Toxicity and Activity of Docetaxel in Anthracycline-Pretreated Breast Cancer Patients

A Phase II Study

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Abstract

Docetaxel has proven effective in advanced breast cancer. Myelosuppression and cumulative fluid retention syndrome are troublesome, potentially avoidable toxicities. In this consecutive cohort study, docetaxel (100 mg/m^2 by 1 hour i.v. infusion, q3 weeks) activity and toxicity was explored in 56 anthracycline-pretreated patients (eligible: 55; median age: 51 years [range: 28–68 years]; median performance status: 0 [range: 0–3]) with metastatic breast cancer, using two different granulocyte colony-stimulating factor and steroid pre- and postmedication schedules. Twenty-nine patients (group A) received a 5-day oral prednisone premedication, and 26 (group B) received 4-day low-dose i.m. dexamethasone; group B patients also received prophylactic granulocyte colony-stimulating factor. All patients were evaluable for toxicity and 53 for response. Prophylactic granulocyte colony-stimulating factor significantly lowered the incidence of grade III–IV neutropenia and neutropenic fever (p = 0.0001 and 0.01, respectively). The incidence of moderate–severe fluid retention syndrome was lower in patients receiving i.m. dexamethasone (p = 0.08). Overall response rate was 53% (4 complete responses/24 partial responses, 95% confidence interval 39.4–66.2%); 32% have stable disease and 15% progressive disease. In 21 anthracycline-refractory/resistant patients, as well as in 10 paclitaxel-pretreated patients, the overall response rate was 50%. Docetaxel is highly active in anthracycline- and paclitaxel-pretreated metastatic breast cancer, with manageable toxicity. Optimal use of both granulocyte colony-stimulating factor support and steroid premedication deserves further investigation.

Breast cancer is the most frequent neoplasm in women in European countries, with an estimated 135,000 new cases per year (24% of all cancer cases) and 58,000 recorded deaths per year (18% of all cancer deaths). [1]

Despite the improvements achieved in the overall outcome of patients with breast cancer, metastatic spread is still frequent. In fact, up to 60% of the patients will ultimately develop distant metastases. Conventional treatments, such as standard chemotherapy or hormone therapy, have no curative impact on advanced disease, with a median survival of approximately 2 years after evidence of metastases. [2]

Besides anthracyclines (doxorubicin and epirubicin), several new active agents, such as taxanes and vinorelbine, have been developed for the treatment of breast cancer in the

last decade. [3] Unlike other antimicrotubule agents, such as vinca alkaloids, taxanes promote the polymerization of stable microtubules and inhibit their disassembly, affecting a number of key cellular functions that depend on the physiologic turnover of tubulin. [4] This unique mechanism of action potentially permits overcoming drug resistance. [5]

Docetaxel is a semisynthetic analogue of paclitaxel, showing a greater in vivo antitumor activity in preclinical studies and a slightly better solubility, as compared with the parent compound. [6] With regard to its clinical activity, several phase II trials of single-agent docetaxel have been carried out in metastatic breast cancer, showing an overall response rate (ORR) of approximately 63% in previously untreated patients and 56% in pretreated patients. [7–13] Moreover, a high level of activity has been reported also in anthracycline-resistant or refractory patients (ORR: 55%), [14,15] demonstrating the lack of a full cross-resistance between these agents.

Docetaxel treatment, however, is accompanied by a number of toxic effects, among which transient neutropenia is the most prominent and dose-limiting. Moreover, characteristic nonhematologic toxicities, such as fluid retention syndrome and skin and nail alterations, are well recognized, cumulative side effects that have often led to treatment discontinuation in the earlier studies. [16] Although the pathophysiologic features underlying the development of the fluid retention syndrome are not yet fully defined, a capillary leak syndrome-like mechanism has been postulated, and corticosteroid pre- and postmedication has proven effective in reducing the incidence and delaying the onset of such a toxicity. [16–18] Optimal steroid dose and schedule is, however, not clearly established.

