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REVIEW ARTICLE

First-Line and Maintenance Therapy for Ovarian Cancer: Current Status and Future Directions

Antonio González-Martín · Luisa Sánchez-Lorenzo · Raquel Bratos · Raúl Márquez · Luis Chiva

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Abstract Paclitaxel and carboplatin combination chemotherapy has remained the standard of care in the frontline therapy of advanced epithelial ovarian carcinoma during the last decade. Maintenance chemotherapy or immunotherapy has not been proven to impact on overall survival and only one clinical trial that explored the administration of monthly paclitaxel for 1 year showed a benefit in terms of progression-free survival (PFS), but at the cost of maintained alopecia and increased peripheral neuropathy. This scenario may be changing with the incorporation of targeted therapy to the frontline therapy of ovarian cancer. In particular, anti-angiogenic therapy has been identified as the most promising targeted therapy, and the addition of bevacizumab to first-line chemotherapy followed by a maintenance period of bevacizumab in monotherapy has shown to prolong PFS. This was considered the proof of concept of the value of anti-angiogenic therapy in the frontline of ovarian cancer, and the results of two additional clinical trials with anti-angiogenic tyrosine-kinase inhibitors have shown results in the same direction.

A. González-Martín (✉) · R. Bratos · R. Márquez
Medical Oncology Department, MD Anderson Cancer Center, C/Arturo Soria 270, 28033 Madrid, Spain
e-mail: agonzalezm@mdanderson.es

L. Sánchez-Lorenzo
Medical Oncology Service, Hospital Central de Asturias, C/Celestino Villamil s/n, 33006 Oviedo, Spain

L. Chiva
Gynecologic Oncology Department, MD Anderson Cancer Center, Madrid, Spain

1 Introduction

Ovarian cancer is still the most common cause of death for gynaecologic cancer in the Western world, and the fifth leading cause of death for cancer mortality in woman [1]. Ovarian cancer is no longer considered a single disease, as it has been described as having several histological subtypes with different morphology, molecular alterations and outcome. Current standard frontline therapy is still the same for all epithelial subtypes and consists of upfront surgery followed by chemotherapy based on a combination of platinum and paclitaxel [2, 3]. If not possible, after adequate evaluation by a well-trained multidisciplinary team, neoadjuvant treatment may be taken into consideration.

Surgery is an essential part of the treatment of advanced ovarian cancer. The main objective of primary surgery is to obtain a complete resection of all macroscopically visible disease. Nowadays, the term 'optimal debulking' or 'optimal cytoreduction' is reserved for those situations in which no macroscopic residual disease has been left after surgery [3]. In fact, the main prognostic factor in patients with advanced ovarian cancer is the amount of residual disease after surgery, as there is a clear and significant difference in overall survival (OS) in patients with optimal cytoreduction (no macroscopic residual disease) in comparison with those with residual disease [4]. For this reason, well-trained and specialized surgical teams should operate on patients with advanced ovarian cancer as it has been demonstrated that the outcome of the patients depends also on the skills and experience of the surgeons [5].

Investigational anti-angiogenic agents are being studied as maintenance therapy in combination with chemotherapy or as single agents in advanced, recurrent and metastatic epithelial ovarian cancer (EOC). The purpose of this article

is to review the current status of first-line and maintenance treatment of ovarian cancer, focusing particularly on the growing number of new molecular-targeted therapeutics in EOC that have demonstrated some efficacy, and discussing some of the ongoing trials.

2 First-Line in Ovarian Cancer: Current Status

The combination of paclitaxel 175 mg/m^2 and carboplatin area under the curve (AUC) 5 or 6 administered intravenously every 3 weeks has been the standard of care in frontline therapy of EOC during the last 15 years [6]. In the mid 1990s, two large, randomized clinical trials demonstrated that the combination of paclitaxel and cisplatin was superior to the regimen of cisplatin and cyclophosphamide [7, 8]. Later on, another three randomized clinical trials confirmed that the substitution of cisplatin by carboplatin in combination with paclitaxel had the same efficacy but a better safety profile and convenience of administration [9–11]. Unfortunately, median time to progression is not fully satisfactory, with a range of 12–18 months depending on the residual disease after surgery, and a 5-year OS of <35 %.

Since the end of the 1990s, several chemotherapy-based strategies have tried to improve the outcome of patients with advanced ovarian cancer. However, neither the substitution of paclitaxel by another drug, such as docetaxel or pegylated liposomal doxorubicin (PLD) [12, 13], or the addition of a third drug to the paclitaxel-carboplatin doublet in the form of triplet or sequential doublets were able to obtain better results [14].

Two different strategies consisting of a change in the route of administration of platinum by intraperitoneal delivery, or the schedule of administration of paclitaxel in a dose-dense regimen of weekly administration, have been shown to improve the outcome of patients with advanced ovarian cancer. However, the results of both strategies are still controversial and have not been widely adopted as standard therapy.

