An open-labeled phase II trial of docetaxel in combination with cisplatin as first-line cytotoxic therapy for anthracycline-naive patients with metastatic breast cancer

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The combination of docetaxel and cisplatin has shown promising results in anthracycline-pretreated patients with advanced breast cancer, but with substantial toxicity. The efficacy and safety in anthracycline-naive patients has not been evaluated. Between October 2003 and January 2006, we enrolled 39 patients. None had undergone chemotherapy for metastatic disease or been exposure to adjuvant anthracycline-based regimens earlier. Eligibility criteria included: histologically proven metastatic cancer; WHO performance status (PS) 0–2; and adequate hematological, hepatic and renal function. Docetaxel (70 mg/m^2) and cisplatin (50 mg/m^2) were administered every 3 weeks until the patient either refused to continue, or progression, or even unacceptable toxicity occurred. Tumor response was assessed every three cycles. One patient was withdrawn from response analysis because of toxicity. Thirty-eight patients had a complete tumor assessment. Median age was 50 years (range, 28–63); 5.1% had a WHO of PS of 0; 87% a PS of 1; 7.7% a PS of 2; in 69%, two or more organs were involved. A total of 291 cycles (range, 1–9) were administered. Three complete responses and 27 partial responses (intent-to-treat response rate 30/39 = 76.9%) resulted; disease remained stable in six patients and two had disease progression. Grade III/IV toxicities included diarrhea in 10.2%, asthenia/fatigue in 2.5%, mucositis in 5.1% and neutropenia in 87.3% of patients. Seven patients developed febrile neutropenia (17.9%). The median time to progression was 11.2 months; the timespan was not sufficient to track the median survival. Docetaxel/cisplatin is an active regimen with acceptable toxicity in the first-line treatment of metastatic breast cancer, but it is not sufficiently promising as a standard. Further randomized study is warranted.
Anti-Cancer Drugs **18:1213–1219**

Anti-Cancer Drugs 2007, **18**:1213–1219

Keywords: breast cancer, cisplatin, docetaxel, metastatic breast cancer, phase II, taxanes

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Received 9 February 2007 **Revised form accepted** 16 June 2007

Introduction

Docetaxel seems to be one of the most promising agents against breast cancer. Docetaxel-based regimens can be used in neoadjuvant, adjuvant and palliative therapy to treat breast cancer [1–6]. To date, combinations of docetaxel with other antineoplastic agents [e.g. docetaxel/anthracycline (TA)] [7] have been regarded as standard regimens. The high single-agent activity of docetaxel and doxorubicin in metastatic breast cancer (MBC) and their lack of cross-resistance might explain why TA or TA plus cyclophosphamide have been proved to be superior to nontaxane regimens in palliative or adjuvant therapy [7,8]. The toxicity of TA-based regimens, however, is substantial; it is mostly due to neutropenia and related complications, and can lead to cardiac complications [7,8]. Infections or toxic death attributable to TA regimens have rarely been reported. In addition, the increasing use of anthracyclines with a single taxane argues for an urgent need for nonanthracycline-based combinations in the treatment of MBC. The problem of untoward cardiac events in patients with human epidermal growth factor receptor-2 (HER-2) overexpressing early breast cancer or MBC using trastuzumab/anthracycline has also suggested the need for a nonanthracycline substitute [9]. Docetaxel/capecitabine and paclitaxel/gemcitabine are thus regarded as promising alternatives [10,11], although these combinations have not been compared with TA in a major trial.

The rationale for combining docetaxel with platinum salts is based on a different mechanism of action: lack of cross-resistance *in vitro*, minimal overlap of toxicities and reported efficacy in solid tumors [12–14]. In general, efficacy of the docetaxel/platinum salt combination was significant, with major responses occurring in the 55–70% range in anthracycline-pretreated advanced breast cancer [15,16]. Cisplatin, however, is known to cause a dose-dependent peripheral neuropathy. Single-agent docetaxel has been reported to cause a mild neuropathy in phase I and II trials. The combination of docetaxel and cisplatin

0959-4973

induces a predominately dose-dependent sensory neuropathy that hinders the progression of this application [17].

