Breast Cancer Research and Treatment **21**: 133–138, 1992.

Report

Weekly low-dose mitoxantrone plus doxorubicin as second-line chemotherapy for advanced breast cancer

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Key words: breast cancer, chemotherapy, doxorubicin, mitoxantrone

Summary

Weekly low dose mitoxantrone (3 mg/m^2) plus doxorubicin (8 mg/m^2) was administered as second-line chemotherapy to 33 patients with advanced breast cancer. Four out of 28 evaluable patients (14%) obtained a partial response with a median duration of 34 weeks (range 18–67$^+$ weeks), while 8 patients (29%) showed stable disease with a median duration of 28 weeks (range 11$^+$–60 weeks). Gastrointestinal toxicity and alopecia were mild. Grade II and III leukopenia occurred in 63% of the courses without serious infectious disease. Four patients experienced an asymptomatic drop of 16–20% in the left ventricular ejection fraction (LVEF) after relatively low cumulative doses of each drug, and one patient with a history of pericarditis carcinomatosa and mediastinal irradiation developed a heart failure. In conclusion, this second-line combination treatment had moderate activity in breast cancer and caused only few subjective side effects, especially with respect to gastrointestinal symptoms.

Introduction

Combination chemotherapy appears to be more effective than single agent therapy in inducing responses in disseminated breast cancer. First-line treatment with cyclophosphamide, methotrexate, and fluorouracil (CMF) induces a response in about 40–50% of the patients with a median duration of response of less than a year [1]. Second-line chemotherapy in CMF-refractory patients often consists of single agent treatment with (4′-epi-) doxorubicin or mitoxantrone in a 3-weekly high-dose schedule. However, only about 20–30% of these patients achieve a remission, frequently of short duration, while toxicity is often considerable especially by treatment with anthracyclines [2–4].

When (4′-epi-)doxorubicin or mitoxantrone are administered in low dose schedules every week or twice a month, the drugs can still be active, with remission rates of about 30% (0–59%) in patients with advanced breast cancer [5–22]. Gastrointestinal toxicity and alopecia are significantly less with these low-dose schedules.

Cardiotoxicity is a major problem of long-term (4′-epi-)doxorubicin treatment, while mitoxantrone occasionally produces such toxicity. Doxorubicin cardiotoxicity is probably induced by the intracellular formation of free radicals and stimulation of membrane lipid peroxidation in the heart

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muscle cells [23]. In experimental studies with hearts of rats, evidence was found that mitoxantrone did not form free radicals, and had a strong inhibitory effect on the lipid peroxidation [24, 25]. In addition mitoxantrone was found to cause a concentration-dependent inhibition of doxorubicin-stimulated lipid peroxidation in liver microsomes of rabbits [26]. These data suggest that mitoxantrone might have an inhibitory effect on the occurrence of doxorubicin-induced cardiotoxicity. Furthermore, low-dose schedules of doxorubicin seem to produce less cardiotoxicity [5, 6, 27, 28]. In view of these data it appeared attractive to combine doxorubicin and mitoxantrone at weekly dosages. Therefore, we initiated a phase II study with the combination of low doses of doxorubicin and mitoxantrone in a weekly schedule as second-line chemotherapy for patients with advanced breast cancer.

Patients and methods

Eligibility criteria of the protocol included: patients with measurable or evaluable lesions, age less than 80 years, World Health Organization (WHO) performance score 2 or less, life expectancy of more than 2 months, serum bilirubin less than 40 µmol/l, WBC above 3.0×10^9/l, platelets above 100×10^9/l, no prior therapy with anthracyclines or mitoxantrone. Patients with a history of recent cardiac disease or with metastases in the central nervous system were excluded. Metastatic disease of all patients had to be resistant to previous endocrine therapy and to first-line chemotherapy with CMF (cyclophosphamide, methotrexate, and fluorouracil). The protocol (DDHK 88-18) was approved by 2 different committees, both a protocol review and a medical ethics committee. All patients gave oral informed consent before entering the study.

On-study evaluation consisted of medical history, physical examination, tumor measurements, complete blood count (Hb, WBC, platelets), automated blood chemistry, left ventricular ejection fraction (LVEF, using radionuclide multigated analysis with intervals of initially 12, subsequently 8 or 4 weeks), bone scan, bone and chest x-rays, and liver CT-scan (in case of liver metastases).

Treatment consisted of mitoxantrone 3 mg/m^2 plus doxorubicin 8 mg/m^2 as weekly sequential intravenous injections via a running infusion with physiologic saline during a few minutes. Responses were defined according to WHO criteria. Duration of partial response was measured from initiation of therapy until time of tumor progression. Drug toxicity was also evaluated according to WHO criteria.

Results

Patient characteristics are indicated in Table 1. Thirty-three patients entered the study. Twenty-eight patients were evaluable for response and toxicity. Five patients were not evaluable because of early withdrawal or lack of response evaluation (within the first 8 weeks). Reasons to stop the treatment were: patient refusal (2), radiation therapy for pain (1), discovery of brain metastasis 1 week after start of treatment (1), and hyperbilirubinemia 1 week after start of treatment (1). These 5 inevaluable patients died between 0.5 and 8 months after start of treatment.

