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Original Article

Outcomes of advanced and recurrent cervical cancer treated with cisplatin and generic topotecan: retrospective analysis in a tertiary care hospital in Thailand

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Objective: Retrospective evaluation of the outcome of stage IVB, recurrent or persistent cervical cancer treated with cisplatin and generic topotecan (CT) in a tertiary care hospital in Thailand.
Methods: The medical records of patients treated with CT regimen at Chiang Mai University Hospital between January 2005 and December 2007 were reviewed and analyzed. The treatment protocol consisted of IV topotecan 0.75 mg/m^2 on days 1, 2, and 3; combined with cisplatin 50 mg/m^2 IV on day 1 and repeated every 21 days until progression or unacceptable toxicity for a maximum of 6 cycles. The outcomes were evaluated based on the response rate, progression free survival (PFS), and overall survival (OS) by using the World Health Organization criteria. The adverse effects of the treatments were also determined.
Results: Twenty-one cervical cancer patients received the CT regimen. The tumor response rate was 28.6%. The median PFS and OS was 4 and 11 months, respectively. With 87 cycles of chemotherapy, the most common grade 3 & 4 hematologic toxicity was neutropenia (57.9%).
Conclusion: Advanced and recurrent cervical cancer patients treated with cisplatin and generic topotecan had a favorable outcome with manageable toxicity.

Key Words: Cervical cancer, Recurrence, Advance, Cisplatin, Topotecan

INTRODUCTION

Cervical cancer with disease recurrence or pelvic metastasis has a poor prognosis with a 1-year survival rate between 15% to 20%, and systematic chemotherapy remains the preferable treatment.[1] In a randomized study of Gynecologic Oncology Group (GOG) 179, the combination of cisplatin and topotecan demonstrated a survival advantage over cisplatin alone in the treatment of advanced and recurrent cervical cancer.[2] Many patients with advanced and recurrent cervical cancer were treated with the same regimen as in the GOG study at the Chiang Mai University Hospital. These patients were given generic topotecan (Topotel®, Fresenius Kabi Oncolgy, Solan, India) which is less expensive than the original brand product. Also, the generic formulation has a convenient package of 2.5 mg/2.5 mL. There have been no previous reports on the outcomes of generic topotecan in treatment of recurrent and advanced cervical cancer. Hence, the present retrospective evaluation was done to assess the outcomes of this treatment regimen.

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MATERIALS AND METHODS

The study protocol was approved by the Research Ethics Committee of the Chiang Mai University Hospital. The medical records (paper records) of all the cervical cancer patients with histologically confirmed of advanced (stage IVB), recurrent, or persistent cervical cancer who received cisplatin and topotecan at Chiang Mai University Hospital between January 2005 and December 2007 were reviewed and recruited for analysis. All the studied patients did not receive curative treatment such as surgery or radiation.

1. Selection criteria for chemotherapy regimen

The schedule of chemotherapy consisted of intravenous (IV) cisplatin 50 mg/m^2 day 1 plus topotecan 0.75 mg/m^2 given for 30 minutes on day 1 to 3, and repeated every 3 weeks until progression or unacceptable toxicity with a maximum dosage of 6 cycles. The protocol consisted of dose reduction of cispla-

tin by 25% if the creatinine clearance was less than 50%, while topotecan in the subsequent cycle was reduced by 25% for grade 3 or 4 hematologic toxicity. All patients were required to have a hemoglobin (Hb) of more than 10 gm%, an absolute neutrophil count (ANC) of more than 1,500/mm^3, and a platelet count (PC) of more than 100,000/mm^3 on the day before beginning chemotherapy. The treatment was to be delayed if blood counts had not returned to acceptable levels prior to the next cycle of chemotherapy. Some patients also received granulocyte-colony stimulating factor (G-CSF) for neutropenia. In cases of tumor progression, further treatment was left to the discretion of the responsible oncologist. The follow-up after the completion of treatment included clinical and pelvic examination every 3 months.

2. Outcome parameters

The objective tumor response was determined by using the WHO criteria.[3] The imaging findings were used for evaluating tumor response. Progression-free survival (PFS) was defined as a period of time between the first administration of chemotherapy and the date of tumor progression or the date of last contact if the patients had not yet developed recurrence; overall survival (OS) was defined as the period of time between the first administration of chemotherapy and the date of last contact or the date of patient's death. The Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events (CTCAE) were used for evaluating all adverse effects.[4]

3. Statistical methods

Descriptive data of all the eligible patients are presented with measurement data expressed as the mean, with range and discrete data as numbers and percentages.

