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ORIGINAL ARTICLE

Phase-II study of weekly schedule of trastuzumab, paclitaxel, and carboplatin followed by a week off every 28 days for HER2+ metastatic breast cancer

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Abstract
Background Addition of carboplatin (C) to trastuzumab (T) and paclitaxel (P) improves the efficacy in HER2+ metastatic breast cancer (MBC). The aim of this phase-II study was to evaluate the efficacy and safety of this combination given weekly (3×) followed by a week off. The primary endpoint was: objective response rate (ORR), and secondary endpoints were: time to progression (TTP), overall survival (OS), and toxicity profile.
Methods HER2+ MBC patients were included in the study. Treatment was as follows: T (loading dose:4 mg/kg per week and 2 mg/kg per day thereafter), P (80 mg/m^2) and C (AUC 2) given weekly 3×, followed by 1 week off until disease progression or unacceptable toxicity.
Results Forty-one patients (pts) were enrolled—median age: 54.5 years (range 29–75); 87.8% PS 0 or 1; 39 (97.5%) had received prior adjuvant or neoadjuvant treatment; 11 (27%) had received one prior CT line for metastatic disease; disease sites: liver (40%), bone (32.5%), lymph nodes (32.5%) and lung (20%); 19 (47.5%) had ≥2 lesions and 97.5% had measurable disease. A total of 37 pts were evaluated for response: 11(26.8%) CR; 12 (29.3%) PR; 9 (22%) SD; 5 (12.2%) PD and 4 NE, resulting in an ORR of 56.1% (95% CI 39.7–71.5%) and tumor growth control rate (RR + SD) of 78% (95% CI 62.4–89.4%). With a median follow up of 39.4 months, 26 (70.3%) patients have progressed. The median time to progression was 12.3 months (95% CI 8.2–15.5). At the time of this report, ten patients have died. Forty patients received 202 cycles (median five cycles). Grades 3–4 toxicities/pts: 3 (7.5%) anemia, 2 (5%) leucopenia, 10 (25%) neutropenia, 1 (2.5%) febrile neutropenia,1 (2.5%) thrombopenia, 2 (5%) asthenia, 2 (5%) diarrhea, 3 (7.5%) nausea, 2 (5%) vomiting, and 3 (7.5%) mucositis.
Conclusions The schedule showed an interesting activity, taking into account that 27% of patients had received previous treatment for MBC. One week of rest may benefit not only the patient but may also improve tolerability and efficacy of the combination.

Keywords Trastuzumab · Paclitaxel · Carboplatin · Metastatic breast cancer

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Introduction

Breast cancer is the most frequent tumor in females in western countries [1]. In Spain, the incidence of breast cancer ranges from 14,000 to 15,000 per year and results in 6,000–7,000 fatalities per year. Over the last few years, there has been a slight decrease in the mortality of breast cancer, which is likely due to early detection and more effective treatments in patients with early disease [1]. Despite this progress, however, there is no current effective treatment to treat advanced disease and patients still invariably succumb, with a median survival of 2–3 years [2].

Breast cancer is a relatively chemosensitive disease [3]. Single agent response rates for classic active compounds such as anthracyclines, alkylating agents, and vinca alkaloids among others, range from 20 to 50% [4–8]. Combination chemotherapy is more effective than single agents in terms of tumor response, and in particular, overall survival with anthracycline-containing regimens [9–14].

Over the last few years, there have been an increasing number of new therapeutic agents added to the breast cancer treatment armamentarium such as taxanes, capecitabine, and gemcitabine. Among these newer agents, paclitaxel has been broadly explored in breast cancer [15]. As a single agent, paclitaxel has a response rate in the 30–50% range in patients with previously anthracycline-treated breast cancer [16,17]. Administered at a dose of 80–90 mg/m^2 per week, the drug is very well tolerated and equally effective as the every 3-week regimen [18–20]. The activity of paclitaxel is also very prominent in combination with other chemotherapeutic agents of common use in breast cancer treatment [21–33].

The biology of breast cancer has been progressively elucidated. Up to 30% of patient tumors carry amplification in the HER2 gene that results in increased HER2 signaling. These tumors are susceptible to treatment with trastuzumab, a monoclonal antibody against the HER2 receptor [34–39]. Consistent synergistic interactions of trastuzumab plus carboplatin, 4-hydroxycyclophosphamide, docetaxel, or vinorelbine across a wide range of clinically relevant concentrations in HER2-overexpressing breast cancer cells indicate that these are rational combinations to test in human clinical trials [40]. In a landmark randomized clinical trial, the combination of trastuzumab with chemotherapy, and either paclitaxel or cyclophosfamide and adriamycin, resulted in higher response rate, time to progression, and overall survival [41]. Based on this trial, the combination of trastuzumab and chemotherapy represent the standard of care for patients with HER2-positive breast cancer. More recently, studies have explored if different chemotherapy regimens in combination with trastuzumab result in levels of activity [42–45]. One regimen that is emerging as very effective in patients with advanced breast cancer is the combination of platinum agents with taxanes and trastuzumab [46]. In phase-III studies, the combination of weekly paclitaxel, carboplatin, and trastuzumab increased the response rate from 36 to 52% and the median survival from 6.9 to 11.2 months [47].

