Chapter 3

Antiangiogenic Therapy in Epithelial Ovarian Cancer

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Abstract

Approximately 75% of women with ovarian cancer are diagnosed at advanced stages (FIGO stage III/IV), with 15-23 months median global survival and 20% 5-year survival. Angiogenesis plays an important role in tumour development and proliferation. Increased angiogenesis is associated with worse clinical outcome in ovarian cancer. Here we review the play of bevacizumab in the treatment of ovarian cancer and also other antiangiogenic drugs. In total, to date there are no promising results for most of the reviewed antiangiogenic agents, except those already known for bevacizumab, trebananib, pazopanib, cediranib and nintedanib. Ongoing research will shed more light on this fascinating tumour process and its control.

Keywords: angiogenesis, ovarian cancer

1. Introduction

Approximately 75% of women with ovarian cancer are diagnosed at advanced stages (FIGO stage III/IV), with 15–23 months median global survival and 20% 5-year survival [1].

Although approximately 80% of patients respond to first-line chemotherapy, more than 70% relapse and develop resistance to chemotherapy [2]. This requires the development of more effective treatments to improve survival in advanced disease. This was not achieved by adding a third cytotoxic agent to the standard treatment [3–7], and so the latest research is focused on new molecular targets.

Angiogenesis plays an important role in tumor development and proliferation. Increased angiogenesis is associated with worse clinical outcome in ovarian cancer.

The vascular endothelial growth factor (VEGF) family comprises VEGF-A (known as VEGF), VEGF-B, VEGF-C, VEGF-D, placental growth factor (PGF), VEGF-E, and VEGF-F (Figure 1).

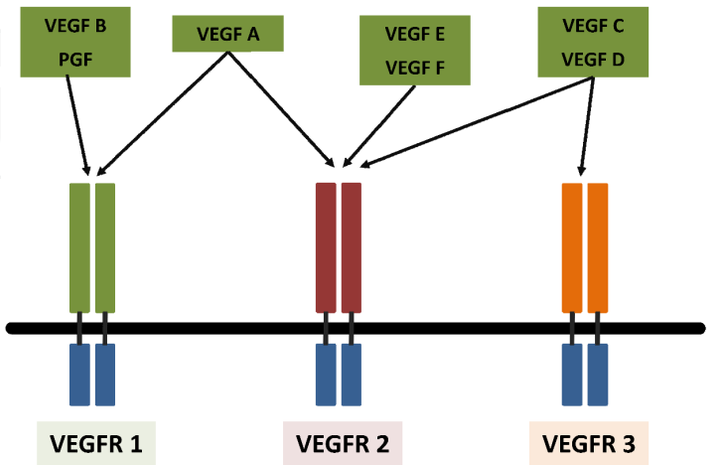

Figure 1. VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, VEGF-F, and PGF bind differentially to receptors VEGFR-1, VEGFR-2, and VEGFR-3.

The relationship between VEGF overexpression, increased angiogenesis, and ovarian cancer development is well established, as well as in peritoneal dissemination and malignant ascites development [8]. Ovarian tumors overexpress several proangiogenic factors such as vascular endothelial growth factor (VEGF), angiopoietin, fibroblast growth factors, platelet-derived growth factors (PDGFs), and proangiogenic cytokines [9].

The most investigated is VEGF, which promotes endothelial cell proliferation and migration for the formation of new blood vessels and increases the permeability of existing blood vessels [10].

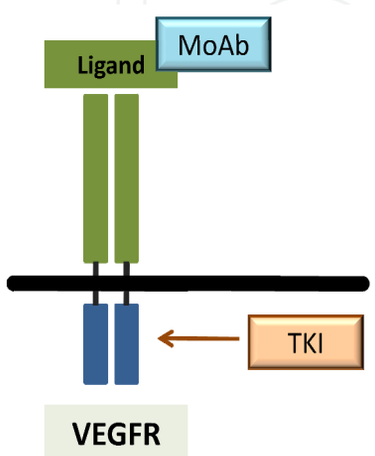

Figure 2. Monoclonal antibodies (MoAb) inhibit VEGF ligand, and TKI inhibits the VEGFR.

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The angiogenesis pathway can be inhibited by two strategies (Figure 2): inhibition of the VEGF ligand with antibodies or soluble receptors and inhibition of the VEGF receptor with tyrosine kinase inhibitors (TKI). Several antiangiogenic drugs have been studied in ovarian cancer in different settings, and we will review them in this chapter.

2. Bevacizumab

Bevacizumab is a recombinant humanized monoclonal antibody that binds to all VEGF isoforms [11]. It has shown its efficacy in different neoplasms, such as colorectal cancer, breast cancer, or kidney cancer.

To date, bevacizumab is the antiangiogenic agent that has shown the best results in the treatment of ovarian cancer.

The first-line efficacy data come from two phase III clinical trials: ICON7 and GOG 218.

