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Pazopanib for the treatment of gynecological malignancies

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Summary

Angiogenesis is a well-established therapeutic target in gynecological malignancies. Vascular growth factor (VEGF) plays a critical role in angiogenesis, but also other growth factor receptors, such as platelet-derived growth factor (PDGF) and fibroblast growth factor (FGF), have been demonstrated to contribute to it. Pazopanib is an oral multi-targeted tyrosine kinase inhibitor (TKI) under clinical investigation in late clinical trials for the treatment of gynecological cancers. Moreover, in 2012 the Food and Drug Administration (FDA) approved pazopanib for the treatment of advanced soft-tissue sarcomas, including uterine leiomyosarcoma. This review aims to provide a complete and updated overview on results of clinical studies of pazopanib for the treatment of gynecological malignancies, highlighting the ongoing trials.

Key words: Angiogenesis; Vascular growth factor (VEGF); platelet-derived growth factor (PDGF); Pazopanib.

Introduction

Angiogenesis consists of the formation of new blood vessels, and it is fundamental for growth and progression of cancer. This process results from the dynamic balance of proangiogenic and antiangiogenic factors. Vascular growth factor (VEGF) is a critical proangiogenic molecule involved in angiogenesis, and currently it is an appealing target for anti-cancer targeted therapy [1]. The most extensively investigated antiangiogenic agent is bevacizumab, a humanized monoclonal antibody that blocks VEGF binding to its receptor, consequently inhibiting angiogenesis and tumor proliferation. The Food and Drug Administration (FDA) has approved bevacizumab for the treatment of several advanced solid tumors, including gynecological cancers [2]. The promising clinical activity of bevacizumab in anti-cancer therapy has stimulated research on the study of additional anti-angiogenic agents, such as tyrosine kinase inhibitors (TKI), small molecules that interact with the intracellular domain of tyrosine kinase receptors, blocking multiple signaling pathways simul- taneously [3].

Pazopanib is a multi TKI that targets vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR) and fibroblast growth factor receptor (FGFR) pathways [4]. The FDA and the European Medicines Agency (EMA) have licensed its use for treatment of advanced renal cell carcinoma [5] and soft tissue sarcoma (STS), including uterine leiomyosarcoma (LMS) [6]. Currently, it is under clinical investigation for the treatment of the other gynecological cancers.

A literature search was performed to find all the published studies evaluating pharmacokinetics, pharmacodynamics, clinical efficacy, and safety of pazopanib for the treatment of gynecological malignancies from inception until November 2017. The following electronic databases were used: Medline, PubMed, Embase, Science Citation Index via Web of Science and the Cochrane Library. The following search terms were used: 'pazopanib' or 'GW786034' alone or in combination with 'epithelial ovarian cancer, 'cervical cancer', 'endometrial cancer', uterine leiomyosarcoma', 'carcinosarcoma', 'efficacy', 'safety', 'toxicity', and 'tolerability'. Current research registers (such as www.cliniclatrials.gov) were also considered. All pertinent articles were carefully evaluated and their reference lists were examined in order to identify other manuscripts that could be included in the present drug evaluation.

Angiogenesis and anti-angiogenic therapy in gynecological cancers

VEGF enhances vascular permeability and stimulates cell migration in macrophage and endothelial cells to form new vessels. Several studies demonstrated that VEGF plays an important role in the growth and spread of tumors. On immunohistochemical examination, VEGF and VEGFRs family have been found to be expressed in about half of the human cancers [7].

Generally, their expression has been associated with genesis and growth of gynecological cancers. In epithelial ovarian cancer (EOC), VEGF levels have been found to be elevated in ascitic fluid, so that VEGF is postulated to play a key role in ascitic fluid formation by increasing endothelial cell permeability [8]. In cervical cancer (CC), VEGF pathway seems directly stimulated during HPV infection by the oncogenic viral protein E6, and by the presence of hypoxia and by other growth factors such as tumor-growth factor-β (TGF-β) and

