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An EORTC Phase II Study of Mitoxantrone in Solid Tumors and Lymphomas

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Abstract—*Mitoxantrone is an anthracenedione, showing structural similarities to doxorubicin. This drug has been proved active against several tumor systems, including some tumors resistant to doxorubicin, and also against human breast xenografts. It is also less cardiotoxic than doxorubicin. Mitoxantrone has been given to* 335 *patients in an i.v. perfusion of* 12 mg/m² *or* 14 mg/m² *every* 3 weeks. *Two hundred and sixty-three patients with advanced disease were evaluable for response: breast* (94 *patients), head and neck* (40), *kidney* (20), *bronchial* (19), *lymphomas* (13) *and various sites* (77). *Most of the patients had been previously treated with radiotherapy and chemotherapy, including/not including doxorubicin. In breast cancer three complete remissions (CR) and* 16 *partial remissions (PR) have been achieved* (20%). *The therapeutic activity was higher in patients who had not received any prior chemotherapy:* 35 *vs* 15% (P = 0.06). *The response rate observed at* 14 mg/m² (32%) *was superior to the response rate observed at* 12 mg/m² (15%). *However, no response has been reported in lung metastases* (0/22). *The median duration of response is* 8 months. *Mitoxantrone shows borderline activity in head and neck tumors (one CR and two PR out of* 40 *patients) but no activity in squamous cells of the lung* (0/19). *One CR and three PR have been seen out of* 13 *malignant lymphomas (four Hodgkin's disease and nine non-Hodgkin's lymphomas). The duration of response ranges from* 10 *to* 24+ months. *Myelosuppression was moderate and no severe leukopenia has been reported. Nausea and vomiting were seen in* 50% *of the patients. Four patients presented cardiac events associated with mitoxantrone, such as reversible congestive heart failure or a significant decrease in the ventricular ejection fraction. Alopecia was observed in* 17 *and* 48% *of the patients treated with* 12 *and* 14 mg/m² *respectively. Due to its anti-tumoral activity, mainly in breast cancer, and its low hematological and cardiac toxicity, mitoxantrone must be considered as a major antimitotic.*

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INTRODUCTION

MITOXANTRONE is a new cytotoxic agent with broad spectrum activity against a panel of experimental tumor systems, including P388 leukemia resistant to doxorubicin and human breast tumor xenografts [1–8]. The drug was selected amongst a series of anthracenedione derivatives showing structural similarities to the anthracyclines but lacking the amino-sugar moiety linked by Adamson to potential cardiotoxicity [9]. In several cardiotoxicity models mitoxantrone showed either none or less toxicity than doxorubicin [10, 11]. Preclinical toxicology suggested that the gastrointestinal tract, the bone marrow, the lymphoid system and the testes were

possible targets for mitoxantrone toxicity [1]. Mitoxantrone intercalates DNA and inhibits DNA and RNA synthesis, but the exact mechanism of action is unknown [12–14].

Von Hoff reported the results of a clinical phase I trial in patients with advanced solid tumors given a single i.v. dose every 28 days. Leukopenia was dose-dependent and was the dose-limiting toxicity. The maximum dose tolerated appeared to be 14 mg/m^2 and the recommended dose for phase II trials was 12 mg/m^2 repeated at 3 or 4-week intervals [15]. Another study did, however, conclude that the maximum tolerated dose was about 19 mg/m^2 and recommended a starting dose of 15 mg/m^2, but the patients were less heavily pretreated than in Von Hoff's study [16].

MATERIALS AND METHODS

Between November 1980 and January 1982, 335 patients with histologically proven solid tumors or lymphomas were entered into the study. Eligibility criteria included age <75 yr, performance status (WHO): 0–2, documented progression of disease, no prior chemotherapy within 3 weeks, no prior radiation therapy within 6 weeks, recovery from toxicity induced by prior treatment, white blood cell counts (WBC) $\geqslant$4000/mm^3, platelet counts $\geqslant$150,000/mm^3, serum creatinine levels $\leqslant$1.5 mg/dl and serum bilirubin $\leqslant$2.0 mg/dl. Patients with second primary tumors, active uncontrolled infection, CNS metastases, congestive heart failure, cardiac arrhythmias, bilateral bundle branch block or history of myocardial infarction were excluded. Measurable and/or evaluable lesions were needed for response evaluation. Pleural effusions, ascites and bone metastases were not accepted as evaluable lesions. Biochemical markers (α-fetoprotein and β-HCG) were accepted as criteria for evaluation in testicular tumors. Informed consent was obtained according to hospital regulations in each participating institution.

A two-stage plan was adopted for defining the number of patients required in the most common disease categories to keep the probability of rejecting a drug active in 20% or more of the patients below 0.05. In the absence of complete and partial response the trial could be discontinued after the first 14 patients. Otherwise, additional patients were to be added to a maximum of 25 [17]. Small numbers of patients with less common tumor types were also entered since anecdotal information about tumor regressions in these diseases could be of interest in orienting the choice of subsequent trials.

