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The Use of FOLFOX4 Regimen in Stage IV Cervical Cancer: A Pilot Study

Ekkasit Tharavichitkul[1*], Ekkapong Tharavichitkul[2], Somvilai Chakrabandhu[1], Pitchayaponne Klunklin[1], Wimrak Onchan[1], Bongkot Supawongwattana[1], Nantaka Pukanhaphan[1], Imjai Chitapanarux[1]

[1]Division of Therapeutic Radiology and Oncology, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand
[2]Department of Medicine, Chiang Rai Prachanukroh Hospital, Chiang Rai, Thailand
Email: *paan_31@hotmail.com

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Abstract

Objective: To evaluate the efficacy and safety of FOLFOX4 (oxaliplatin/5FU/Leucovorin) for the treatment of metastatic cervical cancer. Methods: All patients were designed to receive the FOLFOX4 regimen (Oxaliplatin (Eloxatin®) 85 mg/m² D1, 5-Fluorouracil 400 mg/m² IV push D1-2, 5-Fluorouracil 600 mg/m² IV drip in 22 hours D1-2 and Folinic acid 200 mg/m² IV push in D1-2). The treatment responsiveness and toxicities were evaluated. Results: Thirty patients from January 2010-December 2012 were enrolled into the study. The mean age was 51 years old. Nine patients (31%) achieved objective response. At the mean follow-up time of 13 months, the one-year progression-free and overall survival rates were 20.7% and 65.5%, respectively. The most common grade 3 adverse event reported in this study was anemia (36.7%), thrombocytopenia (16.7%) and fatigue (16.7%). Conclusions: FOLFOX4 regimen in metastatic cervical cancer is feasible.

Keywords

Cervical Cancer, FOLFOX4, Metastasis

1. Introduction

Cervical cancer is one of the most common gynecological cancers in Thailand. From our hospital status, the incidence rate of cervical cancer was 22.7 in the year of 2005 [1]. For locally advanced cervical cancer, concurrent chemo-radiotherapy showed more benefits than radiotherapy alone [2]-[4]. For metastatic disease, chemotherapy

*Corresponding author.

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is the treatment of choice. However, platinum-based regimen has not led to major improvements in clinical outcome and is associated with higher rate of severe toxicities [5]. A randomized study of cisplatin alone versus cisplatin/paclitaxel demonstrated improvements of response and disease-free survival rates in favors of combined regimen, but there was no difference in overall survival rate [6]. Other studies reported lower response rates of re-challenge treatment, and suggested that additional topotecan enhanced the response and survival rates [7]. The randomized trial of four-containing doublet combinations of various cisplatin-based doublets reported no difference of treatment results [8].

Oxaliplatin (Oxaliplatin (L-OHP; trans-oxalate(2-)-O,O platinum)) is platinum-based chemotherapy which found in laboratory that needed less DNA adducts amount to develop toxicity than cisplatin. Oxaliplatin showed efficacy to many cancer cells. From the phase I study program of oxaliplatin, the recommended dose for use in single agent was 130 mg/m^2 [9]. In phase II study, single oxaliplatin in squamous cell carcinoma of the cervix showed around 8% response rate [10]. However, the treatment of metastatic cancer at present is combinations regimen [11]. According to the profiles of oxaliplatin, the use in cervical cancer is interesting. This study planned to evaluate the FOLFOX4 (oxaliplatin/5FU/Leucovorin) for the treatment of metastatic cervical cancer.

2. Materials and Methods

2.1. Patient Selection and Data Collection

This study was approved by Institutional Review Board with the study code of OXALI_L_05049 and conducted in accordance with Good Clinical Practice and the Declaration of Helsinki. The inclusion criteria were as follows: age 18 - 70 years, at least clinically proven metastatic cervical carcinoma, clinical (by clinical examination and imaging) or pathological confirmation of metastasis setting to distant lymph nodes (paraaortic lymph node/ supraclavicular lymph node) or other visceral metastasis**,** no history of allergy. Previous concurrent chemoradiotherapy or systemic chemotherapy was allowed. Written informed consent was obtained from all participants prior to study commencement.

Common Terminology Criteria of Adverse Events (CTCAE) version 3.0 was used to measure adverse events during chemotherapy and during follow-up time [12]. Response rates were evaluated after 6th cycle, 12th cycle and every 3 months until progression with WHO criteria and RECIST criteria according to measured sites [13] [14].

