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ORIGINAL ARTICLE

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Continuous mitoxantrone infusion in pretreated epithelial ovarian cancer

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Abstract Mitoxantrone has shown moderate activity in advanced epithelial ovarian cancer following intermittent i.v. administration. Experiments and clinical data suggest that long-term continuous drug infusion may achieve a better therapeutic result with less toxicity. This hypothesis was tested in patients with advanced ovarian cancer who had been pretreated with other agents. Mitoxantrone was infused continuously in 21-day courses beginning every 6 weeks. If severe toxicity did not occur, the infusion rate was increased by 0.1–0.2 mg/m^2 per day. The mitoxantrone solution proved to be stable over the 21-day infusion period. For ethical reasons an optimal two-stage design was employed. The trial was interrupted at the end of the first recruitment stage because the target of 3 responses out of 13 patients had not been achieved (only 1 patient had a partial response). Hematologic toxicity was observed in 11 patients, and 2 of them had a catheter occlusion. In conclusion, we found that 21-day of infusion of mitoxantrone apparently has no clinical benefit as compared with bolus administration in patients with advanced ovarian cancer.

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Introduction

The prognosis for advanced epithelial ovarian cancer is poor. The survival at 5 years is 15%–20% for patients with macroscopic disease at second-look laparotomy [3, 5]. Although standard chemotherapy treatment (cisplatin, cyclophosphamide, doxorubicin) can initially achieve remission in about 70%–80% of patients, drug resistance is usually responsible for failures and is commonly found at relapse. In the attempt to improve effectiveness and to reduce toxicity, two different approaches can be followed. One is to evaluate new chemotherapic agents with a more favorable pharamacological profile. The other approach is to study new administration modalities that could assure more prolonged and/or more intense tumor drug exposure without increasing toxicity [13].

Mitoxantrone, an anthracenedione introduced only a few years ago into clinical practice, has activity against a wide range of tumors and produces moderate side effects [18]. It has been seen that the in vitro cytotoxic effect of mitoxantrone on human colon carcinoma cells increases during long-term exposure [6]. Therefore, it is conceivable that a dosing schedule based on continuous drug infusion rather than on intermittent bolus injection may improve the efficacy of this drug and, possibly, decrease the incidence of adverse reactions [10]. In fact, after locoregional administration [1, 4, 12, 15], a greater therapeutic response has been reported in patients exhibiting higher plasma drug levels [15]. On the other hand, when given on an i.v. bolus schedule, this drug has been seen to have very limited activity in advanced epithelial ovarian cancer [8, 11].

In patients with end-stage malignancies, Greidanus J. et al. [9] demonstrated that a 21-day i.v. infusion of

mitoxantrone allowed greater intracellular drug uptake (leukocytes) than did repeated bolus injections. Kaminer et al. [10] reported that a 6-day mitoxantrone infusion induced a complete remission in 36% of patients with relapsed acute nonlymphocytic leukemia. On the basis of these promising findings, we studied the therapeutic efficacy and toxicity of long-term mitoxantrone infusion in patients with advanced ovarian cancer.

Patients and methods

Study design

The present investigation was a phase II, noncontrolled, monoinstitutional study. Its primary objective was to evaluate the activity of mitoxantrone infusion in advanced relapsing ovarian cancer. The secondary end point was to evaluate the tolerability of the treatment.

In this kind of study there is the ethical necessity to minimize the number of patients exposed to a treatment that may have low therapeutic activity. To meet these requirements, an optimal two-stage design was employed. The statistical basis of this procedure has been described elsewhere [17]. In brief, patient accrual is carried out in two stages: only if given effectiveness criteria are met at the end of the first stage is the accrual continued during the second stage. The minimal number of patients accrued for each stage and the minimal number of therapeutic responses required for the drug to be considered active depend on the probability level of the statistical hypotheses made. We tested the null hypothesis that the true response probability was less than 20% ("uninteresting" response level) and the alternative hypothesis that the true response probability was at least 40% ("desirable" target level), with the alpha error being set at 5% and the beta error, at 20% (i.e., 1-power). From these constraints, it follows that mitoxantrone treatment should be stopped if (a) at the end of the first stage, 3 or fewer responses have been observed in 13 patients, or (b) at the end of the second stage, 12 or fewer responses have been observed in 43 patients.

