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ภาวะแทรกซ้อนทางระบบโลหิตจากการให้ยาเคมีบำบัดซิสพลาตินร่วมกับรังสีรักษาในการรักษามะเร็งปากมดลูกที่ศูนย์มะเร็งอุบลราชธานี

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Hematologic Toxicities of Cisplatin Concurrent Chemoradiation in Cervical cancer at Ubonrajchathani Cancer Center

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หลักการและเหตุผล: ผู้ป่วยด้วยโรคมะเร็งปากมดลูกลุกลามเฉพาะได้รับการรักษาด้วยการให้ยาเคมีบำบัดซิสพลาตินทุกสัปดาห์ร่วมกับรังสีรักษา แต่พบว่ามีรายงานเกี่ยวกับความชุกของภาวะแทรกซ้อนทางระบบโลหิตในผู้ป่วยไทยอยู่น้อยมาก

วัตถุประสงค์: เพื่อทราบถึงความชุกของภาวะแทรกซ้อนทางระบบโลหิต และผลการรักษาเบื้องต้นจากการรักษามะเร็งปากมดลูกด้วยยาเคมีบำบัดซิสพลาตินร่วมกับรังสีรักษาที่ศูนย์มะเร็งอุบลราชธานี

วัสดุและวิธีการศึกษา: กลุ่มผู้วิจัยได้ทำการเก็บข้อมูลจากเวชระเบียน และแบบบันทึกการให้รังสีรักษาของผู้ป่วยที่ได้รับการรักษาด้วยยาเคมีบำบัดซิสพลาตินร่วมกับรังสีรักษาตั้งแต่วันที่ 1 มกราคม 2546 ถึงวันที่ 31 ธันวาคม 2548 แล้วนำมาวิเคราะห์ผู้ป่วยเหล่านี้ได้รับการรักษาด้วยการให้ยาเคมีบำบัดซิสพลาติน 40 mg/m^2 ทุกสัปดาห์ ร่วมกับการให้รังสีรักษาประมาณ 7500-9000 cGy บริเวณอุ้งเชิงกราน

รูปแบบการศึกษา: เชิงพรรณนาแบบเก็บข้อมูลย้อนหลัง

สถานที่ทำการศึกษาวิจัย: ศูนย์มะเร็งอุบลราชธานี จังหวัดอุบลราชธานี

ผลการศึกษา: มีผู้ป่วยมะเร็งปากมดลูกที่ได้รับการรักษาด้วยยาเคมีบำบัดซิสพลาตินร่วมกับรังสีรักษา ที่ศูนย์มะเร็งอุบลราชธานีจำนวน 95 ราย แต่สามารถนำมาวิเคราะห์ได้

Background: Weekly cisplatin concurrent chemoradiation is a treatment in locally advanced cervical cancer. However, there are only few reports in Thai women about hematologic toxicities of this treatment.

Objectives: To evaluate prevalence of hematologic toxicities and early response accompanying weekly cisplatin concurrent chemoradiation in cervical cancer patients.

Method: Medical records of cervical cancer patients treated between January 2003 to December 2005 were reviewed retrospectively. Patients were treated by weekly cisplatin 40 mg/m^2 accompanying with radiotherapy of total dose 7500-9000 cGy.

Design: Retrospective descriptive study

Setting: Ubonrajchathani Cancer Center, Ubonrajchathani

Results: 89 out of 95 patients diagnosed as locally advanced cervical cancer and treated by weekly cisplatin in concurrent with radiotherapy were eligible and included for analysis. Mean age was 47.5 years (range, 34-71 years). The major histologic types were squamous cell carcinoma (79.8%), and distribution according to International Federation of Gynecology and Obstetrics (FIGO) stage was IB2 19.1%, IIA 6.7%, IIB 38.2%, IIIA 2.2%, IIIB 31.5% and IVA 2.2%, respectively. 80.9% of patients

