Multicenter, phase II, nonrandomized study of docetaxel plus trastuzumab every 21 days as the primary therapy in metastatic breast cancer overexpressing HER2

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Different anthracycline-free regimens have demonstrated activity, without serious cardiac events. This study was conducted to evaluate the activity and toxicity of docetaxel and trastuzumab given every 21 days in patients with metastatic breast cancer (MBC). The primary endpoint was time to progression and the secondary aims included response rate, safety, duration of response, and overall survival. Eligible patients were those with MBC human epidermal growth factor receptor-2+ (HER2+) with no previous chemotherapy for advanced disease. Patients received six cycles of docetaxel (100 mg/m^2) plus trastuzumab (8 mg/kg loading dose and 6 mg/kg every 21 days thereafter), followed by maintenance treatment with trastuzumab monotherapy every 21 days until disease progression. Forty-nine patients with HER2+ MBC were included. The overall response rate was 44.9% (22/49). With a median follow-up of 16.6 months, the median time to progression was 8.3 months and the median overall survival was 25.7 months. Nineteen patients did not receive treatment continuation with trastuzumab monotherapy. The most common toxicity was febrile neutropenia. A total of 10 patients were taken off the study due to treatment-related toxicity, mainly cardiac events. First-line trastuzumab combined with docetaxel is an effective and well tolerated regimen for HER2+ MBC. ***Anti-Cancer Drugs*** **23:239–246 © 2012 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

Anti-Cancer Drugs 2012, **23:**239–246

Keywords: docetaxel, human epidermal growth factor receptor-2, metastatic breast cancer, trastuzumab

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Received 29 July 2011 **Revised form accepted** 15 October 2011

Introduction

Breast cancer is the second most frequent cancer and the third in cancer mortality after lung and colon cancers [1]. In 2006, in Europe, an estimated 3 191 600 cancer cases were diagnosed and there were 1 703 000 deaths from cancer. The most common form of cancers was breast cancer (429 900 cases, 13.5% of all cancer cases) and close to 132 000 women died as a consequence of this disease [2]. Breast cancers are a heterogeneous disease including different subtypes with different outcomes and, despite the advances in the detection and treatment of early-stage breast cancer, approximately one-third of patients will eventually have recurrence and die due to metastatic disease [3].

Metastatic breast cancer (MBC) is commonly believed to be incurable, even though systemic treatments such as chemotherapy and hormonal therapy can promote excellent responses. Nevertheless, their use in metastatic disease is limited to palliative rather than curative purposes with the aim of improving time to progression (TTP) and quality of life [4]. New agents and targets have changed the outcome of patients with MBC. Mainly, for patients with hormonal receptor-positive MBC, endocrine therapy is the first-line treatment, especially when they have large progression-free survival and skeletal or soft tissue metastasis, and this therapy extends survival [5]. For patients with hormonal receptor-negative breast cancers or those whose disease has become resistant to endocrine therapy and visceral metastasis, chemotherapy is the treatment of choice. Anthracyclines are the standard chemotherapeutic agents for MBC [6]. However, some patients do not respond to anthracycline therapy, and anthracyclines have severe toxic effects, especially on the heart.

Anthracycline-based chemotherapy regimens have been widely used in MBC. Some phase II and III studies have provided evidence of other active agents for MBC [7]; thus, docetaxel has shown a response rate that is significantly superior to adriamycin, with lower cardiotoxicity [8].

