RESEARCH COMMUNICATION

Efficacy of Cisplatin in Early Stage Cervical Cancer with a Long Waiting Period for Surgery

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Abstract

This study was undertaken as a prospective trial to evaluate the efficacy and safety of pre-operative cisplatin for controlling the tumor volume of stage IB-IIA cervical cancer patients whose schedule for radical surgery was longer than 3 weeks. Between June 2004 and July 2005, 42 patients were recruited to enter the study. Seventy-five mg/m^2 of cisplatin was administered for 1-2 courses. Cervical tumor volume was measured 1 day before chemotherapy and 1 day before the operation by using 3-dimensional ultrasound. Reduction of cervical tumor volume was noted in 76.2%of cases. The clinical stage, gross appearance of the tumor, histology and number of chemotherapy courses did not significantly affect chemo-responsiveness. The incidence of lymph node metastases was 16.3%. One patient experienced severe vomiting which could be controlled by ondansetron antiemetic. No severe hematologic or other non-hematologic toxicities were identified. In conclusion cisplatin is effective and safe for administration in a pre-operative setting for early stage cervical cancer patients whose surgical schedule is delayed more than 3 weeks.

Key Words: Cervical cancer - early stage - cisplatin - pre-operation

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Introduction

Patients with stage IB-IIA cervical cancer can be treated by either radical hysterectomy plus pelvic lymphadenectomy (RHPL) or radiation therapy with equivalence survival outcome (Landoni, et al.1997). In Chiang Mai University Hospital, surgical treatment is preferred because the ovarian function and vaginal pliability could be preserved (Abitbol, et al.1974). In addition, the duration of treatment is shorter compare with radiation therapy. Annually, this operation is performed in approximately 120-150 patients in our institute. Due to the large number of patients with this cancer and the limitation of the operative room, the surgical schedule after definite diagnosis is usually longer than 3 weeks. This long waiting period is similar for radiation therapy. Previous studies showed that chemotherapy in was effective in reducing cervical tumor size (Eddy, et al.1995., Serur et al.1997., Aoki, et al. 2001., Hwang et al. 2001., Manusirivithaya, et al. 2001.,Tierney J, 2003., Park, et al. 2004). However, these studies used combination chemotherapy which caused severe bone marrow toxicity. Since single cisplatin is efficacy in treatment of cervical cancer and has minimal bone marrow toxicity (Eifel, et al. 1997, Alberts, et al. 2005.,Randall, et al. 2005), this study was accordingly conducted in a prospective setting to evaluate the efficacy and safety of this agent in controlling or decreasing the cervical tumor size in patients with stage IB-IIA cervical cancer whose operative schedule was longer than 3 weeks.

Materials and Methods

From June 1, 2004 to July 31,2005, 157 patients with early stage cervical cancer were scheduled for RHPL at Chiang Mai University Hospital. Inclusion criteria were histological proven squamous cell carcinoma or adenocarcinoma, stage IB-IIA, no prior cervical conization or electrical loop excision, surgical schedule longer than 3 weeks, adequate bone marrow, renal and liver functions. Exclusion criteria were no gross tumor and refusal of chemotherapy. Eligible patients received counseling about preoperative cisplatin chemotherapy. Only patients who gave written inform consent were recruited to enter the study.

Cisplatin was intravenously infused at dosage of 75 mg/m^2 after 12- hours hydration. Premedication included ondansetron and dexamethasone as antiemetics. Furosemide was given as a diuretic. Cisplatin chemotherapy was repeated every 3 weeks if the operative schedule was longer than 35 days. Hematological profile, renal and liver function test were checked before chemotherapy and before the operation.

Cervical tumor volume was measured 1 day before chemotherapy and 1 day before the operation using 3-dimensional ultrasound system (Voluson 730 Pro, GE

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Table 1. Clinicopathological Data for the 42 Patients

Parameter		Number
Stage	IB1	27 (63.6%)
	IB2	10 (23.8%)
	IIA	5 (11.4%)
Mean age (range)		44 (33-62 years)
Gross appearance	Exophytic	25 (59.5%)
	Endophytic	16 (38.1%)
	Ulcerative	1 (2.4%)
Cisplatin	1 course	33 (79.1%)
	2 courses	9 (20.9%)
Interval from cisplatin to surgery (range)		33 (21-50 days)
Mean cervical tumor volume - cm^3 (range)		
	Before cisplatin	39.5 (10.2-90.2)
	After cisplatin	33.3 (5.98-89.5)
Histology	Squamous cell CA	31 (79.1%)
	Adenocarcinoma	11 (26.2%)
Mean number of nodes removed (range)		29 (12-57)
Number of node - positive patients		7 (16.3%)
Number of parametrium - positive patients		4 (9.5%)
Number of LVSI - positive patients		22 (52.4%)

