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Phase II Trial of Weekly Nanoparticle Albumin-Bound Paclitaxel With Carboplatin and Trastuzumab as First-line Therapy for Women With HER2-Overexpressing Metastatic Breast Cancer

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Abstract

Purpose—This multicenter phase II trial evaluated the efficacy and safety of weekly nanoparticle albumin-bound paclitaxel with carboplatin and weekly trastuzumab as first-line therapy for women with HER2-overexpressing metastatic breast cancer (MBC).

Patients and Methods—We treated 32 patients who had measurable MBC that was HER2-positive defined by an immunohistochemical staining score of 3+ or gene amplification by fluorescence in situ hybridization, required for those with an IHC of 2+. Patients were treated with albumin-bound paclitaxel 100 mg/m² and carboplatin at area under the curve (AUC) = 2 on days 1, 8, and 15 of a 28-day cycle. Trastuzumab was administered at 2 mg/kg weekly after a loading dose of 4 mg/kg. Because of hypersensitivity reactions occurring during carboplatin infusion numbers 6-8 in 4 of the first 13 patients with this premedication-free regimen, the protocol was amended for carboplatin and dosed at AUC = 6 day 1 each 28-day cycle, in lieu of introducing steroid prophylaxis. Patients were treated with 6 cycles and allowed to continue with all 3 drugs or trastuzumab alone if free of progression and unacceptable toxicity after 6 cycles.

Results—The overall response rate (ORR) was 62.5% (95% CI, 45.7%-79.3%) with 3 confirmed complete responders (CRs; 9%) and 17 confirmed partial responses (PRs; 53%). An additional 6 patients (19%) had stable disease (SD) for greater than 16 weeks for a clinical benefit rate (ORR + SD > 16 weeks) of 81%. As of April 16, 2009, 20 patients (63%) had progressed with a median progression-free survival (PFS) of 16.6 months (95% CI, 7.5-26.5 months). Antitumor activity was similar for patients treated with weekly carboplatin and every-4-week carboplatin (ORR, 65% vs. 67%, respectively). Hematologic toxicities were the only grade 4 toxicities noted and were

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infrequent with grade 4 neutropenia in 3 patients (9%) and 1 febrile neutropenia. Grade 2/3 peripheral neuropathy was uncommon (13%/3%).

Conclusion—Weekly albumin-bound paclitaxel with carboplatin and trastuzumab is highly active in HER2-overexpressing MBC. In the absence of corticosteroid premedication, which we avoided with albumin-bound paclitaxel, carboplatin seems best dosed every 4 weeks rather than weekly because of carboplatin-associated hypersensitivity reactions. The regimen was very well tolerated with few grade 3 and 4 nonhematologic toxicities experienced, and severe hematologic toxicity and peripheral neuropathy were infrequent.

Keywords

Nab-paclitaxel; Neutropenia; Platinum agents; Progression-free survival

Introduction

Approximately 20%-30% of all human breast cancers overexpress the human epidermal growth factor (HER2) that contributes to tumorigenesis.^{1,2} The humanized monoclonal antibody trastuzumab (Herceptin™, Genentech, Inc.; South San Francisco, CA) targets the extracellular domain of the HER2 protein and in combination with chemotherapy for HER2-overexpressing metastatic breast cancer (MBC) leads to improved response rates, disease-free survival, and overall survival (OS) compared with chemotherapy alone.³⁻⁶ Preclinical evidence has demonstrated synergistic activity between trastuzumab and DNA-damaging agents such as the platinum salts (cisplatin and carboplatin) and alkylating agents.⁷⁻⁸ Trastuzumab increases the sensitivity of HER2-overexpressing cells to damage from these agents, therefore leading to a reduction in the ability of the cells to repair the damage induced. The combination of trastuzumab with cisplatin or carboplatin has shown a 2-log increase in cytotoxic killing of HER2-positive cells in vitro not demonstrated in cells that do not overexpress HER2. Paclitaxel has significant antitumor effects on breast cancer that overexpresses HER2.^{10,11}

The randomized phase III clinical trial CALGB 9840 demonstrating superior efficacy of weekly paclitaxel over every-3-week paclitaxel in MBC has motivated the examination of these combinations with weekly scheduling.¹¹ Two parallel phase II trials of paclitaxel with carboplatin and trastuzumab for first-line therapy in HER2-overexpressing MBC assessed weekly and every-3-week schedules of paclitaxel and carboplatin, both with weekly trastuzumab.¹³ The 48 patients who received 6 cycles of weekly paclitaxel at 80 mg/m² and weekly carboplatin at an area under the curve (AUC) = 2 for 3 weeks on and 1 week off, showed an overall response rate (ORR) of 81% (90% CI, 70%-90%) with a time to progression (TTP) of 13.8 months. The parallel group of 43 women receiving paclitaxel at 200 mg/m² and carboplatin at an AUC = 6 every 3 weeks for 8 cycles experienced an ORR of 65% (90% CI, 57%-77%) and TTP of 9.9 months.

