The Role of HER2 in Metastatic Breast Cancer Treated with a Combination of Taxanes and Cisplatin

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Background: A combination of taxanes and cisplatin have shown modest activity as second-line chemotherapy in breast cancer patients who have been exposed to anthracyclines. The purpose of this study was to retrospectively assess whether HER2 is associated with clinical sensitivity or with prognostic significance in breast cancer patient groups who had received chemotherapy with taxanes and cisplatin.

Methods: Patients were treated either with docetaxel 60 mg/m^2 or paclitaxel 175 mg/m^2 in combination with cisplatin 50 mg/m^2 every 3 weeks. The tumor specimens were checked for estrogen receptor (ER), progestrone receptor (PR), and HER2 status by immunohistochemical stain. Prognostic factors such as performance status, status of metastases, history of prior anthracycline response, and biomarkers such as ER and HER2 were analyzed.

Results: Ninety patients were eligible for HER2 assessment. Only eighty-five patients were eligible for response assessment. The overall response rate to chemotherapy with the taxanes/cisplatin regimen was 52%. In patients who were HER2-positive, the response rate was 62% and in HER2-negative patients, it was 46%, $p = 0.17$. Univariate analysis showed no prognostic factors were significant in predicting a response to chemotherapy. In addition, it appeared that there was no difference in time to progression and overall survival based on HER2 status.

Conclusions: Our results indicated that HER2 status is independent of a response to a taxanes/cisplatin combination and is also not a prognostic factor for survival.
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Key words: breast cancer, taxanes, cisplatin, HER2, chemotherapy

In metastatic breast cancer patients who have been exposed to anthracyclines, taxanes are the first choices when disease recurs or progresses. A number of taxane-based regimens have been reported in the therapy for metastatic breast cancer.[1-3] In one study, a regimen that included platinum had much less activity as a second-line chemotherapy than as a first-line drug.[4] However, there is an interest in combining platinum with taxanes for several reasons, based on the different mechanisms of action, lack of

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cross-resistance *in vitro*[5-7] and reported efficacy in certain solid tumors, such as non-small cell lung cancer.[8] Several phase I and II trials have investigated the combination of taxanes/platinum (cisplatin or carboplatin) in metastatic breast cancers with or without prior exposure to anthracyclines. In general, efficacy of this combination was significant with major response rates in advanced breast cancer patients in the 40-70% range.[9-11] Despite the improvement in response rate as a second-line therapy, about half of patients did not benefit from such a regimen with modest toxicity.

The HER2 gene encodes a transmembrane growth factor receptor that belongs to the epidermal growth factor receptor (EGFR) tyrosine kinase subfamily. Activation of this protein results in the phosphorylation of signal transduction, as well as, regulation of apoptosis via bcl-2.[12,13] The HER2 protein is overexpressed in approximately 30% of breast cancers. Overexpression of the HER2 gene plays a significant role in breast cancer pathogenesis, and the phenomenon is commonly regarded as a predictor of a poor prognosis in early breast cancer. HER2 overexpression has been linked to more sensitivity and/or resistance to hormone therapy and chemotherapeutic regimens, such as those using cyclophosphamide, methotrexate, and fluorouracil (CMF), than anthracycline-based chemotherapy.[14,15] Breast cancer patients with HER2-positive tumors seem to benefit from anthracycline-based adjuvant chemotherapy.[15] Recently, success in the development of a monoclonal antibody against HER2, trastuzumab, to treat HER2-positive breast cancer patients has highlighted the importance of HER2 in the management of breast cancer.[16,17] Nevertheless, the predictive value of taxane sensitivity is not yet clear.[16] Although controversies exist, data from some laboratory and clinical trials of trastuzumab indicate that HER2-positive status confers chemoresistance to certain chemotherapeutic agents such as paclitaxel. One of the molecular mechanisms of HER2 -mediated paclitaxel resistance is that overexpression of the HER2 receptor leads to deregulation of the G2/M cell cycle check-point that inhibits paclitaxel-induced apoptosis.[18] Yu has shown that trastuzumab can effectively sensitize HER2-positive breast cancer cells to paclitaxel by reversing the antiapoptotic function of HER2. In addition, HER2 exposure has been associated with resistance to cisplatin in a breast cancer cell line.[19] Preclinical data also suggested a synergistic effect of trastuzumab and cisplatin through trastuzumab-induced inhibition of the repair of cisplatin-induced DNA damage[20] and an association between HER2 signaling and cisplatin- related DNA repair.[21] Therefore, HER2 could be a potential predictive factor for the response to a taxanes/cisplatin combination. In some phase II clinical trials, the addition of trastuzumab to a combination of cisplatin and taxanes led to a good clinical response in patients with HER2-positive breast cancer.[22,23]

Another gene, excision repair cross complementing-group 1 (ERCC1), encodes nucleotide-excision repair (NER) endonuclease protein and offers resistance to platinum therapy in other cancers such as ovarian cancer, lung cancer and colorectal cancer.[24] Its relationship with cisplatin resistance in breast cancer[25] has not been proved and needs further study.

