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Original article

Front-line treatment of metastatic breast cancer with docetaxel and epirubicin: A multicenter dose-escalation study

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Summary

Purpose: To determine the maximum tolerable dose (MTD) and the dose-limiting toxicity (DLT) of docetaxel (D) in combination with epirubicin (Epi) in patients with advanced breast cancer.

Patients and methods: Forty-seven chemotherapy-naïve metastatic breast cancer patients aged <75 years with PS (WHO) 0–2 and adequate bone marrow, renal, liver and cardiac function, were enrolled in the study. Epi was given as a five-min bolus i.v. infusion on day 1 (d_1) in escalated doses with increments of 10 mg/m^2; D was given in a one-hour infusion after appropriate premedication on either day 1 or on day 2 in escalated doses with increments of 10 mg/m^2. The patients' median age was 60 years, 42 (89%) had a PS (WHO) 0–1, 16 (34%) were premenopausal and 25 (53%) had visceral disease.

Results: When the two drugs were given on the same day, the MTD_1 was reached at the doses of Epi 60 mg/m^2 and D 80 mg/m^2; administration of G-CSF could not result in a dose intensification. When the drugs were given on two consecutive days, the MTD_2 was reached at the doses of Epi 80 mg/m^2 (d_1) and D 90 mg/m^2 (d_2). The dose-limiting events were febrile neutropenia and grade 4 neutropenia, which developed in 30 (64%) patients during the study; among 227 delivered cycles grade 3–4 neutropenia occurred in 64 (28%) cycles but only 22 (10%) of them were complicated by fever. There were no septic deaths. Grade 1–2 neurosensory toxicity occurred in nine (19%) patients, mild edema in eight (17%) and allergic reactions in five (11%). Four (9%) patients presented a greater than 10% decrease of LVEF and treatment discontinuation was required in two of them; none of the patients developed congestive heart failure. Nevertheless, one patient suddenly died 10 days after treatment initiation of myocardial ischemia, and this death is considered treatment-related. Five (14.7%) complete and thirteen (38.2%) partial responses (ORR: 53.9%; 95% confidence interval: 36.1%–69.7%) were observed in 34 evaluable patients. Ten (29.4%) and six (17.6%) patients had stable and progressive disease, respectively. The median duration of response and time to tumor progression were five and seven months, respectively. The median survival has not yet been reached.

Conclusions: The combination of epirubicin and docetaxel is a feasible and well tolerated regimen, but the MTD depends on the administration schedule of the drugs.

Key words: breast cancer, docetaxel, epirubicin

Introduction

Metastatic breast cancer remains an incurable disease despite the considerable amount of research performed in recent years. In addition, current chemotherapy can confer only a slight improvement on the overall survival of patients [1]. Thus, new active agents and regimens are needed in order to improve the prognosis of these patients.

Anthracyclines are among the most active agents when used as single agents in metastatic breast cancer, producing responses ranging from 50% to 60% as front-line treatment. On the other hand, the taxoid docetaxel, a new antimicrotubule agent, is about 1.5-fold more potent, *in vitro,* than paclitaxel or doxorubicin [3]. Indeed, single-agent docetaxel in chemotherapy-naïve patients with metastatic breast cancer resulted in objective response rates ranging from 45% to 60% [4]. Its antitumor activity is similar to that reported with standard combination regimens such as FAC (44%–65%) and FEC (67%) [5]. In addition, docetaxel has yielded an impressive 55% response rate in anthracycline-resistant breast cancer patients [6].

Since docetaxel and anthracyclines are among the most effective agents against breast cancer and have different mechanisms of action, their combination is a logical step in developing new active chemotherapy regimens with the potential to improve the therapeutic results in this disease. A few studies associating paclitaxel and doxorubicin have been reported [7, 8] and the combination showed the significant effect of an up to 90% response rate; these regimens, however, are complicated

by a high incidence of cardiotoxicity [7]. In a phase I study of the paclitaxel and doxorubicin combination, 50% of patients had reductions of left ventricular ejection fraction below the normal levels while 20% of them developed congestive heart failure (CHF) [7]. In contrast, docetaxel is rarely associated with cardiotoxicity [8] and preliminary reports from a few studies have suggested that docetaxel can be effectively combined with doxorubicin [9–11] or epirubicin [12–15]; the incidence of cardiotoxic effects of these regimens is extremely low [9–15].

