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Short communication

A phase II study of mitozantrone in advanced carcinoma of the ovary

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Summary. A total of 37 patients with advanced epithelial ovarian cancer were treated with single-agent mitozantrone at a dose of 12–16 mg/m^2. All patients had received previous chemotherapy, including a platinum compound in 36. In all, 35 patients were evaluable for response. One patient (3%) achieved a partial response lasting 4 months. Treatment was well tolerated, and at the doses used in this study significant bone marrow suppression was uncommon. Our results suggest that mitozantrone has only minimal activity in previously treated ovarian cancer. However, the possibility of its useful activity in first-line treatment or at higher doses has not been excluded.

Introduction

Chemotherapy is well established in the management of advanced carcinoma of the ovary; palliation is often possible and occasional long term disease control is seen. Platinum derivatives are the most effective agents, but platinum resistance typically develops and further chemotherapy in these patients rarely produces a durable remission.

Mitozantrone is a well-tolerated cytotoxic agent with useful activity in breast cancer, lymphoma and leukaemia [7]. Activity in advanced ovarian cancer has recently been reported [3], with responses occurring in patients previously treated with platinum-based chemotherapy; treatment was well tolerated. In view of these encouraging results, we carried out a phase II study of mitozantrone in a similar, pretreated group of patients with advanced ovarian cancer.

Patients and methods

A total of 37 patients with histologically confirmed, advanced epithelial ovarian cancer and a median age of 65 years (range, 37–78 years) were studied, 36 of whom had papillary or mucinous cyst adenocarcinoma and 1, endometrial carcinoma. All patients had received previous platinum-based chemotherapy except one, who had been treated with chlorambucil (Table 1); the median time that had elapsed since their most recent chemotherapy was 3 months (range, 0–27 months). In all, 22 patients had disease confined to the abdomen and pelvis, and 15 had spread of disease outside the abdomen or involving the liver. All patients had adequate bone marrow and liver function. The pretreatment white count (WBC) was required to be $>2.0\times10^9$ cells/l and the platelet count, $>70\times10^9$/l. Patients with a serum bilirubin concentration of >40 μmol/l were ineligible.

Table 1. Patient characteristics (n = 37)

Characteristic	Number of patients	
Previous chemotherapy:		
Cisplatin	21	36 patients had one or the other
Carboplatin	25	
Alkylators	15	
Anthracyclines	2	
Trimelamol	8	
CB 3717	3	
Thiotepa	1	
Methotrexate	1	
Number of previous drugs:		
None	0	
1	13	
2	16	
3	4	
4	2	
5	0	
6	2	
Time elapsed since last chemotherapy treatment:		
0– 6 months	28	
6–12 months	3	
12–18 months	3	
>18 months	3	
Performance status		
UICC grade 0	3	
1	15	
2	14	
3	5	
Sites of disease		
Intra-abdominal/pelvic	34	
Liver	10	
Pleura	8	
Lymphatic	6	
Lung	4	
Skin	1	

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Table 2. Response to data ($n = 37$)

Complete response (CR)	0
Partial response (PR)	1 (4 months)
No change (NC)	8
Progression (PD)	26
Early deaths (<4 months)	1
Not assessable	1

Table 3. Toxicity

WHO grade	Number of patients (worst course; $n = 37$)	Number courses ($n = 117$)
Haematological[a]:		
White blood cells		
Grade 0	17	76
Grade 1	7	22
Grade 2	6	8
Grade 3	3	5
Grade 4	1	2
Not known	3	4
Gastrointestinal[b]:		
Nausea and vomiting		
Grade 0	10	60
Grade 1	7	26
Grade 2	9	17
Grade 3	7	9
Grade 4	0	0
Not known	4	5
Alopecia:		
Grade 0	25	
Grade 1	5	
Grade 2	3	
Grade 3	0	
Grade 4	0	
Not known	4	

[a] Two patients developed grade 2 thrombocytopenia
[b] Four patients developed grade 1 stomatitis

Mitozantrone was given at a dose of 14 mg/m^2 as a bolus i.v. injection every 3 weeks until documentation of progressive disease, patient refusal, or for six courses. In the absence of severe bone marrow suppression (WHO grade >2), the dose of mitozantrone could be increased by 2 mg/m^2. Patients received a median of three courses (range, 1–8); eight patients received only one.