The aim of this phase-II study was to evaluate the response rate of weekly paclitaxel, carboplatin, and trastuzumab in patients with previously treated, advanced breast cancer. Secondary endpoints included time to progression, overall survival, and toxicity profile. Trastuzumab schedule administration was adapted to the chemotherapy treatment administered concomitantly. Hence, trastuzumab, paclitaxel, and carboplatin were administered weekly, with a week off every 28 days. This was based on trastuzumab pharmacokinetics: although a monocompartmental model, with a mean half life of 5–7 days, was initially accepted based on the limited data from phase-I studies, subsequently a bicompartmental model was established, with a mean half life of 28.5 ± 5 days [48]. This model has been validated in both monotherapy and combination treatments [49]. In addition, pharmacokinetic data has also confirmed that steady state is not reached until 24–30 weeks from the beginning of trastuzumab treatment [50,51]. This is due to the long half-life of trastuzumab and is independent of treatment schedule administration (weekly schedule vs. every 3-week schedule). This led to the hypothesis that the use of a treatment schedule that included a week off might not compromise its efficacy while it could benefit the patient's quality of life.

Patients and methods

Patient selection

Patients with cytologically or pathologically documented advanced breast cancer who were not amenable to curative treatment were eligible for this study. Other eligibility criteria included age ≥ 18 years; HER2 overexpression as determined by +++ immunohistochemistry or positive FISH; measurable disease; Karnofsky performance status of ≥70% and life expectancy of at least 12 weeks. A normal bone marrow (absolute neutrophil count ≥ 1.5 × 10^9/l; platelets ≥ 100 × 10^9/l and hemoglobin ≥ 10 g/l); renal (creatinine clearance ≥ 65 ml/min); liver [total bilirubine ≤ 1.25 × upper limit of normal (ULN), AST and ALT < 2.5 × ULN, and alkaline phosphatase < 1.5 × ULN (except for patients with solitary bone metastasis and no other liver problems or abnormality in liver function tests in whom a 5 × ULN was required)]; and cardiac (LVEF > 50% or within institutional limits) function was required. Patients with childbearing potential were required to use an appropriate birth control method before study entry.

Patients were excluded from the study if they had received more than one prior chemotherapy regimen for advanced disease or had received prior platinum or taxane-containing treatment; had received, within 4 weeks before study entry, radiation therapy to areas bearing more than 25% of bone marrow or that included the target lesion. Patients who had received cumulative dose of adriamycin > 340 mg/m^2 and epirubicin > 600 mg/m^2 were also excluded as well as patients with serious preexisting cardiac problems such as congestive heart failure, acute myocardial infarction in the preceding 6 months, cardiac arrythmias or blockage, dyspnea at rest or requiring oxygen administration; symptomatic or progressive brain

metastasis; >grade 2 peripheral neuropathy; pregnant or lactating women; known hypersensitivity reaction to cremophor or with psychiatric disorders that precluded compliance with protocol requirements.

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

Treatment administration

Treatment was administered weekly for three consecutive weeks followed by 1 week of rest every 4 weeks. On the first day of treatment, patients received 4 mg/kg trastuzumab, infused intravenously over 90 min. On subsequent treatments, the dose of trastuzumab was 2 mg/kg, administered over a 30 min infusion. Paclitaxel was administered at a dose of 80 mg/m^2 followed by carboplatin at an area under the curve (AUC) of 2 according to the Calvert equation. A 24-h waiting period between trastuzumab and paclitaxel–carboplatin was required on cycle 1, day 1 to monitor for hypersensitivity reactions. Drugs were administered according to the manufacturer's recommendations with recommended premedications for hypersensitivity reactions. Treatment was maintained until disease progression or intolerable toxicity.

