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ORIGINAL ARTICLE

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Docetaxel plus epirubicin is a highly active, well-tolerated, first-line chemotherapy for metastatic breast cancer: results of a large, multicentre phase II study

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Abstract *Purpose*: In this multicentre phase II study, the efficacy and safety profile of the combination of docetaxel and epirubicin as first-line chemotherapy for metastatic breast cancer (MBC) were evaluated. *Methods*: Epirubicin (75 mg/m^2) and docetaxel (75 mg/m^2) were given intravenously once every 3 weeks for six cycles to 133 patients with MBC. *Results*: The overall clinical response rate was 67% (complete and partial responses were 23% and 44%, respectively). The median time to progression was 10.8 months (95% CI 9.7–12.6) and the median overall survival was 19.5 months. Granulocyte colony-stimulating factor support was administered to 32% of patients and in 22% of cycles. Grade 3/4 neutropenia occurred in 35% of patients and febrile neutropenia in 19%. The most frequent grade 3/4 non-haematological toxicities (as percent of patients) were asthenia (6%), vomiting (5%) and nausea (5%). No patients developed congestive heart failure. *Conclusions*: The combination of docetaxel and epirubicin was highly active as first-line treatment for MBC and showed a manageable toxicity profile.

Keywords Docetaxel · Epirubicin · Metastatic breast cancer · First-line chemotherapy

Introduction

Metastatic breast cancer (MBC) is essentially incurable with standard therapy and patients with MBC have a median survival of about 2 years after metastases have been detected [16]. As a consequence, the treatment goals are to improve the symptoms while trying to

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maintain (or, in some cases, to improve) the quality of life of the patients. Prolonging survival remains a definite goal, but the role of chemotherapy in this setting is still unclear. Complete responses to treatment with anthracycline-containing regimens such as FAC (5-fluorouracil/doxorubicin/cyclophosphamide) as first-line in the metastatic setting may be associated with improved quality of life. Therefore, early effective treatment may be helpful in MBC patients [13]. For example, combination chemotherapy with an anthracycline might be given before hormone therapy [12].

Taxanes are among the most effective agents in MBC. Previous studies have indicated that the maximum overall response rate (ORR) of 40% found with anthracyclines in advanced breast cancer may be achieved with docetaxel alone [5, 6, 9, 23, 25]. Docetaxel has shown high activity in first-line and second-line therapy of MBC, as well as in patients either previously exposed to or resistant to anthracyclines [5, 7, 21, 25]. These results indicate that docetaxel alone is one of the most active chemotherapeutic agents for the treatment of advanced breast cancer. The combined use of taxanes and anthracyclines was the next logical step in the search for a highly effective chemotherapy combination. The administration of an anthracycline in combination with a taxane increases the ORR to at least 50% [10, 14, 22, 23]. Anthracycline/taxane-containing regimens have been developed to test the ability to integrate taxanes into polychemotherapy, to assess their role in MBC and to proceed to adjuvant strategies [20].

The combination of docetaxel and epirubicin has been investigated in six phase I studies, generally using escalating doses of both drugs [15, 26, 28, 30, 33, 34]. Two dose levels were recommended for phase II studies: 75 mg/m^2 of docetaxel plus 75 mg/m^2 of epirubicin, and 75 mg/m^2 of docetaxel plus 90 mg/m^2 of epirubicin. The ORRs reported in these preliminary studies were 52%–75%, which have been confirmed in early [24, 27, 35, 36] and later [29, 37] phase II studies.

The addition of docetaxel to anthracyclines in these phase I/II trials was associated with a lower incidence of non-haematological adverse events and, perhaps most importantly, was not associated with a higher incidence of cardiotoxicity. Docetaxel administered concomitantly or 1 h after anthracyclines had no effect on the latter's pharmacokinetics [3, 30]. Only a transient interference of docetaxel with epirubicin in plasma was found when docetaxel was administered 1 h after epirubicin [1]. Docetaxel is not associated with a higher incidence or severity of cardiotoxicity than doxorubicin monotherapy [19, 22, 23] or with the combination of anthracyclines and paclitaxel [11].

Based on previous studies, we chose to study the combination of epirubicin 75 mg/m^2 and docetaxel 75 mg/m^2. The objective of this prospective phase II study was to evaluate the efficacy and safety profile of this combination as first-line treatment for MBC.

