# The Study of Cisplatin and Vinorelbine in Metastatic Uterine Cervical Cancer

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***Objective:*** *To determine the therapeutic efficacy of cisplatin in combination with vinorelbine in the treatment of patients with metastatic cervical cancer.*
***Material and Method:*** *a total of 17 patients were enrolled in the present study. The median age was 46 years (38-65). There were 6 patients who were diagnosed as stage IVB cervical cancer without previous treatment. The patients were planned to receive cisplatin 80 mg/m$^2$ on day 1 and vinorelbine at 30 mg/m$^2$ on day 1 and 8 every 3 weeks.*
***Results:*** *Fifteen patients were available for evaluation: 2 (13.3%) achieved a complete response, 8 (53.4%) partial responses, 3 (20%) stable diseases and 2 (13.3%) progression of the disease. Myelosuppression was the major toxicity. Grade 3-4 toxicities include 66.7% hemoglobin and 26.7% neutropenia. No other significant side effects were found.*
***Conclusion:*** *Cisplatin-vinorelbine is an active and well-tolerated regimen in metastatic cervical carcinoma. These results require confirmation.*

***Keywords:*** *Uterine cervical neoplasms, Cisplatin, Vinblastine, Vinorelbine*

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Cervical cancer is the leading female cancer in developing countries and the second most common female malignancy worldwide[1]. It is the second major cause of death in women. Surgery and radiation therapy are effective in the majority of the cervical cancer patients. However, there remain a number of women with recurrent and/or metastatic disease, and/or with high-risk disease in early-stage, who need effective chemotherapy. 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[3], but relatively high neuro and/or hematological toxicity[4]. In addition, some clinical studies showed rather low response rates or no response[5,6].

Vinorelbine is a semi-synthetic vinca alkaloid, which differs from other vinca alkaloids by a modification of the catharanthine moiety[7]. 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[8]. The inhibition of tubulin polymerisation with vinorelbine is equal to or greater than that obtained with vincristine or vinblastine. Moreover, the induced spiralization 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. 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

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studies[9]. 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[10].

Based on these data, the Division of Therapeutic Radiology and Oncology, Faculty of Medicine, Chiang Mai University initiated a phase II study of vinorelbine in combination with cisplatin in patients with metastatic or recurrent cervical carcinoma.

## Material and Method

The present study was designed to determine the response rate, the duration of response and the tolerance of vinorelbine in combination with cisplatin in cervical cancer. Patients entering the study were required to have histologically proven cervical carcinoma (both squamous cell carcinoma and adenocarcinoma) and evidence of measurable metastatic and/or recurrent disease outside previously irradiated areas. No prior vinorelbine chemotherapy was allowed. Other eligibility criteria were: age between 18 and 75 years, performance status $\leq 2$, an expected survival of $\leq 3$ months; white blood cell (WBC) count: 4.0 x 10$^9$/l, platelet count 100 x 10$^9$/l; serum creatinine concentration 200 □mol/l and bilirubin level < 25 □mol/l. All patients entering the study gave informed consent.

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 tumor response parameter.

Pre-treatment evaluation included a history and physical examination, assessment of performance status (ECOG), clinical tumor measurements, complete blood cell count, measurement of renal and liver functions as well as chest X-ray and imaging studies necessary for the assessment of indicator lesion(s).

### *Treatment*

Patients in the clinical study received 80 mg/m$^2$ of cisplatin on day 1 and 30 mg/m$^2$ of vinorelbine on days 1 and 8 (cycles repeated every 3 weeks) for a maximum of 6 cycles. Vinorelbine was diluted in 50 ml of normal saline solution, infused intravenously within 5 minutes and followed by venous washing with 250 ml of normal saline. Antiemetic drug therapy was administered before the treatment as the prophylaxis. Patients received the assessments with respect to clinical examination, hematological analysis, and tumor evaluation.