Nanoparticle albumin-bound paclitaxel (Abraxane™; Abraxis BioScience LLC; Santa Monica, CA) is a new taxane formulation of paclitaxel that does not require a solvent for delivery, reducing the risk of hypersensitivity reactions (HSRs) and eliminating the need for steroid and antihistamine premedication. A phase III clinical trial demonstrated a superior ORR (33% vs. 19%; *P* = .001) and TTP (23 weeks vs. 16 weeks; *P* = .006) for albumin-bound paclitaxel given every 3 weeks at 260 mg/m² when compared with Cremophor®-based paclitaxel at 175 mg/m² every 3 weeks in patients with MBC.¹⁴ Additionally, there were no severe HSRs to albumin-bound paclitaxel compared with 5 in the Cremophor-based paclitaxel group, despite standard prophylactic corticosteroid premedication that was not used in the albumin-bound paclitaxel-treated patients.

Like Cremophor-based paclitaxel, albumin-bound paclitaxel appears more effective in MBC when administered weekly. A randomized phase II study of 302 patients with MBC compared docetaxel (100 mg/m²) every 3 weeks, against albumin-bound paclitaxel every 3 weeks (300 mg/m²), and 2 different weekly doses of albumin-bound paclitaxel, 150 mg/m² and 100 mg/m², given “3 weeks on, 1 week off.”¹⁵ Both weekly schedules showed higher response rates compared with both docetaxel and albumin-bound paclitaxel administered every 3 weeks (independent reviewer ORR, 45% and 49% vs. 37% and 35%, respectively). The 100-mg/m² dose of albumin-bound paclitaxel was associated with less neuropathy, arthralgia, and fatigue.

A phase I clinical trial has been conducted to examine the combination of albumin-bound paclitaxel and carboplatin in 3 different treatment schedules.¹⁶ One 21-day albumin-bound paclitaxel schedule and 2-weekly schedules of albumin-bound paclitaxel were examined, all with carboplatin at an AUC = 6 on day 1 of the 21-day cycle; the MTD of albumin-bound paclitaxel was 100 mg/m² when given day 1, 8, and 15 every 28 days, and 125 mg/m² when given days 1 and 8 every 21 days. Therefore, given this established dose combination and the evidence from Perez et al that suggested a possible advantage to weekly paclitaxel in combination with carboplatin and trastuzumab, we initiated this phase II study to examine the efficacy and safety of albumin-bound paclitaxel with carboplatin and trastuzumab all in a weekly schedule as first-line therapy for patients with HER2-overexpressing MBC.

Patients and Methods

Patients

Patients included had measurable, pathologically confirmed adenocarcinoma of the breast that was stage IV at enrollment. Tumor tissue was required to have either 3+ overexpression of HER2 by immunohistochemistry (IHC; Hercep Test™) or demonstrate fluorescence in situ hybridization (FISH) positivity (> 2.0) for HER2 gene amplification (Vysis PathVysion®, Abbott Laboratories, Chicago, IL). Patients with tumors testing 2+ by IHC were required to have a positive FISH test to participate in the study. Patients were not permitted to have previous chemotherapy for MBC but were allowed previous adjuvant or neoadjuvant chemotherapy. Patients must have been > 6 months from previous adjuvant chemotherapy (≥ 9 months if an adjuvant taxane was used); total adjuvant doxorubicin dose could not exceed 360 mg/m². Adequate hematologic, renal, and hepatic function with a normal left ventricular ejection fraction and no history of congestive heart failure or other serious intercurrent medical or psychiatric illness were required. Parenchymal brain metastases were allowed if clinically stable for ≥ 6 months before initiating therapy. Concurrent hormonal or immunotherapy was not allowed, and patients had to be ≥ 4 weeks after radiation therapy or major surgery, with full recovery.