Intraperitoneal chemotherapy consists of the administration of part of the chemotherapy, usually the cisplatin, directly in the abdominal cavity. This approach has a solid pharmacokinetic background as the concentration of the drug obtained in the peritoneal cavity is much higher than when it is administered intravenously. For example, the concentration of cisplatin is tenfold higher after intraperitoneal administration than intravenous administration. The GOG-172 trial compared the administration of an intravenous regimen of paclitaxel and cisplatin every 3 weeks with a regimen that included intravenous paclitaxel on day 1, intraperitoneal cisplatin on day 2 and intraperitoneal paclitaxel on day 8, with cycles repeated every 3 weeks, in patients with stage III disease and macroscopic residual disease no larger than 1 cm [15]. This trial obtained a clear benefit in OS in favour of the intraperitoneal arm (65.6 vs. 49.7 months; $p = 0.03$ by the log-rank test). However, intraperitoneal chemotherapy has not been widely accepted for several reasons [16, 17]. Although the designs of the trials have been methodologically criticized, the principal reason resides in the higher toxicity and complexity of administration of therapy. Actually, only 42 % of patients included in the GOG-172 trial were able to complete the six scheduled cycles. For this reason, some groups are exploring new regimens with better tolerability but without loss of efficacy. In this way, there are three ongoing phase III trials (GOG-252, GOTIC-001/JGOG-3019 and OV-21/Gynecologic Cancer Intergroup [GCIG]) exploring the administration of intraperitoneal carboplatin instead of cisplatin. GOG-252 is a randomized trial assessing the role of intraperitoneal carboplatin, bevacizumab and dose-dense paclitaxel that has recently been closed and for which results are pending.

Dose-dense chemotherapy consists of more frequent administration of some or all of the drugs of the regimen, usually in a weekly or every other week schedule, sometimes obtaining a higher cumulative dose. This strategy was adopted in a randomized clinical trial called NOVEL launched by the Japanese Gynecologic Oncology Group [18, 19]. Patients with stage IIB–IV ovarian cancer were randomized to a standard schedule of paclitaxel 180 mg/m^2 and carboplatin AUC 6 administered every 3 weeks, or the administration of weekly paclitaxel 80 mg/m^2 and carboplatin AUC 6 every 3 weeks. The dose-dense regimen obtained a longer time to progression (28.1 vs. 17.5 months; hazard ratio [HR] 0.76; 95 % confidence interval [CI] 0.62–0.91; $p = 0.0037$) [19] and also OS (5-year OS was 58.7 vs. 51.1 %; HR 0.79; 95 % CI 0.63–0.99; $p = 0.0448$) [19]. Despite the results of this trial, dose-dense regimen has not been widely adopted due to the toxicity reported with this regimen and the potential pharmacogenetic differences between the Japanese and the Caucasian populations. Three large, randomized clinical trials are assessing the dose-dense issue in the Western population—the Italian MITO-7, GOG-262 and ICON8.

Preliminary results of MITO-7 were presented at ASCO (American Society of Clinical Oncology) 2013. In this phase III, open-label, multicentre trial, 822 women were randomly assigned to receive three-weekly carboplatin (AUC 6) plus paclitaxel (175 mg/m^2) for six cycles or a weekly regimen of carboplatin (AUC 2) plus paclitaxel (60 mg/m^2) for 18 weeks. After a median follow-up of 19.9 months, progression-free survival (PFS) was 18.8 and 16.5 months, respectively, a non-significant difference. Nevertheless, one of the primary endpoints, quality of life measured with the Functional Assessment of Cancer Therapy for ovarian cancer, trial outcome index (FACT-O-

TOI) after 9 weeks, was significantly better in the weekly arm [20]. Additionally, GOG-262 compared three-weekly carboplatin (AUC 6) plus paclitaxel (175 mg/m^2) for six cycles or a weekly regimen of paclitaxel (80 mg/m^2) for 18 weeks and carboplatin AUC 6 every 3 weeks in 692 patients with stage II–IV [21]. Bevacizumab 15 mg/kg every 3 weeks was optionally offered to patients, 84 % of whom selected this option. Median PFS was 14.8 months in the dose-dense arm and 14.3 months in the control arm (HR 0.97; 95 % CI 0.97–1.18). These results have maintained an ongoing discussion of dose-dense chemotherapy in the Caucasian population, and the results of ICON8 are awaited with expectancy.

In summary, the combination of paclitaxel and carboplatin administered every 3 weeks is still the most accepted backbone chemotherapy for advanced ovarian cancer. The intraperitoneal regimen and the dose-dense schedule are options that were accepted by the 4th Ovarian Cancer Consensus Conference as potential control arms for future clinical trials but have not been widely adopted in clinical practice [3].

3 Maintenance Chemotherapy

Maintenance therapy has been explored as a strategy to prolong the progression-free interval (PFI) and OS of patients with advanced ovarian cancer. It consists of the administration of additional cycles of chemotherapy beyond the five to six cycles of paclitaxel and carboplatin. Two strategies have been studied: the first option is to continue with some of the agents already used if the patient has not progressed. The rationale behind this approach is that non-resistant, slowly-dividing tumour cells that were inadequately exposed to cycle-dependent cytotoxic agents during the initial treatment period may be substantially reduced in number or completely eliminated with the continuation of chemotherapy. The second option is to introduce a new agent without cross-resistance with those previously used in order to eliminate those clones of cells resistant to upfront chemotherapy.