Materials and methods

Patient eligibility

The study included women between 18 and 75 years of age with a histological or cytological diagnosis of MBC who had not received previous chemotherapy for metastatic disease. Adjuvant chemotherapy and hormone therapy were allowed. Endocrine treatment for metastatic disease was not allowed. Radiotherapy was permitted; however, evaluable lesions had to be located outside the irradiated area. If patients received anthracyclines as adjuvant treatment, disease progression had to have occurred at least 12 months after completion of anthracycline treatment. The cumulative previous anthracycline dose was not to exceed 240 mg/m^2 for doxorubicin or 450 mg/m^2 for epirubicin. Other inclusion criteria were: presence of measurable or evaluable disease, life expectancy of at least 3 months, World Health Organization (WHO) performance status 0–2, adequate haematological function (absolute neutrophil count ≥2000/mm^3, haemoglobin ≥10 mg/dl, platelets ≥100,000/mm^3), renal function (creatinine not more than 1.25 times the upper normal limit) and liver function (total bilirubin not more than the upper normal limit, aspartate (GOT) and alanine aminotransferase (GPT) not more than 2.5 times the upper normal limit), absence of myocardial infarction or unstable angina pectoris in the 12 months before the onset of the study, and normal cardiac function evaluated by multiple-gated-acquisition (MUGA) scan or echocardiography, with a left ventricular ejection fraction (LVEF) ≥50%. Patients with cerebral metastases were allowed to participate if they had received cranial irradiation with clinical and radiographic improvement of their central nervous system disease. Patients with infection, malnutrition or a history of secondary malignant neoplasm other than basal or squamous cell carcinoma of the skin, or carcinoma in situ of the uterine neck, were not included. The ethics and scientific institutional review boards of the participating centres approved the study. All patients signed an informed consent form before entering the study.

Treatment

The patients were treated with 75 mg/m^2 of epirubicin (Farmorubicine; Pharmacia, Milan, Italy) on day 1 administered as a 15-min i.v. infusion followed 1 h later by 75 mg/m^2 of docetaxel (Taxotere; Aventis, Antony, France) as a 60-min i.v. infusion. All patients were given prophylactic corticosteroid premedication to avoid hypersensitivity reactions and to prevent the occurrence of fluid retention; this consisted of either oral dexamethasone (8 mg), methylprednisolone (40 mg), prednisone (50 mg), or prednisolone (50 mg) in a maximum of six doses before and after infusion. Prophylactic antiemetic treatment was administered at the discretion of each investigator. Cycles were repeated every 3 weeks on an outpatient basis. A maximum of six cycles were given for a total cumulative epirubicin dose of no more than 450 mg/m^2 during the study period. Patients with disease progression were immediately withdrawn from the study. Epirubicin administration was discontinued in patients who developed LVEF < 50%, a 15% decrease in LVEF compared to baseline values, or congestive heart failure (CHF). Granulocyte colony-stimulating factor (G-CSF) was not administered prophylactically during treatment, but was given if grade 3/4 neutropenia or febrile neutropenia developed. The dose levels of both drugs were reduced by 20% for grade 4 neutropenia, neutropenia with fever (in spite of G-CSF), grade 4 thrombocytopenia lasting for more than 5 days, or non-haematological toxicity greater than grade 3. Neither hormonal treatment nor cytotoxic maintenance treatments were allowed after chemotherapy.

Assessments

Baseline evaluation included medical history, physical examination, complete differential blood count, serum biochemistry, chest

radiography, computed tomography scan, magnetic resonance imaging, bone scan, ultrasonography, electrocardiography (ECG) and echocardiography or MUGA scan with LVEF measurement. Complete blood count was repeated every 3 weeks in all patients during treatment, and daily in the case of grade 3/4 neutropenia, thrombocytopenia or febrile neutropenia until haematological recovery. Before each cycle, adverse events were documented and a physical examination, differential blood count and blood biochemistry tests were performed. Other tests were carried out as determined by the clinical manifestations. Cardiac monitoring consisted of a physical examination and LVEF measurement every three treatment cycles in patients at cardiac risk and at the discretion of the investigator. LVEF was also measured 3 months later in patients who developed LVEF < 50%, a 15% decrease in LVEF compared to baseline values, or CHF. Response was determined after each cycle if the measurable disease could be evaluated by physical examination, or after every three treatment cycles by repeating the corresponding tests. The patients were considered to be evaluable for response only if they had received at least three treatment cycles, did not have a major deviation from the eligibility criteria or the study procedures and had at least one complete tumour assessment after baseline evaluation. Toxicity analyses were performed on all treated patients. Toxicity and response to treatment were scored using National Cancer Institute Common Toxicity Criteria and WHO criteria, respectively.