Methods

There were 32 patients enrolled and treated in this multicenter, open-label phase II study. Baseline examinations were performed within 4 weeks of study entry, and all female subjects of child bearing potential were required to have a negative serum β-human chorionic gonadotropin test before entry. Written, informed consent was obtained from each participant using an institutional review board approved document from each institution.

An initial cohort of 3 patients were treated with 1 cycle (4 weeks) of albumin-bound paclitaxel at a dose of 75 mg/m² on days 1, 8, and 15 with weekly carboplatin at target AUC = 2 on the same days and trastuzumab given weekly (4-mg/kg load at week 1 and 2 mg/kg on all subsequent weeks). Because no grade 3 nonhematologic or hematologic toxicity requiring dose reduction occurred in those patients, the dose of albumin-bound paclitaxel

was escalated to 100 mg/m² for all subsequent cycles and patients. Trastuzumab was administered before albumin-bound paclitaxel and then was followed by carboplatin. Albumin-bound paclitaxel administration does not require premedication as HSRs are rare. Patients were permitted to receive premedication with dexamethasone and diphenhydramine at the investigator's discretion for the carboplatin administration. On August 31, 2006, after 4 patients of the initial 13 treated on the weekly schedule experienced acute HSRs to carboplatin, the protocol was amended such that the carboplatin schedule was changed from an AUC = 2 given weekly for 3 weeks in a 4-week cycle to an AUC = 6 on day 1 every 4 weeks. Patients who experienced HSRs to carboplatin were permitted to continue on protocol with albumin-bound paclitaxel and trastuzumab and only permitted to be rechallenged with carboplatin after undergoing a desensitization protocol. Patients experiencing HSRs to albumin-bound paclitaxel were rechallenged with premedications typically used for Cremophor-based paclitaxel.

The carboplatin dose was calculated using a modified Calvert formula with creatinine clearance substituted for glomerular filtration rate:

$$\text{Total Dose (mg)} = (\text{Target AUC}) \times (\text{Creatinine Clearance} + 25)$$

Creatinine clearance can either be measured, or estimated using the Cockcroft-Gault formula, as follows: Creatinine clearance (mL/min) = (140 – age) × (weight in kg) / (72 × serum creatinine in mg/dL × 0.85).

Dose Modification

Dose reductions were made according to toxicity as measured by the National Cancer Institute Common Toxicity Criteria for Adverse Events (CTCAE), version 3.0. Patients were specifically assessed for myelosuppression before each albumin-bound paclitaxel dosing (days 1, 8, and 15). Two maximum 20%/25% dose reductions (albumin-bound paclitaxel from 100 mg/m² to 80 mg/m² to 60 mg/m² and carboplatin from AUC = 6 to AUC = 4.5 to AUC = 3) were allowed to patients without the possibility of reescalation. Trastuzumab was not held for toxicities related to albumin-bound paclitaxel or carboplatin. Dose reductions were required for toxicities grade 3, except anemia, and treatment was withheld until resolution to grade 1 or baseline. Treatment was resumed at the next lower dosing level for subsequent cycles after resolution to grade 1. Specific criteria requiring dose modifications were included for neutropenia and thrombocytopenia (Table 1).

Patients with an asymptomatic relative or absolute decline in left ventricular ejection fraction (LVEF) of 15%, but above the lower limit of normal, were continued on trastuzumab therapy but monitored more frequently (every 8 weeks) for cardiac function. Patients whose LVEF decreased below the lower limit of normal had trastuzumab withheld, then resumed if patients were clinically benefitting and symptoms resolved. Trastuzumab was discontinued permanently for patients with symptomatic cardiac dysfunction that required therapy and did not resolve. Chemotherapy with albumin-bound paclitaxel and carboplatin were continued in all cardiac scenarios.

Statistical Methods

The primary efficacy endpoint (ORR) was defined as the percentage of patients that achieved confirmed complete response (CR) or overall response per Response Evaluation Criteria in Solid Tumors (RECIST) guidelines. The primary safety and tolerability endpoints were incidence of toxicity (evaluated per NCI CTCAE, version 3.0), myelosuppression, and dosing modifications for patients receiving weekly albumin-bound paclitaxel and

trastuzumab with carboplatin (weekly, then every 4 weeks) as first-line therapy for HER2-overexpressing MBC. Secondary objectives were progression-free survival (PFS), duration of response (defined as PFS for confirmed responders) and OS.