LVSI = Lympho-vascular invasion

Medical System, USA). The whole cervical tumor was scanned in 3 dimensions via transvaginal probe. The scanner volume was stored digitally on a removable 560 MB magneto-optical hard disc for subsequent analysis. The measurement of cervical tumor volume for 3 dimensional ultrasound was carried out by retrieving the digitally store volume. Tumor circumference in each section was demarcated by moving a roller ball cursor starting from the tumor margin. Serial sections were taken by rotating the tumor axis view 6o each for 30 sections. The tumor volume was computed automatically from the measured surfaces and the distances between them. All the ultrasound measurements were performed by one of the authors (T.T).

The clinical data, the cervical tumor volume before and after chemotherapy, and the toxicity of chemotherapy were recorded. Statistical analysis of the data was carried out by the SPSS for Windows (version 10.0). Clinical variables between the decreased tumor volume group were compared with the increased tumor volume group by using the chi-square, T-test and Fisher's exact test. The differences were judged significant at p value of < 0.05. The study was conducted under approval of the Research Ethics Committee of Chiang Mai University Hospital.

Table 2. Clinicopathological Factors and Response to Cisplatin Chemotherapy

Factors		N	Tumor volume Decreased	Increased	P value
Stage	IB1	27	21	6	
	IB2	10	6	4	
	IIA	5	5	0	0.22
Type of lesion					
	Exophytic	25	18	7	
	Infiltrative	16	13	3	
	Ulcerative		1	1	0
0.68					
Histology	SSC	32	23	9	
	AC	10	8	2	1.00
Chemotherapy					
	1 cycle	32	25	7	
	2 cycles	10	8	2	1.00
Node	Positive	7	5	2	
	Negative	35	27	8	1.00
Status of parametrium					
	Positive	4	4	0	
	Negative	38	28	10	0.56
LVSI*	Positive	22	16	6	
	Negative	20	16	4	0.72

* LVSI = lymphovascular invasion

Results

During the studied period, 42 patients met the eligibility criteria. The clinicopathological characteristics of the patients are showed in Table 1. Nearly two-thirds of the patients had stage IB1 cervical cancer and 60% had exophytic tumor. Among 7 patients (16.3%) with pelvic node metastases, 4 and 3 patients had stage IB1 and stage IIA, respectively.

After cisplatin chemotherapy, reduction of tumor volume was noted in 32 patients (76.2%), the remaining 10 (23.8%) had increased tumor size. Clinical stage, gross appearance of tumor, histology, number of chemotherapy course, node and parametrium status and lympho vascular invasion did not significantly affect response to chemotherapy as shown in Table 2.

Figure 1 demonstrates the percentage of tumor volume change after chemotherapy. In the decreased tumor volume group, the maximum volume reduction was 30 cm3. Half of the patients had tumor size reduction between 20-50%. Two patients had tumor volume decreased more