In our previous work, a phase II randomized trial was performed to compare paclitaxel versus docetaxel with cisplatin in 101 patients with failed anthracycline treatment[26] This study was conducted prior to the introduction of trastuzumab in this country. Thus, it provided us an opportunity to address the role of HER2 in patients with metastatic breast cancer (MBC). Therefore, we conducted this study to retrospectively assess whether HER2-positive status is associated with clinical sensitivity or with prognostic significance in this patient group.

METHODS

The study groups were patients with either a recurrent or metastatic breast cancer with measurable disease. They had failed at least one type of anthracycline treatment, either as adjuvant or palliative chemotherapy. Other eligibility criteria included an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2, age ≥ 18 years, and adequate hematological, hepatic and renal function. Patients were treated with either docetaxel (60 mg/m^2) or paclitaxel (175 mg/m^2) in combination with cisplatin (50 mg/m^2) every 3 weeks. In patients who had received anthracycline treatment in an adjuvant setting, taxane/cisplatin was the first-line chemotherapy for recurrent or metastatic disease, and in patients with failure of anthracycline treatment for recurrent or metastatic disease, taxane/cisplatin was the second

line chemotherapy for recurrent or metastatic disease. The study was approved by the Institutional Review Board of Chang Gung Memorial Hospital. The response evaluation was based on World Health Organization (WHO) criteria and was evaluated every 3 cycles. Partial and complete clinical responses were classified as responsive, while stable disease and progressive disease were classified as non-responsive. The tumor specimens were retrieved from archival paraffin block. Only primary breast tumors that had not been exposed to any chemotherapeutic agent were selected. Immunohistochemical (IHC) stains were performed on formalin fixed, paraffin embedded sections using standardized procedures using an autostainer (Ventana Medical System Inc., AZ, U.S.A.) for estrogen receptor (ER) and progesterone receptor (PR) (Novocastra 1:200), and HER2 oncoprotein (DAKO 1:1000). For interpretation of HER2 staining, a score of 3+ was given when more than 10% of the tumor cells showed a strong and complete membrane staining, while weak to moderate membrane staining was considered 2+. Weak and incomplete membrane staining was given a score of 1+. Only a score of 3+ was classified as positive, and HER2-negative status was defined as a score of 0, 1+, and 2+.

Prognostic factors, such as performance status, status of metastases (sites, number of metastases), history of prior anthracycline response, and biomarkers such as ER and HER2 status on IHC studies were analyzed. The differences in variables between HER2-positive and HER2-negative patients were analyzed with measures of ANOVA. Except for the age, which was analyzed by t-test, the associations between response and categorical variables were analyzed by chi-square or Fisher's exact test. The time to progression (TTP) was measured from the date of treatment to the date of progression. The survival time was calculated from the date of treatment to the date of death. Both TTP and survival curves were established by the Kaplan-Meier method. The differences in TTP and survival between HER2-positive patients and HER2-negative patients were analyzed by log-rank test. A p value of less than 0.05 was considered significant. All reported p values were two-sided. The statistical values in this study were analyzed using SPSS v12.0 software.

RESULTS

A total of 90 patients whose HER2 status was available were included for analysis. The patients were grouped into HER2-positive (with a score of 3+) and HER2-negative (with a score of 0, 1+, 2+) groups. Clinical data on the patients and tumors are summarized in Table 1. There were more HER2-negative patients in the metastatic setting with previous anthracycline treatment than in the adjuvant setting ($p = 0.039$).

