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Efficacy of weekly trastuzumab and paclitaxel in the treatment of women with HER-2/neu overexpressing metastatic breast cancer. The impact of taxane free interval on treatment outcomes

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Purpose. *Trastuzumab is known as an active agent in HER2/neu overexpressing metastatic breast cancer. In the prospective study we investigated efficacy, safety and toxicity of trastuzumab and paclitaxel in metastatic breast cancer progressing on previous therapy.*

Patients and methods. *We accrued 17 patients with histologically confirmed breast cancer, Karnofsky performance status at least 60 %, median age 50 (36-66), pretreated with at least two regimens. HER-2/neu expression was tested by HercepTest (r) (DAKO) in all 17 patients. Fifteen specimens were 3+ positive and 2 specimens 2+ positive. All patients except one were pretreated with taxanes. Taxane free interval (TFI) was defined as a time from last taxane administration until the beginning of the study for every enrolled patient. TFI longer than 1 year was found in 7 patients. TFI shorter than 1 year was observed in 9 patients. Trastuzumab was given 4 mg/kg i.v. as a loading dose followed by 2 mg/kg i.v. weekly. Paclitaxel was given 80 mg/m^2 i.v. weekly until disease progression or unacceptable toxicity. We assessed the response rate (RR), the time to progression (TTP), the survival (OS) and toxicity.*

Results. *In the intent to treat population we found objective response in 10 patients (59 %), including 2 complete responses (CR). In the subset with TFI > 1 year we observed response in 4 cases including 1 CR (RR 57 %). In TFI ≤ 1 year subgroup we observed response in 6 cases also with 1 CR (RR 67 %). TFI was not statistically significant for response ($p < 0,4349$). Median TTP is 6 month with 4 patients remaining progression free. Patients with TFI > 1 year tend to have longer TTP ($p = 0,0201$). Median OS has not been reached with 10 patients surviving. We administered 599 cycles including 473 cycles of trastuzumab and paclitaxel with no dose adjustment. One patient developed hypersensitivity reaction on the first trastuzumab infusion and was excluded from study. The most common toxicity was trastuzumab infusion related pyretic reaction observed in 6 patients. Dose limiting adverse effect which led to the treatment discontinuation was cardiotoxicity. Ejection fraction decline grade 2 occurred in 1 patient and grade 3 also in 1 patient. Six patients experienced grade 3 neuropathy. There were observed 1 episode of grade 4 neutropenia and grade 3 anemia. We noted 4 episodes of grade 3 infection without neutropenia. Grade 3 elevation of liver function tests occurred in 6 patients with no need of dose reduction. There were observed 1 episode of grade 3 hyperglycemia and 1 episode of grade 3 weight gain. Other grade 3 or 4 toxicity was not detected.*

Conclusions. *Trastuzumab and paclitaxel have shown activity and good tolerability in HER-2/neu overexpressing metastatic breast cancer patients. Tumor response in 10 responding taxanes pretreated patients was independent on TFI, but patients with longer TFI tend to be longer progression free.*

Key words: breast neoplasms – drug therapy; paclitaxel; treatment outcome; trastuzumab

Introduction

The HER-2/neu (c-erbB-2) oncogene encodes a 185 kD transmembrane protein with tyrosine kinase activity. This glycoprotein belongs to the family of epidermal growth factor receptors.[1,2] Overexpression of HER-2/neu was found in several solid tumors including breast cancer, lung cancer, prostate cancer, ovarian, gastric and pancreatic cancer.[3,4] In breast cancer overexpression of HER-2/neu has important biological consequences. In preclinical studies HER-2/neu was associated with higher tumorigenicity and metastatic potential.[5,6] HER-2/neu overexpression is considered as a negative prognostic factor in women with breast cancer and in several studies was confirmed the correlation with shorter disease free survival, overall survival and more aggressive tumors.[7,8] HER-2/neu receptor creates homodimers or heterodimers with other members of epidermal growth factor receptor family (EGFR, HER-3, HER-4) on the cell surface which leads to triggering a cascade of growth signals. Studies performed with viral ligands suggest that HER-2/neu evolved as ligandless receptor[9] or this ligand has not been identified so far. The most common and most potent association occurs between HER-2/neu and HER-3. Interestingly, HER-3 has no intrinsic tyrosine kinase activity and cannot respond to ligand binding unless associates with another receptor, such as HER-2, which provides the intracellular signaling.[10]

