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Phase II trial of vinorelbine in patients with advanced and/or recurrent cervical carcinoma: an EORTC Gynaecological Cancer Cooperative Group Study

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Abstract

The objective of this phase II study was to assess the efficacy and toxicity of vinorelbine administered as a single agent in the treatment of chemonaïve cervical cancer patients. 46 patients (41 eligible) with cervical cancer (epidermoid or adenocarcinoma) and measurable metastatic and/or recurrent disease localised outside irradiated areas were treated with weekly intravenous (i.v.) vinorelbine 30 mg/m^2 infused over 20 min. No prior chemotherapy was allowed. Median age was 53 years (range: 33–73), and performance status 1 (0–2). 31 patients (76%) had prior radiation therapy. There were 7 partial responders (17, 95% confidence interval (CI) 7–32) and 8 stable diseases (20%). Median duration of response was 5 months (4–11). Granulocytopenia was the major toxicity, with 47% of patients exhibiting grade 3 or 4 toxicity. Dose reduction and/or treatment delay was necessary in 28 patients (78%). Peripheral neuropathy reported in 10 patients was mild (grade 1 in 9 patients and grade 2 in 1 patient). In conclusion, single agent vinorelbine has moderate activity in recurrent or metastatic cervical cancer, but its reduced neurotoxicity warrants further study in combination with cisplatin.

Keywords: Cervical cancer; Vinorelbine; Phase II; Chemotherapy

1. Introduction

Cervical cancer is the second most common cancer among women worldwide [1] and the leading female cancer in developing countries. It is the second major cause of death in women. Surgery and radiation therapy are effective in most cases of cervical carcinoma. Nevertheless there remain a number of women with metastatic and/or recurrent disease, and/or with early-stage, high-risk disease who need an effective chemotherapy. Unfortunately, reviews of single agent studies have stressed the low activity and the generally short duration of response with such agents [2,3]. Cisplatin is the most active single agent, showing a range of 21–31% response rate when used in first-line chemotherapy and approximately 10% of these responses are complete [2].

Vinca alkaloids represent a family of closely related molecules including vincristine, vindesine and vinblastine. Up to 30% response rates have been reported with vinca alkaloids in patients with minimal or no prior chemotherapy [4], but at a cost of high neuro and/or haematological toxicity [4,5]. In addition, some studies showed rather low response rates or no response [6,7].

Vinorelbine (Navelbine®, Pierre Fabre Medicament, Boulogne, France) is a semi-synthetic vinca alkaloid, which differs from other vinca alkaloids by a modification

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of the catharanthine moiety [8]. The mechanism of action of vinorelbine is similar to that of other vinca alkaloids, i.e. disruption of microtubules by their reversible binding to tubulin, resulting in mitotic spindle dissolution and metaphase arrest in dividing cells [9]. The inhibition of tubulin polymerisation with vinorelbine is equal to or greater than that obtained with vincristine or vinblastine. Moreover the induced spiralisation is lower. Vinorelbine is equally active on mitotic microtubules and less active on axonal microtubules of the tectal plate of mouse embryos than vincristine and vinblastine. This suggests a better efficacy/toxicity ratio and consequently an improved therapeutic index [10] compared with both vinblastine and vincristine. The limiting toxicity of weekly vinorelbine is neutropenia, which is reversible, non-cumulative and of short duration.

Vinorelbine was assessed in a series of phase I studies. With a weekly schedule at 35 mg/m^2/week, the limiting toxicity was neutropenia and some neuropathies were documented. Further studies confirmed these data and permitted a dose of 30 mg/m^2/week to be recommended for phase II studies [11]. More recent dose-finding studies using a 3-weekly schedule reported a maximum tolerated dose (MTD) of 45 mg/m^2. Dose-limiting toxicities were neutropenia and constipation [12].

A number of phase II and phase III trials have shown that vinorelbine is highly effective in the management of advanced breast cancer and non-small cell lung cancer (NSCLC). Antitumour activity has also been demonstrated in head and neck cancer, oesophageal cancer and malignant lymphomas [11].

Based on these data, the EORTC Gynaecological Cancer Cooperative Group (GCCG) initiated a phase II study of vinorelbine as a single agent in chemonaïve patients with advanced or recurrent cervical carcinoma.

