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A Single Arm Prospective Pilot Study Examining the Efficacy and Safety of Bevacizumab Single Maintenance Therapy Following Platinum-Based Chemotherapy in Patients with Advanced or Recurrent Cervical Cancer

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Although the addition of bevacizumab to platinum-based combination chemotherapy has been recommended as a standard regimen for patients with advanced or recurrent cervical cancer, there is no clear evidence regarding the effectiveness of bevacizumab monotherapy as salvage chemotherapy. This study prospectively examined the efficacy and safety of switching from platinum-based chemotherapy combined with bevacizumab to single maintenance therapy in patients with advanced or recurrent cervical cancer. Patients were first treated with standard combination chemotherapy. However, if chemotherapy was discontinued because of an adverse event, bevacizumab monotherapy was continued for patients who agreed to participate in this study and provided written informed consent. The study protocol was approved by the Independent Review Board of Tohoku University School of Medicine (reception number 2017-1-540). A total of 15 patients (median age of 55 years, range 33-69 years) participated in this study. The median number of cycles of bevacizumab single maintenance administration was 8, and the main reasons for discontinuation were disease progression and adverse events. Bevacizumab single maintenance therapy had a disease control rate of 53.3% (CR 40%, PR 6.7%, SD 6.7%). The most frequent grade 3/4 clinical adverse events were proteinuria (5/15) and hypertension (4/15). No treatment-related deaths occurred. Bevacizumab single maintenance therapy was effective as salvage chemotherapy in patients with advanced or recurrent cervical cancer, and the safety profile was generally consistent with those reported in previous studies of bevacizumab monotherapy.

Keywords: advanced or recurrent; bevacizumab; cervical cancer; platinum-based chemotherapy; single maintenance
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Introduction

Cervical cancer, which is a malignant tumor that forms in the cervix, is the fourth most frequently diagnosed cancer and the fourth leading cause of cancer death in women, with an estimated 570,000 cases and 311,000 deaths in 2018 worldwide (Bray et al. 2018). The incidence and mortality rates of cervical cancer have declined over the last few decades (Arbyn et al. 2020). This has been attributed to cytologic screening and DNA testing for high-risk human papilloma virus (HPV) (McGraw and Ferrante 2014). Cervical cancer is preventable and can be expected to be completely cured by radical surgery and/or chemoradiotherapy in patients with early stage or locally limited cancers (Monk and Herzog 2007). In addition, HPV vaccination has been proven to reduce the risk of invasive cervical

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cancer at the population level (Lei et al. 2020). However, once it becomes advanced or recurrent, the median survival of cervical cancer patients is only 9 to 10 months (Long et al. 2005) and systemic chemotherapy with cisplatin combination regimens is being developed for these patients. Based on the two landmark studies, Gynecologic Oncology Group (GOG) 204 (Monk et al. 2009b) and Japanese Clinical Oncology Group (JCOG) 0505 (Kitagawa et al. 2015), paclitaxel plus cisplatin (TP) therapy or paclitaxel plus carboplatin (TC) therapy, respectively, has been recommended as a standard chemotherapeutic regimen for patients with advanced or recurrent cervical cancer. Recently, results from the GOG0240 study revealed the prolongation of overall survival (OS) by the addition of bevacizumab (Bev) to combination chemotherapy (TP therapy or PTX/topotecan) in these patients (Tewari et al. 2014). Based on these results, the triple-drug combination regimen of Bev combined with Paclitaxel therapy was approved for advanced or recurrent cervical cancer as an insurance-covered therapy in Japan in October 2016.

Several observational cohort studies have shown that Bev in combination with chemotherapy is well tolerated and effective in a wide range of patient populations (Godoy-Ortiz et al. 2018; Choi et al. 2020). Chemotherapeutic treatment is continued as long as the effect is observed, since there is no data regarding the optimal number of courses for the initial treatment when using these three-drug combination methods. However, the side effects of chemotherapy are often unacceptable after long-term polypharmacy or decreased physical strength in most patients with advanced or recurrent cervical cancer. In these cases, the available options are (I) lowering the relative dose intensity (RDI), (II) changing the treatment regimen, and (III) pausing chemotherapy. When anti-cancer drugs are effective, lowering RDI may be often selected first, but it has been reported that when the RDI is 85% or less, the prognosis is adversely affected (Bonadonna et al. 1995). If the side effects of chemotherapy are unacceptable even after lowering the RDI, a change in the treatment regimen or discontinuation of treatment should be considered.

In the GOG-0227C trial, Bev monotherapy showed a response rate of 10.9%, which was superior to that of other molecular targeting agents in patients with refractory or recurrent cervical cancer (Monk et al. 2009a). Furthermore, in the JO29569 study, which evaluated the effectiveness of TP plus Bev therapy in Japanese patients with advanced cervical cancer patients, 5 out of 7 cases were administered Bev monotherapy from the halfway, and there was no increase in adverse events (Sugiyama et al. 2017). The effectiveness of TC therapy with Bev followed by Bev single maintenance therapy has been confirmed in patients with ovarian cancer (Perren et al. 2011; Tewari et al. 2019). However, there is currently no clear evidence of the efficacy and safety of switching from TP or TC chemotherapy combined with Bev to single maintenance therapy in patients with cervical cancer. Bev monotherapy is expected to be a useful salvage chemotherapy with a relatively good safety profile over a period of time and the potential to maintain disease control in the long term. Based on this background, this study prospectively examined the efficacy and safety of switching from TP or TC chemotherapy combined with Bev to Bev single maintenance therapy.