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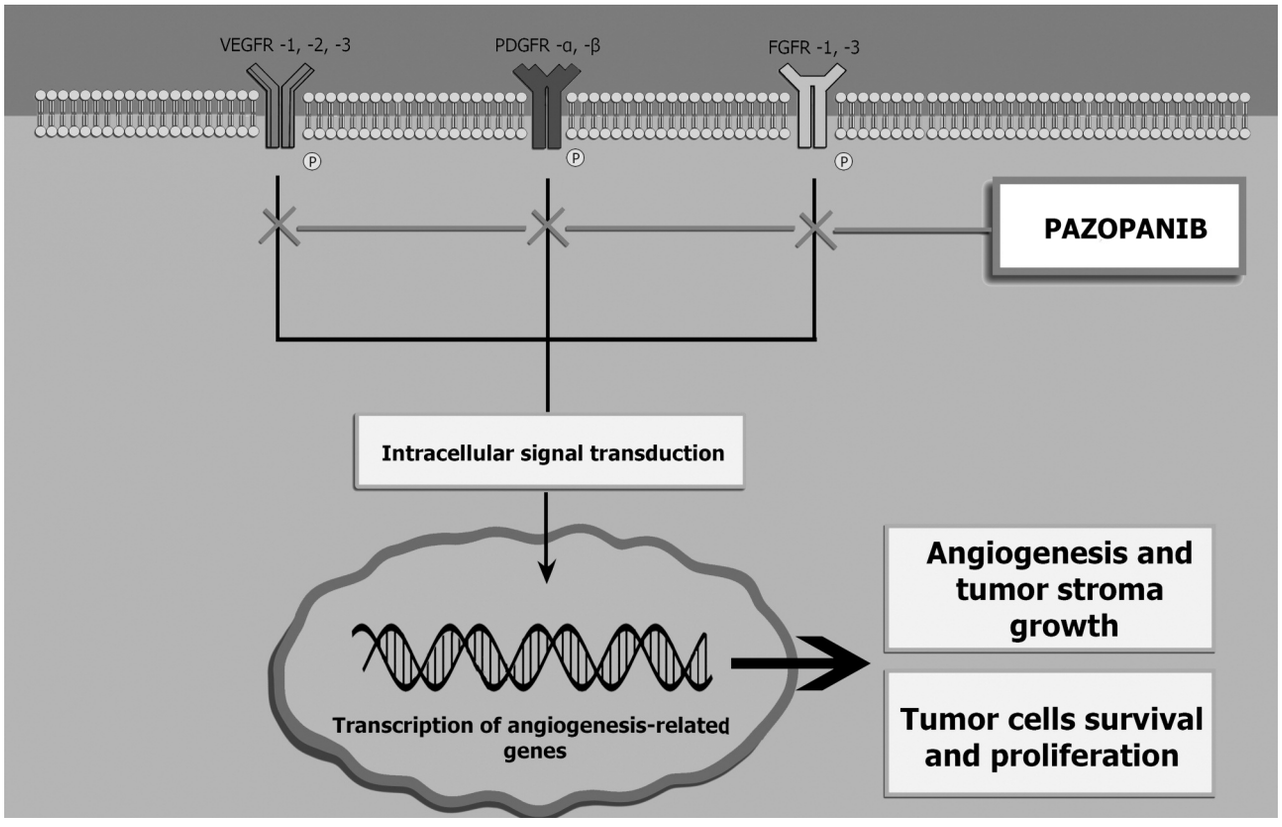

Figure 1. — Mechanism of action of pazopanib.

insulin-like growth factor-1 (IGF-1). Moreover, in CC patients VEGF overexpression has been associated with faster tumor progression and higher risk of pelvic lymph nodal metastasis [9]. In endometrial cancer (EC), VEGF overexpression correlates with poor outcome. An immunohistochemical study has reported that 63% of patients with EC expressed VEGF-A, 55% VEGFR -2, and 26% VEGFR -3. In particular, VEGFR -3 was significantly correlated with advanced FIGO stage and low disease-free survival (DFS) [10].

Two main strategies aim to inhibit the VEGF pathway. The first consists in direct inhibition of circulating VEGF by monoclonal antibodies, such as bevacizumab [11]. The second consists in the inhibition of its receptors by monoclonal antibodies or small TKIs. In particular, TKIs have a wider range of inhibitory effects and may disrupt other secondary pathways that are mediated through receptor kinases responsible for resistance to bevacizumab. Currently, bevacizumab is the only anti-angiogenic drug approved by the FDA for the treatment of recurrent platinum-resistance EOC, and metastatic, recurrent and persistent CC. Although numerous TKIs are under investigation, none of them are approved for the treatment of gynecological cancers.