Response to chemotherapy

All patients received either paclitaxel/cisplatin or docetaxel/cisplatin chemotherapy for MBC. Eighty-five patients were eligible for response assessment. Another five patients were not eligible because they had only bone metastases. The overall response rate was 52%. In HER2-positive patients, the response rate was 62% and in HER2-negative patients, it was 46%, $p = 0.17$. For patients whose anthracycline response could be assessed retrospectively, there was no difference in the response rate between HER2-positive and HER2-negative patients (42% vs. 41%, $p = 0.785$). Univariate analysis showed that performance status, lines of chemotherapy, visceral organ involvement, liver metastasis, ER status and taxane regimens were all not significant factors in predicting a response to chemotherapy (Table 2). We further looked at the two different taxane-based regimens. In 40 patients who were treated with docetaxel/cisplatin, 11/17 (64%) HER2-positive patients responded, while 14/23 (60%) HER2-negative patients responded, as well. For patients with paclitaxel/cisplatin, 7/12 (58%) HER2-positive patients, and 12/33 (36%) HER2-negative patient responded, $p = 0.3$.

Survival

As of this report, disease in all patients has recurred. All patients were included for survival analysis. For HER2-positive patients, the median TTP was 265 days (95% CI: 182 to 348 days), while for patients with negative HER2, the median TTP was 215 days (95% CI: 140 to 290 days), $p = 0.73$. The median overall survival for HER2-positive patients was 699 days (95% CI: 440 to 958 days), and for HER2-negative patients, 715 days (95% CI: 625-809, $p = 0.73$). In the docetaxel/cisplatin group,

Table 1. Patient and Tumor Data

Feature	HER2-positive (N = 30)	HER2-negative (N = 60)	*p* value
Age			
Mean	49.57	46.52	
Range	26-63	25-73	0.187
PS (ECOG)			
0	8 (26.7%)	9 (15.0%)	
1	20 (66.7%)	39 (65.0%)	
2	2 (6.6%)	12 (20.0%)	0.267
Previous anthracyclines			
Adjuvant	12 (40%)	11 (18.3%)	
Metastatic	18 (60%)	49 (81.7%)	0.039
Chemotherapy regimen			
Docetaxel	17 (56.7%)	25 (41.7%)	
Paclitaxel	13 (43.3%)	35 (58.3%)	0.19
No. of metastases			
1	8 (26.7%)	11 (18.3%)	
2	12 (40%)	31 (51.7%)	
3	9 (30%)	13 (21.7%)	
4	1 (3.3%)	5 (8.3%)	0.467
Site of metastases			
Liver (Yes)	11 (36.7%)	19 (31.7%)	
(No)	19 (63.3%)	41 (68.3%)	0.64
Lung (Yes)	16 (53.3%)	27 (45%)	
(No)	14 (46.7%)	33 (55%)	0.46
Lymph node (Yes)	14 (46.7%)	27 (45%)	
(No)	16 (53.3%)	33 (55%)	0.88
Bone (Yes)	16 (53.3%)	43 (71.7%)	
(No)	14 (46.7%)	17 (28.3%)	0.08
Chest wall/breast (Yes)	6 (20%)	15 (25%)	
(No)	24 (80%)	45 (75%)	0.60
Visceral organ involvement			
Yes	22 (73.3%)	41 (68.3%)	
No	8 (26.7%)	19 (31.7%)	0.62
Estrogen receptor			
Negative	24 (80%)	30 (50%)	
Positive	5 (16.7%)	29 (48.3%)	0.004
Missing	1 (3.3%)	1 (1.7%)	
Progesterone receptor			
Negative	22 (73.3%)	32 (53.3%)	
Positive	7 (23.4%)	26 (43.4%)	0.06
Missing	1 (3.3%)	2 (3.3%)	

Abbreviation: PS: performance status.

Table 2. Response Rate according to Patient and Tumor Characteristics

	Response rate	*p* value
Regimen		
Docetaxel/Cisplatin	62.5% (25/40)	0.083
Paclitaxel/Cisplatin	42.2% (19/45)	
Chemotherapy		
First-line	57.7% (15/26)	0.491
Second-line	49.2% (29/59)	
ECOG status		
0	54.9% (39/71)	0.246
1	35.7% (5/14)	
Visceral organ involvement		
Yes	58.3% (14/24)	0.479
No	49.2% (30/61)	
Liver involvement		
Yes	58.2% (32/55)	0.119
No	40.0% (12/30)	
Lung involvement		
Yes	50.0% (21/42)	0.829
No	53.5% (23/43)	
ER status		
Positive	52.8% (28/53)	0.477
Negative	48.4% (15/31)	
PR status		
Positive	56.0% (28/50)	0.641
Negative	45.5% (15/33)	
HER2		
Positive	60.7% (17/28)	0.260
Negative	47.4% (27/57)	

the median TTPs for HER2-negative and positive patients were 320 and 329 days, respectively .In the paclitaxel/cisplatin group, TTPs were 190 and 223 days, respectively. It appeared that there was no difference in TTP and survival according to HER2 status.