Table 1 summarizes the most relevant attempts that have been undertaken with maintenance of chemotherapy and immunotherapy [22–27]. Unfortunately, only one trial has shown some impact in the outcome of patients. The only positive study was an American Intergroup (SWOG–GOG) phase III trial in which 277 patients (262 evaluable) with stage III disease and who had achieved complete clinical remission after five to six cycles of paclitaxel plus cisplatin were randomized to paclitaxel (175 mg/m^2) infused over 3 h every 28 days, for three versus 12 cycles [22]. The median PFS was significantly longer for the group with 12 cycles of paclitaxel (28 vs. 21 months; $p = 0.0023$). The SWOG Data Safety Monitoring Committee closed the study early due to the emerging differences in disease-free survival that were encountered. There were no significant differences in toxicity except for higher peripheral neuropathy in the 12-cycle arm (29 vs. 16 % grade 2–3 neuropathy) [22]. Although this study has been extensively mentioned, the reality is that the use of maintenance paclitaxel after obtaining a complete remission in frontline therapy has not been adopted in routine practice, mainly due to neurotoxicity and the maintained alopecia with this regimen.

4 First-Line and Maintenance Therapy with Anti-Angiogenic Therapy

Anti-angiogenic therapy was identified as one of the most promising targeted therapies in ovarian cancer in the last Ovarian Cancer Consensus Conference held in 2010 in Vancouver [3]. Neoangiogenesis is a necessary step for tumour proliferation and invasion, as a result of an imbalance between pro-angiogenic and anti-angiogenic factors in favour of the former. One of the most important pathways implicated in the initiation of tumour angiogenesis is the interaction of vascular endothelial growth factor (VEGF) with its receptors (VEGFR-1, -2, and -3) [28]. In fact, VEGF overexpression has been demonstrated to be an adverse prognostic factor in ovarian carcinoma as it has been associated with tumour progression and shortened OS [29, 30]. Additionally, other factors and pathways such as platelet-derived growth factor (PDGF) or fibroblast growth factor (FGF) have been implicated in ovarian cancer progression, prognosis and resistance to anti-VEGF therapy [31, 32]. Table 2 summarizes the anti-angiogenic drugs that have been included in randomized clinical trials.

4.1 Bevacizumab

Bevacizumab (Genentech, South San Francisco, CA, USA) is a humanized monoclonal antibody against VEGF-A. It was the first anti-angiogenic therapy used in the clinic and the most extensively studied anti-angiogenic agent in ovarian cancer.

Two prospective, phase II trials in recurrent ovarian cancer showed clear activity of bevacizumab monotherapy in patients with recurrent ovarian cancer [33, 34]. The first, GOG-170D demonstrated a response rate of 21 % in 62 patients with recurrent ovarian cancer (58 % of these were platinum-resistant) and up to two previous chemotherapy lines [33]. The second study showed a response rate of 16 % in 44 patients with platinum-resistant relapse and up to three previous chemotherapy lines [34]. The most common adverse effect associated with bevacizumab has

Table 1 Maintenance therapy with chemotherapy or immunotherapy

References	Study design and intervention	No. of pts	Result
Markman et al. [22]	Randomized trial of 12 vs. 3 months of maintenance paclitaxel after complete response to initial therapy	277	Significantly improved PFS No impact on OS
De Placido et al. [23]	MITO-1: prospective, randomized comparison of topotecan (four cycles) vs. observation	273	No significant difference in survival or PFS
Pfisterer et al. [24]	Prospective, randomized comparison of paclitaxel and carboplatin followed by observation vs. paclitaxel and carboplatin followed by topotecan (four cycles)	1,308	No significant difference in survival or PFS
Hall et al. [25]	Prospective, randomized trial of interferon-α vs. observation	300	No significant difference in survival or PFS
Berek et al. [26]	Prospective, randomized trial of oregovomab vs. observation	373	No significant difference in survival or PFS
Sabbatini et al. [27]	MIMOSA: prospective, randomized trial of abagovomab vs. observation	888	No significant difference in survival or PFS

MITO-1 Multicenter Italian Trials in Ovarian Cancer, *MIMOSA* Monoclonal antibody Immunotherapy for Malignancies of the Ovary by Subcutaneous Abagovomab, *PFS* progression-free survival, *OS* overall survival, *pts* patients

Table 2 Anti-angiogenic agents included in randomized clinical trials

Drug	Targets	Study	No. of pts	Intervention
Bevacizumab	VEGF	GOG-218 [35]	1,873	Frontline associated with chemotherapy followed by a maintenance period
		ICON-7 [36]	1,528	
Pazopanib	VEGFR-1, -2 and -3, PDGFR-α and β, FGFR-1 and -3	AGO-OVAR 16	940	Maintenance after frontline
	c-Kit			
Nintedanib	VEGFR-1, -2 and -3, PDGFR-α and β, FGFR-1, -2 and -3	AGO-OVAR 12/LUME-Ovar 1	1,366	Frontline associated with chemotherapy followed by a maintenance period
	Src and FLT-3			
Sorafenib	c-Raf and b-Raf, VEGFR-2 and -3, PDGFR-β, FLT-3 and c-Kit	Bayer	246	Randomized, phase II of maintenance after frontline
		NCT00791778		
Cediranib	VEGFR-1, -2 and -3, PDGFR-α/β, FGFR-1, and c-Kit	ICON6	486	Second-line associated with chemotherapy followed by placebo or cediranib in platinum-sensitive relapse
Trebananib	Ang-1 and -2	TRINOVA-3	919	Frontline associated with chemotherapy followed by a maintenance period

