Original Article

A retrospective study of anlotinib in patients with persistent, recurrent or metastatic cervical and endometrial cancer

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Background: The prognosis of persistent, recurrent or metastatic cervical and endometrial cancer is poor. Anlotinib is a novel multitarget tyrosine kinase inhibitor (TKI). The efficacy and safety of anlotinib in patients with cervical and endometrial cancer need to be evaluated.

Methods: We retrospectively analyzed the efficacy and safety of anlotinib in patients with persistent, recurrent or metastatic cervical and endometrial cancers between March 2020 and June 2023. The objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS), and adverse events (AEs) were analyzed.

Results: The overall ORR and DCR were 24.14% and 55.17% respectively. The ORR and DCR in patients with cervical cancer were 25.00% and 56.25%; the ORR and DCR in patients with endometrial cancer were 23.08% and 53.85%. The patients received anlotinib plus immunotherapy had significantly higher rate of clinical benefit than those receiving anlotinnb alone (P=0.04). The DCR was significantly higher in patients receiving anlotinib combined with immunotherapy (DCR: 75.00% *vs.* 30.76%) than those without immunotherapy. The overall median PFS and OS were 12.2 months [95% confidence interval (CI): 6.6–17.8] and 22.3 months (95% CI: 20.9–23.7), respectively. The patients receiving anlotinib plus immunotherapy had significantly longer OS than those without immunotherapy [not reached *vs.* 12.5 months; hazard ratio (HR): 0.32 (95% CI: 0.1–0.99); P=0.04]. The most common AEs was fatigue (41.4%).

Conclusions: Anlotinib might be a promising agent for persistent, recurrent or metastatic cervical and endometrial cancers with good tolerability. Moreover, anlotinib combined with immunotherapy showed synergistic antitumor effect.

Keywords: Anlotinib; safety; immunotherapy; cervical cancer; endometrial cancer

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Introduction

The morbidity and mortality of gynecological cancers is growing rapidly worldwide, data from global cancer statistics demonstrated 341,831 and 97,370 new cases of death respectively for cervical cancer and endometrial cancer in 2020 (1). For the newly diagnosed cervical and endometrial cancer patients, the surgery, chemotherapy, and radiotherapy are preferred treatments (2,3). However, for patients with persistent, recurrent, and metastatic cervical and endometrial cancers, the therapeutic strategy is limited and the prognosis is poor (4). Thus, there is unmet need for effective therapeutic regimens for persistent, recurrent, and metastatic cervical and endometrial cancers.

Angiogenesis is an indispensable process of tumor aggressiveness which triggers the development of anti-angiogenesis therapy (5). Anti-angiogenesis therapies target on angiogenic factors such as vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), angiogenin (Ang), hepatocyte growth factor (HGF), hypoxia-inducible factor (HIF), insulin-like growth factor (IGF), transforming growth factor-β (TGF-β), matrix metalloproteinase (MMP), and tumor necrosis factor (TNF) to reduce tumor blood supply and normalize tumor blood vessels, which facilitate conventional treatments (6-9). Since the Food and Drug Administration (FDA) approval of the first antiangiogenic drug (bevacizumab), anti-angiogenesis treatment has enlightened new perspectives and gained remarkable benefits in anti-cancer therapy (10). Until now, bevacizumab is the only anti-angiogenic agent approved for cervical cancer, and no anti-angiogenic agent is approved for endometrial cancer (11). Moreover, previous study indicated that resistance to bevacizumab might attribute to enhanced secretion of other angiogenic factors (12). Therefore, there is growing need for agents targeting multiple angiogenesis pathways.

Anlotinib, a novel multitarget tyrosine kinase inhibitor (TKI) developed in China, inhibits the VEGF receptors 1–3, FGF receptors 1–4, EGF receptor, PDGF receptor, c-kit and c-Met to achieve anti-cancer effect through anti-angiogenesis, regulating tumor microenvironment and promoting tumor cell apoptosis (13,14). Anlotinib has been approved for treating non-small cell lung cancer, small cell lung cancer, and soft tissue sarcoma in China (15-17). A phase II, single-arm, prospective study showed that the objective response rate (ORR) and disease control rate (DCR) of anlotinib were 24.4% and 58.5% in Chinese patients with recurrent or metastatic cervical cancer (18). A phase II clinical trial by Wei *et al.* demonstrated robust therapeutic benefits of anlotinib plus sintilimab [anti-programmed death-1 (anti-PD-1) antibody] in endometrial cancer with an ORR of 73.9% and DCR of 91.3% (19). Given the heterogeneity between real-world practice and clinical trials, and among different centers, we retrospectively investigated the efficacy and safety of anlotinib in cervical and endometrial cancers in our center. We present this article in accordance with the STROBE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-272/rc).

