Original Article

Efficacy and safety of apatinib in patients with recurrent uterine malignancy: a prospective, single-center, single-arm, phase 2 study

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Background: Apatinib, a small-molecule tyrosine kinase inhibitor that selectively targets vascular endothelial growth factor receptor-2, has clinical activity in recurrent/advanced gynecological cancers. However, its efficacy in uterine malignancy remains unclear. This study aimed to determine the efficacy and safety of single-agent apatinib in patients with recurrent uterine malignancy.

Methods: This is a prospective single-center, single-arm, phase 2 study that enrolled patients aged 18–70 years with histopathologically confirmed recurrent endometrial cancer (EC) and recurrent uterine sarcoma (US), received at least 2 chemotherapy regimens, and an Eastern Cooperative Group performance status of 0–1. Apatinib (500 mg) was administered orally once daily. A treatment cycle was defined as 4 weeks. The patients were followed up every 2 cycles for tumor radiological assessment until disease progression. The primary endpoint was the overall response rate (ORR). The secondary endpoints were progression-free survival (PFS) and overall survival (OS). Adverse events (AEs) were recorded throughout the treatment and within 30 days of the last study treatment and graded as per the National Cancer Institute Common Toxicity Criteria Version 4.0.

Results: A total of 33 patients (22 with EC and 11 with US) were enrolled between October 2018 and April 2021. Median follow-up duration was 11.7 months (interquartile range: 6.8–32.5 months). The patients received apatinib for a median of 4.79 cycles (range 2–13 cycles). In the EC and US cohorts, the ORRs were 27.2% [95% confidence interval (CI), 10.7% to 50.2%] and 9.1% (95% CI, 0.2% to 41.3%), the median PFS were 4.4 months (95% CI, 4.2 to 6.7 months) and 7.0 months (95% CI, 3.2 to 11.6 months), and the median OS were 11.7 months (95% CI, 6.8 months to not reached) and 18.1 months (95% CI, 9.2 months to not reached), respectively. The most common treatment-related AEs of all grades were hypertension (36.4%), proteinuria (33.3%), and hand-foot syndrome (30.3%). No treatment-related serious AEs or deaths occurred.

Conclusions: To our knowledge, this is the first prospective study assessing the efficacy and safety of apatinib in patients with uterine malignancy. The results suggested that apatinib might be a potential treatment option for these patients.

Keywords: Apatinib; uterine malignancy; endometrial cancer (EC); uterine sarcoma (US); vascular endothelial growth factor receptor/tyrosine kinase inhibitor (VEGFR/TKI)

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Introduction

Uterine malignancy is one of the most common gynecologic malignancies, and its incidence continues to increase worldwide (1-3). Approximately 80–90% of uterine malignancies are endometrial cancers (ECs), and about 8% are uterine sarcomas (USs) (4). Most patients with EC are diagnosed early and have a good long-term prognosis, but about 13% develop recurrent disease, and have poor outcomes and a mortality rate of about 25% (5). USs are malignant mesenchymal tumors with a poor prognosis, and high rates of recurrence and metastasis (6).

Currently, paclitaxel plus carboplatin remains the standard first-line therapy for patients with advanced, recurrent, or metastatic EC (7,8), while anthracycline (doxorubicin or equivalent) is the standard first-line treatment for advanced US (9). In recent years, biomarker-directed systemic therapies have developed rapidly as second-line treatments for recurrent or advanced EC/US (10). The National Comprehensive Cancer Network guidelines recommend several biomarker-directed treatments, including pembrolizumab for microsatellite-instability-high (MSI-H) or tumor mutation burden-high tumors, nivolumab/dostarlimab-gxly for mismatch-repair-deficient/MSI-H, trastuzumab for human epidermal growth factor receptor 2/neuroglioblastoma positive uterine papillary serous carcinoma, and larotrectinib or entrectinib for neurotrophic tropomyosin-related kinases gene fusion-positive tumors (7,11-15). Additionally, hormonal therapies, including letrozole/everolimus (7), and letrozole plus palbociclib (16), have also shown promising effects in the treatment of advanced or recurrent estrogen receptor-positive EC. More recently, pembrolizumab plus lenvatinib has been approved by the Food and Drug Administration and European Medicines Agency for patients with non-MSI-H or mismatch repair-proficient recurrent EC, and was shown to have compelling efficacy in the KEYNOTE-146, and better progression-free survival (PFS) and overall survival (OS) than traditional chemotherapy in KEYNOTE-775 (17,18).