This study presents our experience with docetaxel for the treatment of patients with metastatic breast cancer pretreated with anthracycline and explores two different steroid schedules as well as the clinical impact of prophylactic granulocyte colony-stimulating factor (G-CSF) administration in a consecutive cohort study design.

PATIENTS AND METHODS

Eligibility Criteria and Pretreatment Evaluation

From July 1995 to December 1997, 56 patients with metastatic breast cancer were entered into the study. All patients provided informed consent.

Eligibility criteria included the following: histologic or cytologic proof of breast cancer with the presence of at least one metastatic lesion, bidimensionally measurable by physical examination and/or radiologic tests, ultrasonography and computed tomography scan; age between 18 and 75 years; performance status (Eastern Cooperative Oncology Group scale) 0–3; adequate bone marrow function (absolute neutrophil count >2,000/μl; platelet count >100,000/μl; hemoglobin >9 g/dl); adequate liver function (total bilirubin <1 × upper normal limit [UNL]; aspartate transaminase and/or alanine transaminase <3.5 × UNL; alkaline phosphatase <6 × UNL; aspartate transaminase <1.5 × UNL together with alkaline phosphatase <2.5 × UNL except in the presence of concomitant bone metastases and normal liver function); and adequate renal (serum creatinine <1.5 × UNL; blood urea nitrogen < 45 mg/dl) and cardiac function. All patients had to have received prior chemotherapy with at least one anthracycline-containing regimen, in either adjuvant or metastatic setting, completed at least 4 weeks before beginning the new treatment. Prior hormone therapy was allowed, as well as prior radiotherapy, provided that at least 4 weeks had elapsed since the last treatment and no more than 20% of the bone marrow reserve

had been irradiated. Irradiated lesions were not used for response assessment, unless clearly progressive.

Patients with brain and/or bone metastases, pulmonary carcinomatous lymphangitis, neoplastic ascites, and/or pleural effusion as the only site of disease were considered not eligible. Other exclusion criteria included: pregnant or lactating women, or women of childbearing potential not using adequate contraception; patients with preexisting more than grade II motosensorial neurotoxicity, or with absolute contraindication to corticosteroid administration; and concomitant treatment with other experimental drugs.

Patient baseline evaluation consisted of: complete medical history and physical examination, neurologic evaluation, and performance status assessment. All of the patients underwent baseline chest radiograms, bone scan, and abdomen ultrasonography as well as other appropriate imaging studies to document the extent of disease.

Laboratory studies at the time patients entered the study included determination of complete blood cell and platelet counts, biochemical profile, serum tumor markers (carcinoembryonic antigen and CA 15-3) and urine analysis. Cardiac function evaluation included electrocardiogram and left ventricular ejection fraction measurement by echocardiography.

Complete blood cell and platelet counts were repeated once weekly during treatment. The patients underwent complete physical examination and biochemical profile before each treatment, and neurologic examinations were repeated only when necessary. Cardiac function assessment was repeated every two cycles.

Treatment

Docetaxel was administered at a dose of 100 mg/m^2 given by 1-hour i.v. infusion in polysorbate 80 (diluted in 5% dextrose solution or 0.9% normal saline).

To prevent hypersensitivity reactions and to reduce skin toxicity and fluid retention syndrome, two different corticosteroid pre- and postmedication schedules were used in two consecutive cohorts of patients. Twenty-nine patients (group A) received oral prednisone (50 mg) 13, 7 and 1 hour before docetaxel administration; postmedication consisting of oral prednisone (50 mg) was given 1 and 12 hours after docetaxel and then twice daily in the following 3 days. No routine prophylactic antiemetic medication was planned in this group. Twenty-six patients (group B) received i.m. dexamethasone (8 mg/day) on days 1, 0, +1, and +2. In this group of patients, prophylactic antiemetic medication with ondansetron 8 mg i.v. 30 minutes before docetaxel administration was routinely given.

In group A, prophylactic G-CSF (lenograstim 150 μg/m^2/day s.c.) was administered in the subsequent cycles in the event of grade IV neutropenia with or without fever. In group B, G-CSF (lenograstim) was included in the treatment schedule at the dose of 150 μg/m^2 every other day starting from day +4 for four doses.

