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Survival Outcomes in Thai Patients with Stage IVB, Persistent or Recurrent Adenocarcinoma of the Uterine Cervix Treated with Platinum-Based Combination Chemotherapy

*Kristsanamon Rittiluechai**

Department of Obstetrics and Gynecology, Phramongkutklao Hospital, Bangkok, Thailand

Abstract

Objective: The main objective of this study was to evaluate the Overall Survival (OS) outcome of Thai patients treated for stage IVB, persistent, or recurrent adenocarcinoma of the uterine cervix in the Phramongkutklao Hospital with standard chemotherapies. Progression Free Survival (PFS), Overall Response Rate (ORR) and prognostic factors were calculated.

Methods: A retrospective chart study was conducted. All patients with stage IVB, persistent, or recurrent disease, treated between July 1993 and June 2013 were included. Patients' baseline characteristics were collected. OS and PFS were calculated by the Kaplan-Meier method.

Results: Forty patients were enrolled with a mean age of 51.4 years. The chemotherapy regimens were cisplatin plus ifosfamide, cisplatin plus irinotecan, platinum-based chemotherapy plus paclitaxel, and 4 other regimens. The median OS of all 40 patients were 7.8 months. The median OS were 6.7, 11.2, 5.5, and 9.3 months for cisplatin/ifosfamide, cisplatin/irinotecan, platinum/paclitaxel, and other regimens group, respectively. Most adverse effects were manageable and hematologic toxicity was the most common. A univariate analysis of various prognostic factors, (age >60 years, hemoglobin level <12 g/dl, relapse inside the irradiation field, and time to relapse within 6 months), was non-contributory.

Conclusion: Cisplatin plus irinotecan achieved the highest response rate and OS without statistical significance compared to the other regimens. However, the observed trend merits confirmation in a larger Thai population.

Keywords: Adenocarcinoma, Metastatic cervical cancer, Cancer recurrence, Chemotherapy

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Correspondence:
Kristsanamon Rittiluechai, Department of Obstetrics and Gynecology, Phramongkutklao Hospital, Bangkok, Thailand,
E-mail: kristsanamon@hotmail.com

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Introduction

In 2012, the Global Burden of Cancer Study (GLOBOCAN) reported 527,600 new cases of cervical cancer worldwide with 265,700 deaths. Ninety percent of these were in developing countries [1]. In Thailand, cervical cancer is the second most common cancer in women, accounting for an estimated 8,184 new cases and 4,513 deaths. The age standardized incidence rate is 17.8 per 100,000 women yearly [2]. In the past 30 years, the implementation of screening programs to detect premalignant disease of uterine cervix has led to a gradual decline in the incidence of squamous cell carcinoma from 10.2 to 3.97 cases per 100,000 women, especially in developed countries. Although the incidence of squamous cell carcinoma has decreased, the proportion of adenocarcinoma of the uterine cervix has increased accounting for 15% to 24% of all cervical cancer cases [3-6]. Data on the prognosis and survival of squamous cell carcinoma and adenocarcinoma of the uterine cervix remain controversial. Some studies report a poorer prognosis for adenocarcinoma [7-9], and others a similar outcome to squamous cell carcinoma [10-12]. Although inconclusive data has been found on survival and increasing incidence of adenocarcinoma of the uterine cervix, few studies have specifically examined survival of adenocarcinoma of the uterine cervix Most of the studies focused on patients with squamous cell carcinoma, and only less than 10% of the study group had adenocarcinoma subtype [13-17]. Survival for adenocarcinoma might differ by stage when compared with squamous cell subtype. Patients with stage IVB adenocarcinoma of the uterine cervix have 1 and 2 year OS rates of 42.9% and 17.1%, respectively, and patients with squamous cell carcinoma 46.1% and 26.2%, respectively [18]. There is no standard treatment for stage IVB,

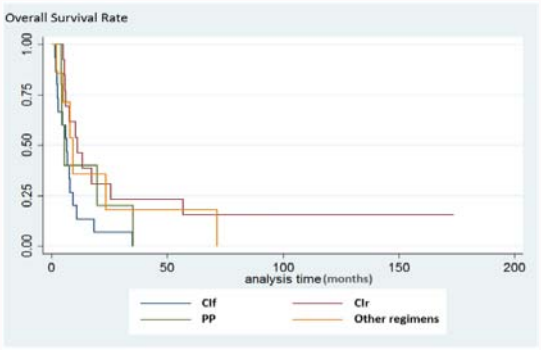

Figure 1: Survival Rates.
Comparison of the OS from combination chemotherapy regimens in adenocarcinoma of the uterine cervix.