Statistical analysis

An ORR of 54% for this combination treatment was found in an early dose-finding study [15]. However, revision by Nabholtz et al. [22] showed an average ORR of 70% in several phase I/II pilot studies. This 70% rate was chosen as the expected ORR. According to Fleming's method [8], the detection of a 16% difference between lower and higher ORRs required enrolling a total of 117 patients. Taking into account a 10% dropout rate, it was established that a total of 129 patients (alpha 0.05 and 95% power) had to be included.

The time to progression was calculated from the onset of treatment until progression or death. Survival was calculated from the onset of treatment to the date of death for any reason. The duration of response was determined from the date when response was documented until disease progression or death. The follow-up time was measured from day 1 of treatment to the most recent contact or death of the patient. The probability of survival was estimated using the Kaplan-Meier method. Confidence intervals (CI) for the ORRs were calculated according to the exact binomial CI.

Results

Patient characteristics

Between June 1998 and August 2000, 133 patients were enrolled. The characteristics of the patients are shown in Table 1. Their median age was 53 years (range 29–75 years), Among the 133 patients, 123 (93%) had a WHO performance status of 0–1, 50 (38%) had one metastatic lesion, 46 (35%) had two metastatic lesions and 33 (25%) had metastatic involvement of three or more organs. Of 74 patients (56%) who had received previous adjuvant or neoadjuvant chemotherapy, or both, 15 (11%) had been pretreated with anthracyclines.

Of the 133 patients included in the study, 102 completed six cycles of treatment and 31 were withdrawn due to early progressive disease ($n=9$), adverse events ($n=7$), death (cancer $n=3$, toxic death $n=3$), consent withdrawal ($n=3$), protocol violation ($n=3$) and lost to follow up ($n=3$).

Table 1 Patient characteristics ($n=133$)

		No.	%
Age (years)			
Median	53		
Range	29–75		
≤ 45		31	23
> 45		102	77
Performance status			
0		73	55
1		50	38
2		10	7
Previous chemotherapy		74	56
Neoadjuvant		1	1
Adjuvant		71	53
Neoadjuvant + adjuvant		2	2
Number of metastatic sites			
One		50	38
Two or more		79	59
Unknown		4	3
Dominant disease sites			
Bone		51	38
Lung		41	31
Liver		38	29
Lymph nodes		33	25
Skin		21	16

Exposure to study medication

Of 700 treatment cycles administered (median 6 cycles per patient, range 1 to 6), 28 (4%) were delayed due to haematological and non-haematological toxicity (9 cycles each) and non-drug-related causes (10 cycles). The median interval between administration of the cycles was 21 days (range 21–30 days). The median duration of treatment delay was 4 days (range 1–18 days). The dose was reduced in 19 of the 700 cycles (3%) due mainly to haematological toxicity (11 cycles). In four patients who underwent dose reduction, the subsequent doses were increased to the initial level. The median relative dose intensity was 98% for both docetaxel and epirubicin.

G-CSF was administered to 35 patients (32%) with grade 3/4 neutropenia or febrile neutropenia or in 134 of 606 cycles (22%).

Safety

The haematological and non-haematological toxicities per cycle and per patient are shown in Table 2. During the first cycle, grade 3/4 neutropenia or febrile neutropenia was observed in nine patients. When all cycles were considered, grade 3/4 neutropenia occurred in 47 patients (35%) and febrile neutropenia in 25 patients (19%) and 28 cycles (4%). Febrile neutropenia occurred in 22 patients in one cycle and in 3 patients in two cycles. In naive patients (without G-CSF support), 17 episodes