The ORR was summarized by the number and percentage of patients who achieved the endpoint and 95% confidence interval (CI) of the ORR. Progression-free survival was defined as the time from the first dose of study drug to the beginning of progression or patient death, whichever occurred first. Patients who did not die or progress were censored at the last known time that the patient was alive and progression free. Patients who initiated new anticancer therapy before progression were censored at the time of the new therapy. Kaplan-Meier methods were used to analyze PFS.

The trial had a planned sample size of 50 patients with measurable disease. This size was based on the assumption of an ORR of 50%, affording a 95% CI of 36%-64%. When only 64% of enrollment was reached after 3 years, accrual was stopped early at 32 patients because it was felt that significant efficacy and safety data had been established. Although the sample size was less than originally planned, there was no effect on the assessment of response rate, the primary endpoint. Actual observed response rate was 62.5% (95% CI, 45.7%-79.3%) with a 95% CI width of $\pm 16.8\%$ that was minimally larger than the $\pm 14\%$ projected, based on the original sample size of 50.

Evaluation of Response and Toxicity

Treatment with protocol therapy (trastuzumab, albumin-bound paclitaxel, and carboplatin) was continued in the absence of disease progression, unacceptable toxicity, patient withdrawal from the study, or until 6 cycles had been administered. Even if chemotherapy was discontinued after 6 or more cycles, trastuzumab monotherapy was continued until progression of disease or unacceptable toxicity (ie, no additional/other cytotoxic agents or anti-estrogens were added). At the investigator's discretion, treatment with chemotherapy (albumin-bound paclitaxel and carboplatin) was continued beyond 6 cycles in the absence of disease progression or unacceptable toxicity.

All patients receiving at least 1 dose of treatment were considered evaluable for response and toxicity. Response assessments were made every 2 cycles, or 8 weeks, using RECIST. Assessment of LVEF was every 2 cycles or per institutional standards. At the time patients were removed from study, laboratory and clinical evaluations to assess adverse events (AEs) were performed. Additionally, radiologic studies for antitumor response were repeated if they had not been done within the previous 28 days. Patients experiencing AEs, either on study or up to 30 days after the last dose of protocol therapy, were followed until the AE had resolved or stabilized. Survival status is monitored monthly for 3 months and subsequently every 3 months thereafter for a total of 2 years.

Results

Patient Characteristics

A total of 32 patients were enrolled between June 2004 and July 2007 and treated at 8 sites across the United States. Therapy has been discontinued for all 32 patients: 15 (47%) for progressive disease, 9 (28%) for patient discretion, 5 (16%) by investigator discretion, 2 (6%) for unacceptable toxicity, and 1 (3%) for other reasons. Table 2 describes the patient characteristics at enrollment.

Efficacy

The response rates are included in Table 3. In total, 3 (9%) patients have had a CR and 17 (53%) have had partial responses. Therefore, the ORR was 62.5% (95% CI, 45.7%-79.3%). An additional 6 patients (19%) achieved a best response of stable disease for more than 16 weeks. Therefore, the calculated clinical benefit rate of this regimen is 81.3% (95% CI, 67.7%-94.8%).

Of the 32 patients treated, 17 were treated solely on the original weekly carboplatin dosing schedule, 3 additional patients began on the original schedule and switched to the revised monthly dosing schedule, and 12 were treated solely on the revised monthly carboplatin dosing schedule (Figure 1). There were 11 confirmed responses in the 17 patients treated solely on the original weekly carboplatin regimen (65%); 8 of the 12 patients (67%) who received the revised schedule (every-4-week carboplatin) had confirmed responses, and 1 of the 3 patients (33%), who originally began on weekly carboplatin, responded after switching to the monthly dosing.

Of the patients who were treated on the monthly carboplatin dosing schedule, either from initiation or after the protocol was amended, steroid premedication was given for the initial cycle in all patients, and by investigator discretion, continued in 5 patients. For 2 patients, steroid premedication was stopped for subsequent cycles without any hypersensitivity reactions.

Though patients were still being followed for progression and OS, as of April 16, 2009, 20 patients (63%) had progressed with a median PFS time of 16.6 months (95% CI, 7.5-26.5 months) (Figure 2). Of the 20 responding patients, only 11 patients (55%) have gone on to progress at this time. The median response duration for these patients was 17.8 months (95% CI, 15.9-37.0 months).

Overall Survival

At the time of data cutoff, April 16, 2009, only 10 patients (31%) of the 32 enrolled in the study had died. The other 22 patients were still alive at the time of analysis.