VEGF vascular endothelial growth factor, *VEGFR* vascular endothelial growth factor receptor, *PDGFR* platelet-derived growth factor receptor, *FGFR* fibroblast growth factor receptor, *FLT-3* fms-like tyrosine kinase 3, *Ang* angiopoietin

been grade $\geq$2 hypertension. Additionally, the second phase II trial was prematurely stopped due to the high rate of gastrointestinal perforations (GIPs) observed. Up to 11 % of patients experienced a GIP and one patient died [34]. An extensive review demonstrated that these perforations occurred only in patients with three previous lines of chemotherapy, and fortunately this high rate has not been observed in subsequent trials.

Two large, prospective, randomized clinical trials have included bevacizumab in the frontline therapy of ovarian, primary peritoneal or fallopian tube cancer in combination with standard chemotherapy followed by a maintenance period with bevacizumab [35, 36]. The main results of both studies are summarized in Table 3.

The GOG-218 trial was a double-blind, randomized clinical trial that included patients with ovarian cancer, fallopian tube cancer or primary peritoneal carcinomatosis with suboptimal or optimal cytoreduction (<1 cm) but with residual macroscopic tumour after frontline debulking surgery [35]. A total of 1,873 patients were included. All patients received standard chemotherapy with intravenous paclitaxel 175 mg/m^2 and carboplatin AUC 6 administered every 3 weeks for six cycles, and were randomized to one of the following three arms: the control arm consisted of the administration of intravenous placebo in cycles 2 through 22; the second group, also called the 'bevacizumab initiation group', consisted of the administration of bevacizumab 15 mg/kg every 3 weeks in cycles 2 through 6

Table 3 Efficacy of bevacizumab in first-line treatment of ovarian cancer in phase III trials

	GOG-218 [35]	ICON-7 [36]
PFS by protocol[a]		
HR (95 % CI)	0.71 (0.625–0.824)	0.87 (0.77–0.99)
Between-group difference[a] (median)	3.8 months	2.5 months
PFS in high-risk patients[b]		
HR (95 % CI)		0.73 (0.60–0.93)
Between-group difference[a] (median)		5.5 months
OS		
HR (95 % CI)	0.88 (0.75–1.04)	0.85 (0.69–1.04)
OS in high-risk patients[b]		
HR (95 % CI)		0.64 (0.48–0.85)
Between-group difference[a] (median)		7.8 months

Between-group differences are for the bevacizumab-throughout group versus the control group in GOG-218, and for the bevacizumab-containing group versus the standard therapy group in ICON7

PFS progression-free survival, *HR* hazard ratio, *OS* overall survival, *FIGO* International Federation of Gynecology and Obstetrics

[a] Progression was defined by RECIST criteria, clinical deterioration or CA-125 criteria in GOG-218, and only by RECIST in ICON7

[b] High risk: suboptimally debulked FIGO stage III or IV disease

concurrently with chemotherapy followed by placebo from cycles 7–22; and the bevacizumab-throughout group was chemotherapy with bevacizumab 15 mg/kg added in cycles 2 through 6 followed by a period of maintenance from cycles 7–22 (approximately 15 months in total). Bevacizumab or placebo was initiated at cycle 2, rather than cycle 1, to reduce the risk of wound-healing complications. The main endpoint of the GOG trial was PFS determined by CA-125 GCIG progression criteria or radiological progression according to RECIST criteria. The bevacizumab initiation group did not obtain any significant benefit in outcome over the control group. However, the bevacizumab group had a significantly longer PFS than the control group (14.1 vs. 10.3 months; HR 0.71; 95 % CI 0.625–0.824; $p < 0.001$). The maximal separation of the PFS curves for the bevacizumab-throughout group and the control group occurred at 15 months, with convergence approximately 9 months later.

In the ICON7 trial, a total of 1,528 patients with EOC, fallopian tube cancer or primary peritoneal carcinomatosis with FIGO (International Federation of Gynecology and Obstetrics) stage I of high risk (defined as grade 3 or clear cell histology) to stage IV were randomized to one of the following arms: the standard arm was intravenous paclitaxel 175 mg/m^2 and carboplatin AUC of 6 every 3 weeks, and the experimental arm was the same chemotherapy regimen with bevacizumab 7.5 mg/kg every 3 weeks added from cycles 1–18 (a total of 12 months) [34]. Patients were stratified according to the extension of the disease and debulking (stage I–III with optimal debulking <1 cm vs. stage I–III with suboptimal debulking >1 cm vs. inoperable stage III and stage IV), timing of treatment initiation (<4 weeks vs. >4 weeks) and GCIG group. The primary endpoint in this trial was also the PFS, but in this case progression was defined by RECIST criteria only. The median PFS was 17.3 months in the standard therapy group and 19.0 months in the bevacizumab group. A comparison of Kaplan–Meier curves for PFS showed a significant difference between the two groups (estimated HR for progression or death in the bevacizumab group, 0.81; 95 % CI 0.70–0.94; $p = 0.004$). The effect of bevacizumab was maximal at 12 months, with an improvement in PFS at this time of 15.1 % compared with the standard arm.