2. Patients and methods

This protocol was designed to determine the antitumour activity, the response rate, the duration of response and the tolerance of vinorelbine in cervical cancer. Patients entering the study were required to have histologically proven cervical carcinoma (both squamous cell carcinoma and adenocarcinoma) and evidence of advanced and/or recurrent measurable disease outside previously irradiated areas. No prior chemotherapy was allowed. Other eligibility criteria were: age between 18 and 75 years, performance status $\leqslant 2$, an expected survival of $\geqslant 3$ months; white blood cell (WBC) count: $\geqslant 4.0\times10^9$/l, platelet count $\geqslant 100\times10^9$/l; serum creatinine concentration $\leqslant 200$ μmol/l and bilirubin level <25 μmol/l. All patients entering the study gave informed consent according to the regulations followed in the individual's participating institutions and countries.

Exclusion criteria were: brain or leptomeningeal involvement, concomitant neurological impairment, history of other malignancies (except adequately treated basal cell carcinoma of the skin), poor medical risk due to non-malignant systemic disease or uncontrolled infection, expected difficulty with follow-up and bone lesion or serious effusions as single tumour response parameter.

Pretreatment evaluation included: a history and physical examination, assessment of performance status (WHO (World Health Organisation)/ECOG), clinical tumour measurements, complete blood cell count and differential, measurement of creatinine, electrolytes, bilirubin, alkaline phosphatase, SGOT, gamma glutamyl transferase as well as chest X-ray and imaging studies necessary for the assessment of indicator lesion(s) and bone scans (if indicated).

2.1. Treatment

Treatment consisted of weekly administration of 30 mg/m^2 of vinorelbine diluted in 125 ml of normal saline solution, infused intravenously (i.v.) over 20 min and followed by venous washing with 125 ml of normal saline. Antiemetic drug therapy was administered during the treatment when necessary. Clinical and haematological toxicities (total and differential WBC) were assessed weekly and biological hepatic and renal tolerance every 4 weeks.

The dose schedule was modified as follows: treatment was delayed for 1 or more weeks until blood cell recovery (WBC $\geqslant 3.0\times10^9$/l; platelets $\geqslant 100\times10^9$/l). Further treatment was continued at a dose of 25 mg/m^2/week only in case of WHO grade 3 or 4 toxicity for myelotoxicity. A maximum of delay of 3 weeks was permitted, but beyond this the treatment was stopped and the patient was taken off the study because of toxicity. If neurotoxicity occurred (neurosensory toxicity and/or muscular weakness) the vinorelbine dose was reduced by 25 or 50% if neurosensory toxicity was moderate or severe, respectively. Treatment was withheld in case of moderate muscular weakness or obviously proprioceptive neurotoxicity (including grade 3 or 4 constipation). Because the vinorelbine is metabolised and excreted by the liver, doses were reduced by 50% if bilirubin was 25–50 μmol/l and by 75% in cases where bilirubin was >50 μmol/l. No dose modifications were necessary for renal dysfunctions.

Patients who had received at least four injections of vinorelbine were assessable for response. All patients who received at least 1 injection were assessable for toxicity. Assessment of response was performed according to WHO criteria [13]. The overall evaluation of response, including measurable and non-measurable manifestations with clinical and imaging procedures, was performed after every four vinorelbine administrations. Complete response (CR) and partial response (PR) had to be

confirmed by the same procedures not less than 4 weeks apart. The duration of CR was dated from the first observation until the documentation of progression; the duration of PR and overall response were determined from the date of first administration of vinorelbine until the documentation of progression. Survival was calculated from the beginning of vinorelbine treatment.

In cases of CR or PR, treatment was continued until progression or unacceptable toxicity. Vinorelbine was discontinued in cases of progression after four injections or stable disease (SD) after eight injections.

To define the number of patients required to detect activity of the treatment, we used the sequential two-step statistical test of Gehan [14]. Duration of response and survival were calculated by the Kaplan–Meier method [15].

The protocol was approved by the EORTC protocol review committee and the study was drawn up according to the ''Declaration of Helsinki, Tokyo, Venise'', and the law and regulations of the country which provided the greatest protection of individual.

3. Results

Between March 1991 and May 1994, 46 patients were registered in 14 centres in Europe and Argentina. 5 patients were ineligible (11%) because of: no measurable lesion present at entry (2 patients), prior irradiation of all marker lesions (1 patient), treatment started 47 days before registration (1 patient), and locally advanced disease (1 patient). The 41 remaining patients (89%) were eligible.