Pazopanib

Pazopanib (known also as GW786034) is a potent and selective multi-TKI that blocks tumor growth inhibiting angiogenesis. Chemically, pazopanib is a synthetic indazolylpyrimidine. Its IUPAC name is 5- [[4-[(2, 3-dimethylindazol-6-yl)-methylamino]pyrimidin-2-yl]amino]-2-methylbenzenesulfonamide is synthetic indazolylpyrimidine. The mechanism of action of pazopanib is the inhibition of VEGFR -1, -2, -3, PDGF-α, -β, and stem cell factor (c-Kit). Pazopanib exerts also low activity against fibroblast growth factor (FGFR) -1 and -3, and c-fms receptor (Figure 1) [12].

Mechanism of action and pharmacodynamics

Tyrosine kinase receptors are responsible for the transduction of extracellular signals into the cell [13]. When a ligand binds to the extracellular domain of the receptor, the ATP recruitment occurs. Consequently, ATP binds to the receptor ATP-binding site and activates intracellular signals, thus causing stimulating effects on angiogenesis. Pazopanib competitively binds to the ATP binding-pocket of specific tyrosine kinase receptors, causing an interference with receptor dimerization, and the block of signal transduction. In preclinical studies, the concentration of pazopanib required producing 50% inhibition (IC50) of VEGFR-1, -2, and -3 was 10, 30 and 47 nM, respectively [14].

Pazopanib is available as film-coated tablets of 200 and

Table 1. — *Main findings of phase II and III trials of pazopanib for the treatment of gynecological malignancies*

Author	Phase	Number of patients	Population	Treatment regimen	Results	Toxicities
EOC						
Friedlander, 2010 [21]	II	36	Recurrent EOC	Pazopanib (800 mg) OD	31% CA-125 response, RR=18%	Grade 3: ALT (8%) and AST (8%) elevation grade 4: peripheral edema (2.7%)
Pignata, 2010 [22]	II	74	Recurrent EOC	Pazopanib (800 mg) OD + paclitaxel (weekly) or paclitaxel (weekly)	PFS 6.35 m vs 3.49 m RR 56% *vs* 25%	Grade 3-4: neutropenia (30% *vs* 3%), fatigue (11% *vs* 6%), leucopenia (11% *vs* 3%)
Richardson, 2014 [23]	II	106	Recurrent EOC	Paclitaxel (weekly) with or without pazopanib (800 mg) OD	PFS 7.5 m *vs* 6.2 m	Grade 3-4: neutropenia (30 vs 3%), fatigue (11 *vs* 6%), hypertension (8 *vs* 0%) and liver transaminases elevation (8 *vs* 0%).
Du Bois, 2014 [24]	III	194	Primary EOC (after CT)	Pazopanib (800 mg) OD (for 24 m)	PFS 17.9 *vs* 12.3 m	Grade 3-4: hypertension (31% *vs* 6%), neutropenia (10% *vs* 1%), hepatic toxicity (9% *vs* 1%) and diarrhea (8% *vs* 1%)
CC						
Monk, 2010 [25]	II	152	Metastatic, recurrent and persistent CC	Pazopanib (800 mg) OD or lapatinib	OS 49.7 vs 44.1 weeks; RR 9% *vs* 5%	Grade 3: diarrhea (11% *vs* 13%) Grade 4: every toxicity (9% *vs* 12%)
EC						
Boom, 2016 [26]	II	74	Progressive EC	Pazopanib (800 mg) OD (for 4 weeks at least)	58% SD; median PFS 5.3 m; OS 9.5 m	Grade 3-4: gastrointestinal (21%)
Uterine LMS						
Sleijfer, 2003 [27] Kawai, 2016 [28]	II-III	EORT 62043: 10 PALETTE: 34	Advanced uterine LMS	Pazopanib (800 mg) OD	PFS 3 m OS 4.5 m	EORT 62043 grade 3-4: fatigue (8%), hypertension (8%), neutropenia (4%) PALETTE grade 3-4: fatigue (13%), hypertension (7%), diarrhea (5%)
CCS						
Campos, 2017 [29]	II	22	Uterine and ovarian CCS	Pazopanib (800 mg) OD	PFS 2 m; OS 8.7 m	Grade 3-4: anemia (16%), hypertension (16%)