Mitoxantrone was supplied by the American Cyanamid Corporation, Pearl River, NJ, U.S.A. as a blue sterile solution containing 2.0 mg/ml of free base. Treatment was given as an i.v. infusion in 100 ml of 5% dextrose over 30 min. The drug was administered as a simple dose of 12 mg/m^2 every 21 days. The dose was reduced if the WBC nadir was less than 1500/mm^3 or the platelet nadir was less than 100,000/mm^3. Interim evaluation of hematological toxicity in May 1981 permitted the starting dose of mitoxantrone to be increased to 14 mg/m^2 in good-risk patients, i.e. those with good performance status (0–1) and with good bone marrow reserve.

A minimum of 2 cycles (6 weeks) of treatment was required for an adequate trial except for patients taken off the study after one cycle because of rapid disease progression. Those cases were considered as treatment failures. Responses were defined as follows: complete response (CR): disappearance of all known disease, determined by two observations not less than 4 weeks apart; partial response (PR): 50% or more decrease of the measurements of all indicator lesions based on two observations not less than 4 weeks apart. In addition, there could be no new lesions or progression of any lesions; no change (NC): less than 50% decrease in total tumor size, unchanged measurements or less than 25% in one or more measurable lesions; progression of disease (PD): a 25% or more increase in the size of one or more measurable lesions, or appearance of new lesions; early death (ED): death within 3 weeks without severe toxicity.

RESULTS

Of the 335 patients admitted to the study, 34 were excluded because they did not fulfil the criteria for eligibility. Thirty-eight patients were considered inevaluable because of incomplete data (16), major protocol violation (9), early death (7), treatment refusal (4) and loss to follow-up (2). The characteristics of evaluable patients are detailed in Table 1. The distribution of tumor types among the 263 evaluable patients shows a substantial number of breast carcinomas, permitting a separate analysis.

Ninety-four patients with breast cancer were evaluable for therapeutic activity. Their characteristics are shown in Table 1. Complete or partial response was seen in 19 patients or 20% (Table 2). In a group of 26 patients who had received no prior chemotherapy, nine patients (35%) responded to mitoxantrone compared to 10/68 patients (15%) who had received prior chemotherapy. The difference in response rate has borderline statistical significance ($P = 0.06$). In the group of patients who had received prior chemotherapy there was a difference, but not statistically significant, between patients with

Table 1. Patient characteristics

Tumor type	No. of evaluable patients	Median age (range) in yr	Performance status (WHO scale) 0–1	2	Prior therapy* RT	CT	Doxorubicin	Initial dose of mitoxantrone(mg/m²) 12	14
Breast	94	57 (31–75)	57	37	68	68	49	66	28
Head and neck	40	54 (35–72)	28	12	20	7	5	39	1
Kidney	20	55 (21–71)	12	8	4	5	1	16	4
Lung squamous cell	19	61 (42–73)	11	8	6	2	0	14	5
Lymphoma	13	37 (26–66)	11	2	11	13	12	13	0
Soft tissue	12	59 (15–65)	8	4	7	10	10	11	1
Colorectum	9	60 (49–75)	4	5	3	5	0	9	0

*No. of patients.

prior exposure to doxorubicin (5/49; 10%) and those without it (5/19; 26%).

Ten of the 66 patients (15%) treated at the dose of 12 mg/m² responded, compared to 9/28 patients (32%) treated at the dose of 14 mg/m². The analysis of response by dominant site or disease does not show a difference in response rate between soft tissue (8/51 patients), bone (4/9 patients) and visceral disease (7/34 patients). However, 5/28 liver metastases (considered as indicator lesions) responded, but no responses were observed in 0/22 lung metastases (Table 3).

Four complete responses were seen, all patients without prior exposure to doxorubicin, including one patient with liver metastases. The median duration of response in brast cancer was 8 months.

Five patients remained in remission, for a duration of 11+ to 18+ months. Two responders were lost to follow-up at 6 months. Of 12 patients known to have relapsed, six died of disease. One died of a cerebrovascular accident and five were still alive at the time of their last follow-up, 1 yr after closing the study.

The majority of patients with head and neck cancer, squamous cell carcinoma of the lung and renal cancer were good-risk patients in terms of performance status and prior treatment (radiation and/or chemotherapy). Most of them were treated at 12 mg/m². The therapeutic activity detected in head and neck cancer does not appear to be clinically useful (Table 2). Of 39 patients with epidermoid carcinomas, only two objective regressions were seen. These occurred in 2/10 patients with tonsillar tumors. Therefore, one cannot exclude the possibility that a subgroup of head and neck tumors might be sensitive to the drug. In addition, a single patient with a cylindroma and pulmonary metastases showed a partial response of over 4 months duration. This suggests that mitoxantrone be tested in this uncommon disease.

