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Evaluation of Oral Etoposide in Combination with Cisplatin for Patients with Recurrent Cervical Cancer: Long-term Follow-up Results of a Japanese Multicenter Study

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Abstract. *Aim: To evaluate the efficacy and toxicities of cisplatin and daily oral etoposide in patients with recurrent cervical cancer. Patients and Methods: Treatment was initiated with oral etoposide 25 mg/day for 21 consecutive days, with intravenous cisplatin at 50 mg/m^2, on day 1, every 4 weeks, then the etoposide dose was increased to 50 mg/day. Results: Thirty patients were enrolled in this study. Twenty-seven (90.0%) patients had a history of prior treatment (cisplatin with concurrent chemoradiotherapy in 15, radiation therapy in 3, chemotherapy in 1, and both radiation therapy and chemotherapy in 9), and 22 (73.3%) patients had a treatment-free interval of less than 6 months. NCI-CTC grade 3/4 hematologic toxicities were leukopenia in 19 (63.3%), neutropenia in 17 (58.6%), anemia in 15 (50.0%) and thrombocytopenia in 6 (20.0%). Four patients developed febrile neutropenia. NCI-CTC grade 3 nonhematologic toxicities consisted of nausea/vomiting in 2 (6.7%), anorexia in 4 (13.3%) and fatigue in 2 (6.7%). The overall response rate was 16.7% including one complete response. The median progression-free survival period and overall survival period were 4.5 and 9.7 months, respectively. Conclusion: Combination chemotherapy consisting of oral etoposide and intravenous cisplatin is safe and effective for recurrent cervical cancer.*

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Previous randomized phase III trials conducted by the Gynecologic Oncology Group (GOG) evaluated cisplatin (CDDP) as a key-drug for chemotherapy of patients with metastatic or recurrent cervical cancer (1), but only the topotecan-CDDP doublet showed survival that was significantly superior to CDDP monotherapy (2). Furthermore, a recent phase III trial comparing four CDDP-containing doublets found that the paclitaxel-cisplatin doublet had a favorable survival effect in advanced, recurrent, or persistent cervical cancer (3). However, the efficacy and safety of other CDDP-containing doublets should be studied to improve the long-term prognosis for recurrent cervical cancer. Oral etoposide (ETP) has been widely used as a topoisomerase 2 inhibitor, and its response rate in patients with recurrent or advanced cervical cancer was reported to be 11.8% (4) to 33% (5) in squamous cell carcinoma and 11.9% in non-squamous cell carcinoma (6). Thus, we initiated a multicenter phase II study to evaluate oral ETP in combination with intravenous CDDP for recurrent cervical cancer.

Patients and Methods

The eligibility criteria were recurrent cervical cancer with a target lesion bidimensionally measurable by computed tomography (CT) or magnetic resonance imaging (MRI) for determination of direct effects, an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2, and age over 20 years. Moreover, the required pretreatment

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Table I. *Patient characteristics.*

Total no. of patients	30
Median age years (range)	50.5 (32-73)
ECOG performance status	
0	23
1	7
Histological subtype	
Squamous cell carcinoma	24
Adenocarcinoma	3
Adenosquamous carcinoma	2
Small cell carcinoma	1
Treatment (%)	
ETP25/CDDP	3 (10.0)
ETP50/CDDP	27 (90.0)
Prior therapy	
Surgery alone	2
CCRT alone	15
Radiation monotherapy	3
Chemotherapy alone	1
Radiation therapy + chemotherapy	9
No. assessable for efficacy[a]	25
No. assessable for survival	30
No. assessable for toxicity[b]	30[c]

ECOG, Eastern Cooperative Oncology Group; ETP25, oral etoposide 25 mg × 21 days; ETP50, oral etoposide 50 mg × 21 days; CDDP, cisplatin; CCRT, cisplatin concurrent chemoradiotherapy. [a]Efficacy determined in accordance with the World Health Organization Criteria. [b]Toxicity determined in accordance with the National Cancer Institute Common Toxicity Criteria. [c]One patient was not evaluated for neutropenia.

