Synergistic therapeutic effect of low-dose bevacizumab with cisplatin-based chemotherapy for advanced or recurrent cervical cancer

Chia-Hao Liu[a,b,c], Yen-Hsuan Kung[a,b], Jeff Chien-Fu Lin[d,e], Chi-Mu Chuang[a,b], Hua-Hsi Wu[a,b,c], Ling-Yu Jiang[a,b,c], Ying-Chu Shih[a,b], Peng-Hui Wang[a,b,c,f], Yi-Jen Chen[a,b,c,*]

[a]Department of Obstetrics and Gynecology, Taipei Veterans General Hospital, Taipei, Taiwan, ROC; [b]Department of Obstetrics and Gynecology, National Yang Ming Chiao Tung University, Taipei, Taiwan, ROC; [c]Institute of Clinical Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan, ROC; [d]Department of Statistics, National Taipei University, Taipei, Taiwan, ROC; [e]Department of Orthopedic Surgery, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan, ROC; [f]Department of Medical Research, China Medical University Hospital, Taichung, Taiwan, ROC

Abstract

Background: Cisplatin-based chemotherapy (CBC) is highly efficacious for advanced cervical cancer; its efficacy can be enhanced by combining with 15 mg/kg (standard dose) bevacizumab (BEV). However, this standard dose is associated with various adverse events (AEs). Therefore, in this retrospective study, we analyzed the survival outcomes and AEs in patients with advanced or recurrent cervical cancer treated with CBC in combination with BEV 7.5 mg/kg.

Methods: Registered patient data were retrieved between October 2014 and September 2019, and 64 patients with advanced or recurrent cervical cancer treated with CBC + BEV (n = 21) or CBC alone (n = 43) were analyzed. The primary endpoints were progression-free survival (PFS) and overall survival (OS); the secondary endpoints were the frequency and severity of AEs. The Cox proportional-hazards model was applied to explore prognostic factors associated with PFS and OS.

Results: The 1-, 2-, and 3-year PFS rates (95% CI) were 36.24% (22.0-50.5), 20.7% (9.8-34.2), and 17.7% (7.7-31.1) for the CBC group; and 71.4% (47.1-86.0), 51.0% (27.9-70.1), and 51.0% (27.9-70.1) for the CBC + BEV group, respectively. The 1-, 2-, and 3-year OS rates were 62.6% (46.4-75.18), 32.4% (18.8-46.9), and 23.2% (11.2-37.6) for the CBC group; and 85.7% (61.9-95.1), 66.6% (42.5-82.5), and 55.5% (27.1-76.7) for the CBC + BEV group, respectively. The CBC + BEV group presented higher PFS and OS rates, $p = 0.003$ and $p = 0.005$, respectively. Proteinuria (6 vs 9, $p = 0.025$) and hypertension (0 vs 10, $p < 0.001$) were less common, but anemia was more common in the CBC group (35 vs 11, $p = 0.021$).

Conclusion: Overall, CBC + BEV significantly improved the PFS and OS compared with CBC alone. CBC + BEV also prevents severe AEs and hence is an efficacious and safe therapeutic option.

Keywords: Advanced cervical cancer; Cisplatin-based chemotherapy; Low-dose bevacizumab; Recurrence

1. INTRODUCTION

Cervical cancer is one of the major causes of cancer-related mortality, and in 2018, there were approximately 570 000 new cases of cervical cancer and 311 000 associated deaths.[1] Angiogenesis, circulating endothelial cells, and pro-angiogenic mediators are essential mediators of malignancy of tumors, supporting the necessity of vasculature for tumor growth and metastasis.[2] Although various treatment modalities have been proposed for locally advanced cervical cancer, the optimal strategy still remains undetermined.[3–5] Systemic platinum-based chemotherapy including cisplatin and carboplatin is the preferred treatment for advanced or metastatic cancer.[6,7] Bevacizumab (BEV), a United States Food and Drug Administration (USFDA)-approved drug for treating advanced cervical cancer is an anti-vascular endothelial growth factor (VEGF) monoclonal antibody, which blocks VEGF-mediated angiogenic signaling pathways.[8–12] Reports have shown that despite the survival advantages of BEV, it is associated with several adverse events (AEs) such as hypertension, proteinuria, and impaired wound healing.[13,14] Besides, BEV may be associated with severe AEs such as gastrointestinal bleeding, perforation, thromboembolic events, and fistula formations.[14–16] Data from GOG 240 revealed that patients treated with standard dose of BEV (15 mg/kg) combined with platinum-based chemotherapy were associated with grade 2 or higher fistula formation.[11] Numerous retrospective studies have also evaluated the efficacy and safety of the standard dose of BEV in patients with advanced cervical cancer and reported varying survival outcomes and AEs.[17–22]

*Address correspondence. Dr. Yi-Jen Chen, Department of Obstetrics and Gynecology, Taipei Veterans General Hospital, 201, Section 2, Shi-Pai Road, Taipei 112, Taiwan, ROC. E-mail address: chenyj@vghtpe.gov.tw; chenyj@nycu.edu.tw (Y.-J. Chen).