Methods

Patients and treatments

In this study, we retrospectively enrolled patients with pathological or cytological confirmed persistent, recurrent or metastatic cervical and endometrial cancers receiving anlotinib as second- or later-line treatment in the General Hospital of Chinese People's Liberation Army (PLA) between March 2020 and June 2023. The inclusion criteria were as follows: pathological or cytological confirmed persistent, recurrent or metastatic cervical and endometrial cancers, Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–2, at least one measurable lesion. The exclusion criteria were as follows: high bleeding risk, serious autoimmune diseases, grade III hypertension, cardiac insufficiency, gastrointestinal dysfunction, intestinal obstruction, failed to be followed up, incomplete clinical information, no measurable lesion. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of General Hospital of Chinese PLA (No. S2021-553-01), the informed consent was waived according to the nature of retrospective study. The demographic and clinical characteristics, such as age, gender, diagnosis, stage, pathology subtypes, presence of liver or brain metastasis, ECOG PS, previous treatment lines and regimens, laboratory and radiological data and adverse events (AEs) were summarized.

Anlotinib was orally taken 8 or 12 mg once daily for 14 consecutive days and withdrawn for 7 days, the initial dosage was determined by the oncologist or gynecologist according to the patient's condition and adjusted if intolerance occurred. The combined regimens were prescribed according to the National Comprehensive Cancer

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Network or Chinese Society of Clinical Oncology guidelines. The last follow-up was on October 1, 2023. Median follow-up time was 14.8 months (range, 3.1–43.3 months).

Assessments

The clinical benefit of anlotinib was evaluated every two cycles. The efficacy indicators were evaluated according to the Response Evaluation Criteria for Solid Tumors (RECIST) version 1.1 by two independent doctors (20), and classified as complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). ORR was calculated as the proportion of CR + PR; DCR was calculated as the percentage of CR + PR + SD. Clinical benefit was defined as patients achieving CR or PR or SD as best response. Non-clinical benefit was defined as patients experienced PD as best response. Progression-free survival (PFS) was defined as the time from anlotinib administration to disease progression or death due to any cause; overall survival (OS) was defined as the time from anlotinib administration to death. The AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0 (CTCAE 5.0).

Statistical analysis

The statistical analysis was conducted by SPSS version 26.0 (IBM Corp., Armonk, NY, USA) and PRISM version 9.0 (GraphPad Software, La Jolla, CA, USA). Continuous data were expressed as mean and 95% confidence interval (CI). Countable data were expressed as frequency or percentage (%). PFS and OS were estimated by the Kaplan-Meier method. The comparison between two or three groups was assessed by the chi-squared test. The survival data between different groups were compared by the log-rank test. The significant difference was defined as $P<0.05$ (two-tails).

Results

Baseline demographics and clinical characteristics of patients

A total of 34 patients were screened for the study, five patients were excluded due to loss of follow-up. Thus, 29 patients were recruited in this study. The median age was 58 years (range, 36–73 years). There were 93.10% (27/29) of patients with stage IV per International Federation of Gynecology and Obstetrics (FIGO) stage system. There were 16 patients diagnosed with cervical cancer, and 13 with endometrial cancer. As for the pathological type, there were 11 and 14 patients with squamous cell carcinoma and adenocarcinoma respectively. Of the whole patients, 86.21% (25/29) were with ECOG PS ≤1, 68.97% (20/29) received two or more lines of previous treatment, and 55.17% (16/29) received anlotinib combined with immunotherapy. The baseline characteristics are summarized in *Table 1*.

Efficacy

Of the whole patients, seven gained PR, nine gained SD, and 13 experienced PD, yielding the ORR of 24.14% and DCR of 55.17%. The ORR in patients with cervical cancer and endometrial cancer were 25.00% and 23.08%, and the DCR were 56.25% and 53.85% (*Table 2*). There was no different anti-tumor effect of anlotinib between patients with cervical cancer and endometrial cancer. Thus, all patients were integrated as a whole for subsequent analysis, given the small sample size of each cancer.