The ICON7 clinical trial [12] randomized 1528 women to receive carboplatin (AUC 5 or 6) and paclitaxel (175 mg/m^2) every 3 weeks for 6 cycles, or the same regimen plus bevacizumab (7.5 mg/kg) every 3 weeks during chemotherapy, followed by 12 cycles or until unacceptable toxicity or disease progression. The study included patients with initial (FIGO I/IIA), high-risk (G3 or clear cells), or advanced (FIGO IIB–IV) cancer stage. The primary objective was progression-free survival (PFS) measured by RECIST criteria, and the secondary objectives included overall survival (OS), response to treatment, toxicity, and quality of life. Most of the patients (94%) had good performance status (ECOG Performance Status 0–1). A total of 70% patients were diagnosed at FIGO stage IIIC/IV.

With a median follow-up of 19.4 months, PFS was greater in the group with bevacizumab, and the difference was statistically significant (19.0 months vs. 17.3 months; HR = 0.81 (95% CI = 0.70–0.94); $p = 0.0041$). This difference in PFS was greater in the high-risk-of-progression group (stage IIIC with suboptimal surgery and IV), 15.9 vs. 10.5 months; HR = 0.68 (95% CI = 0.55–0.85); $p < 0.001$).

In the final analysis, with a median follow-up of 49 months, the increase in PFS is maintained in the high-risk-of-progression group, with an increase of 5.5 months (16.0 vs. 10.5 months; HR = 0.73 (95% CI = 0.61–0.88); $p = 0.001$), and there is an increase of 9.4 months in OS in the high-risk-of-progression group (39.7 vs. 30.3 months; HR = 0.78 (95% CI = 0.63–0.97); $p = 0.03$).

The treatment with bevacizumab was associated with an increase in bleeding (especially grade 1 mucocutaneous bleeding), grade 2 (G2) or greater acute hypertension (18% vs. 2%), grade 3 (G3) or higher thromboembolic events (7% vs. 3%), and gastrointestinal perforation (10 cases vs. 3 cases). The quality of life scores measured by the EORTC QLQ-C30 and QLQ-OV28 questionnaires show that continuation of treatment with bevacizumab appears to be associated with a small but clinically significant decline in quality of life compared to standard chemotherapy, so PFS and quality of life over the period of time in question have to be considered when treatment decisions are made [13].

The GOG 218 clinical trial [14] randomized 1873 women with stage III (incompletely resected) or stage IV epithelial ovarian cancer after cytoreduction surgery in three groups. In the three groups, the patients received carboplatin AUC 6 and paclitaxel 175 mg/m^2 every 3 weeks for 6 cycles and the study treatment. In the first arm (placebo arm), patients received placebo every 3 weeks from cycle 2 to cycle 22; in the second arm (bevacizumab initiation), patients received bevacizumab 15 mg/kg every 21 days from cycle 2 to cycle 6 followed by placebo from cycle 7 to cycle 22; in the third arm (bevacizumab throughout), patients received bevacizumab at the same dose from cycle 2 to cycle 22. The primary objective was PFS according to RECIST, CA-125, or clinical criteria. The secondary objectives included OS, safety, and quality of life. Once again, most of the patients (93%) maintained an ECOG PS 0-1. The group had a relatively poor prognosis, as 40% had stage III disease with residual disease greater than 1 cm and 26% had stage IV disease.

With a median follow-up of 17.4 months, the arm with bevacizumab (bevacizumab throughout) compared with the standard chemotherapy arm (placebo arm) showed a statistically significant increase in PFS (14.1 vs. 10.3 months; HR = 0.717 (95% CI = 0.625–0.824); $p = 0.0001$). In the bevacizumab initiation group, there was no increase in PFS (11.2 vs. 10.3 months; HR = 0.908 (95% CI = 0.759–1.040); $p = 0.080$). OS was similar in the three groups: 39.3, 38.7, and 39.7 months for the placebo arm, bevacizumab initiation group, and bevacizumab-throughout group, respectively, with no statistically significant differences.

G2 or higher hypertension was the only toxicity that was more common in a statistically significant manner in the bevacizumab groups than in the placebo arm (22.9% in bevacizumab throughout vs. 7.2% in the placebo arm). There were no differences in other toxicities such as gastrointestinal perforation or fistula, G3 or higher proteinuria, G4 neutropenia, febrile neutropenia, or venous or arterial thrombosis.

The main open questions left by these two trials are dosage and duration of treatment with bevacizumab. The dosage recommendation is to use the 15 mg/kg dose, which is in the summary of product characteristics, although benefit with bevacizumab is shown in a 7.5–15 mg/kg dose range [14]. As for treatment duration, both studies show that the widest separation of the PFS curves is found at 12 months in ICON7 and 15 months in GOG 218, which is at the termination of the bevacizumab. Thus, it is advisable to maintain bevacizumab treatment up to 15 months and to consider extending this period.

Two phase II studies showed the activity of bevacizumab in patients pretreated with chemotherapy. Those studies included platinum-sensitive and platinum-resistant patients.

A first study conducted by the GOG, GOG 170D, evaluated the efficacy of bevacizumab at 15 mg/kg every 3 weeks in 62 patients with advanced ovarian cancer after having received one or more treatment lines for advanced disease and found a 21% response rate and 10.3 months median response duration, with no intestinal perforation [15].