Conflicts of interest: Dr. Peng-Hui Wang and Dr. Yi-Jen Chen, editorial board members at Journal of the Chinese Medical Association, have no roles in the peer review process of or decision to publish this article. The other authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

Journal of Chinese Medical Association. (2021) 84: 1139-1144.

Received May 11, 2021; accepted August 25, 2021.

doi: 10.1097/JCMA.0000000000000629.

Besides, it is well-known that most patients with advanced cervical cancer have a low social-economic status, and many of these patients cannot afford the high cost of BEV without prior additional health care coverage. A previous cost-effectiveness study has shown that the cost of treatment decreased from $49 831 to $26 472 when the BEV dosage was reduced from 15 to 7.5 mg/kg.[23,24] Therefore, with the aim to increase the affordability of patients with a reduced rate of AEs, we administered BEV at a reduced dose of 7.5 mg/kg, based on the findings of an earlier clinical trial (ICON 7) on ovarian cancer treatment, which attempted to treat women with advanced or recurrent cervical cancer.[25,26] To date, limited studies have investigated the efficacy and safety of BEV at a reduced dose in combination with cisplatin-based chemotherapy (CBC) to treat advanced cervical cancer. Therefore, we aimed to compare the efficacy and safety of CBC with or without BEV 7.5 mg/kg in patients with advanced or recurrent cervical cancer.

2. METHODS

2.1. Patients

This study was approved by the Institutional Review Board on March 5, 2020 (Protocol number: 2020-03-003AC). Patients diagnosed with advanced or recurrent cervical cancer who received CBC + BEV or CBC only between October 2014 and September 2019 were identified using the institutional database. Recurrence was confirmed by both clinical examination and radiological imaging. For cases suspected to have an advanced disease with tumor involvement of the rectum and bladder, cystoscopy and colonoscopy were performed. All patients underwent detailed evaluations before chemotherapy, with adequate performance status, bone marrow reserves, and normal liver and renal functions. Histologically, patients confirmed with squamous cell carcinoma, adenocarcinoma, and adenosquamous carcinoma were enrolled in this study.

2.2. Chemotherapy

Chemotherapy is recommended for patients with metastases or recurrent disease who are not candidates for radiotherapy or exenterate surgery. In this study, CBC or CBC + BEV were administered according to the institutional protocol for the treatment of recurrence or advanced cervical cancer. In CBC group, patients were administered intravenous cisplatin-paclitaxel (50 mg/m^2: 175 mg/m^2); in CBC + BEV group, patients were administered intravenous cisplatin-paclitaxel (50 mg/m^2:175 mg/m^2) with BEV 7.5 mg/kg. Although BEV has demonstrated anticancer activity when combined with CBC, its optimal dose remains undetermined due to its adverse effects. Therefore, in contrast to the standard BEV dose of 15 mg/kg used in previous studies to treat cervical cancer, we administered 7.5 mg/kg BEV to assess whether this low dose can offer similar benefits at a lower cost.[24]

2.3. Outcomes

To assess clinical outcomes, adequate renal and liver functions with complete blood counts were confirmed before each chemotherapy cycle. Contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) was performed every 3 months. Imaging studies such as chest radiographs, CT, MRI, or positron emission tomography (PET-CT) were ordered based on clinical signs or symptoms suggestive of relapse or recurrence. We used Response Evaluation Criteria in Solid Tumors (RECIST) ver. 1.1 to evaluate the response to treatment in patients with measurable diseases.[27,28] Overall survival (OS) indicates the period from the day of the initial chemotherapy cycle to either the day of the final follow-up or the day of patient's death under any circumstances. Progression-free survival (PFS) indicates the period from the day of the initial chemotherapy cycle to either the day of progression or the day of patient's death under any circumstances. Disease control rate (DCR) indicates the proportion of patients who achieved complete response (CR), partial response (PR), and stable disease. Overall response rate (ORR) indicates the proportion of patients with CR and PR.[29–32] We terminated treatment or changed the regimen if the patient presented with disease progression or showed intolerable AEs.

2.4. Adverse events

AEs were evaluated before the start of each chemotherapy cycle based on the National Cancer Institute's Common Terminology Criteria for Adverse Events (version 5.0). Hypertension was defined as the new onset of blood pressure above 140/100 mmHg after the initiation of chemotherapy. Neutropenia (grade 2 or above) was defined as an absolute neutrophil count of less than 1500 cells/mm^3. Anemia (grade 2 or above) was defined as a hemoglobin level of less than 10.0 g/dL. Proteinuria (grade 2 or above) was defined as a urine dipstick reading of 2+ and 3+ or a 24-h urine protein collection greater than 1 g. Fistulas were diagnosed based on clinical examination and confirmation by CT scans. Gastrointestinal bleeding was defined by a positive (at least 1+) occult blood examination in patients with coffee ground vomitus or tarry stool.

2.5. Statistical analysis

Continuous variables are presented as mean and SD and compared with Student's *t* test; categorical variables are presented as number and percentage and compared with Fisher exact test. PFS time was defined as the duration from the date of operation to the date of disease progression. OS time was defined as the duration from the date of operation to the date of patient's death. The PFS probability and the OS probability were estimated and compared using Kaplan–Meier method and log-rank test. The univariate Cox proportional-hazards model was used to quantify the risk effect on the survival for each variable. We could not find any other prognostic factor, except in the CBC + BEV group, associated with PFS and OS from the multivariate Cox model. Data were analyzed using R 4.0.5: A language and environment for statistical computing (R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org/).

