Comparison of Cisplatin-gemcitabine and Cisplatin-paclitaxel Chemotherapy in Stage IVB, Persistent or Recurrent Cervical Cancer

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Abstract

Objectives: To evaluate the treatment outcomes and adverse effects of cisplatin-gemcitabine in comparison with cisplatin-paclitaxel for stage IVB, persistent or recurrent cervical cancer.

Methods: Medical records of patients with stage IVB, persistent or recurrent cervical cancer who were treated with cisplatin-gemcitabine or cisplatin-paclitaxel at Bhumibol Adulyadej Hospital between January 2003 and December 2010 were reviewed.

Results: Ninety-six patients with stage IVB, persistent or recurrent cervical cancer were included in the study. Forty-eight patients (50.0%) received cisplatin-gemcitabine and the remaining received cisplatin-paclitaxel. The majority of patients (68.8%) had squamous cell carcinoma histology. Baseline characteristics of the patients were not significantly different between two groups. There was no statistically significant difference in response rate between cisplatin-gemcitabine and cisplatin-paclitaxel group (47.9% versus 43.7%; p-value = 0.682). The median progression-free survival and median overall survival were also not significantly different: 10 months compared with 9 months (p-value = 0.634) and 12 months compared with 15 months (p-value = 0.606) in patients receiving cisplatin-gemcitabine and cisplatin-paclitaxel, respectively. The hematologic toxicities of leucopenia and thrombocytopenia were significantly higher among patients receiving cisplatin-gemcitabine than those in cisplatin-paclitaxel group.

Conclusion: There was no significant difference in terms of overall response rate, progression-free survival and overall survival among patients with stage IVB, persistent or recurrent cervical cancer receiving cisplatin-gemcitabine regimen compared to cisplatin-paclitaxel regimen. However, the incidences of leucopenia and thrombocytopenia were significantly higher in patients receiving cisplatin-gemcitabine regimen.

Keywords: persistent, recurrent, cervical cancer, chemotherapy, response, survival

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บทคัดย่อ

การเปรียบเทียบผลของการให้ cisplatin และ gemcitabine กับ cisplatin และ paclitaxel ในการรักษามะเร็งปากมดลูกระยะ IVB มะเร็งที่คงอยู่ หรือกลับเป็นซ้ำ

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หน่วยมะเร็งนรีเวช กองสูตินรีกรรม โรงพยาบาลภูมิพลอดุลยเดช

วัตถุประสงค์: เพื่อศึกษาผลการรักษาและอาการข้างเคียงของการให้ cisplatin ร่วมกับ gemcitabine เปรียบเทียบกับการให้ cisplatin ร่วมกับ paclitaxel ในการรักษาผู้ป่วยมะเร็งปากมดลูกระยะ IVB หรือผู้ป่วยที่มะเร็งคงอยู่หรือกลับเป็นซ้ำ

วิธีดำเนินการวิจัย: รวบรวมข้อมูลผู้ป่วยมะเร็งปากมดลูกในระยะ IVB หรือผู้ป่วยที่มะเร็งคงอยู่หรือกลับเป็นซ้ำหลังการรักษาเบื้องต้นที่ได้รับการรักษาด้วย cisplatin ร่วมกับ gemcitabine หรือ cisplatin ร่วมกับ paclitaxel ที่โรงพยาบาลภูมิพลอดุลยเดช ระหว่างเดือนมกราคม พ.ศ. 2546 ถึงเดือนธันวาคม พ.ศ. 2553 จากแฟ้มประวัติผู้ป่วยและนำข้อมูลที่ได้มาศึกษาเกี่ยวกับผลการรักษาและอาการข้างเคียง