Courses were repeated every 3 weeks. A minimum of six cycles were planned, unless progressive disease or unacceptable toxicity occurred. Patients in continuous response and without major toxicity could be administered three more cycles.

Retreatment was allowed, provided that the patients had completely recovered from toxicity, with a maximum acceptable delay of 2 weeks. In both groups, a 25% dose reduction was planned (minimum docetaxel dose: 55 mg/m^2) in the presence of grade IV neutropenia or thrombocytopenia lasting >7 days with or without fever. A 25% dose reduction was also foreseen in the presence of any grade >III nonhematologic toxicity.

Recognized toxic effects were graded by the National Cancer Institute common toxicity criteria. [19] Other toxic effects were graded as mild (asymptomatic or minor symptoms: no treatment required), moderate (moderately symptomatic: minor treatment required), and severe (symptomatic and interfering with function: major treatment required).

Response to treatment was evaluated after every two courses according to World Health Organization criteria. [20] The response duration was calculated from the first day of treatment to the time of progressive disease (PD). Overall survival was calculated from the on-study day to the day of death or last follow-up.

Statistical Analysis

Continuous data were summarized as the median and range, and 95% confidence intervals were calculated. Response duration and survival curves were calculated according to the Kaplan-Meier method. [21] Differences between the curves were analyzed by means of the log-rank *p* test; those between toxicity rates were analyzed by the chi-square test.

RESULTS

Fifty-six patients with metastatic breast cancer were included in the study. One patient was not eligible because of carcinomatous lymphangitis of the lung as the only site of disease.

Patient characteristics are shown in Table 1.

TABLE 1. *Patient characteristics*

Entered	56
Eligible	55
Median age, y (range)	51 (28–68)
Median ECOG PS (range)	0 (0–3)
PS 0-1	46
PS 2-3	9
Metastatic sites	
Dominant visceral	34
Dominant nonvisceral	21
No. of metastatic sites	
1	20
2	19
≥3	16
Prior chemotherapy	
Adjuvant	11
Advanced	21
Adjuvant + advanced	23
Advanced 1 line	22
Advanced ≥ 2 lines	22
Prior anthracyclines	55
Refractory	4
Resistant	18
Sensitive	33
Median doxorubicin dose (range)	300 mg/m^2 (90–400)
Median epirubicin dose (range)	600mg/m^2(300–1080)
Prior paclitaxel	10

ECOG PS, Eastern Cooperative Oncology Group Performance Status.

Table 1: Patient characteristics

Patients who had progressed during treatment with anthracyclines were defined as anthracycline-refractory. Patients whose disease had progressed within 6 months from the completion of an anthracycline-containing adjuvant regimen or had stable disease (SD) as the best response to anthracycline-containing regimens for metastatic disease were defined as resistant. The remaining patients were considered anthracycline-sensitive (Table 2).

TABLE 2. *Definition of anthracycline resistance*

Response to prior anthracyclines	Anthracycline status
Progression while receiving treatment with anthracyclines (either adjuvant or advanced)	Refractory
Progression within 6 months after the completion of adjuvant anthracyclines; stable disease as best response to anthracyclines for advanced disease	Resistant
Progression 6 months or more after the completion of adjuvant anthracyclines; complete or partial response to anthracyclines for advanced disease	Sensitive

Table 2:
Definition of anthracycline resistance

A total of 251 cycles of docetaxel were administered, with a median number of six cycles per patient (range: 1–8 cycles), and a median cumulative dose of 600 mg/m^2 (range: 100–800 mg/m^2).

All the 55 eligible patients were evaluable for toxicity and 53 for antitumor response (one patient was lost to follow-up after cycle 2, and another one died of tumor- and treatment-unrelated causes after cycle 1).

Hematologic Toxicity

Hematologic toxicity data have been analyzed separately, based on the use of prophylactic G-CSF (Tables 3 and 4). In group A patients (n = 29), G-CSF (lenograstim 150 µg/m^2/day) was given as needed in the event of grade IV neutropenia, with or without fever, and then prophylactically in the subsequent cycles. Conversely, group B patients (n = 26) routinely received lenograstim 150 µg/m^2 on alternate days for four doses, starting on day 4.

