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# Phase II trial of paclitaxel, carboplatin, and bevacizumab for advanced or recurrent cervical cancer

Kazuhiro Suzuki, Shoji Nagao *, Takashi Shibutani, Kasumi Yamamoto, Tomoatsu Jimi, Hiroko Yano, Miho Kitai, Takaya Shiozaki, Kazuko Matsuoka, Satoshi Yamaguchi

*Department of Gynecologic Oncology, Hyogo Cancer Center, Hyogo, Japan*

## HIGHLIGHTS

- We evaluated the efficacy and toxicity of paclitaxel/carboplatin/bevacizumab for advanced or recurrent cervical cancer.
- The combination of paclitaxel/carboplatin/bevacizumab has an acceptable toxicitylevel.
- This treatment is effective with an objective response rate and median overall survival of 88% and 26 months, respectively.

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## ABSTRACT

*Objective.* We evaluated the efficacy and safety of the combination of paclitaxel, carboplatin, and bevacizumab in patients with advanced or recurrent cervical cancer.

*Methods.* Subjects included patients with advanced or recurrent cervical cancer not amenable to curative treatment with surgery or radiation therapy. Treatment consisted of paclitaxel 175 mg/m$^2$, carboplatin area under the curve 6 mg/mL/min, and bevacizumab 15 mg/kg every 21 days until disease progression, complete remission, or limiting toxicity. The primary endpoint was the objective response.

*Results.* In total, 34 patients received a median of 6 treatment cycles (range 2–25). The median follow-up period was 18.5 months (range 2–29). The objective response was 88% (95% confidence interval: 72.5%–96.7%). Seventeen patients (50%) experienced complete response, whereas 13 patients experienced (38%) partial response with a median duration of 6 months. Grades 3 and 4 hematologic toxicities manifested as neutropenia in 14 (41.2%), leukopenia in 14 (41.2%), anemia in 11 (32.4%), and thrombocytopenia in 9 (26.5%) patients. One patient who underwent prior pelvic irradiation developed grade 2 rectovaginal fistula.

*Conclusion.* The combination of paclitaxel, carboplatin, and bevacizumab is effective and safe in patients with advanced or recurrent cervical cancer.



## 1. Introduction

Approximately 569,800 women are diagnosed with cervical cancer annually, resulting in 311,400 deaths worldwide in 2018 [1]. Although early-stage and locally advanced cancers may be cured by radical surgery, chemoradiotherapy, or both, patients with metastatic cancers or those with persistent or recurrent disease after platinum-based chemoradiotherapy have limited options. Most women with metastatic cervical cancer or local recurrence after radiotherapy are candidates for palliative chemotherapy.

The Japanese Clinical Oncology Group conducted a phase III trial to evaluate the efficacy and safety of carboplatin–paclitaxel (TC) compared with that of cisplatin–paclitaxel (TP), as well as the patients' quality of life [2]. The median overall survival (OS) was 18.3 months for the TP group versus 17.5 months for the TC group (hazard ratio 0.994; 90% confidence interval (CI), 0.79–1.25), demonstrating the non-inferiority of carboplatin–paclitaxel.

One of the most important recent advances has been the introduction of bevacizumab. This monoclonal antibody targets the vascular endothelial growth factor, the key mediator of tumor angiogenesis [3–5]. Bevacizumab has demonstrated efficacy in a wide range of solid tumor types, including advanced cervical cancer. GOG-240, which investigated the addition of bevacizumab to chemotherapy (either cisplatin–paclitaxel or topotecan–paclitaxel) for advanced cervical cancer, showed that the addition of bevacizumab to chemotherapy resulted in

* Corresponding author at: Department of Gynecologic Oncology, Hyogo Cancer Center, 13-70 Kitaoji-cho, Akashi City, Hyogo 673-8558, Japan.
*E-mail address:* nagao@hp.pref.hyogo.jp (S. Nagao).

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a 3.5-month increase in OS (16.8 versus 13.3 months) and a higher response rate (RR) (48% versus 36%, $p = 0.008$) [6].