Epirubicin has similar efficacy with doxorubicin as first-line treatment of breast cancer, with response rates ranging from 25% to 62% [16]; however, its toxicity profile was more favorable than that of doxorubicin, especially in terms of cardiotoxicity [16–18]. Based on these considerations, we conducted a multicenter phase I study to determine the maximum tolerable dose (MTD) and the dose-limiting toxicities (DLTs) of the docetaxel and epirubicin combination in chemotherapy-naïve patients with metastatic breast cancer.

Patients and methods

Patient selection

Eligible for treatment were previously untreated patients, aged 18–75 years, with histologically proven metastatic breast cancer. Further eligibility criteria were: a cumulative doxorubicin dose received in prior adjuvant treatment of less than 300 mg/m^2 or equivalent; a life expectancy of more than three months; adequate hematologic parameters (absolute neutropenia count $\geq 1500/mm^3$, hemoglobin ≥ 10g/dl, platelets $\geq 100 \times 10^3$) as well as renal (serum creatinine < 1.5 mg/dl) and hepatic (serum bilirubin ≤ 1.5 mg/dl, SGPT, SGOT $\leq 3\times$ normal values) function tests; normal cardiac function with left ventricular ejection fraction (LVEF) $\geq 50\%$; an interval of more than four weeks since the last radiation course; irradiation of less than 25% of bone marrow-containing bones. Bidimensionally-measurable disease was not required for entry into this phase I study. The study was approved by the Ethics and Scientific Committees of the participating centers and all patients gave their written informed consent to participate in the study.

Treatment

The dose escalation scheme is shown in Table 1. Initially, the administration of epirubicin (Farmorubicine; Pharmacia, Milano, Italy) was immediately followed by the administration of docetaxel (Taxotere; Rhône-Poulenc Rorer; Collegeville, PA,USA) in a one-hour infusion, after standard premedication with oral methylpresolone. After MTDI was reached, and since in the meantime it had been reported that the administration of taxanes could modify the clearance of anthracyclines and thereby increase their toxicity [19], we modified the schedule by administering epirubicin on day 1 and docetaxel on day 2. Treatment was given every three weeks on an outpatient basis. There were no intra-patient dose escalations. Three patients were enrolled per dose level, but the number was increased to six if DLT had occurred in at least one of them.

The DLT was defined as the occurrence of one of the following events: grade 4 neutropenia or thrombocytopenia lasting longer than two days; neutropenia and fever > 38.2 °C for more than 24 hours; any grade 3 or 4 non-hematologic toxicity except nausea/vomiting or alopecia. The MTD was defined as the next lower dose level at which DLT occurred during the first chemotherapy course in at least two of three or three of six patients.

Table 1. Dose escalation schedule.

Level	Epirubicin (mg/m^2)	Docetaxel (mg/m^2)	rhG-CSF
1	60 (d_1)	70 (d_1)	–
2	60 (d_1)	80 (d_1)	–
3	70 (d_1)	80 (d_1)	–
3a	70 (d_1)	80 (d_1)	+
4	60 (d_1)	90 (d_1)	–
4a	60 (d_1)	90 (d_1)	+
3b	70 (d_1)	80 (d_2)	–
4b	70 (d_1)	90 (d_2)	–
5b	80 (d_1)	90 (d_2)	–

a – The dose level was repeated with prophylactic G-CSF support.
b – Epirubicin was given on day 1 and docetaxel on day 2.