Toxicity

Overall, the regimen was very well tolerated with neutropenia and leukopenia being the most common toxicities observed (Table 4). Grade 4 hematologic events were uncommon with only 3 patients experiencing grade 4 neutropenia (9%), 1 patient experiencing grade 4 leukopenia (3%), 1 patient experiencing grade 4 anemia (3%), and no grade 4 thrombocytopenia. Febrile neutropenia occurred in only 1 patient (3%).

Fatigue was the most common nonhematologic toxicity with 12 patients experiencing grade 1 (38%), 10 patients experienced grade 2 (31%), and 5 patients experienced grade 3 fatigue (16%). Sensory peripheral neuropathy was observed in 20 patients; 15 grade 1 (47%), 4 grade 2 (13%), and 1 patient with grade 3 peripheral neuropathy (3%). Congestive heart failure did not occur, and only 1 case (3%) of grade 1 left ventricular systolic dysfunction was reported. Other cardiac effects were also rare, with only 1 grade 3 cardiac toxicity, a supraventricular/nodal arrhythmia.

Dose Reductions/Interruptions

Dose reductions for either toxicity or protocol-specified dose modification guidelines were frequent. Twenty-two patients (69%) of the 32 patients treated had at least 1 dose reduction of albumin-bound paclitaxel and 19 patients (59%) had at least 1 dose reduction of carboplatin. For both drugs, hematologic toxicity was the main reason for dose reduction.

Among the patients who required dose reduction, 21 of the 22 patients (95%) with reduced albumin-bound paclitaxel and 18 of the 19 patients (95%) with reduced carboplatin, were for hematologic parameters. These reductions followed specific protocol guidelines (Table 1) including adjustments for nadir counts. Twenty-two of the 32 patients (69%) experienced at least 1 chemotherapy dose delay. Eighteen of the 22 (82%) were for hematologic toxicities, and none for peripheral neuropathy. Two patients experienced albumin-bound paclitaxel dose interruptions, but neither was for HSRs. Four patients had HSRs to weekly carboplatin; out of these, 2 patients had dose interruptions. There were 9 total hypersensitivity reactions that were attributable to carboplatin (5 patients) or trastuzumab (4 patients). No HSRs resulted from albumin-bound paclitaxel administration.

Actual drug delivery for albumin-bound paclitaxel was close to planned. The median delivered dose intensity was 56.9 mg/m²/week, 76% of the planned 75 mg/m²/week. The median delivered dose intensity for carboplatin was 47.6 mg/week, 62% of the planned protocol dose.

Dose interruptions for trastuzumab were also observed. Six patients (19%) had at least 1 missed dose of trastuzumab (3 patients missed only 1 dose and the other 3 patients missed 2, 3 and 4 doses, respectively).

The median number of cycles administered was 8 (range, 2-39 cycles). Of the 20 patients who responded and had at least 6 cycles of albumin-bound paclitaxel and carboplatin, 8 were continued on trastuzumab alone, either weekly or every 3 weeks at the investigator's discretion, until progression of disease.

Discussion

Sequential, single-agent chemotherapy has been the dominant treatment strategy in MBC for the past decade. With the advent of new 'biologic' agents, such as trastuzumab for HER2-overexpressing breast cancer, novel combinations have emerged. The preclinical synergy observed between the taxanes and platinum salts (cisplatin and carboplatin) has motivated the pairing of these 2 classes of chemotherapy for other solid tumor types resulting in this combination of chemotherapy as a first-line standard of care.

Previous phase II and III studies in MBC have demonstrated impressive response rates and PFS with the combination of paclitaxel and carboplatin with trastuzumab for patients with HER2-overexpressing MBC.^{13,17-19} In a randomized phase III study of 196 women with HER2-overexpressing MBC, the addition of carboplatin (AUC = 6, every 3 weeks) to every-3-week paclitaxel (175 mg/m²) and weekly trastuzumab significantly improved ORR (52% vs. 36%; $P = .04$), and median PFS (10.7 months vs. 7.1 months; hazard ratio, 0.66; 95% CI, 0.59-0.75; $P = .03$).¹⁸ The combination of docetaxel with trastuzumab and the platinum salts has also been examined.^{20,21} Phase II studies of weekly trastuzumab with either every-3-week cisplatin or carboplatin given with every-3-week docetaxel, again demonstrated high response rates (ORR, 79% with cisplatin, 58% with carboplatin) and TTP (median TTP, 9.9 months with cisplatin, 12.7 months with carboplatin) with tolerable toxicity profiles. However, preliminary data from the BCIRG 007 phase III study showed no advantage in adding carboplatin (AUC = 6, every 3 weeks) to every-3-week docetaxel (75 mg/m²) and weekly trastuzumab, when compared with a higher dose of docetaxel (100 mg/m² every 3 weeks) and weekly trastuzumab alone (ORR, 72.5% in both arms; median TTP, 11.1 months vs. 10.4 months; $P = .57$).²¹