Assessment of toxicity and dose modifications

The doses of drugs were adjusted based on hematological and non-hematological toxicity. On the day of treatment, patients were required to have an ANC $\geq 1.5 \times 10^9$/l and a platelet count $\geq 100 \times 10^9$/l. Patients who did not meet these criteria had their treatments delayed for a maximum of 2 weeks. Patients who did not recover in 2 weeks were removed from the study. The dose of paclitaxel and carboplatin was reduced by 25% in patients who developed grade-4 neutropenia with fever, grade-4 neutropenia lasting more than 5 days, grade-4 thrombocytopenia (grade 3 if bleeding), or if treatment needed to be delayed by 2 weeks. A second dose reduction of 20% was allowed for patients who presented a second episode of toxicity and were benefiting from the study. Patients who developed non hematological toxicity $\geq$ grade 2 (except alopecia, nausea, and vomiting unless refractory to maximal supportive measurements) had their treatment interrupted for a maximum of 2 weeks until recovery to grade 0 or 1. Patients needing more than 2 weeks treatment delay were taken off the study. Patients with $\geq$grade 3 non-hematological toxicity or grade-2 cardiac toxicity had their dose of paclitaxel and carboplatin reduced by 25%. Patients with grades 3–4 cardiac toxicity were removed from the trial. Patients who developed grade 1 congestive heart failure associated with a >20% decrement in left ventricular ejection fraction (LVEF) had their treatment with trastuzumab discontinued. Patients with $\leq$20% decrement in LVEF and who recovered CHF could be retreated with trastuzumab. Patients with >grade 1 CHF had trastuzumab suspended permanently as were patients with a decrease in the LVEF of >40%.

Concomitant treatment with antiemetics, bisphosphonates in patients with bone metastasis, and hematopoietic growth factor support in patients with febrile neutropenia were allowed.

Patient assessment and follow up

After signing the informed consent and within 2 weeks prior to treatment, patients underwent a complete medical history and physical exam including assessment of prior treatments and toxicities, pregnancy test and a complete blood count, chemistry panel and tumor markers (CEA, CA153) assessment. An EKG, chest X-ray, thoracic and abdominal CT scan, and assessment of LVEF were done 4 weeks prior to study treatment. In patients with clinical suspicion of bone or brain metastasis, a bone scan and/or brain CT were required. Determination of HER2 status from previous specimens was also required.

While on treatment, patients were followed every 4 weeks and patients underwent a physical exam, assessment of concomitant medications as well as toxicity events. Complete blood counts were monitored weekly for the first 3 weeks on cycles 1 and 2 and then at the investigator's discretion. Blood chemistries were determined every 4 weeks. Tumor markers and radiological studies to determine disease status were repeated every 8 weeks. LVEF was measured every 12 weeks.

Outcomes and statistical analysis

The primary endpoint of the study was the response rate with secondary endpoints including toxicity, time to progression, and overall survival. The sample size was calculated using a single stage Fleming design. The expected response rate was 53% and the minimum response rate was 30%. With an alpha error of 0.05 and a power of 80%, a total of 26 patients were required. Assuming that 20% of patients would not be evaluable, the target sample size was 33 patients. Continuous variables were described using the mean and range. Categorical variables were described as frequency and percentage. The Stata statistical program, version 10 (StataCorp. 2007; Stata Statistical Software: Release 10, College Station, Texas: StataCorp LP), was used for all statistical analyses.

Results

Patient characteristics

Between August 2003 and April 2006, a total of 44 patients from five different Spanish hospitals, were enrolled in the study. Baseline clinical characteristics are summarized in Table 1. Median age was 54.5 years (range 29–75) and over 90% had an ECOG of 0–1. Most patients (97.5%) had received prior chemotherapy in the adjuvant or neoadjuvant setting and 11 patients (27%) had also received treatment for advanced disease with a prior regimen and thus, treatment should be considered as second line in these patients. Ninety-two percent of the patients had more than one metastatic lesion, with the liver, lung, and bones as the most frequently affected sites.

Efficacy

A total of 37 patients were evaluated for response. Of those, 11 (26.8%, 95% CI 12.7–41.0) attained a complete response and 12 (29.3%, 95% CI 14.7–43.8) had a partial response accounting for a global response rate (RR) of 56.1% (95% CI 39.7–71.5). In addition, nine patients (22%, 95% CI 8.7–35.2) had stable disease, resulting in a tumor growth control rate (RR + SD) of 78% (95% CI 62.4–89.4). With a median follow up of 39.4 months, 26 (70.3%) patients have progressed. The median time to progression was 12.3 months (95% CI 8.2–15.5). At the time of this report, ten patients had died.