To identify patients most likely benefit from anlotinib, the patients were divided into two groups by achieving clinical benefit or not. The patients received anlotinib combined with immunotherapy had significantly higher rate of clinical benefit than those receiving anlotinnb alone (P=0.04). There were no different rates of clinical benefit between patients in subgroups of age (P=0.53), FIGO stage (P=0.10), liver metastases (P=0.08), brain metastases (P=0.78), pathological types (P=0.19), ECOG PS (P=0.82), number of previous treatment lines (P=0.10) (*Table 3*).

Subsequently, patients were grouped by receiving combined immunotherapy or not. The baseline characteristics were comparable between patients with immunotherapy and without immunotherapy (*Table 4*). The ORR was higher in patients treated with anlotinib combined with immunotherapy than those without immunotherapy (31.25% *vs.* 15.38%, P=0.32); while, the DCR was significantly higher in patients with immunotherapy comparing to those without immunotherapy (75.00% *vs.* 30.76%, P=0.02) (*Table 5*).

The overall median PFS and OS were 12.2 months (95% CI: 6.6–17.8) and 22.3 months (95% CI: 20.9–23.7), respectively (*Figure 1A,1B*). The 6-month survival rates of PFS and OS were 51.7% and 82.8%, the 12-month survival rates of PFS and OS were 34.5% and 51.7%, and the 18-month survival rates of PFS and OS were 17.2% and 37.9%. For patients with cervical cancer, the median PFS and OS were 13.1 months (95% CI: 6.9–19.3) and

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Table 1 Baseline demographics and clinical characteristics of patients enrolled

Characteristics	Total (n=29)	Cervical cancer (n=16)	Endometrial cancer (n=13)
Age (years)			
≤60	13 (44.83)	5 (31.25)	8 (61.54)
>60	16 (55.17)	11 (68.75)	5 (38.56)
FIGO stage			
III	2 (6.90)	1 (6.25)	1 (7.69)
IV	27 (93.10)	15 (93.75)	12 (92.31)
Liver metastases			
No	24 (82.76)	13 (81.25)	11 (84.62)
Yes	5 (17.24)	3 (18.75)	2 (15.38)
Brain metastases			
No	27 (93.10)	14 (87.50)	13 (100.00)
Yes	2 (6.90)	2 (12.50)	0 (0.00)
Pathological types			
Squamous cell carcinoma	11 (37.93)	11 (68.75)	0 (0.00)
Adenocarcinoma	14 (48.28)	3 (18.75)	11 (84.62)
Others	4 (13.79)	2 (12.50)	2 (15.38)
ECOG PS			
≤1	25 (86.21)	14 (87.50)	11 (84.62)
≥2	4 (13.79)	2 (12.50)	2 (15.38)
Number of previous treatment lines			
<2	9 (31.03)	6 (37.50)	3 (23.08)
≥2	20 (68.97)	10 (62.50)	10 (76.92)
Combined with immunotherapy			
Yes	16 (55.17)	10 (62.50)	6 (46.15)
No	13 (44.83)	6 (37.50)	7 (53.85)

Data were present as n (%). FIGO, International Federation of Gynecology and Obstetrics; ECOG PS, Eastern Cooperative Oncology Group performance status.

Table 2 Antitumor activities of anlotinib

Antitumor activity	Total (n=29)	Cervical cancer (n=16)	Endometrial cancer (n=13)
Best overall response			
CR	0 (0.00)	0 (0.00)	0 (0.00)
PR	7 (24.14)	4 (25.00)	3 (23.08)
SD	9 (31.03)	5 (31.25)	4 (30.77)
PD	13 (44.83)	7 (43.75)	6 (46.15)
ORR (%)	24.14	25.00	23.08
DCR (%)	55.17	56.25	53.85

Data were present as n (%) unless specified. CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate.

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Table 3 The comparison of clinical benefit rate in patients of subgroups

Characteristics	Clinical benefit	Non-clinical benefit	P value
Total	16	13	–
Age (years)			0.53
≤60	8	8	
>60	8	5	
FIGO stage			0.10
III	0	2	
IV	16	11	
Liver metastases			0.08
No	15	9	
Yes	1	4	
Brain metastases			0.78
No	15	12	
Yes	1	1	
Pathological types			0.19
Squamous cell carcinoma	8	3	
Adenocarcinoma	7	7	
Others	1	3	
ECOG PS			0.82
≤1	14	11	
≥2	2	2	
Number of previous treatment lines			0.10
<2	7	2	
≥2	9	11	
Combined with immunotherapy			0.04*
Yes	11	4	
No	5	9	

Data were present as n. *, P<0.05. FIGO, International Federation of Gynecology and Obstetrics; ECOG PS, Eastern Cooperative Oncology Group performance status.