A second study in 70 patients evaluated the addition of cyclophosphamide (50 mg orally per day) to bevacizumab (10 mg/kg every 2 weeks) in patients who had received one to three previous chemotherapy lines and found a 24% response rate, 56% of patients relapse-free at 6 months, and 5.7% suffering intestinal perforations [16].

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Subsequently, the OCEANS trial was initiated as a phase II study; after a safety review focused on intestinal perforations, it was converted to a phase III trial. Then 484 patients with platinum-sensitive recurrent ovarian cancer were randomized to receive carboplatin/gemcitabine for 6–10 cycles with bevacizumab (15 mg/m² every 3 weeks) or placebo until disease progression or unacceptable toxicity. Progression was documented by radiological (RECIST 1.0) or clinical criteria but not by CA-12.5 elevations. The primary objective was PFS determined by the investigators. The secondary objectives included response rate and OS. It also included an analysis of the primary objective by an independent committee.

The addition of bevacizumab to carboplatin/gemcitabine showed a median increase in PFS of 12.4 months versus 8.4 months (HR = 0.484, 95% CI = 0.388–0.605). These figures were repeated when evaluated by an independent committee (12.3 months vs. 8.6 months, $p = 0.0001$). This increase benefited all subgroups irrespective of age, ECOG, presence of cytoreduction surgery, time since last recurrence, and CA-12.5 levels. The secondary objectives also showed a 21.1% increase in response rate in the bevacizumab arm (response rate 78.5% vs. 57.4%, $p = 0.0001$). At cutoff date with a small number of events, there were not statistically significant differences in median survival, 35.2 months in the placebo arm and 33.3 months in the bevacizumab arm.

The most relevant G3 toxicities in the bevacizumab arm were proteinuria (0.9% vs. 8.5%) and hypertension (0.4% vs. 17.4%). No gastrointestinal perforation was documented during the study [17].

This study is the first randomized trial to describe the role of bevacizumab in platinum-sensitive disease. In this context, there is an ongoing study, GOG 213, which is evaluating the addition of bevacizumab to carboplatin and paclitaxel in platinum-sensitive relapse, with OS as its primary objective [18].

Two more studies are also evaluating bevacizumab in this context. The MITO-16/Mango OV-2BBP study is evaluating the addition of bevacizumab versus placebo to a carboplatin regimen with gemcitabine or pegylated liposomal adriamycin or paclitaxel in platinum-sensitive disease. Its primary objective is PFS, and OS is one of its secondary objectives [19]. The AGO/OVAR 2.21 study aims to show superiority in PFS for the carboplatin regimen with pegylated liposomal adriamycin and bevacizumab versus carboplatin with gemcitabine and bevacizumab [20].

There is a single phase II study in platinum-resistant disease; 44 patients who had received two or three previous treatment lines that included topotecan or liposomal anthracyclines were treated with bevacizumab, finding a 15.9% response rate and 27.8% of patients disease-free at 6 months. Perforations were found in a large percentage of patients, 11.4%, leading to its premature closure [21].

The AURELIA trial tested the addition of an antiangiogenic drug to chemotherapy in platinum-resistant disease. In this trial, 361 women with platinum-resistant ovarian cancer were randomized to receive single-agent chemotherapy (paclitaxel, pegylated liposomal doxorubicin, or topotecan) or the same chemotherapy with bevacizumab (10 mg/kg every 2 weeks or 15 mg/kg every 3 weeks in the regimen that included topotecan every 3 weeks). The therapeutic regimen was to be decided by the investigators, permitting any of those mentioned above. On

the basis of the high rate of gastrointestinal perforations found in the aforementioned phase II study, the inclusion of both platinum-resistant patients who had received at least two lines of chemotherapy and platinum-refractory patients (progression while being treated with platinum) was ruled out, as well as patients with a history of intestinal obstruction (including subocclusive cases), intestinal perforation, abdominal fistula, intra-abdominal abscess, rectum or sigmoid colon affected by the disease, intestinal affectation by CT, or radiotherapy on the abdomen or pelvis. Its primary objective was PFS evaluated by the investigator. The secondary objectives included radiological response rate according to RECIST 1.0 criteria and CA-12.5, OS, safety, tolerability, and quality of life.

PFS was greater in the bevacizumab arm, with 6.7 months versus 3.4 months (HR = 0.42, $p < 0.001$), showing its efficacy in all the subgroups analyzed. There was also a greater response rate (27.3% in the bevacizumab arm vs. 11.8% in the placebo arm, $p = 0.001$) according to radiologic criteria and also a greater CA-12.5 serologic response rate, 11.6% in the placebo arm and 31.8% in the bevacizumab arm. There were no differences in OS (HR = 0.85; 95% CI = 0.66–1.08; $p = 0.174$). This finding can possibly be explained by the crossover in 40% of the patients assigned to the chemotherapy arm.

Toxicity in the bevacizumab arm included greater proteinuria and G3 hypertension. There was also a 2.2% incidence of gastrointestinal perforations. Overall, this is the first study to evaluate that the addition of an antiangiogenic to chemotherapy has an impact on PFS [22].

