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Carboplatin in Combination Therapy for Metastatic Breast Cancer

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Key Words. *Carboplatin · Taxanes · Trastuzumab · Combination chemotherapy · Metastatic breast cancer · Clinical trials*

LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Describe the single-agent activity of carboplatin for metastatic breast cancer.
2. Discuss the results of phase II trials of taxanes with platinum agents for breast cancer.
3. Explain the hypothesis for the preclinical interaction between trastuzumab and platinum agents.

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ABSTRACT

***Background*. Anthracycline-based regimens have a limited role in patients with metastatic breast cancer due to cumulative cardiotoxicity and their common use in adjuvant chemotherapy. New nonanthracycline regimens are, therefore, needed for metastatic disease. Single-agent carboplatin is active in patients with previously untreated metastatic breast cancer, producing response rates of 20%-35%. Preclinical studies have demonstrated synergistic antitumor efficacy of carboplatin and trastuzumab in HER2+ models.**

***Methods*. Phase II and III clinical trial data of combination therapy with carboplatin (Paraplatin®; Bristol-Myers Squibb; Princeton, NJ), a taxane, and/or trastuzumab (Herceptin®; Genentech, Inc.; South San Francisco, CA) in metastatic breast cancer were identified from multiple sources, including: A) clinical trial data published in peer-reviewed journals within the last 5 years; B) preliminary clinical trial data from abstracts recently presented at national meetings; and C) phase III protocols currently evaluating carboplatin-based combination regimens.**

***Results*. In several phase II studies, combination carboplatin and paclitaxel (Taxol®; Bristol-Myers Squibb) therapy was active and reasonably well tolerated in the first-line treatment of metastatic breast cancer, producing objective response rates of 53%-62%—substantially higher rates than those seen in other phase II trials of either drug alone. Similar phase II data for carboplatin with docetaxel (Taxotere®; Aventis; Bridgewater, NJ) have been reported, and recent phase III data suggest that adding carboplatin to a paclitaxel/trastuzumab regimen produces superior efficacy than paclitaxel/trastuzumab alone for patients with HER2+ metastatic disease. Drug scheduling plays an important role in the therapeutic ratio of this combination treatment.**

***Conclusions*. Incorporation of carboplatin as a standard agent in first-line treatment of metastatic breast cancer has support from several recent studies. Preliminary results of combination carboplatin/taxane therapy with trastuzumab in metastatic disease are encouraging, and other carboplatin combinations are also being investigated in other phase II and III trials in patients selected based on the HER2 status of their cancer. Results are eagerly awaited. *The Oncologist* 2004;9:518-527**

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Introduction

Breast cancer is the most common malignancy affecting women and the second leading cause of cancer death in the U.S., surpassed only by lung cancer [1]. Although only a small minority of patients is initially diagnosed with metastatic breast cancer, it is estimated that 20%-30% of patients with early-stage disease will ultimately progress to metastatic disease [2]. Many different agents are used in this setting—including anthracyclines, taxanes, and antimetabolites—but a single standard of care has not been identified [3]. Anthracycline-based regimens are used commonly in the treatment of metastatic disease, but due to cardiotoxicity, they have a limited role in patients exposed previously to anthracyclines in the adjuvant setting. This underscores the importance of developing new nonanthracycline regimens for the treatment of metastatic disease.

Platinum complexes are active in a wide range of solid tumors [4]. Although both cisplatin (Platinol®; Bristol-Myers Squibb; Princeton, NJ) and carboplatin (Paraplatin®; Bristol-Myers Squibb) have shown activity in breast cancer, carboplatin may be the more appropriate choice for treatment of metastatic disease, because it causes less severe nonhematologic toxicities. Oxaliplatin is also a platinum compound, but breast cancer data are not yet available. Because carboplatin and cisplatin have not yet been directly compared in phase III trials for the treatment of metastatic breast cancer, this review focuses exclusively on the discussion of carboplatin-based combination regimens for metastatic breast cancer. However, without implying carboplatin possesses equivalent activity to cisplatin across all platinum-sensitive tumor types, it is important to note that treatment with carboplatin has demonstrated efficacy comparable with that of cisplatin-based regimens in several tumor types. In suboptimally debulked ovarian cancer, non-small cell lung cancer, and extensive-stage small cell lung cancer, clinical trials have demonstrated that carboplatin can be substituted for cisplatin without a loss of activity [4]. In the metastatic breast cancer setting, phase II data suggest carboplatin- and cisplatin-based regimens may possess comparable activities.

In four phase II studies of previously untreated patients with metastatic breast cancer, single-agent carboplatin produced objective response rates of 20%-35% [5-8]. In three of those trials, carboplatin was administered at a fixed dose of 400 mg/m^2 every 3 or 4 weeks or based on glomerular filtration rate to achieve an area under the concentration-versus-time curve (AUC) of 7 mg/ml minute every 4 weeks in one study. In contrast, objective responses were relatively rare with these carboplatin schedules in patients treated previously with chemotherapy for metastatic disease [8, 9].

In order to provide a topical and focused review of carboplatin-based combination chemotherapy for metastatic breast cancer, discussion of combination regimens administering carboplatin was limited to recent and developing data, including: A) clinical trial data published in peer-reviewed journals during the last 5 years; B) preliminary data from abstracts presented at recent national meetings; and C) ongoing phase III protocols evaluating carboplatin-based combination regimens. The development of the preliminary data presented in this review should provide a more comprehensive description of the role of carboplatin in combination with other agents in this setting.