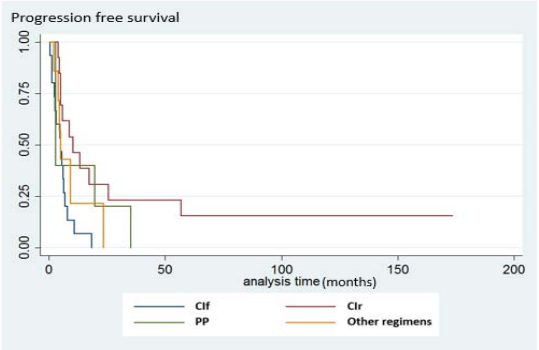

Figure 2: Progression Free Survival Rates.
Comparison of the PFS from combination chemotherapy regimens in adenocarcinoma of the uterine cervix.

persistent, or recurrent cervical carcinoma. Gynecologic Oncology Group (GOG) phase III trials demonstrate a better response rate and PFS with cisplatin-based combination compared to single agent cisplatin [19]. The most active regimens are cisplatin plus topotecan or paclitaxel. GOG protocol 204, which compares four cisplatin-based combination regimens with paclitaxel, vinorelbine, topotecan, or gemcitabine, does not show statistically significant differences, but a trend in favor of the paclitaxel arm [20]. Only 10% to 15% of women in this trial had adenocarcinoma. The few studies of patients with adenocarcinoma do not allow for sound conclusions [21,22]. We conducted this retrospective study to add information on outcomes of patients with adenocarcinoma of the cervix.

Materials and Methods

Patients who were treated at our Institute between July 1993 and June 2013 and had histologically confirmed adenocarcinoma of the uterine cervix were enrolled. The Institutional Review Board dispensed a waiver of consent. Records of patients with stage IVB, recurrent or persistent disease were reviewed. The patients' demographic data included age, initial stage, and previous treatment before receiving chemotherapy, sites of residual or metastatic disease, and performance status before receiving chemotherapy. The initial stage was defined according to the 2009 International Federation of Gynecology and Obstetrics (FIGO) staging system [23], except for patients diagnosed before 2009 where the 1988 FIGO system was used. Persistent disease was defined as any disease that remained after completion of the initial treatment. Recurrent disease was diagnosed when the disease reappeared after a complete remission. Sites of recurrent disease were diagnosed from physical examination, chest X-ray, Computed Tomography (CT) scan, or Magnetic Resonance Imaging (MRI). If a surgical for tissue diagnosis could not be done, disease measured by CT or MRI was accepted. All patients had to receive at least 2 cycles of chemotherapy that included a combination of platinum-based regimens. The choice of chemotherapy regimen was left to the attending physician. The number of cycles, chemotherapy regimen, and complications from chemotherapy were recorded. Patients with 2 primary tumors were excluded from the study. Response to chemotherapy was recorded as complete response, partial response, stable disease and progressive disease, according to the World Health Organization (WHO) criteria. ORR included complete response, disappearance of all known disease. Partial response was defined as 50% or more decrease in total tumor burden that had been bidimensionally measured [24]. OS was the time between the date of the first cycle to the date when the patient died or was last seen at the Institute. PFS was the time between the date of the first chemotherapy cycle to the date of disease progression or when the patient died, whichever came first. Toxicity grading was collected using the WHO grading of acute and subacute toxicity [24]. The statistical analysis for survival used the Kaplan-Meier method to find the difference of OS and PFS among each regimen. Prognostic factors were determined by univariate analysis. A significant prognostic factor was defined when the p-value was less than or equal to 0.05. If any significant prognostic factors were observed from univariate analysis, a Cox regression analysis would be used to calculate the adjusted hazard ratio of those factors.