blood examination values were: leukocytes 3,000/mm^3 to 10,000/mm^3, platelets <100,000/mm^3, hemoglobin ≤9.0 g/dl, serum glutamic oxaloacetic transaminase (GOT) and serum pyruvic transaminase (GPT) <2X the upper limit of normal, and normal bilirubin, and serum creatinine. The treatment effects and toxicities were assessed according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC Version 2.0). The treatment regimen consisted of 4-week cycles of intravenous administration (*i.v.*) of CDDP on day 1, combined with oral ETP on days 1-21 (ETP/CDDP). The CDDP dose was fixed at 50 mg/m^2, while oral ETP was started at 25 mg/day and then escalated to 50 mg/day after confirmation of its safety in regard to dose-limiting toxicities

The primary endpoint of this study was the overall response rate based on the World Health Organization criteria (7). Statistically, the study was designed with a null hypothesis that the true response probability would be less than the clinically significant level of 10% for salvage therapy. If this hypothesis were rejected, we would accept the specified alterative hypothesis that the true response probability was at least a target level of 30% with reference to previous studies of cisplatin monotherapy for patients with recurrent cervical cancer (8, 9). The sample size was calculated as 33 patients, and a one-sided alpha level of 0.05 and 90% power were determined using the Southwest Oncology Group Statistical One Arm Binomial Tool (10). This study was approved by the Internal Review Board of each participating facility. However, we decided to analyze the data as feasibility study because enrollment of patients would remain at 30 cases even if the study period were extended to 3 years.

Table II. *Characteristics of patients with recurrent disease.*

Treatment-free interval (%)	
<6 months	22 (73.3)
6 months to 12 months	5 (16.7)
≥12 months	3 (10.0)
Recurrent site[a]	
Pelvic cavity	11
Distant	28
Both	9
Number of target lesions[b]	
1	12
2	10
3	2
4	6
Prior radiation/CCRT and recurrent site[b] (%)	
Prior irradiated area	11 (40.7)
Outside irradiated area	9 (33.3)
Both	7 (26.0)

CCRT: Cisplatin concurrent chemoradiotherapy. [a]Multiple-site recurrent cases were included. [b]Previously treated with radiation or CCRT.

Results

Table I shows the data on the baseline clinicopathologiccharacteristics of the 30 enrolled patients. Although all patients were assessable for toxicity, 5 patients could not be assessed for efficacy because neither CT nor MRI had been performed post-treatment. Twenty-two (73.3%) patients had a treatment-free interval of less than 6 months, and 18 (60.0%) patients had 2 or more sites of recurrence. Eighteen (66.7%) patients, who had previously undergone either CDDP concurrent chemoradiotherapy (CCRT) or radiation monotherapy had recurrent disease in the prior irradiation area (Table II). Table III shows the toxicities of the ETP/CDDP therapy. Although oral ETP dosing was postponed in 12 patients (due to leukopenia in 11 and elevation of serum creatinine in 1), 8 of those patients were able to resume oral ETP according to the protocol. The median treatment doses of CDDP and oral ETP were 127.5 mg (range: 60.0-308.6 mg) and 1050 mg (range: 350-4200 mg), respectively. The overall response rate of the 25 assessable patients was 16.7% including 1 complete response and 4 partial responses. The median progression-free survival period (Figure 1) and median overall survival period (Figure 2) were 4.5 months (95% confidence interval (CI): 1.0-7.5 months) and 9.7 months (95% CI: 7.0-12.9 months), respectively.

