Randomized Comparison of Fluorouracil Plus Cisplatin vs. Cisplatin as an Adjunct to Radiation Therapy in Stage IIB- IVA Squamous Cell Carcinoma of the Cervix: Pilot Study

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Objective: *To compare the efficacy and toxicity of pelvic radiotherapy with concomitant cisplatin plus fluorouracil versus cisplatin alone in patients with locally advanced squamous cell cervical cancer.*
Material and Method: *Twenty women with squamous cell cervical cancer were randomly assigned to receive ether standard whole pelvic radiotherapy with concurrent cisplatin and fluorouracil infusion every 4 weeks or the same radiotherapy with concurrent cisplatin every 1 week. The primary end point was the response rate.*
Results: *All patients in cisplatin plus fluorouracil regimen and in cisplatin regimen had complete response. In cisplatin group there was higher frequencies of adverse hematologic effects. Grade 3 or 4 neutropenia occurred in 10% of the cisplatin plus fluorouracil group and in 40% of the cisplatin group (p = 0.049).*
Conclusion: *No difference was found in the response rate, but higher frequencies of hemotological adverse effects in the cisplatin group.*

Keywords: *Chemotherapy, Cisplatin, Drug therapy, Fluorouracil, Radiotherapy, Uterine cervical neoplasms*

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Carcinoma of the uterine cervix is the most common malignant neoplasm among Thai women[1]. It is also the most common female cancer detected at Udonthani Cancer Center. Moreover 76 percent of patients with cervical cancer in the Udonthani Cancer Center presented with locally advanced disease (stage IIB through IVA according to the staging system of the International Federation of Gynecology and Obstetrics-FIGO)[2].

As primary treatment for locally advanced invasive carcinoma of the cervix; radiotherapy alone fails in a substantial number of patients so treated. The radiotherapy failure rate for patients with stage IIB disease is 20% to 50%; for patients with more extensive stage III disease, the recurrent rate ranges from 50% to as high as 75%[3,4]. Such treatment failure may be due to unrecognized metastatic disease at the time of original diagnosis. The most common and consequential component of treatment failure is the inability of primary radiotherapy alone to completely eradicate all pelvic disease. Local control may be increased by escalating the radiation dose but at the cost of increased toxicity. Altered fractionation schedules have yet to show significantly increased local control or survival. Hyperbaric oxygen, particle therapy, and hyperthermia are not widely accessible and have shown only marginal improvements.

Theoretically, the concomitant administration of chemotherapy with radiotherapy could increase local control and survival rate. Whitney et al, reported a significant improvement in pelvic control, progression-free interval, and most importantly, survival for

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patients treated with cisplatin plus fluorouracil and radiation therapy compared with patients treated with hydroxyurea with radiotherapy. Thus, a combination between chemo-radiation with cisplatin plus fluorouracil should be the standard treatment of patients with locally advanced cervical carcinoma[5].

In Gynecologic Oncology Group (GOG) Trial 120 investigated the use of standard pelvic radiation with one of three concurrent chemotherapy regimens cisplatin alone, hydroxyurea alone, or cisplatin plus fluorouracil plus hydroxyurea in patients with stage IIB, III or IVA cancer and negative para-aortic lymph nodes. The 3-year survival rate in both cisplatin-containing treatment arms was 65%, compared with 47% for the pelvic radiation plus hydroxyurea treatment group. The relative risk of death was 0.61 for pelvic radiation plus cisplatin, and 0.58 for cisplatin plus fluorouracil plus hydroxyurea plus pelvic radiation, compared with patients treated with pelvic radiation plus hydroxyurea alone. Regimens of radiotherapy and chemotherapy that contain cisplatin had improved the rates of survival and progression-free survival among women with locally advanced cervical cancer[6].

As a result, the authors conducted a randomized control trial to compare cisplatin plus fluorouracil with cisplatin in the treatment of patients with locally advanced carcinoma of the cervix. Response rate was chosen as the primary end point of the comparison and toxicity was selected as secondary end points.