Although the number of events for a mature analysis has not been reached, both trials have shown preliminary data of OS. No significant differences in OS have been found in GOG-218 (HR 0.885; 95 % CI 0.750–1.040) or ICON7 (HR 0.85; 95 % CI 0.69–1.04; $p = 0.11$).

Regarding safety, the most common side effect associated with the administration of bevacizumab was the development of grade $\geq$2 hypertension (22.9 % in GOG-218 and 18.9 % in ICON7). In GOG-218, there were no significant differences among the three groups in the rates of other adverse events, including gastrointestinal perforation or fistula, proteinuria of grade 3 or greater, neutropenia of grade 4 or greater or febrile neutropenia, venous or arterial thrombosis, and wound disruption. Similar conclusions were obtained in ICON7, except for grade $\geq$3 thromboembolic events, which were 7 % with bevacizumab versus 3 % with standard therapy. Finally, the rate of GIP was observed in only 1 % of patients in ICON7 and less than 2 % in the GOG-218 trial [35, 36].

The differences in patient population between the two studies could have influenced the magnitude of the impact of the intervention. Ten percent of patients included in ICON7 had stage I or IIA disease, and the rate of patients with optimal debulking (defined as residual disease <1 cm) after primary surgery was much higher in ICON7 than in the GOG-218 trial (74 vs. 35 %, respectively) [35, 36]. Moreover, in the ICON7 trial there was a heterogeneous mix of patients with different stages and residual disease after surgery, which means differences in prognosis. In fact, the test for interaction suggests that the size of the effect of bevacizumab differed between patients at high risk for progression and the rest of the study population ($p = 0.06$), showing a benefit for the high-risk group. A subanalysis of patients at high risk of progression (defined as stage IV or stage III and suboptimal cytoreduction with residual disease >1 cm) showed that the estimated median

PFS was 10.5 months with standard therapy compared with 16 months with bevacizumab (HR for progression or death in the bevacizumab group, 0.73; 95 % CI 0.60–0.93; $p = 0.002$), and that OS increased from 28.8 months in the standard-therapy group to 36.6 months in the bevacizumab group (HR for death in the bevacizumab group, 0.64; 95 % CI 0.48–0.85; $p = 0.002$) [35].

4.2 Pazopanib

Pazopanib (Votrient™; GlaxoSmithKline, London UK) is an oral small-molecule angiogenesis inhibitor targeting VEGF receptors (VEGFR-1, -2 and -3), PDGF receptors (PDGFR-α and β), FGF receptors (FGFR-1 and -3) and c-Kit.

Activity of this drug in ovarian cancer was demonstrated in a phase II trial that included patients with relapsed ovarian cancer after a previous complete response to first-line platinum-based therapy, with no more than two previous chemotherapy lines, a CA 125 level >42 UI/ml, and small-volume disease (e.g. minimal ascites not causing abdominal distension, mesenteric thickening or not requiring paracentesis, or lesions ≤4 cm by spiral computed tomography or magnetic resonance imaging at baseline) to minimize the potential for bowel perforations observed in previous trials with angiogenesis inhibitors [37]. Overall, 11 of 36 patients (31 %; 95 % CI 16–48) had a CA-125 response that was the primary endpoint of the study. No partial or complete responses were observed in patients with measurable disease based on RECIST. Regarding safety, the most common grade 3 adverse events were fatigue and γ-glutamyl transpeptidase elevation (11 % for both). One patient (3 %) had grade 4 peripheral edema. In contrast, a phase II study conducted by GEICO (Spanish Group for Investigation in Ovarian Cancer) did not show enough activity with pazopanib in a population of patients with platinum-resistant disease and measurable disease by RECIST that had not received more than two previous chemotherapy lines. Only one patient (4 %) obtained a partial response out of 25 patients included, leading to the discontinuation of the second stage of the study [38].

Based on the antitumour activity shown in patients with recurrent and small-volume disease, pazopanib was investigated as maintenance therapy in frontline therapy in an international cooperative AGO-OVAR-16 trial led by the AGO group (Arbeitsgemeinschaft Gynaekologische Onkologiestudiengruppe). In this study, patients without progression after first-line therapy based on platinum/taxanes and a tumour of less than 2 cm in basal evaluation were randomized to maintenance with placebo or pazopanib. The initial duration of treatment with pazopanib or placebo was 1 year but was changed to 2 years during the trial. It is worthwhile to highlight that this trial allowed the inclusion of patients with persistent evidence of disease, provided that there was no progression. Results presented at ASCO 2013 demonstrated that pazopanib as maintenance therapy had a statistically significant PFS benefit (HR 0.766; 95 % CI 0.64–0.91; $p = 0.0021$; median 17.9 vs. 12.3 months, respectively), but OS data are immature and currently show no trend in either direction [39].