Methods

Study design

This study was a prospective pilot study to assess the efficacy and safety of TP or TC therapy combined with Bev followed by Bev single maintenance therapy in patients with advanced or recurrent cervical cancer. Patients were first treated with standard combination chemotherapy (TP plus Bev or TC plus Bev) for advanced or recurrent cervical cancer. If a patient discontinued chemotherapy because of an adverse event of cisplatin, carboplatin, or paclitaxel, Bev could be continued as a single agent for patients who agreed to participate in this study. All participating patients provided written informed consent. In case of preceding chemotherapy resulted in progressive disease (PD), patients were excluded from this clinical trial. This study was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice. The study protocol was approved by the Independent Review Board of Tohoku University School of Medicine (reception number 2017-1-540).

Patients

Eligible patients were aged between 20 and 75 years and had Eastern Cooperative Oncology Group performance status 0 to 2, radiologically confirmed advanced or recurrent cervical cancer that was not amenable to curative treatment with surgery or radiation therapy (including prior concurrent chemoradiotherapy). Patients were required to have adequate hematologic, renal, and hepatic functions. Patients were ineligible if they had received any prior anti-vascular endothelial growth factor (VEGF) or anti-VEGF receptor therapy. Patients were not eligible if they had clinical signs or symptoms of intestinal obstruction requiring parenteral hydration or nutrition, a serious non-healing wound, ulcer, or bone fracture; a history of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 6 months before study entry; bilateral hydronephrosis that could not be alleviated by ureteral stent or percutaneous drainage; complications or history of symptomatic cerebrovascular accident within 6 months before study entry; ongoing grade ≥ 2 peripheral neuropathy according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03; central nervous system metastases that were symptomatic or required treatment; or complications or history of NCI CTCAE grade ≥ 2 hemoptysis within 1 month before study entry. Patients were also excluded if they were considered to be at a high risk of bleeding or if they were pregnant or

nursing. All patients provided written informed consent to participate in the study before participating in the study.

Treatment

Patients were first treated with a TP regimen (cisplatin 50 mg/m^2 combined with paclitaxel administered either at 135 mg/m^2 infused over 24 h) or TC regimen (carboplatin AUC = 5 combined with paclitaxel administered at 175 mg/m^2 infused over 3 h) combined with Bev at a dose of 15 mg/kg. Which regimen to choose was decided by the attending physician. Treatment with all three agents was repeated every 3 weeks, with treatment postponement of up to 2 weeks allowed in the absence of disease progression, unacceptable adverse events, or patient request for discontinuation. If a decision had to be made to discontinue chemotherapy due to adverse events, single-dose Bev maintenance therapy was offered to participants who indicated their willingness to participate in the study.

The regimen was not considered tolerable if patients experienced any of the following adverse events (graded according to NCI CTCAE version 4.03), considered by the investigator to be related to any of the study drugs: grade 4 neutrophil count decrease persisting for ≥ 7 days; febrile neutropenia; grade 4 platelet count decrease or grade 3 platelet count decrease requiring platelet transfusion; grade 4 hypertension; grade ≥ 3 diarrhea, nausea, vomiting, or rash that could not be controlled with appropriate medical management, grade ≥ 3 liver function abnormality, or other grade ≥ 3 non-hematologic toxicity, excluding transient electrolyte abnormality. A ≥ 3-week delay in the administration of cycle 2 due to drug-related adverse events was also considered a qualifying adverse event.

Study objectives

The primary objective was to evaluate the efficacy and tolerability of Bev single maintenance therapy following combination chemotherapy (TP plus Bev or TC plus Bev) in patients with advanced or recurrent cervical cancer. Efficacy was measured as antitumor effect according to Response Evaluation Criteria in Solid Tumors (RECIST version 1.1), progression-free survival (PFS), and overall survival (OS). PFS 1 indicated progression-free survival to first disease progression after the beginning of combination chemotherapy (TP plus Bev or TC plus Bev), and PFS 2 indicated progression-free survival to first disease progression after the beginning of Bev single maintenance therapy.

The secondary objectives were to evaluate safety (frequency, severity, and time to onset of adverse events). The following adverse events were considered to be of special interest for Bev and were reported according to grouped preferred terms: any grade of non-gastrointestinal fistula or abscess; any grade of gastrointestinal perforation; grade ≥ 3 bleeding; grade ≥ 3 congestive heart failure or left ventricular systolic dysfunction; febrile neutropenia; grade ≥ 3 hypertension; grade ≥ 3 proteinuria; any grade of arterial thromboembolic event; grade ≥ 3 venous thromboembolic event; grade ≥ 3 wound healing complications; or any grade of posterior reversible encephalopathy syndrome. Adverse events were classified as serious adverse events if they met any of the following criteria: fatal, life threatening, requiring or prolonging inpatient hospitalization, resulting in persistent or significant disability or incapacity, a congenital anomaly or birth defect in a neonate or infant born to a mother exposed to the study drug; or a significant medical event in the investigator's judgment.