DISCUSSION

We performed this retrospective clinicopathological study of HER2 as a potential marker that might indicate clinical responsiveness to a second-line taxane/cisplatin chemotherapy regimen. Our study has shown HER2 expression is not related to

chemosensitivity to taxanes/cisplatin, time to disease progression or overall survival in MBC patients who have been treated with anthracyclines. Our study did not support pre-clinical findings that HER2 is associated with drug resistance to taxanes and cisplatin. This result further elucidates the discrepancy between bench and clinical studies. Additionally, HER2-positive status is associated with a higher number of negative steroid receptors when compared with HER2-negative patients with MBC. This phenomenon may result from a natural selection bias rather than the biological significance of HER2 in patients with metastatic breast cancer.

In addition, our study showed that there were more HER2-negative patients who received anthracycline treatment for metastasis than received it as adjuvant therapy. However, this result does not seem compatible with clinical data and it is due to selection bias. In the adjuvant group in our study, all patients had disease recurrence within one year after adjuvant therapy with anthracyclines, which means they were more likely to be refractory to adjuvant therapy in general adjuvant group treated with anthracycline. More samples are needed to confirm this.

Although there are several molecular markers with prognostic utility in breast cancer, few have been evaluated as predictors of response to treatment. The most paramount are ER and PR, which predict response to endocrine therapy. HER2 has accrued the most attention because several lines of clinical and pre-clinical evidence have suggested that HER2-positive status might be associated with poor prognosis, aggressive clinical courses and possible drug resistance.[14-16] However, a few clinical reports have found that HER2-positive status was not associated with responsiveness except for a study from Di Leo et al.[27] They compared 176 patients who were randomized to either docetaxel or doxorubicin chemotherapy. They found HER2-positive patients tended to respond to docetaxel more than doxorubicin, while HER2-negative patients had at least equal activity with doxorubicin and docetaxel. However, the results did not support the hypothesis that HER2-positive status is associated with poor response to taxane *in vitro* study. In fact, from our study, HER2-positive patients tended to respond to taxane/cisplatin more than HER2-negative patients, but this was not associated with statistical significance.

Van Poznak et al. studied 144 patients with metastatic breast cancer treated with single-agent paclitaxel using IHC methods to detect HER2. However, there was no significant association between HER2 status and response to paclitaxel.[28] Hamilton et al. analyzed 114 patients with metastatic breast cancer treated with anthracyclines and taxanes by IHC as well. Again, no association between HER2 expression and response to chemotherapy was noted.[29] Sjostrom et al.[30] also studied 131 patients with metastatic breast cancer and found HER2-positive tumors were not uniformly more sensitive to taxanes and claimed that HER2-positive status was not a predictive factor of response to taxane. In addition, Azambuja et al also reviewed a decade of research regarding the role of HER2 in taxane-based chemotherapy and concluded that the predictive value of HER2 in taxane-based chemotherapy has not been validated.[31]

Studying HER2 gene amplification by fluorescent *in situ* hybridization (FISH) was believed to be more clinically relevant than using IHC methods, and was used to evaluate the response to a combination of doxorubicin and paclitaxel in 49 patients with MBC in a prospective study.[27] Patients with HER2–amplified tumor specimens had a higher probability of achieving a complete response and a longer duration of response than patients whose tumor specimens lacked this amplification. However, the clinical relevance of the co-amplification of HER2 and the topoisomerase IIa (topo IIa) gene, which has been associated with sensitivity to anthracylines such as doxorubicin, should be emphasized.[32-34] The largest study that has ever been done was by Konecny et al.[35] They used FISH to study 297 patients treated either with paclitaxel/epirubicin or cyclophosphamide/epirubicin in a randomized trial. Patients with HER2-positive tumors had a significant response using the paclitaxel/epirubicin regimen. Among HER2-positive patients, using paclitaxel resulted in better disease free survival and overall survival. Their study echoed the previous study. However, the relationship of HER2 with topo IIa, rather than the influence of HER2 alone, could not be completely excluded. Whether HER2-positive status predicts a response to a taxane/anthracycline combination is an interesting area for further exploration.