2.2. Treatment

All patients were designed to receive the FOLFOX4 regimen (Oxaliplatin (Eloxatin®) 85 mg/m^2 on D1, 5-Fluorouracil 400 mg/m^2 IV push D1-2, 5-Fluorouracil 600 mg/m^2 IV drip in 22 hours D1-2 and Folinic acid 200 mg/m^2 IV push D1-2) with 2-weeks interval. The planned schedule was 12 cycles of chemotherapy and evaluation was performed after 6th and 12th cycle.

2.3. Statistical Analysis

The goal of this study was to study the efficacy and safety of FOLFOX4 regimen for the treatment of metastatic cervical cancer. The primary endpoints were the one-year progression free and overall survival rates. The secondary endpoint was toxicity profile. Descriptive and qualitative analyses were evaluated by the statistical package for social sciences (SPSS, version 17). Survival analysis data were calculated by Kaplan-Meier method and log-rank test [15] [16].

3. Results

After the approval of the Institutional Review Board, 30 patients were enrolled into the study from January 2010-December 2012. Written informed consent was obtained from all participants prior to study commencement.

The characteristics of enrolled patients are shown in **Table 1**. The mean age was 51 years old. Seventy percent (21/30) had distant lymph node metastasis. Forty-three percent could receive less than 6 cycles and progression of disease was the main reason for treatment discontinuation. One patient died during the first cycle due to non-cancer cause (cardiac problem), so twenty-nine patients could be evaluated in terms of efficacy. One of

29 patients received the FOLFOX4 regimen as second-line treatment. The mean progression-free survival was 7.6 months (interquartile range (IQR): 3 - 12.5 months).

Thirty-one percent of patients (9/29) yielded objective response (CR and PR) and twenty-eight percent of them had stable of disease. Fifty-nine percent of patients could receive at least 6 cycles of chemotherapy. Treatment delayed and/or dose reduction was reported at least one episode in 22 patients. The data are shown in **Table 2**.

Safety could be evaluated in 30 patients. Adverse events during treatment, any grade, during chemotherapy were leucopenia (56.7%), fatigue (50%) and anemia (46.7%). The most common grade 3 adverse events reported in this study were anemia (36.7%), thrombocytopenia (16.7%) and fatigue (16.7%). Grade 3 renal impairment and peripheral neuropathy were developed in 3 patients (10%) and 4 patients (13.3%), respectively. All safety profiles data were showed in **Table 3**.

4. Discussion

Oxaliplatin-based regimen mostly used for treatment of metastatic colorectal and pancreatic cancers with promising results [17]-[20]. In our department, many regimens of chemotherapy were used to treat metastatic cervical cancer. Lorvidhaya *et al.* reported the efficacy of combination chemotherapy using Cisplatin and Epirubicin in carcinoma of the cervix. Fifty-six patients with local recurrent and/or metastatic carcinoma of the cervix have

Table 1. Patient characteristic.

	N = 30	
	n	%
Age, year		
Median (range)	51 (26 - 64)	
Pathological result		
Squamous cell carcinoma	24	80
Adenocarcinoma	6	20
Site of metastasis		
Distant LN metastasis	21	70
Others	9	30
Previous irradiation		
Yes	29	97
No	1	3

Table 2. Treatment results in patients who received FOLFOX4 regimen for metastatic cervical cancer.

	N = 29[a]	
	n	%
Response		
Complete response	5	17.2
Partial response	4	13.8
Stable disease	8	27.6
Progressive disease	12	41.4
Survival		
OS, mean (IQR) months	13 (4 - 22)	
1-year PFS, rate (%)	20.7%	
1-year OS, rate (%)	65.5%	
Compliance		
Complete (12 cycles)	5	18
Partial (6 - 11 cycles)	12	41
Less than 6 cycles	12	41

[a]Excluded one patient who died during the first cycle. Note: OS = overall survival, PFS = Progression-free survival, IQR = Interquartile range.

Table 3. Safety profile of patients.

	N = 30							
	Grade 1		Grade 2		Grade 3		Any grade	
	n	%	n	%	n	%	n	%
Anemia	3	10	-	-	11	36.7	14	46.7
Leucopenia	9	30	8	26.7	-	-	17	56.7
Thrombocytopenia	1	3.3	-	-	5	16.7	6	20
Renal Impairment	-	-	-	-	3	10	3	10
Peripheral neuropathy	2	6.7	-	-	4	13.3	6	20
Fatigue	1	3.3	9	30	5	16.7	15	50
Nausea &Vomiting	-	-	-	-	1	3.3	1	3.3
Cardiac problems	-	-	-	-	-	-	1	3.3

been treated using Cisplatin 60 mg/m^2 and Epirubicin 90 - 100 mg/m^2 every three weeks. The overall response rate was 67.9% (CR 14.3%, PR 53.6%). Four out of fourteen patients in stage IVB had long-term survival ranging from 14 to 85 months. Grade 4 leucopenia occurred in 20% [21].