3. RESULTS

3.1. Patients' baseline clinical characteristics

Sixty-four (n = 64) patients with advanced or recurrent cervical cancer were included in this study. There were no statistically significant differences with respect to patients' age, histopathological type, disease presentation, World Health Organization (WHO) performance status, and prior treatments. Patients' baseline characteristics are presented in Table 1. The median follow-up duration was shorter in the CBC + BEV group than in the CBC group, 934.5 and 1318 days, respectively (p = 0.497).

3.2. Tumor response

According to the RECIST criteria,[27,28] the tumor responses of CBC and CBC + BEV treatment regimens were evaluated and presented in Table 2. Out of 21 CBC + BEV-treated patients, 1 (4.8%), 8 (38.1%), 7 (33.7%), and 5 (23.8%) patients showed a status of complete response, partial response, stable disease, and progressive disease, respectively, whereas in the CBC-treated group, 1 (2.3%), 6 (14.0%), 6 (14.0%), and 30 (69.8%) patients showed complete response, partial response, stable disease, and progressive disease, respectively. The CBC + BEV group showed a significantly better response than the CBC group (p = 0.003). The CBC + BEV group demonstrated a significant improvement

Table 1

Baseline clinical characteristics of CBC and CBC + BEV-treated patients

	CBC	CBC + BEV	*p*
Patients (n)	43	21	
Age (years) (mean [SD])	60.58 (11.88)	56.86 (12.54)	0.252[a]
FIGO stage (%)			
I	12 (27.9)	4 (19.0)	0.514
II	8 (18.6)	5 (23.8)	
III	9 (20.9)	2 (9.5)	
IV	14 (32.6)	10 (47.6)	
Histopathology (%)			
Squamous cell carcinoma	25 (58.1)	13 (61.9)	0.514
Adenocarcinoma	13 (30.2)	4 (19.0)	
Adenosquamous carcinoma	5 (11.6)	4 (19.0)	
Disease presentation (%)			
Advanced stage	17 (39.5)	10 (47.6)	0.596
Recurrence	26 (60.5)	11 (52.4)	
WHO performance status (%)			
0	7 (16.3)	2 (9.5)	0.825
1	31 (72.1)	17 (81.0)	
2	5 (11.6)	2 (9.5)	
Neoadjuvant chemotherapy (%)			
Yes	2 (4.7)	3 (14.3)	0.320
No	41 (95.3)	18 (85.7)	
Prior radical hysterectomy (%)			
Yes	26 (60.5)	15 (71.4)	0.423
No	17 (39.5)	6 (28.6)	
Prior CCRT (%)			
Yes	35 (81.4)	16 (76.2)	0.743
No	8 (18.6)	5 (23.8)	
Prior brachytherapy (%)			
Yes	14 (32.6)	10 (47.6)	0.280
No	29 (67.4)	11 (52.4)	
Radiation dose (Gy) (mean [SD])	51.83 (27.91)	42.55 (29.68)	0.225[a]
Median follow-up days (range)	1318 (112, 1786)	934.5 (198, 2190)	0.497

Categorical variables were presented as number and percentage and compared with Fisher exact test.

CBC = cisplatin-based chemotherapy; BEV = bevacizumab; CCRT = concurrent chemoradiotherapy; FIGO = International Federation of Gynecology and Obstetrics; WHO = World Health Organization.

[a]Continuous variables were presented as mean and SD and compared with Student's *t* test.

(p = 0.032) in the ORR, at 42.9%, compared with the CBC group (16.3%). Similarly, the DCR of the CBC + BEV group (76.2%) was significantly superior (p = 0.001) to that of the CBC group (30.2%).

3.3. Survival outcomes

The 1-, 2-, and 3-year PFS rates (95% CI) were 36.24% (22.0-50.5), 20.7% (9.8-34.2), and 17.7% (7.7-31.1) for the CBC group; and 71.4% (47.1-86.0), 51.0% (27.9-70.1), and 51.0% (27.9-70.1) for CBC + BEV group, respectively (Fig. 1A). The OS also showed a similar trend. Specifically, the 1-, 2-, and 3-year OS rates were 62.6% (46.4-75.18), 32.4% (18.8-46.9), and 23.2% (11.2-37.6) for the CBC group; and 85.7% (61.9-95.1), 66.6% (42.5-82.5), and 55.5% (27.1-76.7) for the CBC + BEV group, respectively (Fig. 1B). We found that the CBC + BEV group had significantly higher PFS rates and OS rates, p = 0.003 and p = 0.005, respectively, than the CBC group.

3.4. Safety and AEs

The AEs between the CBC and CBC + BEV groups are presented in Table 3. Some AEs were significantly less common in the CBC group than in the CBC + BEV group, including proteinuria (6 vs 9, p = 0.025) and hypertension (0 vs 10, p < 0.001). However, anemia was significantly more common in the CBC group than in the CBC + BEV group (35 vs 11, p = 0.021). There was no significant difference between the CBC and CBC + BEV groups for other AEs such as fistula, neutropenia, thrombocytopenia, gastrointestinal bleeding, and bowel perforation.

