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Weekly Docetaxel and Gemcitabine as First-Line Treatment for Metastatic Breast Cancer: Results of a Multicenter Phase II Study

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Key Words
Docetaxel · Gemcitabine · Metastatic breast cancer · Phase II study

Abstract
Objectives: We conducted a multicenter phase II study to evaluate the clinical efficacy, toxicity, and dose intensity of a new weekly schedule of docetaxel and gemcitabine as first-line treatment of metastatic breast cancer patients. ***Methods:*** We enrolled 58 patients, 52% of whom had received a previous anthracycline-containing chemotherapy. The treatment schedule was: docetaxel 35 mg/m^2 and gemcitabine 800 mg/m^2 i.v. on days 1, 8, 15 every 28 days. ***Results:*** All patients were assessable for toxicity and 56 for efficacy. Overall response rate was 64.3% with 16.1% of complete responses and 48.2% of partial responses. Median survival was 22.10 months (95% CI: 15.53–28.67) and median time to tumor progression was 13.6 months (95% CI: 10.71–16.49). The most common hematological toxicity was neutropenia (no febrile neutropenia), which occurred in 28 patients (48.3%) but grade 3–4 in only 8 patients (14%). Alopecia, the most common nonhematological toxicity, occurred in 20 (34.5%) patients, but only 5 patients (8.6%) experienced grade 3 alopecia. ***Conclusion:*** The activity of docetaxel and gemcitabine in metastatic breast cancer is confirmed. The promising results of the employed schedule, in agreement with other published studies, need to be further confirmed within a phase III study.

Introduction

The treatment of metastatic breast cancer (MBC), a typically incurable disease, is one of the main active research fields for medical oncologists. Between the 1970s

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and the mid-1990s, the anthracyclines were the reference chemotherapeutic agents in the treatment of this disease with an overall response rate (ORR) of 35–50% in first-line and 25–30% in second-line treatments [1]. Nonetheless, objective tumor responses are usually short-lived, median survival does not exceed 25 months and the toxicity profile is not very suitable for patients with advanced disease. In the past decade, the introduction of two taxanes, paclitaxel and docetaxel, represented an important advance in the treatment of MBC. Docetaxel as a single agent, in previously untreated patients, provides ORR ranging from 40 to 68% [2, 3], while in anthracycline-resistant patients, the ORR is 53–57% [4, 5]. Although extremely active in terms of ORR, the 3-week schedule of docetaxel 100 mg/m^2 as single agent is associated with grade 3–4 neutropenia in 90–95% of the cases [6]. Weekly administration of docetaxel, evaluated in phase II studies [6–13], represents an interesting alternative schedule, particularly indicated in the metastatic setting, given the opportunity to reduce chemotherapy-related toxicity (especially hematological toxicity) while preserving its high activity.

Gemcitabine has been shown to be safe and effective when used in MBC. As single agent, both in first- and second-line treatments, it has been reported to yield a 12–38% ORR with a good toxicity profile [14–17]. Preclinical evidence of a synergism between gemcitabine and docetaxel on cytotoxicity and apoptosis in breast cancer cells was reported [18]. Due to the activity of the two agents, the different mechanism of action, the nonoverlapping toxicities and the favorable toxicity profile of the weekly schedule, there is a strong rationale to use this drug combination for the treatment of MBC patients, with an attempt to combine the clinical response with the improvement or maintenance of quality of life and prolongation of survival. We have recently carried out a dose-finding study with docetaxel plus gemcitabine on a new weekly schedule (gemcitabine 800 mg/m^2 on days 1, 8 and 15 every 28 days + docetaxel at 3 escalating dose levels of 30, 35 and 40 mg/m^2) in 18 pretreated MBC patients with the aim to determine the maximum tolerable dose (MTD) of docetaxel and the toxicity patterns of this regimen. The MTD for docetaxel was established at 35 mg/m^2. Hematological and nonhematological toxicities were low in number and manageable [19]. With this background, we conducted a multi-institutional phase II study, whose data were partially presented in an abstract form [20], to evaluate the clinical efficacy, the toxicity pattern and the dose-intensity of a new weekly regimen of docetaxel and gemcitabine.