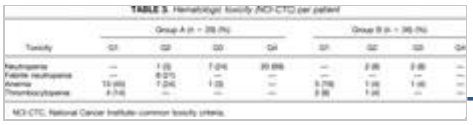

Table 3:
Hematologic toxicity (NCI-CTC) per patient

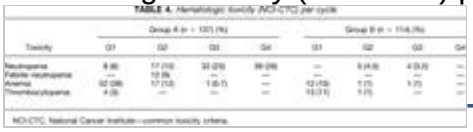

Table 4:
Hematologic toxicity (NCI-CTC) per cycle

Twenty-nine patients and 137 cycles were evaluable for hematologic toxicity in group A. Grade III–IV neutropenia was recorded in 27 (93%) patients and in 71 (52%) cycles. Neutropenic fever occurred in six (21%) patients and in 12 (9%) cycles. Although common, myelosuppression was short lasting, leading to a delay in drug administration in only 3 of 108 (3%) cycles. A 25% dose reduction was performed in three patients (six cycles)

because of complicated neutropenia. G-CSF was required in 11 (38%) patients and in 44 (32%) cycles. Anemia and thrombocytopenia were not common: only 1 patient had grade III anemia, and no patient experienced severe thrombocytopenia.

Twenty-six patients and 114 cycles were evaluable for hematologic toxicity in group B. Grade III–IV neutropenia was observed in two (8%) patients and in four (3.5%) cycles. No episodes of neutropenic fever were recorded. One-week treatment delay was required in 2 out of 88 (2%) cycles, because of myelosuppression. No dose reductions were performed. Grade III anemia occurred in one patient (one cycle), and no patient experienced severe thrombocytopenia.

Comparative analysis of the hematologic toxicity showed a statistically significant reduction in the incidence of both grade III–IV neutropenia (27/29 vs. 2/26 patients, $p < 0.0001$, and 71/137 vs. 4/114 cycles, $p = 0.0001$, respectively) and neutropenic fever (6/29 vs. 0/26 patients, $p = 0.04$, and 12/137 vs. 0/114 cycles, $p = 0.01$, respectively) in group B patients (Fig. 1). No evidence of cumulative toxicity was observed in any of the two groups.

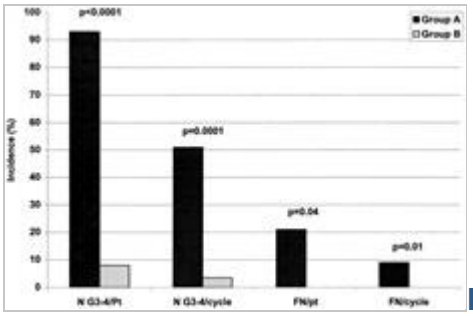

FIG. 1: Comparison of hematologic toxicity between group A and group B patients. N G3–4/pt: grade III–IV neutropenia (maximum toxicity per patient); N G3–4/cycle: grade III–IV neutropenia (toxicity per cycle); FN/pt: febrile neutropenia (maximum toxicity per patient); FN/cycle: febrile neutropenia (toxicity per cycle). *p* value was calculated by chi-square test.

Nonhematologic Toxicity

The nonhematologic toxicity of the docetaxel treatment in the whole population of patients is presented in Table 5. Alopecia was ubiquitous and reversible. Grade III stomatitis was recorded in two (4%) patients (two cycles). Two (4%) patients (two cycles) had grade III–IV diarrhea. The cumulative incidence of emesis was low (25% of all patients and 10% of all cycles, respectively, with only one episode of grade III emesis) and was not affected by the prophylactic use of ondansetron (group B). Significant liver toxicity occurred in two (4%) patients (two cycles), experiencing grade IV transaminase increase and grade III alkaline phosphatase increase, respectively. Moderate to severe asthenia was observed in 21 (38%) patients and 21 (8%) cycles, respectively. Peripheral neuropathy, predominantly of a sensory type and nondisabling, was common, affecting 28 (51%) patients in 79 (31%) cycles, with only 1 patient (1 cycle) experiencing reversible grade III neurotoxicity.