To reduce the severity of sensory neuropathy, we treated 48 patients who had been pretreated with anthracycline for MBC with docetaxel 60 mg/m^2 and cisplatin 50 mg/m^2. The overall response rate was 62% and the time to progression was 7 months, with acceptable toxicity [18]. These promising results suggested that docetaxel with low-dose cisplatin is an active regimen for breast cancer and that, potentially, the dosage of docetaxel as first-line chemotherapy for MBC can be escalated in anthracycline-naive patients. Therefore, a phase II study was conducted.

Patients and methods

The objective of this study was to evaluate the response rate of patients with MBC to docetaxel/cisplatin first-line cytotoxic therapy. This was a prospective, single-center, open-labeled, nonrandomized phase II study. Patients who presented with pathologically confirmed, measurable adenocarcinoma of the breast and who met the following criteria were enrolled: stage IV or recurrent disease; no previous history of chemotherapy or nonanthracycline-containing adjuvant chemotherapy; a WHO performance status (PS) of 0, 1 or 2; age between 18 and 70 years; an absolute neutrophil count $\geq$ 1500 cells/μl, platelet count $\geq$ 100 000 cells/μl, hemoglobin $>$ 9 g/dl and bilirubin within normal limits; aspartate aminotransferase $<$ 2.5 $\times$ upper normal limit or $<$ 1.5 $\times$ upper normal limit if alkaline phosphatase (ALK-P) $>$ 2.5 $\times$ upper limit; ALK-P $<$ 5 $\times$ upper normal limit and creatinine $\leq$ 2.0 mg/dl. Study protocol was approved by the Institutional Review Board of this institution and written consent was obtained from all participants.

A complete medical history and a physical examination, including vital signs, height, weight and assessment of PS, were obtained 2 weeks before study registration. Radiographs used to establish measurable disease were completed 3 weeks before registration. A complete blood count with differential and platelet count, serum creatinine, calcium and serum bilirubin, aspartate aminotransferase, ALK-P, and alanine aminotransferase were obtained 2 weeks before registration.

All patients continued treatment until any evidence of disease progression or unacceptable toxicity occurred, or until such time as patients or investigators decided that it would be in the patient's best interest to stop therapy. All patients were premedicated with dexamethasone to prevent severe hypersensitivity reactions and fluid retention. Premedication consisted of 8 mg of dexamethasone orally, the night before docetaxel infusion, the morning of the infusion and 1 h before docetaxel infusion. Additionally, dexamethasone was given at doses of 8 mg twice daily for 36 h from the end of the infusion (0 h). The chemotherapy consisted of 70 mg/m^2 docetaxel intravenous infusion on day 1 and 50 mg/m^2 cisplatin on day 2. No prophylactic treatment for diarrhea was recommended; however, the patient would receive symptomatic treatment with 4 mg of loperamide after the first episode and 2 mg after each new episode until recovery (no more than 16 mg daily).

Dose reductions were made for objective or subjective toxicities. Toxicities were graded using the National Institute Cancer Common Toxicity Criteria. A maximum of one dose reduction was allowed per patient if nonhematologic toxicity greater than grade III occurred. In cases of prolonged neutropenia (over 3 days) or febrile neutropenia, prophylactic granulocyte colony stimulation factor was given during the next cycles of treatment. If the patients did not recover from grade III/IV toxicity within 2 weeks, they would be removed from the study. The course of chemotherapy was repeated every 3 weeks except if there was a maximal response as judged by a physician, or if disease progression or unacceptable toxicity occurred, or even if the patient refused to continue.

Clinical assessment of the patient's disease (i.e. by physical examination), blood count, biochemistry and side effects were performed after each treatment cycle. Indicator lesions were selected and measured periodically. All unidimensionally or bidimensionally measurable lesions were measured every three cycles. When multiple lesions were present, up to six measurable target lesions that were representative of all the organs involved were selected prospectively, giving priority to bidimensionally measurable target lesions. All evaluable and nonevaluable lesions, however, were assessed when a complete response (CR) occurred.