EOC=epithelial ovarian cancer, CC=cervical cancer, EC=endometrial cancer, LMS=leiomyosarcoma, CCS=carcinosarcoma, RR=response rate, PFS=progression-free survival, m=months, OS=overall survival, OD=once day, ALT=alanine aminotransferase, AST=aspartate aminotransferase.

400 mg [15]. Preclinical studies suggested that the in vivo activity of pazopanib depends on achieving a steady-state concentration > 40 μmol/L [14].

Pharmakokinetics

Pazopanib has low solubility and as consequence low oral bioavailability (14-39%) [16]. Following oral administration at dose of 800 mg, it is rapidly absorbed and it achieves the peak plasma concentrations within 2–4 hours [17]. As the food increases pazopanib bioavailability, it should be administered in the fasting state [17]. It has a poor volume of distribution that ranges between 9 and 13 L and its binding to human plasma proteins is high with a bound fraction of more than 99% [18]. The mean half-life ($t_{1/2}$) of pazopanib is around 31 hours at 800 mg per os (PO). Cytochrome (CYP) 3A4 is the predominant enzyme involved in the hepatic metabolism of pazopanib [15]. Polymorphisms in genes encoding these enzymes might explain some individual differences in its pharmacokinetic parameters. Moreover, the administration of CYP2A4 inhibitors (such as ketoconazole or lapatinib) [19] or inducers (such as carbamazepine) [15] modifies its plasma concentration. Pazopanib is mainly eliminated via feces, and less than 4% is excreted in the urine [16, 20].

Use of pazopanib in gynecological malignancies

Table 1 summarizes the results of clinical trials of pazopanib for the treatment of gynecological malignancies [21-30].

Epithelial ovarian cancer

Pazopanib as long-term maintenance monotherapy for the treatment of recurrent EOC was evaluated in a multi-

center phase II study. In this trial, 36 women, with a complete CA-125 response to initial platinum-based chemotherapy (CT) with subsequent elevation of CA-125 to greater than twice the upper limit of normal and with no measurable or low volume disease on imaging methods, were treated with pazopanib (800 mg) once daily (OD) until progressive disease or unacceptable toxicity. Eleven patients (31%) had a CA-125 response (defined as ≥ 50% decrease from baseline, confirmed ≥ 21 days after the initial evaluation). The median time to response was 29 days and median duration of response was 113 days. Moreover, 56% of patients had stable disease (SD) based on CA-125 criteria, with a median duration of response of 80 days. Among 17 patients with measurable disease at baseline, no partial response (PR) or complete response (CR) were obtained, but there were five SD (29%). The six-month progression-free survival (PFS) rate was 17% [21].

Another multicentric double-arm phase II trial (MITO 11) evaluated a combination of pazopanib and paclitaxel in patients with recurrent EOC. Seventy-four patients with platinum-resistant recurrent disease, treated with a maximum of two previous lines of CT, were randomly assigned to receive paclitaxel (80 mg/m^2 weekly) with or without pazopanib (800 mg OD). After a median follow-up of 16.1 months, there was a significant improvement in PFS in the experimental group compared with the placebo group (6.35 *vs* 3.49 months; HR: 0.42; 95% CI: 0.25–0.69; $p = 0.0002$). Moreover, the response rate (RR) was 56% in the experimental group and 25% in the placebo groups [22].