TABLE 5. *Nonhematologic toxicity (NCI-CTC) per patient*

Toxicity	Group A + Group B (n = 55) (%)			
	G1	G2	G3	G4
Emesis	8 (14)	5 (9)	1 (2)	—
Diarrhea	11 (20)	9 (16)	1 (2)	1 (2)
Mucositis	16 (29)	9 (16)	2 (4)	—
Neurotoxicity	20 (36)	7 (13)	1 (2)	—
Cardiotoxicity	—	—	—	—
Asthenia	3 (5)	12 (22)	9 (16)	—
Alopecia	—	—	55 (100)	—

NCI-CTC, National Cancer Institute—common toxicity criteria.

Table 5:
Nonhematologic toxicity (NCI-CTC) per patient

Cardiac function monitoring failed to show any significant alteration throughout the study period. In particular, no significant change in left ventricular ejection fraction was observed, as assessed by echocardiography.

Two different pre- and postmedication schedules have been used in an attempt to ameliorate characteristic docetaxel-induced nonhematologic toxicities (Table 6).

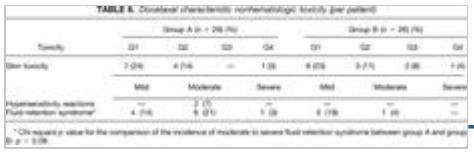

Table 6:
Docetaxel characteristic nonhematologic toxicity (per patient)

In group A patients (n = 29), who received oral prednisone, skin toxicity was recorded in 12 (41%) patients, with only 1 patient experiencing grade IV exfoliative dermatitis of the extremities (hand–foot syndrome), leading to a 25% docetaxel dose reduction. Moderate hypersensitivity reactions were observed in only two patients (four cycles). Mild-to-moderate fluid retention syndrome occurred in 10 (34%) patients, whereas severe fluid retention with bilateral pleural effusion was observed in only 1 patient. Fluid retention syndrome was progressive and related to cumulative dose (median cumulative dose at onset: 400 mg/m^2, range: 100–600 mg/m^2), and usually accompanied by progressive weight gain (median weight gain in patients in whom fluid retention developed: 7.5% of the baseline weight, range: 0–19%). In the patient experiencing pleural effusions, fluid retention syndrome developed after five courses (cumulative dose: 500 mg/m^2; weight gain: 5%) and pleural effusion occurred after seven courses (cumulative dose: 700 mg/m^2; weight gain: 17%).

In group B patients (n = 26), who received i.m. dexamethasone, skin toxicity was observed in 12 (46%) patients, with only 1 patient experiencing grade IV exfoliative dermatitis. No hypersensitivity reactions occurred in this subset. A mild-to-moderate fluid retention syndrome was recorded in five (19%) and one patients, respectively. The median cumulative dose at onset was 600 mg/m^2 (range: 100–600 mg/m^2).

Comparative analysis of moderate-to-severe fluid retention syndrome in the two differently premedicated subsets (groups A and B) showed a trend toward a reduction in its incidence in the patients treated with parenteral dexamethasone (7/29 vs. 1/26 patients in groups A and B, respectively, $p = 0.08$). None of the other toxicities observed was significantly different in any of the two groups, nor was there evidence of cumulative effects.

Response

Fifty-three patients were evaluable for response. Overall response rate (ORR) was 53% (95% confidence interval 39.4–66.2%, 4 complete responses [CRs], 24 partial responses [PRs]). Seventeen (32%) patients had SD and 8 (15%) had PD (Table 7). Of the 25 patients with evaluable liver disease, an overall response (OR) was obtained in 16 (64%, 95% confidence interval 45.2–82.2) patients (5 CRs, 11 PRs).