Among the most significant recent developments in breast cancer, there is the recognition of human epidermal growth factor receptor-2 (HER2) as a prognostic factor and a predictor of response as well as a target

0959-4973 © 2012 Wolters Kluwer Health | Lippincott Williams & Wilkins DOI: 10.1097/CAD.0b013e32834e2fe4

for treatment. Currently, the only two predictive factors with level 1 evidence for clinical use are hormonal receptor status for endocrine therapy and HER2 status for trastuzumab therapy [9]. Approximately 15–20% of breast cancers show HER2 overexpression [3+ by immunohistochemistry and/or amplification of the *HER2/neu* gene by fluorescence in-situ hybridization (FISH)]. HER2-positive breast cancers have a significantly more aggressive course of disease and worse clinical outcome, including shortened overall survival (OS), compared with those that do not overexpress HER2 [10,11]. Trastuzumab is a humanized murine monoclonal antibody that binds specifically to the extracellular domain of the HER2 protein. The clinical efficacy and favorable safety profile of trastuzumab in MBC have been demonstrated as monotherapy [12,13] and in combination with paclitaxel [14]. Trastuzumab is an essential component of the treatment of patients with HER2-positive breast cancer in adjuvant, neoadjuvant, and metastatic settings.

Preclinical studies have shown a synergistic interaction at clinically relevant drug concentrations of docetaxel in combination with trastuzumab [15] and additive cytotoxic effects were observed with paclitaxel in combination with trastuzumab [16,17]. Data from a pharmacokinetic analysis, which was based on a two-compartment model, indicate that trastuzumab has a half-life of 28.5 days [12,18]. These data offer additional support for the use of trastuzumab every 3 weeks.

Trastuzumab with anthracycline-free combinations needs to be evaluated in HER2-overexpressing patients with MBC because of the potential cardiotoxicity that may occur with the concomitant use of anthracycline-based adjuvant therapies. To date, the efficacy, treatment duration, and appropriate dosing schedule for these combinations are still under investigation in this setting [19].

Different phase II studies have evaluated the efficacy and safety of taxanes combined with trastuzumab as the first-line treatment for MBC. On the basis of the current data, this study aimed to evaluate the efficacy and safety of the combination of docetaxel and trastuzumab administered every 21 days as first-line therapy for patients with HER2-positive MBC.

Patients and methods

Patient selection

Inclusion criteria

Women with histologically or cytologically proven locally advanced and/or MBC were eligible. Other eligibility criteria included age above 18 years; life expectancy greater than 12 weeks; Eastern Cooperative Oncology Group (ECOG) performance status 2 or less; adequate bone marrow (absolute neutrophil count $> 1.5 \times 10^9$ l, platelets $> 100 \times 10^9$ l, and hemoglobin > 10 g/dl); liver (total bilirubin $< 1.5 \times$ upper limit of normal, alkaline phosphatase, aspartate transaminase, and alanin transaminase $< 2.5 \times$ ULN); and renal function (serum Cr < 1.5 ULN). Fertile female patients were required to use appropriate contraceptive methods during the study as well as during the three subsequent months. Left ventricular ejection fraction greater than 50% or within the range of normality for each center, as measured by echocardiogram or a multigated acquisition scan.

Patients had to have MBC with measurable disease according to the Response Evaluation Criteria in Solid Tumors and tumors had to overexpress HER2 measured as 3+ by Herceptest in more than 10% of tumors cells or *HER2/neu* gene amplification for FISH. In patients HER2 2+ by Herceptest, a confirmatory FISH test had to be performed. In those cases, the primary or metastatic tumor sample could be used.

Exclusion criteria

Patients who had received prior chemotherapy for MBC or anthracyclines regimens during the 6 months before inclusion in the study were excluded. In any case, adjuvant adriamycin/epirubicin cumulative dose could not be superior to 360/540 mg/m^2, respectively. In addition, patients who had received radiotherapy over the target lesion or over a bone marrow area greater than 25% within the 4 weeks before inclusion in the study were also excluded. Other exclusion criteria were neuropathy grade of at least 2 in the scale National Cancer Institute Common Toxicity Criteria (NCI-CTC), a history of other nonbreast malignancies (except for carcinoma *in situ* of the cervix or nonmelanoma skin cancer or nonrecurrent prior tumor treated at least 5 years ago), cardiac disease (including any cardiac failure of any degree, arrhythmia requiring regular medication, and myocardial infarction within the previous 6 months), or any other concomitant disease that, according to the investigators' criteria, could negatively interfere with study treatment (hypertension, active infection, unstable diabetes mellitus). Pregnant or breast feeding women were excluded.

