Anti-Cancer Drugs 1998, 9, pp. 359–361

Short report

Paclitaxel plus ifosfamide in advanced ovarian cancer: results of a phase I study

U Klaassen, A Harstrick, D Strumberg, H Wilke and S Seeber
Department of Internal Medicine (Cancer Research), West German Cancer Center, University of Essen, Hufelandstrasse 55, 45122 Essen, Germany. Tel: (+49) 201-723-2012; Fax (+49) 201-723-5736.

Patients with advanced ovarian carcinoma and an inadequate response to first-line platinum-based combination chemotherapy (CTX) have a very poor prognosis and effective salvage regimens are clearly needed. This phase I study was performed in order to determine the maximum tolerable dose (MTD) and dose-limiting toxicity (DLT) of the combination paclitaxel (P) and ifosfamide (IFO). After premedication, patients received P as a 3 h i.v. infusion on day 1; IFO was given as 1 h i.v. infusion with the standard dose of mesna i.v. on days 2–5, q day 22. The following dose levels (dl) were investigated: (mg/m^2/day) dl1, P 135/IFO 1500; dl2, P 135/IFO 2000; dl3, P 175/IFO 2000; and dl4, P 175/IFO 1500. Eighteen patients with advanced ovarian cancer entered this trial. In eight patients treated with an IFO dose of 2000 mg/m^2 during dl2 and 3, two required treatment interruptions because of CNS toxicity CTC grade 3 and one patient experienced nephrotoxicity CTC grade 3, Therefore the MTD of IFO used in combination with P and given over 4 days is reached with 2000 mg/m^2/day. In the fourth dl we escalated the P dose up to 175 mg/m^2, reduced the IFO dose to 1500 mg/m^2 and treated an additonal five patients. No DLT occured at that dl. Objective responses were observed at all dls. The combination of P and IFO is feasable and active in pretreated advanced ovarian carcinoma. dl4 is the recommended dose for phase II trials. [© 1998 Lippincott-Raven Publishers.]

Key words: Ifosfamide, ovarian cancer, paclitaxel, phase I.

Introduction

While ovarian cancer is sensitive to cytotoxic drugs in first-line therapy with objective response rates of 60–80% to platinum-based therapy,[1] the majority of individuals with advanced disease will ultimatively relapse. Paclitaxel (P) as an antimicrotubule agent has shown activity as salvage therapy in epithelial ovarian cancer. Moreover, it could be demonstrated that P is active in tumors that have displayed resistance to platinum compounds, with a reported response rate of 20%.[2] Ifosfamide (IFO) has shown activity in the treatment of patients who previously demonstrated clinical resistance to a platinum/cyclophosphamide combination.[3] Furthermore, we demonstrate synergistic interactions of P plus IFO in platinum-resistant ovarian cancer cell lines *in vitro*.[4] Based on these data a phase I study of a combination consisting of P and IFO was performed in patients refractory or recurrent after front-line treatment with cisplatin or carboplatin containing combination chemotherapy.

Correspondence to U Klaassen

Patients and methods

Inclusion criteria

Patients in this study had to have cisplatin or carboplatin pretreatment as frontline therapy for advanced ovarian carcinoma. Other inclusion criteria were: progressive measureable or evaluable disease, age $\leqslant 70$ years, WHO performance status $\leqslant 2$, life expectancy of $\geqslant 3$ months, and adequate renal, liver and bone marrow function (creatinine, bilirubin $\leqslant 1.5 \times$ upper normal limit and ANC $\geqslant 2.0 \times 10^9$/l, platelet count $\geqslant 100 \times 10^9$/l). All patients gave their informed consent prior to study entry.

Staging and follow up

Prior to treatment, all patients had complete medical history and physical examination, ECG, determination and measurements of study parameters by chest X-ray, bone scan, CT scan and/or ultrasound. During treatment, full hematologic blood counts, determination of liver and renal functions, and assessment of non-hematologic toxicities were performed weekly. Response to treatment was assessed prior to each

cycle. The standard WHO/CTC criteria were used for evaluation of response and toxicity, respectively.

Treatment schedule

After standard premedication with dexamethasone (20 mg p.o. 12 and 6 h prior to each P infusion) and cimetidine (400 mg i.v.), clemastine (2 mg i.v.) 30 min before each treatment with P, patients received P, diluted in 1000 ml 0.9% saline solution, as a 3 h i.v. infusion on day 1. IFO, diluted in 500 ml 0.9% saline solution, was given as 1 h i.v. infusion i.v. on days 2-5, q day 22 with mesna at a dose of 400 mg/m^2 prior to and 4 and 8 h after IFO. Prophylactic antiemetic treatment was given according to routine practice. The recommended regimen included 5-HT$_3$ antagonists and steroids on days 2-5 followed by oral metoclopramide for prevention of delayed emesis.

Dose escalation and definition of dose-limiting toxicity (DLT) and maximum tolerated dose (MTD)

We chose the following dose levels (dl): (mg/m^2/d) dl1 P 135/IFO 1500; dl2, P 135/ IFO 2000; dl3, P 175/IFO 2000; and after experiencing IFO-related DLT in three out of eight patients at dl2 and 3, dl4 was chosen for further investigation: P 175/IFO 1500. P was administered if no DLT was present on the day of treatment. DLTs were defined as: neutropenia grade 4 longer than 5 days or febrile neutropenia, anemia and thrombopenia grade 3 or more, other organ toxicity, except alopecia, greater than grade 2 according to CTC criteria. A minimum of three patients were treated at each dl. If no DLT occurred, the next three patients entered the next dl. If one out of three patients at a given dl experienced DLT, three additional patients had to be entered. MTD was reached if DLT occured in two out of six patients.