89 ราย พบว่ามีอายุเฉลี่ย 47.5 ปี (พิสัย 34-71) ผู้ป่วยส่วนมากเป็นมะเร็งชนิด squamous cell carcinoma (ร้อยละ 79.8) โดยมีระยะของโรคเป็นระยะ IB2 ร้อยละ 19.1 ระยะ IIA ร้อยละ 6.7 ระยะ IIB ร้อยละ 38.2 ระยะ IIIA ร้อยละ 2.2 ระยะ IIIB ร้อยละ 31.5 และระยะ IVA ร้อยละ 2.2 ตามลำดับ มีผู้ป่วยที่ได้รับยาเคมีบำบัดซิสพลาตินทุกสัปดาห์อย่างน้อย 5 รอบ ร้อยละ 80.9 พบความชุกของภาวะแทรกซ้อนทางระบบโลหิตจำนวนร้อยละ 78.7 โดยจัดเป็นเกรด 3-4 ร้อยละ 14.4 ภาวะเม็ดเลือดขาวต่ำร้อยละ 64.0 (เกรด 3-4 ร้อยละ 9.0) ภาวะเม็ดเลือดขาวชนิด neutrophil ต่ำร้อยละ 40.4 (เกรด 3-4 ร้อยละ 7.8) ภาวะโลหิตจางร้อยละ 57.3 (เกรด 3-4 ร้อยละ 1.1) ไม่มีภาวะเกล็ดเลือดต่ำเกรด 3-4 มีผู้ป่วยเพียง 1 ราย ที่มีภาวะไข้จากเม็ดเลือดขาวต่ำซึ่งสามารถรักษาได้ ไม่พบปัจจัยที่มีความสัมพันธ์กับผลการรักษาอย่างมีนัยสำคัญทางสถิติ หลังจากให้ยาครบพบว่ามีผู้ป่วยตอบสนองต่อการรักษาโดยสมบูรณ์ร้อยละ 86.5 ตอบสนองต่อการรักษาบางส่วน ร้อยละ 13.5

สรุป: การให้ยาเคมีบำบัดซิสพลาตินทุกสัปดาห์ร่วมกับรังสีรักษาที่ศูนย์มะเร็งอุบลราชธานี พบว่ามีความชุกของภาวะแทรกซ้อนทางระบบโลหิตร้อยละ 78.7 (เกรด 3-4 ร้อยละ 14.4) ซึ่งสามารถยอมรับและดูแลรักษาได้ มีผู้ป่วยตอบสนองทางคลินิกต่อการรักษาโดยสมบูรณ์สูงถึงร้อยละ 86.5

คำสำคัญ: ภาวะแทรกซ้อนทางระบบโลหิต, ซิสพลาติน, มะเร็งปากมดลูก, รังสีรักษาร่วมกับเคมีบำบัด

received five or more cycles of weekly cisplatin. Prevalence of hematologic toxicities was 78.7% and grade 3-4 were found in 14.4% of the patients. There were leukopenia 64.0% (9% grade 3-4), neutropenia 40.4% (7.8% grade 3-4), anemia 57.3% (only 1.1% grade 3-4) and no grade 3-4 thrombocytopenia. Only one patient (1.1%) had febrile neutropenia and this was manageable. There was no significant factor associated with clinical response in this study. Clinical response was evaluated. Complete response was 86.5%, partial response was 13.5%.

Conclusions: Prevalence of hematologic toxicities accompanying with weekly cisplatin concurrent chemoradiation was 78.7% and grade 3-4 were found in 14.4% of the patients. Hemotologic toxicities were acceptable and managable. Complete clinical response rate was high.

Key words: Hematologic toxicity, cisplatin, cervical cancer, concurrent chemoradiation

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Introduction

Cervical cancer is the second most common cancer among women worldwide and the most common cancer among women in Africa, Asia and South America. In 1995-1997, the incidence of cervical cancer of Thai women was 19.5 per 100,000 women population.[1] It is the major health problem in Thailand.

In Ubonrajchathani Cancer Center, about two third of cervical cancer patients were in locally advanced stage.[2] These patients are commonly treated by radiotherapy (RT), but the doses required for eradication of large tumors may exceed the tolerance of normal tissues. Various efforts have been made in the past decades to improve the outcome. Altered fractionation schedules did not prove to be associated with significant better local control or survival.[3] Hyperthermia in combination with standard RT for locally advanced cervical cancer was demonstrated to improve both local control and survival.[4] However, it was not practical in routine implementation at Ubonrajchathani Cancer Center.

Radiotherapy is a conventional treatment for patients with locally advanced stage at the time of diagnosis. Five randomized studies as well as a meta-analysis have demonstrated that chemotherapy administered concurrently with radiotherapy improved overall survival in comparison with radiotherapy alone.[5-9] In Ubonrajchathani Cancer Center, cisplatin concurrent chemoradiation is a routine treatment in locally advanced cervical cancer. Hematologic toxicities are the most common complications. However, there are only few reports in Thai women about hematologic toxicities in treatment of locally advanced

cervical cancer with cisplatin concurrent chemoradiation. The aim of this study was to retrospectively evaluate the hematologic toxicities and response of cisplatin concurrent chemoradiation.

Materials and methods

Medical records of 89 out of 95 patients with clinical FIGO stage IB2-IVA biopsy-proven carcinoma of the uterine cervix, which were treated by cisplatin concurrent chemoradiation at Ubonrajchathani Cancer Center between January 2003 to December 2005, were retrospectively reviewed. Medical records of other six patients were unfortunately absence. Patients with a history of hysterectomy, abdominal or pelvic radiotherapy and neoadjuvant chemotherapy would be excluded. Data were obtained from both out-patient medical records and radiation treatment charts.

