RESEARCH COMMUNICATION

Weekly Cisplatin 20 mg/m^2 in Patients with Carcinoma of Cervix receiving Pelvic Radiotherapy at Srinagarind Hospital: A Randomized Controlled Trial

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Abstract

Objectives: To evaluate treatment response and acute treatment-related toxicity of concurrent chemoradiotherapy with cisplatin 20 mg/m^2, compared to 40 mg/m^2 as the standard, in locally advanced cervical cancer. Study design: A prospective randomized controlled trial in Srinagarind Hospital, Faculty of Medicine, Khon Kaen University, Khon Kaen. Subjects: 140 patients, ≤ 60 years old with biopsy-proven previously untreated invasive carcinoma of cervix, FIGO stage IB2-IVA, undergoing concurrent chemoradiotherapy with adequate bone marrow, renal and liver functions, between April and December 2009. Methods: All patients were randomly assigned (half in each group)to receive weekly cisplatin at a dose of 40 mg/m^2 compared to 20 mg/m^2, concurrent with radiotherapy for 6 cycles. Main outcome measuresincluded clinical response, cytological response, and acute treatment-related toxicity. Results: All 140 patients completed 6 cycles of weekly cisplatin. 80% had squamous cell carcinomas; about half were FIGO stage IIIB. The 40 mg/m^2 group showed unplanned interruptions in 13/70 (18.6%), which was significantly different from the 5/70 (7.1%) in the 20 mg/m^2 group (p=0.02), resulting in prolonged treatment time (p=0.026). Complete responses were found in 69/70 (98.6%) and 68/70 (97.1%), respectively, with no significant difference. Hematological and gastrointestinal toxicities were most frequently observed. Acute toxicities in the first group was significantly higher when compared to the second group (p<0.05) as follows; grade 1-2 leukopenia (14.8% vs. 6.4%), grade 1-2 neutropenia (9.3% vs. 2.6%), grade 2 N/V (3.8% vs. 1%), grade 2 diarrhea (2.4% vs. 0.7%), and grade 1 sensory neuropathy (4.5% vs. 1.2%). No treatment related deaths were encountered. Conclusion: This prospective trial has sufficient data to support the conclusion that concurrent chemoradiotherapy with weekly cisplatin 40 mg/m^2 in locally advanced cervical cancer gives good treatment outcomes. When reducing the cisplatin dose to 20 mg/m^2, treatment responses were still comparable to the standard, but acute toxicity could be reduced. However, there are insufficient data to assess long term treatment outcomes and late treatment related toxicity, because of the short follow-up time.

Key Words: Cervical cancer - cisplatin chemotherapy - concurrent chemoradiotherapy,

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Introduction

Cervical cancer remains a significant health problem and primarily affects socially disadvantage women worldwide, particularly in the developing countries such as those in Africa, South America, and Asia (Parkin et al., 1993; Mohar and Frias-Mendivil, 2000). Undoubtedly, the greatest efforts should be directed toward improving screening campaigns as the most effective means for reducing cervical cancer mortality. (Miller et al., 1981; Deerasamee and Srivatanakul., 1999). In Thailand, similar to many countries with limited health resources, cervical cancer screening coverage is still low. In 2007, the incidence of cervical cancer in Thailand was 24.7 per 100,000 women-years, and it was 18.0 per 100,000 women-years in Khon Kaen. Approximately 6,243 new cases are detected and about 3,000 cases die each year, causing cervical cancer to be an important cause of death from cancer in Thai women (Cancer Unit, Khon Kaen University, 2007; Tangsiriwatthana et al., 2007)

Radiotherapy has been accepted as the standard definitive treatment in patients with cervical cancer since the last 1960s. Published 5-year survival rates in stage IB-IIA after radiotherapy alone are 74-91%, which is similar to 83-91% after radical surgery (Landoni et al, 1997). About 80% of Thai patients are diagnosed with locally advanced cervical cancers, and 5-year survival for stage IIB is only 63-70% after radiotherapy alone. The 5-year survival rate dramatically diminishes in patients with higher stage diseases, e.g. only 16-25% was found in stage IVA after radiotherapy alone (Perez et al, 1998; Mangioni et al., 1999). Furthermore, if the tumor size is more than 3

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cm, 5-year survival is only 30-60% compared to 70-90% in patients with tumor size ≤ 3 cm, presenting poor prognosis in patients with bulky tumors (Stehman et al, 2007).

The limitation of radiotherapy in controlling pelvic diseases for locally advanced cervical cancers is that radiation doses required to treat large tumors in the setting of poor tumor oxygenation exceeds the limit of toxicity in normal tissue. This was the main reason for treatment failure supporting by the fact that about 70% of relapses have pelvic failure as the first sites (Vaupel et al., 2002; Monk et al., 2007). Many strategies have been made trying to improve outcomes in locally advanced diseases such as uses of hypoxic cell sensitizers, hyperbaric oxygen, neutron therapy, and hyper-fractionation. However, results of those mentioned were found limited or unsuccessful. (Vale et al., 2008).