Material and Method

Eligibility

All patients had biopsy-proven invasive squamous cell carcinoma of the uterine cervix. All patients tumor were staged by criteria of FIGO and had stage IIB, III, or IVA disease. Normal renal, hepatic profile and bone marrow function were required for entry. Eligible patients had to be free of clinically significant infection, have no prior exposure to pelvic irradiation or cytotoxic chemotherapy, and have an ECOG performance grade of 2 or lower. Patients with previous or concomitant other cancer, were not eligible for inclusion in the present study.

Other eligibility criteria were as follows: a leukocyte count of at least 3,000 per cu mm^3, a platelet count of at least 100,000 per cu mm^3, a serum creatinine level of no more than 2.0 mg/dL, a serum bilirubin level that was no more than 1.5 times the upper limit of normal at the institution where it was measured and a serum aspartate aminotransferase level that was no more than 3 times the upper limit of normal. All patients gave written informed consent.

Radiotherapy

Radiotherapy was administered to the whole pelvic region in 22 fractions totaling 3,960 cGy (1.8 Gy/fraction/day x 5 fraction a week). Parametrial boost was followed at 1.8Gy/frasction/day for 14.4Gy in 8 fractions.

Patients were to receive 3,960 cGy external beam radiotherapy (EBRT) delivered homogeneously to the whole pelvis in 22 fractions. After completion of EBRT, 3960 cGy was to be delivered to point A via three intracavitary applications (tandem and colpostats) of high dose rate. A parametrial boost was given to bring the point B dose to 54 Gy in 30 fractions. Point A received 22.5 Gy from three intracavitary implants. Point B received 60 Gy from both sources. Those patients treated solely with EBRT were to receive 61.2 Gy in 34 fractions.

Pelvic radiation was delivered by antero-posterior and postero-anterior parallel ports with an X-ray energy of at least 6 MV photons. The pelvic field extended from the upper margin of S1 to the bi-ischial tuberocity or the lowest level of disease, with a 2 cm margin and laterally 2 cm beyond the lateral margins of the bony pelvic wall. The duration of the radiotherapy was 8 weeks. Hemoglobin was greater than 11g/dL. Radiotherapy was withheld if a patient had an absolute neutrophil count less than 1,000/mm^3 or platelet count less than 50,000/mm^3.

The primary end points were response rate. Three months after finishing the treatment, the response rate was evaluated by pelvic examination.

Chemotherapy

Patients were randomized to receive

Arm I: Concurrent chemo-radiation consisting of cisplatin 50 mg/m^2 intravenously and fluorouracil infusion at 1000mg/m^2/day by 96 h infusion was given every 4 weeks for a total of 2 cycles.

Arm II: Concurrent chemo-radiation consisting of cisplatin 40 mg/m^2 intravenously was given every 1 week for a total of 6 cycles.

Treatment modifications

Chemotherapy was not administered until the absolute neutrophil count was $\geq$ 1,500 per cu mm^3 and the platelet count was $\geq$ 100,000 per cu mm^3.

Arm I. If the absolute neutrophil count nadir was between 1,000 and 1,499 per cu mm^3 and/or the platelet count between 50,000 and 74,999 per cu mm^3 and/or creatinine $\geq$ 1.5mg/dL and creatinine clearance 40-50 mg/min and/or grade3 neurotoxicity and/or grade4 emesis toxicity, cisplatin was decreased to 30 mg/m^2. If the absolute neutrophil count was less than 1,000 per cu mm^3 and/or the platelet count less than 50,000 per cu mm^3 and/or creatinine $\geq$ 1.5mg/dL and creatinine clearance $\leq$ 40 mg/min and/or grade3 neurotoxicity, cisplatin dose was omitted. If the absolute neutrophil count nadir was between 500 and 999 per cu mm^3 and/or the platelet count between 25,000 and 49,999 per cu mm^3 and/or grade3 stomatitis or diarrhea toxicity, fluorouracil was decreased to 750 mg/m^2/day. If the absolute neutrophil count nadir was less than 500 per cu mm^3 and/or the platelet count less 25,000 per cu mm^3 and/or grade4 stomatitis or diarrhea toxicity, fluorouracil was decreased to 500 mg/m^2/day.