Some level of HER-2/neu overexpression is found in 25 %-30 % breast cancers with HER-2/neu gene amplification detected in 95 % of the specimens.[7, 11, 12] There are many possible ways to test for HER-2/neu overexpression in tumor cells. Immunohistochemistry measuring protein expression on the cell surface is widely practiced by pathologists around the world and is fast and relatively cheap. Fluorescence in situ hybridization (FISH) measuring gene amplification is easily reproducible but expensive and not widely available. In general, there is a good agreement between the testing strategies. However, there are cases of immunohistochemical "positive" tests with no evidence of gene amplification. There are conversely cases of genetic amplification without increased surface expression.[13] Currently used scoring system for immunohistochemistry has the scale from 0 to 3+. Results 0 and 1+ are understood as negative and 2+ and 3+ as positive.14 Nowadays, there is trend to find only 3+ results as positive because in this subgroup is a concordance with FISH over 75 %[15, 16].

In 2+ subgroup the level of agreement reaches only 24%-39% with significantly lower response rates when treated with monoclonal antibody directed against this protein.[15-17] The definition and standardization of optimal HER-2/neu assay is still in a process.

Using the specific humanized anti-HER-2/neu monoclonal antibody trastuzumab (Herceptin; Roche ®) we can block the activity of HER-2/neu protein and stimulate antibody dependent cellular cytotoxicity.[18] Trastuzumab demonstrated activity in clinical trials in women with HER-2/neu overexpressing metastatic breast cancer as a single agent achieving response rates ranged from 12 % to 27 %.[19-21] Clinical trials based on preclinical evidence of synergy with many chemotherapeutic agents have been conducted. Trastuzumab was combined with cisplatin,[22] or paclitaxel,[16] or vinorelbine[23] in phase II studies with higher response rates than expected for chemotherapy alone. The pivotal phase III trial compared trastuzumab + chemotherapy to chemotherapy alone (either doxorubicin, cyclophosphamide or paclitaxel). Data indicated that trastuzumab in combination with

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chemotherapy produced significantly increased time to progression, response rate and overall survival. Of particular note is that addition of trastuzumab to paclitaxel therapy more than doubled median time to progression and almost doubled the response rate.[24] Regimens with combination of chemotherapy and trastuzumab were generally well tolerated. Pyretic reaction following first trastuzumab infusion occurred in 40 % of patients. Some degree of cardiac dysfunction was observed in 27 % of patients treated with trastuzumab plus doxorubicin and cyclophosphamide which excluded this combination from further clinical use. In trastuzumab plus paclitaxel arm such events were observed in 12 % of patients and only in 2 % were serious.[24] However, trastuzumab plus paclitaxel seems to be a very potent combination, the vast majority of patients in our study were treated with another taxane, docetaxel, in the first or second line treatment. It needs to be clarified whether docetaxel pretreatment and time from the last docetaxel administration have any significant impact on treatment outcomes.

Patients and methods

Eligibility

Women with histologically confirmed metastatic breast cancer overexpressing HER-2/neu were eligible for the purpose of this study. Patients had to be from 18 to 75 years old, with performance status at least 60 % according to the Karnofsky scale. All patients signed written informed consent. Patients were pretreated with two or more regimens for metastatic disease. In case of early recurrence after adjuvant chemotherapy (less than 12 month) also patients pretreated only with one regimen for metastatic disease were eligible. All patients were previously treated with antracyclines (mainly in the adjuvant setting) and all except one with taxanes. Any hormonal treatment except LHRH analogs had to be discontinued before study entry. Laboratory criteria included absolute neutrophile count (ANC) > 1 000/ul, hemoglobin > 80 g/l, platelets > 100 000/ul, adequate hepatic and renal function. Left ventricular ejection fraction had to exceed 50 % with exclusion of patients with history of serious cardiac disease. Patients with clinically unstable metatastases to the brain were not allowed to enter the study. Patients were ineligible if they had a history of other malignancy (except carcinoma in situ of the cervix or nonmelanoma skin carcinoma). Women with childbearing potential had to use reliable contraception while on study and had a negative pregnancy test before entering the study. Baseline evaluation included a complete physical examination, history, complete blood count with differential and platelet count, chemistry, echocardiogram, lesion measurement as appropriate for disease assessment. Her-2/neu status was determined using rabbit 4D5 antihuman HER-2/neu polyclonal antibody (HercepTest).