Patients were required to provide written informed consent before inclusion in the study. The study protocol was approved by the corresponding institutional review board and the studies were conducted in accordance with the principles of the Declaration of Helsinki.

Treatment plan

Patients were treated on the first day of each 21-day cycle as follows: trastuzumab was administered first, followed by docetaxel with a 24-h interval in the first cycle. In further cycles, docetaxel was administered immediately after trastuzumab if the first dose had been well tolerated. Trastuzumab dose was administered in the first cycle as a loading dose of 8 mg/kg intravenously over

60 min and then 6 mg/kg intravenously over 30 min every 21 days in subsequent cycles until disease progression. Docetaxel dose (100 mg/m^2) administered intravenously over 60 min. A maximum of six cycles of the combination were given. Subsequently, trastuzumab as monotherapy was administered every 21 days until disease progression. The dose of docetaxel was reduced to 75 mg/m^2 if investigators considered it necessary, following NCI-CTC. The dose of trastuzumab could not be modified.

Follow-up on completion of treatment

Once treatment was completed, patients were followed up for evaluation of disease status and late-onset toxicity every 3 months until disease progression and/or death.

Study design and endpoints

This was a prospective, multicenter, open label, phase II study following a standard phase II methodology. The study aimed to evaluate the activity and safety of the docetaxel and trastuzumab combination as the primary treatment in patients with MBC overexpressing HER2. The primary endpoint was TTP and was calculated as the time, in months, between patient enrollment and any of the following events, whichever occurred first: disease progression or death due to the MBC. Patients who dropped out of the study before progression were considered events when receiving any other anticancer treatment. For the remaining patients, the last follow-up was considered. The secondary aims included the overall response rate (ORR), OS, response duration, and safety profile. ORR was the percentage of patients who achieved a complete response (CR) or a partial response (PR). OS was calculated as the time interval between enrollment and patient death from any cause. Response duration was defined as the time interval between response occurrence and disease progression or death due to the MBC. The safety profile of the combination was recorded on day 21 of each chemotherapy cycle following NCI-CTC criteria.

Statistical analysis

The sample size target was set at 50 women, and 55 women including a 10% loss of follow-up. With this sample size, it is estimated that the power of the study would be 65.4, 87.1, and 98.8% if the correlation is 0.3, 0.5, and 0.7, respectively (correlation between the TTP with the previous treatment and with the actual treatment). Continuous variables (age, weight, body mass) were described using the mean, median, SD, and range. Categorical variables (sex, ECOG) were described as frequency and percentage. All efficacy endpoints were analyzed in an intention-to-treat analysis. Efficacy analysis included the following endpoints: TTP, OS, response duration, and ORR. Time-dependent variables were analyzed using the Kaplan–Meier method. The SPSS statistical program, version 15.0, was used for all statistical analyses (SPSS Inc., Chicago, Illinois, USA).

Results

Patients' characteristics

A total of 49 HER2-overexpressing locally advanced or MBC were included between January 2002 and February 2006 from the eight participating centers, all of them located in Spain. The most relevant patient characteristics are summarized in Table 1. Approximately half of the patients (51%) had an ECOG = 0, and approximately two-thirds of the patients ($n = 33$, 67.3%) had hormone receptor-positive breast cancer. All patients were HER2-positive, 45 patients (91.8%) had 3 + by immunohistochemistry, and four patients (8.2%) had positive FISH. The median time from the first diagnosis of breast cancer from inclusion in the study was 21.3 months (0.5–121) and the median from the diagnosis of advanced disease was 0.7 months (interval from 0.0 to 15.7 months). A total of 36 patients (73.5%) had undergone previous surgery for resection of the primary lesion and 35 patients had undergone axillary dissection. The median number of previously dissected lymph nodes was 18.5 (3–34) and the median number of affected lymph nodes was 2 (0–23). Twenty-five (51%) patients had received prior radiotherapy treatment and 30 patients (61.2%) had received prior chemotherapy treatment, either adjuvant or neoadjuvant. A total of 20 patients (40.8%) had received prior hormonotherapy, mainly tamoxifen ($n = 19$, 95%). Almost half of the patients had more than one metastatic site involvement (48%), and bone metastases were present in 46% of patients.

