Real-World Outcomes of Different Treatments in the Management of Patients with HER-2 Positive Breast Cancer: A Retrospective Study

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Objective: *To investigate the treatment outcome in terms of relapse free survival and overall survival, and explore the determinants of the clinical outcome in HER-2/neu positive breast cancer patients who received or not received adjuvant trastuzumab.*
Material and Method: *The authors reviewed retrospectively of newly diagnosed non-metastatic breast cancer patients at the Faculty of Medicine, Chiang Mai University between January 2004 and December 2007. Comparisons were made between the two cohorts, women who did not receive adjuvant trastuzumab (100 patients) and women who received adjuvant trastuzumab (14 patients).*
Results: *The median follow-up time was 4.7 years. Four-year relapse-free survival (RFS) and overall survival (OS) in patients receiving trastuzumab was 92.3% and 100%, respectively. In the cohort of HER-2 positive patients who did not receive trastuzumab, the 4-year RFS in this group was 68.2% and 4-year OS was 87.8%. The difference was not statistically significant between the 4-year RFS rates (p = 0.103) and the 4-year OS rates (p = 0.214). By multivariate Cox regression analyses, only nodal status was identified as the independent predictors for superior RFS (hazard ratio 2.93; 95% CI, 1.07 to 5.88; p = 0.034) and none of the clinical parameters were significant predictors for 4-year overall survival.*
Conclusion: *A hospital-based analysis of adjuvant Trastuzumab use in our center does not demonstrate the different treatment outcome. However, there is a trend of favorable outcome in the group receiving adjuvant trastuzumab.*

Keywords: *Breast cancer, Adjuvant trastuzumab, Retrospective study*

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Breast cancer is the most common malignant cancer among women in Thailand. In 2008, 12,566 new breast cancer were diagnosed in Thailand and 4,427 women died of breast cancer[1]. Human epidermal growth factor receptor 2 (HER2) protein overexpression occurs in about 10 to 30% of all breast cancer and is known to be associated with an aggressive phenotype[2-4]. Determination of HER-2/neu status in breast cancer is becoming standard breast cancer clinical practice in Thailand since 2002. Recent randomized controlled studies have shown that trastuzumab, an anti-HER2 monoclonal antibody, given as adjuvant chemotherapy significantly improves the disease-free survival (DFS) and overall survival in patients with HER2-positive primary breast cancer[5,6]. Trastuzumab was licensed for adjuvant therapy in breast cancer in Thailand in 2007. However, because of the scarce resources in Thailand's healthcare system and the high cost of this drug, trastuzumab can be reimbursed as an adjuvant treatment only in the patients who worked for the government. Because of this policy, a retrospective analysis of this patient population was performed in the Faculty of Medicine, Chiang Mai University, a large 1,400 beds hospital, and a tertiary care referral cancer center in Northern Thailand. The primary objective of the present study was to describe the treatment outcome (relapse free survival

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and overall survival), and to explore the determinants of the clinical outcome in HER-2/neu positive breast cancer patients who received or not received adjuvant trastuzumab.

Material and Method

Data was collected for all breast cancer patients newly diagnosed at the Faculty of Medicine, Chiang Mai University between January 2004 and December 2007. The study was approved by medical ethics committee. The inclusion criteria were HER-2/neu positive invasive breast cancers diagnosed by an immunohistochemical (IHC) test, which was the standard clinical practice in Chiang Mai Hospital, stage I-III, and received the treatments in Chiang Mai Hospital. The exclusion criteria were DCIS disease, recurrent disease, or metastatic breast cancer at diagnosis. Patients who were performed only biopsy in Chiang Mai Hospital but received the treatment in other hospitals were excluded. Demographic information, tumor characteristics, and outcomes on all identified patients were obtained from the hospital medical records. Comparisons were made between the two cohorts, women who did not receive adjuvant trastuzumab and women who received adjuvant trastuzumab. Relapse free survival (RFS) was calculated from the date of primary surgery to the date of documented recurrence. The overall survival (OS) was calculated from the date of primary surgery to the date of death. All the known prognostic factors including age, tumor size, hormonal receptor status, and nodal status were analyzed by a Cox regression model for four-year RFS and four-year OS. Univariate analysis and multivariate analysis was carried out using Cox's proportional hazard model. All variables with a p-value <0.20 in univariate analysis were included into a multivariate analysis. All p-values were two-sided, and p-values <0.05 were considered to be statistically significant. Four-year RFS and four-year OS were estimated using the Kaplan-Meier method. The difference in survival rates was determined using the Log-Rank test. All statistics were calculated using STATA.