Patients and Methods

Patients with cytologically and histologically confirmed breast carcinoma at the first diagnosis of metastatic disease were enrolled. The presence of measurable disease was requested. Previous hormone therapy for both adjuvant and anti-metastatic purposes was allowed. Previous adjuvant radiotherapy or for advanced breast cancer was permitted, provided the irradiated lesions were not the only site of disease. With regard to adjuvant chemotherapy, if it did not include a taxane, patients could be enrolled independently of the length of time elapsed from the end of adjuvant therapy; if the adjuvant treatment included a taxane, a 12-month interval at the end of chemotherapy was mandatory. To be eligible, patients had to be aged between 18 and 75 years, have a performance status between 0 and 2 on the ECOG scale and a life expectancy of more than 3 months. Other inclusion criteria included: adequate bone marrow [absolute neutrophil count (ANC) $\geq$1,500/μl, platelet count $\geq$120,000/μl, Hb $\geq$10 g/dl], liver (serum total bilirubin $\leq$2 mg/dl; GOT/GPT $<2\times$ the upper normal value) and renal functions (serum creatinine $\leq$1.2 mg/dl); absence of other concurrent or previous malignant neoplasm, with the exception of adequately controlled in situ uterine carcinoma and/or cutaneous basal cell carcinoma; geographical accessibility to the participating oncology centers and written informed consent. Exclusion criteria: clinically detectable brain metastases, concurrent and uncontrolled cardiovascular, metabolic, renal, neurological or infectious diseases. Previous chemotherapy for metastatic disease, concurrent treatment with other chemotherapeutic, hormonal or immunological antineoplastic agents, and pregnancy also rendered the patient ineligible. The study was approved by an independent ethics committee. Subsequently, an accurate clinical history was taken and all patients underwent a complete clinical examination. Before starting chemotherapy, all eligible patients were extensively staged for accurate definition of disease extension and measurement of disease with two-view chest X-ray, abdomen ultrasound, computed tomography of the involved areas, and bone scan. Complete blood cell counts were performed weekly and routine biochemistry at every cycle. After 3 and 6 cycles, patients underwent re-evaluation of their disease with the same basal staging procedures.

Treatment Schedule

Patients received docetaxel 35 mg/m^2 by intravenous infusion for 60 min on days 1, 8 and 15, and gemcitabine 800 mg/m^2 by intravenous infusion for 30 min after docetaxel infusion on days 1, 8 and 15. The sequence of 3 administrations on days 1, 8, 15, followed by a 2-week rest period, represented a cycle. In order to prevent fluid retention and hypersensitivity reactions, all patients received dexamethasone 8 mg 12 h before administration and on days 1 and 2. Antiemetic treatment was administered at the discretion of each researcher. The routine use of prophylactic G-CSF was not allowed; however, investigators were free to employ growth factors according to individual patients' needs in case of neutropenia (ANC $<$900/μl) and/or infectious complications. The type of objective response achieved and recorded after the first 3 cycles determined the duration of treatment: in the case of a CR, patients received 3 further cycles up to a maximum of 6 cycles of chemotherapy; in the case of partial tumor regression or stabilization, patients received 3 more cycles and were then re-evaluated for response; treatment continued up to a total of 8 cycles, progression or unacceptable toxicity. If progression of disease occurred, patients

dropped out of the study and were followed up to record overall survival.