However, the combination of paclitaxel, carboplatin, and bevacizumab has not been evaluated in patients with cervical cancer. To address this matter, we designed a prospective phase II trial to evaluate the efficiency and safety of this combination in patients with advanced or persistent cervical cancer.

## 2. Patients and methods

### 2.1. Patient eligibility

The eligibility criteria were as follows: patients with advanced or recurrent cervical cancer that was measurable with the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, but was not amenable to curative treatment with surgery or radiation therapy, who were aged ≥20 years with a GOG performance status (PS) score of 0 or 1, adequate bone marrow function [defined as having an absolute neutrophil count (ANC) of ≥1500/μL and platelet (PLT) count of ≥100,000/μL], adequate renal function (defined as having a creatinine level of ≤1.5 mg/dL), and normal hepatic function (defined as having levels of bilirubin ≤1.5 mg/dL, AST ≤100 IU/L, and ALT ≤100 IU/L) [7]. Patients were deemed ineligible if they had other evident malignancies, wounds that do not heal, infection requiring antibiotics, active bleeding, coagulopathy, central nervous system disease, a history of abdominal fistula, gastrointestinal perforation, ongoing grade 2 or higher peripheral neuropathy according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0, proteinuria (≥1 g of protein excreted in the urine per 24 h), prior therapy with bevacizumab, or major surgical procedures within 28 days and if they are pregnant or nursing [8].

The study was reviewed and approved by the institutional review board of our center, and all patients provided informed consent prior to enrollment. The identity of the patients has been protected. This trial was registered in the University hospital Medical Information Network (UMIN) Center Clinical Trials Registry (no. UMIN000024137).

### 2.2. Protocol treatment and evaluation

The patients received paclitaxel 175 mg/m$^2$ intravenously (IV), carboplatin area under the curve (AUC) 6 mg/mL/min IV, and bevacizumab 15 mg/kg IV every 21 days until disease progression, complete remission, or severe adverse events. The carboplatin dose was calculated using the Calvert formula with the creatinine clearance instead of the glomerular filtration rate [9]. Creatinine clearance was calculated using the Cockcroft–Gault formula [10]. If a patient had received prior radiation therapy, the carboplatin dose was reduced to AUC 5 mg/mL/min. Dose modifications were allowed in women of >10% change in body weight.

Toxicity was monitored by history taking, physical examination, and laboratory assessment prior to each treatment cycle, with adverse events defined and graded according to the NCI CTCAE version 4.0 [8]. Patients were required to have an ANC ≥ 1000/μL, a PLT count ≥ 750,000/μL, grade 1 or higher proteinuria, and grade 1 or higher hypertension on the day of re-treatment. There was no dose modification of bevacizumab.

Protocol-specified treatment modifications were permitted in the case of predefined toxic events. Treatment could be delayed for a maximum of 3 weeks. Doses of paclitaxel and carboplatin were reduced to AUC 5 mg/mL/min and 135 mg/m$^2$, respectively, in the event of grade 3 thrombocytopenia or grade 3 febrile neutropenia. In cases of grade 2 peripheral neuropathy, both treatments were delayed until recovery to grade 1, and paclitaxel dose was reduced to 135 mg/m$^2$. Treatment was discontinued if patients experienced either tumor remission or tumor progression and withdrew consent or developed unacceptable toxicity.

Tumor assessment was carried out by conducting clinical examination and performing computed tomography at baseline and after every two cycles. Follow-up was performed every 3 months for 2 years after termination of the treatment protocol. At the time of follow-up, computed tomography was performed after at least every 6 months. The RECIST version 1.1 was used to evaluate tumor response [7].