The response was evaluated using RECIST criteria. A CR was defined as disappearance of all known disease. A patient who had radiographic evidence of bony metastases before therapy had to have normal radiographic findings or complete sclerotic healing of lytic metastases in association with a normal bone scan. A patient with an abnormal bone scan and normal radiographs before therapy had to have normal bone scans. In the case of bidimensionally measurable disease, a partial response (PR) was defined as a decrease of at least 50% in the sum of the products of the largest perpendicular diameters of all measurable lesions. For a unidimensionally measurable disease, a PR was defined as a decrease of at least 50% in the sum of the largest diameters of all lesions. To be deemed a 'PR', not all lesions had to regress; however, none should have progressed and no new lesions should have appeared. For a bidimensionally measurable disease, stable disease (SD) was defined as a less than 50% decrease and a less than 25% increase in the sum of the products of the largest perpendicular diameters of all measurable lesions. For a unidimensionally measurable disease, SD was defined as a

less than 50% decrease and a less than 25% increase in the sum of the diameters of all lesions, and no appearance of new lesions. Progressive disease (PD) was defined as a greater than 25% increase in the size of at least one bidimensionally or unidimensionally measurable lesion, or the appearance of a new lesion. Evidence of PD included the occurrence of pleural effusion or ascites, but not necessarily of pathological fractures or collapse of bone.

Every 3 months after treatment, the patient's disease (assessed by physical examination), indicator lesions and disease status (including current response status, date of relapse or progression, and survival information) were evaluated until the patient died or was lost to follow-up. For PRs and CRs, the duration of response was defined as the interval between the date of documented PR/CR onset and the date of documented disease progression. Time to disease progression was defined as the interval between the date of enrollment (i.e. the date of registration) and the date of disease progression or the date that some other antitumor therapy was started. Survival was defined as the interval between the date of enrollment (i.e. the date of registration) and the date of death. Patients lost to follow-up were censored as of the date of last contact. Evaluable patients included all patients who had received at least three cycles of treatment with at least one follow-up tumor assessment. If PD, lethal toxicity or discontinuation of treatment (secondary to toxicity) occurred before two cycles could be administered, the patient was classified as a treatment failure, but was still evaluated. All efficacy analyses were based on the intent-to-treat and evaluable population. Safety analyses included all patients who had received at least one dose of any study drug.

The primary objective was to assess the response rate and to determine whether the regimen was sufficiently promising. To fulfill this objective, the Fleming method [19] was used in conjunction with the following assumptions: H0: $P \leq 30\%$ (maximal ineffectiveness); H1: $P \geq 54\%$ (minimal effectiveness); and a type I error of 5% and a type II error of 20% (power of 80%). In total, 35 evaluable patients were needed, assuming a 10% dropout rate, we enrolled up to 40 patients in this phase II study. The objective response rate was defined as the CR rate plus the PR rate; 95% confidence intervals (CIs) of the estimate were provided. Duration of response, time to disease progression and survival were estimated using the Kaplan–Meier method. The incidence and types of adverse experiences and changes in physical examination findings and laboratory evaluations were tabulated and summarized using descriptive statistics.

Results

Patient characteristics

Between October 2003 and January 2006, 39 patients with no previous chemotherapy or anthracycline adjuvant therapy for MBC or recurrent breast cancer were enrolled. Out of the 39 patients assessable for safety, one was not evaluable for response owing to acute exacerbation of chronic hepatitis B that prevented the continuation of treatment after the first cycle. Baseline characteristics of the patients are listed in Table 1. Median age was 50 years (range, 28–63) and median PS was 1. Twenty-seven patients (69.2%) had visceral metastases as the dominant site of disease. Twenty-nine (74.4%) patients had undergone adjuvant chemotherapy earlier with a methotrexate-based regimen; the remaining patients were chemonaive. A total of 291 cycles of chemotherapy were administered, with a mean of 7.5 cycles and median of nine cycles (range, 1–9). Twenty (51.3%) patients completed nine cycles of chemotherapy as planned, whereas 10 of the responding patients discontinued chemotherapy because of accumulated toxicity.

Efficacy

Thirty-eight patients received at least three cycles of chemotherapy and were eligible for response assessment. CR was obtained in three patients (7.9%), PR in 27 (71.1%), SD in six (15.8%) and PD in two patients (5.2%). The intent-to-treat analysis, however, showed that the objective response rate was 76.9% [95%