4.3 Nintedanib

Nintedanib (BIBF 1120; Boehringer Ingelheim, Ingelheim, Germany), a 6-methoxycarbonyl-substituted indolinone, is a potent inhibitor of VEGFR-1, -2 and -3, as well as PDGF receptors (PDGFR-α and β) and FGF receptors (FGFR-1, -2 and -3). Additionally, it inhibits Src and fms-like tyrosine kinase 3 (FLT-3).

In order to test the activity of nintedanib in ovarian cancer, a randomized, phase II trial was conducted in patients with response to chemotherapy at relapse but at high risk of recurrence based on a treatment-free interval previous to the last course of chemotherapy of <12 months [40]. Patients responding to chemotherapy for recurrent disease and the abovementioned criteria were randomized to nintedanib 250 mg twice daily or placebo as maintenance therapy until progression or unacceptable toxicity. The PFS rate at 36 weeks was 16.3 % (95 % CI 5.2–27.3) in the nintedanib group and 5.0 % (95 % CI 0–11.8) in the placebo group (HR 0.65; 95 % CI 0.42–1.02; $p < 0.06$). More patients receiving nintedanib experienced diarrhoea, nausea, or vomiting (mainly grade 1 or 2 and no grade 4). There was a higher rate of grade 3 or 4 hepatotoxicity in patients receiving nintedanib (51.2 %) compared with patients receiving placebo (7.5 %; $p < 0.001$), but this was rarely of clinical significance.

A phase I trial carried out in patients with advanced gynaecological malignancies showed that the maximum tolerated dose (MTD) of nintedanib in a 20-day continuous dosing regimen with standard-dose paclitaxel and carboplatin was 200 mg twice daily [41]. This schedule was selected for the international cooperative phase III trial AGO-OVAR 12/LUME-OVAR-1. This trial included patients with an initial diagnosis of ovarian, primary peritoneal or fallopian tube cancer stage IIB–IV after initial debulking surgery, or with only biopsy for patients with stage IV in whom surgery was not considered an option. Patients were randomized to paclitaxel/carboplatin every 3 weeks with placebo or nintedanib for six cycles followed by maintenance therapy with placebo or nintedanib for 120 weeks (including the period of concurrence with chemotherapy) if no progression or intolerance was detected. Recruitment for this trial closed in June 2011, with the inclusion of 1,366 patients. Preliminary results were

presented at ESGO (European Society of Gynaecological Oncology) 2013, asserting that nintedanib added to paclitaxel and carboplatin (TC) chemotherapy significantly increased PFS (HR 0.84; 95 % CI 0.72–0.98; $p = 0.0239$). OS data are immature, with events in 20 % of patients, but currently show no trend in either direction [42].

4.4 Sorafenib

Sorafenib (Bayer, Leverkusen, Germany) is an oral bisaryl urea that inhibits c-Raf and b-Raf, two kinases that function in the mitogen-activated protein kinase (MAPK) pathway. Additionally, sorafenib non-specifically blocks other receptor tyrosine kinases involved in tumour progression and angiogenesis, specifically the VEGF receptors 2 and 3, the PDGF receptor (PDGFR-β), FLT-3 and c-Kit.

Sorafenib was studied in a phase II trial that included 73 patients with ovarian or primary peritoneal cancer that had a recurrence after one or two previous chemotherapy lines and a platinum-free interval of <12 months [43]. Primary endpoints were PFS at 6 months and toxicity. This trial showed a modest activity (response rate 3.4 %, 90 % CI 1–10; PFS at 6 months 24 %, 90 % CI 15–35 and median PFS of 2.1 months) at the expense of substantial adverse events such as grade 3–4 rash ($n = 7$), hand-foot syndrome ($n = 9$), metabolic ($n = 10$), gastrointestinal ($n = 3$), cardiovascular ($n = 2$), and pulmonary ($n = 2$).

A randomized, phase II trial explored the use of sorafenib 400 mg twice daily or placebo as maintenance therapy in patients with epithelial ovarian or primary peritoneal cancer in complete remission after platinum/taxane-based first-line therapy [44]. This trial did not show any improvement in PFS with sorafenib compared with placebo (HR 1.09; 95 % CI 0.72–1.63). Additionally, sorafenib resulted in significantly higher toxicity, especially grade 3 hand-foot syndrome (39 vs. 0.8 %), rash (14.6 vs. 0 %) and hypertension (8.1 vs. 0.8 %).

4.5 Cediranib

Cediranib (AstraZeneca; Wilmington, DE, USA) targets VEGFR-1, -2 and -3, PDGFR-α/β, FGFR-1, and c-Kit. Two phase II trials have shown that cediranib is active in platinum-sensitive (risk ratio [RR] 41 %) and platinum-resistant (RR 17–29 %) recurrent ovarian cancer. The main toxicity observed in phase II studies was grade ≥3 hypertension (46 %), fatigue (24 %), and diarrhoea (13 %) [45, 46].