In Ubonrajchathani Cancer Center, Radiotherapy was routine administered to the whole pelvic region about 25 fractions to total of 50 Gy, followed four weeks later by intracavitary brachytherapy. Two or three times of medium dose intracavitary brachytherapy were scheduled. The total dose delivered to point A (a reference location 2 cm lateral and 2 cm superior to the cervical os) was 75-90 Gy. Pelvic radiation was delivered by anteroposterior and posteroanterior directions. 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). The fields could be modified to include areas of tumor. Radiotherapy was withheld if a patient had an absolute neutrophil count of less than 1,500 cells/mm^3 and delayed until it was more than 1,500 cells/mm^3.

Cisplatin 40 mg/m^2 was prescribed every week for an intended more than five cycles. Chemotherapy and radiation therapy were initiated simultaneously. Before each cycle of chemotherapy, complete blood counts and performance status were obtained. The hematologic toxicities were assesed according to the World Health Organization (WHO) criteria.[10] The clinical responses to treatment were evaluated after completion of cisplatin concurrent chemoradiation for 3 months.

Statistical analysis

We calculated the target sample size from previous data of Serkies and Jassem,[11] incidence of grade 3-4 hematologic toxicities was 6.0%. Precision of error estimation was $\alpha = \pm 0.05$, $Z_{\alpha/2} = 1.96$. The calculated sample size group was 87 patients.

Data were collected and computerized, including generalized characteristic, clinicopathological features, number of cycles of chemotherapy, hematologic toxicities as mean (range) and percentage (%). All data were analyzed by using Pearson's chi-square test, Fisher's exact test and student T test. A p-value of < 0.05 was considered significant.

Results

Eighty nine out of 95 patients diagnosed as locally advanced cervical cancer who have 382 cycles of weekly cisplatin concurrent chemoradiation were completely reviewed. Six patients were unfortunately absence and excluded. Mean age was 47.5 years (range, 34-71 years). The majority of histology were squamous cell carcinoma (79.8%), and distribution according to International Federation of Gynecology and Obstetrics (FIGO) stage was as follows; IB2 19.1%, IIA 6.7%, IIB 38.2%, IIIA 2.2%, IIIB 31.5% and IVA 2.2%, respectively. (Table 1) Most of patients received cisplatin concurrent chemoradiation for five cycles (50.6%). There were 27 patients (30.3%) received six cycles. (Table 2)

The prevalence of hematologic toxicities was 78.7% (70 patients). Leukopenia was the most common hematologic toxicities (57 patients, 64.0%). There were 8 patients (9%) grade 3-4 leukopenia. Anemia were found in 51 patients (57.3%). There was grade 3-4 anemia in only one patient (1.1%). This study showed neutropenia in 36 patients (40.4%) but only 7 patients (7.8%) were with grade 3-4 neutropenia. Only one patient had febrile neutropenia (1.1%) and was treated with antibiotics, G-CSF and supportive care. Thrombocytopenia was less common hematologic toxicities in cisplatin concurrent chemoradiation that was showed in only 6 patients (6.8%) and no grade 3-4 was demonstrated. The hematologic toxicitites were shown in Table 3.

After completion of concurrent chemoradiation for 3 months, we evaluated the clinical response by pelvic examination and Pap smear. We found that complete clinical response rate was 86.5% and partial response rate was 13.5%. There was no significant difference in the clinical characteristics (including age, BMI, total dose of cisplatin, total dose of radiation, tumor size, FIGO staging

Table 1. Clinicopathologic features (N=89)

Characteristics	Number (%)
Histology	
Squamous cell carcinoma	71 (79.8)
Adenocarcinoma	16 (18.0)
Others	2 (2.2)
FIGO stages	
IB2	17 (19.1)
IIA	6 (6.8)
IIB	34 (38.2)
IIIA	2 (2.2)
IIIB	28 (31.5)
IVA	2 (2.2)
Tumor size (cm)	
≤ 4	33 (37.1)
> 4	56 (62.9)
Treatment response	
Complete	77 (86.5)
Partial	12 (13.5)

Table 2. Number of cycle of weekly cisplatin chemotherapy (N=89)

Cycles	Number (%)
6	27 (30.3)
5	45 (50.6)
4	16 (18.0)
3	1 (1.1)

Table 3. Hematologic toxicities (C=total 382 cycles, P=89 patients)