Results

Between January 2004 and December 2007, 1,014 patients with newly diagnosed breast cancer had tissue biopsy at Chiang Mai Hospital. One hundred forty seven patients had HER-2/neu positive (14.5%). Fifteen patients were stage IV at diagnosis, 13 patients were referred to receive treatments in other hospitals, and five patients were ductal carcinoma in situ (DCIS) disease. This left 114 patients who met the study inclusion criteria and were included in this analysis. Only 14 of this group of patients (12.3%) received adjuvant Trastuzumab. The characteristics of the patients are presented in Table 1. There was no significant difference in the distribution of histopathology, tumor size, nodal status, menopausal status, hormonal status, and adjuvant chemotherapy regimen between groups, except the patients who received adjuvant trastuzumab were more likely to receive postmastectomy radiotherapy (p = 0.019). All of them also underwent adjuvant chemotherapy. The majority of patients received Trastuzumab concurrent with chemotherapy (71%) versus sequentially (29%). Eighty six percent (89/100) of patients who did not receive adjuvant trastuzumab underwent adjuvant chemotherapy. The other 11 patients received only hormonal treatment and all of them had negative nodal status. The median follow-up time for both cohorts was 4.7 years (range 0.1-8.4 years). At the time of analysis, June 2012, the median follow-up time for patients who did not receive adjuvant trastuzumab was 4.57 years (range 0.07-8.4 years). Among these patients, there were four loco-regional recurrences (4%, 4/100), 24 distant recurrences (24%, 24/100), and six with both lo-regional and distant recurrences (6%, 6/100). Twelve patients in this group died from breast cancer. Whereas, the median follow-up time for patients who received adjuvant trastuzumab was 4.14 years (range 1.82-6.4 years), only one patient in this group had disease recurrence, and the site of failure was lung metastasis. All 14 patients who received adjuvant trastuzumab were still alive at the time of analysis. Four-year relapse-free survival (RFS) in patients receiving trastuzumab was 92.3% (95% CI, 56.6-98.9) and 4-year overall survival (OS) was 100%. In the cohort of HER-2 positive patients who did not receive trastuzumab, 4-year relapse-free survival (RFS) in this group was 68.2% (95% CI, 57.5-76.8 (Fig. 1) and 4-year overall survival (OS) was 87.8% (95% CI, 78.4-93.3) (Fig. 2). However, the difference was not statistically significant in the 4-year RFS rates (p-value = 0.103) and 4-year OS rates (p-value = 0.214) in the Kaplan- Meier curve between two groups of patients. Clinical parameters, tumor grade, tumor size, menopausal status, estrogen receptor, progesterone receptor, adjuvant radiotherapy, and chemotherapy regimen were not significantly associated with 4-year relapse-free survival, as determined by univariate analysis (Table 2). By multivariate Cox

Table 1. Characteristics of patients

Variables	No adjuvant trastuzumab (%) (n = 100)	Adjuvant trastuzumab (%) (n = 14)
Histopathologic grade of tumor		(p = 0.732)*
Well differentiated	4 (4.00)	-
Moderately differentiated	46 (46.00)	5 (35.71)
Pooly differentiatied	39 (39.00)	8 (57.14)
Not assessed	11 (11.00)	1 (7.14)
Pathological tumor size		(p = 0.124)*
<1 cm	1 (1.00)	1 (7.14)
1-1.9 cm	7 (7.00)	2 (14.29)
2-3 cm	28 (28.00)	2 (14.29)
>3 cm	46 (46.00)	9 (64.29)
Not assessed	16 (16.00)	-
Not palpable	2 (2.00)	-
Nodal status		(p = 0.210)*
Negative	46 (46.00)	4 (28.57)
Positive	40 (40.00)	9 (64.29)
Not assessed	14 (14.00)	1 (7.14)
Menopausal status		(p = 0.737)*
Premenopausal	43 (43.00)	7 (50.00)
Postmenopausal	51 (51.00)	6 (42.86)
Uncertain	6 (6.00)	1 (7.14)
Estrogen receptor		(p = 1.000)*
ER negative	63 (63.00)	9 (64.29)
ER positive	37 (37.00)	5 (35.71)
Progesterone receptor		(p = 0.622)*
PgR negative	64 (64.00)	8 (57.14)
PgR positive	35 (35.00)	6 (42.86)
Not assessed	1 (1.00)	-
Radiotherapy		(p = 0.019)*
No	50 (50.00)	2 (14.29)
Yes	50 (50.00)	12 (85.71)
Chemotherapy		(p = 0.345)*
No	11 (11.00)	-
Yes	89 (89.00)	14 (100)
Regimen		(p = 0.542)*
A	53 (53.00)	6 (42.86)
A/T based	1 (1.00)	-
Not AT based	32 (32.00)	7 (50.00)
No	14 (14.00)	1 (7.14)