Patients inclusion criteria

The following eligibility criteria were adopted: (a) a life expectancy of at least 2 months and a WHO performance status of less than 3; (b) laboratory evidence of normal renal and hepatic functions, with the WBC being more than or equal to 4,000/mm^3 and the platelet count being more than or equal to 100,000/mm^3; and (c) no clinical evidence of cardiac disease as assessed by electrocardiogram, blood pressure, and pre-ejection time/left ventricular ejection time (PEP/LVET).

Treatment

A mitoxantrone stock solution was diluted in 40 ml of normal saline and infused at a constant rate into the subclavian vein (via a permanently implanted catheter) with a portable pump (CADD-1 Pharmacia). Each infusion period comprised 21 days. Preliminarily, we examined the stability of mitoxantrone over this period, keeping a saline solution of the drug (0.2 mg/ml) at 37°C. At proper intervals, 10-µl samples of mitoxantrone were subjected to reverse-phase high-performance liquid chromatography (HPLC) analysis (see below). A fresh drug solution was run as a standard throughout the investigation. The elution pattern of mitoxantrone was almost superimposable on that of the standard for at least 12 days. After this period the area of the mitoxantrone peak decreased by less than 2% after 21 days and a second peak (eluting at about twice the time of mitoxantrone) appeared, accounting for 2.3% of the total absorption. These results indicate that mitoxantrone is rather stable during infusion.

The HPLC assay procedure used was that described by the Van Belle et al. [19] and Peng et al. [16], with the following modifications. Isocratic elution was carried out using 33% of solution A (containing 2 mmol hexanesulfonic acid, 0.5 mmol trifluoroacetic acid, 100 ml MilliQ water, and HPLC-grade acetonitrile to a final volume of 1 l) and 67% of solution B (containing the same amounts of hexanesulfonic and trifluoroacetic acid and milliQ water to a final volume of 1 l). The flow rate was 1.0 ml/min. The lowest detection limit was 10 ng/ml.

The initial infusion rate was 1.1 mg/m^2 per day as recommended by a previous phase I study [9]. The 21-day treatment was repeated every 6 weeks, and the infusion rate was progressively increased by 0.1–0.2 mg/m^2 per day until an evident clinical response was seen after 1–2 cycles or until grade 4 toxicity occurred.

Efficacy evaluation

At least a 50% decrease in the tumor size was the primary treatment end point (partial response). Efficacy was evaluated by echotomography and clinical examination or, in the case of evident disease progression, by clinical examination only. WHO criteria were used for evaluation of response [14]. The tumor stage was assessed according to the 1986 FIGO classification [7]. During therapy, plasma levels of the ovarian-cancer antigen marker CA125 were monitored in all patients by means of radioimmunoassay [2].

Toxicity evaluation

Hematological toxicity, cardiotoxicity, and other gastrointestinal side effects were evaluated according to WHO criteria [14]. Complete blood cell and platelet counts, renal and liver-function tests, and electrolytes were monitored before the start of treatment and weekly during the first cycle. In subsequent cycles the above-mentioned tests were performed only at the beginning and end of each cycle.

Results

Treatment effectiveness

Of the first 72 evaluable patients studied in stage 1, only 1 had a partial response, 6 had stable disease, and 5 had progressive disease. According to the study design, the accrual was interrupted because the target of "3 responses out of 13 patients" was no longer obtainable and mitoxantrone treatment was considered ineffective.

