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Sequential Docetaxel Followed by Epirubicin-Vinorelbine as First-line Chemotherapy in Advanced Breast Cancer

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Abstract. *Background: This phase II study evaluated the efficacy and the tolerability of a sequential regimen of docetaxel followed by epirubicin-vinorelbine combination as first-line chemotherapy in advanced breast cancer. Patients and Methods: Twenty-seven patients received docetaxel 100 mg/m^2 (4 cycles) followed by 4 cycles of epirubicin 90 mg/m^2 (day 1) combined with vinorelbine 25 mg/m^2 (days 1 and 5), with cycles repeated every 3 weeks. G-CSF was administered during epirubicin-vinorelbine treatment. Results: There were 1 (3.7%) CR and 14 (51.9%) PR, for an overall response rate of 55.6% (95% CI, 36.9%-74.3%). Median time to response, time to progression and overall survival were 2, 9 and 25 months, respectively. The dose-limiting toxicity was neutropenia (grade 3 to 4 in 85% of the patients). There was one toxic death due to neutropenic fever. Gastrointestinal side-effects were generally mild. According to the Simon two-stage design the response rate was considered unsatisfactory and patient accrual was terminated. Conclusion: This sequential regimen appears to be moderately effective; possibly, a modulation of the treatment based on objective responses instead of a fixed number of cycles may be more appropriate in order to obtain better results.*

A large body of evidence has demonstrated that the anthracyclines doxorubicin and epirubicin, and the taxanes paclitaxel and docetaxel, are the most active drugs in advanced breast cancer. As first-line treatment, single-agent epirubicin has showed similar efficacy to doxorubicin, with response rates of 30% to 59% (1-3); however, a decreased toxicity has often been reported in comparison to the parent compound (4, 5), and epirubicin is frequently chosen by many investigators. In preclinical studies (6), docetaxel was about 1.5-fold more potent than paclitaxel. This superiority was later confirmed in a number of clinical trials showing a significant single-agent activity in patients with metastatic breast cancer, with overall response rates ranging from 45% to 60% (7, 8). In addition, several reports have indicated that epirubicin and docetaxel lack complete cross-resistance and that better results could be obtained by their simultaneous or sequential administration (9, 10).

From a theoretical point of view, the most efficient method of exploiting the cytoreductive potential of epirubicin and docetaxel, while maintaining toxicity at acceptable levels, should be the sequential use of the two drugs. This is postulated by the Norton-Simon model (11). In this model, which is based on gompertzian tumor growth, the rate of tumor regression is positively correlated with the tumor growth rate just before treatment, and in a cancer that is heterogeneus in growth rate, slower-growing cells tend to regress more slowly in response to a given therapy than faster-growing cells. The Norton-Simon model also suggests that the best way to eradicate the tumor is to first treat the faster-growing population and then the numerically inferior, slower-growing cells. In this regard, the most efficient therapy is the most dose-dense therapy, which may be accomplished by sequential administration of multiple cycles of an active agent followed by multiple cycles of another active agent or regimen, both given at the highest feasible doses (12, 13).

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Sequential therapy has been mainly used in the adjuvant treatment of breast cancer, though less employed in the treatment of advanced disease (14-17). The sequence most frequently employed has been an anthracycline combination followed by a taxane, but also the reverse sequence has been explored with interesting results (18-20). In this regard, it is worth noting that combination regimens including an anthracycline have been shown to be active as second-line therapy in patients previously treated with docetaxel, with a response rate of 30% (21). The combination of epirubicin and vinorelbine has been reported highly active in patients with metastatic breast cancer with no evidence of cardiac toxicity (22).

We undertook this multicenter phase II trial to determine the activity and tolerability of sequential administration of docetaxel followed by the epirubicin-vinorelbine combination as first-line chemotherapy for advanced breast cancer.