Statistical analysis

The PFS curve was estimated using the Kaplan-Meier method for the largest population to be analyzed. In addition, the median PFS and 90% confidence intervals on both sides were calculated. The confidence interval method was used as the criterion for the main analysis. OS was calculated in the same way as the secondary endpoint. The secondary objectives were to define the safety and tolerability of Bev. For safety evaluation, the frequency of reported hematological and non-hematological adverse events was tabulated by grade for the safety set. All analyses are presented for the safety population, comprising all patients who received at least one dose of Bev. SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) was used for statistical analysis.

Results

Patient characteristics

From May 2016 to December 2019, 23 patients underwent TP plus Bev or TC plus Bev combination chemotherapy for advanced or recurrent cervical cancer. Of these, 4 were excluded from this study because the effect judgment of combination therapy was PD. Four patients were used for comparison analysis of the efficacy but excluded from the safety and tolerability analysis because they did not wish to receive Bev single maintenance therapy. Finally, 15 patients with a median age of 55 years (range, 33-69 years) agreed to participate in this study and were eligible to assess efficacy and safety analysis (Fig. 1). The patient characteristics of the study group are listed in Table 1. Total 9 out of 15 patients (60%) had squamous cell carcinoma and 4 (26.7%) had adenocarcinoma. Of the 15 patients, 12 (80%) had received prior radiation, and all these patients received concurrent chemoradiation with weekly cisplatin therapy.

Treatment exposure

A summary of the treatments received by the patients is presented in Table 2. At the time of the primary data cutoff (December 31, 2019), 2 patients remained on the therapy. The median duration of Bev single maintenance therapy was 8 months. The median number of cycles administered was 8. The main reasons for discontinuation of Bev maintenance therapy were disease progression in 7 patients and adverse events in four patients, but there was no case of treatment refusal.

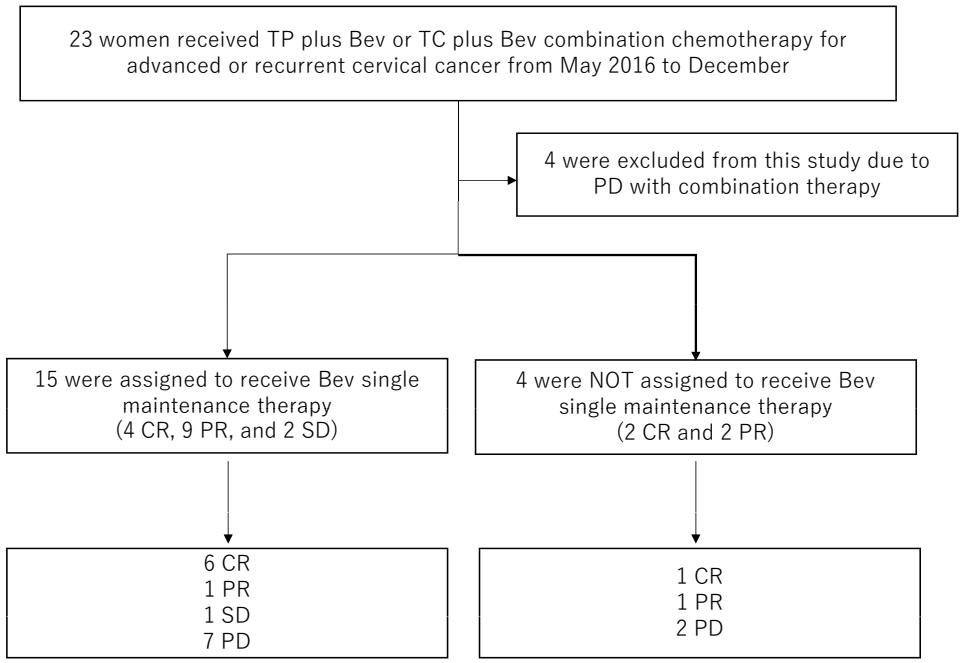

Fig. 1. Selection and outcomes of patients with advanced or recurrent cervical cancer.
Bev, bevacizumab; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; TC, paclitaxel plus carboplatin; TP, paclitaxel plus cisplatin.

Table 1. Patients' characteristics at baseline in 15 patients.

Characteristics	n (%) or n (range)
Median age	55 (33-69)
Histologic subtype (%)	
SCC	9 (60.0%)
Adenocarcinoma	4 (26.7%)
Adenosquamous	1 (6.7%)
SCC + Adenocarcinoma	1 (6.7%)
FIGO stage	
I	2 (13.3%)
II	5 (33.3%)
III	5 (33.3%)
IV	3 (20.0%)
Disease status	
Advanced	4 (26.7%)
Recurrent	11 (73.3%)
Firstline therapy	
Surgery alone	3 (20.0%)
Surgery and CCRT	2 (13.3%)
CCRT alone	10 (66.7%)

CCRT, concurrent chemoradiotherapy; SCC, squamous cell carcinoma; FIGO, The International Federation of Gynecology and Obstetrics.