Mitoxantrone appears inactive against

Table 2. Therapeutic activity (figures are No. of patients)

Tumor type	Entered	Evaluable	Complete response	Partial response	No change	Progression
Breast	121	94	3	16	21	54
Head and neck	50	40	1	2	1	36
Lung squamous cell	25	19	–	–	8	11
Kidney	23	20	–	–	10	10
Lymphoma	17	13	1	3	1	8
Soft tissue	16	12	–	1	2	9
Colorectum	11	9	–	–	–	9
Ovary	10	8	–	–	2	6
Cervix	9	8	–	–	4	4
Testes	9	8	–	–	1	7
Melanoma	8	7	–	–	2	5
Miscellaneous	36	25*	–	2†	9	14

*Lung: small cell (4), adenocarcinoma (5), large cell (1); osteosarcoma (4); bladder (2); esophagus (2); vagina (1); skin (1); penis (1); pancreas (1); small bowel (1); thyroïd (1); prostate (1).

†1/2 in bladder; 1/1 in small bowel.

Table 3. Therapeutic activity in breast cancer according to dominant site of disease

Dominant site	No. of evaluable patients	No. of complete or partial responses (%)	
Soft tissue	51	8	(16)
Bone	9	4	-
Viscera	34	7	(20)
Liver	28	7	(25)
Lung	22	0	-

squamous cell carcinoma of the lung. No tumor regression was noticed in a group of 19 patients, seven having disease limited to one hemithorax. The results were also negative in renal cancer despite the reporting of two minor regressions of short duration among 20 patients. Twelve patients with soft tissue sarcoma including ten patients with prior doxorubicin were evaluable. One patient with a well-differentiated polymorphous sarcoma of the breast, resistant to combination chemotherapy, including doxorubicin, presented a regression of skin and pulmonary metastases that lasted 5 months. No therapeutic activity was detected in the following solid tumor categories, although the number of treated patients was too small to reach any conclusion: carcinoma of the cervix (0/8), colon and rectum (0/9), melanoma (0/7), testicular carcinoma (0/8). In the miscellaneous group, tumor regressions were seen in small bowel carcinoma (1/1) and bladder carcinoma (1/2).

Thirteen patients with lymphomas, including four with Hodgkin's disease, were treated with mitoxantrone at a dose of 12 mg/m^2. Most of them were heavily pretreated with doxorubicin and radiation therapy. Three patients achieved a partial remission, lasting 20+, 10+ and 10 months. The complete remission lasted 24+ months. The patient was still in complete remission in January 1984.

TOXICITY

Hematological indices based on weekly blood counts were analyzed following the first cycle of treatment for 264 patients, 216 patients at 12 mg/m^2 and 48 patients at 14 mg/m^2 (Table 4). Initial WBC counts were comparable for the two dose levels. Although the numbers at 14 mg/m^2 are relatively small, the difference in WBC nadir is significant ($P = 0.05$) when 12 mg/m^2 is compared with 14 mg/m^2. Median values of 3044/mm^3 were recorded at 12 mg/m^2 and 2450/mm^3 at 14 mg/m^2. Neither value represents severe leukopenia. Further analysis of data showed a correlation ($P < 0.05$) between the degree of leukopenia and performance status, prior radiation and prior chemotherapy.

Nausea and vomiting were the most frequent non-hematological toxic effects, but gastrointestinal distress was severe in only less than 10% of patients. Besides a higher incidence of hair loss at 14 mg/m^2, there was no difference between the lower and higher doses of mitoxantrone (Table 5).

Four patients were considered to have cardiac events associated with mitoxantrone therapy. Two patients developed reversible congestive heart failure that responded to diuretic therapy after cumulative doses of 175 and 240 mg/m^2 (Table 5). Neither had received anthracycline treatment, but in one case there was the added risk factor of intrathoracic post-irradiation fibrosis. Endomyocardial biopsies revealed myocardial hypertrophy and increased fibrosis but failed to demonstrate the characteristic lesions of doxorubicin cardiomyopathy. Mitoxantrone was also discontinued in two asymptomatic patients monitored with radionuclide cineangiography after cumulative doses of 75 mg/m^2 because of a decrease in the left ventricular ejection fractions of 15 and 25%. One of them had emphysema and a low baseline left ventricular ejection fraction (56%); the other had doxorubicin discontinued after a total dose of 192 mg/m$_2$ 6 weeks prior to starting mitoxantrone and presented a baseline EKG suggestive of myocardial ischemia. Endocardial biopsies were not obtained.