Table 2

Tumor response of CBC and CBC + BEV-treated patients

	CBC	CBC + BEV	*p*
Patients (n)	43	21	
Response (%)			
Complete remission	1 (2.3)	1 (4.8)	0.003
Partial response	6 (14.0)	8 (38.1)	
Stable disease	6 (14.0)	7 (33.3)	
Progressive disease	30 (69.8)	5 (23.8)	
Overall response rate (%)			
Yes	7 (16.3)	9 (42.9)	0.032
No	36 (83.7)	12 (57.1)	
Disease control rate (%)			
Yes	13 (30.2)	16 (76.2)	0.001
No	30 (69.8)	5 (23.8)	

Categorical variables were presented as number and percentage and compared with Fisher exact test.

BEV = bevacizumab; CBC = cisplatin-based chemotherapy.

3.5. Prognostic factors associated with PFS and OS

The univariate Cox proportional-hazards model for PFS and OS of the CBC- and CBC + BEV-treated patients with cervical cancer are presented in Table 4. Age, FIGO stage, histopathological type, disease presentation, WHO performance status, neoadjuvant chemotherapy, prior radical hysterectomy, prior CCRT, prior brachytherapy, and radiation dose were identified as statistically insignificant prognostic factors for PFS (all p > 0.05), whereas only prior CCRT was significantly associated with better OS. We could not find any other prognostic factor, except the CBC + BEV group, associated with higher PFS and OS from the multivariate Cox model.

4. DISCUSSION

Cisplatin is considered the most effective therapeutic agent for advanced or recurrent cervical cancer, and the response to chemotherapy is a major independent prognostic factor in cervical cancer.[33] However, most patients who develop metastatic disease have received prior CCRT as primary treatment and may no longer be sensitive to CBC. Therefore, cisplatin-containing combination chemotherapy regimens, such as CBC + BEV, have been extensively studied in clinical trials.[34–37] To our knowledge, this retrospective study is the first to treat patients with cervical cancer by synergistically administering CBC and reducing the standard dose of BEV (15 mg/kg) to half (7.5 mg/kg) to assess whether this lower dose might offer similar benefits at lower costs.

Previously, two large studies have retrospectively evaluated the efficacy and safety of standard BEV dose of 15 mg/kg combined with CBC in cervical cancer.[17,20] In a recent study employing CBC + BEV (15 mg/kg) to treat Chinese women with cervical cancer, OS was not reached at 1 year, and it reached 45% at 2 years,[20] which is lower than the OS of our CBC + BEV (7.5 mg/kg), 85.7% and 66.6%, respectively. Furthermore, contrary to our finding, thrombosis/embolism and neutropenia were reported as significant AEs. Chu et al recently reviewed the survival outcomes of CBC +BEV (15 mg/kg) vs CBC alone in postmenopausal women with untreated cervical cancer and showed superior