Treatment

Trastuzumab was administered 4 mg/kg intravenously over 90 minutes as a loading dose with subsequent weekly doses 2 mg/kg over 30 minutes. Paclitaxel 80 mg/m^2 was administered intravenously over 60 minutes the day after trastuzumab loading dose and subsequently the same day after trastuzumab infusion. The treatment was delivered in the outpatient clinic of our department. Treatment was administered every week until disease progression or unacceptable toxicity. Paclitaxel could have been discontinued due to toxicity with further administration of trastuzumab alone until disease progression. Routine premedication before paclitaxel infusion consisted of 8 mg of dexamethasone intravenously (IV), 100 mg cimetidine or 20 mg famotidine IV and 1 mg clemastine IV. Pacli-

taxel was omitted or discontinued for hematologic toxicity (ANC < 1000/ul, platelets < 100000/ul), peripheral neuropathy grade 3 and higher.

Response and toxicity evaluation

Complete blood count was obtained every week and every other week when paclitaxel was discontinued. Serum biochemistry was repeated every four weeks. Echocardiography was performed at least every 16 weeks and at any other time if necessary. Toxicity was graded according to Common Toxicity Criteria National Cancer Institute Version 2.0.

The response was evaluated every three month. The same method as at baseline was used throughout the study. Complete response was defined as a complete disappearance of all signs of tumor confirmed after 4 weeks or later. A partial response was defined as a more than 50 % reduction in the sum of products. Progressive disease was defined as 25 % or bigger increase in the sum of products. All other cases were evaluated as a stable disease.

Immunohistochemical analyses

All specimens of either primary or metastatic tumor were tested for overexpression of HER-2/neu with polyclonal rabbit antihuman antibody (HercepTest DAKO®). We used widely accepted scale when score 3+ is strongly positive, score 2+ is moderately positive, score 1+ means weak positivity, and score 0 is negative. Only patients with 3+ and 2+ results were eligible for protocol. No FISH analyses were performed.

Statistical methods

The primary endpoint of this trial was the overall response to the regimen combining trastuzumab and paclitaxel. The time to progression (TTP) was defined as a time from study entry to progression. Overall survival (OS) was defined as a time from study entry to death. The median time to progression and median overall survival was estimated by the Kaplan-Meier method. TTP was censored in the following circumstances: patient was still receiving treatment without evidence of progression, patient died of unknown cause without evidence of clinical deterioration due to breast cancer and patient discontinued treatment for any reason without evidence of clinical deterioration due to breast cancer before discontinuation. The same criteria was applied for OS. All patients treated with metastatic breast cancer documented at study entry and treated were included in the efficacy intent-to-treat population. Safety analysis included all patients received at least one dose of study drug.

Results

Efficacy data

Between July 1999 and January 2001, 17 eligible patients were enrolled in our institution onto this study. The characteristics are listed in table 1. Only two patients had 2+ Herceptest, all other results were 3+. All patients except one were pretreated with taxanes for metastatic disease (14 with docetaxel and 2 with paclitaxel administered every 3 weeks). Patients were stratified according to the taxane-free interval to two groups: TFI > 1 year; TFI ≤ 1 year.

Altogether 599 cycles of treatment including 473 cycles of trastuzumab plus paclitaxel were delivered. The median number of treatment cycles per patient was 33 (1-78). In one case only first dose of trastuzumab was given with subsequent severe hypersensitive reaction. This patient could not have been evaluated for response. There were no principal protocol deviation. Paclitaxel was discontinued or omitted due to toxicity in 11 pati-

Table 1. Patient characteristics (n = 17)

Characteristics		Patients No.	Patients %
Age			
Median	50		
Range	36-66		
Prior chemotherapy			
2 prior regimens		6	35
≥ 3 prior regimens		11	65
No. of metastatic sites			
1		7	41
2		4	24
≥ 3		6	35
Visceral metastases		11	64
Taxane free interval			
> 1 year		7	41
≤ 1 year		9	53
not pretreated with taxanes		1	6
IHC HER2/neu (Herceptest)			
3+		15	88
2+		2	12
IHC ER			
ER +		4	24
ER -		11	64
Unknown		2	12

Table 2. Response to therapy

Response	Patients No.	Patients %
Overall response	10	59
Complete response	2	12
Partial response	8	47
Stable disease	2	12
Disease progression	4	23
Nonassessable	1	6
Response in patients with TFI ≤ 1 year	6	67
Response in patients with TFI > 1 year	4	57
Response in patients with 3+ IHC	10	67

ents with permanent discontinuation in 6 patients.