Patients and Methods

Eligibility criteria included histologically confirmed metastatic carcinoma of the breast, in women aged 18-75 years, a life expectancy of more than 3 months, a WHO performance status ≤3, a measurable or evaluable disease, adequate bone marrow (absolute neutrophil count ≥1,500 mL, platelet count ≥100,000/mL, hemoglobin ≥11 g/dl), renal and liver (total bilirubin and creatinine <1.25 x upper normal limits) function, and a baseline normal cardiac function as evidenced by left ventricular ejection fraction (LVEF). Exclusion criteria were active cardiac disease, preexistent neuropathy, other prior malignancies, symptomatic brain metastases, previous exposure to anthracyclines, vinca alkaloids and taxanes. Previous chemotherapy for advanced disease was not allowed. Previous adjuvant chemotherapy with CMF or similar regimens was allowed, with an interval of 2 months since the end of therapy. Prior hormonal therapy or radiotherapy must have been discontinued for at least 4 weeks before study entry. The protocol was approved by an independent ethic committee and all patients gave their written informed consent.

Treatment. Treatment consisted of docetaxel, 100 mg/m^2 by one-hour *i.v.* infusion on day 1, with cycles repeated every 3 weeks for four cycles, followed by four cycles of epirubicin, 90 mg/m^2 by *i.v.* bolus on day 1 plus vinorelbine, 25 mg/m^2, diluted in 250 mL of normal saline and administered *i.v.* over 30 minutes on days 1 and 5, with cycles repeated every 3 weeks. In comparison to our previous experience (22), the epirubicin dose was reduced (90 mg/m2 instead of 100 mg/m^2) due to the pretreatment with docetaxel.

For both regimens, antiemetic treatment consisted of an antiserotonin agent plus dexametasone in a 15-minute infusion before starting chemotherapy. Docetaxel premedication consisted of prednisone, 50 mg orally twice a day from the day before to the day after chemotherapy.

Treatment was postponed by a maximum of two weeks if the absolute neutrophil count was less than 1,500/μL or platelet count less than 100,000/μL. A 25% drug dose-reduction was planned in the case of grade 4 neutropenic fever (absolute granulocyte count below 500/mL at the time of a documented temperature of 38˚C or higher) as well as in the case of grade 4 mucositis, grade 3 hepatotoxicity, or grade 2 neurotoxicity. In the case of grade 3-4 neurotoxicity, or significant fluid retention, docetaxel treatment was discontinued. Granulocyte-colony stimulating factor (G-CSF) was planned only in the case of grade 4 neutropenic fever during docetaxel treatment, while it was administered prophylactically on days 7 to 12 of each cycle of the epirubicin-vinorelbine combination.

The docetaxel and epirubicin-vinorelbine regimens were administered for 4 cycles and were discontinued in the case of early disease progression, unacceptable toxicity, treatment delay longer than two weeks, or patient refusal.

A fixed number of four cycles of each regimen was empirically chosen, according to the duration of the majority of chemotherapy regimens in advanced breast cancer.

Study parameters. Pretreatment evaluation included clinical history, physical examination, automated blood cell count, biochemical profile, chest X-ray, abdominal ultrasound, or computed tomography scan, bone scan, ECG, resting LVEF determination by echocardiography or MUGA scan, and other examinations as clinically indicated.

Blood counts were obtained on day 1 and at nadir (docetaxel: d 7; epirubicin-vinorelbine: d 12); the biochemical profile was repeated every 3 weeks. Cardiac monitoring was performed at baseline, and at the end of the study. In the case of a LVEF decrease >10% and/or below the lower limits of normal, a repeat measurement in two months was required and, if necessary, subsequent evaluation was planned during the follow-up.

Objective response was evaluated every two cycles according to standard WHO criteria by at least two observers. Responses were also evaluated separately by single treatment. Patients with disease progression after 1, 2 or 3 cycles of docetaxel were changed to the epirubicin –vinorelbine regimen. Time to progression and survival were calculated starting from the date of first chemotherapy cycle to the date of disease progression or the date of death (or last follow-up evaluation), respectively.

Toxicity was assessed at each treatment cycle and graded using the NCIC-Common Toxicity Criteria.