TABLE 7. *Response to treatment*

Patient population	Response rate (95% C.I.)
Evaluable (n = 53)	53% (39.4–66.2) CR: 4/53 PR: 24/53 SD: 17/53 PD: 8/53
Intent to treat (n = 56)	50% (36.9–63.1)
Liver disease (n = 25)	64% (45.2–82.8) CR: 5/25 PR: 11/25
Anthracycline-refractory (n = 4)	2/4 (50%)
Anthracycline-resistant (n = 17)	8/17 (47%)
Anthracycline-sensitive (n = 32)	18/32 (56%)
Paclitaxel-pretreated (n = 10)	5/10 (50%)

C.I., confidence interval; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Table 7:
Response to treatment

In terms of the anthracycline status, two ORs were observed in the 4 anthracycline-refractory patients (50%) and 8 ORs in the 17 anthracycline-resistant patients (47%), respectively. Eighteen ORs were recorded in the 32 anthracycline-sensitive patients (56%).

Ten patients previously treated with paclitaxel were also included in the present study. All patients had received a combination of paclitaxel (135 mg/m^2, day 1) and 5-fluorouracil plus folinic acid (375 mg/m^2/day and 100 mg/m^2/day, respectively, days 1–3) as second or subsequent metastatic line. The median cumulative dose of paclitaxel was 810 mg/m^2 (range: 675–1,080 mg/m^2) and a median of 20 weeks (range: 8–52 weeks) had elapsed between the last dose of paclitaxel and the first dose of docetaxel. Of the four patients who had a PR to paclitaxel-containing chemotherapy, two responded (PR) to subsequent docetaxel, one had SD, and one had PD; of the six patients who had SD to previous paclitaxel, three had a subsequent response (PR) to docetaxel, one had SD, and two had PD.

The median response duration was 7 months (range: 2–12 months) and the median time to progression was 6 months (range: 1–12 months) (Fig. 2). The median overall survival was 12.5 months (range: 1–29+ months), showing a statistically significant difference (p = 0.04) between responders (median overall survival: 12.5 months, range: 1–29+ months) and nonresponders (median overall survival: 9 months, range: 1–17 months) (data not shown).

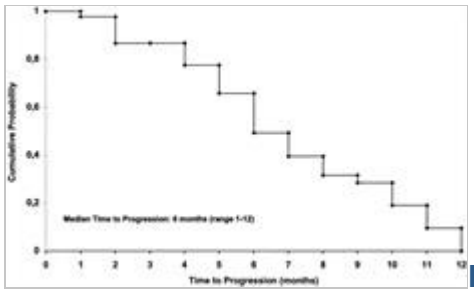

FIG. 2:
Time to progression. Progression-free interval (in months) was calculated according to the Kaplan-Meier method.

DISCUSSION

Our experience with docetaxel at the dose of 100 mg/m^2 every 3 weeks in anthracycline-pretreated patients further confirms the high activity of this drug in advanced breast cancer. The ORR of 53% (95% confidence interval 39.4–66.2%) observed in the present study is consistent with that reported by Valero et al. [15] and ten Bokkel Huinink et al. [8] in I–II line metastatic setting. The activity of docetaxel was not influenced by the presence of dominant visceral versus dominant nonvisceral disease, with an ORR on liver metastasis of 64%, similar to that observed by other authors. [8,9,11,13–15] The median time to progression and median overall survival (6 and 12.5 months, respectively) were also comparable with those reported in previous studies. [22]

During the past few years, anthracycline-containing regimens have been more extensively used for the treatment of patients with breast cancer, either in an adjuvant or metastatic setting. Regardless of the response to anthracycline-based treatment, the majority of patients with breast cancer will, at some time during the course of the disease, require further treatment with non–cross-resistant drugs. The definition of resistance to anthracyclines varies greatly among the different investigators. [23] A recent study from Pivot et al. [24] has shown that only patients progressing during first-line anthracycline treatment have a significantly impaired ORR to second-line treatments as compared with those who progress within 6 months or more. This results in a poorer prognosis only for patients with PD as the best response to an anthracycline-containing regimen. The present trial was designed to assess the efficacy of docetaxel on a representative population of anthracycline-pretreated patients, including refractory (PD during anthracyclines), resistant (SD or PD within 6 months to metastatic or adjuvant anthracyclines, respectively), and sensitive patients. Although the limited number of evaluable patients in each group does not allow drawing any definitive conclusion, ORs were observed in 2 of 4 refractory, in 8 of 17 resistant, and in 18 of 32 sensitive patients, pointing to a substantial activity of docetaxel in this population. These results are consistent with the lack of a full cross-resistance between anthracycline and docetaxel, as reported by other authors. [14,15]