* Fisher's exact test

ER = estrogen receptor; PgR = progesterone receptor; A = anthracycline; T = taxane

regression analyses as shown in Table 2, only positive nodal status was identified as the independent predictors for superior RFS (hazard ratio [HR], 2.93; 95% CI, 1.25-6.90; p = 0.014). When focused to 4-year overall survival, as determined by univariate and multivariate analysis, none of the clinical parameters were significant predictors for 4-year overall survival (Table 3).

Discussion

The role of adjuvant trastuzumab in addition to chemotherapy for patients with HER2 positive tumors has now been clearly established by large appropriately powered studies[5-8]. It is being considered as standard of care in many countries. The results of the meta-analysis of adjuvant trastuzumab[9] indicate that the addition of this drug to anthracycline and

Table 2. Univariate and multivariate analysis of the four-year relapse-free survival rate

Variables	% recurrence (n/N)	Univariate analysis			Multivariate analysis		
		Hazard ratio: HR	95% CI for HR	p-value	Hazard ratio: HR	95% CI for HR	p-value
Tumor grade							
WD & MD	25.45 (14/55)	1					
PD	23.40 (1/47)	0.87	0.39-1.91	0.725	-	-	-
Tumor size (cm)							
≤3	24.39 (10/41)	1					
>3	27.27 (15/55)	1.18	0.53-2.64	0.678	-	-	-
Nodal status							
Negative	16.00 (8/50)	1			1		
Positive	32.65 (16/49)	2.51	1.07-5.88	0.034	2.93	1.25-6.90	0.014
Menopausal status							
Premenopausal	28.00 (14/50)	1					
Postmenopausal	22.81 (13/57)	0.89	0.42-1.89	0.762			
Uncertain	42.86 (3/7)	1.61	0.46-5.62	0.453	-	-	-
ER status							
Negative	26.39 (19/72)	1					
Positive	26.19 (11/42)	0.98	0.47-2.06	0.955	-	-	-
PgR status							
Negative	29.17 (21/72)	1					
Positive	21.95 (9/41)	0.71	0.33-1.55	0.391	-	-	-
Radiotherapy							
No	25.00 (13/52)	1					
Yes	27.42 (17/62)	1.17	0.57-2.40	0.675	-	-	-
Chemotherapy							
No	18.18 (2/11)	1					
Yes	27.18 (28/103)	1.54	0.37-6.47	0.555	-	-	-
Regimen							
A or A&T	26.67 (16/60)	1					
CMF	28.21 (11/39)	1.08	0.50-2.33	0.846	-	-	-
Trastuzumab							
No	29.00 (29/100)	1			1		
Yes	7.14 (1/14)	0.22	0.03-1.62	0.138	0.19	0.03-1.44	0.108

WD = well differentiated; MD = moderate differentiated; PD = poor differentiated; ER = estrogen receptor; PgR = progesterone receptor; A = anthracycline; T = taxane; CMF = cyclophosphamide, methotrexate, 5-FU

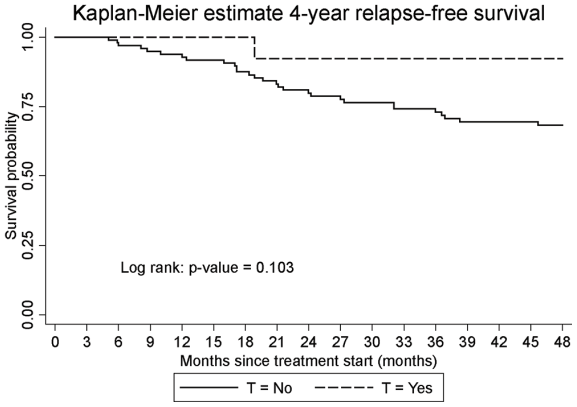

Fig. 1 Four-year relapse free survival by adjuvant Trastuzumab.