In 1999, five large prospective randomized trials performed by the Gynecologic Oncology Group (GOG), Radiation Therapy Oncology Group (RTOG) and the South-West Oncology Group (SWOG) demonstrated significant survival advantage and superiority in reducing risk of death by 30-50% in cisplatin-based therapy given concurrently with pelvic radiotherapy when compared to either radiotherapy alone or radiotherapy in concurrent with non-platinum containing chemotherapy. (Stehman et al., 1997; Keys et al., 1999; Morris et al., 1999; Rose et al., 1999; Whitney et al., 1999). It was stated that cisplatin based chemoradiotherapy also decreased the relative risk of recurrence and the mortality. As a result of these trials, the National Cancer Institute Clinical Announcement established concurrent chemoradiotherapy as the primary mode of therapy instead of radiotherapy alone in locally advanced cervical cancer (Stage IIB-IVA) and as the adjuvant treatment for high risk patients following surgery or locally advanced (Stage I) cervical cancer (Trimble et al., 2007)

Cisplatin is considered as the most active cytotoxic agent and the drug of choice for concurrent chemoradiation (Nias et al., 1985). It is hypothesized of having mechanisms in radiosensitizing activity thus producing a synergistic effect between radiotherapy and chemotherapy. This is due to the additional drug effect in the S-phase of the cell cycle following the effect of radiotherapy in the radiosensitive M-phase cell cycle, which produces sub-lethal cells, inhibition of their repairing process, and hypoxic cell sensitization (Phillips and Tolmach, 1966). Most widely accepted concurrent chemoradiation protocol is the combination of radiation and cisplatin administered once a week at a dose of 40 mg/m2 for 6 weeks, because of its similar effectiveness but more convenient when compare with a daily schedule (Rose et al, 2002; Einstein et al, 2007).

At Srinagarind Hospital, concurrent chemoradiation for locally advanced cervical cancer was initiated in 2002 and the protocol of cisplatin 40 mg/m^2 once a week for 6 weeks in concurrent with pelvic radiation has been applied (Tangsiriwatthana et al., 2007). The main side effects of cisplatin are nephrotoxicity, gastrointestinal toxicity, and bone marrow suppression. From previous studies, those serious toxicities were frequently occurred in considerable numbers of patients and many of their treatments could not be completed (Ikushima et al, 2006; Jones et al, 2009). It has been known that unplanned interruptions of treatment and prolongation of treatment time have compromised the therapeutic result of radiotherapy, treatment cornerstone. A successful treatment schedule without the unplanned interruption was an important factor affecting the best result of treatment (Perez et al., 1995; Chen et al., 2003). There were few reports supported that cisplatin at dose of 20 mg/m^2 could be effectively used concurrent with radiotherapy but with fewer side effects (Bonomi et al., 1985; Dewit et al., 1985).

We hypothesized that by reducing the 40 mg/m^2 cisplatin dose to 20 mg/m^2, more treatment could be completed. In addition, the greater the number of cisplatin treatments, the shorter the treatment time but the lesser the number of side effects should compensate for the lower cisplatin dose. Therefore, in this study, we conducted a prospective randomized controlled trial to evaluate the treatment responses and acute treatment-related toxicities of patients with locally advanced cervical cancer who received concurrent chemoradiotherapy with cisplatin 40 mg/m^2, as standard protocol, compared to 20 mg/m^2 at Srinagarind Hospital, Khon Kaen University, Thailand.

Materials and Methods

This prospective randomized controlled trial was carried out at Srinagarind Hospital between April and December 2009, after approval by the Khon Kaen University Ethics Committee for Human Research. Patients were selected by inclusion criteria that consisting of; age younger than 60 years old with biopsy-proven untreated invasive carcinoma of cervix, FIGO stage IB2 to IVA without evidence of hydronephrosis or ureteric obstruction even on one side, Karnofsky performance status at least 80%, undergoing concurrent chemoradiotherapy with adequate bone marrow function (Absolute Neutrophil Counts at least 1,500 cells/mm^3, platelet counts at least 100,000 cells/mm^3), adequate renal function (serum creatinine less than 1.5 mg/dL, calculated GFR at least 40 ml/min), adequate liver function (serum bilirubin less than 1.5 times of the upper limit, serum aspartate aminotransferase less than 3 times of the upper limit). Patients were excluded from this study if they were immunocompromised such as; HIV-infected, having medical contraindications for chemotherapy, pregnant or breast feeding, having history of prior invasive cancer or prior pelvic irradiation or prior systemic chemotherapy.