Efficacy

The PFS was set as the primary endpoint in this study. At data cut-off, PFS events were observed in 7 patients. One patient had stable disease (SD) (1/15), and 7 patients (47%) showed progressive disease (PD) (Table 2). The median PFS 1 was 16.0 months in the Bev maintenance group and 11.0 months without Bev maintenance (control group) (Fig. 2A and Table 3). Hazard Ratio of the median PFS 1 was 0.753 and p-value was 0.7097. The median PFS 2 was 12.0 months in the Bev maintenance group and 7.0 months in the control group (Fig. 2B and Table 3). Hazard Ratio of the median PFS 2 was 0.734 and p-value was 0.6805. The overall response rate was 47% (7/15), and most of responded patients achieved complete response (CR) (6/15). A total disease control rate of Bev single maintenance therapy was 53.3% (CR 40%, PR 6.7%, SD 6.7%). The median OS since the beginning of combination chemotherapy (TP plus Bev or TC plus Bev) was not reached in 15 patients in the Bev maintenance group and 21.0 months in 4 patients in the control group (Fig. 2C and Table3). Hazard Ratio of the median OS was 0.088 and p-value was 0.0132 which has significant difference.

Safety

There were 4 treatment-related serious adverse events (3 by proteinuria and 1 by gastrointestinal perforation), and there were 13 protocol-specific treatment-related adverse events (Table 4). The most frequent grade 3/4 clinical adverse events were proteinuria (5/15) and hypertension (4/15). The following grade 3/4 adverse events occurred in only 1 patient: bleeding, thrombocytopenia, decreased liver function, and gastrointestinal perforation. No treatment-related deaths occurred. Gastrointestinal perforation was occurred in a patient with stage IIIB cervical cancer. She

Table 2. Treatments and objective responses in 15 patients.

Characteristics	n (%) or n (range)
Combination chemotherapeutic regimen with Bev	
TC	6 (40.0%)
TP	7 (46.7%)
TP→TC	2 (13.3%)
Number of doses (range)	
Combination chemotherapy	5.7 (3-10)
Maintenance chemotherapy	8.9 (3-17)
Of total Bev	14.2 (3-23)
Objective responses of Bev single maintenance	
CR	6 (40.0%)
PR	1 (6.7%)
SD	1 (6.7%)
PD	7 (46.7%)

Bev, bevacizumab; TC, paclitaxel plus carboplatin; TP, paclitaxel plus cisplatin;
CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

was taken concurrent chemoradiotherapy (CCRT) with 3 courses of TP regimen and changed to Bev single maintenance therapy. After taking 14 courses of Bev administration, she complained severe abdominal pain and was diagnosed as gastrointestinal perforation. She took open surgery and has been alive without evidence of disease.

Discussion

VEGF is involved in mitogenesis, angiogenesis, endothelial cell survival, and hematopoiesis induction (No et al. 2009). Bev is a monoclonal antibody against VEGF and is widely used to treat colorectal cancer (Kabbinavar et al. 2005), lung cancer (Sandler et al. 2006), breast cancer (Li et al. 2015), brain tumor (Chinot et al. 2011), and ovarian cancer (Tewari et al. 2019) by targeting tumor neovascularization. In addition to these diseases, results from the GOG0240 study showed that the addition of Bev prolongs OS for advanced or recurrent cervical cancer (Tewari et al. 2014). Increased expression of VEGF and hypoxia-inducible factor 1α was clinically observed in patients with high-grade cervical dysplasia and invasive carcinoma (Tang et al. 2007). Conversely, the invasive phenotype was present only in patients with upgraded VEGF. In addition, the molecular aberrations in predominantly HPV16-driven cervical squamous cell carcinoma and predominantly HPV18-induced cervical adenocarcinoma both favor a proangiogenic tumor environment (Seamon et al. 2018). Based on this background, Bev combined with TP or TC is now considered a standard therapeutic regimen for advanced or recurrent cervical cancer.

For patients with advanced or recurrent cancer, it is necessary to continue anticancer drug treatment as long as the effect is observed, because even strong combination therapy does not result in a complete response. However, long-term treatment is a heavy burden on these patients, and severe side effects sometimes become unacceptable after a long-term combination of multiple drugs. In such cases, continued treatment with molecular targeting drugs with a different side effect profile from conventional anticancer drugs is an option. For example, Bev has minor side effects that are problematic with ordinary anticancer drugs, such as myelosuppression. The usefulness of Bev single maintenance therapy after conventional anticancer chemotherapy is recognized for patients with lung cancer (Sandler et al. 2006), brain tumor (Nagane et al. 2012), and ovarian cancer (Perren et al. 2011; Tewari et al. 2019). Sugiyama et al. (2017) also confirmed the efficacy of Bev single maintenance therapy in treating advanced and recurrent cervical cancer in a phase II study. In our study, Bev single maintenance therapy was administered to 15 patients with advanced or recurrent cervical cancer in whom standard combination chemotherapy was difficult to continue due to side effects, such as pancytopenia or peripheral neuropathy. Results from this study demonstrated that Bev single maintenance therapy had a disease control rate of 53.3% (CR 40%, PR 6.7%, SD 6.7%) and an acceptable toxicity. Although there were 4 cases of postponement of treatment, maintenance therapy was continued for a median of 8 cycles. Bev single maintenance therapy resulted in CR in 6 patients, with a median PFS of 8 months after starting maintenance.