Results

Forty patients who matched the inclusion criteria were enrolled. Patient characteristics are listed in (Table 1). Mean age was 51.4 years (range, 35 to 76 years). Twenty-two patients (55%) had distant metastases, 12 (30.0%) pelvic metastases, and 6 (15%) pelvic and distant metastases. Eighty-five percent of patients had an Eastern Cooperative Oncology Group (ECOG) score of 0, and 15% a score of 1. Treatments before receiving chemotherapy included concurrent chemoradiation (45%), radiation alone (15%), surgery (15%), and surgery with radiation (10%). Ten percent had advanced stage IVB disease, which had not been treated with any chemotherapy before. Another 5% had no data about previous treatments. Fifteen patients received cisplatin and ifosfamide 13 patients received cisplatin and irinotecan, 5 patients received a platinum and paclitaxel, 3 patients received cisplatin and cyclophosphamide, 2 patients received cisplatin and topotecan, and 2 patients received other regimens. The median number of chemotherapy cycles was 4 (range, 2 to 9) (Table 2). Responses to chemotherapy are shown in (Table 3). ORR was 33.3% (no complete response) for cisplatin/ifosfamide regimen, 46.0% (complete response 23.0%, partial response 23.0%) for cisplatin/irinotecan regimen, and 40.0% (complete response 40.0%) for platinum/paclitaxel regimen. In the other regimens group, ORR was 28.6% (complete response 14.3%, partial response 14.3%). There was no statistically significant difference between each group (p=0.87). Analyzed prognostic factors included initial Hemoglobin (Hb) level less than 12 g/dl, age greater than 60 years, relapse inside the radiation field, and relapse time less than 6 months after diagnosis were analyzed (Table 4). Eighty percent of women older than 60 years old, 20.0% of women with a hemoglobin level less than 12 g/dl, 46.2% of patients with relapse inside the radiation field, and 25.0% of patients with relapse within 6 months of diagnosis responded to chemotherapy. Types of disease progression (stage IVB, persistent,

Table 1: Patient Characteristics.

Characteristics	N = 40
Age (years), Mean (Range)	51.4 (35 – 76)
Initial stage, n (%)	
IB1	1 (2.5)
IIA	2 (5.0)
IIB	8 (20.0)
IIIB	19 (47.5)
IVB	5 (12.5)
Unclassified	5 (12.5)
Initial treatment, n (%)	
Concurrent chemo-radiation	18 (45.0)
Radiation alone	6 (15.0)
Surgery	6 (15.0)
Surgery with radiation	4 (10.0)
No previous treatment	4 (10.0)
No data	2 (5.0)
Status of disease for study entry, n (%)	
Stage IVB	4 (10.0)
Persistent disease	11 (27.5)
Recurrent disease	25 (62.5)
Sites of residual or metastatic disease, n (%)	
Pelvic	12 (30.0)
Distant	22 (55.0)
Pelvic and distant	6 (15.0)
ECOG status, n (%)	
0	34 (85.0)
1	6 (15.0)

Table 2: Treatment Regimens.

	N = 40
Chemotherapy, n (%)	
Cisplatin – Ifosfamide	15 (37.5)
Cisplatin – Irinotecan	13 (32.5)
Platinum – Paclitaxel	5 (12.5)
Cisplatin – Cyclophosphamide	3 (7.5)
Cisplatin – Topotecan	2 (5.0)
Others	2 (5.0)
Number of cycles, Median (Range)	4 (2 – 9)

or recurrent) were also analyzed. Twenty-five percent of patients with stage IVB disease, 27.3% with persistent disease, and 44.0% with recurrent disease responded to chemotherapy. In univariate analysis, none of these factors were significant (p>0.05). The median OS 7.8 months for the adenocarcinoma subtype is similar to the one of all histologic subtypes (8.6 months) at our institute. The median OS in each chemotherapy regimen were 6.7, 11.2, 5.5, and 9.3 months in cisplatin/ifosfamide, cisplatin/irinotecan, platinum/paclitaxel, and other regimens group, respectively (Figure 1). Although no significant differences were observed in OS between each regimen, two patients in the cisplatin and irinotecan group were alive with follow-up times of 174 and 117 months. PFS of all 40 patients was

Table 3: Response Rate.

Response	CR (%)	PR (%)	SD (%)	PD (%)
Cisplatin-Ifosfamide (N = 15)	0	33.3	26.7	40
Cisplatin-Irinotecan (N = 13)	23	23	38.5	15.4
Platinum-Paclitaxel (N = 5)	40	0	20	40
Other Regimens (N = 7)	14.3	14.3	42.9	28.6
Total (N = 40)	15	22.5	32.5	30

CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease.

Table 4: Univariate Analysis.

Prognostic factors	Responder (N = 15), n (%)	Non-responder (N = 25), n (%)	p-value
Age			
≤ 60 years	11 (31.4)	24 (68.6)	0.056
> 60 years	4 (80.0)	1 (20.0)	
Hg level			
< 12 g/dl	1 (20.0)	4 (80.0)	0.633
≥ 12 g/dl	14 (40.0)	21 (60.0)	
Relapse inside an irradiation field			
Yes	6 (46.2)	7 (53.8)	0.498
No	9 (33.3)	18 (66.7)	
Relapse time from diagnosis			
< 6 months	1 (25.0)	3 (75.0)	1
≥ 6 months	14 (38.9)	22 (61.1)	
Type of disease			
Stage IVB	1 (25.0)	3 (75.0)	0.543
Persistent	3 (27.3)	8 (72.7)	
Recurrent	11 (44.0)	14 (56.0)	

