Phase II Study of Vinorelbine in Patients With Pretreated Advanced Ovarian Cancer: Activity in Platinum-Resistant Disease

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Purpose: **The aim of the study was to evaluate the activity of vinorelbine (VNLB) in a population of advanced ovarian cancer patients, with particular attention to defining its role in platinum-resistant disease.**

Patients and Methods: **Thirty-three patients were recruited and treated with VNLB 25 mg/m^2 intravenously (IV) weekly. The median age was 53 years, performance status 0 to 2, and number of previous chemotherapy regimens two (range, one to five). Twenty-faur patients were platinum-resistant; the remaining nine either were platinum-sensitive (four cases) or had undetermined sensitivity (five cases).**

Results: **The mean delivered dose-intensity of VNLB was 67% of the planned level, because 60% of the cycles were delayed due to neutropenia or anemia. Four partial responses (PRs) and one complete response (CR) were observed, for an overall response rate of 15% (95% exact confidence interval, 5.1% to 31.9%). All the responses occurred in the subgroup of 24 platinum-resistant cases, in whom the response rate was 21% (95% exact confidence interval, 7.1% to 42.1%). Seven patients became stabilized on VNLB, and 27% of the cases showed a reduction in serum cancer antigen 125 (CA 125) levels. G3/G4 side effects consisted of neutropenia, anemia, and worsening of preexisting peripheral neuropathy. No treatment-related deaths occurred.**

Conclusion: **VNLB led to a 21% response rate in the population of heavily pretreated and platinum-resistant ovarian cancer patients. Further studies of VNLB alone or in combination with taxanes are warranted in patients with less pretreatment.**

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VINORELBINE (VNLB) is a semisynthetic vinca alkaloid analog that acts by promoting depolymerization and inhibiting the assembly of mitotic microtubules at a concentration that does not affect axonal microtubules,[1] and may therefore be active against cancer cells and less neurotoxic than vinca alkaloids. Preclinical studies have shown that VNLB is more active than conventional vinca alkaloids,[2] and phase I studies have ascertained that the drug can be safely given at a dose of 25 to 30 mg/m^2 intravenously (IV) weekly but further dose-escalation is limited by the onset of severe neutropenia and peripheral neurotoxicity.[3] In phase II studies, VNLB has been shown to be active in non–small-cell lung cancer, breast cancer, and Hodgkin's disease.[4]

Two early reports of phase II studies have also suggested that the activity of VNLB (alone or in combination) may be promising in advanced ovarian cancer.[5,6] These data prompted us to study its activity in advanced epithelial ovarian cancer, with particular attention to determining its efficacy in platinum-resistant cases.

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PATIENTS AND METHODS

Eligibility Criteria and Study Protocol

Patients with radiologically measurable advanced epithelial ovarian cancer were eligible for the study; those with only assessable disease were not enrolled. At least one previous first-line treatment with platinum compounds was required, but the number of previous chemotherapy regimens was not limited and previous radiotherapy was also allowed. The other eligibility criteria were as follows: age ≤ 75 years, Eastern Cooperative Oncology Group performance status 0 to 2, absolute neutrophil count (ANC) ≥ 1,500/μL, platelet count ≥ 100,000/μL, hemoglobin level ≥ 8 g/dL, total bilirubin level ≤ 1.5 mg/dL, and serum creatinine level ≤ 1.2 mg/dL. Each patient provided informed consent, and the study was approved by our Institutional Review Board. Concomitant peripheral neuropathy ≥ grade 3 (National Cancer Institute criteria) was a contraindication to study admission.

Eligible patients underwent chest x-ray, radiologic examination of the abdomen and pelvis, gynecologic examination, and electrocardiography, all of which were repeated every 2 months thereafter. Routine hematochemistry (hemogram, blood urea nitrogen, serum creatinine, uric acid, electrolytes, glycemia, transaminases, total bilirubin, alkaline phosphatase, and serum electrophoresis) was undertaken at baseline; the hemogram was repeated weekly and the remaining evaluations were repeated every 3 weeks. Cancer antigen 125 (CA 125) serum levels were assessed at baseline and at monthly intervals. VNLB (Navelbine; Pierre Fabre Pharma, Bizanos, France) was administered as an IV bolus at a dose of 25 mg/m^2 weekly, and tumor response was evaluated after 2 months. In the case of an objective response or disease stabilization, treatment was continued; otherwise, it was stopped. Patients whose disease had stabilized after 4 months of treatment were kept in the follow-up study. Criteria for treatment delays and dose-reductions were as follows. Seven days after the drug infusion, an ANC was conducted. If this resulted in less than 1,500/μL, the second infusion was delayed for a further 3 days and the cycle repeated on the tenth day if the ANC was ≥ 1.500/μL. If the ANC was still less than 1, 500/μL 21 days after