With regard to tumor histology, a meta-analysis of 3 GOG randomized phase III trials revealed that squamous cell carcinoma and adenocarcinoma/adenosquamous cell carcinoma had similar survival rates in recurrent or metastatic cervical carcinoma when treated with chemotherapy doublets (Seamon et al. 2018). In contrast, results from the GOG0240 study did not show a survival impact with the addition of Bev in patients with cervical adenocarcinoma (Tewari et al. 2014). In our study, although 3 out of 4 patients with adenocarcinoma showed PD, 4 out of 9 patients with squamous cell carcinoma maintained CR after

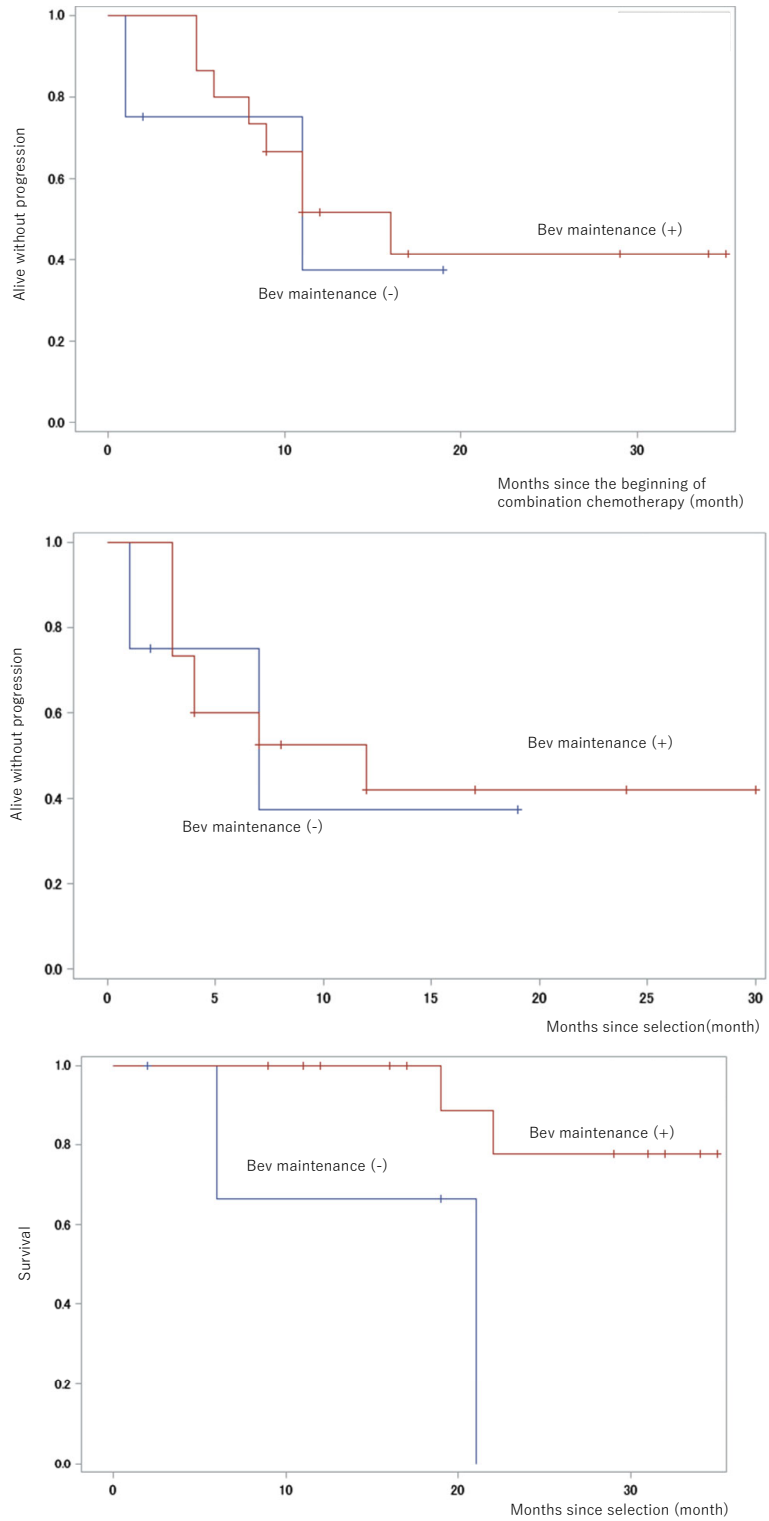

Fig. 2. Kaplan-Meier curves of the bevacizumab (Bev) single maintenance groups (Red) and control group (Blue).
A: Kaplan-Meier curves of the difference in progression free survival to first disease progression after the beginning of combination chemotherapy (PFS1). B: Kaplan-Meier curves of the difference in progression free survival to first disease progression after the beginning of Bev single maintenance therapy (PFS2). C: Kaplan-Meier curves of overall survival (OS) after the beginning of Bev single maintenance therapy.