The promising findings of phase II trials led to the development of a large phase III study to evaluate pazopanib for the treatment of patients with advanced EOC. The international, randomized, double-blind, placebo-controlled phase III trial (AGO-OVAR 16) by de Bois *et al.* evaluated this drug as maintenance monotherapy in patients with primary EOC. Nine-hundred and forty women with EOC in FIGO Stages II–IV with no evidence of disease progression following first-line management were assigned to receive either pazopanib (800 mg OD) or placebo for up to 24 months. Following a median follow-up of 24.3 months, the PFS was significantly improved in the pazopanib arm compared with the placebo arm (17.9 *vs* 12.3 months; HR: 0.77; $p = 0.0021$). Fifty-eight percent of patients in the experimental group required dose reductions compared with 14% of patients in the placebo group. The most frequent Grades 3 and 4 AEs in the pazopanib arm were hypertension (30.8%), neutropenia (9.9%), hepatic toxicity (9.4%), and diarrhea (8.2%). A high rate of patients in the experimental arm (33.3%) discontinued the treatment due to AEs compared with the other arm (5.6%) [24]. An exploratory post hoc analysis of subgroup raised the question of whether the benefit of maintenance therapy with pazopanib was driven by outcomes in the non-Eastern Asian population. In fact, while this group had a PFS benefit of 5.9 month with a HR of 0.69 (95% CI: 0.57–0.84), the subgroup originating from East Asia demonstrated a HR of 1.16 (95% CI: 0.78–1.73). There was also a significant negative impact for OS in the East-Asian population with a HR of 1.71 (95% CI: 1.01–2.89; $p = 0.047$). Moreover, the dose reduction rate was higher for East-Asiatic patients (75%) compared for the other patients (36%) [30]. The differences in outcome and toxicity may be due to different pharmacogenomics and should require further investigation.

Despite the controversial results in terms of efficacy and toxicity reported in previous clinical trials investigating the use of pazopanib, there is still interest in studying this drug in EOC, as demonstrated by latest studies and numerous ongoing trials. Recently, the potential of pazopanib in combination with metronomic oral cyclophosphamide as salvage treatment in patients with recurrent platinum-resistant and previously treated EOC has been recently evaluated in a dose-escalation phase I trial. The maximum tolerated dose (MTD) of pazopanib was found at 600 mg, and the median PFS and OS administering this double regimen were 8.35 and 24.95 months, respectively [31]. Moreover, a single arm phase I/II study is evaluating pazopanib (400-800 mg PO) and topotecan in patients with platinum-resistant or intermediate-sensitive recurrent EOC (NCT01600573). Another randomized phase II study is evaluating pazopanib (600 mg PO) and paclitaxel in patients with platinum resistant and refractory EOC who relapses during bevacizumab maintenance (NCT02383251).

Cervical cancer

Pazopanib has been tested only in a phase II trial for the treatment of patients with advanced CC. In the open-label randomized study VEG105281, 228 patients with CC in FIGO Stage IV were treated with pazopanib (800 mg OD) or lapatinib, a TKI of epidermal growth factor (EGFR) and Her2, (1,500 mg OD) as single agent, or with a combination of pazopanib and lapatinib in two different regimens (lapatinib at 1,000 mg plus pazopanib at 400 mg OD or lapatinib at 1,500 mg plus pazopanib at 800 mg OD). The double regimen was prematurely discontinued due to toxicity and the final analysis was performed only in the two single agent arms. In the pazopanib arm, there was an improvement in PFS (HR: 0.66; 90% CI 0.48–0.91; $p = 0.013$). The median OS and RR were 49.7 weeks and 9% and 44.1 weeks and 5% with pazopanib and lapatinib, respectively (HR 0.96; 90% CI 0.71–1.30; $p = 0.407$). The most common Grade 3 AE was diarrhea (11% for pazopanib and 13% for lapatinib), while Grade 4 AEs were reported by 9% and 12% of patients treated with lapatinib and pazopanib, respectively [25]. Currently, an ongoing phase II study is evaluating the RR using the combination of pazopanib (600 mg/day) and topotecan (0.25 mg PO for 21 days continuously followed by seven days off) in patients with recurrent, persistent or metastatic CC (NCT02348398).

Endometrial cancer

The clinical efficacy of pazopanib in EC was studied only a small prospective open-label phase II clinical trial. In this study, 60 patients with progressive EC and WHO performance status ≤ 2 received pazopanib (800 mg OD PO) until progression, unacceptable toxicity or patient refusal. The patients were evaluable for the primary endpoint of PFS at three months if they had received pazopanib for at least four weeks. Twenty-six of the evaluable patients (58%) had SD at three months and median PFS and OS were of 5.3 and 9.5 months, respectively. The most common severe (Grades 3 or 4) AEs were gastrointestinal (21%), but 80% of patients with gastrointestinal toxicity had peritoneal disease [26].