Four patients were excluded from the analysis of the primary efficacy end-point. Three of them were excluded because the combination docetaxel + trastuzumab was not discontinued after the sixth cycle due to encouraging clinical results (two patients received eight cycles of combined therapy and one received nine). A fourth patient was excluded from the analysis because she has undergone a mastectomy after a full response was achieved following the sixth cycle of combined treatment.

Treatment administration

The total number of cycles of the combination administered to the patients ($n = 49$) was 269 (mean = 5.5 and median = 6). A total of 35 patients received six cycles of the combination, two patients received eight cycles, and only one patient received nine cycles of trastuzumab and docetaxel (all three of them were excluded from the primary analysis). Subsequently, with regard to trastuzumab monotherapy, a total of 30 patients received 363 cycles of trastuzumab (mean = 12.1 and median = 7). A total of 11 patients (22.4%) experienced a treatment delay during the combination treatment. The reasons for the delay were hematological and nonhematological toxicity ($n = 4$) and reasons unrelated to the medication of the study ($n = 7$). During the treatment with trastuzumab alone, 10 patients (33.3%) experienced delays. A total of 25 cycles (6.9%) were delayed, two

Table 1 Baseline demographic and clinical characteristics of the study population

Characteristics ($N=49$)	N (%)
Age: years, median (range)	55.5 (29–76)
Histopathology	
Ductal	40 (82)
Lobulillar	4 (8)
Others	5 (10)
Hormone receptors status	
Positive	33 (67)
Negative	16 (33)
Stage	
I	3 (6)
IIA	11 (22)
IIB	5 (10)
IIIA	2 (4)
IIIB	11 (22)
IV	14 (29)
Unknown	3 (6)
Tumor HER2 status	
Positive IHC 3+	45 (92)
Positive FISH	4 (8)
ECOG performance status	
0	25 (51)
1	19 (39)
2	3 (6)
NA	2 (4)
Time from primary diagnosis to study entry: months, median (range)	21.3 (0.5–121)
Extension of the disease at study entry	
Distant recurrence	24 (50)
Primary disease and metastasis	18 (37)
Loco-regional recurrence and metastasis	6 (12)
No. of organ sites of disease[a]	
1	25 (52)
2	14 (29)
3	6 (12)
4	3 (6)
Dominant metastatic site[a]	
Bone	22 (46)
Lymph nodes	19 (40)
Lung	14 (29)
Liver	13 (27)
Pleura	6 (12)
CNS	3 (6)
Skin	2 (4)
Others	4 (8)

CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; FISH, fluorescence in-situ hybridization; IHC, immunohistochemistry; NA, not available.
[a]Forty-eight patients were analyzed for these variables. One patient did not present metastatic disease.

cycles due to cardiac events, four cycles for nonhematologic toxicity, and 19 cycles for other reasons not related to treatment study. The total number of cycles with a dose reduction of docetaxel was 18 (6.7%), which involved a total of 15 (30.6%) patients. The reasons for dose reduction included hematological and nonhematological toxicity. One patient did not receive the dose of docetaxel due to nonhematological toxicity and four patients (8.2%) did not receive at least one dose of trastuzumab (two patients due to nonhematologic toxicity, one patient due to cardiac toxicity, and one patient due to reduced left ventricular ejection fraction). Over the six cycles of the docetaxel–trastuzumab combination, the mean ranges of the relative dose intensities of docetaxel and trastuzumab were 97% (61–103%) and 96% (76–109%), respectively.