Responses are shown in Table 2. No complete responses were observed. A partial response (PR) was achieved in 4 out of 28 patients (14%) with a median duration of 34 weeks (range 18–67$^+$ weeks), while 8 patients (29%) showed stable disease (SD) with a median duration of 28 weeks

Table 1. Patient characteristics

Number of patients entered:	33
Number of evaluable patients:	28
Menopausal status:	
pre	1
post	26
peri or unknown	6
Age:	
median (range)	57 (40–74)
WHO performance status:	
median (range)	1 (0–2)
Metastatic sites per patient:	
median (range)	3 (1–4)

(range 11+-60 weeks). One patient had early progressive disease after 2 weeks of treatment. Fifteen other patients showed tumor progression within 5–14 weeks after start of treatment. Progression-free survival and overall survival curves of the evaluable patients are shown in Fig. 1. Toxicity is presented in Table 3. Leukopenia grade II occurred in 48% and grade III in 15% of all cycles. Gastrointestinal toxicity was very mild. Serious hair loss grade II and III occurred in only a minority of the patients, and was probably still related to the previous CMF treatment.

In 10 of the 12 patients who achieved a PR or SD, LVEF was repeated at least once. Three patients received a 'doxorubicin equivalent' dose (cumulative doxorubicin dose+ cumulative mitoxantrone dose× 5) of more than 550 mg/m², i.e. 720, 795, and 850 mg/m². LVEF of these patients dropped from 65 to 53%, 76 to 61%, and 80 to 73%, respectively. LVEF of two other patients receiving a cumulative 'doxorubicin equivalent' dose of 195 and 292 mg/m² dropped from 89 to 75% and from 76 to 64% respectively. In four other patients treated with 'doxorubicin equivalent' cumulative doses of 209 to 500 mg/m², LVEF remained stable to the baseline value. Thus, in none of these 9 patients did LVEF decrease to below the critical limit of 50%, and none of them showed any clinical sign of cardiotoxicity.

One patient, with previous mediastinal irradiation and pericarditis carcinomatosa, developed a cardiac failure in the presence of a drop in the absolute level of the LVEF from 78% to 29%, after being treated with a 'doxorubicin equivalent' cumulative dose of 478 mg/m². She was successfully treated with digoxin and diuretics.

Table 2. Type of responses and time to progression (WHO criteria)

	Number of patients (%)	Mean duration in weeks (range)
CR	0	–
PR	4 (14)	34 (18–67+)
SD	8 (29)	28 (11+–60)
PD	16 (57)	within 2–14 weeks

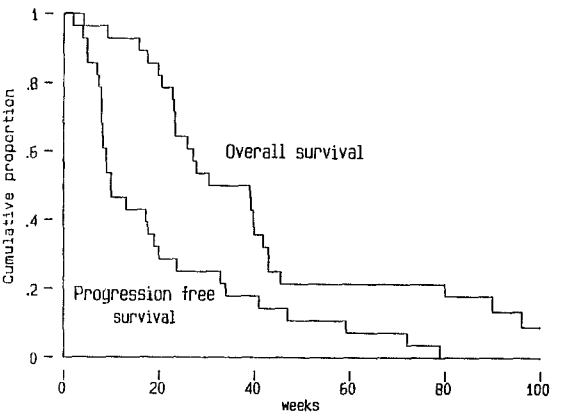

Fig. 1. Progression-free and overall survival of all evaluable patients measured in weeks from start of treatment.

Discussion

Several studies have shown that chemotherapy with weekly low doses of (4′-epi-)doxorubicin or mitoxantrone can be as effective as the 3-weekly high-dose schedules in inducing remissions in patients with advanced breast cancer, whereas toxicity of the low doses is considerable less [5–22, 27, 28]. Treatment results of 18 studies using 'weekly' low dose (4′-epi-)doxorubicin or mitoxantrone in patients with advanced breast cancer are shown in Tables 4 and 5. Table 4 summarizes the treatment results of 7 studies concerning a total of 311 patients of whom less than 50% had been treated before with chemotherapy for advanced disease. Overall, 93 of the 311 patients (30%) treated with weekly low-dose anthracycline or mitoxantrone

Table 3. Percentage of side effects (WHO grading)

Grade	0	1	2	3
Leukopenia*	15	22	48	15
Thrombocytopenia*	80	9	9	2
Mucositis*	96	4	–	–
Diarrhea*	94	6	–	–
Nausea/Vomiting*	84	11	5	–
Alopecia**	82%		18%	

*Percentage of courses with side effect events as recorded in all (100%) weekly chemotherapy courses.