The patients' characteristics are summarized in Tables 1 and 2. All the patients entered into this study had become refractory to multiple chemotherapy regimens, including cisplatin given in combination with anthracyclines and/or cyclophosphamide, and 5-fluorouracil (Table 2). The tumor residua measured before mitoxantrone treatment were less than or equal to 3 cm in three cases, equal to 5 cm in three other cases, and more than 5 cm in seven cases. The

Table 1 Characteristics and clinical outcome of our series of patients (*Histol* Histology, *ND* not defined *NE* not evaluable, *S.P.* serous papillary, *E.* endometrioid, *UD* undifferentiated, *NC* no change, *PR* partial response, *PD* progressive disease)

Patient number	Age (years)	Stage	Residuum	Histol.	Grade	Cumulative dose (mg/m^2)	Number of cycles	Activity	Mean plasma levels (ng/ml)	Present condition
1	66	3C	> 5 cm	N.D.	ND	19	1	NE	–	Dead
2	55	3C	2 cm	S.P.	2	74	3	NC	–	Dead
3	50	3C	3 cm	S.P.	3	69	3	NC	10	Alive
4	66	3C	5 cm	UD	3	109	4	NC	–	Dead
5	39	3C	7 cm	S.P.	1	73	3	PR	20	Dead
6	49	4	8 cm	S.P.	3	28	1.5	PD	–	Dead
7	54	2B	> 5 cm	S.P.	3	82	3	NC	–	Dead
8	65	3C	> 5 cm	S.P.	2	22	1	PD	–	Dead
9	60	3B	5 cm	S.P.	3	69	3	PD	–	Dead
10	65	3C	1 cm	S.P.	2	52	2	PD	–	Dead
11	63	3C	5 cm	E.	3	27	1	NC	–	Dead
12	62	3C	12 cm	S.P.	3	19	0.5	PD	2.5	Dead
13	56	3A	> 5 cm	S.P.	3	82	3	NC	–	Dead

Table 2 Prior treatment (*Adjuv.* Adjuvant chemotherapy)

	Total (*n*)	Prior efficacy		Adjuv.
		Response[a]	No response	
Cisplatin[b]	13	3	9	1
Anthracyclines	13	6	7	–

[a] Partial or complete remission
[b] And/or other platinum-based compounds

Table 3 Correlation among the therapeutic responses, mitoxantrone doses, and residua size (*PR* Partial response, *NC* no change, *PD* progressive disease, *Histopath.* histopathology)

Therapeutic outcome	Number of patients	Mean delivered dose (mg/m^2)	Mean histopath grade (range)	Mean size of disease residua, cm range
PR	1	1, 2	1	7
NC	6	1, 3	3 (2–3)	5 (3–11)
PD	5	1, 1	3 (2–3)	5 (1–12)

histologic type was serous papillary in ten patients, undifferentiated in one case, not defined in one subject, and endometrioid in another patient. Tumors were grade 1 in one case, grade 2 in three cases, not defined in one case, and grade 3 in eight cases. Stage 3C was the most common classification (nine patients), whereas there was one case each in stages 2B, 3A, 3B, and 4 according to the 1986 FIGO classification [7] (Table 1). None of the clinical, pathologic, or pharmacologic factors listed in Tables 1 and 3 was apparently related to the clinical outcome.

There was only one patient with a 2-month response and 6-month survival. Basal CA125 levels were initially elevated in all patients. In the responding patient the basal CA125 level decreased after two cycles. In the other 11 patients, CA125 values did not change significantly after mitoxantrone administration.