The pretreatment characteristics of the eligible patients are listed in Table 1. With the exception of one patient who received low doses of cisplatin administered concomitantly with radiotherapy, no patients had received prior chemotherapy for advanced disease.

A total of 319 courses of therapy (median: 7 (1–27)) were administered to the 41 eligible patients. 28 patients (78%) out of 36 patients who had received vinorelbine for at least 2 weeks had at least one treatment delay. For 7/28 patients a dose reduction was also reported, so a dose reduction was necessary in 7/36 patients (19%), in relation to prior radiotherapy. For 28 patients (78%) a dose reduction, which in 6 cases was due to haematological toxicity. 4/6 of them had received prior radiotherapy. The reason was haematological toxicity in 25 of these patients. Prior radiotherapy was reported in 21/28 patients (75%). Finally, only 8 patients (22%) were treated without treatment delay and/or dose modification. 6 of them (75%) received prior radiotherapy.

Antiemetic therapy was used in 26 patients (63%): prophylactically for 20 patients, symptomatically for 3 and both for 3 patients. In 14 patients (34%) no antiemetic treatment was reported and in 1 the information was not specified. Treatment was discontinued for progressive disease in 26 patients (63%), treatment refusal in 4 (10%), excessive toxicity in 3 (7%), protocol violation in 1, and other causes in 5 patients, while 2 patients were lost to follow-up. No toxic deaths were reported.

Table 2 summarises the antitumour activity of vinorelbine for all eligible and evaluable patients. The response rate in the 41 eligible patients was 17% with a 95% confidence interval (CI) ranging from 7 to 32%. Amongst 8 patients for whom the response could not be evaluated, 2 refused the tumour evaluation and further treatment, 1 had incorrect tumour evaluation and for 5 patients treatment was stopped at the latest after the

Table 1
Pretreatment characteristics of the eligible patients

	n
Entered	46
Eligible	41
Median age (range)	53 (33–73) years
	n (%)
Performance status	
0	10 (24)
1	22 (54)
2	9 (22)
Histology	
Adenocarcinoma	6 (15)
Epidermoid	33 (80)
Unknown	2 (5)
Prior radiotherapy	
No	10 (24)
Yes	31 (76)
Number and localisation of marker lesions	92 (100)
Primary tumour/recurrence	9 (10)
Lymph nodes	35 (38)
Lung	27 (29)
Liver	11 (12)
Other soft tissue	3 (3)
Other	7 (8)

Table 2
Response rate (41 eligible patients) (intent to treat basis)

WHO response	Total	
	n	(%)
PR	7	(17)
SD	8	(20)
PD and early PD	15	(37)
Early death (malignant disease)	2	(5)
Early death (other causes)	1	(2)
Inevaluable	8	(20)
Overall response rate (%)		
Eligible patients ($n=41$) (WHO)	17	95% CI: 7–32
Fully assessable patients ($n=33$)	21	95% CI: 7–35

95% CI, 95% confidence interval; PR, partial responders; PD, progressive disease; SD, stable disease; WHO, World Health Organisation.

Table 3
Tumour response by site of tumour localisation[a] (evaluation based on marker lesion localisation only)

Tumour localisation	Response					Response rate by site (%)
	CR	PR[b]	SD[c]	PD	Inevaluable	
Primary tumour/recurrence	0	1	2	1	5	1/4 (25)
Lymph nodes	7	2	9	7	10	9/25 (36)
Lung	2	8	12	0	5	10/22 (45)
Liver	0	1	3	4	3	1/8 (13)
Other soft tissue	0	0	2	1	0	0/3
Other	3	0	0	3	1	3/6 (50)

CR, complete response; PR, partial response; PD, progressive disease; SD, stable disease.
[a] 41 eligible patients.
[b] Including CR not confirmed by the second measurement.
[c] Including PR not confirmed by the second measurement.

third cycle (week) without further response assessment. In the 33 fully assessable patients, the objective response rate was 21% (95%: CI 7–35). Table 3 presents the tumour response by tumour site of localisation, based on marker lesion analysis.

Median duration of response was 5 months (range 4–11 months). Median time to progression was 2.6 months for all eligible patients.

On the day of the last follow-up (February 1995) information was received, 13 patients had died (32%) and 25 were alive (61%) (3 were lost to follow-up). 11 patients had died because of disease progression, 2 for unknown reasons (14 days after registration for 1 patient).