Table 1 Patient characteristics

Characteristics (n = 44)	
Median age, in years (range)	54.5 (29–75)
ECOG performance status: n (%)	
0	23 (56.1)
1	13 (31.7)
2	1 (2.4)
Unknown	4 (9.8)
Previous treatment: n (%)	
Chemotherapy	37 (92.5)
Radiation therapy	32 (80)
Hormone therapy	20 (50)
Number of metastatic lesions: n (%)	
1	21 (52.5)
2	16 (40)
>2	3 (7.5)
Location of metastatic lesions: n (%)	
Liver	16 (40)
Lung	8 (20)
Bone	13 (32.5)
Lymph nodes	13 (32.5)
Others	13 (32.5)

Toxicity

Overall, the regimen was well tolerated. Table 2 summarizes the principal hematological and non-hematological toxicities. The most frequent toxicities were grades 1–2 neutropenia, anemia, and thrombocytopenia. Overall, 15 (37.5%) patients developed 17 (17.5%) episodes of grades 3 and 4 hematological toxicities. Only two patients developed grade-4 neutropenia and another patient developed an episode of febrile neutropenia. Nine patients developed 12 episodes of grades 3–4 non-hematological toxicities including diarrhea, asthenia, nausea and vomiting. Seventeen patients developed grades 1–2 peripheral neuropathy. It is important to outline the absence of cardiac toxicity.

Discussion

The most appropriate treatment for patients with metastatic breast cancer (MBC) continues to evolve. This study aimed to combine trastuzumab with paclitaxel and carboplatin on a weekly basis every 3 weeks, followed by 1 week of rest schedule. The results of the study show that the regimen is well tolerated and results in a high response rate and time to tumor progression in this patient population.

While the most appropriate chemotherapy treatment for patients with MBC remains to be determined, there is significant evidence that patients with HER2 positive breast cancer do benefit from HER2 targeted-therapies. In randomized phase-III studies, it has been clearly demonstrated that patients with HER2 positive breast cancer benefit from the combination of paclitaxel with trastuzumab. More recently, the oral HER2 tyrosine kinase inhibitor lapatinib

Table 2 Hematological and non-hematological toxicities

	Grades 1–2	Grade 3	Grade 4
Hematological toxicities			
Neutropenia	34 (77.3 %)	8 (20%)	2 (5%)
Febrile neutropenia	0	0	1 (2.5%)
Anemia	28 (70.0 %)	3 (7.5%)	0
Thrombocytopenia	4 (10%)	1 (2.5%)	0
Non-hematological toxicities			
Diarrhea	9 (32.5%)	2 (5%)	0
Neuropathy	17 (42.5%)	0	0
Asthenia	15 (37.5%)	2 (5%)	0
Vomiting	12 (30%)	2 (5%)	0
Nausea	13 (32.5%)	3 (7.5%)	0
Mucositis	12 (30%)	3 (7.5%)	0

has also shown to improve survival in combination with chemotherapy in patients with trastuzumab-resistant breast cancer [52]. This agent opens the prospect for new strategies targeting HER2 positive breast cancer.

Because of concerns with the occurrence of cardiac toxicities when combining trastuzumab with anthracyclines, most regimens in patients with HER2 positive breast cancer are based on taxanes. An area of interest has been the addition of platinum compounds to the taxane–trastuzumab core. In preclinical studies, DNA binding agents such as cisplatin increased the cytotoxicity of trastuzumab [53]. In a recent phase-III study, the combination of trastuzumab with an every 3-week regimen of paclitaxel and carboplatin was well tolerated and improved response rate and time to progression [46]. More recently, adding carboplatin to a docetaxel–trastuzumab regimen allowed a reduction in the docetaxel dose and a better toxicity profile with similar efficacy [54].

The results of the present study compare well with the results of the above mentioned trial with regard to response rate and time to progression. With the every 3-week regimen in patients with no prior treatment for advanced disease, trastuzumab, paclitaxel, and carboplatin regimen resulted in 52% (95% CI 42–62) response rate and a median progression-free survival (PFS) of 10.7 months versus a 56% response rate and 12.3 months PFS in the current study [46]. These data are of even greater interest if we consider that 27% of the patients in this study had received prior treatment for advanced disease. In addition, the rate of grades 3 and 4 toxicities are also reduced with the 3× weekly every 4 weeks regimen. These results are similar to other recently published trials suggesting that the weekly schedule results in less toxicity [55].

In summary, the weekly trastuzumab, paclitaxel, and carboplatin regimen tested in this phase-II study was very well tolerated and resulted in encouraging activity in patients with advanced breast cancer. The long half-life of trastuzumab justifies the excellent activity results attained with a treatment schedule that included a week off. Likewise, it also improved the patient's quality of life by reducing the number of hospital visits. Therefore, this regimen represents an attractive strategy for subsequent phase-III studies.

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