Based on both preclinical and preliminary clinical data showing that patients with PD after paclitaxel therapy may respond to docetaxel, [25] 10 paclitaxel-pretreated patients were included in the present study. Interestingly, 5 patients in this group showed an OR to docetaxel treatment, confirming that the two taxanes might not be fully cross-resistant.

In phase I and II trials of docetaxel, neutropenia is the most commonly reported dose-limiting toxicity. It is usually short lasting, with nadir occurring 5 to 14 days after drug administration and full recovery within 1 week. Febrile neutropenia, defined as fever >38°C with grade IV neutropenia requiring i.v. antibiotics and/or hospitalization, is observed in 16% of patients with normal liver function, often requiring a dose reduction in subsequent cycles and resulting in septic death in 1.4% of patients. [16] The incidence of febrile neutropenia is even higher in anthracycline-pretreated patients (22%). [22]

In the present study, we investigated two different strategies of G-CSF administration in an attempt to reduce hematologic toxicity, avoiding the need for dose reductions. In the first cohort (group A), despite G-CSF administration in 38% of patients and 32% of cycles, respectively, grade III–IV neutropenia occurred in the majority of patients and cycles (93% and 52%, respectively) with neutropenic fever in 21% of patients and 9% of cycles and dose reductions performed in three patients (six cycles). Conversely, routine prophylactic G-CSF use (group B) significantly reduced the incidence of both grade III–IV neutropenia

(8% of patients, $p < 0.0001$, and 3.5% of cycles, $p = 0.0001$) and neutropenic fever (no episodes, $p = 0.04$ and $p = 0.01$ for patients and cycles, respectively). Moreover, in the latter cohort, no dose reductions were necessary. Further studies, involving a cost/effectiveness analysis, are clearly needed to define the role of G-CSF support during docetaxel single-agent chemotherapy.

In terms of characteristic docetaxel-related nonhematologic toxicity, 5-day corticosteroid premedication has been shown to improve hypersensitivity reactions, skin reactions, and fluid-retention syndrome, whereas antihistamines or 1-day corticosteroids have not provided such an effect. Currently ongoing studies are exploring the efficacy of shorter (3 days) steroid schedules. [16–18] In our first cohort of patients (group A), a standard 5-day corticosteroid medication was routinely administered, observing a 41% rate of skin reactions and a 34% rate of mild-to-moderate fluid retention syndrome, with only one case of bilateral pleural effusion and no treatment discontinuation for these reasons. These results are consistent with those reported in other studies using a 5-day corticosteroid premedication. [14,15] In the second cohort of patients (group B), a 4-day premedication using low-dose i.m. dexamethasone (8 mg/day) was used, with a 50% rate of skin toxicity and only one episode of moderate fluid-retention syndrome. Although not reaching a level of statistical significance, a trend toward a reduction in the incidence and a delay in the onset of fluid retention syndrome was evident in the second cohort of patients, suggesting that the low-dose dexamethasone premedication should be further explored in patients receiving docetaxel.

In conclusion, the present study confirms the activity of docetaxel in anthracycline-pretreated patients with metastatic breast cancer and suggests that paclitaxel-pretreated patients might also benefit from this treatment. Both hematologic and nonhematologic toxicities are manageable in an outpatient setting. In addition, prophylactic G-CSF administration significantly reduces the incidence of severe neutropenia, with or without fever, and the need for dose reductions. Both schedules of corticosteroid premedication seem to improve some of the most troublesome drug-related toxic effects, with a trend favoring the low-dose i.m. dexamethasone schedule.

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