A large, phase III study (ICON6) has explored the addition of cediranib to platinum-based chemotherapy in patients with platinum-sensitive recurrent disease (platinum-free interval longer than 6 months). The study had three arms: standard platinum-based chemotherapy plus placebo followed by placebo, standard platinum-based chemotherapy plus cediranib followed by placebo, and standard platinum-based chemotherapy plus cediranib followed by cediranib as maintenance therapy. The original dose of 30 mg/day was reduced to 20 mg/day after the first 30 patients were included due to emerging data regarding safety with this combination. This trial has been prematurely closed with more than 400 patients included of the approximately 2,000 planned. The results were presented at the 17th ECCO (European Cancer Organisation) meeting, showing that the addition of cediranib to chemotherapy followed by a maintenance period with cediranib for 18 months or until progression was associated with an improvement in PFS (HR 0.57; 95 % CI 0.45–0.74; restricted means 9.4 vs. 12.5 months) and OS (HR 0.70; 95 % CI 0.51–0.99; restricted means 17.6 vs. 20.3 months) [47].

4.6 Trebananib (AMG-386)

Trebananib (AMG-386; Amgen, Thousand Oaks, CA, USA) is a first-in-class investigational peptide-Fc fusion protein peptibody that neutralizes the interaction between the Tie2 receptor and angiopoietin-1 (Ang-1) and angiopoietin-2 (Ang-2). The angiopoietin axis promotes vascularization in ovarian cancer by a different pathway than the VEGF–VEGFR interaction. In the first human study of trebananib in solid tumours, one patient with platinum-resistant disease obtained a maintained partial response, by RECIST, in monotherapy [48].

Additional information about the activity of trebananib in recurrent ovarian cancer was provided by a randomized, phase II clinical trial. In this trial, patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer were randomly assigned 1:1:1 to receive paclitaxel (80 mg/m^2 once weekly, 3 weeks on/1 week off) plus intravenous trebananib 10 mg/kg weekly (arm A), trebananib 3 mg/kg weekly (arm B), or placebo (arm C) [49]. The primary endpoint was PFS. Overall, 161 patients were randomly assigned. Median PFS was 7.2 months (95 % CI 5.3–8.1 months) in arm A, 5.7 months (95 % CI 4.6–8.0 months) in arm B and 4.6 months (95 % CI 1.9–6.7 months) in arm C. The HR for arms A and B combined versus arm C was 0.76 (95 % CI 0.52–1.12; $p = 0.165$). Further analysis suggested a dose-response effect. Regarding side effects, the most common side effects were peripheral edema (71, 51 and 22 % in arms A, B and C, respectively, but only 4 % in arm A and 6 % in arm B were grade 3) and grade 3 hypokalemia (12, 11 and 4 % in arms A, B and C, respectively). Interestingly, no GIPs were observed and the rate of hypertension was similar in the experimental and control arms.

Trebananib has entered an extensive programme for clinical development, known as TRINOVA and which includes three different studies. TRINOVA-1, a phase III, randomized, double-blind trial that enrolled 919 patients with 12 months' PFI in advanced ovarian, primary peritoneal or fallopian tube cancer to receive weekly paclitaxel 80 mg/m^2 (3 weeks on/1 week off) plus placebo or intravenous trebananib 15 mg/kg, until progression or unacceptable toxicity. Cutoff date was March 2013 and the first results were presented at ECCO 2013 [50]. The primary endpoint of median PFS was 5.4 months with paclitaxel alone and 7.2 months with paclitaxel plus trebananib (HR 0.66; $p < 0.001$). Despite the fact that mature OS data will not be available until 2014, the interim analysis with 50 % of deaths indicates a non-significant trend in favour of the trebananib arm (19.0 vs. 17.3 months; HR 0.86; $p = 0.19$).

The TRINOVA-2 trial has a similar design to TRINOVA-1 but the backbone of chemotherapy is PLD. This study was temporarily closed due to the shortage of PLD, and was definitively closed later without recruitment being completed. Finally, TRINOVA-3 is an ongoing trial for first-line therapy of patients with stage III or IV ovarian, primary peritoneal or fallopian tube cancer. Patients were randomized to paclitaxel-carboplatin with placebo or trebananib followed by a maintenance period of trebananib/placebo until the completion of 18 months if no progression is detected. This study also allows the inclusion of patients with stage IIIC or IV disease in whom interval debulking surgery is planned after three cycles of therapy.

5 Targeted Agents Beyond Anti-Angiogenic Therapy

The 4th Ovarian Cancer Consensus Conference identified several promising targeted therapies to be studied in ovarian cancer. Of these, angiogenesis and homologous recombination deficiency were considered the most promising [3].