Table 1 Baseline characteristics of patients

Patient characteristics	No. of patients ($N=39$)	(%)
Age		
Median	50	
Range	28–63	
Performance status (WHO)		
0	2	5.1
1	34	87.2
2	3	7.7
Previous adjuvant chemotherapy		
Yes	29	74.4
No	10	25.6
No. of metastases		
1	12	30.7
2	11	28.2
3	13	33.3
4	3	7.7
Site of metastases		
Liver	6	15.4
Lung	21	53.9
Lymph node	20	51.3
Bone	19	48.7
Chest wall	9	23.1
Breast	8	20.5
Visceral organ involvement		
Yes	27	69.2
No	12	30.8
Estrogen receptor		
Negative	24	61.5
Positive	15	38.5
Progesterone receptor		
Negative	25	64.1
Positive	14	35.9
HER2		
Negative	29	74.4
Positive	8	20.5
Unknown	2	5.1

confidence interval (CI), 68–90%, Table 2]. Out of 27 patients with PR, four patients had CR in nonosseous tissue. Owing to bone metastases in these four patients, however, they could not be classified as having CR. All the three patients who obtained a CR had nonvisceral metastatic sites (neck lymph nodes and/or soft tissue lesions). At a median follow-up of 16.5 months, median time to progression was 11.2 months (95% CI, 8.5–13.8 months) and the estimated median overall survival was 31.8 months (95% CI, 15.8–47.5 months), whereas only 10 patients died. Time to progression in responders was 16.7 months. We observed no significant differences in overall response rate or survival between HER-2-positive ($n = 8$) and HER-2-negative ($n = 29$) groups. Tumor response occurred in 22 out of 29 HER-2-negative patients (response rate, 75.9%) and in seven of the eight HER-2-positive patients (response rate, 87.5%).

Toxicity

Evaluation of toxicity was possible in all 39 patients. Ten patients stopped chemotherapy because of intolerable side effects or toxicity. One of these experienced an acute exacerbation of hepatitis B virus (HBV) infection whose serum HBV DNA was undetectable before chemotherapy. Before the second chemotherapy cycle, however, her hepatic transaminase level increased abruptly. Reactivation of the HBV infection was confirmed by the presence of higher serum DNA titers. Her condition subsequently progressed to decompensated liver disease with prolonged jaundice, increased prothrombin time and the presence of ascites. Fortunately, she recovered after the administration of lamivudine. The patient was removed from the study. Fluid retention, cisplatin allergy after seven cycles of chemotherapy and sensory neuropathy led to the withdrawal from chemotherapy in three, one and two patients, respectively. The two patients who discontinued chemotherapy from sensory neuropathy experienced grade II toxicity and withdrew consent themselves. Six patients required docetaxel dose reduction to 60 mg/m^2: for two patients for grade IV diarrhea, two for recurrent febrile neutropenia, one for hand–foot syndrome and one for syncope. The hematological toxicity was monitored weekly for the first two cycles, and every 3 weeks thereafter. Grade III and IV neutropenia was observed in 12.8 and 74.5% of patients, respectively. Seven patients (17.9%) experienced febrile neutropenia. The most common nonhematological toxicities were vomiting, diarrhea, sensory neuropathy and asthenia. The only grade IV toxicities, however, were diarrhea, hepatoxicity and neutropenia. Toxicities observed during the treatment are listed in Table 3.

Table 2 Response to treatment

	Intention to treat population		Evaluable population	
Response	No. of patients (N=39)	(%)	No. of patients (N=38)	(%)
CR	3	7.7	3	7.9
PR	27	69.2	27	71.1
Overall response rate (CR + PR)	30	76.9	30	78.9
Stable disease	6	15.4	6	15.8
Disease progression	2	5.1	2	5.3

CR, complete response; PR, partial response.

Discussion

This is the first study to validate docetaxel/cisplatin as an active first-line regimen for anthracycline-naive patients with MBC. The response rate and time to progression of this study approximate those of other published trials using taxane doublets (e.g. TA) as first-line therapy for MBC. In addition, docetaxel/cisplatin was associated with a lower frequency of sensory neuropathy and other nonhematologic toxicities. Consequently, most of the responding patients were able to complete nine cycles, which might result in a longer interval before disease progression.