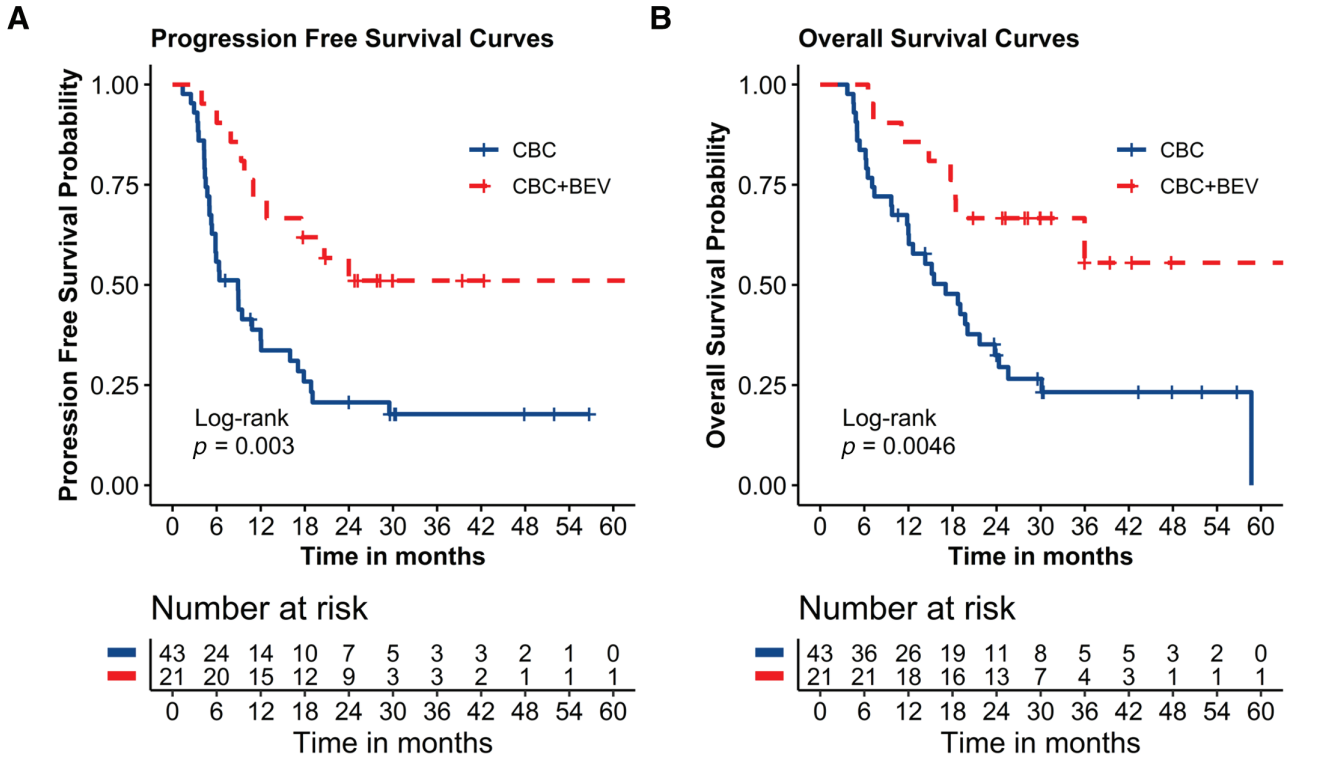

Fig. 1 Kaplan–Meier survival analysis according to chemotherapy regimens. (A) PFS and (B) OS of CBC and CBC + BEV group. With respect to the PFS and OS, $p = 0.003$ and $p = 0.0046$, respectively, according to the log-rank test. BEV = bevacizumab; CBC + BEV = cisplatin-based chemotherapy with bevacizumab; OS = overall survival; PFS = progression-free survival.

Table 3

Adverse events of CBC and CBC + BEV-treated patients

	CBC	CBC + BEV	*p*
Patients (n)	43	21	
Proteinuria (%)			
Yes	6 (14.0)	9 (42.9)	0.025
No	37 (86.0)	12 (57.1)	
Hypertension (%)			
Yes	0 (0.0)	10 (47.6)	<0.001
No	43 (100.0)	11 (52.4)	
Fistula (%)			
Yes	4 (9.3)	2 (9.5)	1.000
No	39 (90.7)	19 (90.5)	
Neutropenia (%)			
Yes	7 (16.3)	8 (38.1)	0.066
No	36 (83.7)	13 (61.9)	
Anemia (%)			
Yes	35 (81.4)	11 (52.4)	0.021
No	8 (18.6)	10 (47.6)	
Thrombocytopenia (%)			
Yes	9 (20.9)	4 (19.0)	1.000
No	34 (79.1)	17 (81.0)	
Gastrointestinal bleeding (%)			
Yes	6 (14.0)	1 (4.8)	0.410
No	37 (86.0)	20 (95.2)	
Bowel perforation (%)			
Yes	1 (2.3)	0 (0.0)	1.000
No	42 (97.7)	21 (100.0)	

Categorical variables were presented as number and percentage and compared with Fisher exact test.

BEV = bevacizumab; CBC = cisplatin-based chemotherapy.

survival benefits in the CBC + BEV group.[17] Notably, the number of AEs (hypertension, neutropenia, and thrombosis/embolism) was significantly more common in the CBC + BEV group. In an open-label single-arm phase II study, 15 mg/kg BEV combined with carboplatin-paclitaxel therapy for advanced cervical cancer caused AEs such as neutropenia, anemia, and hypertension.[38] Besides, this standard dose has also been associated with rectovaginal fistula in a patient with cervical cancer.[39] In a single institution study in Korea, a higher complete response rate was associated with BEV (15 mg/kg) treatment for stage IVB cervical cancer; however, patients with lymph node-only metastasis experienced enhanced bowel toxicities with no improvement in PFS.[40] Interestingly, in a randomized, double-blind, placebo-controlled phase III trial, there was no improvement in the OS of patients with metastatic urothelial carcinoma treated by supplementing BEV to gemcitabine and cisplatin chemotherapy;[41] however, an improvement in PFS was noted. This indicates that BEV at a reduced dose may offer enhanced therapeutic advantages in terms of suppressing complications. In line with the findings of our study, the reduced-dose BEV (5 mg/Kg) monotherapy for patients with glioblastoma resulted in similar OS compared with the standard-dose BEV (10 mg/Kg) with substantial cost savings.[42]

The effectiveness of BEV has also been evaluated in combination with nonplatinum chemotherapy in patients with recurrent, persistent, or metastatic cervical cancer; the results revealed improved OS compared with that achieved by chemotherapy alone.[12] Therefore, reduced dose of BEV should also be investigated with nonplatinum chemotherapy. In a single-arm prospective pilot study, monotherapy of BEV (15 mg/kg) was associated with an ORR and DCR of 47% and 53.3%, respectively, which was also accompanied by AEs of proteinuria and hypertension.[43] Comparatively, our study demonstrated a significantly improved