With evidence that albumin-bound paclitaxel may be more effective than Cremophor-based paclitaxel¹⁴ or docetaxel¹⁵ its combination with these agents is the next logical step.

Evidence supporting superiority of weekly administration of the taxanes in MBC has also motivated examining these combinations weekly. The current trial results that show excellent activity for this combination are a natural evolution of these previous investigations; we observed 63% ORR and, at the time of the manuscript, a median PFS of 16.6 months (95% CI, 7.5-26.5 months).

Previously, Perez et al had demonstrated similar results with weekly Cremophor-based paclitaxel, carboplatin, and trastuzumab (weekly arm, 81% RR; 90% CI, 70%-90%). When examined against an unplanned, parallel study of every-3-week paclitaxel regimen with carboplatin and trastuzumab, the weekly regimen appeared to have favorable results.¹³ The weekly paclitaxel-containing regimen also had a similar PFS (14.7 months for weekly paclitaxel vs. 16.6 months, in this trial) when compared with this albumin-bound paclitaxel weekly combination. A notable difference between the 2 studies is neurotoxicity. Although both studies had a high percentage of patients with at least 1 dose reduction (69% in this study, 75% in the weekly arm of Perez study), none was for grade 3 or 4 peripheral neuropathy in this albumin-bound paclitaxel-containing triplet. In the weekly paclitaxel phase II study, 73% of patients developed grade 1 neuropathy. In this study, 62% of patients experienced grade 1 or greater peripheral neuropathy with only 1 patient experiencing grade 3. Therefore, substituting the albumin-bound paclitaxel may result in similar or possibly less toxicity than a Cremophor-based weekly paclitaxel regimen.

We initially treated patients on a weekly schedule of all 3 drugs, without premedication. However, 4 of the first 13 patients treated experienced HSRs attributable to carboplatin. After switching to carboplatin at an AUC = 6 every 4 weeks, no additional HSRs were seen, and no differences were observed in antitumor response in this unplanned subset of patients treated on the every-4-week carboplatin. The majority of patients did require dose modification of albumin-bound paclitaxel (and carboplatin); however, these adjustments were nearly all for hematologic parameters with only 1 febrile neutropenia. Therefore, the combination of weekly albumin-bound paclitaxel, every 4-week carboplatin, and weekly trastuzumab, perhaps in a lower dose to avoid hematologic toxicities, may be the preferred regimen for those patients with HER2-overexpressing MBC who need or want to avoid premedication.

Conclusion

The results of this trial add to the clinical evidence that the combination of taxanes and carboplatin with trastuzumab has high efficacy in HER2-overexpressing MBC. This trial specifically highlights the advantage of a weekly taxane and the possible advantage of using nanoparticle albumin-bound paclitaxel.

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References

1. Slamon DJ, Clark GM, Wong SG, et al. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/proto-oncogene. *Science*. 1987; 235:177–82. [PubMed: 3798106]
2. Press MF, Bernstein L, Thomas PA, et al. HER-2/neu gene amplification characterized by fluorescence in situ hybridization: Poor prognosis in node-negative breast carcinomas. *J Clin Oncol*. 1997; 15:2894–904. [PubMed: 9256133]

3. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med*. 2001; 344:783–92. [PubMed: 11248153]
4. Vogel CL, Cobleigh MA, Tripathy D, et al. Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer. *J Clin Oncol*. 2002; 20:719–26. [PubMed: 11821453]
5. Cobleigh MA, Vogel CL, Tripathy D, et al. Multinational study of the efficacy and safety of humanized anti-HER2 monoclonal antibody in women who have HER2-overexpressing metastatic breast cancer that has progressed after chemotherapy for metastatic disease. *J Clin Oncol*. 1999; 17:2639–48. [PubMed: 10561337]
6. Marty M, Cognetti F, Maraninchi D, et al. Randomized phase III trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with epidermal growth factor receptor positive metastatic breast cancer administered as first-line treatment: the M77001 study group. *J Clin Oncol*. 2005; 23:4247–50. [PubMed: 15911863]
7. Pietras RJ, Fendly BM, Chazin VR, et al. Antibody to HER-2/neu receptor blocks DNA repair after cisplatin human breast and ovarian cancer cells. *Oncogene*. 1994; 9:1829–38. [PubMed: 7911565]
8. Pietras RJ, Pegram MD, Finn RS, et al. Remission of human breast cancer xeno-grafts on therapy with humanized monoclonal antibody to HER-2 receptor and DNA-reactive drugs. *Oncogene*. 1998; 17:2235–49. [PubMed: 9811454]
9. Arteaga CL, Winnier AR, Poirier MC, et al. p185c-erbB-2 signal enhances cisplatin-induced cytotoxicity in human breast carcinoma cells: association between an oncogenic receptor tyrosine kinase and drug-induced DNA repair. *Cancer Res*. 1994; 54:3758–65. [PubMed: 7913407]
10. Baselga J, Seidman AD, Rosen PP, et al. HER2 overexpression and paclitaxel sensitivity in breast cancer: therapeutic implications. *Oncology*. 1997; 11(suppl 2):43–8. [PubMed: 9110342]
11. Seidman AD, Fornier MN, Esteva FJ, et al. Weekly trastuzumab and paclitaxel therapy for metastatic breast cancer with analysis of efficacy by HER2 immunophenotype and gene amplification. *J Clin Oncol*. 2001; 19:2587–95. [PubMed: 11352950]
12. Seidman AD, Berry D, Cirincione C, et al. Randomized phase III trial of weekly compared with every-3-week paclitaxel for metastatic breast cancer, with trastuzumab for all HER-2 overexpressors and random assignment to trastuzumab or not in HER-2 non-overexpressors: final results of cancer and leukemia group B protocol 9840. *J Clin Oncol*. 2008; 26:1642–9. [PubMed: 18375893]
13. Perez EA, Suman VJ, Rowland KM, et al. Two concurrent phase II trials of paclitaxel/carboplatin/trastuzumab (weekly or every-3-week schedule) as first-line therapy in woman with HER2-overexpressing metastatic breast cancer: NCCTG Study 983252. *Clin Breast Cancer*. 2005; 6:425–32. [PubMed: 16381626]
14. Gradishar WJ, Tjulandin S, Davidson N, et al. Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer. *J Clin Oncol*. 2005; 23:7794–803. [PubMed: 16172456]
15. Gradishar WJ, Krasnojon D, Cheporov S, et al. Significantly longer progression-free survival with *nab*-paclitaxel compared with docetaxel as first-line therapy for metastatic breast cancer. *J Clin Oncol*. 2009; 22:3611–9. [PubMed: 19470941]
16. Stinchcombe TE, Socinski MA, Walko CM, et al. Phase I and pharmacokinetic trial of carboplatin and albumin-bound paclitaxel, ABI-007 (Abraxane®) on three treatment schedules in patients with solid tumors. *Cancer Chemother Pharmacol*. 2007; 60:759–66. [PubMed: 17285317]
17. Burris H, Yardley D, Jones S, et al. Phase II trial of trastuzumab followed by weekly paclitaxel/carboplatin as first-line treatment for patients with metastatic breast cancer. *J Clin Oncol*. 2004; 22:1621–9. [PubMed: 15117984]
18. Robert N, Leyland-Jones B, Asmar L, et al. Randomized phase III study of trastuzumab, paclitaxel, and carboplatin compared with trastuzumab and paclitaxel in women with HER-2-overexpressing metastatic breast cancer. *J Clin Oncol*. 2006; 24:2786–92. [PubMed: 16782917]
19. Loesch D, Robert N, Asmar L, et al. Phase II multicenter trial of weekly paclitaxel and carboplatin in patients with advanced breast cancer. *J Clin Oncol*. 2002; 20:3857–64. [PubMed: 12228205]

20. Pegram MD, Pienkowski T, Northfelt DW, et al. Results of two open-label, multicenter phase II studies of docetaxel, platinum salts, and trastuzumab in HER2-positive advanced breast cancer. *J Natl Cancer Inst.* 2004; 96:759–69. [PubMed: 15150304]
21. Pegram M, Forbes J, Pienkowski T, et al. BCIRG 007: First overall survival analysis of randomized phase III trial of trastuzumab plus docetaxel with or without carboplatin as first line therapy in HER2 amplified metastatic breast cancer (MBC). *J Clin Oncol.* 2007; 25(34 suppl):18s. (abstract LBA1008).