Biological Rationale and Clinical Background for Combining Carboplatin with a Taxane and Trastuzumab

The promising activity of single-agent carboplatin in previously untreated patients led to the investigation of its activity in combination with a taxane and, more recently, to evaluation of a carboplatin/taxane regimen in combination with trastuzumab (Herceptin®; Genentech, Inc.; South San Francisco, CA) in women with HER2$^+$ metastatic disease. The rationale for combining carboplatin with a taxane is based on their single-agent activities in metastatic breast cancer, their complementary mechanisms of action, and the activity of this combination in other malignancies [7, 8, 10, 11]. Interestingly, when used in combination, paclitaxel (Taxol®; Bristol-Myers Squibb) appears to have a platelet-sparing action that reduces the thrombocytopenia seen with carboplatin alone [12]. The addition of trastuzumab to the carboplatin/taxane doublet is partially based on preclinical observations. In SK-BR-3 human breast carcinoma cells overexpressing HER2, synergistic cytotoxic activity was observed between carboplatin and trastuzumab, and additive interactions were seen between paclitaxel and trastuzumab [13, 14]. In these cells, trastuzumab reduced repair of platinum-induced DNA damage, thereby promoting platinum cytotoxicity against target cells [15]. The positive interaction between trastuzumab and chemotherapy seen in human cancer cells in vitro was also evident in HER2-transfected MCF-7 human breast cancer xenografts in athymic mice [13, 14]. In this animal model, trastuzumab potentiated the reduction in tumor growth seen with maximally tolerated doses of a platinum or taxane alone [13, 14].

Carboplatin and Paclitaxel in First-Line Treatment

Although there are currently no large phase III trials comparing carboplatin/paclitaxel combination therapy with paclitaxel alone for metastatic breast cancer, several phase II studies have shown that combination therapy with carboplatin and paclitaxel is active and reasonably well tolerated as first-line treatment of patients with metastatic breast cancer (Table 1) [16]. The Hellenic Cooperative Oncology Group (HCOG)

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Table 1. Phase II studies of carboplatin/paclitaxel in patients with advanced breast cancer

Study	Regimen	*n* of patients	Response	Outcome	Grade 3/4 toxicity (% patients)
Fountzilas et al. [16]	P: 175 mg/m^2 over 3 hours; C: AUC 6 q3w	66	OR: 53% CR: 12% PR: 41%	MTTP: 8.9 months	Leukopenia (25); nausea/vomiting (7); thrombocytopenia (5); anemia (5); arthralgia/myalgia (4)
Perez et al. [11]	P: 200 mg/m^2 over 3 hours; C: AUC 6 q3w	53[a]	OR: 62% CR: 16% PR: 46%	MDR: 8.6 months MTTP: 7.3 months 1-year OS: 72%	Neutropenia (82); leukopenia (52); thrombocytopenia (18); arthralgia/myalgia (16); neurosensory (16); nausea/vomiting (8)
Loesch et al. [17]	P: 100-135 mg/m^2 over 1 hour C: AUC 2 on days 1, 8, 15 q4w	100[b]	OR: 62% CR: 8% PR: 54%	MDR: 13.3 months MTTP: 4.8 months MOS: 16.0 months 1-year OS: 64% 18-month OS: 47%	Neutropenia (35); leukopenia (17); neuropathy (11); infection (6); weakness (6); anemia (5); paresthesia (3)

Abbreviations: P = paclitaxel; C = carboplatin; OR = overall response; CR = complete response; PR = partial response; MTTP = median time to tumor progression; MDR = median duration of response; MOS = median overall survival; OS = overall survival.

[a]50 patients evaluable.

[b]95 patients evaluable including 19 treated with 135 mg/m^2 and 76 treated with 100 mg/m^2 paclitaxel.

treated 66 patients with a regimen of paclitaxel (175 mg/m^2 infused over 3 hours) followed by an infusion of carboplatin (to an AUC of 6 mg/ml min over 30 minutes) [16]. Treatment was repeated every 3 weeks (q3w) in an outpatient clinic. Eight (12%) patients achieved complete responses and 27 (41%) patients had partial responses for an overall response rate of 53% (95% confidence interval [CI] = 41%-65%) [16]. The median time to progression was 8.9 months (range 0.5 to 14.6+ months), whereas the median survival time had not been reached at the time of the study report [16]. The most common grade 3/4 toxicities were leukopenia (25% of patients), nausea/vomiting (7%), thrombocytopenia (5%), and anemia (5%) [16]. Notably, 38 patients who had been treated previously with adjuvant chemotherapy, including 21 patients who had received an anthracycline- or mitoxantrone-containing regimen, were enrolled and treated with carboplatin/paclitaxel [16]. In the latter subgroup, four (19%) patients achieved complete responses and nine (43%) patients had partial responses. Complete responses were observed in patients with soft tissue, bone, liver, and lung metastases [16].