Besides specific biomarker-directed strategies, several multi-target vascular endothelial growth factor (VEGF) signaling pathway inhibitors (e.g., aflibercept, bevacizumab, thalidomide, sunitinib, sorafenib, pazopanib, and lenvatinib) have become popular research areas and their use in treating recurrent or metastatic EC or US is currently being examined (19-27). However, with response rates of 7–14.3%, only modest or minimal responses have been achieved (19-27). Thus, there is a substantial unmet need for second- or later-line therapies that use new VEGF/vascular endothelial growth factor receptor (VEGFR)-targeted agents to treat and improve the prognosis of patients with recurrent uterine malignancies.

Apatinib (also known as rivoceranib) is a small-molecule tyrosine kinase inhibitor (TKI) that targets the adenosine triphosphate binding site in VEGFR-2 cells, has a high binding affinity and inhibits VEGFR-2, which may decrease the tumor micro-vessel density and thus slow down or even stop tumor development (28,29). Recent studies have shown that apatinib has a promising clinical efficacy and a manageable safety profile in the treatment of patients with untreated or chemotherapy-refractory soft tissue sarcoma, advanced non-small cell lung cancer, or recurrent/advanced gynecological cancers, including cervical and ovarian cancer (28,30-32). Currently, anlotinib (a multi-kinase angiogenesis inhibitor) has been approved for soft-tissue sarcoma in China (33,34), which suggests that angiogenesis inhibitors might have good efficacy in the treatment of US. However, the therapeutic effect apatinib, which is also a multi-kinase inhibitor with an anti-angiogenic effect, on uterine malignancy has not yet been reported.

Thus, we conducted a single-center, single-arm, phase-II study to assess the activity and safety of apatinib in the treatment of patients with recurrent uterine malignancy in whom chemotherapy had previously failed. We present the following article in accordance with the TREND reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-6463/rc).

Highlight box

Key findings

- Apatinib showed modest antitumor efficacy and acceptable safety profile in patients with recurrent endometrial cancers and uterine sarcoma.

What is known and what is new?

- The prognosis for patients with recurrent uterine malignancy is poor, while targeting vascular endothelial growth factor receptor signaling pathway may potentially be a viable therapeutic strategy.
- This study investigated the efficacy and safety of the anti-angiogenic apatinib in patients with uterine malignancy.

What is the implication, and what should change now?

- Apatinib can become a potential treatment for patients with advanced/recurrent endometrial cancers or uterine sarcoma.

Methods

Study design and ethical statement

This single-center, single-arm, phase-II trial was conducted by Fudan University Shanghai Cancer Center and registered at the Chinese Clinical Trial Registry Centre (registration No. ChiCTR1800018965). This trial was conducted in accordance with the Declaration of Helsinki (as revised in 2013), Good Clinical Practice, and approved by the Ethics Committee of Fudan University Shanghai Cancer Center (No. 1805185-8). All the patients provided written informed consent.

Inclusion and exclusion criteria

Women with histopathologically confirmed recurrent EC or US who had received at least 2 chemotherapy regimens were eligible for this trial. More specifically, to be eligible for inclusion in this study, patients had to meet the following inclusion criteria: (I) be a female aged 18–70 years; (II) have an Eastern Cooperative Group (ECOG) performance status of 0 or 1; (III) have shown disease progression during a second-line or later treatment, or within 3 months of the last treatment; (IV) have at least 1 extracranial measurable lesion according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1; (V) have not undergone radiotherapy within 4 weeks of starting treatment; and (VI) have adequate hematologic, cardiac, hepatic, renal, and thyroid function, which were defined as hemoglobin ≥90 g/L (no blood transfusion within 14 days), an absolute neutrophil count $\geq 1.5\times10^9$/L, platelets $\geq 75\times10^9$/L, total bilirubin ≤1.5× the institutional upper limit of normal (ULN), alanine transaminase, aspartate aminotransferase ≤3× ULN, and serum creatinine ≤1× ULN.