Response data are listed in Table 2. There was 2 CRs and 8 PRs with an objective response rate 59 % in the intent-to-treat population. Two patients had stable disease for at least 24 weeks and 4 patients progressed on therapy. The first CR occurred in 53 years old woman with infiltration of soft tissues of chest wall, and the second CR occurred in 36 years old woman with liver involvement. The first CR was maintained for 47 weeks and the second CR was still maintained at the time of analysis (45 weeks from the first documentation). One patient with PR after 16 cycles was referred to surgery for removal of residual disease in contralateral breast. She remains disease free at the time of analysis. In the subgroup with TFI > 1 year was observed 3 PRs and 1 CR. In the subgroup with TFI ≤ 1 year

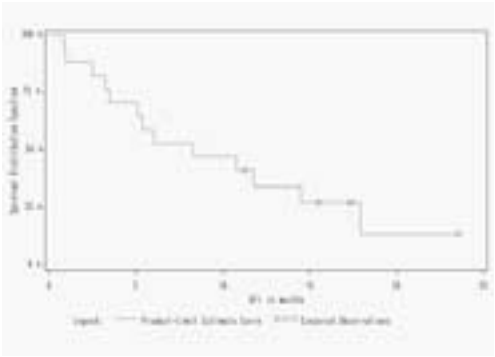

Figure 1. Time to progression in month.

were achieved 5 PRs and 1 CR. TFI does not have any impact on the overall response ($p < 0,4349$).

The median time to tumor progression in the intent-to-treat population was 6 month (range: 1-23,5) (Figure 1). At the time of analysis 4 patients (3 with TFI > 1 year 1 with TFI ≤ 1 year) remained free of progression. Patients with TFI > 1 year tended to stay longer progression free ($p = 0,0201$).

The median survival was not reached at the time of analyses when 10 patients were alive. The 1-year survival in the intent-to-treat population was 53 % and the 2-year survival 12 %.

Safety and toxicity data

All 17 patients were evaluated for toxicity (Table 3). In total there were delivered 599 cycles including 473 cycles of paclitaxel plus trastuzumab with no dose adjustments to 17 patients. The median number of cycles per patient was 33 (range: 1-78). Paclitaxel was omitted or discontinued in 11 patients. Paclitaxel toxicity, mainly neurotoxicity, led to permanent discontinuation of this drug in 6 patients. The most common adverse event was infusion related pyretic reaction after the first trastuzumab infusion in 6 patients (35 %). One patient experienced serious hypersensitivity reaction with dyspnea, shortness of breath and hypertension when receiving first trastuzumab infusion. This event led to treatment discontinuation. The dose limiting adverse effect was also cardiotoxicity. Ejection fraction decline grade 2 occurred in 1 and grade 3 in 1 patient. The treatment was discontinued in both cases when one patient was in CR and one in PR with no further tumor regression. Hematological toxicity was very modest. We noted only 1 episode of grade 4 neutropenia and 1 episode of grade 3 anemia. No growth factors were administered and only 3 units of blood transfusion were gi-

Table 3. Toxicity profile of weekly trastuzumab and paclitaxel

		NCI Grade (% of patients)		
Toxicity		2	3	4
Neutropenia		-	-	1 (6 %)
Leucopenia		3 (18%)	-	-
Anemia		1 (6%)	1 (6%)	-
Neuropathy		2 (12%)	6 (35%)	-
Cardiotoxicity		1 (6%)	1 (6%)	-
Infection		5 (29%)	4 (24%)	-
Hypacusis		2 (12%)	-	-
Edema		4 (24%)	-	-
Nausea/Vomiting		1 (6%)	-	-
Heartburns		1 (6%)	-	-
Onycholysis		1 (6%)	-	-
Weight gain		6 (35%)	1 (6%)	-
Transaminitis		3 (18%)	6 (35 %)	-
High glucose		-	1 (6%)	-
Infusion related reaction:	6 (35%)			

ven. There were observed 3 episodes of grade 3 infection without neutropenia treated with antibiotics with no further complications. Grade 3 elevation of liver function tests occurred in 6 patients with no need of dose reduction. Six patients experienced grade 3 neuropathy, which led to paclitaxel discontinuation in 5 patients. Other serious toxicity was very rare. We observed grade 3 weight gain in 1 patient, grade 2 weight gain in 6 patients and 1 episode of grade 3 hyperglycemia. It remains to be answered whether weight gain is related either to dexamethasone used as a premedication or to study drugs. Other toxicity was only marginal (Table 3).