Table 2 Haematological and non-haematological toxicity per cycle and patient

	Cycle ($n=700$)		Patient ($n=133$)	
	Grade 1/2 (%)	Grade 3/4 (%)	Grade 1/2 (%)	Grade 3/4 (%)
Haematological				
Anaemia	3	0	3	0
Febrile neutropenia	–	4	–	19
Neutropenia	3	11	5	35
Neutropenia with infection	1	1	2	5
Non-haematological				
Allergy	1	0	5	1
Alopecia	72	–	85	–
Asthenia	31	0	45	6
Cutaneous	1	0	4	0
Diarrhoea	6	0	20	0
Fever without neutropenia	5	0	13	0
Infection without neutropenia	2	0	8	2
Nail disorders	3	0	6	0
Nausea	31	1	56	5
Neuromotor	3	1	5	3
Neurosensory	1	0	3	0
Pain	5	1	10	2
Peripheral oedema	6	0	16	1
Stomatitis	19	1	39	4
Vomiting	16	1	36	5

of febrile neutropenia (61%) occurred. The median duration of grade 3/4 neutropenia was 4 days (range 1–12 days); this value includes all patients despite G-CSF support. Grade 1/2 anaemia occurred in 4 patients (3%) and no patient had thrombocytopenia. Non-haematological toxicity was mild (mainly grade 1/2). The most frequent non-haematological toxicities were seen in 6 patients (5%) who developed grade 3/4 nausea and vomiting, and in 8 patients (6%) who had grade 3/4 asthenia. Mild fluid retention or oedema was observed in 21 patients (16%). The median LVEF was 65% (range 63–88%) at baseline and 58% (range 37–68%) at the end of treatment (cycle 6).

Seven patients were withdrawn from the study following adverse events: cardiac toxicity ($n=2$), hypersensitivity reaction ($n=1$), vomiting ($n=1$), stomatitis ($n=1$), peripheral oedema ($n=1$), and both investigator decision and severe asthenia ($n=1$). Cardiac toxicity was found in one patient with LVEF reduction to less than 50% in the fifth treatment cycle and another patient with ECG disturbances after the first cycle; however, neither patient developed CHF.

Three deaths could be related to the treatment. The first patient was a 63-year-old woman with cutaneous and bone recurrence after adjuvant treatment with an anthracycline-containing regimen and haematopoietic stem cell transplantation (TASPE). After the first cycle, she developed febrile neutropenia followed by septic shock and died 5 days later. The second patient was a 51-year-old woman with liver and bone metastases. She developed high fever, dyspnoea, hypoxia and bilateral lung infiltrates 2 days after the second cycle. A third death occurred in a 69-year-old woman who developed intense asthenia after four cycles of treatment. Although the patient was hospitalized, she did not recover and entered a terminal situation that resulted in death 28 days later.

Table 3 Summary of response (intent-to-treat population, $n=133$) (*ORR* objective response rate)

Parameter	No.	%
Complete response	31	23
Partial response	58	44
Stable disease	21	16
Progressive disease	11	8
Non-evaluable	12	9
ORR (95% CI)	89	67 (59–75)
ORR with or without previous chemotherapy		
With ($n=74$)	48	65
Without ($n=59$)	41	69
ORR with or without previous anthracyclines		
With ($n=15$)	10	67
Without ($n=59$)	38	64
ORR specific by metastatic site		
Liver ($n=34$)	18	53
Lung ($n=37$)	22	59
Lymph nodes ($n=30$)	26	87
Skin ($n=20$)	16	80

Efficacy

Of the 133 patients included in the study, 2 showed major protocol violation (non-measurable or non-evaluable disease), and 10 were considered non-evaluable for response because they did not receive a minimum of three cycles. The reasons for early withdrawal were adverse events ($n=6$) and toxic death ($n=2$), as previously specified, and patient decision ($n=2$). The intent-to-treat analysis of efficacy (Table 3) showed complete responses (CR) in 31 patients (23%) and partial responses (PR) in 58 (44%), resulting in an ORR of 67% (95% CI 59–75). Stable disease (SD) was seen in 21 patients (16%) and progressive disease (PD) in 11 (8%) during or after completion of treatment. In 89 patients who responded to the treatment, the median duration of response was 9.0 months (95% CI 7.5–11.6) with 52% of events recorded.

The ORR did not differ significantly in patients with or without previous chemotherapy (65% vs 69%, respectively), or with or without previous anthracyclines (67% vs 64%, respectively). Responses were observed in all metastatic sites, with an ORR of 53% for liver metastasis, 59% for lung metastasis, 87% for lymph node metastasis and 80% for skin metastasis. With a median follow-up of 6.4 months, the median time to progression was 10.8 months (95% CI 9.7–12.6; Fig. 1) and the median overall survival was 19.5 months (Fig. 2).