the last drug injection, the dose was reduced by 25% for the next cycle. No granulocyte colony-stimulating factors were used during the trial. For hemoglobin levels less than 8 g/dL at the moment of drug infusion, a RBC transfusion was given, and the cycle was repeated after 3 days if the hemoglobin level was ≥ 8 g/dL; otherwise, further transfusions were given until the hemoglobin level was ≥ 8 g/dL. Treatment was stopped in the case of grade 3 or 4 peripheral neurotoxicity or constipation. Tumor response was assessed according to standard criteria[7]; in the case of lesions that were measurable by physical examination, response was confirmed radiologically. Toxicity was graded according to the National Cancer Institute classification.[8] Patients were considered assessable only if they had undergone at least three cycles of chemotherapy. Response duration was calculated from the time of response documentation, whereas the time to treatment failure and overall survival were calculated from the time of treatment initiation and estimated using the Kaplan-Meier method. Exact 95% confidence intervals were computed for the response rates in the whole population and in the subgroup of platinum-resistant patients.

Criteria to Define Platinum Responsiveness

The criteria used to assess platinum responsiveness have been previously reported[9] and can be summarized as follows. Patients were defined as platinum-resistant if the disease had progressed during administration of a platinum-containing regimen, or had stabilized or regressed by less than 50% after platinum-containing chemotherapy given until the cumulative dose of cisplatin or carboplatin had reached a total of 450 or 1,800 mg/m^2, respectively. Patients were defined as platinum-sensitive if they had responded at least partially after a treatment that included platinum compounds. The status of patients without radiologic or surgical evidence of response or progression after a previous platinum therapy was defined as undetermined. The platinum-free interval was not used in the assessment of responsiveness to platinum compounds. The responsiveness of patients who had received two lines of platinum-containing regimens before entering the study was evaluated on the basis of results achieved with the last regimen.

RESULTS

Patient Characteristics

Thirty-three patients were recruited between January 1993 and December 1994; their main characteristics are listed in Table 1. All patients had received previous chemotherapy, the median number being two (range, one to five). All patients had been previously treated with platinum compounds, and 10 had received previous treatment with paclitaxel.

All of the patients had radiologically measurable disease as required by the eligibility criteria; furthermore, the disease in 16 patients was also measurable by physical examination (12 cases with abdominal-pelvic masses and four with superficial lymph nodes). Eight patients had concomitant assessable sites (two with diffuse abdominal skin infiltration, one with lytic bone lesions, and five with pelvic masses).

On the basis of the criteria for platinum responsiveness used in this study, there were 24 platinum-resistant, four platinum-sensitive, and five undetermined cases. It should be pointed out that two of four sensitive cases had been in pathologically complete remission for 10 and 11 months, respectively, whereas the remaining two were in partial remission and were treated with VNLB 1 year after the last platinum dose. No radiologic or surgical evaluation of responsiveness to a platinum-containing chemotherapy was available for the five undetermined cases, but all were treated with VNLB at least 7 months after the last platinum-containing cycle (range, 7 to 84). Comparison to the conventional criteria for determining platinum responsiveness[10] showed no difference in the evaluation of responsiveness, except for the fact that the conventional criteria would have divided the group of 24 platinum-resistant patients into two different subgroups of 15 primary- and nine secondary-resistant cases.