Homologous recombination comprises several pathways implicated in DNA repair of double-strand breaks. BRCA 1 and BRCA 2 are an important component of the homologous recombination repair system, but other proteins and pathways are also involved [51]. Up to 50 % of patients with high-grade serous ovarian cancer have a homologous recombination deficiency, 15–20 % of patients have a germ-line mutation in BRCA1 or BRCA2, and the rest include BRCA somatic mutations, epigenetic silencing via hypermethylation of BRCA and deficiency in other proteins and pathways, such as, for instance, EMSY [52]. Patients with homologous recombination deficiency, with or without germ-line BRCA mutation, can be treated with inhibitors of poly-ADP-ribose polymerase (PARP). PARP1 is an enzyme that plays a critical role in the repair of DNA single-strand breaks through base-excision repair [53]. Loss of PARP1 activity leads to accumulation of single-strand breaks, subsequent double-stranded breaks, and cellular death. In normal cells, double-stranded breaks are repaired through homologous recombination. However, in patients with homologous recombination deficiency, such as those with BRCA mutation, the inhibition of PARP produces an accumulation of single- and double-strand DNA breaks that leads the cell to apoptosis [54]. This concept is called 'synthetic lethality', and basically means that a cell can survive if two different genetic alterations are not concurrent, but if both occur at the same time the cell is unable to survive [55, 56].

Several PARP inhibitors are under study in clinical trials (Table 4). Of these, olaparib (AZD2281; AstraZeneca, Wilmington, DE, USA) has been the most extensively studied. The administration of olaparib 400 mg twice daily in patients with recurrent ovarian cancer has produced clinical responses, not only in patients with BRCA mutations (response rate 41 %) but also in patients with high-grade serous ovarian cancer who were non-carriers of the BRCA mutation (response rate 26 %) [57].

One phase II, randomized, placebo-controlled clinical trial evaluated maintenance treatment with olaparib 400 mg twice daily in patients with platinum-sensitive, relapsed, high-grade serous ovarian cancer who had received two or more platinum-based regimens and had had a partial or complete response to their most recent platinum-based regimen [58]. The primary endpoint was PFS according to the RECIST guidelines, and was significantly longer with olaparib than with placebo (median 8.4 vs. 4.8 months; HR 0.35; 95 % CI 0.25–0.49; $p < 0.001$). Unfortunately, a longer follow-up of the study has not shown any difference in OS. Olaparib is generally well-tolerated, although the incidence of nausea (68 vs. 35 %), fatigue (49 vs. 38 %), vomiting (32 vs. 14 %), and anaemia (17 vs. 5 %) was higher than with placebo; the majority of adverse events were grade 1 or 2. In another randomized, phase II trial, olaparib 200 mg twice daily was added to paclitaxel-carboplatin followed by a maintenance phase of olaparib

Table 4 PARP inhibitors in clinical development

Drug	Company	Administration route
O-9201 (Olaparib)	Astra Zeneca	Oral
PF-0137 (Rucaparib)	Clovis/Pfizer	IV/oral
ABT 888 (Veliparib)	Abbott	Oral
INO-1001	Inotek	IV
GP1201	Eisai	Oral
CEP 9722	Cephalon	Oral
MK 4827 (Niraparib)	Merck/Tesaro	Oral
BMN 673	BioMarin	Oral

PARP poly-ADP-ribose polymerase, *IV* intravenous

400 mg twice daily, and compared with paclitaxel-carboplatin in patients with platinum-sensitive recurrent ovarian cancer and no more than three previous platinum-based regimens [59]. The BRCA status was unknown for the majority of patients and the PFS determined by RECIST criteria was significantly longer in the olaparib arm (12.2 vs. 9.6 months; HR 0.51; 95 % CI 0.34–0.77; $p = 0.0012$). Immature data of OS have not shown any between-group differences. The tolerability profile was considered acceptable and manageable. In the combination phase, both arms had generally similar toxicity profiles, and in the maintenance phase, olaparib tolerability was consistent with the known monotherapy profile.

Although the majority of PARP inhibitors are under study in the context of relapsed disease, a randomized clinical trial called SOLO-1, which tests the administration of olaparib versus placebo as maintenance therapy after frontline therapy in patients with BRCA 1 or 2 germline mutation, has been initiated.

6 Conclusions

Frontline chemotherapy for EOC has not changed in the last decade and the combination of paclitaxel and carboplatin administered every 3 weeks has remained the standard of care. Alternative schedules, such as, for instance, intraperitoneal administration of chemotherapy or dose-dense regimen, are still controversial and have not been adopted widely in clinical practice. Additionally, maintenance therapy with chemotherapy or immunotherapy after the completion of first-line platinum-paclitaxel has not been proven to benefit the outcome of patients with advanced ovarian cancer. This scenario has recently changed due to the introduction of targeted agents, especially anti-angiogenic agents. Data from two large, randomized clinical trials have shown that adding bevacizumab, a monoclonal antibody against VEGF, to the chemotherapy regimen followed by a maintenance period of bevacizumab prolongs the PFS, mainly in patients considered at high risk of relapse. The results of the clinical trials with bevacizumab have been considered the proof of concept of the value of anti-angiogenic therapy in the frontline therapy of ovarian cancer. However, several questions have risen about the optimal setting, dose and duration of bevacizumab. Additionally, we already have positive results of other phase III trials with anti-angiogenic agents, in frontline (pazopanib and nintedanib) and second-line (cediranib and trebananib) therapy. The great challenge for the near future will be the selection of patients with advanced ovarian cancer obtaining more benefit from these different options in frontline therapy and in recurrent disease.

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