The North Central Cancer Treatment Group (NCCTG) evaluated carboplatin/paclitaxel in the first-line treatment of metastatic breast cancer (trial NCCTG 95-32-52, Fig. 1) [11]. Patients received paclitaxel (200 mg/m^2 via a 3-hour infusion) followed immediately by carboplatin (dosed to an AUC of 6 mg/ml minute over 30 minutes) [11]. Treatment was repeated q3w. Among 50 evaluable patients, eight (16%) had complete responses and 23 (46%) had partial responses for an overall response rate of 62% (95% CI = 48%-75%) [11]. Three of the patients with complete responses had received anthracycline-based therapy in the adjuvant setting. As in the previous study, responses were observed at all metastatic sites [11]. The median time to progression was 7.3 months, with 36% of patients being free of disease progression at 12 months. The 1-year overall survival rate was 72% [11]. Neutropenia (82% of patients) was the most common toxicity, but it was usually of short duration and uncomplicated [11]. Other toxicities included grade 3/4 thrombocytopenia (18%), grade 3 neurosensory toxicity (16%), and grade 3 arthralgia/myalgia (16%). Notably, the response rate observed in this study with carboplatin/paclitaxel appeared higher than that reported for either carboplatin or paclitaxel as a single agent [11].

Weekly administration of paclitaxel is active in patients with metastatic breast cancer, including patients treated previously in the adjuvant or metastatic setting, and produces a mild toxicity profile [10]. Accordingly, a weekly schedule of carboplatin/paclitaxel was evaluated in 100 previously untreated patients with advanced breast cancer to ascertain if it could produce a response rate similar to that with the q3w schedule but with less toxicity [17]. The first 20 patients received paclitaxel (135 mg/m^2 via a 1-hour infusion) followed by carboplatin (to an AUC of 2 mg/ml minute over 30-60 minutes) on days 1, 8, and 15 of a 4-week cycle [17]. On the basis of the toxicity profile seen in these patients, the subsequent 80 patients received paclitaxel at a dose of 100 mg/m^2 [17]. Among 95 evaluable patients, eight (8%) had complete responses and 51 (54%) had partial responses for an overall response rate of 62% [17]. The response rates did not differ between those receiving the 135 mg/m^2 paclitaxel dose and those receiving the 100 mg/m^2 dose. The median time to progression was 4.8 months (range <1 to 26 months) and median survival was 16 months (range <1 to 27 months) [17]. Neutropenia (35%)

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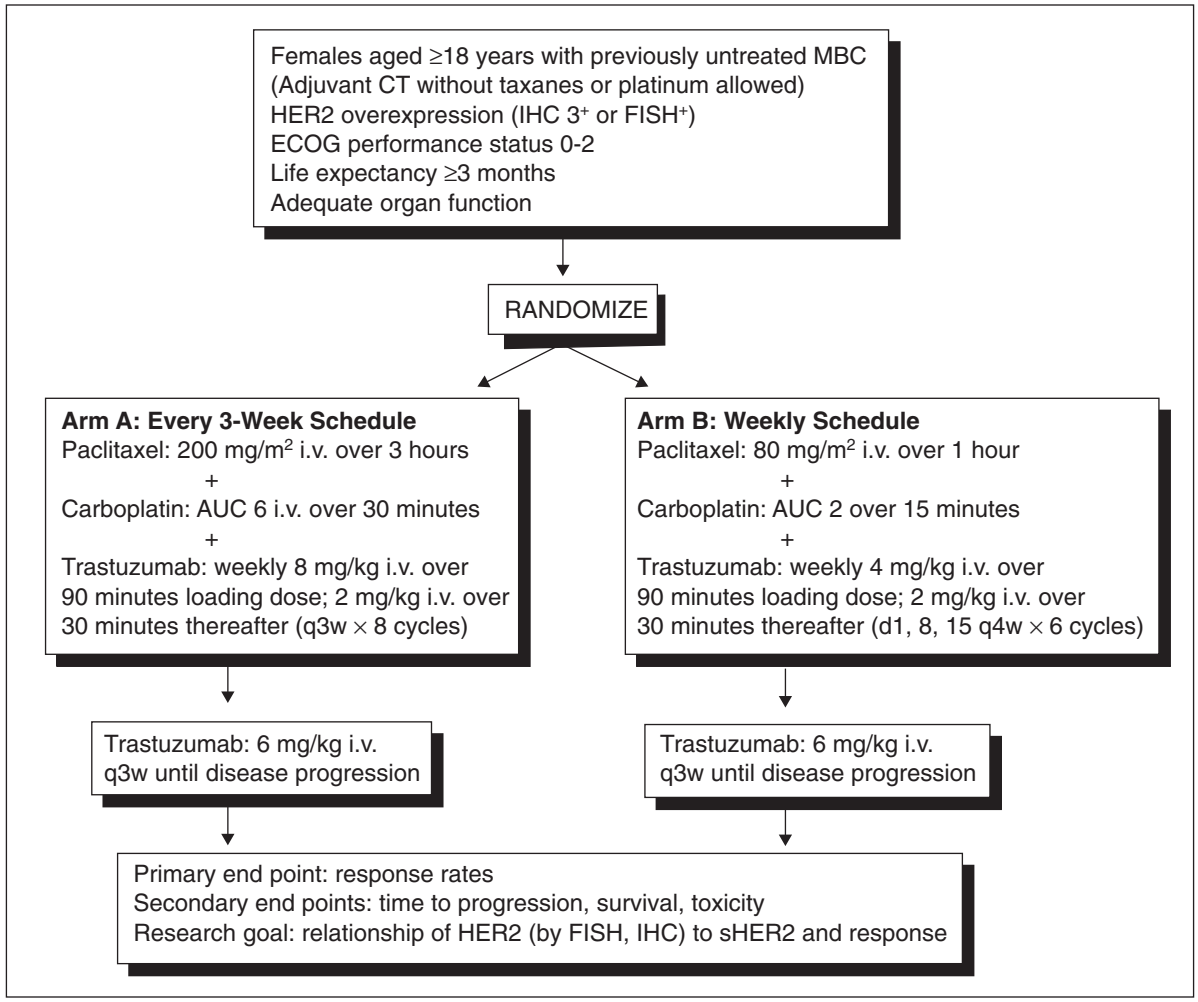