Patients were excluded from the study if they met any of the following exclusion criteria: (I) had histologically proven low-grade endometrial stromal sarcoma, or a diagnosis of any malignancy within the last 5 years (except for cured skin basal cell carcinoma); (II) had participated in clinical trials of unapproved drugs within 4 weeks before enrollment, had previously received treatment with a VEGFR inhibitor (except bevacizumab); (III) had symptomatic central nervous system metastases, or had been stable without clinically relevant symptoms of brain metastases for at least 8 weeks, and had received neither mannitol nor glucocorticoid to reduce intracranial pressure before the study; (IV) had severe cardiopulmonary insufficiency, severe liver or kidney insufficiency, severe or uncontrolled infections, long-term unhealed injuries, or fractures; (V) had antihypertensive drug-treated but uncontrolled hypertension (a systolic blood pressure >140 or diastolic blood pressure >90 mmHg), myocardial ischemia, myocardial infarction above grade I, or arrhythmia of grade I and above (including women with a corrected QT interval >440 ms), and cardiac insufficiency; (VI) had issues affecting oral drug absorption, such as an inability to swallow, post-gastrointestinal resection, chronic diarrhea or intestinal obstruction; (VII) had abnormal coagulation functions (prothrombin time >16 s, activated partial thromboplastin time >43 s, thrombin time >21 s, and fibrinogen <2 g/L), had received thrombolytic or anticoagulant therapy, or had a bleeding tendency and were at risk of gastrointestinal bleeding [e.g., had active ulceration combined with a positive fecal occult blood test (++)]; (VIII) had a history of a thrombotic event, such as cerebrovascular accidents (including transient ischemic attacks), deep vein thrombosis, or pulmonary embolism within 6 months before study entry; (IX) had a history of psychotropic drug abuse and dependence, or being mentally disturbed; and/or (X) were pregnant or lactating, were of childbearing age, or could not use an effective contraceptive method.

Treatment

The enrolled patients received apatinib (500 mg) orally once daily, until disease progression, they developed inability to tolerate toxicity, or they refused to continue treatment. A treatment cycle was defined as 4 weeks. Apatinib was provided by Jiangsu HengRui Medicine Co., Ltd. Dose interruption and dose reduction were allowed for the management of treatment-related adverse events (TRAEs). The patients were monitored for toxicity; if a patient could not tolerate the drug, the dose was reduced to 250 mg once daily. If the toxicity was still intolerable after the dose reduction and/or dose interruption, apatinib was discontinued.

Statistical methods and endpoints

The primary endpoint of this study was the confirmed overall response rate (ORR), which was defined as the proportion of patients whose best overall response was complete response or partial response as per the RECIST v1.1. The secondary endpoints were PFS, which was defined as the time from the first dose of apatinib treatment

to objective disease progression or death, and OS, which was defined as the time from the first dose of apatinib treatment to all-cause death. Tumor responses were defined using the RECIST v1.1, and included complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). The disease control rate (DCR) was defined as the proportion of patients with CR, PR, and SD. Confirmation of progressive disease by radiological assessment was required preferably 4 weeks after a diagnosis of progression per RECIST v1.1. Adverse events (AEs) were recorded throughout the treatment and within 30 days of the last study treatment and graded as per the National Cancer Institute Common Toxicity Criteria Version 4.0. The patients were followed up every 2 cycles for tumor radiological assessment until disease progression. After disease progression, the patients were monitored for OS every 3 months until death, lost to follow-up, or study completion.