Uterine sarcomas

LMS is an aggressive STS derived from smooth muscle cells typically of uterine, gastrointestinal or soft tissue origin. A phase II trial (EORTC 62043) evaluated the efficacy and safety of pazopanib (800 mg OD) in 142 patients with advanced STS. The patients were divided into four cohorts, based on STS subtype: adipocytic sarcomas, LMS, synovial sarcomas, and a group of miscellaneous STS histotypes. The PFS at 12 weeks was 44% (18/41 patients) in the LMS group, 49% (18/37 patients) in the synovial sarcomas, and 39% (16/41 patients) in the other STS types. Compared with historical controls treated with second-line CT, PFS and OS were prolonged in all the three cohorts in which PFS at 12 weeks was reached [27]. A randomized double-blind placebo-controlled multicenter phase III trial (PALETTE) evaluated pazopanib in 369 patients with metastatic STS (excluding gastrointestinal stromal tumors and adipocytic sarcomas) who had not received a previous angiogenesis targeted therapy and had progressed during previous standard CT. The median PFS was significantly greater in the pazopanib group (4.6 months) compared with the placebo group (1.6 months). Moreover, there was no significant difference in the median OS between the pazopanib (12.5 months) and the placebo (10.7 months) groups, respectively [28].

A retrospective analysis on pooled data from EORTC 62043-study and PALETTE study evaluated whether the response to pazopanib in women with uterine LMS differs from that of patients with other STS. There were ten patients with uterine LMS in the EORTC 62043 trial and 34 patients with uterine LMS in the PALETTE trial. Most patients with uterine LMS had high-grade tumors (n=37, 84.1%) compared to patients with non-uterine disease (n=164, 54.8%). Patients with uterine LMS were heavily pretreated, having 61.3% received greater than or equal to two lines of CT prior to pazopanib compared to 40.8% in the non-uterine population. Median PFS and OS were three and 17.5 months in uterine LMS group versus 4.5 and 11.1 months in the other group, respectively. Prognostic factor analysis was performed. Univariate prognostic factor analysis was performed for best overall response, PFS and OS, looking at the role of age, performance status, tumor grade and the presence of several sites of metastases, but none of these prognostic factors were found to be significant [32].

Although carcinosarcoma (CCS) is a relatively rare tumor among gynecologic malignancies, a phase II study from the Gynecologic Oncology Group (GOG) evaluated the efficacy and safety of pazopanib in the management of patients with recurrent or persistent CCS of the uterus. Pazopanib (800 mg OD for 28 days cycle) was administered to 22 women. No patients had a PR or CR. Three patients (15.8%) had PFS ≥ 6 months. The median PFS was 2.0 months and the median OS was 8.7 months [29]. Recently, a single institutional study reported the results of pazopanib administration as second line treatment for uterine and ovarian CCS. Eight patients received pazopanib (800 mg/day PO), showing a median administration period of 84.5 (range: 23–330) days. The clinical benefit rate (PR and SD) and disease control rate, indicated by more than 12 weeks of SD, were 50% (four) patients. The median PFS was 2.8 months, ranging from 0.8 to 11 months [33].

Discussion

Identifying and developing novel agents with limited toxicity that target specific mechanisms of tumor progression such as angiogenesis represent high priority goals of the oncologic therapy of advanced gynecological cancers. Currently, most of the data on the action of antiangiogenic drugs come from studies evaluating bevacizumab. A major challenge in the success of antiangiogenic therapy is the development of resistance to this drug, probably due to the induction of tumor escape mechanisms by the upregulation of growth factors pathways, such as FGFR and PDGFR. Multi-target TKIs, such as pazopanib, offers the advantage of blocking all these pathways at the same time.