24.0 months (95% CI: 20.3–27.7); for patients with endometrial cancer, the median PFS and OS were 8.2 months (95% CI: 0–17.0) and 22.3 months (95% CI: 10.7–33.9). The patients receiving anlotinib combined with immunotherapy had significant longer OS than those without immunotherapy [not reached *vs.* 12.5 months; hazard ratio (HR): 0.32 (95% CI: 0.1–0.99); P=0.04]. In addition, the PFS was also longer in patients receiving anlotinib with immunotherapy comparing to those without immunotherapy, though not significant [12.2 *vs.* 5.6 months; HR: 0.76 (95% CI: 0.30–1.96); P=0.58] (*Figure 1C,1D*).

Safety

The AEs were reported in 23 (79.3%) patients, and there was no treatment-related death and anlotinib discontinuation. The seven most common AEs were fatigue (41.4%), hand-foot syndrome (17.2%), oral mucositis

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Table 4 Baseline characteristics between patients with and without immunotherapy

Characteristics	With immunotherapy (n=16)	Without immunotherapy (n=13)	P value
Age (years)			0.90
≤60	7 (43.75)	6 (46.15)	
>60	9 (56.25)	7 (53.85)	
FIGO stage			0.88
III	1 (6.25)	1 (7.69)	
IV	15 (93.75)	12 (92.31)	
Liver metastases			0.45
No	14 (87.50)	10 (76.92)	
Yes	2 (12.50)	3 (23.08)	
Brain metastases			0.19
No	14 (87.50)	13 (100.00)	
Yes	2 (12.50)	0 (0.00)	
Pathological types			0.47
Squamous cell carcinoma	7 (43.75)	4 (30.77)	
Adenocarcinoma	7 (43.75)	7 (53.85)	
Others	2 (12.50)	2 (15.38)	
ECOG PS			0.19
≤1	15 (93.75)	10 (76.92)	
≥2	1 (6.25)	3 (23.08)	
Number of previous treatment lines			0.98
<2	5 (31.25)	4 (30.77)	
≥2	11 (68.75)	9 (69.23)	

Data were present as n (%). FIGO, International Federation of Gynecology and Obstetrics; ECOG PS, Eastern Cooperative Oncology Group performance status.

Table 5 Tumor response in patients with or without immunotherapy

Antitumor activity	With immunotherapy (n=16)	Without immunotherapy (n=13)	P value
Tumor response			–
CR	0 (0.00)	0 (0.00)	
PR	5 (31.25)	2 (15.38)	
SD	7 (43.75)	2 (15.38)	
PD	4 (25.00)	9 (69.23)	
ORR (%)	31.25	15.38	0.32
DCR (%)	75.00	30.76	0.02*

Data were present as n (%) unless specified. *, P<0.05. CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate.