ผลการวิจัย: ผู้ป่วยที่นำมาศึกษา 96 ราย ได้รับยาเคมีบำบัดสูตรละ 48 ราย ผู้ป่วยส่วนใหญ่ (ร้อยละ 68.8) เป็นมะเร็งชนิด squamous cell carcinoma ผู้ป่วยทั้ง 2 กลุ่มมีลักษณะข้อมูลพื้นฐานไม่แตกต่างกัน ผู้ป่วยที่ได้รับยา cisplatin ร่วมกับ gemcitabine มีอัตราการตอบสนองต่อการรักษา ร้อยละ 47.9 ซึ่งแตกต่างอย่างไม่มีนัยสำคัญทางสถิติกับผู้ป่วยที่ได้รับ cisplatin ร่วมกับ paclitaxel ซึ่งตอบสนองต่อการรักษา ร้อยละ 43.7 (p-value = 0.682) มัธยฐานของเวลาที่โรคไม่ลุกลามเพิ่ม และมัธยฐานของการรอดชีวิตของผู้ป่วยที่ได้รับยา cisplatin ร่วมกับ gemcitabine ก็แตกต่างอย่างไม่มีนัยสำคัญทางสถิติกับกลุ่มที่ได้รับ cisplatin ร่วมกับ paclitaxel คือ 10 เดือน เทียบกับ 9 เดือน (p-value = 0.634) และ 12 เดือนเทียบกับ 15 เดือน (p-value = 0.606) ตามลำดับ ผู้ป่วยที่ได้รับ cisplatin ร่วมกับ gemcitabine มีภาวะเม็ดเลือดขาวต่ำ และเกล็ดเลือดต่ำ มากกว่าผู้ป่วยที่ได้รับยา cisplatin ร่วมกับ paclitaxel อย่างมีนัยสำคัญทางสถิติ

สรุป: ผู้ป่วยที่ได้รับยา cisplatin ร่วมกับ gemcitabine มีอัตราการตอบสนองต่อการรักษา ระยะเวลาที่โรคไม่ลุกลามเพิ่ม และระยะเวลาการรอดชีวิต แตกต่างจากผู้ป่วยที่ได้รับ cisplatin ร่วมกับ paclitaxel อย่างไม่มีนัยสำคัญทางสถิติ แต่มีผลข้างเคียงด้านเม็ดเลือดขาวต่ำและเกล็ดเลือดต่ำมากกว่าอย่างมีนัยสำคัญทางสถิติ

Introduction

Cervical cancer remains one of the major health burdens in many developing countries including Thailand. In most developing countries, higher overall incidence as well as higher proportion of patients presenting with advanced stage cervical cancer has been noted compared to that in developed countries.[1]

Clinical stage of diseases is an important prognostic factors for cervical cancer. Patients who were in stage IB-IIA had a 5-year overall survival of 75-80% while those of stage III and IV were only 50% and 20%, respectively.[2] Similarly found in a retrospective study of Lorvidhaya et al[3] from Thailand, in which 1,992 patients with cervical cancer of various stages who received radiotherapy were reviewed. The 5-years overall survival of patients with stage III and stage IV cancer were only 50% and 30%, respectively. Risk of recurrence was also strongly associated with stage. Approximately 30-45% and 20-25% of patients with stage III-IV developed pelvic recurrence and distant metastasis. Even in the era of concurrent chemoradiation which is a current standard treatment for advanced stage disease, a high rate of uncontrolled disease is still encountered. This may present as persistent tumors or recurrent diseases after primary treatment.

Treatment options for cervical cancer patients who have stage IVB, persistent, or recurrent diseases vary from surgery, radiation, or chemotherapy depending on many factors e.g. site and extent of diseases, patient's performance status, and type of initial treatment. Unfortunately, certain numbers of these patients are found to have distant metastatic lesion or extensive disease. This leads systemic chemotherapy as the only possible option for further management.