Toxicities	Set	WHO Grading (%)					Grade 3+4 (%)	95%CI
		0	1	2	3	4		
Anemia	C	57.8	37.4	4.5	0.3	0	0.3	0.02 - 1.74
	P	42.7	42.7	13.5	1.1	0	1.1	0.05 - 6.94
Leukopenia	C	69.2	14.7	13.4	2.4	0.3	2.7	1.39 - 5.02
	P	36.0	22.5	32.5	7.9	1.1	9.0	4.25 - 17.45
Neutropenia	C	85.3	9.7	2.6	0.8	1.6	2.4	1.18 - 4.64
	P	59.6	23.6	9.0	2.2	5.6	7.8	4.25 - 17.45
Thrombocytopenia	C	97.1	1.9	1.0	0	0	0	-
	P	93.2	3.4	3.4	0	0	0	-

C=Maximum grade over all cycles

P=Maximum grade of over all cycles within patients

CI= Confidence interval

Table 4. Relation between clinical characteristics and treatment responses

Characteristics	Complete response (N=77)	Partial response (N=12)	p-value
Age (year, mean±SD)	47.15±9.68	48.57±12.67	0.65
BMI (kg/m^2, mean±SD)	23.75±4.21	22.54±3.46	0.35
Total dose of cisplatin (mg, mean+SD)	289.27±52.9	291.7±44.4	0.88
Total dose of external radiation (cGy, mean+SD)	5405.33±482.08	5550±320.51	0.32
Total dose of brachytherapy (cGy, mean+SD)	2996.67±802.75	2708±396.48	0.23
Histologic subtypes			
Squamous cell carcinoma	61 (85.92)	10 (14.18)	0.94
Non-squamous cell carcinoma	16 (88.89)	2 (11.11)	
Tumor size (cm)			
≤ 4	28 (84.85)	5 (15.15)	0.76
> 4	49 (87.50)	7 (12.50)	
FIGO stage			
Early stage (IB2,IIA)	22 (95.65)	1 (4.35)	0.27
Locally advanced (IIB,IIIA,IIIB,IVA)	55 (83.33)	11 (16.67)	
WHO hematologic toxicities grade			
Grade 0-2	68(86.08)	11(13.92)	0.60
Grade 3-4	9(90.00)	1(10.00)	

Value are number (percentage) unless stated otherwise.
Chi-square test, $p < 0.05$ was considered significant.

and WHO hematologic toxicities) among treatment responses. (Table 4)

Discussion

After the National Cancer Institute (NCI) clinical alert, concurrent platinum based chemotherapy is the accepted standard treatment of locally advanced cervical cancer undergoing radiation therapy.[12] Hematologic toxicities are the most common adverse effects in these patients and are the leading causes to delayed chemotherapy or radiation therapy.

A total of 89 cases and 382 cycles received cisplatin concurrent chemoradiation at Ubonrajchathani Cancer Center during the study period. The prevalence of hematologic toxicities was 78.7%. There was no treatment related deaths. Leukopenia grade 3-4 were 9.0% while Serkies's study showed lower (6.0%).[11] Anemia of grade 3-4 was less common. The frequencies of grade 3-4 neutropenia were lower than Cetina's study (9% vs 30% respectively).[13]

Regarding treatment compliance, the cycles of chemotherapy were scheduled in the first week day of radiation. Most of patients received 5 cycles of chemotherapy same as study of Maharaj Nakorn Chiang Mai Hospital.[14] The effects of chemotherapy should not interfere the planed course of radiation, and the advantage of cisplatin is that it has limited adversed effect on bone marrow. We found only 1 case who received only 3 cycles of chemotherapy because of severe bone-marrow suppression.

Cisplatin is recommended to augment the effects of radiation by inhibiting the repair of radiation induced sublethal damage and by sensitizing hypoxic cells to radiation. Because of its cytotoxic effect, this agent reduces the bulky tumors, which lead to reoxygenation of the tumor and entry of the cells into a radiation sensitive phase of the cell cycle again. Our study showed clinical complete response in 86.5% by clinical pelvic examination and Pap test, the accuracy of response may be limited by this follow up program. Fortunately, hemoglobin level is a

prognostic factor in patients treated by radiation therapy for cervical cancer.[15] Our study demonstrated grade 3-4 anemia in only one patient. There was high clinical complete response rate but no significance difference in the clinical characteristics.

This study is the first report of Northeastern Thailand. Because the study design was retrospective, some data such as time to follow up, survival, and progression free survival were incomplete for analysis. The sample size was quite smaller than previous studies. Further study should be focused on survival in a randomized controlled trial comparing two or more of treatment modalities.

Conclusion

Hematologic toxicities of concurrent chemoradiation with weekly cisplatin 40 mg/m^2 during external radiation were acceptable and manageable. The clinical complete response rate was high.

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