The dose schedule was modified as follows: treatment was delayed for 1 or more weeks until blood cell recovery (WBC 3.0 x 10$^9$/l; platelets 100 x 10$^9$/l). Further treatment of vinorelbine was continued at a dose of 25 mg/m$^2$/dose and 15% reduction of cisplatin dosage 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. Patients who had received at least 2 cycles of chemotherapy were assessable for response. All patients who received at least 1 cycle were assessable for toxicity. Assessment of response was performed according to WHO criteria[11]. The overall evaluation of response, including measurable and non-measurable manifestations with clinical and imaging procedures, was performed after 3 cycles of chemotherapy. Complete response (CR) 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 partial response (PR) and overall response were determined from the date of the first administration of chemotherapy until the documentation of progression. Survival was calculated from the beginning of the treatment. In cases of CR or PR, treatment was continued to the maximum of 6 cycles and discontinued in cases of progression or unacceptable toxicity. Duration of response and survival were calculated by the Kaplan-Meier method[12].

## Results

Between January and August 2006, 17 patients were registered into the present clinical study. The median age was 46 years (38-65). Prior to the study entry, 7 patients were treated with radiochemotherapy, 3 patients were treated with radiation alone and one patient was treated with chemotherapy alone. There were 6 patients who were diagnosed as stage IVB cervical cancer without previous treatment. The sites of metastases were 7 in the para-aortic lymph nodes, 5 in the supraclavicular lymph nodes, 2 in liver, 1 in the lungs, 1 in the inguinal lymph node and 1 in the sacral bone. The pretreatment characteristics of the eligible patients are listed in Table 1. No patients had received prior vinorelbine chemotherapy for advanced disease.

A total of 71 cycles of therapy (median: 4 (1-6)) were administered to all patients. Fifteen patients (88.2%) out of 17 patients received chemotherapy for

**Table 1.** Pretreatment characteristics of the eligible patients

| Characteristics | Total n = 17 | (%) |
|---|---|---|
| Age, years | | |
| Median | 46 | |
| Range | 38-65 | |
| ECOG PS | | |
| 0 | 7 | 41.1 |
| 1 | 8 | 47.1 |
| 2 | 2 | 11.8 |
| Metastatic site (s) | | |
| Para-aortic lymph nodes | 7 | 41.1 |
| Supraclavicular lymph nodes | 5 | 29.4 |
| Liver | 2 | 11.8 |
| Lungs | 1 | 5.9 |
| Inguinal lymph nodes | 1 | 5.9 |
| Sacral bone | 1 | 5.9 |
| Previous treatments as first line | | |
| Concurrent radiochemotherapy | 7 | 41.1 |
| Radiotherapy alone | 3 | 17.6 |
| Chemotherapy alone | 1 | 5.9 |
| None | 6 | 35.4 |
| Previous treatment as second line | | |
| Chemotherapy | 4 | 23.5 |
| Histopathology | | |
| Squamous cell carcinoma | 15 | 88.2 |
| Adenocarcinoma | 2 | 11.8 |

Note: ECOG PS, Eastern Cooperative Oncology Group performance status

at least 3 cycles. For 7/17 patients experienced at least one dose delay, showing that a delayed dose was necessary in 41.1%, in relation to prior definitive concurrent radiochemotherapy. The reason for 7 patients (41.1%), who had a delayed dose, was due to hematological toxicity and all of them had received prior radiotherapy plus chemotherapy. Ten patients (58.9%) were treated without treatment delay and/or dose modification. Three of them (17.6%) received prior radiotherapy alone and 1 patient received prior chemotherapy. Treatment was discontinued for progressive disease in 2 patients (11.8%) and for treatment refusal in 2 patients (11.8%). No toxic deaths were reported.

Table 2 summarizes the anti-tumor activity of this regimen for all and evaluative patients. The response rate (CR+PR) in the 17 eligible patients was 58.8%. Amongst 2 patients for whom the response could not be evaluated, both refused further treatment after 1 and 2 cycles, respectively. In the 15 fully assessable patients, the objective response rate (CR+PR) was 66.7%.