Figure 1. Schema for NCCTG 98-32-52 [27]. *Abbreviations: MBC = metastatic breast cancer; IHC = immunohistochemistry; ECOG = Eastern Cooperative Oncology Group; sHER2 = shed extracellular domain of HER2.*

and leukopenia (17%) were the most common grade 3/4 toxicities, but they occurred more commonly in the group treated with the higher paclitaxel dose [17]. Other grade 3/4 toxicities included neuropathy (11%), infection (6%), weakness (6%), anemia (5%), and paresthesia (3%). Three (3%) patients had drug-related sepsis [17]. That study showed that weekly carboplatin/paclitaxel produces response rates comparable with those seen with the q3w schedule, but with a more favorable toxicity profile [17]. The median time to progression, however, was somewhat shorter than that observed with the q3w schedule. In a study by *Perez et al*. that used the q3w schedule, the median time to progression was 7.3 months, versus 4.8 months observed in the study using the weekly regimen [11, 17]. However, response rates for both groups were the same at 62% [11, 17]. Longer follow-up is necessary to determine whether there is indeed an apparent difference in time to progression using the weekly approach. A phase III trial would be required to avoid the inherent difficulties of comparing data across phase II studies with different treatment regimens. Leaving carboplatin aside, there are suggestive data indicating a higher rate of pathologic complete response in patients receiving weekly paclitaxel compared with those receiving an q3w dose of 225 mg/m^2 when administered before four cycles of FAC chemotherapy [18]. Moreover, recent data from the CALGB 9840 study also demonstrated the statistically significant improvements in response rate and time to progression, with a trend for improved survival using weekly instead of q3w paclitaxel as first-line therapy for metastatic disease [19].

Carboplatin and Docetaxel in First-Line Treatment

Two independent phase II studies have shown that the combination of carboplatin and docetaxel (Taxotere®; Aventis Pharmaceuticals, Inc.; Bridgewater, NJ) is active in the first-line treatment of metastatic breast cancer. *Brufsky et al*.

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[20] enrolled 40 patients with advanced breast cancer in a trial that evaluated docetaxel (75 mg/m^2) and carboplatin (AUC 6) given q3w. An overall response rate of 59% was observed in 39 evaluable patients: six patients (15.4%) had complete responses after six cycles of treatment, 17 patients (43.6%) had partial responses, and nine patients (23%) had stable disease. The mean duration of response was 8.8 months and the mean time to progression was 6.5 months. The primary toxicity was hematologic: 28 patients had grade 4 neutropenia, four of whom had febrile neutropenia; four patients had grade 4 thrombocytopenia. There were no treatment-related deaths.

The NCCTG continued investigating the role of a carboplatin/taxane regimen in patients irrespective of HER2 status. In a phase II trial to determine the efficacy of carboplatin and docetaxel as first-line therapy for metastatic breast cancer, the NCCTG 9932 trial evaluated docetaxel (75 mg/m^2) and carboplatin (AUC 6) administered on day 1 of a 3-week cycle [21]. Fifty-three patients (median age: 60 years; range 31-83 years) were enrolled in the trial. Prior adjuvant treatments included chemotherapy (47%) and anthracycline therapy (43%). Visceral disease was observed in 74% of the women. The overall response rate was 58% (95% CI = 44%-72%), including three complete responses and 28 partial responses. With a median follow-up of 10.6 months (range 21 days to 21.8 months), at last contact, 26 patients had no disease progression while disease had progressed in 13 patients. Fourteen patients had progressed and died. The median progression-free survival time was 9.8 months and the 1-year survival rate was 72% (95% CI = 59%-88%). Grade 3/4 hematologic toxicities included neutropenia (94%), febrile neutropenia (15%), thrombocytopenia (15%), and anemia (11%). Severe nonhematologic toxicities included grade 3 fatigue (21%), infection (11%), and diarrhea (11%), and grade 3/4 neurotoxicity (4%).

Investigators from both phase II studies concluded that the combination of docetaxel and carboplatin showed activity in the first-line setting for metastatic breast cancer. The toxicities of this regimen were deemed to be acceptable.

Carboplatin and Paclitaxel in Anthracycline-Resistant Metastatic Breast Cancer

The HCOG administered carboplatin/paclitaxel to 37 women with metastatic breast cancer resistant to anthracyclines [22]. Eligible patients had either relapsed within 12 months of adjuvant anthracycline therapy or progressed during treatment of advanced disease with an anthracycline [21]. Paclitaxel (200 mg/m^2) was infused over a 3-hour period followed by carboplatin dosed to an AUC of 7 mg/ml minute over 30 minutes [21]. Five (14%) patients achieved complete responses and 11 (30%) had partial responses for an overall response rate of 43% (95% CI = 27%-60%) [21]. The median time to progression was 8 months (range 0.26 to 16.8+ months) and the median survival time was 12 months (range 0.5 months to 19.6$^+$ months). Leukopenia (27%) was the most common grade 3/4 toxicity, followed by thrombocytopenia (10%) and diarrhea (5%) [21]. These results suggest that carboplatin/paclitaxel is an active and well-tolerated option for patients with decreased progression to anthracycline-based therapy [21].