### 2.3. Statistical design and analysis

The primary endpoint of this phase II study was the objective response (OR) of the regimen. The secondary endpoints were as follows: safety, progression free survival (PFS), and OS. Results from JCOG-0505 revealed that paclitaxel and carboplatin had an RR of 63% [2]. GOG-240 demonstrated an improvement in the RR from 36% to 48% with the addition of bevacizumab to chemotherapy [6]. Based on a 12% improvement in the RR (from 63% to 75%) with a one-sided 0.05 significance and 80% power, the accrual of 28 subjects would be required. The duration of response was measured from the day of the first documentation of response to chemotherapy until disease progression. The PFS was measured from study entry until the day of the first evidence of disease progression, and the OS was measured from study entry to death or last contact. PFS and OS calculations were performed using the Kaplan–Meier method. Statistical analysis was performed using IBM SPSS statistics version 24.0 (IBM Corp.; Armonk, New York, USA).

## 3. Results

### 3.1. Patient characteristics

Between July 2016 and February 2019, a total of 34 patients were enrolled. Patient and disease characteristics of the study cohort are presented in Table 1. The median age of the patients was 53 years (range 31–73); 31 of them (91.2%) had a PS score of 0. Nineteen patients (55.9%) had received radiotherapy and 18 received platinum chemotherapy. All patients received at least two cycles of study treatments. In total, 260 cycles were administered with a median of six cycles per

**Table 1**
Patient characteristics.

| | No. | % |
|---|---|---|
| Age (years) | | |
| Median (range) | 53 (31–73) | |
| Performance status | | |
| 0 | 31 | 91.2 |
| 1 | 3 | 8.8 |
| Histologic type | | |
| Squamous cell carcinoma | 21 | 61.8 |
| Adenosquamous cell carcinoma | 2 | 5.9 |
| Adenocarcinoma | 7 | 20.6 |
| Others | 4 | 11.8 |
| Disease status | | |
| IVB or persistent | 9 | 26.5 |
| First recurrence | 22 | 64.7 |
| Second recurrence | 3 | 1.3 |
| Prior irradiation | | |
| Yes | 19 | 55.9 |
| No | 15 | 44.1 |
| Prior platinum chemotherapy | | |
| Yes | 18 | 52.9 |
| No | 16 | 47.1 |
| Prior hysterectomy | | |
| Yes | 12 | 35.3 |
| No | 22 | 64.7 |

patient (range 2–25). As of February 2019, all patients have discontinued therapy: nine due to disease progression, five due to toxicity, four due to refusal of further therapy, and one due to carboplatin allergy. Ten patients died of disease progression. Twenty-one patients (62%) are alive; 10 of whom are without progression.

### 3.2. Adverse events

All patients were evaluable for toxicity. Overall, the treatment was well tolerated and the recorded adverse events were anticipated, given the toxicity profiles of paclitaxel, carboplatin, and bevacizumab. Table 2 shows all adverse effects observed during the study. Grade 3 to 4 hematologic toxicities were frequent. Grade 3 to 4 hematologic toxicities were manifested as neutropenia in 14 (41.2%), leukopenia in 14 (41.2%), anemia in 11 (32.4%), and thrombocytopenia in 9 (26.5%) patients. There were one episode of grade 3 bronchopulmonary hemorrhage and one grade 2 rectovaginal fistula that did not lead to surgical emergencies nor sepsis. One patient developed a deep venous thrombosis, without fatal pulmonary embolus. Only one grade 2 hypertension was observed.

### 3.3. Activity of paclitaxel, carboplatin, and bevacizumab

All 34 patients were evaluated for treatment response. The OR was 88% (95% CI: 72.5–96.7%) (Table 3). In total, 17 patients confirmed complete response (CR) (50%, 95% CI: 32.4–67.6%), whereas 13 partial responses (38%, 95% CI: 22.2–56.4%) lasting a median 6 months (range 1–15 months) were documented (Supplementary Figs. 1, 2). In addition, three patients (9%, 95% CI: 1.9–23.7%) had a stable disease course with a median duration of 5 months (range 2–10 months) and one had progressive disease (PD) (3.0%). The median follow-up period was 18.5 months (range 2–29 months). The median PFS and OS for all patients were 9 months (95% CI: 6.7–11.5 months) and 26 months (95% CI: 14.3–37.7 months), respectively (Fig. 1).