Assessment of Response, Toxicity and Dose Intensity

Complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) were assessed according to the WHO criteria [21]. CR was defined as complete regression of all lesions and signs and symptoms of disease. PR was defined as a reduction $\geq 50\%$ in the sum of the product of the two principal diameters of all measurable lesions, including partial healing of lytic lesions or reduction in the number of the uptake areas, lasting at least 2 months. SD was considered as a <50% reduction or <25% increase in the above sum, lasting at least 3 months. PD was defined as an increase >25% in the sum of the product of the two principal diameters of all measurable lesions, and/or the appearance of new lesions. Toxicity was assessed at every cycle according to the WHO. If, on the planned day of therapy, ANC was <1,500/μl and/or platelet count was less than 100,000/μl, chemotherapy was delayed for 1 week; in the case of slow recovery despite delay, subsequent doses of both gemcitabine and docetaxel were reduced by 25%. If grade 2 liver toxicity occurred, docetaxel and gemcitabine dosages were both reduced by 50%; in the case of persistent grade 2 or de novo grade 3 hepatic toxicity, treatment was delayed by 1 week to allow recovery; if no recovery was verified within 2 weeks, treatment was stopped and patients dropped out. In the case of grade 1–2 neurotoxicity, the dose of docetaxel was reduced by 50% for subsequent administrations, while gemcitabine dosage remained unaltered. If neurotoxicity of more than grade 2 occurred, treatment withdrawal was considered. The actual dose intensity was calculated for docetaxel and gemcitabine using the following formula: dose (mg) × number of administrations/total interval between courses (weeks).

Statistical Analysis

The primary end-point of this phase II study was the evaluation of clinical efficacy in terms of clinical response, survival, time to progression (TTP) and time to treatment failure (TTF); secondary end-points were considered: analysis of toxicity profile and of dose intensity. The study was designed to detect a 60% ORR applying a two-step minimax design according to Simon. Considering a type 1 error of 0.05 and a type 2 error of 0.20, at least 8 objective responses had to be recorded in the first cohort of 16 patients in order to proceed to the second step, after which a total of 30 responses had to be achieved in the whole population before being able to reject the hypothesis that the ORR was less than the estimated 60%. A total of 50 assessable patients were to be enrolled in the trial. Duration of CR was calculated from the first assessment of CR until the appearance of PD. Duration of PR or SD was defined from the time of starting chemotherapy until disease progression. TTP was calculated from the date of starting chemotherapy until clinical and/or instrumental evidence of progressive disease, while overall survival was calculated from the date of starting chemotherapy until death or last documented follow-up. TTF was calculated from the date of starting chemotherapy until the date of progression, death (by any cause), adverse event, loss to follow-up, whichever occurred first. The follow-up time was measured from the day of the administration of first the treatment to the last contact or death.

All data concerning TTP, TTF and overall survival were analyzed by computer to generate curves according to the Kaplan and Meier method by the SPSS statistical package (version 8.0, 1997).

Results

Patients' Characteristics

Between January 2001 and June 2003, 58 patients with MBC were enrolled into the study. All patients were chemotherapy naive for metastatic disease. Fifty-six (96.5%) patients were assessable for response and all for toxicity. Two patients were not assessable for response because they refused to continue therapy. The characteristics of this cohort of patients are summarized in table 1. The median age was 58.5 years (35–75) and PS according to ECOG was 0 in 32 patients (55.2%), 1 in 24 (41.4%), 2 in 2 (3.4%). Thirty (52%) patients had received an anthracycline-based chemotherapy (3 in a neoadjuvant and 27 in an adjuvant setting). With regard to the other adjuvant treatments, 2 (3%) patients had received a taxane (paclitaxel). In this group, an adequate interval (>12 months) from the adjuvant treatment, as per protocol, was respected. No patient had received previous docetaxel-containing therapy. Two patients had received adjuvant high-dose chemotherapy plus peripheral blood stem cell reinfusion. Thirty-six (62%) patients had multiple sites of disease: 15 (26%) had 2 sites of disease, 21 (36%) had >3 sites of disease. The sites of metastases were: lung in 27 (46%), lymph nodes in 21 (36%), liver in 18 (31%), bone in 20 (34%), pleura in 13 (22%), skin in 12 (21%), breast in 11 (19%), pericardium in 3 (5%), and peritoneum, ovary and adrenal gland in 1 (2%). At least 1 visceral site of metastasis was present in 45 (77.6%) patients.