Discussion

This is the largest phase II study to date in which the efficacy and toxicity profile of docetaxel/epirubicin has

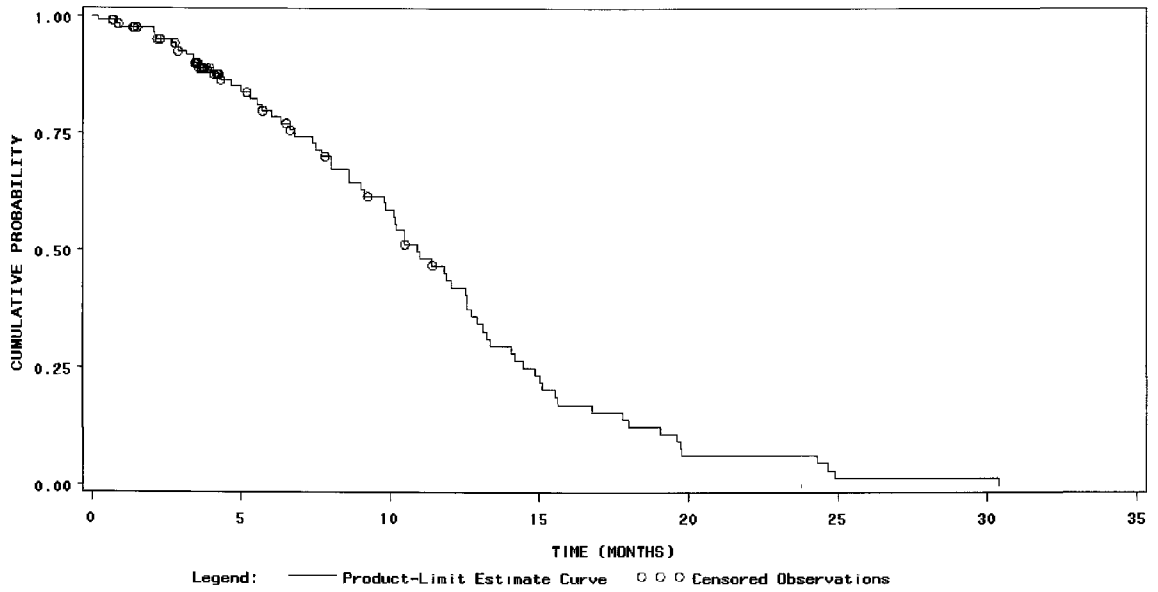


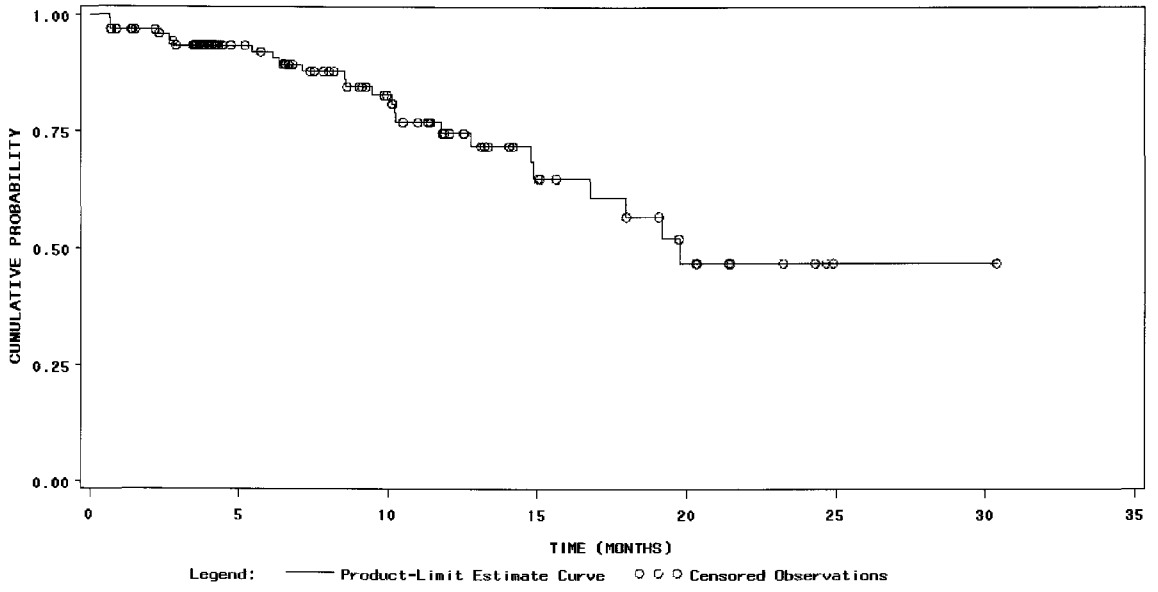
Fig. 1 Time to progression

been evaluated for first-line treatment of MBC. The ORR found with this schedule was 67% (95% CI 59–75). CR and PR rates were 23% and 44%, respectively. Responses were observed for liver (53%), lung (59%), lymph node (87%) and skin metastases (80%). The median time to progression was 10.8 months (95% CI 9.7–12.6) and the median overall survival was 19.5 months.