Hematological and non-hematological toxicity analysis amongst all eligible patients is presented in Table 3. Grade 4 anemia and neutropenia were reported in 4 (23.5%) and 3(17.6%) patients, respectively, while Grade 3 anemia and neutropenia were reported in 5 (29.4%) and 1(5.9%) patients, respectively. The 2 patients with grade 3 other non-hematological toxicities had significant fatigue and refused to receive further chemotherapy. No late side-effects were reported.

With a median follow-up time of 10.4 months (0.9-23.3 months), the authors found the median time to progression of 6.6 months (1.2-22.6 months) and the median overall survival time of 18.9 months (1.2-23.3 months) (Fig. 1, 2).

**Table 2.** Response rates of the treatment

| Response | n (%) |
|---|---|
| Evaluable patients (n = 15) | |
| Complete response (CR) | 2 (13.3) |
| Partial response (PR) | 8 (53.4) |
| Stable disease (SD) | 3 (20.0) |
| Progression of disease (PD) | 2 (13.3) |
| Intention to treat basis (n = 17) | |
| CR | 2 (11.8) |
| PR | 8 (47.0) |
| SD | 3 (17.6) |
| PD | 2 (11.8) |
| Not evaluable (NE) | 2 (11.8) |

**Table 3.** Toxicity and side-effects during treatment (17 eligible patients)

| Toxicities: | Grade 2 | % | Grade 3 | % | Grade 4 | % |
|---|---|---|---|---|---|---|
| Haematological toxicities | | | | | | |
| Anemia | 4 | 23.5 | 5 | 29.4 | 4 | 23.5 |
| Neutropenia | 4 | 23.5 | 1 | 5.9 | 3 | 17.6 |
| Thrombocytopenia | 0 | 0 | 0 | 0 | 0 | 0 |
| Febrile neutropenia | 0 | 0 | 0 | 0 | 0 | 0 |
| Nonhaematologic toxicities | | | | | | |
| Fatigue | 7 | 41.7 | 2 | 13.3 | 0 | |
| Nausea/Vomiting | 3 | 17.6 | 0 | | 0 | |
| Alopecia | 12 | 70.6 | 0 | | 0 | |
| Constipation | 3 | 17.6 | 0 | | 0 | |
| Renal | 1 | 5.9 | 0 | | 0 | |
| Liver | 0 | | 0 | | 0 | |