Another question to be investigated is the combination of bevacizumab with other strategies that have shown good results in the first-line treatment of ovarian cancer, such as intense doses of chemotherapy or intraperitoneal chemotherapy.

The combination of bevacizumab with intense-dose chemotherapy was studied in the OCTAVIA phase II clinical trial [23]. The primary objective was PFS according to RECIST criteria; the secondary objectives included the overall response rate, response duration in responder patients, OS, progression defined by CA-125, safety, and tolerability. The study included 189 patients diagnosed with stage I/IIA (grade 3/clear cells) or stages IIB–IV (any grade) ovarian cancer who underwent surgery. The patients received 6–8 cycles of bevacizumab (7.5 mg/kg, day 1 every 3 weeks) with weekly paclitaxel (80 mg/m^2, days 1, 8, and 15 every 3 weeks) and carboplatin (AUC 6, day 1 every 3 weeks); bevacizumab continued at the same dose as a single agent every 3 weeks up to a total of 17 cycles (1 year). A PFS of more than 18 months was considered to be clinically significant. Most of the patients were stage IIIC/IV (74%). With a median follow-up of 26.3 months, PFS was 23.7 months (95% CI = 19.8–26.4). PFS in the patients with stage III disease and >1.0 cm of residual disease after debulking surgery, or with stage IV disease, was 18.1 months. The response rate by RECIST in the 91 patients with measurable disease was 84.6% (95%CI = 75.5–91.3%), with 30.8% (95% CI = 21.5–41.3%) of complete responses. OS at 1 and 2 years was 97.8% and 92.1%, respectively. The most common grade ≥ 3 undesirable effects related to bevacizumab were hypertension (4.2%) and thromboembolic events (6.3%). In the study update [24], the limited number of events (17% of patients) for the planned final study analysis means that the OS results would be premature.

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The combination of bevacizumab and chemotherapy at intense doses was also studied in the phase III GOG 262 clinical trial, which compared the standard chemotherapy regimen with carboplatin and paclitaxel every 3 weeks versus carboplatin every 3 weeks and paclitaxel weekly. The patients could also receive bevacizumab at the investigator's discretion [25].

The combination of bevacizumab and intraperitoneal chemotherapy is being studied in the GOG 252 phase III clinical trial [26].

3. Trebananib

Angiopoietins 1 and 2 (Ang1 and Ang2) are ligands of the Tie2 receptor, which is expressed in endothelial and some hematopoietic and lymph cells, mediating in vascular remodeling; it has a different signaling pathway from VEGF.

Trebananib (AMG 386) is a peptibody that inhibits angiopoietin 1 and 2, preventing interaction with the Tie2 receptor; it shows antiangiogenic effects in preclinical ovarian cancer models.

Having shown its safety and efficacy when administered intravenously in monotherapy at a maximum dose of 30 mg/kg weekly in phase I studies [27], and increasing PFS in phase II studies that used a dose of 10 mg/kg [28], it can be inferred that this benefit will be even greater using higher doses (such as 15 mg/kg), as doses of up to 30 mg/kg are tolerated without an increased toxicity.

The phase III study (TRINOVA-1) [29] examines the addition of trebananib to weekly paclitaxel versus weekly paclitaxel, showing a significant increase in PFS. It is a randomized, double-blind, placebo-controlled study. The inclusion criteria are as follows: woman over 18 years of age with histological diagnosis of epithelial ovarian cancer; primary peritoneal cancer or Fallopian tube cancer; having previously received chemotherapy based on a platinum regimen and progressed to 2 treatment lines; performance status 0–1; correct hematological, hepatic, and renal function; correct blood pressure figures (accepting appropriate control by taking antihypertensive treatment); and life expectancy of 3 months or more. Platinum-sensitive patients (platinum-free interval of more than 12 months) and platinum-refractory patients (disease recurrence or progression in the first 6 months or less after starting first-line platinum-based chemotherapy) were excluded and were also excluded in other histologies such as borderline, mucous and clear-cell tumors, patients who had presented a thromboembolic or hemorrhagic event in the last 12 months, unhealed wound, ulcer, fracture or infection, metastasis in the central nervous system, presence of grade 1 or higher neuropathy, presence of hepatitis B or C virus, and HIV infection. A total of 912 patients were randomized to receive in a 1:1 proportion of placebo and paclitaxel weekly or trebananib and paclitaxel weekly. The patients were stratified by platinum-free interval (0–6 months, or more than 6 months but less than 12), geographic region, and presence of radiologically measurable disease or not.

Patients received 80 mg/m² of paclitaxel IV (3 weeks on and 1 week off) and placebo or 15 mg/kg i.v. trebananib weekly, until progression according to RECIST 1.1 criteria, toxicity, or withdrawal of consent. A reduction in the dose of paclitaxel was allowed, but not of the placebo

or trebananib. If necessary due to toxicity (e.g., edema), the drug was suspended until the toxicity was resolved, and it was definitively suspended if the delay due to toxic effects lasted more than 28 days. The patients were reassessed every 8 weeks by computerized tomography (CT) of the chest, abdomen, and pelvis. The tumor marker (specific cancer antigen (CA-125)) did not contribute to the assessment of disease response and progression. The primary objective was PFS, and the secondary objectives are survival and response rate.