Table 4

Hazard ratios for PFS and OS using univariate Cox proportional-hazards model

	PFS			OS		
Covariate	**Hazard ratio**	**95% CI**	***p***	**Hazard ratio**	**95% CI**	***p***
Group						
CBC	1.00			1.00		
CBC + BEV	0.36	0.18, 0.73	0.004	0.34	0.16, 0.74	0.007
Age (years)	1.00	0.98, 1.03	0.825	0.99	0.96, 1.02	0.538
FIGO stage						
I	1.00			1.00		
II	1.32	0.55, 3.18	0.537	0.93	0.34, 2.58	0.892
III	0.99	0.37, 2.60	0.979	1.32	0.48, 3.64	0.596
IV	1.49	0.68, 3.26	0.320	1.84	0.79, 4.29	0.156
Histopathology						
Squamous cell carcinoma	1.00			1.00		
Adenocarcinoma	0.63	0.30, 1.34	0.232	0.78	0.37, 1.67	0.525
Adenosquamous carcinoma	0.51	0.20, 1.33	0.167	0.56	0.20, 1.60	0.279
Disease presentation						
Advanced stage	1.00			1.00		
Recurrence	1.26	0.68, 2.33	0.459	0.75	0.40, 1.42	0.377
WHO performance status						
0	1.00			1.00		
1	1.01	0.45, 2.29	0.972	0.81	0.37, 1.79	0.605
2	0.60	0.16, 2.33	0.463	0.91	0.27, 3.07	0.881
Neoadjuvant chemotherapy						
Yes	1.00			1.00		
No	2.41	0.58, 9.98	0.225	1.58	0.38, 6.57	0.530
Prior radical hysterectomy						
Yes	1.00			1.00		
No	1.54	0.83, 2.83	0.169	1.62	0.86, 3.05	0.132
Prior CCRT						
Yes	1.00			1.00		
No	1.21	0.60, 2.46	0.592	2.50	1.22, 5.11	0.012
Prior brachytherapy						
Yes	1.00			1.00		
No	1.22	0.66, 2.23	0.529	1.83	0.93, 3.59	0.079
Radiation dose (Gy)	1.00	0.99, 1.02	0.424	0.99	0.98, 1.00	0.152

BEV = bevacizumab; CBC = cisplatin-based chemotherapy; CCRT = concurrent chemoradiotherapy; OS = overall survival; PFS = progression-free survival; WHO = World Health Organization.

ORR and DCR of 42.9% and 76.2%, respectively, in the CBC + BEV group, which are superior to those in the CBC group. This also implies that reduced dose of BEV may offer enhanced therapeutic advantages in terms of ORR and DCR. Furthermore, in the univariate Cox proportional-hazards model, we did not find age, FIGO stage, histopathological type, disease presentation, WHO performance status, neoadjuvant chemotherapy, prior radical hysterectomy, prior brachytherapy, and total radiation dose as significant prognostic factors, except for prior CCRT. However, in a previous study, a univariate analysis of BEV combined with radical chemoradiotherapy showed improved OS, local relapse-free survival, and distant metastasis-free survival rates, without significant difference between any of the baseline characteristics.[44] This finding implies that a prior CCRT in patients with advanced or recurrent cervical cancer may have a potential prognostic role in patients treated with CBC + BEV; however, further analysis with larger samples is needed for confirmation.

Our study had some limitations, such as retrospective nature and small number of patients. Therefore, further studies such as randomized controlled trials are necessary to confirm similar or enhanced efficacy and safety of reduced dose of BEV compared with the standard dose.

Conclusively, our study revealed that compared with CBC, the reduced dose of BEV (7.5 mg/kg) combined with CBC showed significant therapeutic effects in patients with advanced or recurrent cervical cancer, in terms of improved OS, PFS, and tumor response. Our findings also indicate that reducing BEV has acceptable AE rates, and this reduced dose might be a preferable, cheaper alternative with better tolerability.

ACKNOWLEDGMENTS

This study was supported by the Ministry of Science and Technology, Executive Yuan (MOST 109-2314-B-010-041-MY3 and MOST 109-2314-B-010-042), Taipei Veterans General Hospital (V109C-097, V109EP-001, VN109-13), Szu-Yuan Research Foundation of Internal Medicine (Grant number: 109002, 110), and National Health Research Institute, Biobank Consortium Matching Fund (NHRI-109BCCOMF-202014-06).

The authors thank Na-Rong Lee, Shu-Yun Huang, and Ping-Chun Lin for their contributions and the data management for conducting this study.

REFERENCES

1. Bonjour M, Charvat H, Franco EL, Piñeros M, Clifford GM, Bray F, et al. Global estimates of expected and preventable cervical cancers among girls born between 2005 and 2014: a birth cohort analysis. *Lancet Public Health* 2021;**6**:e510–21.
2. Eskander RN, Tewari KS. Targeting angiogenesis in advanced cervical cancer. *Ther Adv Med Oncol* 2014;**6**:280–92.