Carboplatin and a Taxane in Combination with Trastuzumab in HER2$^+$ Advanced Breast Cancer

The benefit of adding trastuzumab to first-line chemotherapy of metastatic breast cancer that overexpresses HER2 was established in a well-conducted phase III study [23]. A total of 469 patients were randomly assigned to receive chemotherapy either with or without trastuzumab. Patients who had not received adjuvant chemotherapy were treated with an anthracycline plus cyclophosphamide, whereas those previously treated with an adjuvant anthracycline received paclitaxel. The addition of trastuzumab to chemotherapy resulted in a significantly higher response rate (50% versus 32%, $p < 0.001$), longer median time to disease progression (7.4 versus 4.6 months, $p < 0.001$), longer median duration of response (9.1 versus 6.1 months, $p < 0.001$), and longer median survival time (25.1 versus 20.3 months, $p = 0.046$) [23]. Statistically significant differences in the overall rate of response, duration of response, and time to treatment failure were observed in the subgroup treated with trastuzumab/anthracycline/cyclophosphamide and in the subgroup receiving trastuzumab/paclitaxel, versus the subgroups treated with an anthracycline plus cyclophosphamide or paclitaxel alone, respectively [23].

The incidences of severe adverse events were generally comparable between the groups treated with or without trastuzumab with the exception of cardiotoxicity [23]. A higher incidence of cardiotoxicity was observed, particularly in patients receiving trastuzumab concurrently with an anthracycline plus cyclophosphamide [23].

Based on these promising results of combining trastuzumab with chemotherapy, nonanthracycline alternatives were investigated, with many of them incorporating platinum agents. The Breast Cancer International Research Group (BCIRG) conducted two pilot phase II trials of patients with advanced breast cancer overexpressing or with amplified HER2, in which trastuzumab was administered in combination with carboplatin/docetaxel or cisplatin/docetaxel [24]. One prior chemotherapy regimen for metastatic breast cancer was allowed in the study of carboplatin/docetaxel but not in the study of cisplatin/docetaxel [24]. Docetaxel (75 mg/m^2) was administered followed by either carboplatin (AUC 6) or

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Table 2. Activity of carboplatin/docetaxel/trastuzumab and cisplatin/docetaxel/trastuzumab in phase II studies conducted by the BCIRG in advanced breast cancer [24]

Regimen	*n* of patients (*n* FISH$^+$)	Performance status	Prior chemotherapy	Response All Pts	Response FISH$^+$ Pts	Median TTP All Pts	Median TTP FISH$^+$ Pts
Carboplatin/ docetaxel/ trastuzumab	59 (40)	0: 58% 1: 40% 2: 2%	Adjuvant anthracycline: 45% Adjuvant taxane: 15% CT for MBC: 5%	OR: 58% CR: 20% PR: 37%	OR: 64% CR: 19% PR: 44%	12.8 months	17.0 months
Cisplatin/ docetaxel/ trastuzumab	62 (35)	0: 65% 1: 32% 2: 3%	Adjuvant anthracycline: 32% Adjuvant taxane: 0 CT for MBC: 0	OR: 79% CR: 5% PR: 74%	OR: 77% CR: 6% PR: 71%	9.9 months	12.7 months

Abbreviations: FISH$^+$ = patients with HER2$^+$ status analyzed by FISH; Pts = patients; CT = chemotherapy; OR = overall response; CR = complete response; PR = partial response; TTP = time to progression.

cisplatin (75 mg/m^2) on day 1 of a 3-week cycle. Up to eight cycles were administered. Trastuzumab was administered at a loading dose of 4 mg/kg on the first day of the first cycle and then continued at a weekly dose of 2 mg/kg for 1 year or until disease progression [24].

Both regimens were active, but it is important to recognize that the two studies were not identical with respect to the patient populations enrolled (Table 2). The overall response rates were 79% (95% CI = 66%-88%) for the cisplatin/docetaxel/trastuzumab group and 58% (95% CI = 40%-70%) for the more heavily pretreated carboplatin/docetaxel/trastuzumab group [24]. In the subgroup of patients in whom HER2 gene amplification was analyzed by fluorescent in situ hybridization (FISH), the response rates were numerically higher in the cisplatin/docetaxel/trastuzumab group (77% versus 64%), but the median time to progression was longer in the carboplatin/docetaxel/trastuzumab group, (17.0 versus 12.7 months) [24]. In the subgroup of patients with FISH-negative disease for HER2, the response rate was n = 16/19 (84%) for the cisplatin study and n = 7/17 (41%) for the carboplatin trial. Grade 3/4 thrombocytopenia was more common with the carboplatin regimen, but gastrointestinal, renal, and neurosensory toxicities occurred more frequently with the cisplatin regimen [24]. Grade 3/4 renal toxicity, ototoxicity, neurosensory toxicity, and constipation were not observed with the carboplatin regimen. One patient in each group developed congestive heart failure. These studies showed that adding trastuzumab to a platinum/taxane combination is active in HER2-overexpressing advanced breast cancer, leading to high response rates and notable times to progression, forming the basis for further phase II and phase III clinical trials as outlined below. The regimens containing cisplatin and carboplatin showed similar activities, but nonhematologic toxicities appeared to be less frequent with the carboplatin regimen [24].