When the patients were recruited, informed consent was obtained and then pretreatment evaluations including complete medical history, physical and pelvic examination, performance status assessment, clinical tumor measurement and laboratory work up (complete blood count, urinalysis, liver and renal function test, intravenous pyelography, chest radiography, cystoscopy and proctoscopy) were done. Abdominal CT or lymphangiography was not performed routinely unless clinically indicated. After that, all patients were staged clinically according to the FIGO staging criteria by a gynecological oncologist and a radiation oncologist

without general anesthesia. Radiotherapy was administered in a manner consistent with guideline of Radiotherapy Division at Srinagarind Hospital. The radiotherapy consisted of External Beam Radiotherapy (EBRT) followed by High Dose Rate Intracavitary Brachytherapy (HDRICB).

Initially, EBRT was delivered to the whole pelvis 5,000 cGy in 25 daily fractions using a high energy photon machine (10-25 MV) with an additional 600-1,000 cGy boost to the sides of grossly parametrial involvement. If tumor size was greater than 5 cm, EBRT was delivered without midline shielding. If tumor was 4-5 cm, the midline block was used after 4,000 cGy. If tumor was about 3-4 cm, the midline block was used after 3,000 cGy and if tumor size was less than 3 cm, the midline block was used after 2,000 cGy.

EBRT was delivered by a four-field-box technique (anteroposterior, posteroanterior, and two lateral fields). The pelvic field extended from the L4-L5 interspace to the midportion of the obturator foramen or the lowest level of disease with a 3-cm margin and laterally 1.5 cm beyond the lateral margins of the bony pelvis. For the lateral fields, the anterior border was at anterior part of the pubic symphysis and the posterior border included the anterior sacral silhouette (the space between S2-S3). The field could be modified for better coverage of lower vagina and uterine extension.

After adequate tumor regression or completion of EBRT, HDRICB was performed using an Ir-192 remote afterloading technique at 1 week intervals. The standard prescribed dose to point A for each HDRICB was 600 cGy for 4 insertions and 720 cGy for 3 insertions. Point A was defined as 2 cm above the cervical os marker and 2 cm perpendicular to the uterine axis along the plane of the uterus. During each insertion, the posterior and anterior vagina was packed with radio-opaque gauze to reduce rectal and bladder exposures and to visualize the posterior vaginal septum. No EBRT was performed on the same day of HDRICB.

All patients were randomly assigned to receive weekly cisplatin at a dose of 40 mg/m^2 compared to 20 mg/m^2, by computer-generated sequence and allocation concealment by opaque-envelopes. The drugs were given intravenously in concurrent with EBRT and the treatment plan included a total of 6 cycles. The first cycle of cisplatin was initiated on the first treatment day of radiotherapy if possible, not later than the third day then every week. Cisplatin was given within a 1-hour infusion after adequate prehydration by 2,000 ml of 5% dextrose in half strength saline intravenous infusion within 12-hour overnight. Prophylactic anti-emetics consisted of dexamethazone 8 mg and ondansetron 8 mg were routinely used intravenously at least 30 minutes before cisplatin infusion. The dose of cisplatin was based on the Body Surface Area but not exceed 2.0 m^2.

Treatment related toxicities were weekly monitored and graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0. If the granulocyte count was less than 1,500 cells/mm^3, platelet count was less than 100,000 cells/mm^3, creatinine clearance was less than 40 ml/min, or the patient could not tolerate acute gastrointestinal toxicities during the course of treatment, cisplatin administration would be suspended until these were return to normal. All patients were followed-up in an outpatient clinic to assess treatment responses at about 4 weeks after completion of treatment. When residual disease was suspected on pelvic or cytological examination results, a biopsy should be taken for confirmation whenever possible.

Treatment responses, either clinical or cytological, were classified using National Institute Response evaluation criteria in solid tumors that consisting of; Complete Response (CR) defined as disappearance of all lesions and no cytological evidence of disease, Partial Response (PR) defined as decrease in size at least a 30% of the longest diameter of lesions, Progressive Disease (PD) defined as increase in size at least a 20% of the longest diameter of lesions or appearance of one or more new lesions, and Stable Disease (SD) defined as neither sufficient shrinkage to reach partial response nor sufficient increase to reach progressive disease.

The baseline characteristics and demographic data of all patients were analyzed as descriptive statistics; in percentages for nominal data, but in mean + SD, median, and range for continuous data. Comparisons of categorical variables between the groups were performed using Pearson's chi-squared test, Fisher's exact test, and independent sample t-test, or nonparametric equivalents where appropriate. All data were analyzed using SPSS version 17.0 statistical software. P-values of less than 0.05 were considered as having statistical significance.

Results

Between April and December 2009, 140 patients with carcinoma of cervix were enrolled: 70 were assigned to receive weekly cisplatin 40 mg/m^2 (first group) and 70 were assigned to receive weekly cisplatin 20 mg/m^2 (second group). All of them were treated concurrently with radiotherapy and nobody dropped out. Baseline characteristics and demographic data of all patients were summarized in Table1. There was no significant difference in the baseline characteristics of the patients between the two groups except for the patient's age. All 140 patients completely received 6 cycles of cisplatin. Therefore all analyses were adjusted for age.