Toxicity

The type and severity of the toxicity observed is summarized in Table 4. The most common and severe reactions were of hematologic type, with leukopenia being the most frequent (11 of 13 patients). The occurrence of severe toxicity required treatment withdrawal in three cases. Two of these patients had grade 4

Table 4 WHO toxicity socres recorded for 13 patients

Toxicity	WHO grade				
	0	1	2	3	4
Anemia	11	1	–	–	1
Leukopenia	2	1	4	4	2
Thrombocytopenia	7	2	1	2	1
Infections	10	3	–	–	–
Arrhythmia	11	2	–	–	–
Mucosal	11	2	–	–	–
Hair loss	10	1	1	–	–
Gastrointestinal	10	2	1	–	–
Local[a]	11	–	2	–	–
Renal	12	1	–	–	–
Nail pigmentation	(2 cases)				

[a] Subclavian vein thrombosis

leukopenia (associated in one case with grade 4 thrombocytopenia), and the third patient had anemia due to enteric hemorrhage that required blood transfusion. The drug infusion rates at the moment of toxicity were 1.1 mg/m^2 per day in one patient and 1.3 mg/m^2 per day in the other two patients. Two patients suffered from cardiac extrasystolic arrhythmia but none had signs of pump failure. No liver toxicity appeared in any patient. Two patients developed subclavian vein thrombosis and catheter occlusion. In one case, a thrombus was lysed with urokinase and the catheter was used for two additional courses. In the other patient, therapy was stopped (for 1 week) at 5 days after the start of treatment and the catheter had to be substituted.

Discussion

The working hypothesis of this study was that long-term mitoxantrone constant-rate infusion could induce some beneficial effects in patients with advanced epithelial ovarian cancer who had been pretreated with multiple drug chemotherapy. Mild drug toxicity was another expected outcome. In spite of the numerous experimental and theoretical considerations that backed up this hypothesis, our experimental data could not confirm it. The poor response rate observed in the face of moderate to severe drug toxicity prompted us to interrupt patients' accrual in the early stage of the optimal two-stage design. Of the 12 evaluable patients studied, only 1 had a partial response and 6 had stable disease. In addition to the severe and frequent hematologic toxicity encountered, another major side effect was the occurrence (in 2 of 13 patients) of subclavian vein thrombosis requiring thrombolytic treatment and, in 1 case, catheter substitution.

In a previous study on end-stage disseminated malignancies in which the same therapeutic protocol was used, Greidanus et al. [9] reported that 1 of the 13 evaluable patients had a partial response and 4 had stable disease. Those results must be interpreted with caution, as that study did not specifically aim at assessing clinical efficacy, but the findings are in agreement with our data.

Some possible reasons for such a disappointing outcome can be analyzed. First, the patient population studied had advanced disease and had previously been treated with multiple drugs. It is therefore possible that multidrug resistance ensued. Were this true, another trial should be carried out at an earlier stage of disease. A second (and, in our opinion, more likely) hypothesis is that contrary to what has been found in leukocytes [9], drug accumulation in ovarian tumor cells during long-term exposure to low drug plasma levels occurs only to a slight extent, if at all. It follows that a threshold mitoxantrone plasma level should exist under which no therapeutic response is attainable. In keeping with this view, we found in our previous work [15] that even when mitoxantrone was given i.p. to patients with advanced ovarian cancer, responders had significantly greater areas under the concentration-time curve and higher peak plasma concentrations than did nonresponders; it may be that the only patient who responded in the present series had higher plasma levels.

According to this interpretation, the maintenance of low, constant plasma levels of drug would achieve only hematologic (leukocyte) toxicity without providing a therapeutic advantage. Whatever the explanation, our data indicate that in advanced ovarian cancer, no substantial clinical benefit can be gained with a 21-day infusion of low mitoxantrone doses. It cannot be excluded, however, that the shorter term infusion of a higher dose could result in a more favorable outcome.