Cisplatin has been recognized as an active agent for treating patients with persistent, recurrent or stage IVB cervical cancer.[4,5] However, the cisplatin-based combination chemotherapy has become increasingly common particularly after the Gynecologic Oncology Group (GOG) reported their randomized controlled trial showing a significant improvement of response rate, progression-free and overall survivals in patients receiving cisplatin-based combination chemotherapy (cisplatin plus topotecan) compared to those who had only cisplatin single agent.[6,7] Other chemotherapeutic agents which were added in cisplatin-based combination chemotherapy in patients with stage IVB, persistent or recurrent cervical cancer include paclitaxel, gemcitabine, vinorelbine, and 5-fluorouracil (5-FU).[4-6,8-15]

Cisplatin-paclitaxel and cisplatin-gemcitabine are common combination chemotherapy regimens used in patients having stage IVB, persistent, or recurrent cervical cancer in Bhumibol Adulyadej Hospital, Bangkok, Thailand. The aim of this study was to evaluate the treatment outcomes of these two chemotherapeutic regimens in terms of objective response rate, progression-free survival, overall survival, and related toxicities.

Methods

After an approval from the Research Ethics Committee, medical records of the patients with persistent, recurrent, or stage IVB cervical cancer in Bhumibol Adulyadej Hospital between January 2003 and December 2010 were reviewed. Inclusion criteria were: (1) histological confirmed squamous cell carcinoma, adenocarcinoma or adenosquamous cell (2) receiving cisplatin plus paclitaxel or cisplatin plus gemcitabine. Exclusion criteria were patients with incomplete medical data.

The dosages and schedules of chemotherapy used in our institute were: cisplatin 50 mg/m^2 given before paclitaxel 135 mg/m^2 over a 3-hour infusion or cisplatin 50 mg/m^2 given on day 1 plus gemcitabine 1,000 mg/m^2 on day 1 and 8. The two regimens of chemotherapy were repeated every 3 weeks. Before initiating chemotherapy, all of the following conditions must be met: (1) good performance status which was defined as having Eastern

Cooperative Oncology Group (ECOG) score ≤ 2 (2) normal bone marrow function (hemoglobin level ≥ 9.0 g/dl, white blood cell ≥ 3,000/ml, absolute neutrophil count ≥ 2,000/ml, platelet ≥ 100,000/ml (3) normal renal function (serum creatinine ≤ 1.5 x upper normal limits (4) normal liver function (aspartate and alanine aminotransferases, alkaline phosphatase ≤ 2.5 x upper normal limits).

Pretreatment laboratory studies were repeated before each treatment cycle. Complete blood count every 2 weeks was obtained during the 3 week-treatment for toxicities evaluation. Response to treatment was assessed using gynecological examination and/or radiologic studies including chest x-ray, computed tomography (CT) scan or magnetic resonance imaging (MRI) which were performed after every 3 treatment cycles.

The abstracted data included age, stage, histology, type of primary treatment and its response, site of diseases, type and course of chemotherapy, time to progression of disease, death or last contact. Response to chemotherapy treatment and severity of chemotherapy-related toxicity were determined using World Health Organization (WHO) criteria.[16]

Statistical analysis was carried out using SPSS version 16 (SPSS, Chicago, IL, USA). Baseline characteristics were described using number with percentage or mean with standard deviation (SD) and were compared by unpaired t-test, chi-square test or Fisher's exact test as appropriate. Survival was estimated using the Kaplan-Meier method. Progression-free survival was obtained from a time interval between initiation of protocol chemotherapy treatment to the time of documented progressive disease or started further treatment or last patient contact. Overall survival was calculated from a time interval from an initiation of protocol chemotherapy treatment to the time of last patient contact or death. Differences in survival were estimated using the log-rank test. P-value < 0.05 was considered statistically significant.

Results

In this study, a total of 96 patients with stage IVB, persistent or recurrent cervical cancer were reviewed. Half of the patients received each chemotherapy regimen of cisplatin-gemcitabine or cisplatin-paclitaxel. The majority of patients (68.8%) had squamous cell carcinoma histology. The most common initial treatment was concurrent chemoradiation (66.7%). Of 64 patients who received concurrent chemoradiation, 28 patients (43.8%) received cisplatin, other concurrent chemotherapy were carboplatin and xeloda. Only one woman in this study received primary chemotherapy as an initial treatment. Baseline characteristics of the patients according to the types of chemotherapy, cisplatin-gemcitabine or cisplatin-paclitaxel are displayed in Table 1.