Discussion

The efficacy of ETP/CDDP for gynecologic cancer has mainly been studied in recurrent or advanced epithelial ovarian cancer, and the overall response rate was reported

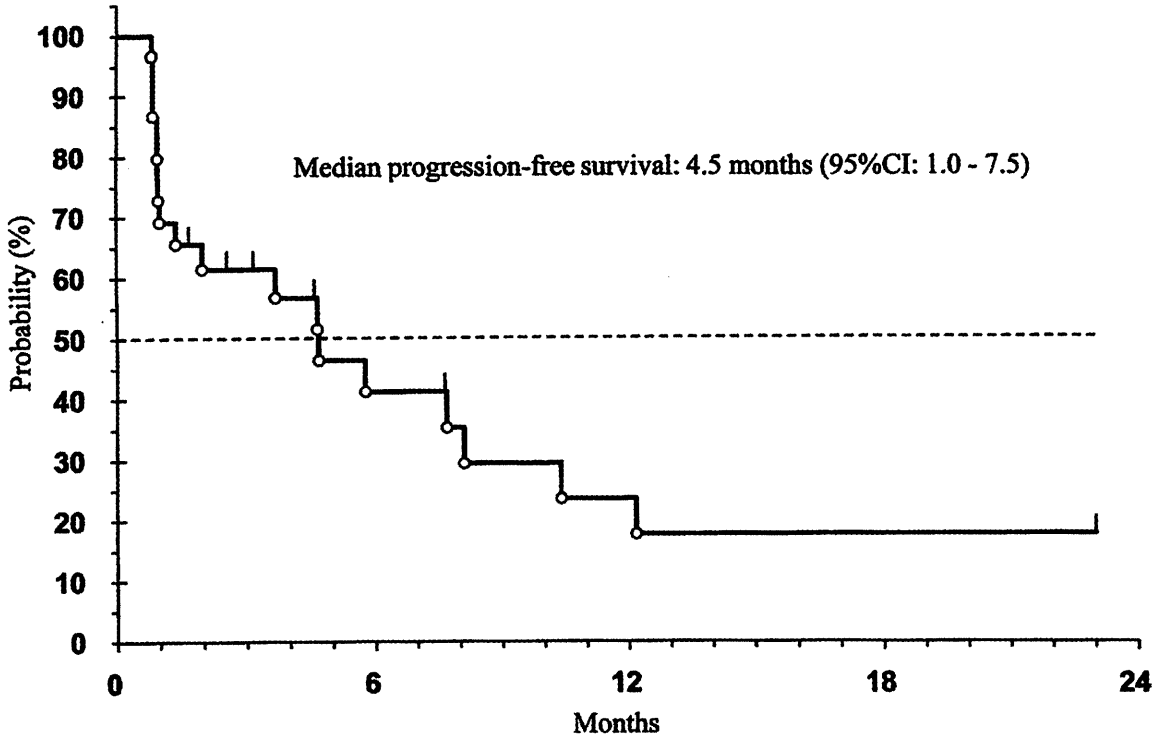

Figure 1. *Progression-free survival of enrolled patients.*

to range from 9.1% (11) to 27% (12) in previously treated patients and from 52% (13) to 54% (12) in therapy-naïve patients. Furthermore, this regimen was modified to daily oral etoposide and weekly cisplatin *i.v.*, and the rate of direct effects in recurrent epithelial ovarian cancer was reported to range from 78% (14) to 92% (15) in platinum-sensitive relapse and 44% (16) to 46% (14,15) in platinum-resistant relapse. Al-Saleh *et al.* (17) investigated *i.v.* etoposide/cisplatin chemotherapy fr recurrent or primary advanced cervical cancer and reported an overall response rate of 39%, including 7 complete responses, and an overall survival period of 9.8 months. However, no studies had evaluated oral ETP/*i.v.* CDDP for recurrent cervical cancer. Although the optimal administration schedule for etoposide in combination with CDDP has not been established, daily oral administration is thought to be effective because a previous in vivo study found that the antitumor activity of etoposide increased in proportion to the duration of drug exposure at the same total dose (18). Bone marrow suppression, especially thrombocytopenia, must be kept in mind when administering etoposide, but the incidence and the median duration of NCI-CTC grade 3/4 thrombocytopenia in the present study were only 20.0% and 5 days, respectively.