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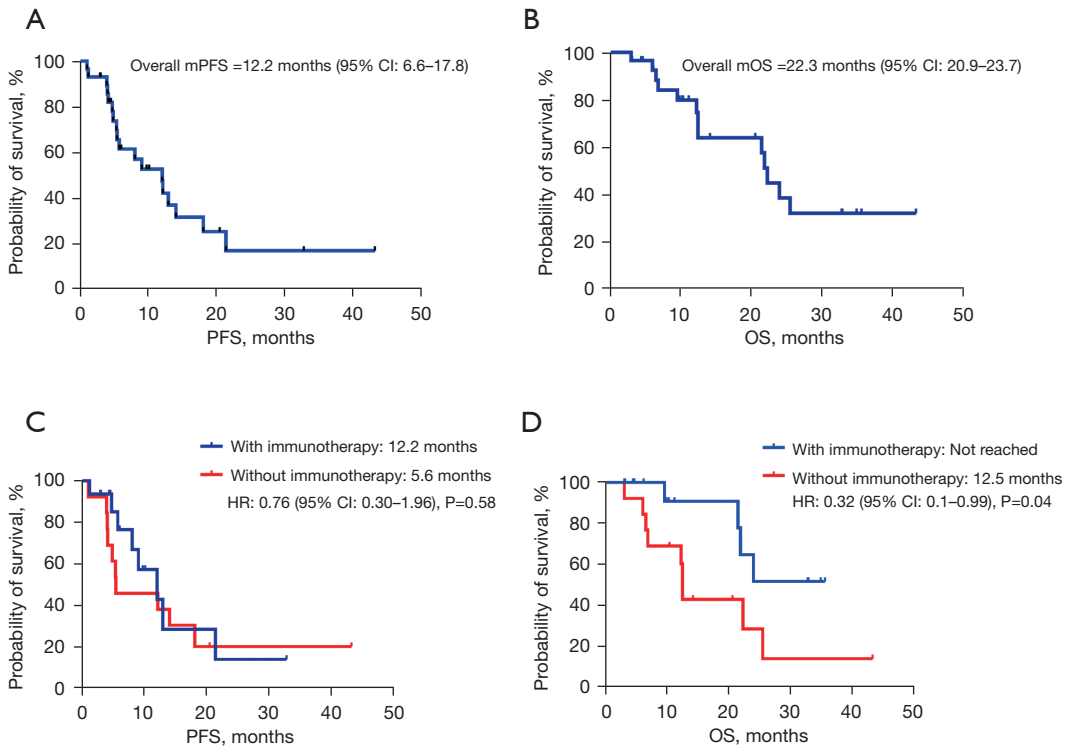

Figure 1 The Kaplan-Meier curves of PFS and OS of all patients and immunotherapy stratified patients. (A) The Kaplan-Meier curves of overall mPFS of patients. (B) The Kaplan-Meier curves of overall mOS of patients. (C) The Kaplan-Meier curves of PFS of patients stratified by with or without immunotherapy. (D) The Kaplan-Meier curves of OS of patients stratified by with or without immunotherapy. mPFS, median progression-free survival; CI, confidence interval; PFS, progression-free survival; mOS, median overall survival; OS, overall survival; HR, hazard ratio.

(17.2%), neutropenia (17.2%), anemia (13.8%), hoarseness (13.8%), and hypertension (13.8%). Grade 3–4 AEs were observed in 4 (13.8%) patients treated with anlotinib combined with immunotherapy; three suffered grade 3 hypertension and were managed well by antihypertensive drugs, one suffered grade 4 anemia and received transfusion and dose reduction. All the safety data are summarized in *Table 6*.

Discussion

Persistent, recurrent, or metastatic gynecological cancers are associated with poor prognosis and have limited treatment options (21-23). For the recurrent or metastatic cervical cancer, the 5-year survival rate is 17%; for the stage IV endometrial cancer, the 5-year survival rate ranges from 15% to 17% (24,25). Novel antitumor strategies remain an unmet clinical need. In our study, anlotinib exhibited compelling antitumor effect with ORR of 24.14% and DCR of 55.17% in patients with cervical cancer and endometrial cancer. Moreover, anlotinib plus immunotherapy demonstrated synergistic antitumor effect.

Sufficient clinical trials have confirmed the efficacy of anti-angiogenic therapy in solid tumors. In our study, the efficacy outcomes are similar with previous studies. As for cervical cancer, the ORR and DCR were comparable to those reported by Zhu *et al.* (18). In endometrial cancer, our results showed an ORR of 23.08% and DCR of 53.85%, which were slightly inferior to those reported by Cui *et al.* (26) and Wei *et al.* (19). The differences might attribute to the followings: firstly, the sample size of endometrial cancer in our study was relatively small; secondly, in the study by Wei *et al.*, all patients were treated with anlotinib plus immunotherapy and lower proportion of patients received three or more lines of previous treatments (19). However, the survival benefits of our study are superior to previous studies. In present study, the median PFS and OS were 13.1 and 24.0 months in cervical cancer; while, the median

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Table 6 Safety analysis

AEs	Any grade, n (%)	Grade 1, n	Grade 2, n	Grade 3, n	Grade 4, n
Hoarseness	4 (13.8)	4	0	0	0
Fatigue	12 (41.4)	9	3	0	0
Oral mucositis	5 (17.2)	5	0	0	0
Hand-foot syndrome	5 (17.2)	5	0	0	0
Rash	2 (6.9)	2	0	0	0
Nausea	1 (3.4)	1	0	0	0
Diarrhea	0 (0.0)	0	0	0	0
Hemorrhage	3 (10.3)	3	0	0	0
Hypertension	4 (13.8)	0	1	3	0
Proteinuria	2 (6.9)	0	2	0	0
Increased AST	0 (0.0)	0	0	0	0
Increased ALT	2 (6.9)	1	1	0	0
Increased Scr	0 (0.0)	0	0	0	0
Neutropenia	5 (17.2)	1	4	0	0
Anemia	4 (13.8)	2	1	0	1
Thrombocytopenia	2 (6.9)	1	1	0	0

AEs, adverse events; AST, aspartate aminotransferase; ALT, alanine aminotransferase; Scr, serum creatinine.