Among the patients in cisplatin-gemcitabine group, a total of 239 cycles were given with a median number of 5 cycles (range 2-8 cycles). For cisplatin-paclitaxel group, a total of 243 cycles were administered with a median of 5 cycles (range 2-9 cycles). Overall response rate was noted in 47.9% in cisplatin-gemcitabine group comparing to 43.7% in cisplatin-paclitaxel group, which was not statistically significant different (p-value = 0.682) The rate of stable disease and progressive disease were also comparable in both groups (Table 2)

At the end of the study, with the median follow up time of 11 months (2-34 months), 62 patients (64.6%) were dead, while 25 (26.0%) were alive with disease and 9 (9.4%) were alive without disease. The median progression-free survival was 10 months (95% confidence interval (CI): 4.2 - 15.8 months) in cisplatin-gemcitabine group and was 9 months (95% CI: 6.1 - 11.9 months) in cisplatin-paclitaxel group (p-value = 0.634). The median overall survival of the patients in both groups were also not significantly different: 12 months (95% CI: 9.2-14.8 months) in patients receiving cisplatin-gemcitabine chemotherapy and 15 months (95% CI: 11.2 - 18.8 months) in those receiving cisplatin-paclitaxel (p-value = 0.606). Figure 1 and 2 displays progression-free

Table 1 Baseline characteristics (n=96)

Characteristics	cisplatin-gemcitabine (n=48)		cisplatin-paclitaxel (n=48)		p-value
	number	%	number	%	
Age, mean ± SD (years)[a]	52.0 ± 12.4		50.3 ± 8.9		0.441
Stage[b]					0.079
IB	5	10.4	5	10.4	
IIA	0	0	2	4.2	
IIB	28	58.3	16	33.2	
IIIA	0	0	2	4.2	
IIIB	12	25.0	20	41.7	
IVA	3	6.3	2	4.2	
IVB	0	0	1	2.1	
Histology[b]					0.104
Squamous cell carcinoma	30	62.5	36	75.0	
Adenocarcinoma	14	29.2	12	25.0	
Adenosquamous	4	8.3	0	0	
Primary treatment[b]					0.508
RHPL	4	8.3	6	12.5	
CCRT	31	64.6	33	68.7	
ERT + ICRT	13	27.1	8	16.7	
Chemotherapy only	0	0	1	2.1	
Status of disease before inclusion[b]					0.837
Stage IVb	0	0	1	2.1	
Persistent tumor	22	45.8	20	41.7	
Recurrent tumor	26	54.2	27	56.2	
Site of disease(s)[c]					0.452
Local	34	52.4	29	60.4	
Distant	9	13.9	10	20.8	
Local and distant	5	7.7	9	18.8	

Abbreviation: RHPL, radical hysterectomy with pelvic lymphadenectomy; CCRT, concurrent chemoradiation; ICRT, intracavitary radiation; ERT, external radiation

[a] p-value by unpaired t-test

[b] p-value by Fisher's exact test

[c] p-value by chi-square test

Table 2 Response to treatment according to the World Health Organization criteria (n=96)

Responses	cisplatin-gemcitabine (n=48)		cisplatin-paclitaxel (n=48)		p-value[a]
	number	%	number	%	
Overall response	23	47.9	21	43.7	0.682*
Complete response	8	16.7	10	20.8	
Partial response	15	31.2	11	22.9	
Stable disease	12	25.0	15	31.3	
Progressive disease	13	27.1	12	25.0	

[a] p-value by chi-square test compared response vs nonresponse between cisplatin-gemcitabine and cisplatin-paclitaxel

Table 3 Hematologic toxicities according to the World Health Organization criteria (n=96)