References

1. Alberts DS, Surwit EA, Peng YM, Closkey TM, Riviest R, Graham V, McDonald L, Roe D (1988) Phase I clinical and pharmacokinetic study of mitoxantrone given to patients by intraperitoneal administration. Cancer Res 48: 5874
2. Bast RC Jr, Klug TL, St. John ES, Jenison E, Niloff JM, Lazarus H, Berkowitz RS, Leavitt T, Griffiths CT, Parker L, Zurawski VR (1983) A radioimmunoassay using a monoclonal antibody to monitor the course of epithelial ovarian cancer. N Engl J Med 309: 883
3. Bertelsen K, Hansen MK, Pedersen PH, Larsen G, Nyland M, Jacobsen M, Andersen JE (1988) The prognostic therapeutic value of second-look laparotomy in advanced ovarian cancer. Br J Obstet Gynecol 95: 1231
4. Blochl-Daum B, Rainer EH, Jakesz R, Salzer H, Steger G, Schuller J, Gunther E, Proksch B, Ehninger G (1988) Escalating dose regimen of intraperitoneal mitoxantrone: phase I study—clinical and pharmacokinetic evaluation. Eur J Cancer Clin Oncol 24: 1133
5. Copeland LJ, Gershenson DM (1986) Ovarian cancer recurrences in patients with no macroscopic tumor at second-look laparotomy. Obstet Gynecol 68: 837
6. Drewinko B, Yang LY, Barlogie B, Trujillo JM (1983) Comparative cytotoxicity bisantrene, mitoxantrone, ametantrone, dihydroxyanthracenedione, dihydroxyanthracenedione diacetate, and doxorubicin on human cells in vitro. Cancer Res 43: 2648
7. FIGO Cancer Committee (1986) Staging announcement. Gynecol Oncol 25: 383
8. Fiorentino MV, Nicoletto MO, Stefani GP, Salvagno L, Tredese F (1988) A phase II trial with mitoxantrone in pretreated epithelial ovarian cancer. Proceedings 6th Mediterranean Congress of Chemotherapy, Taormina, 22–27 May, p 504
9. Greidanus J, Vries EGE de, Mulder NH, Sleijfer DT, Uges DRA, Oosterhuis B, Willemse PHBM (1989) A phase I pharmacokinetic study of 21-day continuous infusion mitoxantrone. J Clin Oncol 7: 790
10. Kaminer LS, Choi KE, Daley KM, Larson RA (1990) Continuous infusion mitoxantrone in relapsed acute nonlymphocytic leukemia. Cancer 65: 2619
11. Lawton F, Blakledge G, Mould J, Latief T, Watson R, Chetiyawardana AD (1987) Phase II study of mitoxantrone in epithelial ovarian cancer. Cancer Treat Rep 71: 627

12. Markman M, George M, Hakes T, Reichman B, Hoskins W, Rubin S, Jones W, Almadrones L, Lewis L Jr (1990) Phase II study of intraperitoneal mitoxantrone in the management of refractory ovarian cancer. J Clin Oncol 1: 146
13. McVie JG, Rodenhuis S, Dubbelman R, Varossieau FJ, Bokkel Huinink WW ten (1987) Clinical pharmacokinetics of intraperitoneal mitoxantrone in ovarian cancer. Proc Am Soc Clin Oncol 6A: 156
14. Miller AB, Hoogstraten B, Staquet M, Winkler A (1981) Reporting results of cancer treatment. Cancer 47: 207
15. Nicoletto MO, Padrini R, Ferrazzi E, Nascimben O, Visonà E, Tumolo S, Palumbo M, Costa L, Vinante O, Monfardini S, Fiorentino MV (1993) Phase–II study of intraperitoneal mitoxantrone in advanced pretreated ovarian cancer. Eur J Cancer 29A: 1242
16. Peng YM, Ormberg D, Alberts DS (1982) Improved high-performance liquid chromatography of the new antineoplastic agents bisantrene and mitoxantrone. J Chromatogr 233: 235
17. Simon R (1989) Optimal two-stage designs for phase II clinical trials. Controlled Clin Trials 10: 1
18. Smith IE (1983) Mitoxantrone (Novantrone): a review of experimental and early clinical studies. Cancer Treat Rev 10: 103
19. Van Belle SJP, Schoemaker TJ, Verwey SL, Paalman ACA, McVie JGJ (1985) ion-paired high performance liquid chromatographic determination of mitoxantrone in physiological fluids. J Chromatogr 337: 73