

Vinorelbine and Cisplatin in Advanced Squamous Cell Carcinoma of the Cervix: The South African Experience

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Abstract. *Background:* This phase II trial was performed to assess the activity and safety of the cisplatin and vinorelbine combination in patients with advanced cervical carcinoma. *Patients and Methods:* Forty-two patients with advanced cervical cancer were included in the study to receive vinorelbine at 30 mg/m² on d 1 and d 8 and cisplatin 100 mg/m² on day 1 every 4 weeks. *Results:* Thirty-seven patients were evaluable for response and 40 patients for tolerance. Twenty-four patients (64.8%) achieved objective responses. The median duration of response was 17.5 months (range 2.5-57 months), median time to progression was 13.2 months (range 0.4-57 months) and median survival was 20.6 months (range 0.4-55 months). This regimen was well-tolerated; no WHO grade 4 neutropenia was observed, grade 3 nausea and vomiting occurred in 50% of patients and grade 2 peripheral neuropathy in 5% of patients. *Conclusion:* Vinorelbine-cisplatin is an active and well-tolerated regimen in advanced cervical carcinoma.

Cervical carcinoma is a health problem in developing countries, where more than 80% of all cervical cancers are diagnosed (1). The estimated incidence rate (age-standardized) of cervical cancer per 100,000 women in Republic of South Africa was 28.8 which represents an estimated 4654 new cases of invasive cervix cancer in 2001 (1). Chemotherapy is the standard therapy for advanced or metastatic disease. Unfortunately results are disappointing and response rates are poor, varying between 10 to 35%, and are of short duration (2, 3). Nevertheless, among various older cytotoxic agents, cisplatin is considered to be the most active chemotherapeutic agent as a single agent or in combination. (4, 5).

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Vinorelbine is of a new generation of vinca alkaloids, which exerts its biological effects by inhibiting microtubule assembly (6). It is an active agent against several human malignancies (7-17). As a single agent at 30 mg/m² weekly, vinorelbine has shown a consistent efficacy in non-small cell lung cancer and in advanced breast cancer (12-17).

An interesting activity has also been reported with vinorelbine in cervical carcinoma (18-20).

Based on the efficacy of both agents, this phase II trial was performed to assess the activity and safety of the combination in patients with advanced cervical carcinoma.

Patients and Methods

Eligible patients included women with histologically confirmed FIGO stage III or IV squamous carcinoma of the uterine cervix, WHO performance status ≤ 2 , age between 18 and 75 years, life expectancy more than 3 months, not previously treated by radiotherapy, chemotherapy or surgery. Patients had to have at least one bidimensionally measurable lesion and had to give informed consent. Ineligible patients included those with malignancies of the cervix other than squamous, previous or concurrent cancer at other sites (except adequately treated basal cell carcinoma of the skin), a serum creatinine level >1.25 N (or creatinine clearance <60 ml/minutes), absolute neutrophils counts $<2 \times 10^9$ /l and/or platelets count $<100 \times 10^9$ /l, bilirubin >1.25 N and/or transaminases $>1.25 \times$ N, peripheral neuropathy ≥ 2 , any sign of brain involvement or uncontrolled hypercalcemia. Patients with uncontrolled infectious diseases, or who were pregnant or nursing, as well as those with family, social or environmental conditions impairing adequate follow-up and protocol compliance, were excluded from this study. This protocol was reviewed and approved by an independent ethics committee. It was conducted under the terms of the declaration of Helsinki.

Treatment regimens. Vinorelbine was administered intravenously on days 1 and 8 at 30 mg/m², in short infusion over 6 to 10 minutes and cisplatin on day 1 at 100 mg/m² in 250 ml of normal saline infused over at least one hour. All patients were given hydration and antiemetic therapy according to accepted clinical practice. Chemotherapy was repeated every 4 weeks. For cases in which the absolute neutrophil count was less than 1.5×10^9 /l or/and platelet

Table I. Patient characteristics.