The groups comprised 458 patients in the control arm (paclitaxel–placebo) and 461 in the experimental arm (paclitaxel–trebananib); median patient follow-up was 10.1 months.

Median PFS was greater in the group that received trebananib (5.4 vs. 7.2 months, HR = 0.6, 95% CI = 0.57–0.77), $p < 0.0001$, with all patient subgroups benefiting. The response rate by RECIST was greater in the experimental group (30% vs. 38%), and this difference was greater according to CA-125 levels, with a significant reduction of this (49% vs. 56%, $p = 0.03$). The interim overall OS analysis showed no differences between the groups (17.3 months vs. 19 months, HR = 0.86, 95% CI = 0.69–1.08, $p = 0.19$). Grade 3 or more side effects were described in 28% of the control subjects (paclitaxel–placebo) and 34% of the experimental group (paclitaxel–trebananib). The most common adverse reaction to the study drug was edema, which even became a cause of suspension of the treatment. Cases of hypertension, bleeding, pulmonary and arterial thromboembolism, proteinuria, and gastrointestinal perforations were also described. Trebananib added to paclitaxel for the treatment of recurring ovarian cancer significantly increases PFS versus placebo.

There are 2 phase III studies in which trebananib is added to pegylated liposomal doxorubicin (TRINOVA-2) [30] and trebananib in the first line associated to carboplatin–paclitaxel (TRINOVA-3) [31], although no conclusions have yet been reached.

4. Pazopanib

Pazopanib is an orally administered multikinase inhibitor of vascular endothelial growth factor receptor (VEGFR)-1/-2/-3 and of platelet-derived growth factor receptor (PDGFR)-α/-β and of c-Kit.

This drug has been approved for the treatment of metastatic renal cancer and soft tissue sarcomas.

Its role in several combinations has been analyzed, initially in a phase I/II study in combination with carboplatin and paclitaxel, after surgery, in order to increase the disease-free interval. This open-label phase I/II study was conducted to evaluate the safety and efficacy of paclitaxel 175 mg/m^2 plus carboplatin (AUC 5 (group A) or AUC 6 (group B)) once every 3 weeks for up to six cycles, with either 800 or 400 mg per day of pazopanib. Dose-limiting toxicities (DLT) were detected in two of the first six patients included in the pazopanib 800 mg plus paclitaxel 175 mg/m^2 plus carboplatin AUC 5 arm. There was also DLT in 2 of these first 6 patients at the lowest dosage level (pazopanib 400 mg plus paclitaxel 175 mg/m^2 plus carboplatin AUC 5).

Two of the 4 DLTs were gastrointestinal perforations, and severe myelotoxicity was reported in 6 of the 12 patients, leading to suspension of the study [32].

Subsequently, its use in monotherapy was investigated in a multicenter, nonrandomized, phase II study (VEG104450; NCT00281632) in patients with recurrence of epithelial ovarian or Fallopian tube cancer or primary peritoneal carcinoma who had presented complete response of CA-125 levels with platinum-based chemotherapy regimens. At relapse, patients with CA-12 levels reaching ≥42 U/mL (>2 × ULN) were treated with pazopanib 800 mg/day until progression or toxicity. Inclusion criteria were ECOG 0–1 and good hepatic and renal function. The primary objective was the response rate (determined by normalization of CA-125 levels or not), and the secondary objectives were overall response (measured as biochemical, radiological, and physical response) and PFS. Eleven out of 36 patients (31%) presented CA-125 response with a mean duration of 113 days; the overall response rate in patients with measurable disease was 18%. The most common adverse events leading to suspension of the treatment were transaminase elevation, with only 1 case of grade 4 edema [33].

This led to the study of the role of pazopanib as maintenance therapy in ovarian cancer patients who had not progressed during first-line chemotherapy. A total of 940 patients were included, with epithelial ovarian, Fallopian tube, or primary peritoneal cancer; FIGO stages II–IV, with no evidence of progression after surgery; and 6 cycles of platinum plus taxane chemotherapy. They were randomized 1:1 to receive pazopanib 800 mg once daily or placebo for 24 months. The primary objective was PFS by RECIST 1.0 criteria. It was shown that maintenance therapy with pazopanib increased PFS compared with placebo: 17.9 vs. 12.3 months, HR = 0.77; 95% CI = 0.64–0.91; $p = 0.0021$. Grades 3 and 4 adverse events were hypertension (30.8%), neutropenia (9.9%), transaminase elevation (9.4%), diarrhea (8.2%), fatigue (2.7%), thrombocytopenia (2.5%), and palmoplantar erythrodysesthesia (1.9%) in the pazopanib arm. Suspension of the treatment was significantly greater in the pazopanib arm (33.3%) versus placebo (5.6%) [34].