The statistical analyses were conducted using SAS® software (version 9.4, SAS Institute Inc., Cary, USA). For the efficacy analysis, the primary analysis set was the full analysis set, which was defined as all of the patients who were enrolled in the study and received at least 1 dose of the study treatment. While the safety set included those patients who received at least 1 dose of the study treatment, and for whom safety data had also been recorded after the dose. The patients that discontinued treatment were considered to have no response. No matter the point, any missing value was imputed as a non-response, except for those for which the preceding and subsequent measurements indicated that the treatment was successful, and the data were censored in such cases. PFS and OS were estimated using the Kaplan-Meier method, and the corresponding 95% confidence intervals (CIs) were calculated using the Brookmeyer-Crowley method. For the objective response rate, the 95% CIs were calculated using the Clopper-Perason method. A sample size of 33 gives 79% power to observe an ORR increase from 7% (single-agent chemotherapy) to 20% (apatinib monotherapy) at a significance level (alpha) of 0.05 (1-sided).

Results

Clinical characteristics

Between October 10, 2018, and April 19, 2021, 40 patients were screened to determine their eligibility, of whom 35 eligible patients were enrolled and received at least 1 dose of apatinib (5 patients were enrolled but withdrew informed consent without treatment). Of the 35 patients, 2 discontinued treatment after <1 cycle without efficacy and safety evaluations (1 patient withdrew from the study for personal reasons, and 1 patient withdrew due to headache after taking apatinib for 3 days). Ultimately, a total of 33 patients (22 with EC and 11 with US) received at least 1 cycle of apatinib and were assessable for toxicity and response. The results of 1 EC patient were not evaluated for efficacy and were only evaluated for toxicity, as that patient refused to continue the treatment after 1 cycle of apatinib. Patients with histologic subtypes of endometrioid carcinoma (13 cases), serous carcinoma (5 cases), carcinosarcomas (2 cases), clear cell carcinoma (1 case), and neuroendocrine carcinomas (1 case) were enrolled in the EC cohort. Patients with the histologic subtypes of uterine leiomyosarcomas (uLMS, 9 cases) and high-grade endometrial stromal sarcomas (ESS, 2 cases) were enrolled in the US cohort. The clinical characteristics of the EC and US cohorts are shown in *Table 1*.

Efficacy and survival analysis

As of the data cut-off date of September 16, 2021, the median follow-up duration was 11.7 months (interquartile range, 6.8–32.5 months), and 6 (18.2%) of the 33 patients were still receiving the treatment, and 2 (6.1%) had withdrawn from the study due to TRAEs. The patients received apatinib for a median of 4.79 cycles (range, 2–13 cycles). The antitumor activity results for apatinib in the 2 cohorts as assessed by the RECIST v1.1 are presented in *Table 2*. In the EC cohort, 6 (27.2%) of the 22 patients achieved a PR, 9 (40.9%) had SD, and 6 (27.2%) had PD as their best responses, giving a confirmed ORR of 27.2% (95% CI, 10.7% to 50.2%) and a DCR of 68.2% (95% CI, 45.1% to 86.1%). The results of 1 patient could not be evaluated. The median PFS and OS were 4.4 months (95% CI, 4.2 to 6.7 months) and 11.7 months (95% CI, 6.8 months to not reached), respectively (*Figure 1*).

In the US cohort of patients, 1 (9.1%) of the 11 patients achieved a PR, giving a confirmed ORR of 9.1% (95% CI, 0.2% to 41.3%). Further, 8 patients (72.7%) had SD and 2 patients (18.2%) had PD as their best responses with a DCR of 81.8% (95% CI, 48.2% to 97.7%). The median PFS and OS were 7.0 months (95% CI, 3.2 to 11.6 months) and 18.1 months (95% CI, 9.2 months to not reached), respectively (*Figure 2*). The US cohort comprised 9 patients with uLMS and 2 patients with high-grade ESS. The uLMS