In instances of DLT, the lower dose level was administered in the next cycle. Epirubicin administration was discontinued in patients with LVEF < 50% or a 15% decrease of LVEF in comparison with the pretreatment values, or congestive heart failure (CHF). The total cumulative dose of epirubicin allowed was defined at 850 mg/m^2, including the equitoxic received dose of anthracycline in the adjuvant setting.

Patient evaluation

Baseline evaluations included: patient history, physical examination, chest X-rays, complete blood count with differential and platelet count (CBC), blood chemistry, ECG and echocardiography or MUGA with LVEF measurement. Computed tomography scans or abdomen ultrasounds were performed when clinically indicated. CBCs were performed twice weekly for all patients or daily in patients with grades 3 or 4 neutropenia, thrombocytopenia or febrile neutropenia. Toxicity was graded according to the WHO criteria [20]. Cardiac monitoring consisted of physical examination and ECG performed every three weeks, LVEF measurement after the third and the sixth chemotherapy courses and then every three months for a maximum of nine months after the completion of treatment. Response to treatment was assessed according to the WHO criteria [20].

Statistical analysis

The duration of response was calculated from the first documentation of response until disease progression. Overall survival was measured from study entry to death. The actuarial probability of survival was estimated by the Kaplan–Meier method. The confidence intervals for response rate were calculated using methods for exact binomial confidence intervals.

Results

From November 1996 to April 1998, 47 patients were enrolled. Their median age was 60 years (Table 2); 31 (66%) patients were post-menopausal and 42 (89%) had a PS 0–1. Twenty-seven (58%) patients had not received prior chemotherapy. Twenty (42%) patients had received adjuvant chemotherapy (nine of them an anthracycline-containing regimen with a median received cumulative doxorubicin dose of 200 mg/m^2; range 170–280 mg/m^2). The median interval between the completion of adjuvant chemotherapy and the administration of the docetaxel/epirubicin regimen was 33 months (range 7–132).

Table 2. Patient characteristics.

	Number of patients	%
Patients enrolled	47	
Age (years)		
Median	60	
Range	30–74	
WHO performance status		
0	23	49
1	19	40
2	5	11
Hormonal status		
Pre-menopausal	16	34
Post-menopausal	31	66
Receptor status		
ER+	30	64
ER−	17	36
Prior treatment		
Adjuvant chemotherapy: CMF[a]	11	23
Adjuvant chemotherapy: CAF[b]	9	19
Hormone treatment for metastatic disease	15	32
None	12	26
Number of disease sites		
0	11	23
1	13	28
2	14	30
⩾3	9	19
Visceral disease	25	53

[a] Cyclophosphamide, methotrexate, 5-fluorouracil.
[b] Cyclophosphamide, doxorubicin, 5-fluorouracil.

Two hundred twenty-seven chemotherapy courses were administered with a median of six courses per patient (range 1–9). The median cumulative dose of epirubicin administered was 525 mg/m^2 (range 100–1350) and of docetaxel 660 mg/m^2 (range 125–1350). Four (9%) patients discontinued treatment after the first course because of septic shock due to acute neutropenic enterocolitis (one patient), progressive disease (one patient), death due to acute myocardial ischemia (one patient) and treatment refusal because of grade 4 neutropenia (one patient).

The hematologic toxicity in all delivered courses at each dose level is presented in Table 4. There was no significant difference in the incidence of grade 4 neutropenia at different dose levels. A total of 30 (64%) patients developed grade 4 neutropenia and two (4%) patients grade 3–4 thrombocytopenia. Sixty-four (28%) of two hundred twenty-seven administered chemotherapy cycles were complicated by grade 3–4 neutropenia; however only twenty-two (10%) of these neutropenic episodes, corresponding to twenty (43%) patients, were complicated by fever (Table 4). Thirteen (6%) neutropenic episodes occurred during the first course and nine (4%) during subsequent courses; all patients with febrile neutropenia were hospitalized and uneventfully treated with antibiotics and G-CSF; the median duration of hospitalization was four days (range 3–10). There were no septic deaths. Dose reductions, most of them due to hematologic toxicity, were performed in 15 (7%) and 12 (5%) courses for epirubicin and docetaxel, respectively (Table 4).