A phase II study assessed weekly trastuzumab added to a combination of paclitaxel and carboplatin as first-line treatment in metastatic breast cancer [24]. Sixty-one metastatic breast cancer patients showing 2$^+$ or 3$^+$ HER2$^+$ expression by immunohistochemistry received induction therapy with trastuzumab followed by weekly paclitaxel (70 mg/m^2), carboplatin (AUC 2), and trastuzumab (2 mg/kg) for 6 of every 8 weeks. The overall response rate for all patients was 66%, with a median overall survival time of 29.3 months and a median time to tumor progression of 12 months. Grade 3/4 leukopenia was observed in 33% of patients, with no patients showing febrile neutropenia. Grade 3/4 nonhematologic toxicities were rare, with fatigue, diarrhea, and neuropathy noted in 7%, 4%, and 4% of patients, respectively. The study indicated that the combination of paclitaxel/carboplatin/trastuzumab was effective and tolerated in the first-line setting of metastatic breast cancer.

Ongoing Phase III Trials of Carboplatin-Based Therapy in Metastatic Breast Cancer

The benefit of adding carboplatin to paclitaxel and trastuzumab in the first-line treatment of HER2-overexpressing metastatic breast cancer was further shown in results from an ongoing phase III study [26]. A total of 191 patients were randomly assigned to treatment with paclitaxel (175 mg/m^2 infused over 3 hours) either with or without carboplatin (AUC of 6 mg/ml minute) [26]. Treatment was repeated q3w for up to six cycles. Trastuzumab was administered at a loading dose of 4 mg/kg followed by weekly doses of 2 mg/kg until disease progression. Nearly half the patients had received prior adjuvant chemotherapy [26], and 66% had 3$^+$ IHC for HER2. Updated data indicate that the group receiving carboplatin had a significantly higher response rate (52% versus 36%, p = 0.03) and a longer median time to progression (10.3 versus 7.0 months, p = 0.016) [26] than the group receiving only paclitaxel and trastuzumab. A similar advantage of carboplatin was observed in the subgroup with HER2 scored as 3$^+$ by immunohistochemistry: the response rates were 57% versus 37% (p = 0.03) and the median times to progression were

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14 versus 7.1 months ($p = 0.007$) [26]. The study was not powered statistically to show a survival advantage between treatments, but at the latest update, the median overall survival time was 42.1 months (range 1.8-45.7) with paclitaxel/carboplatin/trastuzumab versus 33.3 months (range 1.8-45.7) with paclitaxel/trastuzumab ($p = 0.41$). In the 3^+ HER2 patients, the paclitaxel/carboplatin/trastuzumab group showed a trend for longer median survival (42 months [range 5.6-51.8] versus 29 months [range 1.8-55.3], $p = 0.15$) [26].

As expected, the addition of a third drug to paclitaxel and trastuzumab resulted in greater myelosuppression; grade 4 neutropenia (36% versus 12%, $p \leq 0.01$) and grade 3 thrombocytopenia (9% versus 1%, $p \leq 0.01$) were significantly more common with carboplatin/paclitaxel/trastuzumab than with paclitaxel/trastuzumab. Fatigue (10% versus 4%), anemia (5% versus 2%), and nausea (6% versus 1%) also occurred somewhat more frequently [26]. Thus, these preliminary results suggest that adding carboplatin to paclitaxel and trastuzumab provides a statistically and clinically significant higher response rate and longer time to progression than paclitaxel and trastuzumab in patients with a high degree of HER2 overexpression, as well as an important trend toward better survival, all associated with a very modest increase in myelosuppression.

The NCCTG is conducting a parallel phase II study (NCCTG 98-32-52) to evaluate the efficacy and tolerability of carboplatin/paclitaxel/trastuzumab delivered on a q3w schedule with those of a weekly schedule to patients with $HER2^+$ metastatic breast cancer (Fig. 1) [27]. In the first arm, paclitaxel (200 mg/m^2) is infused over 3 hours followed immediately by carboplatin (AUC 6 mg/ml minute over 30 minutes) [27]. Treatment is repeated q3w for eight cycles. In the other arm, paclitaxel (80 mg/m^2 infused over 1 hour) followed by carboplatin (AUC 2 mg/ml minute infused over 15 minutes) is administered on days 1, 8, and 15 of a 4-week cycle. Treatment is repeated for six cycles [27]. In the q3w arm, patients are administered an 8-mg/kg loading dose of trastuzumab. In the weekly arm, a 4-mg/kg loading dose of trastuzumab is administered following carboplatin on the first day of the first cycle. In both arms, a 6-mg/kg maintenance dose of trastuzumab (day 1, q3w) is given until disease progression. Preliminary results from the first 91 ($n = 43$ for the q3w schedule; $n = 48$ for the weekly schedule) patients suggest the weekly schedule is better tolerated than the q3w schedule [28]. Neutropenia was the most common toxicity, with grade 4 neutropenia (67% versus 12%) and febrile neutropenia (16% versus 2%) occurring more frequently with the q3w schedule [28]. In addition, grade 3/4 thrombocytopenia (30% versus 4%), the need for red blood cell transfusions (26% versus 6%), and sensory neuropathy (19% versus 2%) were also more common with the q3w schedule [28].