The starting dose of mitozantrone was 14 mg/m^2 in 25 patients; in 11 others, treatment was started at 12 mg/m^2 (9 patients) or 10 mg/m^2 (2 patients) because of heavy pretreatment with chemotherapy and a previous history of marrow suppression. One patient started treatment at 16 mg/m^2. Subsequent doses were based on the blood count at day 21; full doses were given if the WBC was $>3.5 \times 10^9$ cells/l or the platelet count, $>120 \times 10^9$/l. A dose reduction of 50% was undertaken at a WBC of $2.0–3.5 \times 10^9$ cells/l or a platelet count of $70–120 \times 10^9$/l, and treatment was postponed for 1 week if the blood count was below these ranges. Of 12 patients receiving more than two courses, 7 had their dose of mitozantrone increased in accordance with the protocol. Response was assessed clinically and radiologically using UICC criteria [6]. Toxicity was assessed according to WHO criteria [9].

Results

A total of 35 patients were evaluable for response (Table 2). One patient (3%) with abdominal and lung disease achieved a partial response lasting 4 months. In all 7 patients (20%) had stable disease for 4–10 months (median, 6 months) and 25 (71%) progressed. Two patients were not evaluable for response; one refused treatment and assessment after two courses, and another committed suicide. A total of 27 patients died, and the median duration of survival was 5 months (range, 0–13+ months).

Treatment was well tolerated on an out-patient basis (Table 3). WHO grade 4 bone marrow suppression occurred in only one patient. Treatment reductions or delays were necessary in two patients. Nausea and vomiting were mild, with standard doses of metaclopramide and dexamethasone used as antiemetics.

Discussion

Mitozantrone had minimal activity in this cohort of previously treated patients with advanced epithelial ovarian cancer. Our results do not confirm those of Lawton et al. [3], in whose study 10/41 (25%) patients previously treated with cisplatin responded. The two studies do not appear to differ in terms of the age, performance status, histology or distribution of disease in patients.

The number of previous treatments may have been greater in our study. It is our normal practice to use single-agent chemotherapy for ovarian cancer, the number of drugs thus equating closely with the number of treatments. A total of 10 patients had received both cisplatin and carboplatin, and 24 had received mitozantrone as third-line (or greater) treatment. Multi-drug resistance could be expected after such extensive prior treatment and probably accounts for our poor results [4]. Patients received mitozantrone for disease relapsing within 6 months of their most recent chemotherapy; however, at least three patients in this study subsequently responded to treatment with carboplatin.

Mitozantrone was a well tolerated out-patient treatment. Dose-limiting bone marrow suppression was not seen at starting doses of 12–14 mg/m^2 or, in those selected for dose escalation, doses of 16–18 mg/m^2. The recommended dose of 12–14 mg/m^2 was largely derived from experience in patients with advanced breast cancer [7], in whom impaired bone marrow function secondary to infiltration and prior radiotherapy are common. Higher doses may be possible in ovarian cancer, but we are unaware of evidence in solid tumours that shows an increased response rate with high-dose mitozantrone.

It should be stressed that our results do not exclude mitozantrone activity in ovarian cancer. We have seen responses in previously untreated patients [2], and i.p. mitozantrone therapy has been effective in some patients [5]. In advanced breast cancer, mitozantrone had a response rate of 33% when given as first-line treatment [7], a result confirmed by us [1, 8]. However, activity in pretreated patients was lower, with a response rate of 20% at the Royal Marsden Hospital and that of 0 at Guy's Hospital (unpublished observations).

In conclusion, mitozantrone cannot be recommended for heavily pretreated patients with advanced ovarian cancer. However, in view of its low toxicity, further study may

be indicated to determine the activity of mitozantrone used as first-line treatment.

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