The acceptance of taxane doublet regimens has been slow. One of the major reasons is that the toxicities that result from these regimens are difficult to manage. For example, docetaxel combined with doxorubicin or vinorelbine has caused high frequencies of grade III/IV

Table 3 Toxicities according to National Cancer Institute Common Toxicity Criteria

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Toxicities	N=39					Cycle=291				
	Percent of patients					Percent of cycles				
Neutropenia	2.5	2.5	7.7	12.8	74.5	39.2	12.2	12.8	10.8	25
Anemia	28.2	53.8	15.5	2.5	0	43.0	48.1	8.6	0.3	0
Thrombocytopenia	79.5	20.5	0	0	0	98.3	1.7	0	0	0
Nausea/vomiting	15.4	18.0	56.4	10.2	0	48.1	33	17.2	1.7	0
Mucositis	43.6	28.2	23.1	5.1	0	77.7	16.5	5.1	0.7	0
Diarrhea	18.0	18.0	53.8	5.1	5.1	63.2	17.5	17.2	1.4	0.7
Neuropathy	15.4	53.8	30.8	0	0	41.3	40.2	18.5	0	0
Myalagia/arthralagia	38.5	38.5	23.0	0	0	76.6	18.9	4.5	0	0
Asthenia/fatigue	18.0	41.0	38.5	2.5	0	63.2	22.0	14.4	0.4	0
Hand–foot syndrome	87.3	2.5	7.7	2.5	0	95.9	1.7	2.1	0.3	0
Hepatotoxicity	61.6	35.9	0	0	2.5	83.9	15.8	0	0	0.3
Edema	74.5	20.5	5.0	0	0	94.5	4.5	1.0	0	0

neutropenia and febrile neutropenia [7,20]. Critics also point to the lack of evidence showing the superiority of two-drug combinations over their sequential use. The results of two large randomized trials in anthracycline-pretreated MBC patients were promising [10,11]. Docetaxel/capecitabine or paclitaxel/gemcitabine treatments have attracted greater interest owing to their superior activity over single taxanes, as well as their more manageable toxicities (except for the palmar–plantar erythema reaction). The reported higher rate of adverse effects from the combinations might, nevertheless, be due to both overlapping toxicity profiles and intensive pretreatment. In anthracycline-naive patients, these regimens have yet to be fully tested; however, their efficacy should be anticipated.

Despite the well-known synergistic effect and clinical activity of docetaxel/cisplatin in the treatment of other solid tumors (such as nonsmall cell lung cancer), this combination is not as commonly used as other agents in the treatment of MBC. Cisplatin is not among the most active of drugs used in breast cancer and has questionable efficacy in the treatment of anthracycline pretreated patients. The substantial neurotoxicity and myelosuppression associated with this combination are some of the obstacles [7]. Early studies of docetaxel/cisplatin used relatively high doses of cisplatin with docetaxel. In a phase I trial, Crown *et al.* [21] was able to reach a maximum tolerated dose of 100 mg/m^2 docetaxel and cisplatin; however, a lower dose of cisplatin has been suggested to diminish the dose-limiting toxicities (i.e. emesis and renal toxicity). Bernard *et al.* [15] treated 32 patients with 100 mg/m^2 docetaxel and 100 mg/m^2 cisplatin. Despite the promising 50% response rate, grade III/IV neutropenia occurred in 55% of patients; 72% required granulocyte colony-stimulating factor and 65% required dose reduction. Additional toxicities including cutaneous and neurological toxicities occurred in 78 and 75% of patients, respectively. Spielmann *et al.* [16] conducted a phase I/II study to determine the maximum tolerated dose and the activity profile of docetaxel and cisplatin in anthracycline-resistant patients. The dose-limiting toxicity was found to be febrile neutropenia at 75/80 mg/m^2 of docetaxel and cisplatin. Ninety-three percent of the patients experienced grade III/IV neutropenia (20% febrile) and 12%, grade III/IV peripheral neuropathy. One patient died of septic shock.

The following studies reduced the dosage of both docetaxel/cisplatin owing to their substantial toxicities. Vassilomanolakis *et al.* [22] reported a trial of docetaxel (75 mg/m^2) and cisplatin (75 mg/m^2) as first-line chemotherapy in chemonaive patients with MBC, 16 (32%) of whom received anthracyclines as adjuvant. Prophylactic recombinant human granulocyte colony-stimulating factor was, nevertheless, administered. The overall response rate was 68% (95% CI, 55–81%), which was close to the rate in our study [22]. Recently, two studies from Korea used lower doses of docetaxel/cisplatin in anthracycline pretreated patients with MBC. In the study of Park *et al.* [23] patients with MBC were treated with 75 mg/m^2 docetaxel and 60 mg/m^2 cisplatin. The objective response rate was 31% and neutropenia was the most frequently observed toxicity (39%) [23]. In the study by Ahn *et al.* [24], 50 younger MBC patients (median age, 43 years) were first treated with anthracycline, and then with 75 mg/m^2 docetaxel and 75 mg/m^2 cisplatin as first-line (23 patients) or second-line (27 patients) therapy. The overall response rate was 40%, and toxicities included grade III/IV neutropenia in 38% of the patients and febrile neutropenia in 14%. In summary, docetaxel/cisplatin is an active regimen in anthracycline-pretreated patients. Although these studies cannot be directly compared with ours, the response rate to docetaxel/cisplatin in our study approximates the response rates to docetaxel/capecitabine or gemcitabine combinations in the above studies [10,11]. The higher doses of cisplatin, the toxicity increased accordingly.