In EOC, antiangiogenic therapies show promising efficacy for treating primary EOC as well as platinum-sensitive and platinum-resistant recurrent diseases. The ICON 7 [34] and GOG 218 [35] studies demonstrated that adding bevacizumab to first-line chemotherapy increased PFS of patients with advanced EOC. Moreover, the AURELIA study showed significant improvement in PFS and objective response rate with addition of bevacizumab to chemotherapy in women with recurrent platinum-resistant EOC. In the phase II MITO-11 [22] the magnitude of PFS benefit administering pazopanib was similar to that observed with the addition of bevacizumab to patients with platinum-resistant EOC in the AURELIA study [36]. In AGO-OVAR 16 [24], although pazopanib as monotherapy provided a significant improvement of PFS (17.9 *vs* 12.3 months) for the treatment of patients with primary advanced EOC, it should not be recommended for general clinical use due to the lack of OS benefit and significant toxicity which led a high rate of women to interrupt the treatment. Lower doses of pazopanib may be worth considering for further clinical investigation. Moreover, in AGO-OVAR 12 [37] phase III trial, nintedanib, another multi-TKI, showed a similar

extension of PFS (seven months) compared with conventional CT in patients with low postsurgical tumor burden. Differently, nintendanib was administered in combination with carboplatin and paclitaxel. Therefore, it would be rational to investigate also pazopanib in a triple regimen to treat patients with primary EOC after surgery. Although pazopanib reported controversial clinical results, currently there is still interest in studying this drug in EOC as showed by numerous ongoing trials.

Despite availability of primary and secondary preventive approaches, CC persists as one of the most common cancers among women around the world, and more than 70% of cases are diagnosed at advanced stages. These patients have a poor prognosis, and, for this reason, the research of new drugs is mandatory. Pazopanib, administered to treat metastatic, persistent and recurrent CC in the VEG105281 [25] study, showed modestly activity (RR=11%), but was well-tolerated, reporting rare Grade 3 and 4 AEs. Moreover, it obtained as monotherapy a longer OS (11.6 weeks more) than lapatinib. In the near future, pazopanib may have a role in the salvage treatment of patients with metastatic, progressive, and persistent disease. Moreover, a clinical trial is ongoing to test pazopanib in combination with cytotoxic drugs (NCT02348398).

The majority of women diagnosed with EC have early-stage disease with relatively good survival rates. However, novel therapies are being investigated to combat the increasing incidence of advanced endometrial carcinoma. First results of a small single-arm phase II trial of pazopanib for the treatment of advanced EC have shown encouraging results (OS 9.5 months), but this study was uncontrolled and the population included in the study was heterogeneous. For this reason, it not possible to draw a conclusive evaluation of pazopanib for the treatment of advanced EC.

Pazopanib has been the first targeted drug approved by the FDA for the treatment of STS, including uterine LMS. The retrospective analysis on pooled data from EORTC 62043 and PALETTE studies [32] have shown that women with uterine LMS treated with pazopanib had better results (RR of 11.4% and a median PFS of three months) that patients with other STS. These findings may be considered similar to those obtained in patients with uterine LMS with other conventional cytotoxic drugs, such as doxorubicin (first-line RR 14%, PFS 4.6 months, all STS) [38], gemcitabine and docetaxel (first-line LMS, RR 25%, PFS 7.1 months) [39], gemcitabine and docetaxel (pretreated LMS, RR 53%, median time to progression 5.6 months) [40], trabectedin (RR 10% ULMS median PFS 5.8 months) [41]. However, cross comparison among these trials is difficult due to a selection bias and the heterogeneous study populations. It may be interesting to study whether response rates might have been higher if pazopanib had been administered in an earlier treatment line and in a greater percentage of women with a performance status of 0. As more patients with LMS included were classified as high-grade (84.1%), a possible future option would be to investigate the response of those patients with low grade uterine disease.

CCS is a relatively rare tumor among gynecologic malignancies. The two clinical trials on pazopanib evaluation for the treatment of patients with CCS have some limitations, as they enrolled few patients and were uncontrolled. Thus, it is not possible to draw a conclusive evaluation on this drug for this setting.

Conclusion

Having a poor prognosis using the conventional available treatments, the investigation of targeted drugs with novel mechanisms of action is a priority of clinical research for the treatment of advanced gynecological cancers. Among TKIs, pazopanib has shown controversial results in terms of both efficacy and safety, as shown in several studies. However, there is still interest in this drug as demonstrated by numerous ongoing clinical trials. Further results are awaited to complete its clinical evaluation.

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