Toxicities	cisplatin-gemcitabine (n=48)				cisplatin-paclitaxel (n=48)				p-value[a]
	grade 3		grade 4		grade 3		grade 4		
	number	%	number	%	number	%	number	%	
Anemia	13	27.1	3	6.3	9	18.8	0	0	0.120
Leucopenia	17	35.4	4	8.3	6	12.5	0	0	0.001
Neutropenia	22	45.8	6	12.5	17	35.4	2	4.2	0.133
Thrombocytopenia	5	10.4	3	6.3	0	0	0	0	0.006

[a] p-value by Fisher's exact test compared grade 0-2 vs grade 3 vs grade 4 between cisplatin-gemcitabine and cisplatin-paclitaxel

survival and overall survival, respectively.

The hematologic toxicities found in the patients who received cisplatin-gemcitabine or cisplatin-paclitaxel are summarized in Table 3. Incidence of grade 3 & grade 4 leucopenia and thrombocytopenia were significant higher among patients receiving cisplatin-gemcitabine (leucopenia 43.7%, thrombocytopenia 16.7%) than those in cisplatin-paclitaxel group (leucopenia 12.5%, thrombocytopenia 0%). Grade 3-4 anemia was also higher in cisplatin-gemcitabine group but did not reach statistical significant difference (33.4% vs 18.8%). Febrile neutropenia was observed in one patient receiving cisplatin-gemcitabine chemotherapy. There was no drug toxicity-related death.

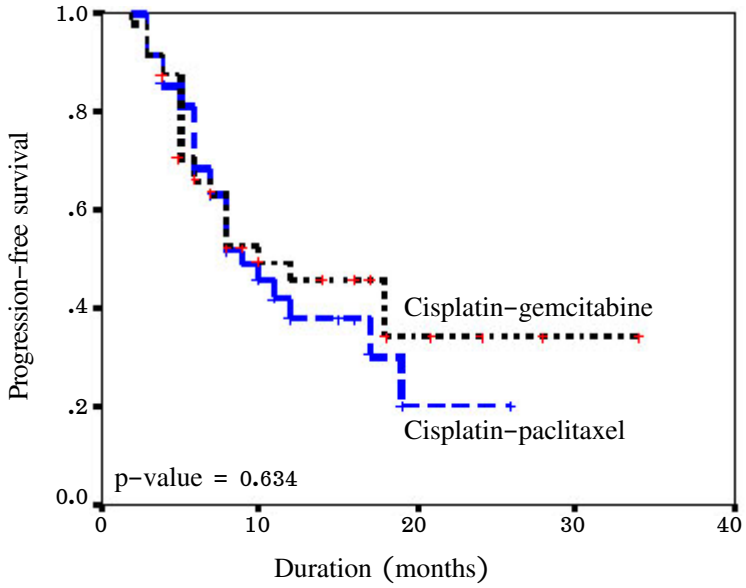

Fig. 1 Progression-free survival compared between cisplatin-gemcitabine and cisplatin-paclitaxel