3. Liu CH, Lee YC, Lin JC, Chan IS, Lee NR, Chang WH, et al. Radical hysterectomy after neoadjuvant chemotherapy for locally bulky-size cervical cancer: a retrospective comparative analysis between the robotic and abdominal approaches. *Int J Environ Res Public Health* 2019;**16**:E3833.
4. Abu-Rustum NR, Yashar CM, Bean S, Bradley K, Campos SM, Chon HS, et al. NCCN guidelines insights: cervical cancer, version 1.2020. *J Natl Compr Canc Netw* 2020;**18**:660–6.
5. Wang PH, Chang YH, Yang YH, Chang WH, Huang SY, Lai CR, et al. Outcome of patients with bulky IB (≥ 6 cm) cervical squamous cell carcinoma with and without cisplatin-based neoadjuvant chemotherapy. *Taiwan J Obstet Gynecol* 2014;**53**:330–6.
6. Rose PG, Bundy BN, Watkins EB, Thigpen JT, Deppe G, Maiman MA, et al. Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. *N Engl J Med* 1999;**340**:1144–53.
7. Rose PG, Lappas PT. Analysis of the cost effectiveness of concurrent cisplatin-based chemoradiation in cervical cancer: implications from five randomized trials. *Gynecol Oncol* 2000;**78**:3–6.
8. Garcia J, Hurwitz HI, Sandler AB, Miles D, Coleman RL, Deurloo R, et al. Bevacizumab (Avastin®) in cancer treatment: a review of 15 years of clinical experience and future outlook. *Cancer Treat Rev* 2020;**86**:102017.
9. Li X, Hu Z, Shi H, Wang C, Lei J, Cheng Y. Inhibition of VEGFA increases the sensitivity of ovarian cancer cells to chemotherapy by suppressing VEGFA-mediated autophagy. *Onco Targets Ther* 2020;**13**:8161–71.
10. Sopo M, Anttila M, Hämäläinen K, Kivelä A, Ylä-Herttuala S, Kosma VM, et al. Expression profiles of VEGF-A, VEGF-D and VEGFR1 are higher in distant metastases than in matched primary high grade epithelial ovarian cancer. *BMC Cancer* 2019;**19**:584.
11. Tewari KS, Sill MW, Penson RT, Huang H, Ramondetta LM, Landrum LM, et al. Bevacizumab for advanced cervical cancer: final overall survival and adverse event analysis of a randomised, controlled, open-label, phase 3 trial (Gynecologic Oncology Group 240). *Lancet* 2017;**390**:1654–63.
12. Tewari KS, Sill MW, Long HJ 3rd, Penson RT, Huang H, Ramondetta LM, et al. Improved survival with bevacizumab in advanced cervical cancer. *N Engl J Med* 2014;**370**:734–43.
13. Eskander RN, Tewari KS. Development of bevacizumab in advanced cervical cancer: pharmacodynamic modeling, survival impact and toxicology. *Future Oncol* 2015;**11**:909–22.
14. Minion LE, Tewari KS. The safety and efficacy of bevacizumab in the treatment of patients with recurrent or metastatic cervical cancer. *Expert Rev Anticancer Ther* 2017;**17**:191–8.
15. Ganapathi AM, Westmoreland T, Tyler D, Mantyh CR. Bevacizumab-associated fistula formation in postoperative colorectal cancer patients. *J Am Coll Surg* 2012;**214**:582–8.
16. Spigel DR, Hainsworth JD, Yardley DA, Raefsky E, Patton J, Peacock N, et al. Tracheoesophageal fistula formation in patients with lung cancer treated with chemoradiation and bevacizumab. *J Clin Oncol* 2010;**28**:43–8.
17. Chu G, Liu X, Yu W, Chen M, Dong L. Cisplatin plus paclitaxel chemotherapy with or without bevacizumab in postmenopausal women with previously untreated advanced cervical cancer: a retrospective study. *BMC Cancer* 2021;**21**:133.
18. Tao W, Yang J, Jiang Y, Chen W, Wang Y. Paclitaxel, carboplatin, and bevacizumab in advanced cervical cancer: a treatment response and safety analysis. *Dose Response* 2020;**18**:1559325820941351.
19. Godoy-Ortiz A, Plata Y, Alcaide J, Galeote A, Pajares B, Saez E, et al. Bevacizumab for recurrent, persistent or advanced cervical cancer: reproducibility of GOG 240 study results in "real world" patients. *Clin Transl Oncol* 2018;**20**:922–7.
20. He X, Liu J, Xiao L, Zhao M, Su T, Liu T, et al. Cisplatin-based chemotherapy with or without bevacizumab for Chinese postmenopausal women with advanced cervical cancer: a retrospective observational study. *BMC Cancer* 2020;**20**:381.
21. Lee N, Kim SI, Lee M, Kim HS, Kim JW, Park NH, et al. Bevacizumab efficacy and recurrence pattern of persistent and metastatic cervical cancer. *In Vivo* 2019;**33**:863–8.
22. Tinker AV, Fiorino L, O'Dwyer H, Kumar A. Bevacizumab in metastatic, recurrent, or persistent cervical cancer: the BC cancer experience. *Int J Gynecol Cancer* 2018;**28**:1592–9.
23. Gyawali B, Iddawela M. Bevacizumab in advanced cervical cancer: issues and challenges for low- and middle-income countries. *J Glob Oncol* 2017;**3**:93–7.