More patients in the first group met unforeseen

Table 1. Baseline Characteristics

Characteristics		40 mg/m^2	20 mg/m^2	P-value
Age (Mean ± SD)		50.0±7.52	46.4±6.97	0.002
Tumor size	≤4 cm	39 (55.7%)	40 (57.1%)	0.865
	>4 cm.	31 (44.3%)	30 (42.9%)	
Histological type				0.775
Squamous cell carc		56 (80.0%)	57 (81.4%)	
Adenocarcinoma		13 (18.6%)	11 (15.7%)	
Adenosquamous carc		1 (1.4%)	2 (2.9%)	
Tumor Characteristics				0.726
Exophytic		43 (61.4%)	45 (64.3%)	
Infiltrative		27 (38.6%)	25 (35.7%)	
FIGO stage	IIA	5 (7.1%)	6 (8.6%)	0.399
	IIB	28 (40.0%)	35 (50.0%)	
	IIIB	37 (52.9%)	29 (41.4%)	

Table 2. Treatment Schedule Details

Characteristic	40 mg/m^2	20 mg/m^2	P-value
Unplanned interruptions			
No	57 (81.4%)	65 (92.9%)	0.02
Yes	13 (18.6%)	5 (7.14%)	
Treatment time (days)			
Mean (days)	80.3±15.7	75.8±11.3	0.026
Treatment responses			
Complete response	69 (98.6%)	68 (97.1%)	0.599
Partial response	1 (1.4%)	2 (2.9%)	0.500
Progressive disease	0	0	
Stable disease	0	0	

treatment schedule interruptions when compared to the second group (13/70 vs. 5/70, p=0.02) as shown in Table 2. Almost all of these patients (11/13 vs. 4/5) had durations of delayed treatments equal or less than 1 week. As the result of treatment schedule interruptions and delayed treatments, treatment time of the first group was longer than the second group's. Treatment responses did not between the two groups (Table 2).

All patients came for follow-up in outpatient clinic at about 4 weeks after treatment completed. Complete responses were found in 69/70 (98.6%) of the first group and 68/70 (97.1%) of the second group, therefore, no significant difference was found in this comparison. Consequently, 3/140 patients were classified as having partial responses, one in the first group had suspected residual disease on pelvic examination, and the other two in the second group had detected residual disease on pelvic examination in one and on abnormal cytology (AGC-favor neoplasia) without gross lesion in another one. Diagnoses of these 3 patients were confirmed by colposcopic directed biopsies that show histological results of adenocarcinoma in all of them. After these, additional HDRICB and hyperthermia were delivered to these three patients upon the decision making of radiation oncologists. Nobody was classified as having progressive or stable disease.

As shown in Table 3, both weekly cisplatin regimens were well tolerable among the patients who were treated concurrent with radiotherapy. There was no treatment related death. Hematological toxicity was most frequently observed and was similarly found among both groups. However, there was no significant difference in numbers of grade 1-2 anemia and grade 1-2 thrombocytopenia found between the groups. Nobody had grade 3-4 hematological toxicity. 14.8% of 420 courses in the first group had grade1-2 leukopenia and 9.3% had grade 1-2 neutropenia, which were significantly higher than 6.4% of grade 1-2 leukopenia and 2.6% of grade 1-2 neutropenia found in 420 courses in the second group (p=0.029). All of these problems could be solved with oral iron-supplement therapy, blood component transfusion if clinically indicated, and supportive care, without any use of colony-stimulating growth factor or platelet transfusion. Among non-hematological toxicities, gastrointestinal toxicity was most frequently observed in both groups.

Unfortunately, grade 3 gastrointestinal toxicity was observed in only one patient of the second group. This patient suffered from diarrhea with dehydration requiring intravenous fluid replacement and hospitalization about 1 week. The incidence of grade 1-2 gastrointestinal toxicity consisting of nausea, vomiting, and diarrhea, was significantly higher in the first group when compared to the second group. 2 patients in the first group developed renal insufficiency due to calculated GFR being less than 40 ml/min in the last cycles of chemotherapy. Fortunately, renal function was return to normal after adequate hydration and supportive care in these 2 patients. During the course of treatment, 4.5% of the first group were found having grade 1 sensory neuropathy, which was significantly higher than 1.2% of the second group (p=0.004), without any measure, all were spontaneously recovered after treatment completed. The first group had slightly higher incidence of electrolyte imbalances when compared to the second group, however, there was no significant difference found in this comparison.