Outcomes

The median TTP was 8.3 months [95% confidence interval (CI): 4.6–11.9] (Fig. 1) for the 45 patients evaluated. Table 2 summarizes the response rates for the intention-to-treat population. A total of three patients were not evaluated for treatment response due to withdrawal of consent or physician decision ($n = 2$) and drug toxicity ($n = 1$). The ORR (PR + CR) was 44.9% (95% CI: 31–58.8). At a median follow-up time of 16.6 months (1.9–53.4 months), the median OS was 25.7 months (95% CI: 9.1–42.2) (Fig. 2). The 1-year OS was 80.6% (95% CI: 69.2–92.0) and the 2-year OS was 53.4% (95% CI: 37.4–69.4). Duration of response has been evaluated in those patients who reached a CR or a PR as the best response ($n = 22$). The median response duration was 11 months (95% CI: 7–15) (Fig. 3).

Treatment toxicities

The most relevant toxicities are listed in Table 3. The most frequent toxicity associated with the combination was hematological ($n = 18$, 37%), mainly neutropenia (12% grade III). Of those patients with neutropenia ($n = 17$), 28.6% presented febrile neutropenia. The majority of nonhematological adverse events were grades I–II (alopecia, stomatitis, transaminitis, diarrhea, and asthenia). Diarrhea grade III was present in five patients (10%). No neurotoxicity grade III was reported, and 16% were grades I–II. No nonhematological grade IV toxicity was reported. In total, 10 patients (20.4%) were excluded from the study due to treatment-related adverse events. Of these, five patients were excluded from the study while receiving the combination treatment mainly due to cardiac toxicity ($n = 4$) and allergic reaction to trastuzumab ($n = 1$).

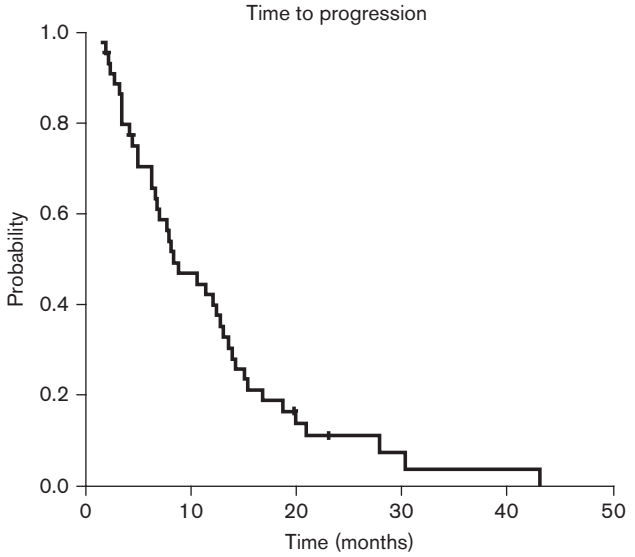
Five patients were excluded from the study while receiving monotherapy with trastuzumab due to cardiac conditions, which were reversible when trastuzumab was discontinued.

Discussion

This multicenter, phase II study tested the safety and efficacy of combining trastuzumab and docetaxel, both administered every 21 days, in patients with HER2- + MBC. The results show that the tested regimen is effective and safe and can be an alternative for subsequent phase III studies.