Arm II. If the absolute neutrophil count nadir was between 1,000 and 1,499 per cu mm^3 and/or the platelet count between 50,000 and 74,999 per cu mm^3 and/or creatinine $\geq$ 1.5mg/dL and creatinine clearance 40-50 mg/min and/or grade3 neurotoxicity and/or grade 4 emesis toxicity, cisplatin was decreased to 30 mg/m^2. If the absolute neutrophil count was less than 1,000 per cu mm^3 and/or the platelet count less than 50,000 per cu mm^3 and/or creatinine $\geq$ 1.5mg/dL and creatinine clearance $\leq$ 40 mg/min and/or grade 3 neurotoxicity, cisplatin dose was omitted.

Results

Between March 2006 and August 2007, 20 patients were entered into the present study. Of these, 10 were randomized to a regimen of radiotherapy with concurrent cisplatin plus fluorouracil and 10 to radiotherapy with concurrent cisplatin. There were no differences in the clinical characteristic among the two treatment groups (Table 1). All patients in the cisplatin plus fluorouracil group and in the cisplatin group had complete response.

There were no treatment-related deaths. The type and frequencies of adverse effects are shown in Table 2. Grade 3 or 4 hematologic toxic effects were more frequent in the cisplatin group than in the cisplatin plus fluorouracil group. Grade 3 or 4 neutropenia occurred in 10% of the cisplatin plus fluorouracil group and in 40% of the cisplatin group ($p = 0.049$). Grade 3 or 4 diarrhea was more frequent in the cisplatin plus fluorouracil group than in the cisplatin group ($p = 0.057$). The incidence of non-hematologic toxic and other hematologic toxic effects did not differ significantly between the two groups.

Discussion

There is no curative surgical option for patients with locally advanced invasive carcinoma of uterine cervix. Primary radiotherapy to the pelvis cures many, but not all of these patients. The more common and consequential component of treatment failure occurs within the field of pelvic radiation. Neither adjuvant surgery nor increasing dose of radiotherapy alone is likely to increase the rate of pelvic control in patients without the consequence of increased early and late complications. Altered fraction schedules have yet to offer significant improvement, may increase complications, and are not convenient for patients. Technical equipment and cost limitations have constrained the widespread use of particle beams, hyperbaric oxygen, and hyperthermia; in any events, they are not readily accessible. A large number of trials have explored the use of combination chemotherapy with radiotherapy. The most commonly reported combinations include cisplatin plus fluorouracil or cisplatin. Chemo-radiation has proven to be of value for patients with locally advanced cervical carcinoma[5-10].

The present study is a comparison of both the standard chemo-radiation regimens. The treatment group randomly formed was balanced on the known prognostic variable of patients. None of the radiotherapy variables are different between the treatment arms.

Table 1. Characteristic of the patients

Characteristic	Treatment regimen			
	Cisplatin plus fluorouracil		Cisplatin	
	No.	%	No.	%
Total	10	100	10	100
Stage				
IIB	6	60	6	60
IIIB	4	40	4	40
GOG performance status				
0	0	0	2	20
1	10	100	7	70
2	0	0	1	10
Tumor size, cm				
≤ 4	4	40	4	40
> 4	6	60	6	60

Table 2. Adverse effects**

Adverse effect	Cisplatin plus fluorouracil (n = 10)					Cisplatin (n = 10)					p-value*
	Grade					Grade					
	1	2	3	4	3 or 4	1	2	3	4	3 or 4	
	No.	No.	No.	No.	%	No.	No.	No.	No.	%	
Hemoglobin	6	2	0	0	0	5	3	1	0	10	0.146
WBC	5	2	2	0	20	3	2	4	1	50	0.069
Neutrophils	5	2	1	0	10	2	2	3	1	40	0.049
Platelets	0	1	0	0	0	2	3	0	1	10	0.146
Febrile neutropenia	0	0	1	0	10	0	0	0	0	0	0.146
Vomiting	3	3	1	0	10	2	2	2	0	20	0.264
Creatinine	1	0	0	0	0	3	0	0	0	0	-
Neurologic	0	0	0	0	0	0	1	0	0	0	-
Weight loss	6	1	0	0	0	5	1	0	0	0	-
Diarrhea	0	4	2	0	20	1	2	0	0	0	0.057
Other	1	0	0	0	0	0	0	0	0	0	-

* p-values are for the comparison between the two study groups of the incidence of grade 3 or 4 toxic effects
** Adverse effects were assessed with use of the Common Terminology Criteria for Adverse Events version 3.0

Radiotherapy concurrent cisplatin plus fluorouracil is equally in complete response rate as radiotherapy concurrent cisplatin for the treatment of locally advanced cervical cancer.

Myelosuppression was the most frequent toxic effect in both groups and was more frequent in the cisplatin group than in the cisplatin plus fluorouracil group. There was a significantly higher incidence of grade 3 or 4 neutropenia among the patients who received cisplatin than among those who received cisplatin plus fluorouracil. More grade 3 or 4 diarrhea toxicity was present in cisplatin plus fluorouracil but had no significant difference between the two groups.

However, the sample size was too small to draw meaningful conclusions. In the future research, sample size should be increased. Furthermore, clinical aspect of overall survival should be explored.

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การศึกษาเปรียบเทียบแบบสุ่มอิสระในการรักษามะเร็งปากมดลูกชนิดเซลล์แบนระยะ IIB-IVA ระหว่างการฉายแสงพร้อมกับการให้ยาเคมีบำบัดสูตร cisplatin และ fluorouracil เทียบกับผู้ป่วยที่ได้รับการฉายแสงพร้อมกับให้ยาเคมีบำบัดสูตร cisplatin

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วัตถุประสงค์*: เพื่อเปรียบเทียบประสิทธิผลและความเป็นพิษของรังสีรักษาในอุ้งเชิงกรานพร้อมกับ cisplatin บวก fluorouracil กับ cisplatin อย่างเดียวต่อมะเร็งปากมดลูกชนิดเซลล์แบนระยะลุกลาม*

วัสดุและวิธีการ*: ได้ศึกษาในผู้ป่วยหญิงจำนวน 20 คนที่เป็นมะเร็งปากมดลูกชนิด เซลล์แบน โดยให้รับการฉายแสงวิธีการเหมือนกัน แต่ต่างกันที่สูตรยาเคมีที่ให้พร้อมกับการฉายแสง โดยทำการสุ่มให้กลุ่มหนึ่งได้รับยาเคมี cisplatin ร่วมกับ fluorouracil ทุก 4 สัปดาห์ กับอีกกลุ่มได้รับยาเคมี cisplatinทุก 1 สัปดาห์ เป้าหมายหลักเป็นอัตราการตอบสนอง*

ผลการศึกษา*: ผู้ป่วยทั้งสองกลุ่มให้ผลการรักษาตอบสนองจนไม่พบรอยโรคทุกคน แต่ในกลุ่มที่ได้ ยาเคมี cisplatin ทุก 1 สัปดาห์ พบมีผลแทรกซ้อนทางด้านโลหิตวิทยามากกว่าอีกกลุ่ม โดยผลแทรกซ้อนระดับ 3 หรือ 4 ของเม็ดเลือดขาวชนิด neutrophil ต่ำพบ 10% ในกลุ่มที่ได้ยาเคมี cisplatin ร่วมกับ fluorouracil ส่วนกลุ่ม cisplatin พบ 40% (p = 0.049)*

สรุป*: ไม่มีความแตกต่างในการตอบสนองต่อการรักษาของยาเคมีทั้งสองกลุ่มแต่ กลุ่มcisplatin พบมีผลแทรกซ้อนทางโลหิตวิทยาบ่อยครั้งกว่า*