Discussion

After a 1999 National Cancer Institute (NCI) Clinical alert was issued, chemoradiotherapy has become widely used in treating women with cervical cancer (Trimble et al, 2007). Cisplatin is considered the most active cytotoxic agent and the drug of choice for concurrent chemoradiation (Nias et al, 1985; Rose et al, 2000). The effects of equivalent doses of cisplatin administered on schedules every three weeks, weekly and daily, were also studied with more frequent administration either weekly or daily resulting in greater therapeutic gain (Bonomi et al., 1985). However, weekly cisplatin administration was

Table 3. Acute Cisplatin Treatment Related Toxicity in the 140 Patients

Toxicity	40 mg/m^2 (n=420 courses)				20 mg/m^2(n=420 courses)				P-value
Grade	0	1	2	3	0	1	2	3	
Anemia	66.2	26.7	7.14	0	66.20	25.5	8.33	0	0.607
Leukopenia	85.2	11.9	2.86	0	93.57	5.23	1.20	0	0.032
Neutropenia	90.7	6.67	2.62	0	97.38	2.14	0.48	0	0.029
Thrombocytopenia	98.6	1.19	0.24	0	99.52	0.24	0.24	0	0.261
Nephrotoxicity	96.9	3.09	0	0	98.81	1.19	0	0	0.057
Hepatotoxicity	97.6	2.38	0	0	97.15	2.85	0	0	0.666
Nausea/Vomiting	74.5	21.7	3.81	0	85.72	13.3	0.95	0	0.032
Diarrhea	73.6	24.1	2.38	0	87.38	11.7	0.71	0.24	0.034
Sensory neuropathy	95.5	4.52	0	0	98.81	1.19	0	0	0.004
Hyponatremia	97.4	2.62	0	0	99.29	0.71	0	0	0.055
Hypokalemia	90.5	9.52	0	0	91.67	8.33	0	0	0.545

as effective as daily administration and was a more convenient schedule (Einstein et al., 2007). Most widely accepted protocol is the combination of irradiation and cisplatin at dose of 40 mg/m^2, once a week, until completion of the treatment course (Rose et al., 2002).

Cetina et al reported 83% complete response with weekly cisplatin 40 mg/m^2 in concurrent with radiotherapy (Cetina et al., 2006). Ozsaran et al reported early results with an excellent overall response rate (97.4%) of concurrent chemoradiotherapy in patients with locally advanced cervical cancer (Ozsaran et al., 2003). Chiara et al (1994) reported a response rate of only 78% after treatment of FIGO stage IIB-III cervical cancer. Tangsiriwattana et al reported a 97% overall response rate with complete responses in 86% of patients with carcinoma of cervix stage IB2-IVA receiving concurrent chemoradiotherapy with weekly cisplatin 40 mg/m^2. (Tangsiriwattana et al., 2007). In this study, the results were similar to several published trials mentioned above. Early results of treatment responses revealed 98.6% complete-response rate in the group of patients received concurrent weekly cisplatin 40 mg/m^2 as the standard protocol. Interestingly, our data have demonstrated the highest complete response rate that maybe due to excellent treatment compliance.

Excellent treatment compliance which showed 140 (100%) patients able to complete 6 cycles of weekly cisplatin could be achieved, because nobody dropped out during data collection. This should be merit of most of patients (70%) were enrolled by well-set inclusion criteria, and had good performance status enough to tolerate treatment's toxicities until completion of the treatment course. In addition, radiotherapy in our institute was delivered in a manner consistent with guideline of the Radiotherapy Division at Srinagarind Hospital that differs from previous study (Vale et al., 2008). Our guideline has been in consistent with The American Brachytherapy Society (ABS) that recommended using a minimum total of 7500 cGy to point A with EBRT and HDRICB 600 cGy/fraction about 3-4 times to achieve optimum tumor control. (Nag et al., 2000) Therefore, this study has sufficient data to support that the use of weekly cisplatin 40 mg/m^2 in concurrent with radiotherapy in patients with locally advanced cervical cancer had excellent treatment outcomes.

From a meta-analysis of 18 randomized trials done in 2008, neither evidences of a difference in the size of the benefit by radiotherapy, nor chemotherapy dose and schedule was seen. (Vale et al., 2008) Many studies are being undertaken to ascertain the optimal dose schedules and trying to decrease the total dose of cisplatin administered in order to minimize its toxicities. Bonomi et al reported that the effects of different cisplatin doses at 100 mg/m^2, 50 mg/m^2, and 20 mg/m^2 repeated every 21 days, showed no appreciable differences in complete response rate, but the higher dose regimen was associated with greater myelosuppression and nephrotoxicity (Bonomi et al., 1985). Moreover, a dose response relationship was not seen. Salem et al had also reported that cisplatin dose at 20 mg/m^2 per 24 hour continuous infusion could be used concurrently with radiotherapy in head and neck cancer. (Salem et al, 1984) It was assumed that tumor biology of squamous cell carcinoma of the cervix and head/neck are similar. Mitra et al reported that 88% complete response rate was found in patient with carcinoma of cervix received weekly cisplatin 30 mg/m2 plus external radiotherapy, which was significantly higher than only 73% in patients received radiotherapy alone. (Mitra et al., 2006) Nyongesa et al had also reported that a weekly cisplatin dose at 25 mg/m^2 was the maximum tolerated dose (MTD) when used in combination with pelvic radiotherapy and the dose limiting toxicity (DLT) was observed at weekly cisplatin dose of 30 mg/m^2. (Nyongesa et al., 2006) These all were lower than the recommended dose of weekly cisplatin at 40 mg/m^2.