5.6 months (Figure 2). The most common side effect was hematologic toxicity. In the cisplatin and ifosfamide group, 13.3% experienced grade 3 anemia (hemoglobin level <7.9 g/100 ml), 6.7% experienced grade 4 neutropenia (absolute neutrophil count <1,000/mm^3), 6.7% experienced grade 3 renal toxicity (elevated serum creatinine), and 13.3% experienced grade 3 hematuria. In the cisplatin and irinotecan group, 15.3% experienced grade 3 anemia, 7.7% experienced grade 3 neutropenia, 7.7% had elevated serum creatinine, and 15.3% had grade 3 diarrheas. There was no grade 4 hematotoxicity by using platinum with paclitaxel regimen. Two patients who received this regimen had grade 3 neutropenia, 1 patient had grade 3 anemia, and 1 patient had grade 3 thrombocytopenia (platelet count <50,000 / mm^3). All adverse events were manageable and no chemotherapy-related death occurred.

Discussion

Patients with advanced disease stage IVB, persistent, or recurrent cervical cancer have poor prognosis. Most studies evaluating cytotoxic agents in this setting have usually included patients with all histologic subtypes, mostly squamous cell carcinoma, and few studies have focused on the outcomes of patients with adenocarcinoma. Our results demonstrate that patients with advanced stage IVB, persistent or recurrent adenocarcinoma of the uterine cervix after treatments

Table 5: Grade 3 and 4 Adverse Events.

	CIf	CIr	PP	Other regimens
	(N = 15)	(N = 13)	(N = 5)	(N = 7)
Anemia, n (%)	2 (13.3)	2 (15.3)	1 (20.0)	2 (28.6)
Neutropenia, n (%)	1 (6.7)	1 (7.7)	2 (40.0)	1 (14.3)
Thrombocytopenia , n (%)	0 (0)	0 (0)	1 (20.0)	1 (14.3)
Elevated serum creatinine, n (%)	1 (6.7)	1 (7.7)	0 (0)	0 (0)
Diarrhea, n (%)	0 (0)	2 (15.3)	0 (0)	0 (0)
Hematuria, n (%)	2 (13.3)	0 (0)	0 (0)	0 (0)

CIf: Cisplatin and Ifosfamide; CIr: Cisplatin and Irrinotecan; PP: Platinum-based and Paclitaxel

Table 6: Comparison of Various Chemotherapy Regimens**.**

Study	Year	Regimen	N	AdenoCA (%)	CR (%)	PR (%)	ORR (%)	PFS (months)	OS (months)
Omura, et al. GOG 110(14)	1997	Cisplatin	140	0	6.4	11.4	17.8	3.2	8.0
		Cisplatin + Mitolactol	147	0	9.5	11.6	21.1	3.3	7.3
		Cisplatin + Ifosfamide	151	0	12.6	18.5	31.1	4.6	8.3
Bloss, et al. GOG 149 (26)	2002	Cisplatin + Ifosfamide	146	0	NA	NA	32.2	4.6	8.5
		Cisplatin + ifosfamide + Bleomycin	141	0	NA	NA	32.1	5.1	8.4
Moore, et al. GOG 169 (16)	2004	Cisplatin	134	0	6.0	13.0	19.0	2.8	8.8
		Cisplatin + Paclitaxel	130	0	15.0	21.0	36.0	4.8	9.7
Long, et al. GOG 179 (17)	2005	Cisplatin	146	6	2.9	10.1	13.0	2.9	6.5
		Cisplatin + Topotecan	147	6	10.4	16.3	26.7	4.6	9.4
		MVAC	63	Discontinued	-	-	-	-	-
Monk, et al. GOG 204 (20)	2009	Cisplatin + Paclitaxel	103	13	2.9	26.2	29.1	5.8	12.9
		Cisplatin + Vinorelbine	108	14	7.4	18.5	25.9	3.9	9.9
		Cisplatin + Gemcitabine	112	15	0.9	21.4	22.3	4.7	10.3
		Cisplatin + Topotecan	111	10	1.8	21.6	23.4	4.6	10.3
Tewari, et al. GOG 240 (25)	2014	Cisplatin + Paclitaxel							
		Topotecan + Paclitaxel	114	20	10.3	34.7	45.0	5.9	14.3
		Cisplatin + Paclitaxel + Bevacizumab	111		5.5	21.5	27.0		12.7
			115	19	19.5	30.5	50.0	8.2	17.5
		Topotecan + Paclitaxel+ Bevacizumab	112		12.3	34.7	47.0		16.2
This study	1993-2013	Cisplatin + Ifosfamide	15	100	0	33.3	33.3	5.6	6.7
		Cisplatin + Irinotecan	13	100	23.0	23.0	46.0	-	11.2
		Platinum + Paclitaxel	5	100	40.0	0	40.0	2.9	5.5
		Other regimens	7	100	14.3	14.3	28.6	-	9.3