Response and Survival

A total of 270 cycles was administered with a median number of 4.5 cycles (1–12) per patient. Planned dose intensity for docetaxel was 26.25 mg/m^2/week and 600 mg/m^2/week for gemcitabine. The median actual dose intensity for docetaxel was 26.25 (13.12–26.25) mg/m^2/week (100% of the planned dose) and 600 (300–600) mg/m^2/week (100% of the planned dose) for gemcitabine. Thirty-eight patients (65%) received treatment with a >90% dose intensity.

Following the research protocol, we proceeded to the second step of the study after obtaining 8 objective responses in the first group of 16 patients. Among the 56 assessable patients, 9 (16.1%) achieved a CR, 27 (48.2%) obtained a PR with an ORR of 64.3%.Twelve (21.4%) patients had SD while PD occurred in 8 (14.3%) patients. Patients with CR had a median TTP of 12.3 months (95% CI: 5.15–19.45); in patients with PR the median TTP was 15.5 months (95% CI: 9.54–21.46). In patients with SD

Table 1. Patients' characteristics

Patient characteristics	n	%
Number of patients enrolled	58	100
Assessable for activity	56	96
Assessable for toxicity	58	100
Age, median (range)	58.5 (35–75)	
Performance status (ECOG)		
0	32	55.2
1	24	41.4
2	2	3.4
Histological type		
Ductal invasive	40	69
Lobular invasive	7	12.1
Medullary	2	3.4
NOS	9	15.5
Previous treatments		
Surgery	49	84
Radiotherapy	15	26
Adjuvant chemotherapy	42	72
Neoadjuvant chemotherapy	3	5
Taxol-containing chemotherapy	2	3
Anthracycline-containing chemotherapy	30	52
High-dose chemotherapy + PBSC	2	3
Hormone therapy adjuvant/first-line	27/6	46/10
Radiotherapy adjuvant/first-line	15/7	26/12
Metastatic sites		
1	22	38
2	15	26
≥ 3	21	36
Sites of disease		
Lung	27	46
Nodes	21	36
Bone	20	34
Liver	18	31
Pleura	13	22
Skin	12	21
Breast	11	19
Pericardium	3	5
Ovary	1	2
Peritoneum	1	2
Adrenal gland	1	2
Cycles administered		
Median (min–max)	4.5 (1–12)	
Total	270	

Table 2. Response and survival

Objective response	Patients		TTP, months		Survival, months	
	n	%	median	95% CI	median	95% CI
CR	9	16.1	12.3	5.15–19.45	22.27	13.84–30.70
PR	27	48.2	15.5	9.54–21.46	29.30	18.74–30.61
SD	12	21.4	9.77	2.25–17.28	24.57	16.43–32.70
PD	8	14.3	2.7	1.42–3.98	7.43	3.96–7.63

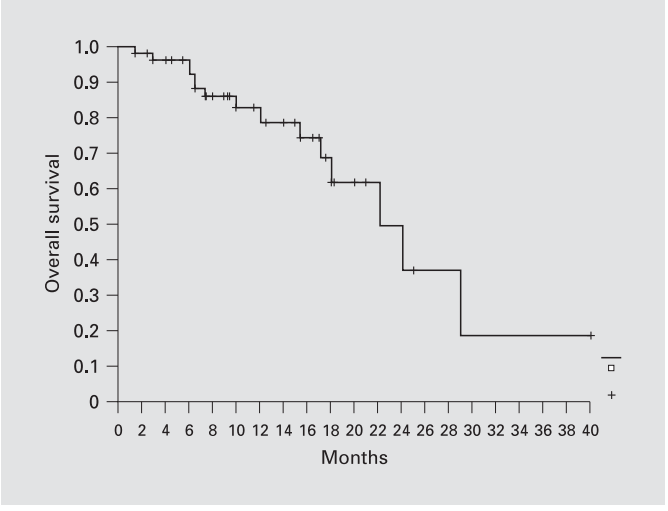

Fig. 1. Kaplan-Meier curve of overall survival. The median survival was 22.10 months (95% CI: 15.53–28.67).