Several published trials reported that hematological toxicities and gastrointestinal toxicities were the principle acute treatment related toxicities that were found similarly in our study (Ikushima et al., 2006; Tangsiriwatthana et al., 2007; Jones et al., 2009). Chen et al reported that prolongation of treatment time in cervical cancer resulted in a daily decrease in local control rate of 0.67% overall per day of treatment prolongation and median treatment time is about 63 days for all stages of disease (Chen et al, 2003). Peres et al reported that the overall treatment time may be related to biological factors such as cell repopulation and increased proliferation resulting from treatment interruptions (Peres et al., 1995). Therefore, radiotherapy should be delivered in the shortest possible overall treatment time. In our study, median treatment times were 80.5 and 77.0 days in the group of weekly cisplatin 40 mg/m^2 and 20 mg/m^2, respectively. Fortunately, the early results good, due to the fact that about 40% of our patients had tumor size larger than 4 cm.

Gasinska et al reported that treatment prolongation negatively influences causes-specific survival and pelvic control rate (Gasinska et al., 2004). In general, more extensive tumors which have a higher local failure rate required longer overall treatment time and shorter treatment time could be achieved in patients with smaller tumors. (Petsuksiri et al., 2008) The cause of delayed treatments in our study were due to the unplanned interruptions during cycles resulted from acute treatment related toxicities, the radiotherapy machine breakdown, extended weekends due to public holidays, and the break between EBRT to first HDRICB required to improve the geometry of the residual tumors.

As result in high complete response rate, this study showed that no one had grade 3-4 anemia and more than half of all patients (66.2%) had initial hemoglobin levels of at least 11.0 g/dL. Choi et al reported the impact of the hemoglobin levels of at least 10 g/dL on better survival of patient with carcinoma of cervix without lymph node metastasis treated with concurrent chemoradiotherapy (Choi et al., 2006). Veerasarn et al also reported that the only prognostic factor predicting better complete response rate was the baseline hemoglobin levels >10 g/dL (Veerasarn et al., 2007). On the other hand, Obermair et al reported that only patients with nadir hemoglobin levels > 11 g/dL throughout chemoradiotherapy had a more than 90% chance of achieving a complete clinical response and

the nadir hemoglobin level was the most predictive factor for treatment failure while the hemoglobin level at the time of presentation is prognostically not significant (Obermair et al., 2001). From these mentioned reasons, we have never let our patient's hemoglobin level to be lower than 10 g/dL.

Several reports have considered adenocarcinoma differently from other histological subtypes because its biology is more aggressiveness and relatively radioresistant (Shingleton et al, 1995; Nakanishi et al, 2000). In our study, adenocarcinoma was found in 13/70 and 11/70 in the first group and in the second group, respectively, and all three partial responses were found in 3 of them (1 in the first group and 2 in the second group) supporting its radioresistancy. There is also still controversy about the most effective primary treatment for adenocarcinoma of cervix because of a concern of this relatively radioresistant nature of adenocarcinoma (Peters et al, 2000; Stehman et al, 2007; Petsuksiri et al, 2008) However, there were no significant difference in pelvic recurrence between squamous cell carcinoma and adenocarcinoma in patients who have bulky tumor of larger than 4 cm (Eifel et al, 1995; Peres et al, 1998).

The most important strength of this study is that it was a prospective randomized controlled trial, therefore, there was no recall bias and the outcomes or any variables could be completed without data missing. The basic characteristics and demographic data among the two groups were similarly found, except age, which should not be an important factor in prognosis. In addition, a uniform classification system was used for reporting data about treatment responses and toxicities making outcome assessor comfortable for evaluation and no one had miscommunication during data collection and analysis. However, the limitation is that there were insufficient data available to assess long term treatment outcomes such as survival rate, loco-regional relapses, or distant metastases, and serious late treatment related toxicities, due to only short follow-up times were gained. As a result, in the nearly future, the author will continue collecting data and information on these patients such as survival rate, loco-regional relapses, or distant metastases, and also serious late treatment related toxicities, until we can receive complete information, sufficient to evaluate all issues mentioned above, because these information are essential for patients when choosing treatment options. Authors believe that the results of this prospective randomized controlled trial would have had some benefits and uses to be applied in concurrent chemoradiotherapy for improvement of treatment tolerability and quality of life in cervical cancer patients.

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References

Bonomi P, Blessing JA, Stehman FB, et al (1985). Randomized trial of three cisplatin dose schedules in squamous-cell carcinoma of the cervix: a Gynecologic Oncology Group study. *J Clin Oncol*, **3**, 1079-85.

Cancer Unit, Khon Kaen University (2007). Statistical report. Khon Kaen, Tumor registry, Cancer Unit, Khon Kean University, 8-10.