Our findings are nearly identical to those reported for the docetaxel arm in a phase III trial in which doxorubicin (50 mg/m^2) and docetaxel (75 mg/m^2) (AT) was compared with doxorubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2) (AC) for a maximum of eight cycles in 423 patients with MBC [20]. Patients included in the docetaxel arm showed a significantly improved ORR (60%, $P=0.012$) and median time to progression (37.1 weeks, $P=0.0153$). In the phase II study performed by Mavroudis et al. [17], treatment with 70 mg/m^2 of epirubicin and 90 mg/m^2 of docetaxel resulted in an ORR of 66% with a median time to progression of 11 months.

The combination of docetaxel and epirubicin without G-CSF support resulted in febrile neutropenia in approximately 15% of cycles in a trial by Pagani et al. [26] and in 7% of cycles in a trial by Mavroudis et al. [17]. In our study, febrile neutropenia was observed in 25 patients (19%) and 28 cycles (4%). This result is very promising, considering that we did not use prophylactic G-CSF and that G-CSF support was given in only 22% of cycles for the treatment of grade 3/4 neutropenia or febrile neutropenia. In a study by Sparano et al. [31], prophylactic G-CSF was used with a lower docetaxel dose (60 mg/m^2) and doxorubicin 60 mg/m^2, and severe granulocytopenia was observed in 76% of patients. Nabholtz and Riva [20] found a 33% incidence of febrile

Fig. 2 Overall survival



neutropenia for AT, and prophylactic G-CSF was not used. Combination regimens with epirubicin at doses of 75–90 mg/m^2 without G-CSF show less neutropenia than with doxorubicin, and the incidence of febrile neutropenia is acceptable and similar to that found for other chemotherapy combinations.

A clear dose response relationship for single-agent epirubicin (up to a dose of 90 mg/m^2) has been found in postmenopausal women with MBC [2]. Doubling the epirubicin dose (100 mg/m^2 vs 50 mg/m^2) in the FEC (5-fluorouracil/epirubicin/cyclophosphamide) regimen significantly increased CR and ORR but not overall survival, especially in patients with visceral metastases or multiple sites of organ metastasis [4]. Similar results have been found for docetaxel, as the 100 mg/m^2 dose was associated with a higher ORR than the 75 mg/m^2 dose [32]. The same relationship has been found in other trials in which prophylactic G-CSF was given in order to deliver a high dose of both drugs [18, 31]. This strategy reduced the incidence of severe febrile neutropenia in subsequent cycles and allowed the administration of full doses for both drugs to most patients. In a study performed by Milla-Santos et al. [18] with docetaxel 100 mg/m^2 and epirubicin 130 mg/m^2, an ORR of 87% and a high CR rate were achieved; however, this high dose of epirubicin with a standard dose of docetaxel required lenograstim (a glycosylated form of rHuG-CSF) support to stimulate leucopoiesis and reduce side effects.

The median duration of response (9.0 months), time to progression (10.8 months) and overall survival (19.5 months) found in our trial are very acceptable for patients with an incidence of visceral metastases close to 60% and a high rate of adjuvant chemotherapy, including anthracyclines. However, caution is required when interpreting the results of phase II studies. Milla-Santos et al. [18] have reported a median survival of 604 days, and in other studies with three-drug schedules (docetaxel, doxorubicin and cyclophosphamide [9]), an ORR of 77% with a median time to progression of 42 weeks has been found.

In our study, we demonstrated that the combination of docetaxel and epirubicin is highly active in MBC and has a manageable toxicity profile even when given without prophylactic G-CSF support. Furthermore, the results are very similar to those found in other studies using higher doses of these agents with G-CSF support. In conclusion, we consider that the combination of epirubicin and docetaxel might be considered as an important alternative in the treatment of MBC.

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