Haematological and non-haematological toxicity analysis amongst all eligible patients is presented in Table 4. Granulocyte nadir values varied from 0.2 to 7.1×10^9/l (median 1.1). The 2 patients with grade 3 other non-haematological toxicity had thrombosis of a pelvic artery and epigastric pain, respectively. No late side-effects were reported.

Table 4
Toxicity and side-effects during treatment (41 eligible patients)

Toxicity	WHO grading					Grade 3–4
	0	1	2	3	4	*n* (%)[a]
Haematological[b]						
Leucocytes	5	2	15	13	4	17 (44)
Granulocytes	7	3	9	8	9	17 (47)
Platelets	36	1	2	0	0	0
Haemogloblin	14	7	9	6	3	9 (23)
Haemoglobin[c]	14	6	4	3	2	5 (17)
Non-haematological[d]						
Nausea/vomiting	20	10	5	2	0	2 (5)
Alopecia	23	6	6	1	0	1 (3)
Local reaction	27	6	2	1	0	1 (3)
Drug fever	35	0	1	1	0	1 (3)
Neurotoxicity	27	9	1	0	0	0
Diarrhoea	27	5	3	0	0	0
Infection	29	2	4	0	0	0
Mucositis	31	4	2	0	0	0
Bone pain	32	2	1	0	0	0
Cutaneous reaction	33	2	1	0	0	0
Renal toxicity	32	1	1	0	0	0
Liver toxicity	32	1	1	0	0	0
Pulmonary toxicity	35	1	0	0	0	0
Cardiotoxicity	35	1	0	0	0	0
Other toxicities	16	7	8	2	0	2 (6)

[a] % of patients with available data for each toxicity.
[b] Evaluated for 39 patients with at least one laboratory value reported after treatment start.
[c] Evaluated for 29 patients with initial haemoglobin value >6.6 mmol/l.
[d] Evaluated for 41 eligible patients who received at least one cycle of vinorelbine treatment.

4. Discussion

Chemotherapy for patients with metastatic or recurrent cancer of the uterine cervix is in most instances merely given for palliative reasons. At present, there is no indication that aggressive combination chemotherapy regimens given to such patients are superior to the most active single agent, cisplatin, in terms of survival [16,17].

Therefore, single agent cisplatin has generally been accepted as a reasonable standard therapy to palliate such patients [18]. In that setting, cisplatin i.v. to chemonaive patients at a dose of 50–100 mg/m^2 every 3 weeks induces 20–30% objective responses of short duration (range: 3.9–4.8 months) and leads to a median survival of approximately 7 months [19]. It is, therefore, essential to study further new agents in such patients, and in particular to look for more tolerable and less toxic drugs.

Vinca alkaloids have been used in many combination chemotherapy regimens for cervical cancer. Data on vincristine as a single agent has been controversial [20–22] and data on vinblastine were disappointing [6,23].

Vindesine showed more promise in two phase II studies using i.v. bolus schedules [4,5]. Response rates varied from 17 to 30%. However as we observed in the EORTC-GCCG study dose-limiting toxic effects were not only leucopenia, but also peripheral neuropathy. In fact, neurotoxicity was observed in 39% of patients, and was severe in 7% of these patients. Vinorelbine evaluated in the present series seems to have a comparable moderate activity (response rate = 17% in all eligible patients, 21% in the fully assessable patients and 20% of stable disease in the 41 eligible patients) in similar patients, i.e. those metastatic and/or recurrent disease outside previously irradiated areas. Moreover, the drug was reasonably well tolerated, i.e. grade 3 or 4 non-haematological toxicity was rare.

In the present study vinorelbine was given in a weekly regimen. Our results, i.e. moderate activity and good tolerance are in agreement with those of others using the same schedule [24]. The advantage of vinorelbine appears to be the lower rate of disabling neurotoxicity. This reduced neurotoxicity will enable us (and others) to study combinations with other active agents in the treatment of this disease, in particular cisplatin.

The most appropriate clinical situation to test whether such a combination is superior over cisplatin alone is either in patients with only lung or lymph node metastases and no locoregional recurrence or in untreated patients, i.e. in the neoadjuvant setting. In the latter setting a very promising response rate (45%) has been reported by Lacava and colleagues [25], again without serious non-haematological toxicity. Therefore in both settings it seems worthwhile to study the combination of vinorelbine with cisplatin.

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