Cetina L, Rivera L, Hinojosa J, et al (2006). Routine management of locally advanced cervical cancer with concurrent radiation and cisplatin. Five-year results. *BMC Womens Health*, **6**, 3.

Chen SW, Liang JA, Yang SN, Ko HL, Lin FJ (2003). The adverse effect of treatment prolongation in cervical cancer by high-dose-rate intracavitary brachytherapy. *Radiother Oncol*, **67**, 69-76.

Chiara S, Bruzzone M, Merlini L, et al (1994). Randomized study comparing chemotherapy plus radiotherapy versus radiotherapy alone in FIGO stage IIB-III cervical carcinoma. GONO (North-West Oncologic Cooperative Group). *Am J Clin Oncol*, **17**, 294-7.

Choi YS, Yi CM, Sin JI, et al (2006). Impact of hemoglobin on survival of cervical carcinoma patients treated with concurrent chemoradiotherapy is dependent on lymph node metastasis findings by magnetic resonance imaging. *Int J Gynecol Cancer*, **16**, 1846-54.

Dewit L, Begg AC, Kohler Y, Stewart FA, Bartelink H (1985). Influence of cis-diamminedichloroplatinum (II) on mouse duodenal crypt stem cell survival after multifraction X ray treatment. *Int J Radiat Oncol Biol Phys*, **11**, 1809-16.

Deerasamee S, Srivatanakul P (1999). Cervix uteri in: Deerasamee S, Martin N, Sontipong S, Sriamporn S, Sriplung S, Srivatanakul P, et al, editors. Cancer in Thailand, Vol II 1992-1994, Lyon, IARC, 56-9.

Eifel PJ, Burke TW, Morris M, Smith TL(1995). Adenocarcinoma as an independent risk factor for disease recurrence in patients with stage IB cervical carcinoma. *Gynecol Oncol*, **59**, 38-44.

Einstein MH, Novetsky AP, Garg M, et al (2007). Survival and toxicity differences between 5-day and weekly cisplatin in patients with locally advanced cervical cancer. *Cancer*, **109**, 48-53.

Gasinska A, Fowler JF, Lind BK, Urbanski K (2004). Influence of overall treatment time and radiobiological parameters on biologically effective doses in cervical cancer patients treated with radiation therapy alone. *Acta Oncol*, **43**, 657-66.

Ikushima H, Osaki K, Furutani S, et al (2006). Chemoradiation therapy for cervical cancer: toxicity of concurrent weekly cisplatin. *Radiat Med*, **24**, 115-21.

Jones B (2009). Toxicity after cervical cancer treatment using radiotherapy and chemotherapy. *Clin Oncol (R Coll Radiol)*, **21**, 56-63.

Keys HM, Bundy BN, Stehman FB, et al (1999). Cisplatin, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage IB cervical carcinoma. *N Engl J Med*, **340**, 1154-61.

Landoni F, Maneo A, Colombo A, et al (1997). Randomised study of radical surgery versus radiotherapy for stage Ib-IIa cervical cancer. *Lancet*, **350**, 535-40.

Mangioni C, Landoni F, Colombo A, et al (1999). Concurrent platinum-based chemo- and radiotherapy for locally advanced cervical cancer: a new gold-standard treatment? *Ann Oncol*, **10**, 647-8.

Miller AB, Hoogstraten B, Stequet M, Winkler A (1981). Reporting results of cancer treatment. *Cancer*, **47**, 207-14.

Mitra D, Ghosh B, Kar A, et al (2006). Role of chemoradiotherapy in advanced carcinoma cervix. *J Indian*