Table 3. Efficacy profiles of each endpoint.

		Bev maintenance (+)	Bev maintenance (-)
		n =15	n =4
PFS 1	Median (95%CI)	16.0 (6.0 - N/A)	11.0 (1.0 - N/A)
	HR (95%CI) (cox)	0.753 (0.159-3.569)	
	Two-side p-value (Log-rank test)	P = 0.7097	
PFS 2	Median (95%CI)	12.0 (3.0 - N/A)	7.0 (1.0 - N/A)
	HR (95%CI) (cox)	0.734 (0.154-3.489)	
	Two-side p-value (Log-rank test)	P = 0.6805	
OS	Median (95%CI)	N/A	21.0 (6.0-21.0)
	HR (95%CI) (cox)	0.088 (-)	
	Two-side p-value (Log-rank test)	P = 0.0132	
	One year survival rate	100%	66.67%
	Two year survival rate	77.78%	0%

Bev, bevacizumab; PFS, progression free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; N/A, not applicable.

Table 4. Bevacizumab specific adverse events in 15 patients.

	n (%)	Note (n)
Hypertension	4 (26.7%)	Continued treatment with antihypertensive drugs
Proteinuria	5 (33.3%)	Postponement of treatment (2)
		Treatment discontinuation (3)
Bleeding	1 (6.7%)	Continued treatment
Gastrointestinal perforation	1 (6.7%)	Treatment discontinuation
Thrombocytopenia	1 (6.7%)	Postponement of treatment
Decreased liver function	1 (6.7%)	Postponement of treatment

Bev single maintenance therapy, thus suggesting that histological subtype might affect the outcome of patients with cervical cancer who underwent Bev maintenance following combination chemotherapy. Although many authors have reported that histological subtype affects survival outcomes in patients with cervical cancer (Kleine et al. 1989; Eifel et al. 1995; Vinh-Hung et al. 2007; Shimada et al. 2020), the NCCN guidelines (Cervical Cancer. Version 1. 2021: https://www.nccn.org/) do not recommend treatment based on histological subtypes for patients with cervical cancer. The question of whether the effect of anti-angiogenesis therapy differs depending on the histological type needs to be verified in future studies.

In this small pilot study, Bev single maintenance therapy was tolerable in patients with advanced or recurrent cervical cancer, and the safety profile was generally consistent with those reported in previous studies (Tewari et al. 2014; Sugiyama et al. 2017). As reported in a previous study, hypertension, hemorrhage, and proteinuria are the most common adverse events associated with Bev treatment (Hatake et al. 2016). In accordance with these studies, the main adverse events in this study were hypertension and proteinuria. Three patients discontinued maintenance therapy because of grade ≥ 2 proteinuria. In addition, we observed 1 case of bowel perforation in the control group, and Bev single maintenance therapy was discontinued for this patient. Radiation therapy is known to be a risk factor for gastrointestinal perforation and vesicovaginal/rectovaginal fistulas in Bev-containing regimens. The incidence of fistula/gastrointestinal perforation was 13.3% in the GOG0240 study (Tewari et al. 2014) and 11.3% in the CECILIA study (Redondo et al. 2020). In the GOG0240 study, all 14 patients who developed gastrointestinal-vaginal fistula (1 chemotherapy alone and 13 chemotherapy plus Bev) had received prior pelvic irradiation (Tewari et al. 2014). Careful attention should be paid to Bev administration after concurrent chemoradiotherapy in patients with cervical cancer.

This study had some limitations. It was a single-arm pilot study conducted at a single institution and due to the

small sample size, various biases are likely to have affected the results. In this study, for example, PFS was similar between the Bev maintenance therapy group and the control group, but there was a difference in OS. There may be several reasons for this, but it is possible that selection bias occurred because it was not a randomized trial. Another possibility was that maintenance therapy could often be administered in patients with high reserve capacity rather than the direct therapeutic effect of Bev. Such a group of patients with high reserve capacity had more chances to receive second-or-third line treatment even after Bev maintenance therapy. Another limitation of this study was that it did not assess the quality of life and cost-effective analysis associated with long-term Bev-containing therapy. Nonetheless, the results of this study investigating the usefulness of Bev single maintenance therapy could provide some insight into clinical problems for patients with advanced or recurrent cervical cancer.

In conclusion, Bev single maintenance therapy following standard chemotherapy (TP plus Bev or TC plus Bev) was well tolerated and effective as salvage chemotherapy for advanced or recurrent cervical cancer. The safety profile in this trial was generally consistent with previous reports of Bev monotherapy. Treatment was discontinued due to rectal perforation or severe proteinuria, and careful management of adverse events is required for this regimen.

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Conflict of Interest

The authors have no conflict of interest.