the median TTP was 9.77 months (95% CI: 2.25–17.28). After a median follow-up of 10.6 months, 15 patients died (all for tumor-related causes) and 43 patients (74.1%) are still alive at the cut-off date of 36 months; 24 patients experienced PD. The median survival was 22.10 months (95% CI: 15.53–28.67). The median survival for patients with CR was 22.27 months (95% CI: 13.84–30.70). Patients who achieved a PR had a median survival of 29.30 months (95% CI: 18.74–30.61). In patients with SD median survival was 24.57 months (95% CI: 16.43–32.70). The median survival in patients who experienced PD was 7.43 months (95% CI: 3.96–7.63). Objective response and survival data are reported in table 2. The Kaplan-Meier curve of overall survival is represented in figure 1. The median TTP was 13.6 months (95% CI: 10.71–16.49). The median TTF was: 8.60 months (95% CI: 4.79–12.41).

Compliance to Treatment and Toxicity

Treatment discontinuation occurred in 2 patients for refusal. The most common hematological toxicity was neutropenia, which occurred in 28 patients (48.3%) but grade 3–4 in only 8 patients (14%). No case of febrile neutropenia was reported. Twenty patients (34.5%) experienced anemia, grade 3 in 2 patients (3.4%). Grade 3 thrombocytopenia was registered in 4 patients (6.9%). Hematological toxicity is reported in table 3.

Table 3. Hematological toxicity (assessable patients: n = 58)

Type (assessable patients = 58)	Grade	Patients	
		n	%
Neutropenia	G1/G2	20	34.5
	G3/G4	8	13.8
Anaemia	G1/G2	18	31
	G3/G4	2	3.4
Thrombocytopenia	G1/G2	19	32.7
	G3/G4	4	6.9

Table 4. Non-haematological toxicity (assessable patients: n = 58)

Type	Grade	Patients	
		n	%
Nausea/vomiting	G1/G2	11	18.9
	G3/G4	1	1.7
Diarrhea	G1/G2	4	6.9
	G3/G4	3	5.2
Stomatitis	G1/G2	4	6.9
	G3/G4	2	3.4
Renal	G1/G2	1	1.7
	G3/G4	–	–
Hepatic	G1/G2	7	12.1
	G3/G4	–	–
Alopecia	G1/G2	15	25.9
	G3/G4	5	8.6
Fever	G1/G2	8	13.8
	G3/G4	–	–
Cardiac	G1/G2	2	3.4
	G3/G4	–	–
Neurotoxicity	G1/G2	3	5.2
	G3/G4	1	1.7
Asthenia	G1/G2	12	20.7
	G3/G4	1	1.7
Skin	G1/G2 (nail changes)	2	3.4
	G3/G4	1	1.7
Flu-like syndrome		1	1.7

With regard to nonhematological toxicity, alopecia was the most common: it occurred in 20 (34.5%) patients, but only 5 patients (8.6%) experienced grade 3 alopecia. Asthenia was registered in 13 (22.4%) patients but was of grade 3 in only 1 case (1.7%). Twelve patients (20.6%) experienced nausea/vomiting, mostly of grade 1–2 (18.9%). Mild hepatic toxicity occurred in 7 patients (12%). With respect to grade 3–4 nonhematological toxicities, the most frequent were: alopecia as previously cited, diarrhea in 3 (5%) patients (grade 3 in 2 patients and grade 4 in 1 patient) and stomatitis in 2 (4%) cases (grade 3 in 1 patient and grade 4 in 1 patient). No case of fluid retention syndrome was seen. No patient experienced eye tearing toxicity (table 4). There was no treatment-related death. The addition of gemcitabine and/or the length of treatment did not affect the toxicity profile.

Discussion

The difficulties which medical oncologists have in finding an optimal treatment for MBC, still an incurable illness, are witnessed by the large amount of studies performed in this area in which it is necessary to combine the need for effective therapies with the goal of the improving quality of life and survival.