	No.	%
Entered in study	42	100
Age (years)		
Median	46	
Range	26 - 72	
Histology		
Squamous cell carcinoma	42	100
Stage of disease		
III A	1	2.4
III B	34	81
IV A	3	7.1
IV B	4	9.5

Table II. Efficacy.

	n	ITT (42 pts) %	Evaluable (37 pts) %
Complete response	3	7	8.1
Partial response	21	50	56.7
Objective response	24	57	64.8
Stable disease	8	19	21.6
Progressive disease	5	12	13.5
Non-evaluable patient	5	12	-

count was less than $75 \times 10^9/l$, chemotherapy was postponed by 1 week with respect to the treatment schedule. If treatment could not be given after a 3-week interval because of haematological toxicity, the treatment was discontinued. In case of WHO grade 2 neurological toxicity, vinorelbine was delayed for 1 week; if this toxicity persisted for more than 3 weeks or in the case of grade 3 toxicity, the treatment was discontinued. In case of WHO grade 3 hepatic toxicity the treatment was postponed by 1 week, while with grade 4 or persistence of grade 3 for more than 3 weeks, the treatment was discontinued. For cases in which creatinine clearance was between 40 and 60 ml/minute, the cisplatin dose was reduced by 50%, if the creatinine clearance was <40 ml/min, the cisplatin dose administration was delayed, and if still at the same level after 2-week delay, the patient was excluded from the study.

Toxicity was evaluated according to WHO criteria (21). Haematological assessment including complete blood count (CBC); WBC differential and platelet count on day 1 and day 8. Serum chemistry analysis (ASAT/ALAT, LDH, serum creatinine, electrolytes and calcium) was done on day 1 of each course.

Objective responses were evaluated according to WHO criteria (21) every 2 cycles of chemotherapy by repeating the staging procedures performed at entry, including pelvic magnetic resonance imaging. Confirmation of response was established after 4 weeks.

Table III. Survival.

	Months	
Median duration of response	17.5	(2.5 - 57)
Median time to progression	13.2	(0.4 - 57)
Median survival	20.6	(0.4 - 55)

Responding patients were treated for a maximum of 6 cycles of chemotherapy, or until progression or unacceptable toxicity occurred.

If a patient had stable disease (SD) after the first assessment, the investigator was free to decide whether or not to continue the same combination.

The objective response rate (ORR) was the main endpoint criteria for the efficacy of this regimen and was conducted on the whole study population.

Statistical analysis. The study was a non-randomized phase II study in which an overall response rate (complete response + partial response) of 21% or greater would be clinically significant. The study was conducted in 2 stages using Fleming tests (22); Survival time was measured from the start of treatment to death or loss to follow-up. The time to progression was defined as the time elapsed from registration on the study until progression. Survival, time to progression and duration of response was calculated using the Kaplan-Meier method.

Results

Between April 1996 and November 1998, 42 patients were enrolled into the study. The patient characteristics are shown in Table I. The median patient age was 46 years (range 26-72 years); all patient had squamous tumours; 83.5% had clinical stage III and 16.5% had stage IV; no patient had had prior radiotherapy or surgery. Thirty-seven patients were evaluable for response and 40 for toxicity. Of the patients unassessable for response, one patient was lost to follow-up after day 1 of the first cycle; 2 patients died after the first cycle for reasons not related to treatment; one patient died after the second cycle due to renal failure, and one patient refused to continue chemotherapy after day 8 of the second cycle. In the total study population, there were 3 complete response (CR) (7%), 21 partial response (PR) (50%) and 8 stable disease (SD) (19%). The overall response (OR) rate (CR + PR) was 57%. In evaluable patients, overall responses were recorded in 24 patients (64.8%) including 3 (8.1%) CR (Table II).

The median duration of response was 17.5 months (range 2.5- 57 months). The median time to progression was 13.2 months (range 0.4-57 months) and median survival was 20.6 months (range 0.4-55 months) (Table III).

Table IV. Haematological toxicity according to WHO grade.