Table 1. Patient Characteristics

Characteristic		No. of Patients
Entered/assessable		33/33
Age, years		
Median	53	
Range	40-73	
Performance status		
1		25
2		8
Histology		
Serous		24
Clear cell		5
Mucinous		2
Undifferentiated		2
No. of previous regimens		
1/2		5/17
3/≥ 4		6/5
No. of previous cycles per patient		
Mean	12	
Range	3-38	
Platinum responsiveness		
Resistant/sensitive		24/4
Undetermined		5

Treatment Administration

A total of 260 VNLB cycles were given, with a mean number of eight per patient. The mean delivered dose-intensity was 2.4 mg/m^2/d, 67% of the planned amount (3.6 mg/m^2/d), because 60% of the cycles were delayed (a mean of five delayed cycles per patient). Twenty-one of 33 patients (64%) required a treatment delay in accordance with the criteria already described; in particular, the causes of delay were neutropenia (ANC < 1,500/μL at the moment of drug infusion) in 16 patients, anemia (hemoglobin level < 8 g/dL at the moment of drug infusion) in three, and anemia plus neutropenia in two. No dose-reductions were needed.

Table 2. Characteristics of Responding Patients

Age	Best Response	No. of Previous Regimens	Platinum Responsiveness	Response Duration (mo)	Response Sites	Method of Assessment	CA 125 Reduction	Baseline CA 125/ Lowest Value (U/L)	% Reduction
49	PR	2	Progression on 2nd-line carboplatin	8	Liver, peritoneum, retroperitoneal nodes, pelvic mass	MRI	Yes	2,200/220	90
40	PR	2	Stabilization after cisplatin 500 mg/m^2	3	Peritoneum	MRI	Not assessable	—	—
68	PR	2	Progression on 2nd-line carboplatin	—*	Retroperitoneal nodes, abdominal mass	CT	Yes	831/216	74
43	PR	2	Stabilization after cisplatin 640 mg/m^2	5	Superficial nodes, abdomino-pelvic mass	Echography	Yes	635/235	63
73	CR	1	Progression on cisplatin	2	Superficial nodes, peritoneum, pelvic mass	MRI	Yes	245/110	55

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging.
*Response duration not ossessable because of lack of further CT scans.

Antitumor Activity

All 33 eligible patients were assessable for response: there were one complete response ([CR] 3%), four partial responses ([PRs] 12%), seven cases of stable disease (21%), and 21 cases of progressive disease (64%), for an overall response rate of 15% (95% exact confidence interval, 5.1% to 31.9%). The five responses were among the 24 resistant cases (21% OR; 95% exact confidence interval 7.1% to 42.1%). There was no response among the four platinum-sensitive patients or the five patients whose responsiveness was undetermined. Characteristics of the responding patients are listed in Table 2, and it must be emphasized that all but one had received VNLB as a third-line therapy. With regard to the activity of VNLB among the 10 patients who had been previously treated with paclitaxel, one whose disease had progressed on paclitaxel, responded to VNLB, and two who had previously responded to paclitaxel had disease progression on VNLB. According to the conventional criteria of platinum responsiveness, two of five responses were achieved by nine secondary-resistant cases, and the remaining three occurred in the group of 15 primary-resistant patients.

For the seven patients whose disease stabilized, the median duration of stabilization was 6 months (range, 4 to 12). It is important to point out that one of the stabilizations lasted for 12 months (VNLB being a fifth-line treatment); another in a platinum-resistant patient lasted for 6 months and was associated with a decrease in serum CA 125 levels of 67% from baseline values; and a third, in a patient who also received VNLB as fifth-line therapy, was a minor response (tumor reduction in the liver and stabilization of a pelvic mass) associated with a 44% reduction in CA 125 levels. Serum CA 125 levels decreased in a total of seven of 26 assessable patients, the mean reduction being 63%. According to criteria reported by Rustin et al[11] to define tumor response on the basis of multiple serum CA 125 evaluations, two of 20 patients achieved a tumor remission, one of whom also showed a radiologic response. The median time to treatment failure and overall survival duration were 4 months (range, 1 to 14) and 10 months (range, 2 to 20), respectively. Ten patients received further treatment after disease progression during VNLB (four with paclitaxel, two with docetaxel, and four with tamoxifen), with only a minor response observed in one of the patients on paclitaxel.

Tolerability

Side effects experienced by 33 assessable patients are listed in Table 3. Neutropenia, anemia, and worsening of a preexisting peripheral neuropathy were the only G3 side effects. Five patients needed RBC transfusions. Two patients stopped VNLB treatment because of toxicity (G3 peripheral neurotoxicity in both cases). No toxic deaths were reported, and none of the patients refused to continue VNLB or to receive the treatment at the due time.