The analysis of the NCCTG 98-32-52 trial indicated that the weekly schedule ($n = 48$) provided clinical responses numerically better than the q3w schedule ($n = 41$), although direct comparisons are not appropriate based on the parallel phase II design of this trial. The overall response rates were 65% (complete response = 12%; partial response = 53%) for the q3w schedule and 77% (complete response = 23%; partial response = 54%) for the weekly schedule [28]. The median progression-free survival time appeared longer for patients receiving the weekly schedule, and more patients were progression free after 1 year on the weekly schedule. The 1-year and 2-year overall survival rates also favored the weekly schedule. These data are summarized in Table 3. Based on the interim safety and efficacy analyses, which suggest the weekly regimen is better tolerated and is at least as effective as the q3w regimen, the NCCTG and the National Cancer Institute stopped accrual to the q3w arm, leading to the overall imbalance of 43 patients receiving q3w therapy versus 48 of those on the weekly regimen.

Finally, the BCIRG is currently conducting a phase III study to further explore the activity of the platinum/taxane/trastuzumab combination in the first-line treatment of advanced breast cancer [29]. In study BCIRG 007 (Fig. 2), patients with tumors overexpressing HER2 (as shown by FISH) are being randomly assigned to treatment with docetaxel and trastuzumab either with or without a platinum (carboplatin AUC 6 or cisplatin 75 mg/m^2 at the discretion of the study center) (Fig. 2) [29]. Treatment will be repeated q3w for eight cycles. The planned accrual is 466 patients—233 per treatment arm [29].

Summary

An increasing number of phase II studies and one phase III study support incorporation of carboplatin as a standard agent in the management of patients eligible to receive first-

Table 3. NCCTG 98-32-52: preliminary analysis of efficacy (carboplatin/ paclitaxel/trastuzumab)

Clinical response	q3w schedule ($n = 43$)	Weekly schedule ($n = 48$)
Overall response (%)	65	77
Complete response (%)	12	23
Partial response (%)	53	54
Progression-free survival		
Median (months)	9.9	13.8
1-year (%)	40	58
Overall survival (%)		
1-year	91	100
2-year	54	73

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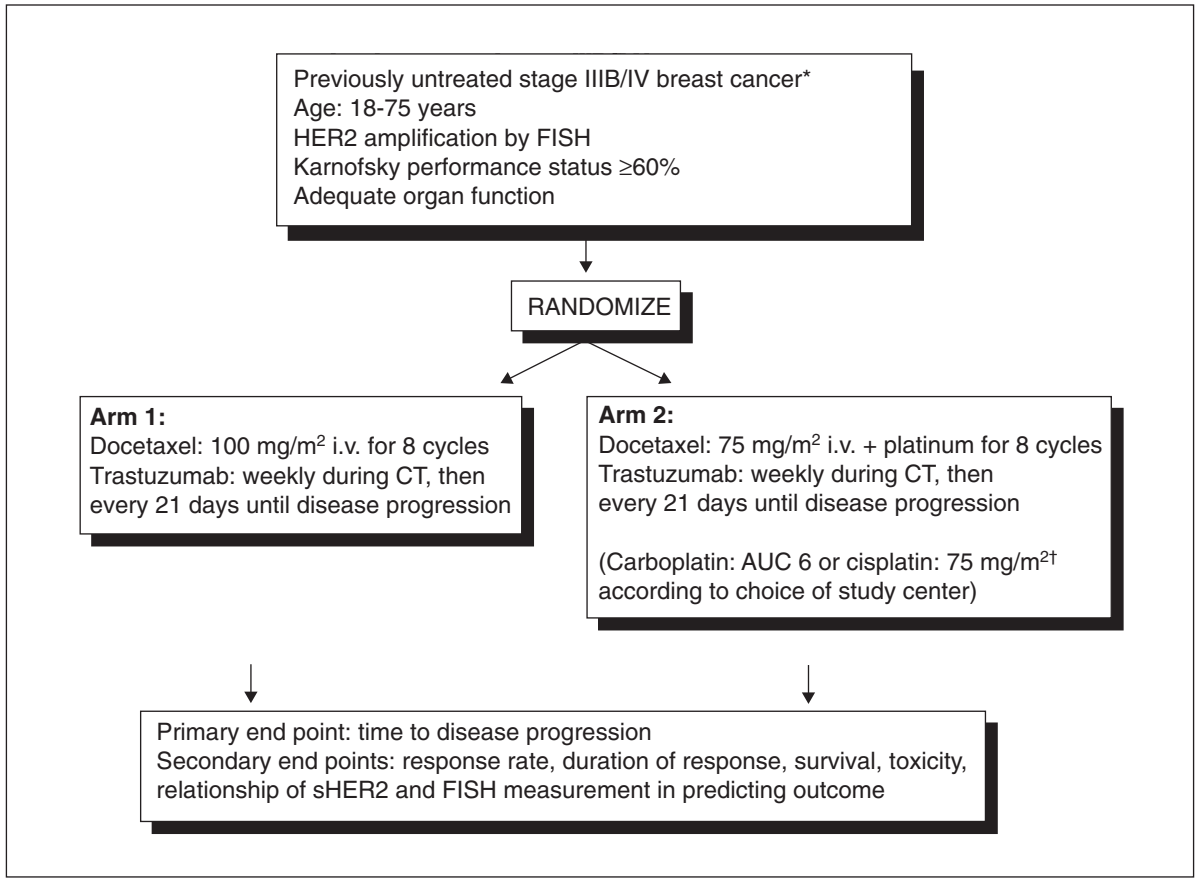