	WHO Grade (% of patients) n=42				
	0	1	2	3	4
Neutropenia	38	17	26	19	-
Anemia	26	17	45	12	-
Thrombocytopenia	88	10	-	2	-

Table V. Non-haematological toxicity according to WHO grade.

		WHO Grade (% of patients)				
		0	1	2	3	4
Nausea / Vomiting	(n=40)	5	10	35	45	5
Infection	(n=38)	42	26	21	8	3
Constipation	(n=38)	61	18	21	-	-
Creatinine	(n=36)	78	19	3	-	-
Peripheral neuropathy	(n=38)	84	11	5	-	-

A total of 171 courses were administered with a median number of 5 cycles per patient. Hematological toxicity was manageable; only WHO grade 3 neutropenia was observed in 19% of patients with 4 cases of grade 3/4 infection. Grade 3 anaemia was recorded in 12% of patients (Table IV). Non-haematological toxicity was mild; grade 3 nausea/vomiting was recorded in 50% of patients. Grade 2 peripheral neurotoxicity occurred in 5% of patients and was reversible (Table V).

Discussion

Despite an improvement in overall survival for cervical carcinoma, recurrent or metastatic disease remains incurable, and chemotherapy is only palliative at this stage. As yet, there is no evidence that cisplatin-based regimens increase survival compared to cisplatin single agent. Two randomised trials have compared cisplatin-based regimens to cisplatin alone; Omura *et al.* have compared cisplatin and ifosfamide *versus* cisplatin and dibromodulcitol *versus* cisplatin alone. They have shown that the cisplatin-ifosfamide combination produced a higher response rate and a longer progression-free survival than the other arms, however this was achieved at the cost of significantly greater toxicity without overall survival benefit (5). The second randomised study, reported by Vermorken *et al.*, compared cisplatin as single agent or in combination with bleomycin, vindesine and mitomycin. The highest response was in favour of the combination, but with no impact on survival (4). Therefore, it is essential to evaluate more active and less toxic new agents as single agents and in combination with cisplatin.

Vinorelbine as a single agent has been tested in advanced cervical carcinoma. Morris *et al.* reported the activity of weekly vinorelbine 30 mg/m² in 33 patients previously treated by radiation therapy for advanced or recurrent cervical carcinoma. The response rate in this study was 18% with an acceptable toxicity (18). Similar results have been confirmed by the EORTC Gynaecological Cancer Cooperative Group Study in radiotherapy pretreated patients (19). However, in non-pretreated patients vinorelbine produced a higher response rate of 45% (20). In our study, the combination of vinorelbine and cisplatin produced a 64.8% response rate in patients with a bulky disease. Similar outcomes have been reported by Pignata *et al.* In 50 stage IB-IVB patients treated with vinorelbine at 25 mg/m² on day 1 and day 8 and cisplatin 80 mg/m² on day 1 every 3 weeks, 64% responded. Moreover, impressive activity was observed in early stages, 81.4% of patients achieving objective responses (23). We agree that comparable results were obtained with other cisplatin-based regimens, however, we have to point out that the vinorelbine-cisplatin regimen was safe and manageable, which was not the case with other cisplatin-based regimens (24, 25). Data comparable to that reported by Pignata and our group were also obtained by Sineiro *et al.* using vinorelbine at 30 mg/m² on day 1 and day 8 plus cisplatin at 80 mg/m² on day 1 every 3 weeks in 20 cases of recurrent and metastatic cervical cancer (26).

In the present study, the disease free survival and median survival were 13.2 months and 20.6 months, respectively. These data are very encouraging, particularly at this stage of the disease.

This combination was well-tolerated; haematological toxicity was mild and no prophylactic growth factors were needed. Non-haematological toxicity was not significant and never caused therapy discontinuation. Nausea-vomiting episodes were quite frequent in these young patients but were of short duration and well-managed. Peripheral neurotoxicity was mild and reversible.

A combination of vinorelbine and cisplatin should be considered as an option therapy, with or without radiation therapy, for patients with advanced or metastatic cervical carcinoma.

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