References

Arbyn, M., Weiderpass, E., Bruni, L., de Sanjose, S., Saraiya, M., Ferlay, J. & Bray, F. (2020) Estimates of incidence and mortality of cervical cancer in 2018: a worldwide analysis. *Lancet Glob. Health*, **8**, e191-e203.

Bonadonna, G., Valagussa, P., Moliterni, A., Zambetti, M. & Brambilla, C. (1995) Adjuvant cyclophosphamide, methotrexate, and fluorouracil in node-positive breast cancer: the results of 20 years of follow-up. *N. Engl. J. Med.*, **332**, 901-906.

Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R.L., Torre, L.A. & Jemal, A. (2018) Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J. Clin.*, **68**, 394-424.

Chinot, O.L., de La Motte Rouge, T., Moore, N., Zeaiter, A., Das, A., Phillips, H., Modrusan, Z. & Cloughesy, T. (2011) AVAglio: phase 3 trial of bevacizumab plus temozolomide and radiotherapy in newly diagnosed glioblastoma multiforme. *Adv. Ther.*, **28**, 334-340.

Choi, H.J., Lee, Y.Y., Choi, C.H., Kim, T.J., Lee, J.W., Bae, J.H., Bae, D.S. & Kim, B.G. (2020) Triplet chemotherapy vs doublet chemotherapy plus bevacizumab in metastatic, recurrent, and persistent cervical cancer. *Curr. Probl. Cancer*, **44**, 100557.

Eifel, P.J., Burke, T.W., Morris, M. & Smith, T.L. (1995) Adenocarcinoma as an independent risk factor for disease recurrence in patients with stage IB cervical carcinoma. *Gynecol. Oncol.*, **59**, 38-44.

Godoy-Ortiz, A., Plata, Y., Alcaide, J., Galeote, A., Pajares, B., Saez, E., Alba, E. & Sanchez-Munoz, A. (2018) Bevacizumab for recurrent, persistent or advanced cervical cancer: reproducibility of GOG 240 study results in "real world" patients. *Clin. Transl. Oncol.*, **20**, 922-927.

Hatake, K., Doi, T., Uetake, H., Takahashi, Y., Ishihara, Y. & Shirao, K. (2016) Bevacizumab safety in Japanese patients with colorectal cancer. *Jpn. J. Clin. Oncol.*, **46**, 234-240.

Kabbinavar, F.F., Hambleton, J., Mass, R.D., Hurwitz, H.I., Bergsland, E. & Sarkar, S. (2005) Combined analysis of efficacy: the addition of bevacizumab to fluorouracil/leucovorin improves survival for patients with metastatic colorectal cancer. *J. Clin. Oncol.*, **23**, 3706-3712.

Kitagawa, R., Katsumata, N., Shibata, T., Kamura, T., Kasamatsu, T., Nakanishi, T., Nishimura, S., Ushijima, K., Takano, M., Satoh, T. & Yoshikawa, H. (2015) Paclitaxel plus carboplatin versus paclitaxel plus cisplatin in metastatic or recurrent cervical cancer: the open-label randomized phase III trial JCOG0505. *J. Clin. Oncol.*, **33**, 2129-2135.

Kleine, W., Rau, K., Schwoeorer, D. & Pfleiderer, A. (1989) Prognosis of the adenocarcinoma of the cervix uteri: a comparative study. *Gynecol. Oncol.*, **35**, 145-149.

Lei, J., Ploner, A., Elfstrom, K.M., Wang, J., Roth, A., Fang, F., Sundstrom, K., Dillner, J. & Sparen, P. (2020) HPV vaccination and the risk of invasive cervical cancer. *N. Engl. J. Med.*, **383**, 1340-1348.

Li, Q., Yan, H., Zhao, P., Yang, Y. & Cao, B. (2015) Efficacy and safety of bevacizumab combined with chemotherapy for managing metastatic breast cancer: a meta-analysis of randomized controlled trials. *Sci. Rep.*, **5**, 15746.

Long, H.J. 3rd, Bundy, B.N., Grendys, E.C. Jr., Benda, J.A., McMeekin, D.S., Sorosky, J., Miller, D.S., Eaton, L.A. & Fiorica, J.V.; Gynecologic Oncology Group Study (2005) Randomized phase III trial of cisplatin with or without topotecan in carcinoma of the uterine cervix: a Gynecologic Oncology Group study. *J. Clin. Oncol.*, **23**, 4626-4633.

McGraw, S.L. & Ferrante, J.M. (2014) Update on prevention and screening of cervical cancer. *World J. Clin. Oncol.*, **5**, 744-752.

Monk, B.J. & Herzog, T.J. (2007) The evolution of cost-effective screening and prevention of cervical carcinoma: implications of the 2006 consensus guidelines and human papillomavirus vaccination. *Am. J. Obstet. Gynecol.*, **197**, 337-339.

Monk, B.J., Sill, M.W., Burger, R.A., Gray, H.J., Buekers, T.E. & Roman, L.D. (2009a) Phase II trial of bevacizumab in the treatment of persistent or recurrent squamous cell carcinoma of the cervix: a gynecologic oncology group study. *J. Clin. Oncol.*, **27**, 1069-1074.