DISCUSSION

Identification of active second-line drugs for the treatment of ovarian cancer is a priority because approxi-

Table 3. Side Effects

Side Effect	No. of Patients		% of Patients With G3-G4 Toxicity
	G1-G2	G3-G4	
Neutropenia	12	6	18
Anemia	2	5	15
Onset of paresthesia	1	—	—
Worsening of paresthesia	6	2	6
Constipation	5	—	—
Stomatitis	8	—	—
Nausea/vomiting	11	—	—
Alopecia	5	—	—
Diarrhea	1	—	—
Phlebitis	5	—	—
Mandibular pain	3	—	—
Flushing	3	—	—
Pneumonia	1	—	—
Neutropenic fever	6	—	—

mately 80% of advanced ovarian cancer patients will need second-line therapy during the treatment program. Unfortunately, the discovery of active drugs in platinum-resistant disease is rare, although the use of taxanes over the last few years has led to important data.[12-21]

In this study of VNLB in a population of heavily pretreated patients, we observed a 15% response rate with a mean delivered dose-intensity that was 67% of the planned level. The main result was a 21% response rate in 24 platinum-resistant cases; in fact, all of the responses occurred in this subset of patients, although it is impossible to evaluate the drug's activity in the group of patients with platinum-sensitive disease because this included only four cases. Two trials that evaluated VNLB in advanced ovarian cancer have been reported.[5,6] The first evaluated VNLB 30 mg/m^2 weekly in a population of 32 pretreated patients[5] and recorded five objective remissions (one CR), for an overall response rate of 15%; three of these responses occurred in patients whose disease had progressed while on previous chemotherapy. Twenty-six percent of the cycles were delayed and 12% were given at reduced dose, mainly as a result of neutropenia. The other trial combined VNLB with hexamethylmelamine in a group of 17 pretreated patients, with VNLB given at a dose of 20 mg/m^2 weekly.[6] There were one pathologic PR and five clinical responses (two CR), for a response rate of 36%; two of the remissions were obtained in platinum-resistant patients.

Both of these studies suggested that VNLB may be active in advanced ovarian cancer, but they lack a clear description of the platinum-responsiveness of the treated patients. The difference in the present study is that patients were classified according to previous response to platinum compounds, and this has made it possible to investigate the activity of VNLB in platinum-resistant disease, which is the ideal target to evaluate new drugs in ovarian cancer.

The criteria used to determine platinum responsiveness in this study virtually overlap with the conventional criteria,[10] the only differences being the further division of platinum resistance into primary- and secondary-resistant cases (used in the conventional criteria) and the admission of patients whose disease had stabilized/regressed less than 50% when treated with platinum into the category of resistant cases only if they had received a determined cumulative dose of platinum compounds (used in the criteria of this study). Nevertheless, whichever criteria for platinum responsiveness are used, the response rate to VNLB in the platinum-resistant patients of this study remains at 21%.

As is also suggested by the conventional criteria for platinum responsiveness,[10] patients who experienced tumor remission during treatment with platinum compounds but had a platinum-free interval of less than 6 months were not considered resistant, because such patients may still respond to platinum compounds even if the probability of response is directly related to the platinum-free interval and the extremely brief response obtained may not be meaningful.[22-25] Noninclusion of these patients in the category of resistant cases makes the criteria to assess platinum resistance very rigid and therefore the evaluation of the investigated drug very accurate. This choice may be supported by an editorial that analyzed the results of a second-line paclitaxel study in which platinum resistance was classified as either absolute (progression during platinum) or relative (relapse within 6 months or stabilization after platinum). It is interesting that the responses to second-line paclitaxel varied and seemed to be better in relatively resistant patients, although the analysis is limited by the small number of patients included in the two categories.[26]

In terms of future investigations, it would be interesting to study the activity of VNLB at a higher dose-intensity. In this subset of heavily pretreated patients it seems difficult to improve dose-intensity, because even though we planned to administer the drug to patients with grade 1 neutropenia (ANC $\geq$ 1,500/μL), it was not possible to give more than 67% of the originally planned dose. An improvement in dose-intensity might be obtained in less heavily pretreated patients or if weekly VNLB is associated with administration of a granulocyte colony-stimulating factor. However, although it might theoretically improve the drug's antitumor activity, a greater dose-intensity might also lead to increased toxicity (peripheral neurotoxicity and anemia), and since the second-line treatment of ovarian cancer is only palliative, this may be a major concern.

