Cancer Chemother Pharmacol (2000) 45: 513–515

CLINICAL TRIAL REPORT

Mario Nardi · Salvatore De Marco · Alessandra Fabi
Alessandra Aloe · Elena Magnani · Pierpaolo Grandinetti
Francesco Cognetti

Ifosfamide and vinorelbine in advanced pretreated ovarian cancer: a phase II study

Received: 1 December 1999 / Accepted: 25 January 2000

Abstract *Purpose*: The response rate to salvage chemotherapy in advanced ovarian cancer (AOC) has been disappointing in patients who do not respond or relapse after platinum-containing regimens. Ifosfamide (IFO) showed an overall response rate of 20% and vinorelbine (VNR) 15.6%. Trials of the association of these two drugs for AOC have not yet been published. *Patients and methods*: Between April 1996 and August 1997, 17 patients with AOC were treated with intravenous IFO 2000 mg/m^2 per day, days 1 to 3, with mesna uroprotection, and VNR 25 mg/m^2 per day, days 1 and 8, every 3 weeks. All patients but one had been heavily pretreated. All patients had been treated with platinum compounds and 16/17 with taxanes. *Results*: All 17 patients were evaluable for toxicity, and 16 for response (one lost to follow-up). One patient showed a partial response, 12 progressive disease and three stable disease. No complete responses were observed. The main toxicity was neutropenia (grade 3-4 in 82% of patients) with neutropenic fever in 17.6% of patients. In 70.5% of patients (19/59 of courses) VNR was not administered on day 8. In four patients (10/59 courses) the dose was reduced by 25% for persistent leukopenia grade 2-3. Other toxicities were not significant. *Conclusions*: This combination showed no activity in this set of patients. The poor outcome, as compared with the significant activity reported with the agents used singly, could be ascribed to the patients' characteristics, the low dose intensity of VNR administered and possible cross-resistance between the study drugs and previously used agents.

Key words Ovarian cancer · Ifosfamide · Vinorelbine · Salvage chemotherapy

M. Nardi (✉) · S. De Marco · A. Fabi · A. Aloe · E. Magnani
P. Grandinetti · F. Cognetti
Division of Medical Oncology I, Regina Elena National,
Cancer Institute, Viale Regina Elena 291, 00161 Rome, Italy
e-mail: mdb@crs.ifo.it
Tel.: +39-06-49852201; Fax: +39-06-4462655

Introduction

Over the last 20 years only a few agents, ifosfamide [5] taxanes [6] and topotecan [1], have produced a significant number of responses when used as salvage therapy for ovarian cancer patients with recurrent or refractory disease after primary cisplatin-based chemotherapy. As demonstrated by a Gynecologic Oncology Group study, ifosfamide shows an overall response rate of 20% in patients with progressive disease or disease refractory to cisplatin-containing therapy [5]. Vinorelbine as a single agent shows significant activity in second-line treatment, producing an objective response rate of 29% [2]. The combination of ifosfamide and vinorelbine has been tested in different solid tumours including non-small-cell lung cancer [4] and breast cancer [3]. Trials on the association of these two drugs as salvage therapy for advanced ovarian cancer have not yet been published. The aims of this study were to evaluate the antitumour activity and the toxicity of this combination as salvage treatment in patients with advanced epithelial ovarian cancer.

Materials and methods

Eligibility criteria included: histologically confirmed epithelial ovarian carcinoma relapsing or refractory after platinum-containing combination therapy; bidimensionally measurable disease by physical examination, computed tomography scan, ultrasonography or radiography; ECOG performance status ≤2; an interval of at least 4 weeks from prior chemotherapy; adequate renal, hepatic and haematological function tests; and a life expectancy of at least 12 weeks. Written informed consent was required from all patients.

Before each course, medical history and physical examination with assessment of evaluable lesions, performance status, neurological examination, complete blood count (CBC), chemistries and Ca 125 assay were performed. CBCs were repeated weekly, while tumour assessment by imaging studies was carried out every three courses. Standard response criteria were employed.

Patients received ifosfamide 2000 mg/m^2 per day on days 1 to 3 as an intravenous (i.v.) infusion in 500 ml Ringer's solution over 30 min in association with adequate hydration and mesna

uroprotection. Vinorelbine was given at a dose of 25 mg/m^2 per day i.v. on days 1 and 8 over 20 min. Cycles were repeated every 3 weeks. Toxicity and response were defined according to WHO standard criteria. At least two courses were administered except in cases of rapid progressive disease.

Results

Between April 1996 and August 1997, 17 patients entered this study. The characteristics of the 17 patients are summarized in Table 1. All patients were evaluable for toxicity and 16 for response (one lost to follow-up). Of the 17 patients, 6 (35.3%) had received three or more regimens, 10 (58.8%) two previous chemotherapy combinations and 1 had received only one regimen. All patients had received primary chemotherapy including platinum compounds, 15 patients had received alkylating agents, 16 patients had been pretreated with paclitaxel, and 7 patients had received anthracyclines. The group deemed to be clinically sensitive to platinum included patients who had previously shown a complete response (CR) to platinum-based first-line therapy and disease recurrence >6 months after discontinuing the treatment. The clinically resistant group consisted of those whose disease progressed while receiving platinum-based therapy, whose best response was stable disease or a partial response (PR), and those with CR whose disease recurred within 6 months of interrupting the treatment. On this basis, 13 patients were considered clinically resistant to platinum compounds as initial chemotherapy. A total of 59 courses were administered (median three, range one to six). Of the 16 patients evaluable for response, 1 showed a PR (confidence interval 0–17.6%) lasting more than 8 months, 3 had stable disease and 12 progressed. The only PR was observed in a platinum-sensitive patient.

The median relative dose intensity was 1.8 g/m^2 per week for ifosfamide (90%) and 10.9 mg/m^2 per week for vinorelbine (65.5%). A high dose intensity of both drugs was reached in the only responder (ifosfamide 95%, vinorelbine 87.3%).

Table 1 Patient characteristics

No. of patients	
Total entered	17
Platinum-sensitive	4
Platinum-resistant	13
Age (years)	
Median	54
Range	32–69
Histology	
Serous	15
Mucinous	1
Undifferentiated	1
Stage (WHO)	
III	13
IV	4
Prior chemotherapy regimens	
1	1
2	10
≥3	6

Table 2 Toxic effects of the combination of ifosfamide and vinorelbine presented as the number (%) of patients

Toxicity	WHO grade			
	1	2	3	4
Neutropenia	1 (5.8)	–	4 (23.5)	10 (58.8)
Anemia	3 (17.6)	3 (17.6)	3 (17.6)	–
Thrombocytopenia	3 (17.6)	–	–	–
Neurotoxicity	2 (11.7)	2 (11.7)	–	–
Alopecia	–	5 (29.3)	–	–
Nausea/vomiting	4 (23.5)	1 (5.8)	–	1 (5.8)
Fever	2 (11.7)	–	–	–
Mucositis	1 (5.8)	–	–	–

All patients were evaluable for toxicity. Table 2 shows the toxic effects. The main haematological toxicity was grade 3-4 neutropenia in 82% of patients, with neutropenic fever in 17.6%, not requiring hospitalization. Three patients (17.6%) had grade 3 anemia. In 70.5% of patients (19/59 courses, 32.2%) vinorelbine was not administered on day 8. A 25% dose reduction of both drugs was needed in four patients (10/59 courses, 16.9%) for a leukopenia lasting more than 1 week. Other toxic effects were negligible.

Discussion

The combination of ifosfamide and vinorelbine tested in the present study showed no activity. Despite the demonstrated efficacy of these two drugs as single agents in cisplatin-pretreated ovarian cancer patients, some hypotheses may be proposed to explain the poor outcome following their use in combination. First, the compromised bone-marrow reserve of these heavily pretreated patients did not allow the administration of the projected dose intensity. The omitted administration of vinorelbine on day 8 in 32.2% of cycles led to a low dose intensity of this drug (65.6%). Second, our cohort of patients had particularly unfavourable characteristics. In 60% and 35% of patients the study regimen was given as third-line and fourth-line chemotherapy, respectively, and a high proportion (76.5%) of the patients were platinum-resistant. Furthermore, the only patient who responded to treatment was platinum-sensitive, and had previously received two combination regimens including platinum compounds, paclitaxel and alkylating agents. In particular, the dose intensity delivered to this patient was high: 95% for ifosfamide and 87% for vinorelbine.

Although in other malignancies this combination has proven active, our results in ovarian cancer, compared with those obtained with ifosfamide and vinorelbine as single agents, raise the question as to whether their simultaneous administration might interfere with their pharmacokinetics and mechanisms of action. The elucidation of drug-resistance mechanisms and their

implications in cross-resistance among front-line drugs (platinum compounds and paclitaxel) and salvage therapy agents could be interesting aims of further trials.

The results of this study suggest that the combination of vinorelbine and ifosfamide is not suitable in this subset of patients, but further study may be useful in more selected patient populations.

References

1. Bolis G, Malstrom H, Mangioni C, Carter J, Gordon A, Hall J, Hudson I, Broom C, Bookman M (1996) Efficacy of topotecan in advanced epithelial ovarian cancer after failure of platinum and paclitaxel: International Topotecan Study Group Trial. Ann Oncol 7 [Suppl 5]: 3210
2. Burger RA, Di Saia PJ, Roberts JA, O'Rourke M, Gershenson DM, Homesley HD, Lichtman SM, Barnes W, Moore DH, Monk BJ (1999) Phase II trial of vinorelbine in recurrent and progressive epithelial ovarian cancer. Gynecol Oncol 72: 148
3. Campisi C, Fabi A, Papaldo P, Massidda B, Tomao S, Zappalà A, Ionta MT, Cognetti F (1998) Ifosfamide given by continuous intravenous infusion in association with vinorelbine in patients with anthracycline-resistant metastatic breast cancer: a phase I-II clinical trial. Ann Oncol 9: 565
4. Hoffman P, Drinkard L, Masters G, Samuels B, Krauss S, Watson S, Golomb H, Vokes E (1995) Ifosfamide plus vinorelbine: a phase I study in advanced non-small cell lung cancer (NSCLC). Proc Am Soc Clin Oncol 1092: 358
5. Sutton GP, Blessing JA, Homeseley HD, Berman ML, Malfetano J (1989) Phase II trial of ifosfamide and mesna in advanced ovarian carcinoma: a Gynecologic Oncology Group study. J Clin Oncol 7: 1672
6. Thigpen JT, Blessing JA, Ball H, Hummel SJ, Barret RS (1994) Phase II trial of paclitaxel in patients with progressive ovarian carcinoma after platinum-based chemotherapy: a Gynecologic Oncology Group Study. J Clin Oncol 12: 1748