DISCUSSION

Mitoxantrone administered at a dose of 12–14 mg/m^2 appears to be an effective drug against advanced breast cancer. The overall response rate of 20%, as well as the higher response rate (35%) seen in patients not previously treated with chemotherapy, is similar to that obtained with those drugs used as first-line chemotherapy with the possible exception of doxorubicin [18, 19]. The median duration of response of 8 months is better than that observed with most single agents and may be partially explained by the inclusion of patients who had never received chemotherapy before. The tumor regressions seen in patients with prior doxorubicin treatment suggest a lack of complete cross-resistance between mitoxantrone and doxorubicin. The difference in response rate between the doses of 12 and 14 mg/m^2 of mitoxantrone, although not statistically significant, does not exclude a dose–response relationship. In view of the moderate toxicity encountered at these doses and the results reported by some phase I investigators with higher doses, the possibility exists, at least for patients with a good bone marrow reserve, that the optimal dose of mitoxantrone may be 14 mg/m^2 [16–24].

Table 4. Hematological toxicity

Mitoxantrone dose (mg/m²)	No. of patients	WBC nadir (× 10³/mm³) median (range)	Platelets nadir (× 10³/mm³) median (range)
12	216	3.0 (0.1–7.7)	240 (52–621)
14	48	2.4 (1.2–6.5)	205 (22–358)

Table 5. Non-hematological toxicity

Toxic effect	Incidence % Mitoxantrone 12 mg/m² ($n = 216$)	Mitoxantrone 14 mg/m² ($n = 48$)
Nausea/vomiting	42 (4)*	54 (6)*
Diarrhea	5	10
Stomatitis	4	14
Alopecia	17	48 (2)*
Fever	5	2
Cardiac	2	-

*( ) severe.

The therapeutic activity observed in metastatic liver disease, including a complete remission, is particularly noteworthy. There is no ready explanation for the absence of response in pulmonary metastases. A larger number of patients need to be treated to define the activity of mitoxantrone in metastatic visceral disease of breast cancer.

Lymphomas, including Hodgkin's disease, appear sensitive to mitoxantrone therapy, despite an inadequate number of patients to enable evaluation of the level of activity. Remarkably, this activity was detected in patients receiving mitoxantrone as second- or third-line chemotherapy, after having been exposed to doxorubicin. One may assume a high incidence of doxorubicin resistance in this group of patients, which further suggests a lask of cross-resistance between the two drugs. Further phase II trials in Hodgkin's disease and non-Hodgkin's lymphomas are needed.

The therapeutic activity detected in other tumor categories sensitive to doxorubicin, i.e. soft tissue sarcoma and bladder carcinoma, deserves further investigation. The number of patients with squamous cell carcinomas of the head and neck and of the lung, as well as patients with renal cancer, was adequate for statistically valid inferences. It is unlikely that mitoxantrone would be active in these malignancies.

Mitoxantrone at the dose of 12–14 mg/m² every 3 weeks was well tolerated. The acute dose-limiting toxicity was neutropenia. The level of toxicity observed would allow further dose escalation, at least in patients with an adequate bone marrow reserve. Gastrointestinal side-effects were well controlled by symptomatic treatment and hair-loss was moderate. Whether mitoxantrone is better tolerated by the patients than doxorubicin is a question to be addressed in future trials.

The similarities in chemical structure as well as potential mechanisms of action of two intercalating agents such as mitoxantrone and doxorubicin raise questions about cross-resistance between the two drugs as well as their respective spectrum of therapeutic activity.

Therefore, a carefully selected methodology for those tumor categories for which doxorubicin alone or in combination is standard first-line therapy needs to be defined. If the accumulated data of on-going trials support the hypothesis that mitoxantrone has a broad spectrum of activity overlapping with doxorubicin but with less toxicity and especially less cardiotoxicity than doxorubicin, a head-on comparison of the two drugs will be necessary. This appears to be the case for breast cancer.

The administration of 12–14 mg/m² of mitoxantrone given as a single agent every 3 weeks may be recommended as a regimen that is well tolerated and active in breast cancer and lymphomas. The definition of an optimal dose according to risk factors of toxicity remains an open question. So is the cardiotoxicity of mitoxantrone. Animal models would suggest reduced toxicity rather than an absence of cardiotoxicity, but the extrapolation from animal models is hazardous [10, 11]. The data of this study, as well as those reported by others [25], do not permit us to answer this question. Certainly, anthracycline-like induced cardiomyopathy has not been substantiated by available biopsy material. Reversible cardiac failure has occurred, mostly in patients having received prior anthracycline treatment. The availability of non-

invasive accurate monitoring methods permits the follow-up of responding patients, while biopsies of patients showing alteration of the left ventricular function could settle the matter of whether mitoxantrone does indeed cause cardiomyopathy.

Mitoxantrone appears to be a useful adjunct to existing major anticancer drugs.

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