Figure 1. Protocol Treatment Schema

The protocol was revised after 4 patients in the first 13 treated experienced hypersensitivity reactions to carboplatin given weekly. **(A)** Original protocol schema with weekly albumin-bound paclitaxel, carboplatin, and trastuzumab; **(B)** revised protocol schema to amend the carboplatin dose to AUC = 6 every 4 weeks.

Abbreviation: AUC = area under the curve

Figure 2.
Progression-Free Survival of the Treated Population

Figure 3. Computerized Tomography Scans of a Patient With Lung Metastases Who Had a Partial Response

Baseline and after 4 cycles. Computed tomography scan of the lungs of a patient enrolled and treated on this protocol at baseline, before initiating treatment, and then again after 4 cycles of treatment, 32 weeks later.

Table 1**Hematologic Parameter Dose Modification Scheme**

ANC, Cells/mL		Parameter Count		Febrile Neutropenia	Albumin-Bound Paclitaxel Dose, mg/ m ²	Carboplatin Dose (AUC)
Nadir 500	and	Nadir 50,000	and	No	No change	No change
Nadir < 500	or	Nadir < 50,000	or	Yes	↓ 100 to 80 or ↓ 80 to 60	↓ 6 to 4.5 or ↓ 4.5 to 3
Day 1, 1500	and	Day 1, 100,000	–	–	No change	No change
Day 1, 500-1499	or	Day 1, 50,000-99,000	–	–	↓ 100 to 80 or ↓ 80 to 60	↓ 6 to 4.5 or ↓ 4.5 to 3
Day 1, < 500	or	Day 1, < 50,000	–	–	Withhold; resume at lower dose	Withhold; resume at lower dose
Day 8/15, < 1000	–	–	–	–	Withhold; resume at lower dose	Withhold; resume at lower dose

Schema used in the protocol to dose adjust albumin-bound paclitaxel and carboplatin based on day 1, day 8, day 15, and nadir absolute neutrophil count and platelet counts.

Abbreviations: ANC = absolute neutrophil count; AUC = area under the curve

Table 2

Patient Characteristics (N = 32)

Characteristic	Number of Patients (%)
Age, Years	
Median	52
Range	29-76
ECOG Performance Status	
0	19 (59)
1	12 (38)
2	1 (3)
3	0
4	0
Race	
White, Non-Hispanic, Non-Latino	26 (81)
Black	4 (13)
Hispanic/Latino	2 (6)
Asian	0
Previous Adjuvant/Neoadjuvant Therapy	
Anthracycline	14 (44)
Taxane (paclitaxel or docetaxel)	11 (34)
Menopausal Status	
Premenopausal	7 (22)
Postmenopausal	25 (78)
Sites of Metastatic Disease	
Lymph node	24 (75)
Skin/soft tissue/breast	21 (66)
Liver	15 (47)
Lung	19 (59)
Bone	22 (69)

Abbreviation: ECOG = Eastern Cooperative Oncology Group

Table 3

Confirmed Overall Response Rates (N = 32)

Confirmed ORR (CR + PR), N (%); 95% CI	20 (63%); 45.7-79.3
CR	3 (9%)
PR	17 (53%)
Patients With SD for 16 Weeks	6 (19%)
Clinical Benefit Rate (ORR + SD 16 Weeks)	26 (81%)

Abbreviations: ORR = overall response rate; CR = complete response; PR = partial response; SD = stable disease

Table 4

Incidence of Adverse Events by Percentage

Adverse Events, %	Grade 1	Grade 2	Grade 3	Grade 4
Hematologic^{a,b}				
Neutropenia	13	34	41	9
Leukopenia	22	28	44	3
Anemia	25	63	3	3
Thrombocytopenia	38	34	3	0
Nonhematologic				
Sensory neuropathy	47	13	3	0
Nausea	56	16	0	0
Diarrhea	19	25	0	0
Rash/desquamation	22	9	0	0
Arthralgia	16	3	0	0
Fatigue	38	31	16	0
Stomatitis	28	13	0	0
Elevated ALT	9	6	3	0
Elevated AST	9	0	0	0

^aBased on laboratory data graded by National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.

^b1 episode of febrile neutropenia was observed.

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase