Weekly versus Three-Weekly Cisplatin as an Adjunct to Radiation Therapy in High-Risk Stage I-IIA Cervical Cancer after Surgery: A Randomized Comparison of Treatment Compliance

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Objectives: *To compare weekly and three-weekly cisplatin as an adjunct to radiation therapy in high-risk early-stage cervical cancer after surgery with regard to treatment compliance.*
Material and Method: *From June 1st, 2003 to February 29th, 2004, the authors performed a randomized trial of radiotherapy in combination with two concurrent chemotherapy regimens - weekly or three-weekly cisplatin - in patients with high-risk cervical cancer FIGO stage I-IIA after surgery. Women with primary invasive squamous-cell carcinoma, adenocarcinoma, or adenosquamous carcinoma of the cervix were enrolled. The patients also had to have an absolute neutrophil count of at least 1,500 cells per cubic millimeter, a platelet count of at least 75,000 cells per cubic millimeter, a creatinine clearance higher than 40 milliliter per minute, and adequate hepatic function. All patients received external-beam radiotherapy according to a strict protocol. Patients were randomly assigned to receive one of two chemotherapy regimens: 75 mg per square meter of cisplatin on days 1, 22, 43 and 64 or every three weeks for 4 cycles (group 1) or 40 mg per square meter of cisplatin per week for six cycles (group 2).*
Results: *The analysis included 40 women. The first group that received three-weekly cisplatin had a higher rate of incomplete and delayed treatments than the second group that received weekly cisplatin ($p < 0.001$ and $p = 0.0236$ respectively). The relative risks of delayed courses were 2.06 (95 percent confidence interval, 1.15 to 3.68) for group 1, compared with group 2. The toxicity-related incomplete treatments rate and G-CSF doses used were significantly higher in group 1 than in group 2.*
Conclusion: *Concurrent chemoradiation with weekly cisplatin regimen has more complete treatment rate and less delayed courses than that with three- weekly cisplatin among women with high-risk cervical cancer after surgery.*

Keywords: *Cisplatin, Concurrent chemoradiation, High-risk cervical cancer*

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Current primary treatments of cervical cancer are either surgery or radiation or both, depending on the clinical stage and surgico-pathologic characteristics. The authors usually give adjuvant radiation therapy to patients with any of the high-risk factors such as positive pelvic nodes, positive surgical margins, and parametrial invasion or two intermediate-risk factors of lymph-vascular space invasion (more than 10 spaces) and deep cervical stromal invasion (less than 3 mm from serosa). This is for better disease control and also improved cure rate[1]. The National Cancer Institute of the US has recommended that cisplatin-based chemotherapy should be given in concurrent with adjuvant radiation as a new standard since February 1999[2]. This is based on consistent findings from many studies that by adding the cisplatin-based chemotherapy to pelvic radiation, a 36% improvement in survival could be achieved[3-8]. As an adjunct to radiation, regimens that include cisplatin alone or in combination with other cytotoxic agents can be given with a one to three or four-week interval by different dosages. Commonly, 75 mg/m^2 of cisplatin for 4 cycles was given in the three-weekly regimen[3,4,7,9-11] while 40 mg/m^2 of cisplatin for 6 cycles was given in the weekly regimen[5,6,12].

Concurrent chemoradiation with cisplatinum was introduced to the Faculty of Medicine, Chiang Mai University in 1999. At first, The authors gave cisplatin in a dosage of 75 mg/m2 for 4 cycles on a three-weekly basis. Then, the authors began to give 40 mg/m2 of cisplatin at a one-week interval for 6 cycles in 2002. The authors have consistently observed that in both regimens, there would be substantial cases that could not receive complete chemotherapy due to subsequent adverse effects. However, definite information about the number of these patients, number of delayed courses and toxicity found in each group were not available. Thus, the authors decided to conduct the present study to examine and compare these adjunctive chemotherapeutic regimens in terms of compliance and toxicities.

Material and Method

Eligibility

Women with the International Federation of Gynecology and Obstetrics (FIGO) stage I - IIA invasive squamous-cell carcinoma, adenocarcinoma, or adenosquamous carcinoma of the cervix after surgery who were found to have any high-risk factors or 2 intermediate-risk factors from histopathological examination of the surgical specimens, were enrolled in the present study from June 2003 to February 2004. All cancers were confirmed histologically by the Gynecologic Pathology Unit. Each patient was required to undergo a complete physical examination, a pelvic examination, chest radiography, to determine the clinical stage of the cancer. Patients' ages were not more than 60 years old and were required to have a ECOG (Zubrod) performance status of 0, 1, or 2 (equivalent to Karnofsky performance scores of 90 or 100, 70 or 80, and 50 or 60, respectively) and to have no history of other cancers, previous chemotherapy or previous radiation.

Other eligibility criteria were as follows: an absolute neutrophil count of at least 1,500 cells per cubic millimeter, a platelet count of at least 75,000 cells per cubic millimeter, a creatinine clearance of higher than 40 milliliter per minute, the serum bilirubin, SGOT, SGPT and alkaline phosphatase level that were no more than 1.25 times the upper normal limit. Additional pretreatment evaluations included assessment of performance status and measurements of the cervical tumor and serum electrolytes and magnesium. All patients gave written informed consent according to institutional regulation. The conduct of the present study was approved by the Institutional Review Board (IRB) of Faculty of Medicine, Chiang Mai University.

Radiotherapy

Radiotherapy was administered to the whole pelvic region in 25 fractions totaling 50 Gy, followed two weeks later by intracavitary brachytherapy. Four times of HDR technique intracavitary brachytherapy were used only if hysterectomy was abandoned or positive surgical margin. The total dose delivered from this method was 24 Gy. The total dose delivered to point A (a reference location 2 cm lateral and 2 cm superior to the cervical os) was 85-90 Gy; the total dose delivered to point B (the pelvic wall) was 55-60 Gy. Pelvic radiation was delivered by anteroposterior and posteroanterior parallel ports or a four-field box technique (anteroposterior, posteroanterior, and two lateral fields) with an x-ray energy of at least 4-MV photons. The pelvic field extended from the lower margin of L5 to the 2 cm below the obturator foramen, and laterally 2 cm beyond the lateral margins of the bony pelvic wall (at least 7 cm from the midline). For the lateral fields, the anterior border was the anterior border of the pubic symphysis and the posterior border was the space between S2 and S3. The fields could be modified to include areas of known tumor.

The duration of the radiotherapy was not more than 10 weeks. Radiotherapy was withheld if a patient

had an absolute neutrophil count of less than 1,500 cells per cubic millimeter, and delays of up to one week were also allowed in the event of radiation-related gastrointestinal or genitourinary toxicity. The length of radiotherapy, in days, was calculated for the duration of whole pelvic (external-beam) radiotherapy only.

Chemotherapy

The patients were randomly assigned to receive one of two chemotherapy regimens, which were given concomitantly with external-beam radiotherapy. Treatment with cisplatin was delayed if the absolute neutrophil count dropped below 1,500 cells per cubic millimeter (grade 2), hemoglobin level dropped below 9.5 milligram per deciliter, or the platelet count dropped below 75,000 cells per cubic millimeter (grade 2), and it was resumed once the counts rose above these levels. Treatment with cisplatin was discontinued if the absolute neutrophil count dropped below 1000 per cubic millimeter (grade 3), the platelet count dropped below 50,000 per cubic millimeter (grade3), creatinine clearance dropped below 40 milliliter per minute, sensorineural hearing loss of any grade, there were medical complications that delay the course more than 7 days or the patient requested to stop, and then the patient was given radiotherapy alone. The followings are the steps employed in giving chemotherapy:

Day 0: 8:00 pm Hydration with 5% D/N/2 1000 ml + 50% MgSO4 1 gm + KCL 20 mEq IV drip in 30 d/min x II

Day 1: Premedication 30 minutes before chemotherapy with

1. Lorazepam 1 mg orally
2. Dexamethasone 20 mg + ondansetron 8 mg + 5% D/W 100 ml IV drip in 50 d/min
3. Ondansetron 8 mg slow IV push

IV fluid of 5% D/N/2 1000 ml + 50% MgSO4 1 gm + KCL 20 mEq IV drip in 15 d/min

Furosemide 20 mg before cisplatin

Cisplatin of 75 mg/m^2 or 40 mg/m^2 + 0.9% NSS 500 ml IV in 30 d/min

Furosemide 20 mg after cisplatin

* If creatinine clearance dropped below 50 milliliter per minute mannital will be given instead of furosemide.

Statistical Analysis

The authors calculated the target sample size of 20 patients for each regimen on the basis of 40 percent different with the statistical power of 80%, the rate of incomplete treatment from the pilot study (70% vs 30%) with the use of either radiotherapy combined with treatment with three-weekly cisplatin or radiotherapy combined with treatment with weekly cisplatin. This design provided the study with a statistical power of 80 percent. At the time of analysis, 14 patients (70%) had had incomplete treatment in the three-weekly group (group 1) and 3 patients (15%) had that in the weekly cisplatin group (group 2). Thus, because of the larger difference in outcome among the treatment groups, this sample size was adequate.

Double blind randomization was carried out by random number, table 1 with equal numbers assigned to each treatment group. The physicians who gave chemotherapy to the new patient did not know which regimen was given. At that time of allocation, the authors would not know who the patient was. Prognostic variables of interest include patient age, FIGO stage, surgical procedures, pathologic examination details. Outcome variables of interest included rate and reasons of delayed courses (2nd-6th cycle), rate and reason of incomplete treatment, amount of G-CSF and PRbc used, amount and severity of toxicities found in each group.

General characteristics among groups, three-weekly and weekly, were described using mean (range) and frequency (%) for continuous and categorical variables, respectively. Independent t-test, Pearson's chi-square test or Fisher's exact test were used to compare characteristics among groups. All reported p values are two-tailed unless otherwise stated. A p value of < 0.05 was considered significant.

Results

Characteristics of the Patients

From June 2003 to February 2004, 128 new cervical cancer patients had primary surgery for treatment. After thorough pathological examination, 46 patients were considered to be high-risk and could benefit from receiving concurrent chemoradiation. However, only 40 patients were enrolled: 20 were assigned to receive radiotherapy and concomitant chemotherapy with three-weekly cisplatin; 20 were assigned to receive radiotherapy and concomitant chemotherapy with weekly cisplatin (Fig. 1). Six of these 46 patients (13 percent) were found to be ineligible for the following reasons: small cell carcinoma (3 patients), previous chemotherapy (2 patients), creatinine clearance of less than 40 milliliter per minute (1 patient).

There were no significant differences in the baseline clinical characteristics among the two treatment groups (Table 1).

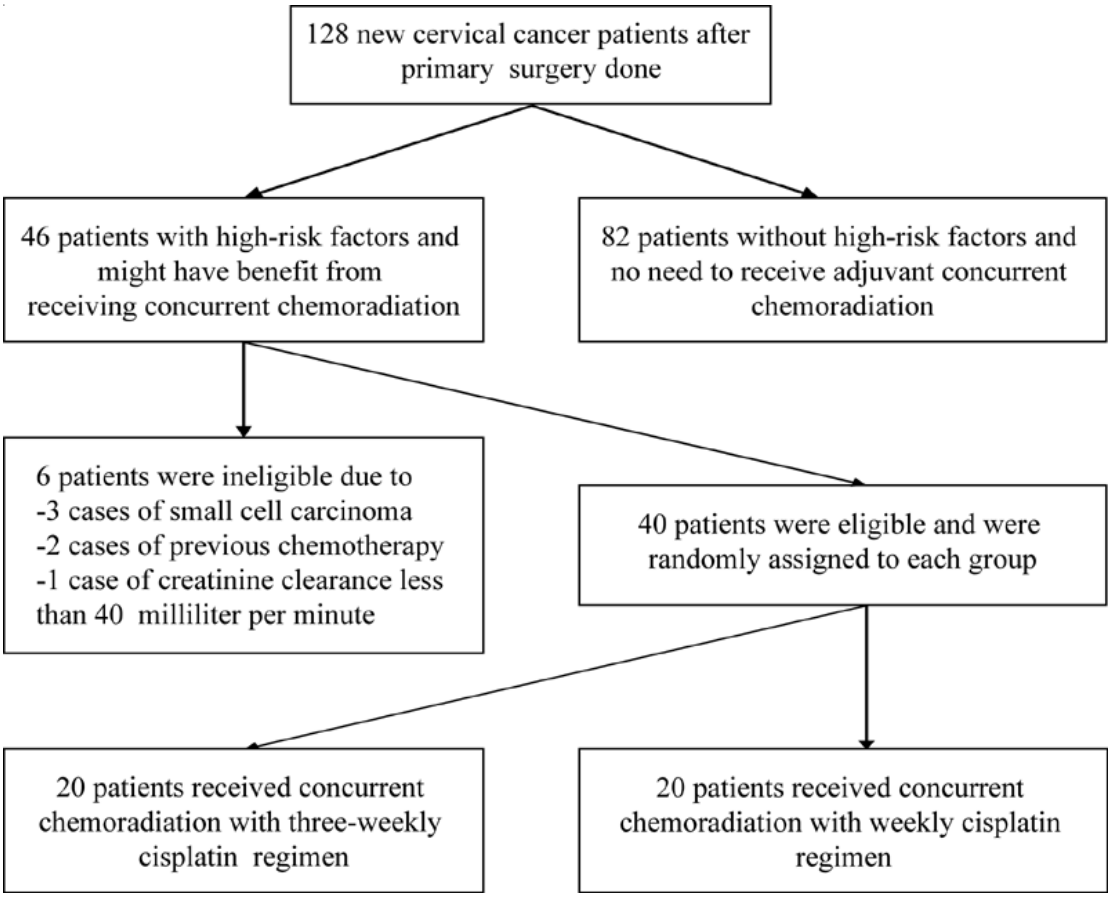

Fig. 1 Treatment scheme of high-risk cervical cancer patients enrolled and randomly assigned in both groups

Radiotherapy

All patients received a complete course of radiation therapy. The mean duration to start external-beam treatment in the three-weekly group was 27.5 days (14-43 days) compared with 28.0 days (18-43 days) in the weekly group. This was not significantly different ($p = 0.83$).

The median duration of whole pelvic radiation was 42.2 days (33-64 days) in the three-weekly group and 41.2 days (33-62 days) in the weekly group given radiotherapy combined with treatment with cisplatin. There was also no significant difference ($p = 0.534$).

Chemotherapy

In the three-weekly group, there were 33 courses delivered as 2nd-4th cycles. Of these, 10 courses were delayed. For the weekly group, there were 93 courses delivered as 2nd-6th cycles. Of these, 12 courses were delayed. There was significant difference in the rate of total delay courses ($p = 0.0236$, RR = 2.06, 95%CI 1.15 to 3.68).

If the comparison was made only for delay due to chemotherapeutic-induced toxicities, 7 courses in the three-weekly group and 4 courses in the weekly group, the significant difference was still observed ($p = 0.007$). However, if the authors compared between delays due to factors other than those associated with treatment (i.e. patient came late, laboratory results delayed, wrong appointments), there was no significant difference among the two groups ($p = 1.000$). Table 2 shows the number of the 2nd-6th cycles of chemotherapy (i.e., weeks) administered, and the number and reason for delays in each group.

Toxicity-related delay in the 2 groups was then examined in detail. It appeared that 5 of the 7 delays in the three-weekly group, were due to neutropenia grade 2, and 2 were due to anemia grade 2, while in the weekly group, there were 3 with neutropenia grade 2 and 1 of radiation diarrhoea grade 2.

Table 1. Baseline characteristics of patients who received three-weekly cisplatin versus those received weekly cisplatin concurrent chemoradiation

Characteristics	Three-weekly group	Weekly group	p-value
Age (years) mean (range)	44.2 (27-60)	43.5 (30-59)	0.609
Body mass index (kg/m^2) mean (range)	23.7 (19.3-26.6)	23.4 (18.2-29.5)	0.078
Hemoglobin (mg/dl) mean (range)	11.2 (9.5-14.1)	11.5 (9.5-15.5)	0.596
FIGO staging (%)			
IB1	17 (85)	12 (60)	0.155
IB2	1 (5)	5 (25)	
IIA	2 (10)	3 (15)	
Procedures received (%)			
Radical hysterectomy	13 (65)	18 (90)	0.242
Bilateral pelvic node dissection	20 (100)	20 (100)	
Para-aortic node sampling	5 (25)	0 (0)	
Bilateral salpingo-oophorectomy	15 (75)	10 (50)	
Unilateral salpingo-oophorectomy	1 (5)	1 (5)	
Appendectomy	12 (60)	13 (65)	
Cell types (%)			
Squamous cell carcinoma	14 (70)	13 (65)	0.929
Adenocarcinoma	4 (20)	5 (25)	
Adenosquamous carcinoma	2 (10)	2 (10)	
Differentiation (%)			
Well	3 (15)	7 (35)	0.322
Moderately	14 (70)	10 (50)	
Poorly	3 (15)	3 (15)	
Tumor sizes (%)			
Microscopic-1 cm	1 (5)	1 (5)	0.355
1 cm-4 cm	18 (90)	15 (75)	
More than 4 cm	1 (5)	4 (20)	
Risk factors (%)			
Para-aortic nodes positive	3 (15)	0 (0)	0.377
Pelvic nodes positive	16 (80)	14 (70)	
Surgical margins positive	1 (5)	1 (5)	
Parametrial invasion	6 (30)	10 (50)	
2 intermediate risks (LVSI and deep stromal invasion)	5 (25)	6 (30)	

Table 2. Numbers of delay courses during 2nd-6th cycles in each group and reasons

Details of cycles and delay reasons	Three-weekly group	Weekly group	p-value
Total courses during 2nd-6th cycles	33 (100)	93 (100)	
Total delay courses of 2nd-6th cycles	10 (30.3)	12 (12.9)	0.0236
Adverse effects	7 (21.2)	4 (4.3)	0.0070
Administrative delay	3 (9.1)	8 (8.6)	1.0000

Fourteen (70%) versus 3 patients (15%) had incomplete treatment with cisplatin in the three-weekly and the weekly group respectively. There was significant difference in the rate of incomplete treatment ($p < 0.001$).

If the comparison was made only for incomplete treatment due to toxicities,12 cases in the three-weekly group and 2 cases in the weekly group, there was also significant difference ($p < 0.001$). Table 3 shows the number of incomplete treatment cases, and the number and reasons for discontinuation in each group.

The toxicity-related discontinuation in the 2 groups were then examined in more details. For the 12 cases in the three-weekly group, there were 7 neutropenia grade 3, 2 prolonged neutropenia grade 2 (> 7 days), and 3 sensorineural hearing loss. Of 2 additional cases that had medical complications, one had infective diarrhoea and another had viral hepatitis. From these reasons, 6 cases had chemotherapy stopped after the 1st course, 1 after the 2nd course, and 7 after the 3rd course. There remained only 6 cases who had complete treatment (i.e. receiving the full 4 courses). For the 3 cases in the weekly group, there were 1 neutropenia grade 3, 1 sensorineural hearing loss, and 1 patient who refused further treatment. In this latter case, she had fatigue symptoms of grade 2. From these reasons, 1 case had chemotherapy stopped after the 3rd course, and 2 after the 4th course. There were 17 cases who completed the 6 courses of cisplatin.

G-CSF and PRbc used

The mean doses of G-CSF (granulocyte-colony stimulating factor) used in the three weekly group was 0.2 doses (0-1 doses) compared with 0 doses in the weekly group (never been used). There was significant difference ($p = 0.036$). However, no significant difference ($p = 0.233$) was found for the mean unit of PRbc (packed red blood cells) used, 0.45 unit (0-2 units) in the three-weekly group and 0.2 unit (0-2 units) in the weekly group.

Adverse effects

There were no treatment-related deaths. The types and frequencies of adverse effects are shown in Table 4. The frequencies of both grade 3 neutropenia in the three-weekly group were significantly more than the frequencies in the weekly groups (7 versus 2 cases respectively, $p = 0.005$). But the frequencies of sensorineural hearing loss of any grade in the three-weekly group were similar in both groups of patients ($p = 0.09$).

Table 3. Numbers of incomplete treatment patients in each group and reasons

Details of incompleteness and reasons	Three-weekly group	Weekly group	p-value
Total patients (%)	20 (100)	20 (100)	<0.001
Total incomplete treatment patients	14 (70)	3 (15)	<0.001
Adverse effects	12 (60)	2 (10)	
Medical complications	2 (10)	0 (10)	
Patient's request	0 (0)	1 (5)	

Table 4. Adverse effects and their severity in each group according to WHO recommended toxicity grading

Adverse effects	Three-weekly group (53 cycles)				Weekly group (113 cycles)			
Grades	0	1	2	3	0	1	2	3
Leukopenia	10	19	20	4	73	29	10	1
Thrombocytopenia	37	1	15	0	112	1	0	0
Neutropenia	23	6	17	7*	77	26	8	2*
Anemia	16	27	9	1	69	37	6	1
Nausea/ vomiting	7	17	29	0	82	27	4	0
Fatique	50	3	0	0	111	1	1	0
Hearing loss	50	0	2**	1**	112	0	1**	0
Diarrhoea	53	0	0	0	112	0	1	0

* $p = 0.005$, ** $p = 0.09$

Discussion

The FIGO staging classifications and clinical practice guidelines in the management of gynecologic cancers that was first published in September 2000[13], and last revised in December 2003[14] has recommended adjuvant concurrent chemoradiation to high-risk cervical cancer patients following surgery. The three-weekly regimen of 5-FU in combination with cisplatin 75 mg/m^2 or the weekly regimen of cisplatin 40 mg/m^2 alone may be used. However, from the NCI Clinical announcement in February 1999[2], any regimen with cisplatin was recommended.

Concurrent chemoradiation has been given to our patients with high-risk cervical cancer following surgery since 1999. The authors began with the three-weekly regimen of cisplatin 75 mg/m^2, modified from the 5-FU in combination with cisplatin regimen. The 5-FU was excluded to reduce overall toxicities. That regimen was used for a period of approximately 3 years during which the number of patients that could not complete chemotherapy due to toxicities were found to be substantive. Since June 2002, the authors have started to use the weekly cisplatin regimen and found that it might provide a more complete treatment rate and less toxicities than the three-weekly regimen. Therefore, the authors did this study to prove this hypotheses.

From the present study, the authors found a higher rate of incomplete treatment among patients who were treated with radiotherapy and three-weekly cisplatin than among patients who were treated with radiotherapy and weekly cisplatin regimen. The number of delays due to toxicities in the three-weekly group was higher than that in the weekly group. The G-CSF used in the three-weekly group was also more than that of the weekly group. In addition, the number of treatment cycles that cause grade 3 neutropenia in the three-weekly group was also higher than that in the weekly group.

To the authors' knowledge, there is no study in the literature that compares these two regimens with regard to treatment compliance. But still there were studies of other three-weekly regimens that had a similar result as described next.

Morris et al[4] used the regimen of 5-FU in combination with cisplatin every 3 weeks for 3 cycles during radiation therapy to 193 patients. They found that there were 131 patients reaching 3 cycles (68%). In the present study, there were 13 patients (65%) reaching 3 cycles.

Peter III et al[7] used the regimen of 5-FU in combination with cisplatin 70 mg/m2 every 3 weeks for 4 cycles during radiation therapy to 127 patients. They found that there were 37 patients received chemotherapy less than 3 cycles (29%). In the present study, there were 7 patients (35%) received less than 3 cycles. There were other studies of other three to four-weekly regimens that had the different results from the present study which could be briefly summarized below.

Whitney et al[3] used the regimen of 5-FU in combination with cisplatin 50 mg/m2 every 4 weeks for 2 cycles during radiation therapy to 177 patients. They found that 161 patients received chemotherapy reaching 2 cycles (91%).

Rose et al[5] used the regimen of 5-FU in combination with hydroxyurea and cisplatin 50 mg/m^2 every 4 weeks for 2 cycles during radiation therapy to 173 patients. They found that 157 patients received chemotherapy reaching 2 cycles (91%) that was the same as Whitney's studies[3].

Killackey et al[10] used the regimen of bleomycin or bleomycin and ifosfamide in combination with cisplatin every 3 weeks for 2 cycles during radiation therapy to 22 patients. He found that there were 20 patients reached 2 cycles (91%) that was the same as Whitney's[3] and Rose's[5]. In the present study, there were only 14 patients (70%) reached 2 cycles.

Park et al[9] used the regimen of 5-FU and cisplatin 100 mg/m^2 for SCCA or cyclophosphamide with adriamycin and cisplatin 70 mg/m^2 every 3 weeks for 6 cycles during radiation therapy to 395 patients. They found that the mean cycles received was 3.42, whereas the present in our study it was 2.65.

The reasons for the differences between the studies mentioned above[3,5,10] and the present study may be from the difference in cisplatin dosage and interval used. Our dosage appeared to be higher (75 mg/m^2 vs 50 mg/m^2) and our interval was shorter (3 weeks vs 4 weeks). However, for the Park's study[9], more courses of chemotherapy were given. Thus, this results in higher mean cycles received.

From the literature review, there were three studies about the weekly cisplatin regimen. All of them had a similar result to the present study and is described next.

Rose et al[5] used the weekly cisplatin regimen of 40 mg/m2 for 6 cycles during radiation therapy to 176 patients. They found that 146 patients received chemotherapy reaching 5 cycles (82.9%). In the present study, there were 17 patients who received chemotherapy reaching 5 cycles (85%).

Keys et al[6] used the same weekly cisplatin regimen of 40 mg/m2 for 6 cycles as Rose et al[5] during

radiation therapy to 183 patients. They found that 165 patients received chemotherapy up to 4 cycles (90%). In the present study, 19 patients who received chemotherapy reached 4 cycles (95%).

Pearcey et al[12] used the weekly cisplatin regimen of 40 mg/m^2 for only 5 cycles during radiation therapy to 127 patients. They found that there were 89 patients (70%) that received complete chemotherapy and without modification of planned schedule. In the present study, there were 13 (65%) patients who received chemotherapy that reached 5 cycles without modification of planned schedule.

From the literature review summarized above, and the comparison and analysis done, the present study had a similar result to the previous studies that used a similar dosage and interval of cisplatin given during the radiation therapy. The duration of radiotherapy and the dose of radiation were similar among the two regimens, implying that the differences in incomplete treatment and delayed courses rate were related to the chemotherapy (three-weekly or weekly regimen).

The present results demonstrate that treatment with the weekly cisplatin regimen had more complete treatment rate and fewer delays than treatment with the three-weekly regimen. The authors recommend the weekly cisplatin as the more appropriate regimen adjunctive to radiation in high-risk early-stage cervical cancer following primary surgery. These results will lead to changs in our concurrent chemoradiation strategy in Maharaj Nakorn Chiang Mai Hospital. The present study will also be a preliminary to future researches on progression free survival, overall survival and 5-years survival of this patient group in our institution. Moreover, whether or not concurrent chemoradiation given on a out-patient basis can be established with this weekly cisplatin regimen is one of the interesting questions that could be examined further.

The present study has many strengths that it was a randomized controlled trial with an adequate sample size and there were no loss to follow-up. The present results did not differ from one larger study conducted previously. Any differences that occurred could be explained by acceptable reasons. However, some study weaknesses exist. For one thing, the method of treatment could not be blinded from the patients and the assessors, thus could introduce some degree of bias. In addition, the follow-up period was too short to provide any meaningful information and conclusion on the effect of these regimens on long term outcome such as survival.

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เคมีบำบัดด้วยยาซิสพลาตินร่วมกับรังสีรักษาเพิ่มเติมหลังการผ่าตัดในผู้ป่วยมะเร็งปากมดลูกระยะที่ I-IIA ที่มีความเสี่ยงสูง แบบทุกสัปดาห์กับแบบทุกสามสัปดาห์: การศึกษาเปรียบเทียบจำนวนการได้ยาตามเกณฑ์

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วัตถุประสงค์: *เพื่อเปรียบเทียบจำนวนการได้ยาเคมีบำบัดซิสพลาตินร่วมกับรังสีรักษาตามเกณฑ์ ระหว่างแบบทุกสัปดาห์กับแบบทุกสามสัปดาห์ ในผู้ป่วยมะเร็งปากมดลูกระยะที่ I-IIA ที่มีความเสี่ยงสูงหลังการผ่าตัด*

วัสดุและวิธีการ: *ระหว่างวันที่ 1 มิถุนายน พ.ศ .2546 ถึงวันที่ 29 กุมภาพันธ์ พ.ศ. 2547 ผู้วิจัยได้ทำการศึกษาทดลองทางคลินิกเชิงเปรียบเทียบการให้รังสีร่วมกับยาเคมีบำบัด 2 แบบ- แบบทุก 3 สัปดาห์ หรือ แบบทุก 1 สัปดาห์- ในผู้ป่วยมะเร็งปากมดลูกระยะที่ I-IIA ที่มีความเสี่ยงสูงหลังการผ่าตัด ผู้ป่วยมะเร็งปากมดลูกรายใหม่ที่มีมะเร็งชนิด squamous-cell, adenocarcinoma, หรือ adenosquamous carcinoma จะได้เข้าร่วมในการศึกษานี้ ผู้ป่วยเหล่านี้จะต้องมี absolute neutrophil count อย่างน้อย 1,500 cells per cubic millimeter, platelet count อย่างน้อย 75,000 cells per cubic millimeter, creatinine clearance สูงกว่า 40 milliliter per minute, และการทำงานของตับปกติ ผู้ป่วยทั้งหมดจะได้รับรังสีรักษาภายนอกตามตารางเวลาแบบเดียวกัน ผู้ป่วยแต่ละคนจะถูกสุ่มจัดให้ได้รับยาเคมีบำบัดร่วมด้วยในแบบใดแบบหนึ่งต่อไปนี้คือ: 75 mg ของ cisplatin per square meter ในวันที่ 1, 22, 43 และ 64 หรือทุก 3 สัปดาห์ 4 ครั้ง (กลุ่มที่ 1) หรือ 40 mg ของ cisplatin per square meter ทุกสัปดาห์ 6 ครั้ง (กลุ่มที่ 2)*

ผลการศึกษา: *มีผู้ป่วยในการวิเคราะห์ข้อมูลรวม 40 คน กลุ่มแรกที่ได้รับ cisplatin ทุก 3 สัปดาห์มีอัตราการได้ยาไม่ครบสูงกว่าและอัตราการเลื่อนยาเคมีบำบัดก็สูงกว่ากลุ่มที่ 2 ซึ่งได้รับยาเคมีบำบัดทุก 1 สัปดาห์ ($p < 0.001$ และ $p = 0.0236$ ตามลำดับ) ความเสี่ยงสัมพัทธ์ของการเลื่อนยาเคมีบำบัดในกลุ่มที่ 1 เป็น 2.06 (95 percent confidence interval, 1.15 to 3.68) เมื่อเปรียบเทียบกับกลุ่มที่ 2 อัตราการได้ยาไม่ครบเนื่องมาจากพิษข้างเคียง และจำนวนยากระตุ้นเม็ดเลือดขาวที่ใช้ไปของกลุ่มที่ 1 ก็มากกว่ากลุ่มที่ 2 อย่างมีนัยสำคัญ*

สรุป: *รังสีรักษาร่วมกับยาเคมีบำบัดด้วย cisplatin แบบทุก 1 สัปดาห์มีอัตราการให้ยาได้ครบสูงกว่า ในขณะที่มีจำนวนการเลื่อนการให้ยาเคมีบำบัดออกไปต่ำกว่าแบบทุก 3 สัปดาห์ ในผู้ป่วยมะเร็งปากมดลูกระยะที่ I-IIA ที่มีความเสี่ยงสูงหลังการผ่าตัด*