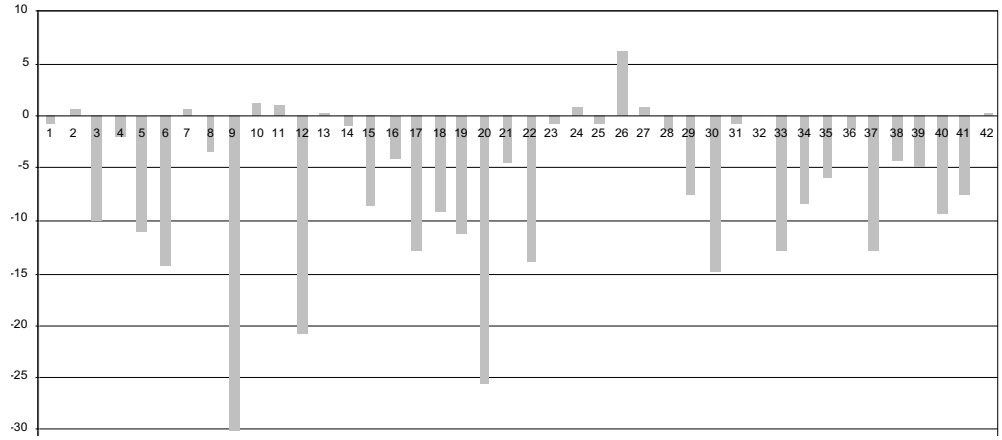

Figure 1. Percentage Change in Tumor Size after Chemotherapy

than 50%. One with stage II A cervical cancer had initial tumor volume 29.85 cm3 and decreased to 8.95 cm3. The other one was in stage IB1 cervical cancer, the tumor volume was reduced from 24.88 cm3 to 10.72 cm3. Both patients had exophytic tumors received 2 courses of cisplatin chemotherapy. Surgical pathology showed negative pelvic nodes in both patients. Among the 10 patients with increased tumor size, the volume changed was in a range of 0.07-6.39 cm3 or 1.99-13.79%.larger from the initial tumor size. Two patients (20%) in this group had pelvic node metastases and none had parametrial involvement. Only 1 patient experienced severe vomiting which could be controlled by additional intravenous ondansetron. No severe hematologic and other non hematologic toxicities occurred.

Discussion

This study shows that cisplatin chemotherapy is effective in controlling or delaying tumor growth and can be safely administered in early stage cervical cancer patients who have long waiting period for surgical treatment. About three-fourth of patients had decreased tumor volume after cisplatin chemotherapy. Despite an increase of tumor volume, the incidence of pelvic node metastases in these patients (20%) is not significantly higher than that of 15% in patients with decreased tumor volume. Overall, the incidence of positive nodes (16%) in this study is in the range of 15-30% of those reports in the literature (Landoni, et al. 1997, Eifel, et al.1997., Randall, et al. 2005.)Previous studies showed that chemotherapy given in an neoadjuvant setting was highly effective in cervical cancer with response rate (complete and partial responses) of 80-95% (Zanetta, et al. 1998, Aoki, et al. 2001.,Duenas-Gonzalez, et al. 2001.,Termrungruanglert, et al. 2005).

These studies differed from our study which showed response rate of only 4.7% when using WHO response criteria. The discrepancy may be caused by different course and number of chemotherapeutic agents. In our study, only single cisplatin was given for 1-2 cycles, while combination cisplatin-based chemotherapy, e.g. gemcitabine, ifosfamide, paclitaxel, and bleomycin was administered for 2-3 cycles in the other studies (Zanetta, et al. 1998, Aoki, et al. 2001.,Duenas-Gonzalez, et al. 2001.,Termrungruanglert, et al. 2005).

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In addition, the purpose of the study was also different. The aim of chemotherapy administration in our study was to control or delay tumor progression in patients whose surgical schedule was deferred, while the aim of chemotherapy in the previous studies was to down the clinical stage to improve operability. In our study using single cisplatin preoperatively, stable disease could be achieved as high as 95% and most of the patients showed a decrease in tumor volume.

Single cisplatin chemotherapy is quite safe and inexpensive. No severe hamatologic and non-hematologic toxicities except for severe vomiting were found in our study. In combination of cisplatin and gemcitabine chemotherapy given in neoadjuvant setting, grade 3 or 4 neutropenia, anemia, and thrombocytopenia were observed in 18.5%, 7.4%, and 3.7% of patients, respectively (Termrungruanglert, et al. 2005) .

Cervical tumor volume estimation by 3 – dimensional ultrasound has shown that the true volume of cervical cancer can be measured with high accuracy (Chou, et al.1997) . We used this technique to evaluate the cervical tumor volume before and after administration of cisplatin chemotherapy. We believed that this technique would most likely decrease the error of measurement in our study.

Benedetti - Panici et al reported among cervical cancer patients who received neoadjuvant chemotherapy before radical surgery, larger tumor size (more than 5 cm.) was most likely to respond to chemotherapy (Panici, et al. 1991). In our study, no clinicopathologic variable was a significant predictor for chemoresponsiveness of cervical cancer. However, this might be from small number of patients, fewer cycles, numbers, and types of chemotherapeutic agents.

Some others reported the lower incidence of lymph node metastases in patients receiving neoadjuvant chemotherapy (Panici, et al. 1991, Eddy et al., 1995). However, a study from Chiang Mai University Hospital showed that the incidence of pelvic node metastases was similar at 16% in cervical cancer patients who received and did not received neoadjuvant chemotherapy (Manusirivithaya, et al. 2001). This figure was also identical with this study.

The limitations of this study were the small number of patients and no comparison with patients who did not receive chemotherapy. The operability and survival analysis were not carried out to evaluate the benefit of cisplatin chemotherapy in cervical cancer patients whose surgical schedule was delayed. Furthermore, the sonographic tumor size was not compared with the actual pathologic tumor size.

In conclusion, cisplatin chemotherapy can be used effectively and safely to delay tumor progression in stage IB-IIA cervical cancer patients who have long waiting period for surgical treatment.

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