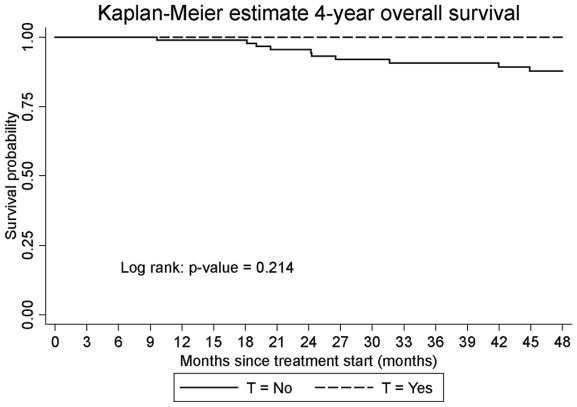

Fig. 2 Four-year overall survival by adjuvant Trastuzumab.

Table 3. Univariate and multivariate analysis of the four-year overall survival rate

Variables	% death (n/N)	Univariate analysis			Multivariate analysis		
		Hazard ratio: HR	95% CI for HR	p-value	Hazard ratio: HR	95% CI for HR	p-value
Tumor grade							
WD & MD	34.55 (19/55)	1					
PD	40.43 (19/47)	1.20	0.63-2.26	0.580	-	-	-
Tumor size (cm)							
≤3	39.02 (16/41)	1					
>3	43.64 (24/55)	1.16	0.61-2.18	0.654	-	-	-
Nodal status							
Negative	34.00 (17/50)	1			1		
Positive	44.90 (22/49)	1.57	0.83-2.95	0.166	1.70	0.90-3.22	0.103
Menopausal status							
Premenopausal	44.00 (22/50)	1					
Postmenopausal	35.09 (20/57)	0.81	0.44-1.49	0.496			
Uncertain	57.14 (4/7)	1.38	0.48-4.02	0.550	-	-	-
ER status							
Negative	40.28 (29/72)	1					
Positive	40.48 (17/42)	1.04	0.57-1.89	0.906	-	-	-
PgR status							
Negative	40.28 (29/72)	1					
Positive	41.46 (17/41)	1.05	0.58-1.92	0.865	-	-	-
Radiotherapy							
No	42.31 (22/52)	1					
Yes	38.71 (24/62)	0.98	0.55-1.75	0.943	-	-	-
Chemotherapy							
No	45.45 (5/11)	1					
Yes	39.81 (41/103)	0.83	0.33-2.09	0.689	-	-	-
Regimen							
A or A&T	61.54 (24/60)	1					
CMF	38.46 (15/39)	0.97	0.51-1.86	0.934	-	-	-
Trastuzumab							
No	43.00 (43/100)	1			1		
Yes	21.43 (3/14)	0.42	0.13-1.34	0.143	0.41	0.13-1.35	0.144

WD = well differentiated, MD = moderate differentiated, PD = poor differentiated, ER = estrogen receptor, PgR = progesterone receptor, A = anthracycline, T = taxane, CMF = cyclophosphamide, methotrexate, 5-FU

taxane-containing chemotherapy provides substantial benefit for women with HER2-positive breast cancer, in terms of disease recurrence and survival. In Thailand, having node-positive and being government officials (or retired officials) are standard criteria for patients to receive reimbursement for adjuvant trastuzumab treatment. Other node-positive patients who also meet the criteria, but carry only the standard gold medicare card, cannot receive reimbursement for adjuvant trastuzumab. This card, under the Thai national healthcare policy, allows all Thais, except for those already covered under other government benefits, to receive only basic medical protection. Most Thais fall under this category. The most common reasons for not receiving this drug in the present study were national universal coverage cases. The presented data demonstrate that the relapse free survival rate that has been observed in HER2-positive breast cancer was higher with the adjuvant trastuzumab group (92.3% versus 68.2%). However, this did not reach the statistically significant difference. Kiess et al[10] reported the benefit of adjuvant trastuzumab that reduced markedly of loco-regional failure rates. This study included women who received breast-conservation therapy for lymph node negative, HER2 positive breast cancer. The 3-year loco-regional recurrence free survival rate was 90% (95% CI, 83%-97%) for the non-trastuzumab cohort and 99% (95% CI, 97%-100%) for the trastuzumab cohort. Our patients had more aggressive tumor characteristics