Statistical analysis. The Simon two-stage phase II design was used to determine the sample size (23). Treatment would be considered worthy of further testing if at least 17 out of 27 evaluable patients had an objective response (63%), with a significance level of 5% and a power of 80%. In the second stage, 40 additional patients would be needed, with an overall sample size of 67 patients. Time to progression and overall survival curves were assessed by the Kaplan-Meier method.

Results

This trial was initiated in January 1999 and accrued 27 patients with advanced breast cancer according to the number required by the first stage of the study design. All of the patients received both docetaxel and the epirubicin-vinorelbine combination. The patient characteristics are listed in Table I. The median age was 58 years (range, 35 to 71 years) and median WHO performance status was 0 (range, 0 to 2). None of the patient included in the study

Table I. *Patient characteristics.*

Characteristic	No. of patients
Entered/evaluable	27/27
Median age, years (range)	58 (35-71)
Median WHO performance status (range)	0 (0-2)
Pre/postmenopausal	5/22
Receptor status	
positive	11
negative or unknown	16
Prior surgery	22
Prior radiotherapy	7
Prior hormonal therapy	
Adjuvant	10
Advanced disease	3
Prior adjuvant CMF	11
Dominant disease site	
Soft tissue	7
Bone	4
Viscera (liver)	16 (5)
Number of disease sites	
1	14
2	10
3	3
Disease-free interval (years)	
< 1	9
1-5	13
> 5	5

Table II. *Objective responses in 27 patients.*

	No. of responses		
	D	EV	ORR (%)
CR	-	1	3.7
PR	11	14	51.9
NC	11	9	33.3
PD	5	3	11.1

CR, complete response; PR, partial response; NC, no change; PD, progressive disease; D, docetaxel; EV, epirubicin-vinorelbine; ORR, overall response rate.

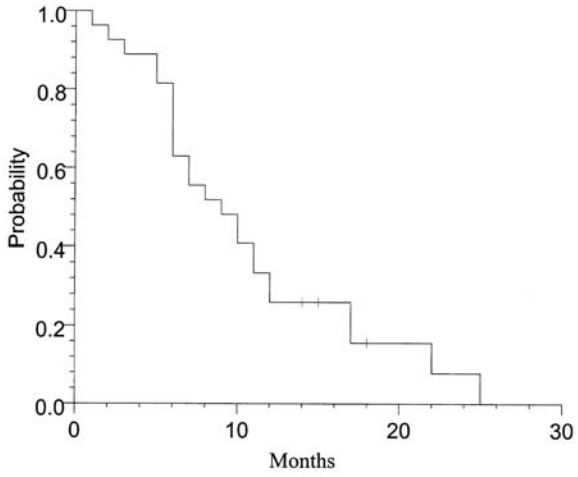

Figure 1. *Time to progression.*

had previously received chemotherapy for metastatic disease. Eleven patients had received adjuvant CMF, and 3 patients had hormonal treatment for advanced disease. Fifty-nine percent of the patients had visceral metastases, with liver involvement in 5 patients (18.5%).

The median number of cycles of docetaxel administered was 4 (range, 2-4), and the median number of cycles of the epirubicin-vinorelbine regimen was 4 (range, 1-4).

As outlined in Table II, among the first 27 enrolled and evaluable patients, 1 (3.7%) had complete and 14 (51.9%) had partial responses, for an overall response rate of 55.6% (95% CI, 36.9%-74.3%). Disease remained stable in 9 (33.3%) patients, while a progressive disease was observed in 3 (11.1%) patients. According to the Simon two-stage design of the study, this response rate was considered unsatisfactory and patient accrual was terminated.

Evaluating response according to treatment phases showed that the complete response rate increased from 0% after docetaxel to 3.7% at the end of the sequence, whereas the 40.7% objective response rate after initial treatment increased to 55.5% after the epirubicin-vinorelbine combination. The median time to first response was 2 months (range, 2-4 months). As expected, the highest response rate was observed in soft-tissue lesions (71%), but the treatment schedule was also highly effective in visceral disease (62.5%), whereas no responses were observed in the small number of patients with disease confined to bone. An objective response was observed in 6/14, 6/10 and 3/3 patients with 1, 2 or 3 metastatic sites, respectively. The median duration of response was 8 months (range, 2-18 months), and the median time to progression was 9 months (range, 2-25 months) (Figure 1). Overall survival was 25 months (range, 4-29 months) (Figure 2).