A further area of development for VNLB is the possibility of combining it with taxanes. VNLB acts by inhibition of microtubule assembly and promotion of microtubule depolymerization, whereas the taxanes promote the assembly and inhibit the depolymerization—both agents inhibit cell mitosis. In vitro studies have demonstrated that VNLB and paclitaxel act synergistically when exposed to two human breast cancer cell lines, but it is important to stress that the combination loses activity when cells are exposed to paclitaxel 24 hours before addition of VNLB.[27] Preclinical models have confirmed the synergistic activity of the VNLB-paclitaxel combination,[28] and synergy has also been demonstrated when docetaxel and VNLB are concomitantly given to mice bearing solid tumors.[29] In a recent clinical study that tested the combination of VNLB and paclitaxel,[30] seven patients with pretreated lung or breast cancer were enrolled onto a dose-finding study that evaluated fixed-dose VNLB (25 mg/m^2 IV on days 1 and 8) plus paclitaxel given at two different doses (90 mg/m^2 over 3 hours for the first three patients and 175 mg/m^2 over 3 hours for the last four); granulocyte colony-stimulating factors were also routinely used. All of the patients received VNLB before paclitaxel. It is clear from this preliminary experience that the combination of the two drugs leads to severe granulocytopenia despite the use of granulocyte colony-stimulating factors, and therefore other schedules might be explored, particularly in chemotherapy-naive patients.

In conclusion, in the present trial VNLB led to a 15% response rate in a population of heavily pretreated ovarian cancer patients and, more importantly, a 21% response rate in the subgroup of 24 patients with platinum-resistant disease. Together with the data from two previous trials, these results suggest that VNLB may be useful in ovarian cancer and that future studies in a less heavily pretreated population are warranted. Furthermore, preclinical and early clinical data suggest that the association of VNLB and taxanes may lead to a synergy that should soon be tested in ovarian cancer.