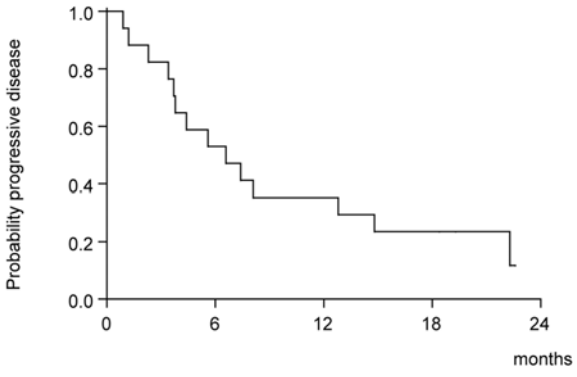


**Fig. 1** The time to progression curve

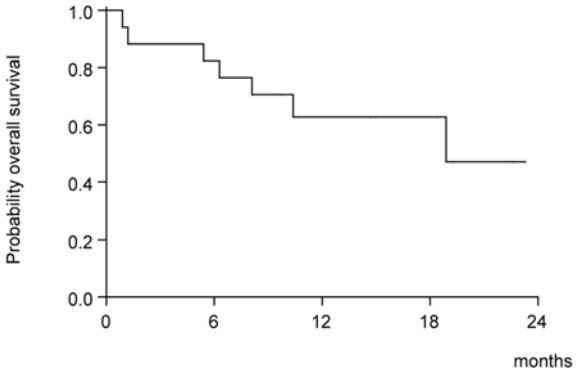


**Fig. 2** The overall survival curve

## Discussion

Systemic chemotherapy for patients with metastatic or recurrent cervical cancer is in most circumstances prescribed for palliative goals. At present, there is no definite indication that aggressive combination chemotherapy regimens administered to the patients are superior to the most active single agent, cisplatin, in terms of survival[13,14]. Therefore, single agent cisplatin has generally been accepted as an appropriate treatment to palliate these patients[15]. In that situation, intravenous cisplatin administered to chemonaive patients at a dose of 50-100 mg/m$^2$ every 3 weeks yields 20-30% objective responses of short duration (range: 3.9-4.8 months) and demonstrates a median survival time of approximately 7 months[16]. It is, therefore, necessary 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[17-19] and data on vinblastine were disappointing[5,20]. The appropriate clinical situation to study 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 neo-adjuvant setting, which has been reported by Lacava et al, yields a very promising response rate (45%)[21], without severe non-hematological toxicity.

In the present study vinorelbine was given in a 3-weekly regimen, dividing into days 1 and 8. The present results show moderate activity with a major response rate of 58.8% and relatively good tolerance. The combination of cisplatin and vinorelbine has been shown to provide a significant improvement in response rates, with acceptable toxicity, compared with either single agent in patients with non-small-cell lung cancer[22-24]. This combination has been studied in the phase II setting in patients with untreated cervix cancer and was found to have an overall response rate of 64%[25]. In a similar trial, patients whose uterine cervix cancer recurred within the radiated field had a response rate of 28%, and those with no prior radiation or recurrence outside of the pelvis had an overall response rate of 57%[26].

While more aggressive dosing might have yielded better response rates, patients with advanced cervical cancer often tolerate the drugs less well than other patient populations because of previous radiation and predisposition to some bladder and bowel complications. The present study reports the 41.1% of delayed dosing in 7 patients, who received prior definitive concurrent radiochemotherapy, due to hematological toxicity. The authors found the median time to progression of 6.6 months and the median overall survival time of 18.9 months with the median follow-up of 10.4 months. There are several clinical aspects and possibilities to study the combination of vinorelbine and cisplatin. The present phase II study demonstrated that this regimen is an active and well-tolerated regimen in metastatic cervical carcinoma. These results require confirmation in larger number of patients.

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## การศึกษายาเคมีบำบัดซีสพลาติน ร่วมกับไวโนเรลบีนในโรคมะเร็งปากมดลูกระยะแพร่กระจาย

**พิมพ์ขวัญ กำเนิดศุภผล, อิ่มใจ ชิตาพนารักษ์, เอกสิทธิ ธราวิจิตรกุล, วิมล สุขถมยา, วิชาญ หล่อวิทยา**

***วัตถุประสงค์:*** *เพื่อประเมินประสิทธิภาพของยาเคมีบำบัดซีสพลาตินร่วมกับยาไวโนเรลบีนในโรคมะเร็งปากมดลูกระยะแพร่กระจาย*

***วัสดุและวิธีการ:*** *ผู้ป่วยในการศึกษาจำนวน 17 คน โดยมีอายุเฉลี่ย 46 ปี (พิสัย 38-65 ปี) ชุดของการรักษา ผู้ป่วยจะได้รับยาซีสพลาติน 80 mg/m$^2$ ในวันที่ 1 ร่วมกับยาไวโนเรลบีน 30 mg/m$^2$ ในวันที่ 1 และ 8 ทุก 3 สัปดาห์*

***ผลการศึกษา:*** *ผู้ป่วยจำนวน 15 คน สามารถประเมินประสิทธิภาพการรักษาได้ มีการตอบสนองโดยรวม 10 คน (66.7%) ไม่ตอบสนองต่อการรักษา 2 คน (13.3%) ผลข้างเคียง ส่วนใหญ่เกิดจากภาวะการกดไขกระดูก พบภาวะซีด 66.7% ภาวะเม็ดเลือดขาวต่ำระดับ 3 ถึง 4 พบ 26.67%*

***สรุป:*** *ยาเคมีบำบัดซีสพลาตินร่วมกับไวโนเรลบีน มีประสิทธิภาพในการรักษามะเร็งปากมดลูกระยะแพร่กระจาย ซึ่งผู้ป่วยสามารถทนต่อการรักษาได้ดี*