Monk, B.J., Sill, M.W., McMeekin, D.S., Cohn, D.E., Ramondetta, L.M., Boardman, C.H., Benda, J. & Cella, D. (2009b) Phase III trial of four cisplatin-containing doublet combinations in stage IVB, recurrent, or persistent cervical carcinoma: a Gynecologic Oncology Group study. *J. Clin. Oncol.*, **27**, 4649-4655.

Nagane, M., Nishikawa, R., Narita, Y., Kobayashi, H., Takano, S., Shinoura, N., Aoki, T., Sugiyama, K., Kuratsu, J., Muragaki, Y., Sawamura, Y. & Matsutani, M. (2012) Phase II study of single-agent bevacizumab in Japanese patients with recurrent malignant glioma. *Jpn. J. Clin. Oncol.*, **42**, 887-895.

No, J.H., Jo, H., Kim, S.H., Park, I.A., Kang, D., Han, S.S., Kim, J.W., Park, N.H., Kang, S.B. & Song, Y.S. (2009) Expression of vascular endothelial growth factor and hypoxia inducible factor-1alpha in cervical neoplasia. *Ann. N. Y. Acad. Sci.*, **1171**, 105-110.

Perren, T.J., Swart, A.M., Pfisterer, J., Ledermann, J.A., Pujade-

Lauraine, E., Kristensen, G., Carey, M.S., Beale, P., Cervantes, A., Kurzeder, C., du Bois, A., Sehouli, J., Kimmig, R., Stahle, A., Collinson, F., et al. (2011) A phase 3 trial of bevacizumab in ovarian cancer. *N. Engl. J. Med.*, **365**, 2484-2496.

Redondo, A., Colombo, N., McCormack, M., Dreosti, L., Nogueira-Rodrigues, A., Scambia, G., Lorusso, D., Joly, F., Schenker, M., Ruff, P., Estevez-Diz, M., Irahara, N., Donica, M. & Gonzalez-Martin, A. (2020) Primary results from CECILIA, a global single-arm phase II study evaluating bevacizumab, carboplatin and paclitaxel for advanced cervical cancer. *Gynecol. Oncol.*, **159**, 142-149.

Sandler, A., Gray, R., Perry, M.C., Brahmer, J., Schiller, J.H., Dowlati, A., Lilenbaum, R. & Johnson, D.H. (2006) Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N. Engl. J. Med.*, **355**, 2542-2550.

Seamon, L.G., Java, J.J., Monk, B.J., Penson, R.T., Brown, J., Mannel, R.S., Oaknin, A., Leitao, M.M., Eisenhauer, E.L., Long, H.J., Liao, S.Y. & Tewari, K.S. (2018) Impact of tumour histology on survival in advanced cervical carcinoma: an NRG Oncology/Gynaecologic Oncology Group Study. *Br. J. Cancer*, **118**, 162-170.

Shimada, M., Tokunaga, H., Kigawa, J. & Yaegashi, N. (2020) Impact of histopathological risk factors on the treatment of stage IB-IIB uterine cervical cancer. *Tohoku J. Exp. Med.*, **252**, 339-351.

Sugiyama, T., Mizuno, M., Aoki, Y., Sakurai, M., Nishikawa, T., Ueda, E., Tajima, K. & Takeshima, N. (2017) A single-arm study evaluating bevacizumab, cisplatin, and paclitaxel followed by single-agent bevacizumab in Japanese patients with advanced cervical cancer. *Jpn. J. Clin. Oncol.*, **47**, 39-46.

Tang, X., Zhang, Q., Nishitani, J., Brown, J., Shi, S. & Le, A.D. (2007) Overexpression of human papillomavirus type 16 oncoproteins enhances hypoxia-inducible factor 1 alpha protein accumulation and vascular endothelial growth factor expression in human cervical carcinoma cells. *Clin. Cancer Res.*, **13**, 2568-2576.

Tewari, K.S., Burger, R.A., Enserro, D., Norquist, B.M., Swisher, E.M., Brady, M.F., Bookman, M.A., Fleming, G.F., Huang, H., Homesley, H.D., Fowler, J.M., Greer, B.E., Boente, M., Liang, S.X., Ye, C., et al. (2019) Final overall survival of a randomized trial of bevacizumab for primary treatment of ovarian cancer. *J. Clin. Oncol.*, **37**, 2317-2328.

Tewari, K.S., Sill, M.W., Long, H.J. 3rd, Penson, R.T., Huang, H., Ramondetta, L.M., Landrum, L.M., Oaknin, A., Reid, T.J., Leitao, M.M., Michael, H.E. & Monk, B.J. (2014) Improved survival with bevacizumab in advanced cervical cancer. *N. Engl. J. Med.*, **370**, 734-743.

Vinh-Hung, V., Bourgain, C., Vlastos, G., Cserni, G., De Ridder, M., Storme, G. & Vlastos, A.T. (2007) Prognostic value of histopathology and trends in cervical cancer: a SEER population study. *BMC Cancer*, **7**, 164.