Table 1 Baseline characteristics

Characteristics	Endometrial cancer (n=22)	Uterine sarcoma (n=11)
Age (years), median [range]	61 [31–69]	54 [34–65]
Clinical stage, n (%)		
I–II	11 (50.0)	10 (91.0)
III–IV	11 (50.0)	1 (9.0)
ECOG performance status, n (%)		
0	13 (59.1)	10 (91.0)
1	9 (40.9)	1 (9.0)
Histologic subtype, n (%)		
Endometrioid adenocarcinoma	13 (59.1)	–
Grades 1–2	8 (61.5)	–
Grade 3	4 (30.8)	–
Not confirmed	1 (7.7)	–
Non-endometrioid adenocarcinoma[a]	9 (40.9)	–
Leiomyosarcoma	–	9 (81.8)
High-grade endometrial stromal sarcomas	–	2 (18.2)
Lymph-vascular space invasion, n (%)		
Positive	9 (40.9)	3 (27.3)
Negative	12 (54.5)	7 (63.6)
Missing	1 (4.5)	1 (9.1)
Treatment-free interval, n (%)		
<3 months	11 (50.0)	7 (63.6)
≥3 months	11 (50.0)	4 (36.4)
Metastatic site, n (%)		
Lung	9 (40.9)	6 (54.5)
Retroperitoneal lymph node	8 (36.4)	0 (0.0)
Abdomen	8 (36.4)	1 (9.1)
Pelvis	7 (31.8)	6 (54.5)
Liver	3 (13.6)	0 (0.0)
Prior chemotherapy, n (%)		
Platinum-taxane combination*	21 (95.5)	5 (45.5)
Anthracyclines	5 (22.7)	4 (36.4)
Docetaxel-gemcitabine combination*	0 (0.0)	4 (36.4)
Others[b]	4 (18.2)	1 (9.1)
Prior radiation, n (%)		
Yes	14 (63.6)	4 (36.4)
No	8 (36.4)	7 (63.6)
Previously treated with Bevacizumab, n (%)	1 (4.5)	0 (0.0)

[a], non-endometrioid adenocarcinoma included serous carcinoma (5 cases), carcinosarcomas (2 cases), clear cell carcinoma (1 case), and neuroendocrine carcinomas (1 case); [b], other chemotherapy agents included pemetrexed, irinotecan, and etoposide; *, with or without other anticancer medication. ECOG, Eastern Cooperative Group.

Table 2 Antitumor activity of apatinib in patients with recurrent EC and recurrent US

Antitumor activity	Endometrial cancer (n=22*)	Uterine sarcoma (n=11)
ORR, n (%)	6 (27.2)	1 (9.1)
95% CI	10.7% to 50.2%	0.2% to 41.3%
DCR (%)	68.2	81.8
95% CI	45.1% to 86.1%	48.2% to 97.7%
Median PFS (months)	4.4	7.0
95% CI	4.2 to 6.7	3.2 to 11.6
Median OS (months)	11.7	18.1
95% CI	6.8 months to not achieved	9.2 months to not achieved
Best overall response, n (%)		
PR	6 (27.2)	1 (9.1)
SD	9 (40.9)	8 (72.7)
PD	6 (27.2)	2 (18.2)

*, no post-baseline assessment was available for response evaluation in one patient. EC, endometrial cancer; US, uterine sarcoma; ORR, overall response rate; DCR, disease control rate; CI, confidence interval; PFS, progression-free survival; OS, overall survival; PR, partial response; SD, stable disease; PD, progressive disease.

patients had a confirmed ORR of 11.1% [n=1/9, (95% CI, 0.3% to 48%)], and median PFS and OS of 8.3 months (95% CI, 3.2 months to not reached) and 18.0 months (95% CI, 9.2 months to not reached), respectively. Among the high-grade ESS patients, 1 patient (1/2) had SD as their best response, and no patient achieved CR or PR. The median PFS and OS were 3.2 months (95% CI, 2.0 months to not reached) and 14.8 months (95% CI, not reached to not reached), respectively.