Med Assoc, **104**, 432-36.
Mohar A, Frias-Mendivil M (2000). Epidemiology of cervical cancer. *Cancer Invest*, **18**, 584-90.
Monk BJ, Tian C, Rose PG, Lanciano R (2007). Which clinical/pathologic factors matter in the era of chemoradiation as treatment for locally advanced cervical carcinoma? Analysis of two Gynecologic Oncology Group (GOG) trials. *Gynecol Oncol*, **105**, 427-33.
Morris M, Eifel PJ, Lu J, et al (1999). Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer. *N Engl J Med*, **340**, 1137-43.
Nag S, Erickson B, Thomadsen B, et al (2000). The American Brachytherapy Society recommendations for high-dose-rate brachytherapy for carcinoma of the cervix. *Int J Radiat Oncol Biol Phys*, **48**, 201-11.
Nakanishi T, Ishikawa H, Suzuki Y, et al (2000). A comparison of prognoses of pathologic stage Ib adenocarcinoma and squamous cell carcinoma of the uterine cervix. *Gynecol Oncol*, **79**, 289-93.
Nias AH (1985). Radiation and platinum drug interaction. *Int J Radiat Biol Relat Stud Phys Chem Med*, **48**, 297-314.
Nyongesa C, Ruff P, Donde B, Kotzen J (2006). A phase I study of concurrent cisplatin chemotherapy in patients with carcinoma of the cervix receiving pelvic radiotherapy. *Int J Gynecol Cancer*, **16**, 1614-9.
Obermair A, Cheuk R, Horwood K, et al (2001). Impact of hemoglobin levels before and during concurrent chemoradiotherapy on the response of treatment in patients with cervical carcinoma: preliminary results. *Cancer*, **92**, 903-8.
Ozsaran Z, Yalman D, Yurut V, et al (2003). Radiochemotherapy for patients with locally advanced cervical cancer: early results. *Eur J Gynaecol Oncol*, **24**, 191-4.
Parkin DM, Pisani P, Ferlay J (1993). Estimates of the worldwide incidence of eighteen major cancers. *Int J Cancer*, **54**, 594-606.
Pearcey R, Miao Q, Kong W, et al (2007). Impact of adoption of chemoradiotherapy on the outcome of cervical cancer in Ontario: results of a population-based cohort study. *J Clin Oncol*, **25**, 2383-8.
Perez CA, Grigsby PW, Castro-Vita H, Lockett MA (1995). Carcinoma of the uterine cervix. I. Impact of prolongation of overall treatment time and timing of brachytherapy on outcome of radiation therapy. *Int J Radiat Oncol Biol Phys*, **32**, 1275-88.
Perez CA, Grigsby PW, Chao KS, Mutch DG, Lockett MA (1998). Tumor size, irradiation dose and long-term outcome of carcinoma of uterine cervix. *Int J Radiat Oncol Biol Phys*, **41**, 307-17.
Peters WA, Liu PY, Barrett RJ, et al (2000). Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. *J Clin Oncol*, **18**, 1606-13.
Petsuksiri J, Chansilpa Y, Therasakvichya S, et al (2008). Treatment options in bulky stage IB cervical carcinoma. *Int J Gynecol Cancer*, **18**, 1153-62.
Phillips RA, Tolmach LJ (1966). Repair of potentially lethal damage in x-irradiated HeLa cells. *Radiat Res*, **29**, 413-32.
Rose PG, Bundy BN, Watkins EB, et al (1999). Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. *N Engl J Med*, **340**, 1144-53.
Rose PG (2000). Chemoradiotherapy: the new standard care for invasive cervical cancer. *Drugs*, **60**, 1239-44.
Rose PG (2002). Chemoradiotherapy for cervical cancer. *Eur J Cancer*, **38**, 270-8.
Salem P, Khalyl M, Jabboury K, Hashimi L (1984). Cis-diamminedichloroplatinum (II) by 5-day continuous infusion. A new dose schedule with minimal toxicity. *Cancer*, **53**, 837-40.
Shingleton HM, Bell MC, Fremgen A, et al (1995). Is there really a difference in survival of women with squamous cell carcinoma, adenocarcinoma, and adenosquamous cell carcinoma of the cervix? *Cancer*, **76 (10 Suppl)**, 1948-55.
Stehman FB, Bundy BN, Kucera PR, et al (1997). Hydroxyurea, 5-fluorouracil infusion, and cisplatin adjunct to radiation therapy in cervical carcinoma: a phase I-II trial of the Gynecologic Oncology Group. *Gynecol Oncol*, **66**, 262-7.
Stehman FB, Ali S, Keys HM, et al (2007). Radiation therapy with or without weekly cisplatin for bulky stage 1B cervical carcinoma: follow-up of a Gynecologic Oncology Group trial. *Am J Obstet Gynecol*, **197**, 5031-6.
Tangsiriwatthana T, Chumworathayi B, Yuenyao P, Luanratanakorn S, Pattamadilok J (2007). Srinagarind Hospital experience in concurrent chemoradiation for 100 patients with stage IB2 to IVA uterine cervical cancer. *Radiat Med*, **25**, 502-10.
Trimble E, Gius D, Harlan LC (2007). Impact of NCI announcement upon use of chemoradiation for women with cervical cancer. *J Clin Oncol*, **25**, 2835.
Vaupel P, Thews O, Mayer A, Hockel S, Hockel M (2002). Oxygenation status of gynecologic tumors: what is the optimal hemoglobin level? *Strahlenther Onkol*, **178**, 727-31.
Vale C (2008).Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: a systematic review and meta-analysis of individual patient data from 18 randomized trials. *J Clin Oncol*, **26**, 5802-12.
Veerasarn V, Lorvidhaya V, Kamnerdsupaphon P, et al (2007). A randomized phase III trial of concurrent chemoradiotherapy in locally advanced cervical cancer: preliminary results. *Gynecol Oncol*, **104**, 15-23.
Whitney CW, Sause W, Bundy BN, et al (1999). Randomized comparison of fluorouracil plus cisplatin versus hydroxyurea as an adjunct to radiation therapy in stage IIB-IVA carcinoma of the cervix with negative para-aortic lymph nodes: a Gynecologic Oncology Group and Southwest Oncology Group study. *J Clin Oncol*, **17**, 1339-48.