Maintenance therapy with pazopanib leads to an improvement in the median PFS of 5.6 months (HR = 0.77), with a 23% risk reduction for 2 years in women with FIGO stages II–IV who had not progressed to the first line of treatment. An increase in OS has not yet been shown, so the use of pazopanib is not currently recommended for this clinical situation.

5. Nintedanib

Nintedanib (BIBF 1120) is a powerful triple angiokinase inhibitor. It inhibits VEGFR-1, VEGFR-2, and VEGFR-3; PDGFR α and β; and FGFR-1, FGFR-2, and FGFR-3. The first data, obtained in a phase I study, in combination with carboplatin and paclitaxel administered twice a day, with doses of 100–250 mg, in 22 patients with locally advanced or recurring metastatic ovarian cancer, indicated that the maximum tolerated dose was 200 mg/12 h. Higher doses were related to higher significant gastrointestinal toxicity in the form of diarrhea, alanine aminotrnasferase (ALT) and aspartate aminotransferase (AST) elevation, and hematological toxicity, basically in white blood cells [35].

Nintedanib 250 mg/12 h was studied in a phase II randomized trial versus placebo in 83 women with recurring (in second or subsequent lines) ovarian cancer who had responded to chemotherapy but presented high risk of relapse. The primary objectives were PFS, OS, and toxicity. The patients received at least 9 cycles of the treatment or placebo, continuing until disease progression (unless the patient withdrew from the study). PFS at 36 weeks was 16.3% versus 5%, with HR = 0.65, 95% CI = 0.42–1.02, and $p = 0.06$. The reported G3/4 adverse events were similar in both arms (34.9% vs. 27.5%, respectively, $p = 0.49$), but in the nintedanib group, there was greater gastrointestinal toxicity in the form of diarrhea, nausea, and vomiting ($p < 0.001$) versus placebo. Likewise, there was greater G3/4 hepatotoxicity with nintedanib versus placebo (51.2% vs. 7.5%, $p < 0.001$ [36]).

There is currently an ongoing phase III, randomized, double-blind trial (AGO-OVAR 12/LUME) in first-line treatment of locally advanced or metastatic ovarian cancer (stages IIB–IV) that compares the combination of carboplatin, paclitaxel, and nintedanib 200 mg/12 h and maintenance with nintedanib for 120 weeks versus the same chemotherapy regimen with placebo and maintenance with placebo, also for 120 weeks. A total of 1366 patients have been included, and to date, it has reported an advantage in PFS in favor of the arm with the combination of nintedanib with chemotherapy and subsequent maintenance (17.3 months vs. 16.6 months), HR = 0.84 and 95% CI (0.72–0.98), $p = 0.0239$, versus placebo [37].

Another phase II trial is being conducted with this drug in recurrent or persistent disease or disease already treated with bevacizumab [38].

6. Cediranib

Cediranib (AZD 2171) is a tyrosine kinase agent with antiangiogenic activity, blocking the VEGF receptor (VEGFR 1, VEGFR2 and VEGFR3) and c-Kit.

Although women were included in the phase I study of the drug, they did not have ovarian cancer. It was found that the dose was tolerable up to 45 mg/24 h [39]. The phase II studies used both this and lower doses.

At the 2008 ASCO meeting, Hirte et al. presented data from 60 patients with relapse of ovarian or Fallopian tube carcinoma or peritoneal carcinomatosis treated with cediranib, showing that the 30 mg/24 h dose was well tolerated and active in this patient group [40].

In 2009, the results of a phase II study were published, including 46 patients with platinum-sensitive and platinum-resistant relapse of ovarian carcinoma, Fallopian tube carcinoma, or peritoneal carcinomatosis. The patients received cediranib 45 mg/24 h until progression, intolerable toxicity, or withdrawal of consent. After the toxicity seen in 11 patients, the dose was reduced to 30 mg/24 h. More than 20% of the patients presented G3 adverse events, the most common being hypertension (46%), fatigue (24%), and diarrhea (13%); 8.7% of them presented G4 adverse events [41].

The randomized, double-blind ICON 6 study compares a platinum-based chemotherapy arm with cediranib (concurrent), another similar arm (concurrent) plus continuation (for 18 months

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or until progression) of maintenance cediranib, and the same chemotherapy regimen with placebo in relapse of platinum-sensitive disease. The preliminary data (60 women enrolled) show benefit with the combination of cediranib and its maintenance versus the arm in which placebo was added, both in PFS (11.4 vs. 9.4 months, HR = 0.68, $p = 0.0022$) and in OS (20.3 vs. 17.6 months, HR = 0.70, $p = 0.049$). The dose of cediranib had to be reduced during the study to 20 mg/24 h due to toxicity and reduced adherence to treatment [42]. The results update at the 2013 ESMO congress show greater benefit in PFS (12.5 vs. 9.4 months, HR = 0.57, $p = 0.00001$) and a benefit of 2.7 months in OS in the cediranib maintenance group. It is the first oral antiangiogenic agent to date to show benefit in terms of OS. The most common adverse events were diarrhea, nausea, and fatigue [43].