Safety

During the treatment, 19 patients (57.6%) experienced dose reduction, 27 (81.8%) needed a dose interruption, and 2 (6.1%) discontinued treatment due to AEs. A summary of the TRAEs for all patients is provided in *Table 3*. AEs of any grade were reported in 30 patients (90.9%). The most common TRAEs of all grades were hypertension (36.4%), proteinuria (33.3%), hand-foot syndrome (30.3%), increased aspartate transaminase (27.3%), and increased alanine transaminase (24.2%). Moreover, 9 patients (27.3%) experienced TRAEs of grade ≥3, the most common of which were hypertension, proteinuria, and hand-foot syndrome. Most TRAEs were mild in severity and clinically acceptable, and no treatment-related serious AEs or deaths

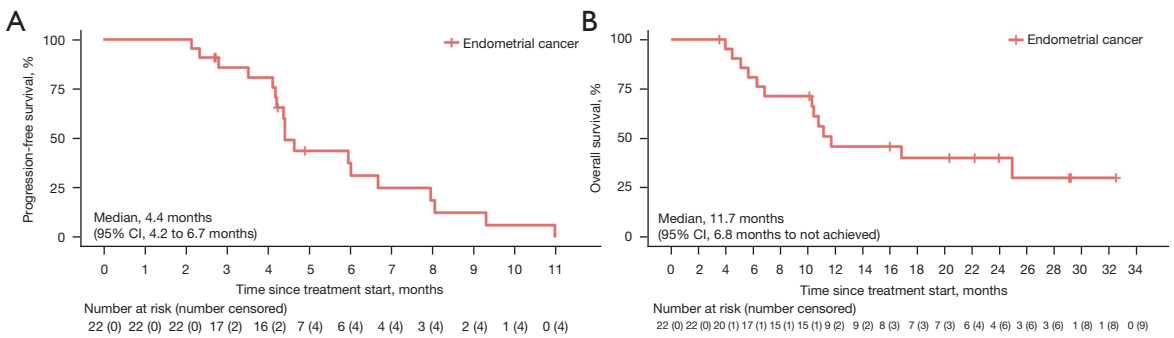

Figure 1 Kaplan-Meier plots depicting the PFS (A) and OS (B) for the 22 evaluable patients with EC. OS, overall survival; PFS, progression-free survival; CI, confidence interval; EC, endometrial cancer.

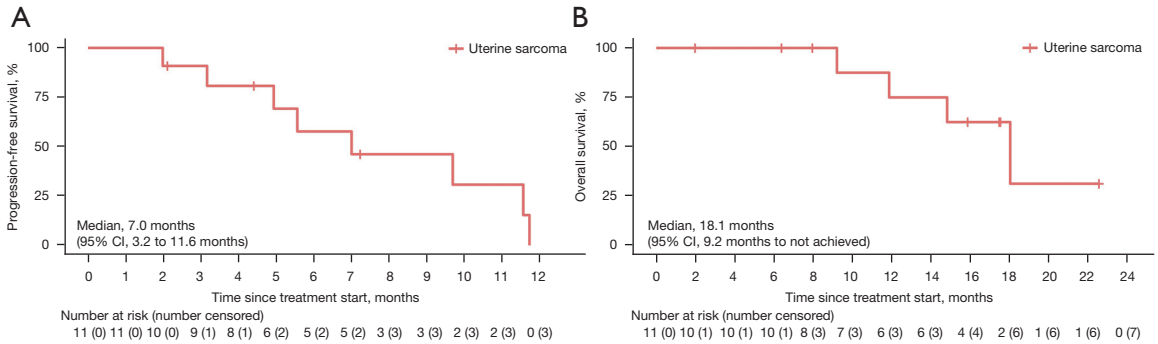

Figure 2 Kaplan-Meier plots depicting the PFS (A) and OS (B) for the 11 evaluable patients with US. OS, overall survival; PFS, progression-free survival; CI, confidence interval; US, uterine sarcoma.

Table 3 Adverse events

TRAEs	Patients (n=33), n (%)	
	All grade	Grade ≥3
Any event	30 (90.9)	9 (27.3)
Hypertension	12 (36.36)	5 (15.15)
Proteinuria	11 (33.33)	2 (6.06)
Hand-foot syndrome	10 (30.30)	2 (6.06)
Increased aspartate transaminase	9 (27.27)	–
Increased alanine transaminase	8 (24.24)	–
Asthenia	6 (18.18)	–
Stomachache	6 (18.18)	–
Decreased neutrophil count	6 (18.18)	–
Decreased white blood cell count	4 (12.12)	1 (3.03)
Oral ulcer	4 (12.12)	–
Diarrhea	3 (9.09)	1 (3.03)
Toe numbness	2 (6.06)	–
Rash	2 (6.06)	–
Positive fecal occult blood	2 (6.06)	–
Hemoptysis	1 (3.03)	–
Sore throat	1 (3.03)	–
Increased creatinine	1 (3.03)	–
Tongue numbness	1 (3.03)	–
Insomnia	1 (3.03)	–
Decreased platelet count	1 (3.03)	–

TRAEs, treatment-related adverse events.

occurred in the trial.