PFS and OS were estimated by the Kaplan-Meier Method. Statistical analysis of the data was done using the SPSS ver. 11.5 (SPSS Inc., Chicago, IL, USA).

RESULTS

Twenty-one cervical cancer patients received cisplatin plus topotecan during the study period. The profiles of the patient characteristics are shown in Table 1. About one-third of the patients was diagnosed as stage IVB and had never received any treatment before. Tumor stage was unknown for two patients during the initial staging, one of those had previously received whole pelvic radiation and brachytherapy as primary treatment at another hospital 16 years ago. The other had been diagnosed with early stage cervical cancer and had been treated with simple hysterectomy. Two years after surgery she developed recurrence at the vagina and the left groin node. The histology of the recurrence site was poorly differentiated adenocarcinoma. In this study, the most common histology was squamous cell carcinoma followed by adenocarcinoma (Table 1).

Most patients received concurrent chemoradiation or radiation alone as the initial treatment. About half of the patients had one site of recurrence, and the affected sites included local and distant metastases. The most common site of recurrence was the supraclavicular lymph node and lung.

Table 1. Patients' characteristics (n=21)

	No. (%)
Mean age (range), yr	47 (26-65)
Tumor stage	
IB1	1 (4.8)
IB2	2 (9.5)
IIA	1 (4.8)
IIB	5 (23.8)
IIIB	1 (4.8)
IVA	1 (4.8)
IVB	8 (38.1)
Carcinoma in situ	1 (4.8)
Unknown	1 (4.8)
Tumor grade	
Well differentiated	3 (14.3)
Moderately differentiated	11 (52.4)
Poorly differentiated	4 (19.0)
Unknown	3 (14.3)
Histopathological type	
Squamous cell carcinoma	15 (71.4)
Adenocarcinoma	5 (23.8)
Clear cell carcinoma	1 (4.8)
Mean tumor size (range), cm	4 (0-8)
Previous treatment	
Radical hysterectomy	1 (4.8)
Radical hysterectomy & pelvic CCRT	1 (4.8)
Radiation	3 (14.3)
CCRT	6 (28.6)
Abandoned radical hysterectomy & pelvic CCRT	1 (4.8)
Simple hysterectomy	1 (4.8)
None	8 (38.1)
Previous chemotherapy	
Cisplatin	5 (23.8)
Non-cisplatin	3 (14.3)
None	13 (61.9)
The number of metastatic site(s)	
1	11 (52.4)
2	6 (28.6)
3	2 (9.5)
4	2 (9.5)
Site of recurrent/metastasis	
Local	1 (4.8)
Regional	3 (14.3)
Distant	5 (23.8)
Combine	12 (57.1)
Mean size of recurrent lesion (range), cm	4.8 (2-13)

CCRT: concurrent chemoradiation.

1. Chemotherapy regimen

Seven patients (33.3%) were given a 6-cycle cisplatin and topotecan regimen with a total chemotherapeutic course of 87

cycles.

2. Tumor response & survival

The overall response rate was 28.6%. Complete response (CR) was observed in only 1 (4.8%) patient, partial response in 5 (23.8%) patients, and stable disease in 1 (4.8%) patient. After tumor progression, further therapy consisted of re-irradiation (19%), chemotherapy in (38%), and supportive care (42%). All but one died from disease progression. There was only one patient who was alive with disease. The median PFS was 4 months and median OS was 11 months (Fig. 1).

3. Toxicity

Of the 87 cycles of chemotherapy, the hematological toxicity data was available for 69 cycles (80% cycles). The most common grade 3 & 4 hematologic toxicity was neutropenia (Table 2). However, febrile neutropenia was seen in only 1 cycle. Granulocyte stimulating factor was administered in five cycles for those patients with neutropenia. The adjusted dosage of cisplatin, topotecan, or both of them in subsequent cycles according to toxicities were 10.3%, 21.8%, and 3.4%, respectively Other serious toxicity was found in one patient who developed bilateral sensory neural hearing loss after receiving 2 cycles of chemotherapy.

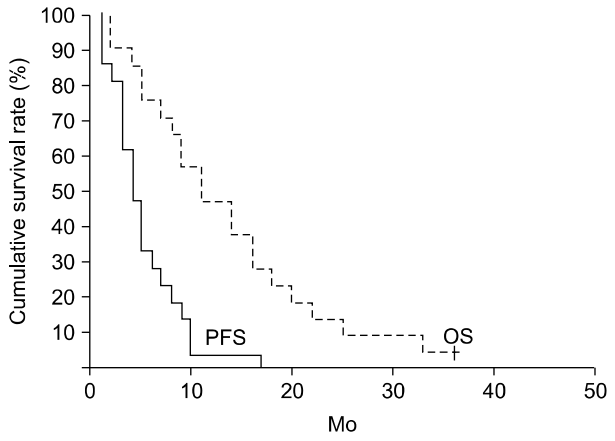

Fig. 1. Progression free survival (PFS) and overall survival (OS) of the studied patients. The median PFS was 4 mo (range, 1 to 17 mo) while the median OS was 11 months (range, 2 to 36 mo).