Table III. *Treatment toxicities.*

Adverse event	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
	N (%)	N (%)	N (%)	N (%)	N (%)
Leukopenia	3 (10.0)	2 (6.7)	6 (20.0)	13 (43.3)	6 (20.0)
Neutropenia[a]	4 (13.8)	4 (13.8)	4 (13.8)	7 (24.1)	10 (34.5)
Anemia	4 (13.3)	4 (13.3)	7 (23.3)	10 (33.3)	5 (16.7)
Thrombocytopenia	16 (53.3)	6 (20.0)	2 (6.7)	5 (16.7)	1 (3.3)
Nausea/Vomiting	2 (6.7)	10 (33.3)	16 (53.3)	2 (6.7)	0 (0.0)
Anorexia	6 (20.0)	8 (26.7)	12 (40.0)	4 (13.3)	0 (0.0)
Fatigue	9 (30.0)	15 (50.0)	4 (13.3)	2 (6.7)	0 (0.0)
Febrile neutropenia	26 (86.7)	–	–	4 (13.3)	0 (0.0)

[a]A total of 29 patients were assessable for neutropenia. Toxicities were determined in accordance with the National Cancer Institute Common Toxicity Criteria v2.0.

Furthermore, although the incidence and median duration of NCI-CTC grade 3/4 neutropenia were 58.6% and 8 days, respectively, that incidence was considerably lower than those reported with paclitaxel/cisplatin therapy (78.2% (5)) and topotecan/cisplatin therapy (82.6% (5) and 70.1% (2)).

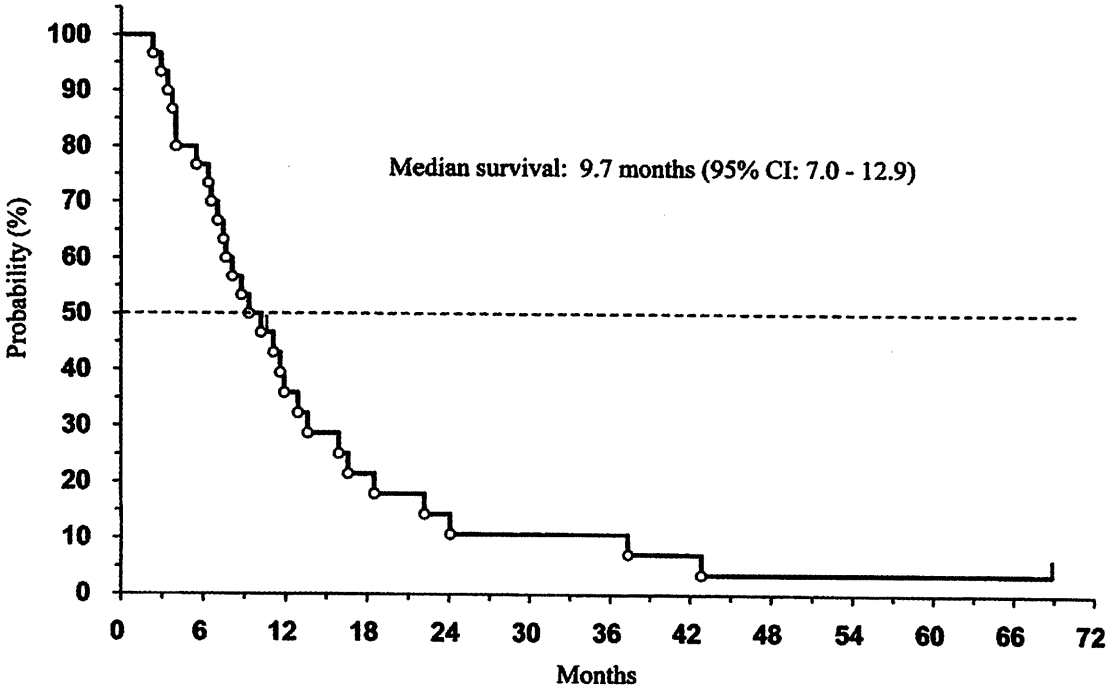

Figure 2. *Overall survival of enrolled patients.*

Our findings indicate that O-ETP/CDDP therapy has potential as a treatment option for patients with recurrent cervical cancer, especially for patients who were previously treated by CCRT.

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