For chemonaive patients, Lee *et al.* [25] used docetaxel and cisplatin both at 70 mg/m^2 for four courses as primary chemotherapy for locally advanced breast cancer. Pathologic CR in the breast was achieved in 15 patients (26%). This result was promising as a pathological complete remission rate of over 20% was rarely seen in patients on regular dose schedules of docetaxel-based regimens. In combination with our results, these results suggest that docetaxel/cisplatin is a very active regimen for first-line MBC and the role of docetaxel/cisplatin as an alternative to anthracycline in patients for whom anthracycline is not suitable should be further investigated.

The docetaxel dosage of 70 mg/m^2 in this study was selected on the basis of studies in Asian populations. Goh *et al.* [26] reported that people of Chinese ethnicity have lower docetaxel clearance. In addition, the optimal dosage in Japanese patients was published as 55–60 mg/m^2 [27]. Our previous experience using single docetaxel at a dose of 75 mg/m^2 every 3 weeks also revealed that 25% of patients with MBC who had been pretreated with anthracycline and paclitaxel developed grade III/IV neutropenia [18,28]. The effect of taxane/cisplatin on the frequency and severity of neuropathy remains obscure. A phase I study in locally advanced solid tumors found that varying degrees of neuropathy developed in 26 out of 35 (74%) patients treated with cumulative doses of both cisplatin and docetaxel above 200 mg/m^2 [17]. We therefore maintained a higher dosage of docetaxel and reduced cisplatin to 50 mg/m^2 to delay the occurrence of neuropathy and to prolong the treatment period. No grade III/IV sensory neuropathy was observed in this study, but two patients withdrew owing to neuropathy.

The concern of compromising treatment efficacy as a result of reducing cisplatin dose was unfounded as both the response rate and time to progression remained promising in this study. The sensory neuropathy might, nevertheless, be overcome by replacing cisplatin with carboplatin. The docetaxel/carboplatin combination has attracted significant attention for its high activity with a lower frequency of neuropathy in a few phase II trials [29,30]. Unfortunately, carboplatin has only limited approved indication in this country. If feasible, substitution in place of cisplatin would be a reasonable approach; however, this deserves further investigation.

The role of this combination is of particular importance in the postanthracycline era and as a cotreatment with trastuzumab in HER-2-positive patients [31,32]. The regimen might be further optimized with docetaxel/carboplatin to reduce the frequency of neuropathy, as the BCIRG 006 study suggested [33]. Of note is that 75.9% of the 29 HER-2-negative patients included in this study responded to docetaxel/cisplatin. Therefore, the regimen should not be limited to HER-2-positive patients as part of trastuzumab-based regimens.

No direct comparisons have been made between the docetaxel/platinum combination and docetaxel single agent for MBC. Published data have shown promising findings with response rates ranging from 42 to 68% for the docetaxel single agent [34–36]. Additionally, the response of docetaxel monotherapy in MBC seems to be dose dependent [36]; therefore, whether the effect of docetaxel/cisplatin combination in reduced dosage is comparable with the effect of docetaxel single agent at 100 mg/m^2 remains inconclusive.

In summary, the promising results shown in this study suggest a possible active combination using docetaxel with cisplatin in combating MBC. The data, however, generated so far may not be sufficient to establish this combination as a potential standard. In particular, the possible advantages of the combination regimen over docetaxel single agent remains unclear at present. Further randomized controlled studies are warranted to confirm the activity of docetaxel combined with cisplatin.

Acknowledgement

This work was partly supported by Sanofi-Aventis.

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