PFS and OS were 8.2 and 22.3 months in patients with endometrial cancer. In Gynecologic Oncology Group (GOG) 240 trial, bevacizumab combined with chemotherapy achieved 17 months of median OS and 8.2 months of median PFS in patients with refractory, recurrent, or metastatic cervical cancer (27). Cui *et al.* reported the median PFS and OS of anlotinib in endometrial cancer were 6 and 13.3 months respectively (26). The promising survival benefit demonstrated the efficacy of anlotinib, while the difference due to small sample size cannot be ruled out.

Immunotherapy, especially for anti-PD-1/programmed death ligand-1 (PD-L1) blockades, has achieved remarkable success in solid tumors and revolutionized the treatment of cancers in recent years (28). In gynecological cancers, efficacy of immunotherapy has been validated by numerous studies (29,30), especially in endometrial cancer patients harboring deficient mismatch repair or high microsatellite instability (31,32). Thus, immunotherapy is recommended as the first-line treatment for advanced or metastatic endometrial cancer (33). Furthermore, anti-angiogenic therapy combined with immunotherapy shows synergistic anti-tumor effects, for the anti-angiogenic therapy could alleviate immunosuppression by T-cell infiltration, decrease regulatory T cells, and downregulate PD-L1 expression (34,35). As reported by Xu *et al.* (36), anlotinib plus sintilimab showed promising efficacy with ORR of 54.5% and DCR of 100% in patients with persistent, recurrent, or metastatic cervical cancer. Yang *et al.* showed that the anlotinib plus sintilimab achieved an ORR of 40% and a DCR of 100% in patients with persistent, recurrent, or metastatic cervical cancer as second-line treatment (37). In the KEYNOTE-146 study (38), lenvatinib plus pembrolizumab showed compelling antitumor activity with an ORR of 38% in patients with advanced or metastatic endometrial cancer regardless of microsatellite status. In line with above-mentioned studies, our study showed that the ORR and DCR were also superior in patients treated with anlotinib plus immunotherapy. The patients receiving anlotinib plus immunotherapy had longer PFS and OS than those without immunotherapy, which are similar to results reported by Wei *et al.* (19). Thus, anlotinib plus immunotherapy might be a promising regimen in cervical and endometrial cancers.

In our study, the most common AEs were fatigue (41.4%),

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hand-foot syndrome (17.2%), oral mucositis (17.2%), neutropenia (17.2%), anemia (13.8%), hoarseness (13.8%), and hypertension (13.8%), all of which were typical AEs of anlotinib reported in previous studies, and no unreported complications and death occurred. In present study, three patients suffered treatment-related grade 3 hypertension, which was reported ranging from 39% to 68% in previous studies (39-41), and all the three patients were managed well. Furthermore, all the grade 3–4 AEs were observed in patients treated with anlotinib plus immunotherapy, suggesting that the combination therapy might increase the incidence of grade 3–4 AEs. However, our study showed that anlotinib exhibited well tolerability and low toxicity.

Some limitations should be noted. First, the small sample size and self-limitation of single-center retrospective study lower the significant power, and further large-scale prospective studies are needed to confirm our findings. Second, prognostic indicators involving the microsatellite status, PD-L1 expression, and genetic status were not analyzed in this study, which could help to identify patients more likely to benefit from anlotinib with immunotherapy.

Conclusions

Anlotinib might be a promising therapy for persistent, recurrent, or metastatic cervical and endometrial cancers with low toxicity. Moreover, anlotinib combined with immunotherapy showed synergistic antitumor effects in persistent, recurrent, or metastatic cervical and endometrial cancers.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-272/rc

Data Sharing Statement: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-272/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-272/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of General Hospital of Chinese PLA (No. S2021-553-01), the informed consent was waived according to the nature of retrospective study.

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