REFERENCES

1. Fellons A, Ohayon R, Vacassin T, et al: Biochemical effect of Navelbine on tubulin and associated proteins. Semin Oncol 16:9-14, 1989
2. Cros S, Wright M, Moromoto M, et al: Experimental antitumor activity of Navelbine. Semin Oncol 16:15-20, 1989
3. Mathè G, Reizenstein P: Phase I pharmacologic study of a new vinca-alkaloid: Navelbine. Cancer Lett 27:285-293, 1985
4. Cvitkovic E, Izzo J: The current and future place of vinorelbine in cancer therapy. Drugs 44:36-45, 1992 (suppl 4)
5. George MJ, Heron JF, Kerbrat P, et al: Navelbine in advanced ovarian epithelial cancer: A study of the French Oncology Centers. Semin Oncol 16:30-32, 1989
6. Pinon G, Pinel MC, Goudier MJ, et al: Etude de la vinorelbine associèe à l'hexamèthylmèlamine dans les adènocarcinomes de l'ovaire: rèsultats d'un essai phase I-IIA, NH0-88, du groupe "ovaire" de l'ARTAC. Bull Cancer 78:1119-1131, 1991
7. WHO/UICC Handbook for Reporting Results of Cancer Treatment. WHO Offset Publication No. 48 Geneva, Switzerland, WHO, 1979, pp 14-27
8. Wittes RE (ed): Appendix A: Grading of toxicity, in Manual of Oncologic Therapeutics. Philadelphia, PA, Lippincott, 1991, pp 445-448
9. Di Leo A, Bajetta E, Biganzoli L, et al: An I.T.M.O. group study on second-line treatment in advanced epithelial ovarian cancer: An attempt to identify clinical and biological factors determining prognosis. Eur J Cancer 31A:2248-2254, 1995
10. Markman M, Hoskins W: Responses to salvage chemotherapy in ovarian cancer: A critical need for precise definitions of the treated population. J Clin Oncol 10:513-514, 1992 (editorial)
11. Rustin GJ, van der Burg MEL, Berek JS: Tumour markers. Ann Oncol 4:S71-S77, 1993 (suppl 4)
12. McGuire WP, Rowinsky EK, Rosenshein NB, et al: Taxol: A unique antineoplastic agent with significant activity in advanced ovarian epithelial neoplasms. Ann Intern Med 111:273-279, 1989
13. Trimble EL, Adams JD, Vena D, et al: Paclitaxel for platinum-refractory ovarian cancer: Results from the first 1,000 patients registered to National Cancer Institute Treatment Referral Center 9103. J Clin Oncol 11:2405-2410, 1993
14. Einzig AI, Wiernik PH, Sasloff J, et al: Phase II study and long-term follow-up of patients treated with Taxol for advanced ovarian adenocarcinoma. J Clin Oncol 10:1748-1753, 1992
15. Thigpen JT, Blessing JA, Ball H, et al: Phase II trial of paclitaxel in patients with progressive ovarian carcinoma after platinum-based chemotherapy: A Gynecologic Oncology Group study. J Clin Oncol 12:1748-1753, 1994
16. Sarosy G, Kohn E, Stone DA, et al: Phase I study of Taxol and granulocyte colony-stimulating factor in patients with refractory ovarian cancer. J Clin Oncol 10:1165-1170, 1992
17. Kohn EC, Sarosy G, Bicher A, et al: Dose-intense Taxol: High response rate in patients with platinum-resistant recurrent ovarian cancer. J Natl Cancer Inst 86:18-24, 1994
18. Francis P, Schneider J, Hann L, et al: Phase II trial of docetaxel in patients with platinum-refractory advanced ovarian cancer. J Clin Oncol 12:2301-2308, 1994
19. Piccart MJ, Gore M, Ten Bokkel Huinink W, et al: Docetaxel: An active new drug for treatment of advanced epithelial ovarian cancer. J Natl Cancer Inst 87:676-681, 1995
20. Aapro M, Pujade-Lauraine E, Lhomme C, et al: Phase II study of taxotere in ovarian cancer. Proc Am Soc Clin Oncol 12:256, 1993 (abstr 809)
21. Kavanagh J, Kudelka A, Freedman R, et al: Taxotere: Activity in platin refractory ovarian cancer and amelioration of toxicity. Proc Am Soc Clin Oncol 13:237, 1994 (abstr 732)
22. Gore ME, Fryatt I, Wiltshaw E, et al: Treatment of relapsed carcinoma of the ovary with cisplatin or carboplatin following initial treatment with these compounds. Gynecol Oncol 36:207-211, 1990
23. Markman M, Rothman R, Hakes T, et al: Second-line platinum therapy in patients with ovarian cancer previously treated with cisplatin. J Clin Oncol 9:389-393, 1991
24. Kjorstad K, Harris A, Bertelsen K, et al: A multicenter phase

II study of carboplatin in advanced ovarian carcinoma: Final report. Ann Oncol 3:217-222, 1992

25. Kavanagh J, Tresukosol D, Edwards C, et al: Carboplatin reinduction after taxane in patients with platinum-refractory epithelial ovarian cancer. J Clin Oncol 13:1584-1588, 1995

26. Cannistra SA: Paclitaxel in ovarian cancer: How can we make it better? J Clin Oncol 12:1743-1744, 1994 (editorial)

27. Adam DJ: Synergy of Navelbine-Taxol combination treatment in two human breast cancer cell lines. Proc Am Assoc Cancer Res 35:327, 1994 (abstr 1944)

28. Knick VC, Eberwein DJ, Miller CG: Preclinical activity of Navelbine and Taxol drug combinations. Proc Am Assoc Cancer Res 35:327, 1994 (abstr 1945)

29. Bissery MC, Vrignaud P, Bayssas M, et al: Preclinical in vivo activity of docetaxel-containing combinations. Proc Am Soc Clin Oncol 14:489, 1995 (abstr 1599)

30. Chang AY, Garrow GC: Pilot study of vinorelbine(Navelbine) and paclitaxel (Taxol) in patients with refractory breast cancer and lung cancer. Semin Oncol 22:66-71, 1995