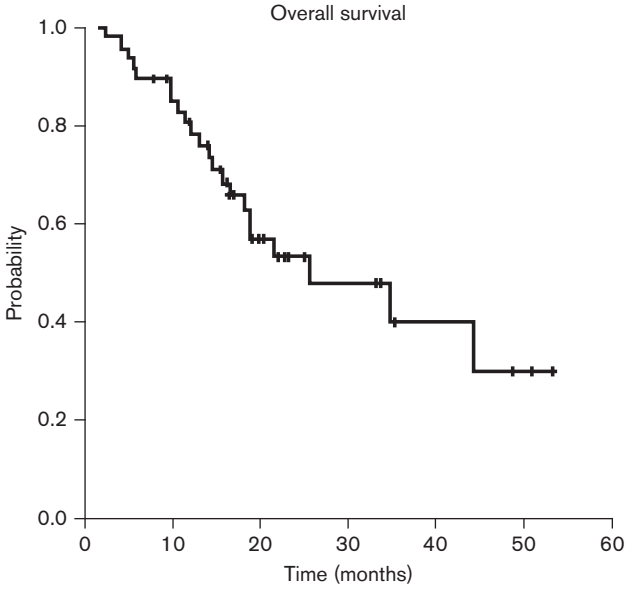
The combination of docetaxel–trastuzumab every 3 weeks as the first-line treatment for MBC resulted in a 45% response rate, slightly lower than that in other phase II trials, and 86% of clinical benefit. The median TTP was 8.3 months and the median OS was 25.7 months with 16.6 months of median follow-up. These results are similar to the findings in other phase II studies of the combination of trastuzumab with taxanes in MBC [19]. The taxane–trastuzumab combination has been widely

Fig. 1



Kaplan–Meier analysis of time to progression.

Fig. 2



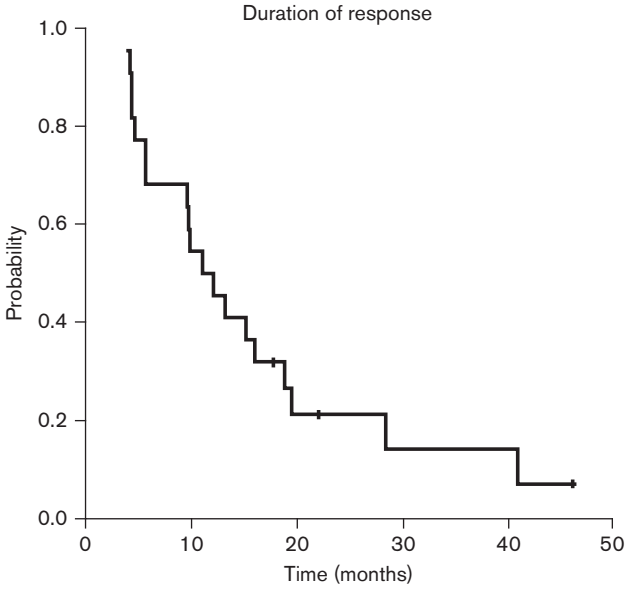
Kaplan–Meier analysis of overall survival.

Table 2 Response rate for the intention-to-treat population

Response rate	*N* (%)
Complete response	6 (12.2)
Partial response	16 (32.7)
Stable disease	18 (36.7)
Disease progression	6 (12.2)
Not evaluable[a]	3 (6.1)
Total	49 (100.0)

Responses were established by the physicians participating in the study.
[a]Three patients were not evaluated: one was excluded from the study due to toxicity, two patients withdrew consent, or their physicians decided to take them off the study.

Fig. 3



Kaplan–Meier analysis of response duration.

studied, with different schedules and ORR ranges between 29 and 75% and median TTP between 8.5 and 12.3 months (Table 4).

Although most of the other phase II published studies that have evaluated trastuzumab–taxanes combinations used weekly trastuzumab, we designed the trial using 3-weekly trastuzumab administration, because the result of trastuzumab exposure is similar to that of the a standard weekly regimen, and was also likely to be well tolerated and more convenient than the weekly schedule for the combination with docetaxel. Previous pharmacokinetic studies with trastuzumab have shown that at the dose and schedule used in this trial, trastuzumab trough levels were more than 20 μg/ml by the end of cycle 1. The half-life of trastuzumab was estimated to be 18–27 days and the cumulative dose over a 3-week interval is identical for the regimens administered weekly and every 3 weeks; the average exposure and time to steady state are also similar. Different pharmacokinetic studies conclude that the regimen administered every 3 weeks is a feasible alternative to the weekly regimen on the basis of pharmacokinetic parameters [31]. These data do indeed support the administration of trastuzumab every 3 weeks. Only another phase II study, conducted by Leyland-Jones *et al.* [18] used the 3-weekly trastuzumab schedule, combined with paclitaxel in first-line MBC. In this study, which included 32 patients, the ORR was 59% and the median TTP was 12.2 months.