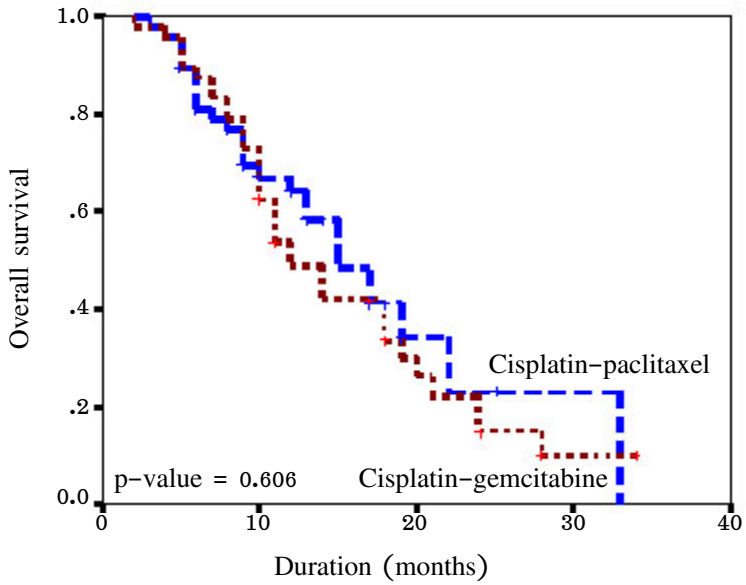

Fig. 2 Overall survival compared between cisplatin-gemcitabine and cisplatin-paclitaxel

Discussion

This study failed to demonstrate any superiority with respect to response rate or survival outcomes between patients with stage IVB, persistent, or recurrent cervical cancer who received either cisplatin-gemcitabine or cisplatin-paclitaxel. Our finding was in accordance with the results from a large phase III trial comparing four cisplatin-based chemotherapy regimens including cisplatin-paclitaxel, cisplatin-gemcitabine, cisplatin-topotecan, and cisplatin-vinorelbine in patients with stage IVB, recurrent or persistent cervical cancer patients.[10] There was no significant superiority in terms of overall survival among these four treatment arms.

In this study, cisplatin-paclitaxel combination chemotherapy provided a clinical objective response rate

of 43.7% while the response obtained from cisplatin-gemcitabine was 47.9%. These figures were in the ranges as had been reported from other studies: 28%-47% from cisplatin-paclitaxel[11-13,17,18] and 22%-63% from cisplatin-gemcitabine.[9,10,19,20] A wide variation in treatment response to either cisplatin-paclitaxel or cisplatin-gemcitabine chemotherapy in the literature might be partly explained by differences among the studies including baseline patients' characteristics, severity of disease, type of primary treatment, details of drug administration and the number of patients in each trial.

The higher incidence of hematologic toxicity of cisplatin-gemcitabine combination chemotherapy has been acknowledged. In previous study of Brewer et al,[19] hematologic toxicity was the most common toxicity among patients with previously treated cervical squamous cell carcinoma who received cisplatin-gemcitabine combination chemotherapy. Grade 4 neutropenia, anemia, and thrombocytopenia were noted in 18.8%, 9.4%, and 6.3%, respectively. In this study, grade 4 neutropenia, anemia, and thrombocytopenia were noted in 12.5%, 6.3%, and 6.3% in patients receiving cisplatin-gemcitabine, which was higher than those receiving cisplatin-paclitaxel. Although one patient having cisplatin-gemcitabine experienced febrile neutropenia, no other serious side effect including death was observed in this study. One previous study reported a significant higher risk of death among women who had cisplatin-based combination chemotherapy in recurrent cervical cancer within an irradiated area.[10] These information regarding the toxicities specific to each type of chemotherapy should be clearly given during patients' counseling about treatment decision and planning.

The limitations of this study are worthy of note. First, data were collected retrospectively. Some provocative information were incomplete including non-hematologic toxicity profile, details of supportive treatment e.g. the use of granulocyte colony stimulating factor (G-CSF), dose adjustments, medical co-morbidities, and quality of life. Second, this observational study was not able to identify the patient's or clinician's preferences regarding the selection of chemotherapy regimen. Third, this study comprised of small sample size with low power to detect the difference between the groups. A small study size also makes an employment of multivariable analysis unfeasible. Finally, although baseline parameters between the groups appeared to be comparable, the effects of unmeasured confounders in observational study however could not be understated.

In conclusion, there was no significant difference in terms of overall response rate and survival outcomes among patients with stage IVB, persistent, or recurrent cervical cancer receiving cisplatin-gemcitabine compared to those receiveing cisplatin-paclitaxel. However, these findings should be viewed with caution in the presence of several limitations in the study. Compared to cisplatin-paclitaxel group, the incidence of severe hematologic toxicities in patients receiving cisplatin-gemcitabine was significantly higher.

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