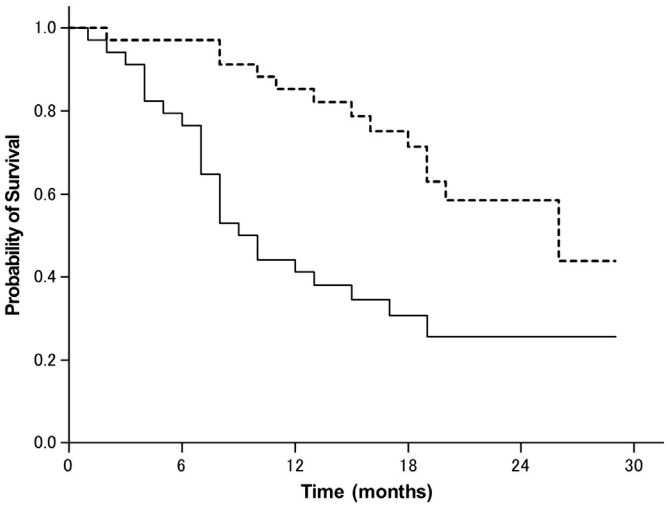


**Fig. 1.** Kaplan–Meier curves for overall survival and progression-free survival.

## 4. Discussion

The combination of paclitaxel, carboplatin, and the anti-angiogenic agent bevacizumab, given every 21 days, was safe, feasible, and relatively well tolerated in patients with advanced or recurrent cervical cancer. Furthermore, the median PFS and OS of 9 months and 26 months, respectively, were observed in the current study, which were favorable than recent historic data in the same patient population. In GOG-240, the cisplatin–paclitaxel–bevacizumab arm had an RR of 50%, PFS of 8.2 months, and OS of 17.5 months, respectively [11]. In JCOG-0505, the carboplatin–paclitaxel arm had an RR of 63%, PFS of 6.2 months, and OS of 17.5 months, respectively [2].

A significant improvement in treatment efficiency may be attributed to two factors. First, a striking difference between the population of patients enrolled in the present study and those in GOG-240 is their PS. Almost all patients in the current study had a PS score of 0, whereas in GOG-240, almost 50% of the patients had a PS score of 1 [6]. The difference in PS may reflect some degree of selection bias for the present study. Second, the rate of chemotherapy-naive patients in this study was higher than in both GOG-240 and JCOG-0505. In the present study, 47.1% of patients had not received prior platinum treatment including cisplatin-based chemoradiotherapy. In the present study, the rate of chemotherapy-naive patients was 24.5%. Rate of chemotherapy-naive patients was 24.5% of the combination of paclitaxel–cisplatin backbone in GOG-240, whereas it was 34.1% of the combination paclitaxel–carboplatin arm in JCOG-0505. [2,6]. The high rate of chemotherapy-naive patients might indicate a good outcome.

In this study, severe adverse events were not evident. It is important to minimize toxicities, which are the main focus of studies assessing chemotherapy in patients with advanced or recurrent cervical cancer. The rate of grade 3 to 4 hematologic toxicities was 41.2% in neutropenia, 41.2% in leukopenia, 32.4% in anemia, and 26.5% in thrombocytopenia. In GOG-240, particularly in the chemotherapy–bevacizumab arm, the rate of grade 3 to 4 hematologic toxicities was 58% in neutropenia and 36% in leukopenia [6,11]. In JCOG-0505, specifically in the carboplatin–paclitaxel arm, the rate of grade 3 to 4 hematologic toxicities was 76.2% in neutropenia, 44.4% in anemia, and 24.6% in thrombocytopenia [2]. Compared to other studies, the hematologic toxicities of this study are within the acceptable range. Nineteen patients (55.9%) had received prior pelvic irradiation and thus were given carboplatin that was reduced to AUC 5 mg/mL/min. The rate of prior pelvic irradiation therapy was 80% of the combination of paclitaxel and cisplatin backbone in GOG-240 and 86% of the carboplatin–paclitaxel arm in JCOG-0505 [2,6,11]. The low rate of prior irradiation therapy may have resulted in allowable hematologic toxicity.