Table 3 Adverse reactions associated with the combination treatment as well as with the maintenance treatment with trastuzumab

	Docetaxel + trastuzumab (*N* = 49)				Trastuzumab (*N* = 30)			
	Grade I/II *N* (%)	Grade III *N* (%)	Grade IV *N* (%)	Grade III/IV *N* (%)	Grade I/II *N* (%)	Grade III *N* (%)	Grade IV *N* (%)	Grade III/IV *N* (%)
Hematologic								
Anemia	27 (55.1)	1 (2.0)	–	1 (2.0)	10 (33.3)	–	–	–
Leukopenia	6 (12.2)	6 (12.2)	5 (10.2)	11 (22.4)	2 (6.7)	–	–	–
Neutropenia	3 (6.1)	6 (12.2)	11 (22.4)	17 (34.7)	–	–	–	–
Trombocytopenia	1 (2.0)	–	1 (2.0)	1 (2.0)	1 (3.3)	–	–	–
Nonhematologic								
Allergy	–	1 (2.0)	–	1 (2.0)	–	–	–	–
Cardiovascular								
Atrial fibrilation	–	1 (2.0)	–	1 (2.0)	–	–	–	–
Cardiac toxicity	3 (6.1)	1 (2.0)	–	1 (2.0)	4 (13.3)	–	–	–
Edema	7 (14.3)	1 (2.0)	–	1 (2.0)	4 (13.3)	–	1 (3.3)	1 (3.3)
Phlebitis	1 (2.0)	–	–	–	–	–	–	–
Deep venous thrombosis	–	1 (2.0)	–	1 (2.0)	–	–	–	–
Dermatology/skin								
Alopecia	37 (75.5)	–	–	–	23 (76.7)	–	–	–
Nail Changes	5 (10.2)	2(4.1)	–	2 (4.1)	1 (3.3)	2 (6.7)	–	2 (6.7)
Pain								
Arthralgia	1 (2.0)	1 (2.0)	–	1 (2.0)	1 (3.3)	–	–	–
Myalgia	10 (20.4)	1 (2.0)	–	1 (2.0)	1 (3.3)	–	–	–
Gastrointestinal								
Anorexia	6 (12.2)	–	–	–	1 (3.3)	–	–	–
Diarrhea	16 (32.7)	5 (10.2)	–	5 (10.2)	1 (3.3)	–	–	–
Stomatitis	21 (42.9)	–	–	–	1 (3.3)	–	–	–
Nausea	18 (36.7)	–	–	–	1 (3.3)	–	–	–
Vomiting	14 (28.6)	1 (2.0)	–	1 (2.0)	1 (3.3)	–	–	–
Hepatic	24 (49.0)	1 (2.0)	–	1 (2.0)	9 (30.0)	–	–	–
Infection/febril neutropenia	–	6 (12.2)	8 (16.3)	14 (28.6)	–	–	–	–
Metabolic								
Hyperglucemia	18 (36.7)	2 (4.1)	–	2 (4.1)	1 (3.3)	–	–	–
Neurological								
Sensor neuropathy	8 (16.3)	–	–	–	5 (16.7)	–	–	–
Constitutional symptoms								
Asthenia	31 (63.3)	3 (6.1)	–	3 (6.1)	13 (43.3)	–	–	–
Fever	9 (18.4)	–	–	–	1 (3.3)	–	–	–

Table 4 Phase II studies for human epidermal growth factor receptor-2–positive metastatic breast cancer treated with trastuzumab plus taxanes