To our knowledge, only one study published to date has assessed HER2 expression and response to single-agent taxane as primary therapy. Estevez et al. evaluated the predictive role of HER2 protein expression using IHC in 56 patients with AJCC Stage II and III breast carcinoma who received preoperative weekly docetaxel. They found that HER2-positive status was not predictive of response to therapy.[36] It is interesting to note that five of the six patients who achieved a partial clinical response had HER2-negative tumor specimens. Formenti et al.[37] studied a total of 36 patients with locally advanced breast cancer treated with paclitaxel and radiation. A pathological response in the mastectomy specimen was achieved in 12 of these 36 patients (33%). Only tumors with low HER2/neu gene expression were associated with a pathological response. They concluded that HER2 expression cannot yet be applied clinically as a predictive factor for response in advanced breast cancer.

In an adjuvant setting, Guarneri et al.[38] studied patients treated with high-dose chemotherapy and autologus stem cell support. Despite a high complete response rate, HER2-positive status was associated with a shorter median time to progression. However, this could just reflect the nature of HER2 patients rather than the correlation with chemosensitivity.

Our study had a confounding factor, since this regimen was a combination of taxanes and platinum. So, our results should be interpreted to mean there is no association between HER2-positive status and response to a taxane/cisplatin regimen, rather than a response to single taxanes. It is possible that the synergetic effect of this combination may overcome HER2 drug resistance. However, there is a lack of such evidence from laboratory study. Instead, HER2 has been linked with cisplatin resistance *in vitro*. Therefore, specifically, the results of our study should conclude that HER2 status is independent of the response to or prognosis of a cisplatin/taxanes combination in patients with MBC.

In conclusion, although HER2-positive status is a known prognostic factor in early breast cancer, it is not a predictive factor for response to chemotherapy with taxanes or a prognostic factor for patients with MBC. In light of current clinical data, HER2-positive status should be considered a predicting factor for trastuzumab therapy only.

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HER2 接受體陽性在接受 taxanes 及 cisplatin 合併化學治療的轉移性乳癌病人的作用

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背 景： 對於曾接受 anthracycline 治療的乳癌病人，合併 taxanes 及 cisplatin 的化學治療已被證實當作第二線化學治療時，有不錯的療效。本研究的目的在於回溯及評估此類病人，其 HER2 接受體陽性與其臨床治療反應或預後的關係。

方 法： 病人皆曾接受每三週一次 docetaxel 合併 cisplatin 或 paclitaxel 合併 cisplatin 的化學治療，其劑量爲 docetaxel (60 mg/m^2) 或 paclitaxel (175 mg/m^2) 及 cisplatin (50 mg/m^2)。而每位病人的腫瘤標本是採用免疫化學染色法，來分析賀爾蒙接受體 ER，PR 及 HER2 接受體的表現程度。同時也分析病人的一些預後因子與其 HER2 接受體表現程度的關係，例如活動能力，轉移程度，之前對 anthracycline 治療的反應，一些生物標記如賀爾蒙接受體 ER、HER2 接受體的表現程度。

結 果： 本次研究共 90 個曾接受此類化療的病人接受 HER2 接受體的評估，有 85 個可評估其化學治療反應，其中對化學治療反應良好佔有 52%。在 HER2 接受體陽性表現的病人中，其化學治療反應良好佔有 62%，HER2 接受體陰性表現的病人則有 46%，p 值是 0.17。單變項分析顯示其他預後因子，例如年齡、活動能力、做過幾線化學治療、內臟器官是否被侵犯、肝臟轉移、賀爾蒙接受體表現及使用 taxanes 的種類，與預測化學治療的反應無關。在 HER2 接受體陽性表現的病人中，其腫瘤自治療至惡化的時間中位數爲 265 天 (95% 信賴區間爲 182 至 348 天)，而 HER2 接受體陰性表現的病人，其腫瘤自治療至惡化的時間中位數爲 215 天 (95% 信賴區間爲 140 至 290 天)，p 值是 0.73。至於 HER2 接受體陽性表現的病人其存活期中位數爲 699 天 (95% 信賴區間爲 440 至 958 天)，HER2 接受體陰性表現的病人其存活期中位數爲 715 天 (95% 信賴區間爲 625 至 809 天)，p 值是 0.73。

結 論： 所以我們的研究結果顯示 HER2 接受體陽性與其 taxanes/cisplatin 合併治療的反應率無明顯相關，HER2 接受體的表現也不是存活期的預後因子。

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關鍵詞：乳癌，taxanes，cisplatin，HER2，化學治療

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