Non-hematologic toxicity was mild. Alopecia (grade 2) was almost universal at all dose levels. Grade 3 nausea/vomiting occurred in five (11%) patients; grades 2 and 3 diarrhea was observed in seven (15%) and one (2%) patients, respectively. Twenty-one (45%) and two (4%) patients reported grades 2 and 3 asthenia, respectively, lasting for up to 13 days; asthenia seems to be cumulative since it always occurred after the third chemotherapy course. Mild (grade 1–2) mucositis occurred in nine (19%) patients, grade 2 neurosensory toxicity in 9 (19%) patients, constipation in 10 (21%) patients, eodema in 8 (17%) patients, and mild or moderate allergic reactions in 5 (11%) patients. The median LVEF was 56% at baseline (range 51%–70%) and 52% after six courses (range 41%–68%). Four (9%) patients presented a greater than 10% decrease of the LVEF during treatment; in two of them the LVEF was decreased by more than 25% of the pre-treatment values after the eight and nineth chemotherapy courses; in both patients treatment was discontinued (the received cumulative doses of epirubicin were 630 mg/m^2 and 472 mg/m^2, respectively). None of the patients developed congestive heart failure. Moreover, another patient with no predisposing factors died of a probable acute myocardial ischemia five days after the administration of the first chemotherapy course; autopsy was not authorized. Finally, another patient died of a massive pulmonary thrombosis 12 days after the third chemotherapy course.

Thirty-four patients with bidimensionally measurable disease were evaluable for response. Thirteen (28%) patients were not evaluable (four patients received only one cycle of treatment and nine had not measurable disease). Responses were observed at all dose levels (Table 4); 5 (14.7%) complete (CR) and 13 (38.2%) partial responses (PR) were documented (overall response rate 53.9%; 95% confidence interval (95% CI): 36.16%–69.72%). Ten (29.4%) and six (17.6%) patients had stable (SD) and progressive disease (PD), respectively. Among the 22 evaluable patients who received epirubicin and docetaxel on day 1, 13 (59%) achieved an objective (CR + PR) response and nine (41%) SD and PD; in contrast, 5 (41%) of 12 evaluable patients who received epirubicin on day 1 and docetaxel on day 2 achieved CR + PR and 7 (58%) SD and PD. The difference between the objective response rates of the two different schedules was not statistically significant (P = 0.33). Responses were observed in lymph nodes (9 of 15 patients; 60%), lung (three of eight patients; 38%), skin (seven of nine patients; 78%) and liver (two of seven patients; 29%). The median duration of response was five months (range 1.5–14.5) and the median time to tumor progression seven months (range 2–16). At the time of this analysis (with a median follow-up time of seven months; range 1–16), 12 (26%) patients remain progression-free and 37 (79%) are still alive. The median survival has not yet been reached.

Table 3. Hematologic toxicity and dose-limiting events of docetaxel–epirubicin combination during the first chemotherapy course.

Dose level	E/D (mg/m^2)	Number of patients	Number of patients with adjuvant CT	Nadir (mean ± SD)			DLEs
				Neutrophils (/dl)	Platelets (× 10^3/dl)	Hemoglobin (g/dl)	
1	60/70	3	3 (1)[a]	4057 ± 4671	249 ± 58	11.3 ± 1.670	–
2	60/80	7	2 (2)	3554 ± 2682	266 ± 95	11.4 ± 1.502	FN (1)[b]
3	70/80	7	1 (1)	1013 ± 1708	313 ± 115	11.6 ± 2.339	NG4 (5), TG4 (1), DG3 (1), FN (3)
3a	70/80	4	3 (2)	1927 ± 3118	174 ± 140	11.1 ± 1.266	NG4 (3), TG4 (1), FN (1)
4	60/90	3	1 (0)	418 ± 285	234 ± 85	10.7 ± 1.966	NG4 (2)
4a	60/90	3	–	413 ± 299	163 ± 55	10.2 ± 1.261	NG4 (2), FN (1)
3b	70/80	10	3 (1)	1419 ± 1400	197 ± 56	11.7 ± 1.655	NG4 (4), FN (3)
4b	70/90	6	–	2190 ± 2078	215 ± 114	12.0 ± 1.738	NG4 (2), FN (2)
5b	80/90	4	2 (1)	317 ± 201	173 ± 66	10.0 ± 1.300	NG4 (4), FN (2)