Discussion

The prognosis for patients with advanced or recurrent EC or US is poor, and the targeting of the VEGF/VEGFR signaling pathway represents a potentially viable therapeutic strategy. Pembrolizumab plus lenvatinib has been an established second-line therapy for advanced/recurrent metastatic EC; however, the VEGF inhibitor may still provide value for patients for whom the PD-1/PD-L1 antibody is not suitable, for whom specific biomarkers are not known, or for whom biomarker detection is unavailable. A series of VEGF/VEGFR inhibitors, such as aflibercept (20,21), bevacizumab (22), thalidomide (23), sunitinib (24), sorafenib (25), pazopanib (26), and lenvatinib (27), have been developed (*Table 4*), which have shown minimal or modest activity (ORR: 7.0% to 14.3%; median PFS: 1.5 to 5.6 months; median OS: 5.0 to 15.1 months) in recurrent EC or US.

As apatinib has been demonstrated to have a promising clinical efficacy and a manageable safety profile in the treatment of recurrent or advanced gynecological cancers (28,32), this phase-II study was designed to verify the antitumor activity of apatinib in patients with recurrent EC and US in whom chemotherapy had previously failed. The final data from this phase-II study demonstrated an acceptable antitumor efficacy in patients with EC (ORR: 27.2%) and potential antitumor activity in patients with US (ORR: 9.1%). The toxicity was acceptable.

In the EC cohort, 6 of the 22 patients achieved a PR and 9 patients had SD, giving an ORR of 27.2% and a

Table 4 Partial research results of VEGF/VEGFR inhibitor therapies to treat uterine malignancy

Time	Regimen	Target	Disease	Phase	Sample size	ORR	Median PFS (months)	Median OS (months)
2007	Thalidomide (23)	VEGF	Endometrial cancer	II	24	–	1.7	6.3
2009	Sunitinib (24)	VEGFR	Uterine leiomyosarcoma	II	23	8.7%	1.5	15.1
2010	Sorafenib (25)	VEGFR	Uterine carcinoma	II	40	–	3.2	11.4
			Uterine carcinosarcoma		16	–	1.8	5.0
2011	Bevacizumab (22)	VEGF-A	Endometrial cancer	II	52	13.5%	4.2	10.6
2012	Aflibercept (21)	VEGF-Trap	Endometrial cancer	II	44	7.0%	2.9	14.5
2014	Pazopanib (26)	VEGFR	Uterus carcinosarcoma	II	19	–	2.0	8.7
2020	Lenvatinib (27)	VEGF	Endometrial cancer	II	19	14.3%	5.6	10.6

VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; ORR, overall response rate; PFS, progression-free survival; OS, overall survival.

DCR of 68.2%. The median PFS and OS were 4.4 months (95% CI, 4.2 to 6.7 months) and 11.67 months (95% CI, 6.8 months to not reached), respectively. Apatinib exhibited an acceptable antitumor activity compared to other VEGF-targeted therapies in clinical studies for EC. For example, in patients with unresectable EC, the lenvatinib treatment resulted in a confirmed ORR of 14.3%, a median PFS of 5.6 months, and median OS of 10.6 months (27). A phase-II study of bevacizumab for patients with recurrent or persistent EC showed an ORR of 13.5%, a median PFS of 4.2 months, and a median OS of 10.6 months (22).