Cediranib was combined with olaparib in a randomized phase II study versus olaparib in monotherapy in women presenting platinum-sensitive relapse of ovarian cancer associated with BRCA mutation. The patients received olaparib 200 mg/24 h and cediranib 30 mg/24h in the combination arm and olaparib 400 mg/24 h in the monotherapy arm. PFS was 17.7 months with the combination and 9 months with olaparib in monotherapy, HR = 2.9 and 95% CI (1.5–5.6), $p = 0.001$. There were 2 complete and 21 partial responses, 56% objective responses with the monotherapy, and 3 complete, 33 partial, and 84% objective responses in the experimental group. The incidence of G3/4 adverse events was 70% with the combination and only 7% with olaparib; the most common were fatigue, diarrhea, and hypertension [44].

7. Aflibercept

Aflibercept is a recombinant fusion protein, also called VEFG-Trap, that binds to and neutralizes all forms of VEGF-A and VEGF-B and inhibits placental growth factor (PGF) activation. In several preclinical models, it was seen to inhibit tumor growth and metastasis formation, and another study showed evident reduction in ascites and tumor size in murine models that developed human ovarian tumors [45].

Various phase II studies have tested the activity of this drug in ovarian cancer. In the first of these, aflibercept is combined with docetaxel in 49 patients with platinum-resistant relapse with a maximum of two previous chemotherapy regimens. It was administered at a dose of 6 mg/kg until progression or intolerable toxicity. There was a 54% response rate; 10 cases presented complete response, and relapse was not detected in 4 of them at 1-year posttreatment (range 5–22 months). Median PFS was 6.2 months, and OS was 24.3 months [46].

Gotlieb et al. published a multicenter, randomized, double-blind phase II study that included 55 patients with relapse of platinum-resistant ovarian cancer, who had received a median of at least 4 previous lines (range 2–12) that compared aflibercept 4 mg/kg every 14 days versus placebo. The patients were stratified according to the need for paracentesis in 2 periods, ≤2 weeks and >2 weeks. The primary objective was time to new paracentesis. Time to paracentesis from randomization was significantly greater in the aflibercept arm (55.1 vs. 23.3 days), and in two patients, new paracentesis was not required until 6 months later. There was more toxicity in the form of dyspnea (20% vs. 8%) in the aflibercept arm and also intestinal perfo-

ration (3 patients vs. 1). However, there was more fatigue or asthenia (13% vs. 44%) and more dehydration (10% vs. 12%) with placebo [47].

Similar to the previous study, and with the same doses, another multicenter group tried to answer the same question in another phase II study: the utility of aflibercept in control of gynecologic tumor ascites. They included 16 platinum-resistant and very pretreated patients, with similar results obtained [48].

These last two studies show the activity and effect of the drug in reducing the need for paracentesis, although a small risk of intestinal perforation in peritoneal carcinomatosis cannot be ruled out. It should only be used after thoroughly evaluating the risk/benefit ratio in each specific case.

8. Sorafenib

Sorafenib is a multikinase inhibitor with activity on different tyrosine kinase receptors, including VEGFR-2 and VEGFR-3, PDGFR-β, c-Kit, and Flt-3 receptor and the v-raf oncogene.

Limited activity of this drug has been shown in 71 women who presented ovarian tumor relapse within 12 months of completing platinum treatment (after one or two previous regimens). The primary objectives were PFS at 6 months and safety; the secondary objectives were percentage response and duration of PFS and OS. The dose used was 400 mg/12 h. Efficacy was evaluated only in the 59 patients with measurable disease: 14 women (24%) presented PFS of at least 6 months. Partial response was obtained in 2 women, stabilization in 20, while 30 patients presented progression; response could not be measured in 7 patients. The most common G3/4 adverse events were as expected (rash, hand/foot syndrome, gastrointestinal, and metabolic and, to a lesser extent, cardiovascular and pulmonary toxicity) [49].

A Canadian group from the Princess Margaret Hospital studied sorafenib, at the same doses, in combination with gemcitabine weekly in a phase II trial in 43 pretreated patients with platinum-resistant relapse; 2 of them presented partial response, and the disease remained stable for at least 6 months in 10 of them. However, the proportion of responses was only 4.7%. The most common G3/4 events were hematological (28% lymphocytopenia and 26% neutropenia), leading to significant delays in the administration of the therapeutic regimen [50].

German investigators tested the addition of the drug to the carboplatin–paclitaxel combination in the neoadjuvant context in patients with large disease volume and ascites. This phase II trial included only 4 patients, as it was stopped due to severe G3/4 toxicity, largely cardiovascular [51].

The combination with topotecan in platinum-resistant patients was also evaluated. There was important hematologic toxicity and G3/4 toxicity in the form of transaminase elevation [52].

The possibility of continuation or maintenance treatment was evaluated in women after they completed the first-line treatment with carboplatin and paclitaxel and had presented complete response. Two hundred and forty-six patients were included and randomized to receive

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Sorafenib 400 mg/12 h or placebo until progression, intolerable toxicity, or withdrawal of consent. The patient was withdrawn from the study if there was more than a 30-day delay in the administration of the treatment or if more than two dose reductions were required. The primary objectives were to evaluate the efficacy and safety of this approach. There were no differences between the two groups in PFS, with a trend toward better results in the placebo arm, and there were clearly more adverse events with sorafenib, with a toxicity profile similar to that found in previous studies. The conclusions of the study were that maintenance therapy with this drug could not be recommended [53].