Abbreviations: DLEs – dose-limiting events; N – neutropenia; T – thrombocytopenia; D – diarrhea; FN – febrile neutropenia; G – grade.
[a] Number of patients with anthracycline-based adjuvant chemotherapy.
[b] Number of patients.

Table 4. Hematologic toxicity and responses of the docetaxel–epirubicin combination in all patients and all courses at the different dose levels.

Dose level	E/D (mg/m^2)	Number of patients (courses)	Nadir (mean ± SD)			Dose reduction (courses)		Grade 3–4 (number of courses)			CR + PR
			Neutrophils (/dl)	Platelets (× 10^3/dl)	Hemoglobin (g/dl)	Epirubicin	Docetaxel	Neutropenia	Hb	Thrombocytopenia	
1	60/70	3 (13)	2127 ± 2449	220 ± 45	10.9 ± 1.6	–	–	2 (2)[a]	–	–	0/2
2	60/80	7 (38)	3410 ± 3293	207 ± 61	11.0 ± 0.9	–	–	1 (1)	–	–	4/5
3	70/80	7 (35)	3266 ± 3886	228 ± 71	11.3 ± 1.3	3	3	6 (6)	–	1	5/6
3a	70/80	4 (16)	2741 ± 2156	176 ± 90	11.0 ± 1.0	2	2	3 (1)	–	1	0/3
4	60/90	3 (22)	3472 ± 3049	224 ± 53	11.5 ± 1.0	1	1	1 (1)	–	–	2/3
4a	60/90	3 (19)	2779 ± 2642	211 ± 61	10.6 ± 1.4	3	3	2 (1)	–	–	2/3
3b	70/80	10 (46)	3069 ± 3114	214 ± 70	11.2 ± 1.4	2	1	7 (3)	–	–	3/7
4b	70/90	6 (26)	3436 ± 4965	198 ± 66	15.0 ± 1.8	2	2	4 (4)	–	–	2/4
5b	80/90	4 (12)	2124 ± 1424	235 ± 63	10.3 ± 0.9	2	–	4 (2)	–	–	0/1
		47 (227)				15	12	30 (20)[a]	0	2	18/34

[a] In parentheses: courses complicated with fever > 38.2 °C for more than 48 hours.

Discussion

The results of the present study indicate that epirubicin can be effectively combined with docetaxel as front-line chemotherapy in patients with metastatic breast cancer. The MTD of this combination clearly depends on the administration schedule of the two drugs. Indeed, two different MTDs could be established: the MTD1 is epirubicin 60 mg/m^2 and docetaxel 80 mg/m^2 when the two drugs are given sequentially on day 1 (with epirubicin infused first) whilst the MTD2 is epirubicin 70 mg/m^2 and docetaxel 90 mg/m^2 when the drugs are given separately on days 1 and 2, respectively. Gianni et al. [19] have reported that paclitaxel perturbs the metabolism of doxorubicin when doxorubicin is given 15 minutes but not 24 hours prior to the paclitaxel infusion, resulting in an approximately 30% increase in doxorubicin exposure with the shorter interval. A similar phenomenon has also been reported by Itoh et al., who randomized patients with advanced breast cancer to receive either the sequence of docetaxel followed by doxorubicin or vice-versa; the MTD (docetaxel 60 mg/m^2 and doxorubicin 40 mg/m^2) was exceeded in the first but not in the second arm of the study [11]. This phenomenon may be responsible for the toxicity differences observed with the administration schedules used in the present study. Therefore, the recommended doses for further phase II studies are either epirubicin 60 mg/m^2 followed by docetaxel 80 mg/m^2 on the same day or epirubicin 70 mg/m^2 on day 1 and docetaxel 90 mg/m^2 on day 2.