Docetaxel is a highly active agent in advanced breast cancer. It has demonstrated a superior activity when compared both to single agent doxorubicin [22] or paclitaxel [23] and polichemotherapy as mitomycin C plus vinblastine [24] or methotrexate plus 5-fluorouracil [25].

Although extremely active, the 3-week schedule of docetaxel 100 mg/m^2 as single agent is associated with a high incidence of myelosuppression [6]. Weekly administration of docetaxel has an efficacy at least comparable with the standard 21-day administration with lower myelotoxicity [6–13, 26]. The better toxicity profile of weekly docetaxel makes it particularly suitable for combination with other active drugs as gemcitabine in MBC patients.

The combination of docetaxel and gemcitabine as first- and second-line therapy for MBC has been evaluated in phase II trials [27–36]. Mavroudis et al. [27] enrolled 52 patients previously treated for metastatic disease. Their patients received gemcitabine 900 mg/m^2 i.v. on days 1 and 8 and docetaxel 100 mg/m^2 on day 8, every 3 weeks and prophylactic G-CSF from the 9th to the 15th day. The ORR was 54%, with 14% CR and 40% PR. Four patients, who had PD after a paclitaxel or docetaxel monotherapy, achieved a PR after treatment with the combination of docetaxel and gemcitabine. The median duration of response was 3.6 months and the median TTP 8 months. Regarding the hematological toxicity, neutropenia of grade 3–4 occurred in 29% of patients despite the

Table 5. Phase II studies with gemcitabine-docetaxel combination in MBC

Author and year of publication	Patients	Prior therapy	Schedule	ORR %	TTP months	Toxicities, %
Mavroudis et al. [27] 1999	52	anthracyclines 100%	G 900 mg/m^2 1, 8 + T 100 mg/m^2 8 q21	54	8	neutropenia G3/4 = 29 thrombocytopenia G3/4 = 21
Fountzilas et al. [31] 2000	39	anthracyclines 100%	G 1,000 mg/m^2 1, 8 + T 75 mg/m^2 1 q21	36	7	neutropenia G3/4 = 49 FN = 18 alopecia G3 = 77.5
Laufman et al. [32] 2001	39	anthracyclines 85%	G 800 mg/m^2 1, 8, 15 + T 100 mg/m^2 1 q28	79	7.6	neutropenia G3/4 = 39 FN = 7.7 alopecia = 100
Kornek et al. [33] 2002	52	anthracyclines 19%	G 1,500 mg/m^2 1, 15 + T 50 mg/m^2 1, 15 q28	60.5[a] 43[b]	8.5[a] 6.6[b]	neutropenia G3/4 = 29 alopecia G3 = 35
Garle et al. [30] 2003	48	anthracyclines 33%	G 2,500 mg/m^2 1, 14 + T 65 mg/m^2 1, 14 q14	71	9.1	neutropenia G3/4 = 44 FN = 4 fatigue G3/4 = 15
Alexopoulos et al. [34], 2004	50	docetaxel 100%	G 900 mg/m^2 1, 8 + T 100 mg/m^2 8 q21	46	7.5	neutropenia G3 = 24
Pelegri et al. [28] 2004	71	anthracyclines 28%	G 2,500 mg/m^2 1 + T 65 mg/m^2 1 q14	66	NR	neutropenia G3/4 = 45
Brandi et al. [35] 2004	53	anthracyclines 100%	G 1,000 mg/m^2 1, 8 + T 80 mg/m^2 8 q21	53	7.5	neutropenia G3/4 = 43 anemia G3/4 = 8
Slee et al. [36] 2004	26	anthracyclines 100%	G 1,000 mg/m^2 1, 8 + T 75 mg/m^2 8 q21	61	7.7	leucopenia G3/4 = 23/184 cycles
Palmeri, present study	58	anthracyclines 52%	G 800 mg/m^2 1, 8, 15 + T 35 mg/m^2 1, 8, 15 q28	64.3	13.6	neutropenia G3/4 = 13.8 diarrhea G3/4 = 5.2

G = Gemcitabine; T = docetaxel; NR = not reported; FN = febrile neutropenia.
[a] First-line treatment.
[b] Second-line treatment.

prophylactic use of G-CSF and thrombocytopenia of grade 3–4 was registered in 21% of patients. The median dose intensity was 26.5 and 513 mg/m^2/week for docetaxel and gemcitabine, respectively.