Toxicity is reported in Table III. Although this sequential regimen appeared feasible, myelosuppression was striking with neutropenia occurring in virtually all patients. The incidence of grade 3-4 neutropenia was more frequent in patients given docetaxel. Febrile neutropenia (grade 4

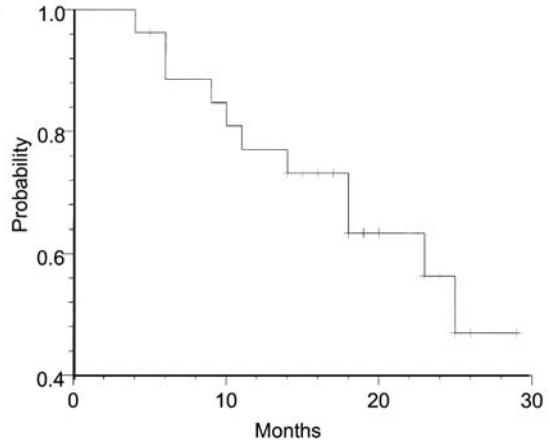

Figure 2. *Patient overall survival.*

Table III. *Overall toxicity (%) in 27 evaluable patients.*

Toxic effect	Grade		
	1/2	3	4
Leukopenia	33	52	15
Neutropenia	15	15	70
Thrombocytopenia	4	4	4
Anemia	89	4	-
Nausea/vomiting	85	7	-
Mucositis	67	15	4
Diarrhea	26	-	-
Peripheral neurotoxicity	48	-	-
Alopecia	-	100	-
Arthralgias/myalgias	15	-	-

Neutropenic fever = 33

neutropenia concomitant with grade 2 fever) was experienced by 9 patients (33%). All these patients received G-CSF and parenteral antibiotics. Unfortunately, 1 patient developed sepsis and died 20 days after the third cycle of epirubicin-vinorelbine. Anemia and thrombocytopenia were generally mild; platelet transfusions were not required. Overall, a high mean relative dose-intensity for both regimens was administered. The mean docetaxel dose-intensity was 31.2 mg/m^2/week (93.69% of the planned dose-intensity); the mean epirubicin-vinorelbine dose-intensities were 26.9 and 15.2 mg/m^2/week (89.6% and 91.2% of the planned dose-intensities), respectively.

Gastrointestinal side-effects were generally mild, and only in rare instances grade 3-4 nausea and vomiting or stomatitis were observed. Alopecia was universal. Neurotoxicity was only of grade 1 or 2. Astenia and nail disorders, although common, were generally mild. Hypersensitivity reactions and fluid retention were not encountered. No clinical or laboratory cardiotoxicity was recorded.

Discussion

The most extensively used approach to treat advanced breast cancer has been the concomitant administration of multiple drugs in an effort to overcome the heterogeneity in drug sensitivity characteristic of this neoplasia. Although simultaneous combination chemotherapy has generally proven to be more effective than single agents, failure to eradicate the disease has been tantamount to failure to cure or even to alter the long-term outcome of this slow-growing tumor. The Norton-Simon model suggests that innovative dose-schedule schemes, namely sequential chemotherapy, might be able to improve the clinical results. Sequential therapy has been successful in the laboratory (24), and has been already reported as effective in the adjuvant treatment of breast cancer (14). However, the experience in advanced disease is lower (15-20, 25-31), especially when taxanes followed by anthracyclines are considered (18-20, 28, 31).