The dose-limiting events were grade 4 neutropenia, neutropenic fever and, occasionally, grade 4 diarrhea or thrombocytopenia. There was no significant difference in the incidence of grade 4 neutropenia or febrile neutropenia between the different dose levels (Table 4). It is interesting to note that the prophylactic administration of rhG-CSF could not prevent the development of dose-limiting neutropenia when the two drugs were given on day 1. However, neutropenia was rapidly reversible, since by day 20 the mean neutrophil count had returned to normal range (data not shown) and it was possible to

deliver the next chemotherapy without significant delay or significant dose reductions for epirubicin and docetaxel. In addition, myelotoxicity did not appear to be cumulative.

Some preliminary studies have investigated the combination of anthracyclines (anthracyclines or epirubicin) and docetaxel. In all such studies neutropenia and neutropenic fever were the main dose-limiting events, indicating that severe myelosuppression is the main toxic effect of this combination. In all of the other reported phase I studies investigating the epirubicin-docetaxel combination, the MTD was reached at docetaxel 75 mg/m^2 and epirubicin 90 mg/m^2 without rhG-CSF [14], at docetaxel 75 mg/m^2 and epirubicin 75 mg/m^2 [15], at docetaxel 75 mg/m^2 and epirubicin 100 mg/m^2 [12] while it has not been reached at the docetaxel 75 mg/m^2 and epirubicin 80 mg/m^2 in the fourth study [13]. Despite the fact that docetaxel was given at a lower dose than in our study, grade 4 neutropenia was almost universal in the two trials reporting detailed results [12, 14]. The hematologic toxicity profile of the present study compares favorably with the studies cited above, since grade 3–4 neutropenia occurred in 28% of the administered courses. The reasons for this difference may be related to the lower dose of epirubicin administered in our trial. In addition, severe neutropenia was not associated with a high incidence of infection, since only 10% of the administered courses were complicated by neutropenic fever; furthermore, no septic deaths were observed. However, one patient required hospitalization in ICU because of septic shock due to acute neutropenic enterocolitis. The relatively low infection rate despite the high incidence of severe myelosuppression is in accord with the observation of Kerbrat et al. [12] who reported febrile neutropenia in only 3.2% of the 340 delivered chemotherapy courses.

The cardiotoxicity of this epirubicin-docetaxel combination was low, as has been reported by others; indeed, Kerbrat et al. [12] reported a 16% to 19% decrease in LVEF in three patients, whilst Raab et al. [13] observed a 25% LVEF decrease in one patient who received a cumulative epirubicin dose of 320 mg/m^2. Although in our study four patients showed a greater than 10% decline in the LVEF, none of the patients developed clinical signs of congestive heart failure. However, one patient without predisposing factors died suddenly, probably of myocardial ischemia. Whether this episode is directly related to the chemotherapy regimen is not known, but we consider this event as treatment-related since it was observed within 10 days after the treatment.

Objective responses were observed at all dose levels, with an overall response rate of 54%, which is not significantly different from that of Kerbrat et al. (ORR 69% in 62 patients) [12]. However, this response rate is lower than that reported with the combination of docetaxel and doxorubicin (81% ORR with 95% CI, 63%–93%) [21]. This difference in response rate may be explained by the fact that in the present trial the administered dose of anthracycline is lower than the one used in the docetaxel/doxorubicin combination. Alternatively, we cannot exclude that the administration of the drugs on two different days may lead to a lack of synergism between them; however, despite the fact that the number of patients is relatively low, the response rate of the combination given on either one or two consecutive days is not statistically different. However, the efficacy of each regimen has to be evaluated in a subsequent phase II trial. The Greek Cooperative Breast Cancer Group is now conducting such a trial combining epirubicin (70 mg/m^2, d_1) and docetaxel (90 mg/m^2, d_2).

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