Figure 2. Schema for the BCIRG 007 trial [29]. **Prior hormonal and adjuvant and/or neoadjuvant chemotherapy (CT) allowed. If chemotherapy was either a taxane or trastuzumab, it was allowed ≥ 6 months prior to study registration. If chemotherapy was a taxane plus trastuzumab, it was allowed ≥12 months prior to study registration. If an anthracycline was used, the cumulative dose was as follows—doxorubicin ≤360 mg/m², epirubicin ≤ 720 mg/m², or mitoxantrone <72 mg/m²—and treatment was stopped at least 4 weeks prior to study registration. †Carboplatin or cisplatin was initially allowed based on the choice of the study center, but the protocol was amended to use carboplatin due to toxicity issues with cisplatin.*

line chemotherapy for metastatic breast cancer. In three phase II studies of patients whose HER2 status was unspecified, combination therapy with carboplatin and paclitaxel produced objective response rates of 53%-62% [11, 16, 17]. These rates are substantially higher than those seen in other phase II trials of either single-agent carboplatin or paclitaxel [7, 8, 10]. Moreover, another study showed that combination carboplatin/paclitaxel therapy was active in patients with

Table 4. Activity of carboplatin/taxane combinations in metastatic breast cancer irrespective of HER2 status: phase II studies

Study	Regimen	Response rate	TTP (months)	Median survival (months)	1-year survival
Perez et al. 2000 [11] NCCTG 98-32-52	Paclitaxel (200 mg/m²) + carboplatin (AUC 6) q3w	62%	7.3	16	72%
Fitch et al. 2003 [21] NCCTG N9932	Docetaxel (75 mg/m²) + carboplatin (AUC 6) q3w	58%	9.8	Not reached	72%
Brufsky et al. 2002 [19]	Docetaxel (75 mg/m²) + carboplatin (AUC 5) q3w	68%	7.9	20.6	NR
Loesch et al. 2002 [17]	Paclitaxel (100 mg/m²) + carboplatin (AUC 2), 3 weeks of a 4-week cycle	62%	4.8	16	NR

Abbreviations: TTP = time to progression; NR = not reported.

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Table 5. Activity of carboplatin/taxane with trastuzumab in patients with HER2+ metastatic breast cancer

Study	Regimen	Response rate	TTP (months)	Median survival (months)
Robert et al. [26] US Oncology 98012 Phase III	Arm A: Paclitaxel (175 mg/m^2) + carboplatin (AUC 6) Arm B: Paclitaxel (175 mg/m^2) q3w	52% versus 36% $p = 0.03$	11.3 versus 6.3 $p = 0.003$	42.1 versus 33.3 $p = 0.41$
Perez et al. [28] NCCTG 98-32-52 Phase II	Arm A: Paclitaxel (200 mg/m^2) + carboplatin (AUC 6) Arm B: Paclitaxel (80 mg/m^2) + carboplatin (AUC 2) days 1, 8, 15 q4w	A: 65% B: 77%	A: 9.9 B: 13.8	A: 25 B: 38
Burris et al. 2004 [25] Phase II	Paclitaxel (70 mg/m^2) + carboplatin (AUC 2) weekly for 6 of 8 weeks	76%	14.5	29.3
Pegram et al. 2001 [24] Phase II	Docetaxel (75 mg/m^2) + carboplatin (AUC 6) q3w	63%	12.7	NR

Abbreviations: TTP = time to tumor progression; NR = not reported.

anthracycline-resistant disease [21]. Results from phase II studies also suggest that the combination of carboplatin and docetaxel is effective in the first-line treatment of metastatic disease [19, 20]. Table 4 summarizes the activities of carboplatin/taxane combinations in patients with metastatic breast cancer irrespective of HER2 status.

Trastuzumab potentiates the activity of chemotherapy in patients with HER2+ metastatic breast cancer [30]. Preclinical data have demonstrated the synergistic interaction of carboplatin with trastuzumab in a large number of breast cancer cell lines. The biological explanation for this favorable response may be related to a decrease in DNA repair, leading to improved cellular cytotoxicity. These preclinical and biological data have been translated into the clinical setting. The results of phase II and phase III clinical trials corroborate the observations of preclinical studies. Table 5 summarizes available data on the activity of carboplatin/paclitaxel/trastuzumab in patients with HER2+ metastatic breast cancer. Specifically, phase II studies conducted by the BCIRG showed that combining trastuzumab with a platinum/docetaxel regimen is active in HER2+ metastatic disease [24]. Moreover, results from an ongoing phase III study showed that adding carboplatin to paclitaxel/trastuzumab yields a significantly higher response rate and almost doubles the median time to progression versus paclitaxel/trastuzumab, especially in those with high-level HER2 expression [26], confirming the activity of first-line carboplatin/paclitaxel/trastuzumab reported in an earlier phase II study [25]. Myelosuppression was more common with the three-drug regimen. However, preliminary results from the NCCTG 98-32-52 trial suggest that a weekly schedule of carboplatin/paclitaxel plus trastuzumab produces much less toxicity than, and is at least as effective as, the q3w schedule [28]. Studies evaluating the carboplatin/taxane combination, with or without trastuzumab, in metastatic breast cancer are ongoing. Current data on carboplatin-based regimens indicate that this is an important clinical option in the management of patients with metastatic breast cancer.

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Author's note: A recent randomized phase III trial of paclitaxel with epirubicin (taxane-anthracycline) vs. paclitaxel with carboplatin in 327 patients with metastatic breast cancer corroborated that the carboplatin combination lead to similar median survival (27.8 months for the carboplatin combination and 22.4 months for the anthracycline regimen), and better time to progression than the anthracycline- taxane combination (10.8 vs. 8.1 months, respectively) [31].

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