Results

Eighteen patients with advanced ovarian cancer entered this study. The median age was 52 years (range 37-66), the median performance status according to WHO criteria was 1 (range 0-1). Sixteen out of 18 patients had bidimensionally measurable disease (nine of 18 visceral metastases, seven of 18 lymph node involvement). Prior chemotherapy consisted of a median of 1.5 chemotherapy regimens for advanced disease (range 1-3). Fourteen out of 18 patients had platinum refractory disease defined as disease progression while receiving platinum-containing chemotherapy prior to study entry.

The observed toxicity at each dose level is outlined in Table 1. All patients experienced alopecia CTC grade 3. No DLTs were seen in five patients treated at dl1 (28 treatment cycles). After we performed dose escalation of IFO up to 2000 mg/m^2 during dl2 and 3, in two out of eight patients treatment interuptions had to be performed due to CNS toxicity CTC grade 3 and an additional patient showed nephrotoxocity CTC grade 3. According to protocol guidelines the MTD of IFO used in combination with P was reached at 2000 mg/m^2/day. Therefore we reduced the dose of IFO to 1500 mg/m^2/day within dl4 and escalated the dose of P to 175 mg/m^2 (3 h i.v. infusion). Five additional patients were included at that dl. No further DLT were observed at dl4 within 25 treatment cycles (Table 1).

Table 1. Frequency of toxicity in (*n*) cycles per dose level

CTC grade	dl1 (*n*=5, 28 cycles)		dl2 (*n*=5, 24 cycles)		dl3 (*n*=3, 14 cycles)		dl4 (*n*=5, 25 cycles)	
	1/2	3/4	1/2	3/4	1/2	3/4	1/2	3/4
Neutropenia	6	22	–	24	–	14	–	25
Anemia	17	–	14	–	–	–	12	–
Thrombopenia	6	–	8	–	6	–	9	–
Nausea/vomiting	28	–	24	–	14	–	25	–
Cental nervous system toxicity	–	–	–	1[a]	–	1[a]	1	–
Peripheral neuropathy	28	–	24	–	14	–	25	–
Diarrhea	3	–	20	–	10	–	15	–
Mucosistis	20	–	20	–	14	–	18	–
Alopecia	–	23	–	19	–	11	–	20
Myalgia	20	–	14	–	14	–	25	–
Nephrotoxicity	–	–	–	1[a]	–	–	–	–

[a]Grade 3.

Table 2. Study treatment results

dl	No. of patients (*n*)	Treatment duration (cycles/patient)	Response
1	5	5.6 (3–8)	SD 3, PR 2
2	5	4.8 (2–6)	PD 1, SD 3, CR 1
3	3	4.6 (4–6)	PR 2, CR 1
4	5	5 (2–6)	PD 1, SD 1, PR 2, CR 1

All patients had a defined progression according to WHO criteria of their disease prior to study entry. Out of 18 patients, three had a complete remissions (CR), six had partial remissions (PR), seven had stable disease (SD) and only two patients experienced progressive disease (PD). Responses could be observed at all dls. At dl4, which is recommended for phase II, one CR, two PR, one SD and one PD could be observed among the five patients treated. An improvement of tumor-related symptoms (pain, weight loss, reduction of ascites in five out of 18 patients) was seen in all patients with an objective tumor response and in patients with stable disease.

Conclusions

Ovarian cancer belongs to the most responsive human malignancies to cytotoxic chemotherapy, with objective response rates of 60–80% being reported for a variety of platinum-based chemotherapy regimens. Despite this high chemosensitivity, the majority of patients will show progression in the later course of their disease,[5] and there is clearly a need to develop effective salvage chemotherapy regimens. The aim of our study was to determine the MTD for the combination of P given as a 3 h i.v. infusion on day 1 and IFO given as a 1 h i.v. infusion for 4 consecutive days (days 2–5) to be used as salvage chemotherapy in pretreated advanced ovarian cancer patients. Based on our study results the combination of P and IFO is feasible and active as salvage treatment in advanced ovarian carcinoma with an acceptable level of toxicity. dl4 is recommended for phase II trials, to further determine the value of this regimen in terms of efficacy.

References

1. Ozols B, Schwartz PE, Eifel PJ. Ovarian cancer, fallopian tube carcinoma and peritoneal carcinoma. In: DeVita VT, Hellman S, Rosenberg SA, eds. *Cancer, principles and practice of oncology,* 5th edn. Philadelphia, PA: Lippincott Raven 1997; **1**: 1502–34.
2. du Bois A, Lück H, Buser K, *et al.* Extended phase II study of paclitaxel as a 3-h infusion in patients with ovarian cancer previously treated with platinum. *Eur J Cancer* 1997 **33**: 379–84.
3. Markman M, Hakes T, Reichman B, *et al.* Ifosfamide and mesna in previously treated advanced epithelial ovarian cancer: activity in platinum resistant diseaase. *J Clin Oncol* 1992; **10**: 243–8.
4. Klaassen U, Harstrick A, Schleucher N, *et al.* Activity and schedule dependent interactions of paclitaxel, etoposide and ifosfamide in cisplatin-sensitive and cisplatin-resistant human ovarian cancer cell lines. *Br J Cancer* 1996; **74**: 224–8,
5. Markman M, Hoskins W. Responses to salvage chemotherapy in ovarian cancer: a critical need for precise definitions of the treated population. *J Clin Oncol* 1992; **10**: 513–4.

(Received 12 February 1998; accepted 17 February 1998)