Chitapanarux *et al.* reported the efficacy and tolerability of irinotecan plus cisplatin as first-line chemotherapy in metastatic or recurrent cervical cancer. Thirty "chemotherapy-naïve" patients with metastatic or recurrent disease and at least one measurable tumor site received irinotecan (60 mg/m^2 IV infusion over 90 min) on D1, D8, and D15, followed by cisplatin (60 mg/m^2 IV infusion over 90 minutes) on D1, every 28 days for a maximum of six cycles. The median (range) age was 45 years (34 - 65). Nineteen patients had metastatic disease, 6 presented with locally recurrent disease, and 5 presented with locally recurrent plus metastatic disease. The overall response rate was 66.7%. Stable disease and progression disease were observed in 2 patients (6.7%) and 8 patients (26.7%), respectively. Median time to relapse was 13.4 months, with a median survival time of 16.9 months. One-year disease-free survival and overall survival were 26.7% and 65.1%, respectively. Dose-limiting toxicity was observed in 4 patients (13.3%) with grade 3 renal toxicity. Nine patients (30%) developed grade 3 neutropenia, and only grade 1-2 acute and late diarrhea were observed in 20% and 40%, respectively [22].

Kamnerdsupaphon *et al.* reported the therapeutic efficacy of cisplatin in combination with vinorelbine in the treatment of patients with metastatic cervical cancer. Seventeen patients were enrolled in the present study. The median age was 46 years (38 - 65). There were 6 patients who were diagnosed as stage IVB cervical cancer without previous treatment. The patients were planned to receive cisplatin 80 mg/m^2 on D1 and vinorelbine at 30 mg/m^2 on D1 and D8 every 3 weeks. Fifteen patients were available for evaluation: 2 (13.3%) achieved a complete response, 8 (53.4%) partial responses, 3 (20%) stable diseases and 2 (13.3%) progression of the disease. Myelosuppression was the major toxicity Grade 3/4 toxicities include 66.7% hemoglobin and 26.7% neutropenia. No other significant side effects were found [23].

The use of oxaliplatin-based regimen was further evaluated. Kuo *et al.* reported the efficacy and toxicity of paclitaxel and oxaliplatin in patients with recurrent or metastatic cervical cancer. Treatment consisted of paclitaxel 175 mg/m^2 IV and oxaliplatin 130 mg/m^2 IV every 21 days. Of the 35 patients enrolled, 32 were evaluable. The median (range) age was 56 (27 - 78) years; 30 had prior radiation (23 concomitant with cisplatin). Patients completed a mean of 4.2 cycles (1 - 11). There were 2 complete and 5 partial responses for a total response rate of 7/32 (22%; 95% CI: 9.3 - 40.0). Eight patients had stable disease for an overall clinical benefit rate of 15/32 (47%; 95% CI: 29.1 - 65.3). The mean time to best response was 13.5 weeks (95% CI: 10.6 - 16.4). The mean progression-free survival was 21 weeks (95% CI: 14.7 - 27.2) and mean overall survival was 52 weeks (95% CI: 39.4 - 64.8). A total of 135 cycles were administered. There were 28 (20.1%) grade 3/4 hematologic toxicities and 46 (34.1%) grade 3/4 non-hematologic toxicities, which were predominantly sensory neuropathy. There were 13 treatment delays, 4 dose reductions, and no treatment-related deaths. The author concluded that the combination of paclitaxel and oxaliplatin is an effective regimen in patients with recurrent or persistent cervical cancer including a majority previously exposed to cisplatin [24].

For our experiences of using FOLFOX4 in recurrent or metastatic cervical cancer, 31% of our patients re-

ceived objective response after treatment with the mean time to progression of 7.6 months. Fifty-nine percents received more than six cycles. With the mean follow-up time of 13 months, the 1-year progression-free survival and overall survival rates were 20.7% and 65.5%, respectively. Common toxicities, any grade, during chemotherapy were leucopenia (56.7%), fatigue (50%) and anemia (46.7%). When we compared these results to our previous studies, [21]-[23] the treatment results were comparable.

5. Conclusion

In conclusion, FOLFOX4 regimen can be used in metastatic cervical cancer with manageable safety profile.

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Conflict of Interests

No conflict of interests is reported for the author.

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