study that should be considered when interpreting the findings including no control treatment arm, small sample size, and the retrospective design. Also, this study did not evaluate whether the shorter treatment course resulted in decreases in overall medical costs.

In conclusion, we found that adjuvant therapy with trastuzumab for 6 months in patients with HER2-positive breast cancer resulted in clinical benefit as assessed by tumor recurrence and favorable tolerability. Further, larger scale randomized controlled studies are needed to confirm these results.

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