Study	Schedule	*n*	ORR (%)	Median TTP (months)	Median OS (years)
Leyland-Jones *et al.* [18]	T/3w + P 175 mg/m^2/3w	32	59	12.2	NR
Fountzilas *et al.* [20]	T/w + P 90 mg/m^2/w	35	29	9	NR
Seidman *et al.* [21]	T/w + P 90 mg/m^2/w	95	57	NR	NR
Esteva *et al.* [22]	T/w + D 35 mg/m^2/w	30	63	9	NR
Gori *et al.* [23]	T/w + P 80 mg/m^2/w	25	56	8.6	NR
Montemurro *et al.* [24]	T/w + D 75 mg/m^2/3w	35	67	9	NR
Sato *et al.* [25]	T/w + D 70 mg/m^2/3w	40	65	6.8	NR
Tedesco *et al.* [26]	T/w + D 35 mg/m^2/w	26	64	12.3	1.8
Raff *et al.* [27]	T/w + D 33–40 mg/m^2/w	17	59	8.5	NR
Gasparini *et al.* [28]	T/w + P 80 mg/m^2/w	118	75	12.3	NR
Marty *et al.* [29]	T/w + D 100 mg/m^2/3w	168	61	11.7	2.6
Janku *et al.* [30]	T/w + P 80 mg/m^2/w	17	59	9	1.9
Servitja *et al.*, 2010 (current study)	T/3w + D 100 mg/m^2/3w	49	45	8.3	2.14

D, docetaxel; NR, not reported; ORR, overall response rate; OS, overall survival; P, paclitaxel; T, trastuzumab; TTP, time to progression; w, week.

The combination was well tolerated; no unexpected toxicities were reported. The most common hematological toxicities were leukopenia and neutropenia, but the incidence of grade III/IV hematological toxicity was lower than that reported by Sato *et al.* [25], using a weekly docetaxel–trastuzumab combination. We reported 28.6% grade III/IV febrile neutropenia, all the cases manageable on reducing the dose of docetaxel or on using granulocyte-colony stimulating factor. No other remarkable nonhematologic grade III/IV toxicity was reported. Indeed, the toxicity that occurred was mild and easy to manage.

Cardiotoxicity is the most important toxicity related to trastuzumab. Only one patient (2%) experienced grade III cardiotoxicity with the docetaxel–trastuzumab

combination. The trial protocol allowed continuation of trastuzumab monotherapy after six cycles of the combination. In this setting, four patients (13.3%) developed grade I/II cardiotoxicity and no grade III/IV was reported. These data support the cardiac safety.

The importance of introduction of trastuzumab as an essential part of the regimens used for the HER2-positive breast cancer treatment is widely recognized. The addition of trastuzumab to the chemotherapy schedules in an adjuvant setting improves disease-free survival and OS; when administered as a neoadjuvant treatment, it increases pathological complete responses; and for MBC, the use of trastuzumab benefits TTP and OS. We have learned that trastuzumab is indispensable for HER2-positive breast cancer, but it is not yet known whether it is essential to maintain trastuzumab as monotherapy afterward. In this sense, some retrospective analysis aimed to evaluate the benefit to maintain trastuzumab beyond progression [32]. Von Minckwitz *et al.* [33] published the first randomized phase III trial to confirm whether patients who were treated with trastuzumab beyond progression and second-line chemotherapy showed an improved response and experienced longer TTP than those treated with chemotherapy alone. Their results support maintenance of trastuzumab until disease progression.

In summary, the results of the study provide strong evidence that the combination of trastuzumab every 3 weeks plus docetaxel is safe and effective as a first-line treatment for patients with HER2 – + MBC. The 3-week schedule is more convenient and should be tested in future randomized trials.

Acknowledgements

The present study was funded by Roche Farma and Aventis Pharma.

Conflicts of interest

There are no conflict of interest.

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