Table 2. Hematologic toxicity

	Per cycle (69 cycles)		Per patient (n=22)	
	Grade 3	Grade 4	Grade 3	Grade 4
Anemia	3 (4.3)	-	3 (13.6)	-
Leukopenia	19 (27.5)	1 (1.4)	10 (45.5)	1 (4.5)
Neutopenia	23 (33.3)	17 (24.6)	9 (40.9)	10 (45.5)
Thrombocytopenia	1 (1.4)	-	1 (4.5)	-

Values are presented as number (%).

DISCUSSION

Topotecan is a semisynthetic derivative of camptothecin that is isolated from the Chinese yew tree, *Camptotheca acuminate*.[5] It acts by two mechanisms, firstly, topotecan binds to the topoisomerase I-DNA complex and prevents religation of these single strand breaks; and secondly it inhibits the hypoxia-inducible factor (HIF). This HIF induces expression of gene encoding proteins enabling cell survival in hypoxic conditions.[6] This mechanism is of particular significance in cervical cancer since HIF tends to be expressed in previously irradiated tumors, which frequently results in tumor hypoxia. Furthermore, topotecan and cisplatin have non-overlapping toxicities; hence they are administered together in the treatment of recurrent and advanced cervical cancers. A superior outcome is observed with the topotecan and cisplatin combination compared to cisplatin monotherapy in a randomized phase III study by the GOG.[2] In this study, the median overall and progression-free survivals were 9.4 months and 4.6 months respectively, in patients receiving cisplatin plus topotecan, but were only 6.5 and 2.9 months, respectively, for the patients who received cisplatin monotherapy. In the present study, the median overall and progression-free survivals were 11 months and 4 months, respectively, with generic topotecan along with cisplatin. Thus, the results with generic topotecan are similar to those with other formulations as used in the GOG study.[2]

In another phase II study of topotecan as a single agent in second line therapy for persistent or recurrent carcinoma of the cervix in 25 patients, the median progression-free survival was 2.4 months for the patients with progressing disease and 6.2 months for those with stable disease.[7] The most frequent severe adverse events were grade 3 anemia (28%) and grade 4 (4%), along with grade 3 neutropenia (8%) and grade 4 (8%). Two patients had grade 4 thrombocytopenia.

The toxicity findings in the present study also are more or less similar to the GOG study[2]; the present study revealed grade 3 & 4 anemia in 13.6%, leukopenia in 50.0%, neutropenia in 86.4%, and thrombocytopenia in 4.5%, whereas in the GOG study, grade 3 & 4 anemia, leukopenia, neutropenia, and thrombocytopenia reported were 40%, 66%, 74%, and 28%, respectively. In the present study less frequency of grade 3 & 4 anemia and thrombocytopenia are reported compared to the GOG study. The GOG study also reported non-hematologic toxicity but these events were not considered attributable to the protocol anti-cancer therapy. The differences in these outcomes are likely due to the smaller sample size in the present study. Also, the differences in the population characteristics in the present study and the GOG study may explain the differences in the outcomes observed in the present study and the GOG study.

For patients with stage IVB, recurrent, or persistent cervical carcinoma, the regimen of topotecan along with cisplatin has been shown to provide comparable outcomes to those of pacli-

taxel 135 mg/m^2 over 24 hours plus cisplatin 50 mg/m^2 day 2 every 3 weeks, vinorelbine 30 mg/m^2 days 1 and 8 plus cisplatin 50 mg/m^2 day 1 every 3 weeks, and gemcitabine 1,000 mg/m^2 day 1 and 8 plus cisplatin 50 mg/m^2 day 1 every 3 weeks.[8] The present study reports similar outcomes of generic topotecan used along with cisplatin. However, the smaller sample size of the study limits the generalization of the results of this study. Also, the retrospective nature of this study precludes any inferences to be drawn in favour of generic topotecan.

In conclusion, there seem no obvious differences in response, median PFS or toxicity when generic topotecan was used as a substitute for the original one.

CONFLICT OF INTEREST

The generic topotecan used in this study was provided by the company. However, the study design and data analysis were independent, were developed and conducted entirely by the authors.

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