than their study. Almost half of our patients were node positive. However, their results are consistent with our current study and suggest that the impact of adjuvant trastuzumab is not confined to only distant metastasis but also to loco-regional relapse. The limitation of our study was the imbalance number of patients between the two cohorts. The statistical analysis of all the treatment outcomes was limited by a low number of events in trastuzumab group.

Conclusion

A hospital-based analysis of adjuvant Trastuzumab use in our center does not demonstrate the different outcome at the 4.7-year follow-up period. However, there is a trend of favorable outcome in the group receiving adjuvant trastuzumab. Although retrospective in nature, this is one of the first studies in our country to observe breast cancer outcomes in a more generalized population with the use of trastuzumab being limited by public funding.

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Potential conflicts of interest

None.

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การศึกษาแบบย้อนหลังถึงการรักษาที่แตกต่างกันในผู้ป่วยมะเร็งเต้านมที่มี HER-2 positive

อิ่มใจ ชิตาพนารักษ์, ห้องสิน ตระกูลทิวากร, ทรงพล ศรีสุโข, อารีวรรณ สมหวังประเสริฐ, กีรติ วัชราชันย์, จิรวัฒนา ศรีกาวิน, เบญจพร ไชยวรรณ, ภัทรินี ไตรสถิตย์

วัตถุประสงค์: *เพื่อศึกษาผลของการรักษาในแง่ของอัตราการรอดชีวิตโดยปราศจาก การกลับเป็นซ้ำและอัตราการรอดชีวิตโดยรวม และประเมินหาปัจจัยที่กำหนดผลการรักษาในผู้ป่วยมะเร็งเต้านมที่มี HER-2/neu positive ที่ได้รับและไม่ได้รับยาเสริม trastuzumab*

วัสดุและวิธีการ: *ทำการศึกษาย้อนหลังในผู้ป่วยมะเร็งเต้านมในระยะที่ไม่แพร่กระจายที่มารับการรักษาที่คณะแพทยศาสตร์ มหาวิทยาลัยเชียงใหม่ ในระหว่างเดือนมกราคม พ.ศ. 2547 จนถึง ธันวาคม พ.ศ. 2550 และทำการเปรียบเทียบผู้ป่วยสองกลุ่ม คือ กลุ่มที่ได้รับยาเสริม trastuzumab กับกลุ่มที่ไม่ได้รับยาเสริม trastuzumab*

ผลการศึกษา: *จากการติดตามผลไปที่ระยะเวลา 4.7 ปี พบว่าอัตราการรอดชีวิตโดยปราศจากการกลับเป็นซ้ำที่ 4 ปี และอัตราการรอดชีวิตที่ 4 ปี ในกลุ่มที่ได้รับยาเสริม trastuzumab มีค่า 92.3% และ 100% ตามลำดับ ในขณะที่กลุ่มที่ไม่ได้รับยาเสริม trastuzumab มีค่า 68.2% และ 87.8% ตามลำดับ อย่างไรก็ตามไม่พบความแตกต่างกันอย่างมีนัยสำคัญทางสถิติ ในระหว่างผู้ป่วยสองกลุ่มนี้ จากการใช้สถิติวิเคราะห์พหุตัวแปรพบว่ามีเพียงสถานะของต่อมน้ำเหลืองเท่านั้นที่มีผลต่ออัตราการรอดชีวิตโดยปราศจากการกลับเป็นซ้ำ และไม่พบตัวแปรใดมีผลต่ออัตราการรอดชีวิตโดยรวม*

สรุป: *การศึกษาย้อนหลังนี้ถึงแม้จะไม่มีความแตกต่างกันทางสถิติอย่างมีนัยสำคัญ แต่มีแนวโน้มถึงผลการรักษาที่ดีกว่าในผู้ป่วยมะเร็งเต้านมที่มี HER-2/neu positive และได้รับยาเสริม trastuzumab*