Discussion

At the time we started to accrue patients to this trial there were no phase II or III data published about the efficacy of trastuzumab plus weekly paclitaxel. We assumed sufficient efficacy based on results of pivotal trial combining trastuzumab with chemotherapy.[24]

This pivotal, multicentre phase III trial randomized 469 HER2 positive (2+, 3+) previously untreated metastatic breast cancer patients either to receive chemotherapy alone or chemotherapy plus trastuzumab. Four arms were designed as follows: AC every 3 weeks alone, AC plus trastuzumab weekly, paclitaxel every 3 weeks alone, or paclitaxel plus trastuzumab. The addition of trastuzumab to chemotherapy almost doubled response rate and prolonged overall survival. When we compare paclitaxel alone to paclitaxel plus trastuzumab the response rate was even more than doubled however the response rate in paclitaxel alone was lower than expected. Most potent has been the combination of AC and trastuzumab but high proportion of cardiac events excluded this combination from further investigation. Nevertheless some grade of cardiac dysfunction occurred in both trastuzumab arms.

In another pivotal phase II trial trastuzumab was administered as a single agent to 222 metastatic breast cancer patients who had failed on previous 1st or 2nd line chemotherapy.[20] The overall response rate in pretreated population was 15 % and 18 % in 3+ population. In the subset with positive FISH response rate was even 20 % and furthermore no FISH negative patient responded to therapy.

The evaluation of HER2 expression was further investigated. There was found 75-89 % concordance between FISH positivity and 3+ result of immunohystochemistry[16,17] but only 24-39 % of patients who were 2+ positive by immunohistochemistry had also positive FISH result. The relative lack of benefit in 2+ population implicated the suggestion that all 2+ results should be confirmed by FISH before the treatment initiation.

The results from preclinical studies showed that trastuzumab has synergic or additive effect with some other drugs including vinorelbine, carboplatin, cisplatin, docetaxel, gemcitabin etc. Interesting data has come up from the trial with weekly trastuzumab and vinrolebine as the 1st, 2nd and 3rd line therapy of metastatic breast cancer with overall response rate exceeding 70 %.[23] Just recently there were published data from trastuzumab and gemcitabine phase II trial.[25] In several ongoing trials is trastuzumab combined with weekly docetaxel or carboplatin plus minus docetaxel.[26]

Because of promising safety and efficacy profile of trastuzumab combinations in the metastatic setting, this novel biologic agent now entered adjuvant breast cancer trials in the United States and Europe. Breast Cancer International Research Group conducts a clinical trial (BCIRG 006) for node positive early breast cancer patients.[27] Other examples of this approach include the National Surgical Breast and Bowel Project clinical trial B-31, the North Central Cancer Treatment Group adjuvant trial 9831 and the Eastern Coopera-

Figure 2. Trastuzumab adjuvant trials.

PTX = paclitaxel; T = trastuzumab; AC = doxorubicin and cyclophosphamide; DTX = docetaxel, CBDCA = carboplatin
q3w = every 3 weeks; w = weekly;
S = surgery; RT = radiotherapy; CT chemotherapy

1) ECOG 2198 (N+)
PTX q3w × 4 + T → AC × 4 → No T
→ T × 52 w
2) Intergroup NCCTG N 9831 (N+)
AC q3w x 4 → PTX w × 12
→ PTX w × 12 → T x 52 weeks
→ PTX w × 12 + T w → T × 40 weeks

3) NSABP B-31 (N+)
AC q3w × 4 → PTX × 4
→ PTX × 4 + T × 52 weeks
4) BCIRG (N+)
á AC × 4 → DTX × 4
á AC × 4 → DTX × 4 + T × 52 weeks
á DTX + CBDCA × 6 + T × 52 weeks
5) BIG HERA
S + CT + RT →T q3w 1 year → T q3w 2nd year
→ observation
→ observation

tive Oncology Group trial 2198 (Figure 2).[26] The Breast International Group conducts an adjuvant trial called HERA which slightly differs from other trials mentioned before because trastuzumab is planned to be administered every 3 weeks (Figure 2).[26,28] Completion of these ongoing trials through collaborative efforts between patients and scientific community will allow us to obtain the results we so eagerly await.

Conclusions

In this small single institution prospective open labeled clinical trial we showed that trastuzumab and paclitaxel is active in the treatment of HER-2/neu overexpressing metastatic breast cancer patients with only limited number of adverse event. As the first group we assessed the effect of this combination with respect to the interval from the last taxane administration – taxane free interval. We did not found any statistically significant correlation between taxane free interval and overall response rate. Nevertheless, patients with longer taxane free interval tended to stay longer progression free.

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