The results of the present phase II study, using the sequential administration of a fixed number of cycles of docetaxel followed by a fixed number of cycles of epirubicin and vinorelbine, should be considered unsatisfactory as first-line treatment in advanced breast cancer, because of the relatively low objective response rate (55.6%), along with a very low complete response rate (3.7%). These results are at variance with those reported by a similar phase II trial, in which sequential docetaxel followed by doxorubicin and cyclophosphamide (AC) were evaluated with an overall response rate of 71% (28). It should be considered, however, that in this study patients with progressive disease in the first phase of treatment were withheld from the study, whereas a consolidation treatment was delivered to patients who responded to docetaxel and still were in response under AC. This allowed a progressive selection of patients with sensitive tumors, thus increasing treatment results. Contrasting results were reported in two recent phase II trials, of sequential docetaxel followed by AC with response rates of 35% and 73%, respectively (29, 31).

The role of sequential compared with simultaneous administration of taxanes and anthracyclines in metastatic breast cancer has so far been investigated in four prospective trials. In a randomized trial of simultaneous *versus* sequential doxorubicin and docetaxel (17), the response rates were almost superimposible in both arms (66% *vs* 65%) and there was no significant difference in time to progression and overall survival between the two treatment schedules. In another randomized trial (30) comparing simultaneous *versus* sequential epirubicin and paclitaxel, no significant difference was observed between the two arms in overall response rate (42% *vs* 55%), time

to progression and median survival, although the complete response rate was higher in the sequential group. Recently, a phase III randomized trial comparing sequential with concomitant doxorubicin and docetaxel as first-line treatment showed lower toxicity in the sequential arm, but no significant differences in activity were found (26). Finally, results from a phase II randomized trial of combination, alternating and sequential regimens of doxorubicin and docetaxel as first-line chemotherapy showed that all three schedules are feasible and active without any significant difference in efficacy (27).

The present study and the results of these four randomized trials failed to demonstrate a superiority of the sequential treatment in patient with metastatic breast cancer. Several reasons may be postulated as a possible explanation for the poor outcome of the present trial. First, the number of cycles given in each treatment phase might have been too small. It has previously been reported that, with continued treatment, complete response rates may increase (32), and certainly some patients could have benefited from more cycles of one or both regimens. Second, delivering a fixed number of treatment cycles may be not appropriate in the metastatic setting. This strategy is commonly applied in the adjuvant setting, where the burden of the disease is presumably small and the log-kill is greater in comparison to large tumors. Gompertzian tumors are difficult to eradicate unless the impact of therapy is so great that regrowth is precluded. In a large tumor, as is the case of advanced breast cancer, the regression rate is low and four treatment cycles, even if very effective, may be not enough to eradicate cancer cells sensitive to the first regimen, allowing the residual cells to regrow while the subsequent regimen is delivered. Therefore, a better approach could be a longer treatment until maximum response to each regimen under study, with a consolidation phase in patients achieving complete response.

A limit to this type of thinking may be an increased toxicity of the whole treatment. However, sequential therapy by itself does not imply more frequent or severe toxic effects. Indeed, the toxicity profile of the sequential treatment was considered safe in phase II studies (28), and somewhat better than the concurrent regimen in randomized trials (17, 26, 27, 30). In the current study, although myelotoxicity was relevant, the sequential regimen appeared quite feasible and nonhematological toxicity was generally mild to moderate, with the exception of a few instances of stomatitis. Nevertheless, the epirubicin-vinorelbine combination given after four cycles of docetaxel seemed to be somewhat worse tolerated than the same regimen used as first treatment, as was the case in our previous study in which the epirubicin dose was even higher (22).

From the body of evidence so far accumulated in studies addressing the issue of sequential chemotherapy in metastatic breast cancer, it seems that, although the superiority of this approach could not be demonstrated, data have not emerged to refute the Norton-Simon hypothesis. Indeed, the results of our study, as well as those of several other trials (15-20, 26-28, 30, 31), provided persuasive evidence that the design of studies exploring the sequential administration of taxanes and anthracyclines may be improved in the search for the optimal regimen to be used as first-line chemotherapy in advanced breast cancer. Ongoing and future randomized trials will hopefully give appropriate answers to relevant questions related to this important issue.

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