A regimen of docetaxel and gemcitabine every 2 weeks was used as first line therapy in 3 phase II trials. Pelegri et al. [28] treated 71 patients with docetaxel 65 mg/m^2 and gemcitabine 2,500 mg/m^2 on day 1 of a 14-day cycle. An objective response rate of 66% was registered. Grade 3–4 neutropenia occurred in 45% of patients. In the study of Mavroudis et al. [27], 47 patients (37 assessable for response) were enrolled to receive docetaxel 65 mg/m^2 and gemcitabine 1,500 mg/m^2 on day 1 every 2 weeks. The intent-to-treat ORR was 75.6%. Grade 3–4 neutropenia was registered in 14 (30%) patients with febrile neutropenia in 2 (5%) cases [29]. Garle et al. [30] administered docetaxel 65 mg/m^2 and gemcitabine 2,500 mg/m^2 on day 1 of a 14-day cycle to 48 patients obtaining an objective response rate of 71%. In this study grade 3–4 neutropenia was also registered in 44% of patients. Grade 3–4 fatigue (15% of cases) was the most frequent nonhematological toxicity. For comparison with the present study, table 5 lists previous studies with the gemcitabine-docetaxel combination in MBC.

In our dose-finding study [19], 18 heavily pretreated patients received 3 escalating weekly doses of docetaxel (30, 35 and 40 mg/m^2) with a weekly fixed dose of gemcitabine 800 mg/m^2 on days 1, 8 and15 of a 28-day cycle. The MTD for docetaxel was reached at the 40 mg/m^2 dose and the recommended dose for subsequent phase II studies was established at the 35 mg/m^2 dose. Leucopenia was prevalent at the highest dose of 40 mg/m^2. The promising

activity data obtained (ORR = 58%) in a heavily pretreated population of patients, even if small, encouraged the exploration of this innovative schedule in a phase II setting.

The present study focuses on a new combination therapy administered weekly as first line treatment in MBC patients. At least 1 visceral site of metastasis was present in 45 (77.6%) patients. In the 56 assessable patients, the ORR was 64.3% with 9 patients (16.1%) achieving a CR, 27 (48.2%) a PR response and 12 (21.4%) patients with SD. The median survival was 22.10 months (95% CI: 15.53–28.67) with 43 (74.1%) patients still alive at the cut-off date of 36 months. Noteworthily, the TTP was 13.6 months (CI 95%: 10.71–16.49). The median TTF was: 8.60 months (95% CI: 4.79–12.41). At the time of cutting off, 24 patients experienced PD. Another remarkable point is the length of response in patients with SD: in fact, in this subgroup, the median duration of response was 19.27 months. Furthermore, the median survival of patients who achieved PR was 29.30 months.

The data from this study seem to confirm that the combination of docetaxel and gemcitabine is active in advanced breast cancer. This weekly schedule seems to be active and well tolerated, the median actual dose intensity being 26.25 mg/m^2/week (100% of the planned dose) for docetaxel and 600 mg/m^2/week (100% of the planned dose) for gemcitabine.

These results, with 56 assessable patients, are in agreement with other published studies. Grade 3–4 neutropenia occurred in only 8 patients (14%). Regarding nonhematological toxicity, grade 3 alopecia was experienced by only 5 cases (9%). No case of fluid retention syndrome was seen. Furthermore, this schedule is manageable in an outpatient setting.

The need to perform adequately designed and sized phase III trials is strongly felt in order to confirm the promising results of this study, considering two study populations: patients who have received prior anthracycline-containing therapy and anthracycline-naive patients.

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