In 2019, anlotinib (a multi-kinase angiogenesis inhibitor) was approved by the National Medical Products Administration for the treatment of advanced soft-tissue sarcoma (33,34). Apatinib, which is also a multi-kinase inhibitor anti-angiogenic agent, was investigated in the treatment of US (a subtype of soft-tissue sarcoma) in this study. The result showed that the median PFS and OS were 7.0 months (95% CI, 3.2 to 11.6 months) and 18.1 months (95% CI, 9.2 months to not reached) respectively, suggesting that a clinical benefit might be achieved from apatinib in this population, especially for patients with uLMS. In this trial, we found a 11.1% ORR and a 81.8% DCR for apatinib in patients with recurrent uLMS.

The recent-developed VEGFR inhibitor, sunitinib, was introduced into a clinical trial of recurrent or persistent uLMS but did not achieve a sufficient objective response (ORR: 8.7%, 90% CI: 1.6–24.9%) or sustained disease stabilization as a second- or third-line treatment (24). Sunitinib is a multi-targeted tyrosine kinase inhibitor that selectively inhibits VEGFR-1, VEGFR-2, VEGFR-3, platelet-derived growth factor receptor α (PDGFRα), PDGFRβ, and so on, with a 50% inhibitory concentration (IC_{50}) of 0.005 μM *in vitro* (35,36). Conversely, apatinib mainly targets VEGFR-2, which is the major factor in the pathological over-formation of blood vessels, with an IC_{50} of 0.001 μM *in vitro* (36,37). Thus, the single-agent apatinib exhibited an antitumor activity in patients with recurrent uLMS in this study. However, as the number of patients was small, further evaluations are required.

The overall toxicity profile reported in this study was consistent with that of previous studies on apatinib (28,30-32), and no new safety signals were identified. The severity of most TRAEs were mild to moderate, and relatively few (2/33, 6.1%) patients discontinued treatment because of these events. Hypertension (12/33, 36.4%), proteinuria (11/33, 33.3%), and hand-foot syndrome (10/33, 30.3%) were the most frequently observed TRAEs of apatinib in this trial. Hypertension and proteinuria were the most common toxicities associated with dose modifications. In addition to dose reduction, an angiotensin receptor blocker (with or without calcium antagonists) was able to control hypertension well. Patients with proteinuria also recovered to normal rapidly, and proteinuria was well tolerated after dose reduction. In addition, apatinib was associated with hematologic AEs, including a decreased neutrophil count, a decreased white blood cell count, and a decreased platelet count from mild to moderate. Of the 33 (27.3%) patients, 9 experienced grade 3 or higher TRAEs. However, there were no treatment-related serious AEs or treatment-related deaths.

This phase-II study had some limitations. First, the

present study was a preliminary exploration of the clinical activity and safety of apatinib in patients with recurrent EC and US. The current data were not mature because of the nature of the study (i.e., it was a single-arm and single-center study) and its small sample size. Further research with expanded cohorts of patients with recurrent EC and US needs to be conducted to confirm the findings presented in this study. Second, both recurrent EC and US patients were enrolled, which is arguably the major weakness of this study. Patients with either recurrent EC or US, who might gain benefits from apatinib, were all included. While patients with low-grade endometrial stromal sarcoma, who might gain benefits from hormone therapy instead of VEGF/VEGFR inhibitors, were excluded. Further, recurrent EC and US were analyzed separately in the results. As an initial exploratory analysis, our findings might provide a direction and some data for the later-line treatment for different subtypes of uterine malignancies. More research needs to be conducted to provide clearer guidance on the patients who may benefit from this anti-angiogenesis therapy according to molecular profiling.

Conclusions

In summary, for patients in whom chemotherapy had previously failed, apatinib showed acceptable antitumor efficacy in recurrent EC and potential antitumor activity in recurrent US. The toxicity was acceptable. A well-designed ongoing clinical trial is currently being conducted to further confirm the present results.

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Footnote

Reporting Checklist: The authors have completed the TREND reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-6463/rc

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Conflicts of Interest: All the authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-6463/rc). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work, including ensuring that any questions related to the accuracy or integrity of any part of the work have been 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 Fudan University Shanghai Cancer Center (No. 1805185-8). Informed consent was obtained from all the patients.

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