**Alopecia is expressed as the percentage of patients experiencing various grades (0/1 and 2/3) of hair loss.

Table 4. Low-dose doxorubicin (Dox), 4′-epi-doxorubicin (Epi-dox), or mitoxantrone (Novantrone) mainly used as first-line chemotherapy in advanced breast cancer

Drug	Dosage	Treatment interval (weeks)	Number of eval. pts	Responses (CR/PR)		Prior chemother. (% pts)	Ref.
				(n)	(%)		
Dox	15 or 20 mg	1	50	7	14	44	(5)
Dox	20 mg	1	62	19	31	0	(6)
vs							
VAC		3	66	24	35		
Dox	20 mg	1	81	29	36	0	(7)
vs							
Epi-dox	50 mg	2	68	15	22		
Epi-dox	12 mg/m²	1	42	18	43	12	(8)
Epi-dox	20 or 40 mg	1	25	12	48	<24	(9)
Epi-dox	20 mg	1	41	4	10	17	(10)
Novantrone	3.3–6 mg/m²	1	10	4	40	0	(11)

Number of eval. patients: 311.
Number of patients achieving CR/PR: 93/311 (30%).
Mean % CR/PR of all 7 individual series: 32% (range 10–48%).

responded objectively. The mean percentage of response of the 7 separate series of patients was 32% (range 10–48%). Table 5 shows the treatment results of 11 studies concerning 361 patients of whom more than 50% had been pretreated with various types of chemotherapy. During this second-line chemotherapy 110 out of 361 patients (30%) responded. The mean percentage of response of the individual series was 29% (range 0–59%). Response durations in the studies vary widely. Based on response data available in 12 of these 18 studies, the median duration of response is about 6–7 months.

In our study we combined mitoxantrone and

Table 5. Low-dose doxorubicin (Dox) or 4′-epi-doxorubicin (Epi-dox) mainly used as second-line chemotherapy in advanced breast cancer

Drug	Dosage	Treatment interval (weeks)	Number of eval. pts	Responses (CR/PR)		Prior chemother. (% pts)	Ref.
				(n)	(%)		
Dox	0.4 mg/kg*	1	29	11	38	100	(12)
Dox	0.5–1 mg/kg	1	31	11	35	heavily pretreated	(13)
Dox	20 mg/m²	1, 3, 1, 3	60	16	27	87	(14)
Dox	6–12 mg/m²	1	34	20	59	>62	(15)
Dox	5–11.5 mg/m²	1	20	3	15	100	(16)
Dox	8–12 mg/m²	1	17	2	12	70	(17)
Dox	10 mg/m²	1	24	0	0	>96	(18)
Dox	12 mg/m²	1	30	8	27	97	(19)
Dox	20 mg	1	48	9	19	56	(20)
Epi-dox	20 mg	1	39	20	51	51	(21)
Epi-dox	15 mg/m²	1	29	10	34	52	(22)

Number of eval. patients: 361.
Number of patients achieving CR/PR: 110/361 (30%).
Mean % CR/PR of all 11 individual series: 29% (range 0–59%).
*Therapy with initial loading course (days 1–3 and 8–10).

doxorubicin in weekly low-dose schedules in order to achieve a low toxicity profile with preserved activity. Subjective side effects, gastrointestinal toxicity, and alopecia were mild with this combination therapy, but leukopenia regularly needed postponement of the chemotherapy. In spite of these clear toxic effects on bone marrow function, the combination of weekly low-dose mitoxantrone and doxorubicin showed 'moderate' antitumor activity (14% PR) as second-line chemotherapy in patients with metastatic breast cancer. However, in an additional 29% of the patients a SD was observed for 11+-60 weeks with nearly the same median duration of progression-free survival as for partial responders (28 vs 34 weeks). This median duration of SD (about 6–7 months) in our patients is not different from that of the objective responders reported in the other studies (Table 4 and 5), i.e. 6–7 months. The overall response rate (CR/PR/SD) of 43% also is generally not different from that reported in other studies, even in comparison with high-dose mitoxantrone 3-weekly in the first-line (40%) as reported by Harris *et al.* [29].

Striking in our study was the clear dose-limiting bone marrow depression in spite of the low dosages of the drugs used. However, it has to be noted that the relatively high incidence of leukopenia compared to 3-weekly schedules is influenced by the frequent weekly measurement of WBC in this weekly dose regimen.

In vitro studies with the combination of both drugs had suggested a possible protective effect of mitoxantrone towards doxorubicin-induced cardiotoxicity [26]. This possible protective effect of mitoxantrone towards doxorubicin-induced cardiotoxicity, however, was not observed in two clinical studies that combined the drugs in 3-weekly 'high-dose' schedules [30, 31]. From our study we cannot make definite conclusions in this respect. Although 4 patients showed a significant relative decrease (16–20% of the pretreatment value) of LVEF, none of them decreased below an absolute value of 50% with the exception of the patient with previous mediastinal irradiation and carcinomatous pericarditis.

It can be concluded that second-line combination treatment of weekly low-dose mitoxantrone plus doxorubicin is a well tolerated drug regimen for patients with CMF-resistant tumors. The antitumor efficacy is comparable to that of other second-line chemotherapeutic regimens in the absence of serious side effects, but postponement of drug administration was regularly needed because of the occurrence of leukopenia.

Acknowledgements

We wish to thank P.J. van Assendelft and J. Vuik for preparing the print, and DG Lederle Netherlands for support.

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