The combination of paclitaxel, carboplatin, and sorafenib was investigated in first-line treatment for metastatic disease in women with stages III and IV. After two treatment cycles, the patients with stabilization or partial response continued the chemotherapy for six cycles, and sorafenib was maintained for 52 weeks; 85 patients were included. Efficacy was similar in proportion of responses, PFS, and 2-year survival. The addition of sorafenib clearly increased toxicity: EPP, mucositis, and HT, and so its use was not recommended [54].

9. Sunitinib

Sunitinib is also another multikinase inhibitor that binds to VEGF, PDGF, c-Kit, and Ftl-3. As with sorafenib, the response rates of therapy with this drug are low.

In a phase II trial that included 30 women with platinum-sensitive (73%) and platinum-resistant (27%) relapse who had received one or two previous lines, treated with the standard 50 mg/day dose for 4 weeks and 2 weeks of rest, there was one partial response and 16 stabilizations [55].

In another phase II study with 73 platinum-resistant patients who had received three or more previous lines, they were randomized to receive sunitinib at standard dose or 37.5 mg/day continually. There were differences in median PFS in favor of the standard administration (4.8 vs. 2.9 months) but not in OS (13.6 vs. 13.7 months). The pattern and the frequency of adverse events were similar in the two groups and as expected: fatigue, cardiovascular and gastrointestinal toxicity, hematological alterations, and hepatic function disorders [56].

The continuous administration of 37.5 mg/day was also evaluated in another Dana–Farber phase II study in 18 platinum-resistant patients, continuing to find a response (partial and complete) rate of around 8% and median PFS of just 10 weeks. There was also considerable toxicity in the form of hypertension and gastrointestinal events [57].

10. Imatinib mesylate

Imatinib belongs to the tyrosine kinase inhibitor family; it prevents PDGF from binding to its receptor and prevents the triggering of the AKT intracellular signaling cascade responsible for tumor growth and metastatic dissemination.

Its possible therapeutic effect on platinum-resistant ovarian tumors after progression to other treatments has also been studied. Most studies treated patients at the standard dose of 600 mg/day after selecting them according to immunohistochemical c-Kit expression. They included a small number of patients, and the drug was tested in monotherapy [58, 59] and in combination with docetaxel [60] or paclitaxel [61]. Few responses were obtained (0–2%), primarily obtaining stabilizations, with repeated dose reductions required due to toxicity in the form of edemas, gastrointestinal, or hematological adverse events.

More recently, Anderson's work found that there was no correlation between responses in platinum-refractory patients who had progressed to taxanes and expression of the aforementioned biomarkers. The efficacy and toxicity results were similar to those of previous studies, concluding that it was not an active treatment in this group of patients [62].

11. Vandetanib

Vandetanib (ZD6474) also belongs to the oral tyrosine kinase inhibitor family and inhibits VEGFR-2 and VEGFR-3, EGFR, and RET.

In a phase I/II study in combination with pegylated liposomal doxorubicin (50 mg/m², day 1/28 days), at a dose of 100 mg/24 h in platinum-resistant patients, 14 patients were included and few responses (around 10%) were found, with close to 40% stabilizations, but significant toxicity led to discontinuation of the treatment in nearly 30% of patients [63].

Combined with concomitant docetaxel, the SWOG S0904 study compared it to docetaxel in monotherapy. A total of 131 patients were included and randomized to one of the arms; no benefit was found from the addition of vandetanib in PFS; there was G4 hematological toxicity in nearly 30% of the included women [64].

12. Ramucirumab

Ramucirumab, or IMC-1121B, is an Ig G1 humanized monoclonal antibody that has affinity for the extracellular domain of VEGFR-2 and prevents VEGF from binding to its ligands, thus inhibiting endothelial cell proliferation and migration and new vessel formation.

A multicenter study with 70 women with platinum-resistant relapse in 75% of them only obtained 5% partial responses, nearly 60% stabilizations, and 25% 6-month PFS (both primary end points); ramucirumab was not found to be particularly active in this context [65].

13. Zibotentan

Zibotentan or ZD4054 is an oral ET-A receptor antagonist that is involved in activation of endothelin growth, and thus in cell proliferation and tumor invasion and migration.

In a multicenter study that combines the drug (at a dose of 10 mg/24 h) with carboplatin and paclitaxel versus the same chemotherapy and placebo, no benefit was found in PFS, percentage of responses, or reduction of CA-125 in women with platinum-sensitive disease. The toxicities most commonly found with the drug were anemia and neutropenia, alopecia, nausea, and headache in nearly 50% of patients [66].

In total, to date there are no promising results for most of the reviewed antiangiogenic agents, except those already known for bevacizumab, trebananib, pazopanib, cediranib, and nintedanib. Ongoing research will shed more light on this fascinating tumor process and its control.

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