24. Phippen NT, Leath CA 3rd, Havrilesky LJ, Barnett JC. Bevacizumab in recurrent, persistent, or advanced stage carcinoma of the cervix: is it cost-effective? *Gynecol Oncol* 2015;**136**:43–7.
25. Oza AM, Cook AD, Pfisterer J, Embleton A, Ledermann JA, Pujade-Lauraine E, et al; ICON7 Trial Investigators. Standard chemotherapy with or without bevacizumab for women with newly diagnosed ovarian cancer (ICON7): overall survival results of a phase 3 randomised trial. *Lancet Oncol* 2015;**16**:928–36.
26. Perren TJ, Swart AM, Pfisterer J, Ledermann JA, Pujade-Lauraine E, Kristensen G, et al; ICON7 Investigators. A phase 3 trial of bevacizumab in ovarian cancer. *N Engl J Med* 2011;**365**:2484–96.
27. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009;**45**:228–47.
28. Schwartz LH, Litière S, de Vries E, Ford R, Gwyther S, Mandrekar S, et al. RECIST 1.1-Update and clarification: from the RECIST committee. *Eur J Cancer* 2016;**62**:132–7.
29. Basu P, Mukhopadhyay A, Konishi I. Targeted therapy for gynecologic cancers: toward the era of precision medicine. *Int J Gynaecol Obstet* 2018;**143**(Suppl 2):131–6.
30. Kagabu M, Nagasawa T, Fukagawa D, Tomabechi H, Sato S, Shoji T, et al. Immunotherapy for uterine cervical cancer. *Healthcare (Basel)* 2019;**7**:E108.
31. Kim M, Suh DH, Lee KH, Eom KY, Toftdahl NG, Mirza MR, et al. Major clinical research advances in gynecologic cancer in 2018. *J Gynecol Oncol* 2019;**30**:e18.
32. Xiao Y, Cheng H, Wang L, Yu X. Clinical response and safety of apatinib monotherapy in recurrent, metastatic cervical cancer after failure of chemotherapy: a retrospective study. *J Gynecol Oncol* 2020;**31**:e2.
33. Thigpen T, Shingleton H, Homesley H, Lagasse L, Blessing J. Cisplatinum in treatment of advanced or recurrent squamous cell carcinoma of the cervix: a phase II study of the Gynecologic Oncology Group. *Cancer* 1981;**48**:899–903.
34. Monk BJ, Sill MW, McMeekin DS, Cohn DE, Ramondetta LM, Boardman CH, et al. 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* 2009;**27**:4649–55.
35. Moore DH. Chemotherapy for advanced, recurrent, and metastatic cervical cancer. *J Natl Compr Canc Netw* 2008;**6**:53–7.
36. Moore DH, Blessing JA, McQuellon RP, Thaler HT, Cella D, Benda J, et al. Phase III study of cisplatin with or without paclitaxel in stage IVB, recurrent, or persistent squamous cell carcinoma of the cervix: a gynecologic oncology group study. *J Clin Oncol* 2004;**22**:3113–9.
37. Tao X, Hu W, Ramirez PT, Kavanagh JJ. Chemotherapy for recurrent and metastatic cervical cancer. *Gynecol Oncol* 2008;**110**(3 Suppl 2):S67–71.
38. Redondo A, Colombo N, McCormack M, Dreosti L, Nogueira-Rodrigues A, Scambia G, et al. Primary results from CECILIA, a global single-arm phase II study evaluating bevacizumab, carboplatin and paclitaxel for advanced cervical cancer. *Gynecol Oncol* 2020;**159**:142–9.
39. Tomizawa K, Ando K, Shimada H, Kaminuma T, Murata K, Oike T, et al. Rectovaginal fistula in a cervical cancer patient treated with sequential radiotherapy and bevacizumab: a dose-volume analysis. *Clin Case Rep* 2021;**9**:2099–104.
40. Youn SH, Kim YJ, Seo SS, Kang S, Lim MC, Chang HK, et al. Effect of addition of bevacizumab to chemoradiotherapy in newly diagnosed stage IVB cervical cancer: a single institution experience in Korea. *Int J Gynecol Cancer* 2020;**30**:764–71.
41. Rosenberg JE, Ballman KV, Halabi S, Watt C, Hahn OM, Steen PD, et al. CALGB 90601 (Alliance): randomized, double-blind, placebo-controlled phase III trial comparing gemcitabine and cisplatin with bevacizumab or placebo in patients with metastatic urothelial carcinoma. *J Clin Oncol* 2019;**37**(Suppl 15):4503.
42. Gleeson JP, Keane F, Keegan NM, Mammadov E, Harrold E, Alhusaini A, et al. Similar overall survival with reduced vs. standard dose bevacizumab monotherapy in progressive glioblastoma. *Cancer Med* 2020;**9**:469–75.
43. Toyoshima M, Shimada M, Sasaki S, Ishibashi M, Shigeta S, Tsuji K, et al. 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. *Tohoku J Exp Med* 2021;**254**:145–53.
44. Yang H, Zhang Y, Liu C, Feng B, Zhang J, Zhou Y, et al. The integration of bevacizumab improves tumor response and survival in patients with refractory cervical cancer treated with radical chemoradiotherapy. *Ann Transl Med* 2021;**9**:1184.