CR: Complete Response; PR: Partial Response; ORR: Overall Response Rate; PFS: Progression Free Survival; OS: Overall Survival

with platinum-based chemotherapy have a similar outcome to patients with other subtypes. Our results are supported by a previous study that showed a similar outcome of both squamous and non-squamous cell carcinoma with advanced stage IV and recurrent disease [22]. ORR is significantly better for patients receiving a combination of cisplatin-based chemotherapy than patients receiving cisplatin alone. Response rates of combination regimens vary widely, from 16% to 60% and the ORR we observed (37.5%) is in this range [14-17]. Many phase III trials (GOG protocols 110, 149, 169, 179, 204, and 240), which studied various treatment outcomes in patients with advanced stage IVB, persistent or recurrent cervical cancer, included only 20% of adenocarcinomas (Table 6). GOG 110 and GOG 149 tested cisplatin and ifosfamide regimen [14,25]. ORR for this cohort in our study had a similar outcome (ORR, 33.3%). A slight difference in median OS (GOG, 8.3 and 8.5 months and this study, 6.7 months) is likely related to the delivery of concurrent chemo-radiation in first line. In our study, 45.0% of patients *vs.* 13.9 and 20.5% in GOG 110, GOG 149, respectively, had received concurrent chemo-radiation. While cisplatin plus paclitaxel showed a promising outcome in squamous cell carcinoma of the uterine cervix with an ORR of 46.3% in the GOG phase II trial [26] and 36% in GOG protocol 169 (16) (36% in cisplatin plus paclitaxel arm versus 19% in cisplatin arm), there was no OS benefits for the combination. Cisplatin plus paclitaxel became the first line therapy in patients with advanced stage or recurrent disease. Carboplatin plus paclitaxel could be used instead of cisplatin plus paclitaxel without compromising outcomes [27]. However, in patients with cisplatin-naïve disease, the cisplatin plus paclitaxel combination yielded significantly higher OS. In our study, the platinum and paclitaxel regimen had an ORR of 40% and a median OS of 5.5 months. Again, 45% of patients had received concurrent chemo-radiation versus 23.8% in the equivalent GOG study, explaining differences in outcomes for treatment of relapsed disease. The latest study, GOG 240, showed a significant improvement in OS when antiangiogenic therapy is combined with chemotherapy regimens [28]. In our study, the most active regimen was cisplatin and irinotecan with an ORR of 46.1% and a median OS of 11 months. The combination was given in cycles of 4 weeks. Weekly administration of cisplatin and irinotecan regimen yielded an ORR of 66.7% (20 of 30 patients with metastatic disease), but only 27% of patients had the adenocarcinoma cell type [15]. The median OS was 16.9 months. Another study showed a lower ORR of 16.2% [29]. Differences in outcome may be due to the different schedules. Interestingly, two of our patients had very long survivals of 174 and 117 months. The first case was 49 years old at the time of diagnosis and treatment. She had stage IVB disease with lung metastases. She received cisplatin and irinotecan regimen as the first line treatment. Her performance status was good throughout the treatment. The last status was alive with disease. The second case was a 65-year-old woman with initial stage IIB disease. The primary treatment was radiation, which yielded a complete response. She had recurrent disease in the lungs 7 years later. She received cisplatin and irinotecan regimen and achieved a complete response after the sixth cycle. Her

last status was alive without disease.

Conclusion

Because adenocarcinoma of the uterine cervix is rare, our study has obvious limitations; few patients; lack of long term follow-up; various regimens. Cisplatin and irinotecan regimen might yield a better outcome in Thai patients with stage IVB, persistent, or recurrent adenocarcinoma of the uterine cervix especially among patients with lung metastases; however, statistically significant differences of OS or ORR in this histologic subtype have not been demonstrated. With the dissemination of newer therapeutic approaches such as antiangiogenic drugs or immunotherapy, the outcome of such patients might improve. However, the national health insurance of Thailand allows few chemotherapy regimens for each cancer. Administering other regimens with newer or more promising drugs causes unaffordable costs for the patient and the hospital. Thus, assessing the best chemotherapy combination remains a benefit for our patient population.

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