In GOG-240, an exploratory analysis of the clinicopathologic characteristics associated with the development of fistulae revealed that all of the patients who developed gastrointestinal–vaginal fistulae had received prior pelvic irradiation [6]. The ongoing CECILIA study also revealed a 10% fistula rate, whereas GOG-0240 observed 13.3% [12]. In

**Table 2**
Adverse events.

| Adverse effects | Grade (no. of patients) | | | | |
|---|---|---|---|---|---|
| | 0 | 1 | 2 | 3 | 4 |
| Hematologic | | | | | |
| Leukopenia | 4 | 1 | 15 | 8 | 6 |
| Neutropenia | 2 | 5 | 13 | 9 | 5 |
| Thrombocytopenia | 6 | 10 | 9 | 7 | 2 |
| Anemia | 0 | 11 | 12 | 7 | 4 |
| Nonhematologic | | | | | |
| Peripheral neuropathy | 27 | 5 | 2 | 0 | 0 |
| Hypertension | 32 | 0 | 2 | 0 | 0 |
| Proteinuria | 34 | 0 | 0 | 0 | 0 |
| Thromboembolic event | 33 | 0 | 1 | 0 | 0 |
| Gastrointestinal perforation | 0 | 0 | 0 | 0 | 0 |
| Fistula | 33 | 0 | 1 | 0 | 0 |
| Bronchopulmonary hemorrhage | 33 | 0 | 0 | 1 | 0 |

**Table 3**
Treatment efficiency.

| | No. | (%) | Median duration (range) |
|---|---|---|---|
| Complete response | 17 | (50.0) | 8 (2–14) |
| Partial response | 13 | (38.2) | 6 (1–15) |
| Stable disease | 3 | (8.8) | 5 (2−10) |
| Progressive disease | 1 | (3.0) | |

our study, among 19 patients with prior pelvic irradiation, one patient developed rectovaginal fistula that could be associated with bevacizumab administration. In addition, one patient developed pulmonary embolism that could also be associated with bevacizumab administration.

There are some limitations to this study. First, this was a single-center study that exclusively consisted of Japanese women. The ongoing CECILIA study will provide additional data on the tolerability and activity of bevacizumab in populations from different geographic regions [12]. Second, the patient-reported subjective quality of life evaluation was not prospectively measured, which could have elucidated the relative effect. Although the objective evaluation might be possible with non-hematological toxicities and hospitalization periods, it was not sufficient by itself. Finally, chemotherapy was discontinued when CR was obtained in the current study. Most studies in patients with advanced or recurrent cervical cancer continue chemotherapy even when CR is obtained, and continue chemotherapy until PD. Even if chemotherapy was discontinued when CR was obtained, it was the result of CR lasting a median of 8 months. The chemotherapy-free duration indicates the maintenance and promotion of the quality of life. The subjective quality of life evaluation and chemotherapy discontinuation still remain to be clarified.

Our study demonstrates that the combination of paclitaxel, carboplatin, and bevacizumab is effective and safe in patients with advanced or recurrent cervical cancer. Although the patients who had received prior irradiation therapy need to be vigilant with regard to the development of gastrointestinal–vaginal fistula, the combination of paclitaxel, carboplatin, and bevacizumab can be a standard treatment option in patients with advanced or recurrent cervical cancer.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2019.05.018.

## Author contribution

K. Suzuki designed the study, analyzed the data, and wrote the initial draft of the manuscript. S. Nagao contributed to design of the research, analysis and interpretation of the data, and assisted in the preparation of the manuscript. T. Shibutani, K. Yamamoto, T. Jimi, H. Yano, M. Kitai, T. Shiozaki, K. Matsuoka, and S. Yamaguchi have contributed to data collection and interpretation, and critically reviewed the manuscript. All authors approved the final version of the manuscript.

## Declaration of Competing Interest

None of the authors report a conflict of interest.

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