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REVIEW

Bevacizumab in the Treatment of Ovarian Cancer

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ABSTRACT

Introduction: In the past decade there have been many attempts to improve systemic treatment and thus the outcome of patients with ovarian cancer. However, neither the sequential addition of non cross-resistant drugs to standard chemotherapy comprising carboplatin and paclitaxel, nor triplet combination therapies with conventional chemotherapeutic drugs have improved outcomes. Instead, such approaches have led to an increase in the incidence of side effects. We are currently experiencing a shift toward the addition of molecularly targeted and biological anticancer therapies to standard treatment. Vascular endothelial growth factor (VEGF), which improves vitally important tumor vasculature, is secreted by a range of tumors, and a high level of VEGF is known to be an independent risk factor for aggressive disease in ovarian cancer. This finding led to the development in the 1990s of bevacizumab, a humanized monoclonal antibody against VEGF.

Discussion: Several phase II trials and four phase III trials have demonstrated that bevacizumab is active in patients with advanced and recurrent ovarian cancer. Both phase III trials of bevacizumab as first-line therapy in advanced ovarian cancer (ICON 7/AGO-OVAR 11 and GOG-0218) have shown that the addition of bevacizumab to chemotherapy and as maintenance therapy improves progression-free survival (PFS). The phase III trials in platinum-sensitive (OCEANS) and platinum-resistant, relapsed disease (AURELIA) have also demonstrated a benefit for bevazicumab with respect to PFS. The administration of bevacizumab to improve survival in patients with ovarian cancer is not without side effects and a broad discussion on the cost-effectiveness of this approach is ongoing.

Conclusion: This article presents clinical trial data on bevacizumab in the treatment of ovarian

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cancer and discusses the indication and pitfalls in the application of bevacizumab in patients with this malignancy.

Keywords: Antiangiogenic therapy; Bevacizumab; Carcinoma; Ovarian cancer

INTRODUCTION

Vascular endothelial growth factor (VEGF) is an important molecule in angiogenesis. VEGF antibodies inhibit physiological and pathological angiogenesis. Bevacizumab, the first humanized VEGF antibody was introduced into clinical practice for the treatment of colorectal cancer in 2004. It is approved for the treatment of five cancers in Europe (metastatic colon cancer, metastatic breast cancer, lung cancer, advanced/metastatic renal cell cancer, advanced ovarian cancer) and four cancer entities in the USA (advanced colon, lung, kidney, and glioblastoma). Here we discuss the clinical data and therapeutic impact of bevacizumab as first-line therapy for ovarian cancer and for the treatment of recurrent disease.

A SHORT GLANCE AT THE HISTORY OF ANGIOGENESIS INHIBITION

The term angiogenesis was first introduced by John Hunter in 1787 when he observed the growth of new blood vessels in reindeer gut [1]. The science of tumor angiogenesis began at the end of the 19th century, when a couple of German pathologists, including Carl Thiersch, recognized that some human tumors show heavy vascularization [2]. In 1928, the development of the transparent chamber by J. C. Sandison made it possible to observe the growth of blood vessels in vivo [3], and in 1939 Gordon Ide set up the hypothesis that tumor cells excrete growth factors, which enhance blood vessel growth [4]. The first experiments involving the excretion of angiogenic factors by cancer cells were conducted in 1968, and the hypothesis that tumor growth is dependent on angiogenesis was published by Folkman et al. in 1971 [5]. In their paper, Folkman et al. [5] introduced the term antiangiogenesis, defined as the inhibition of recruitment of capillary sprouts in new implanted tumors. The authors concluded that an antibody directed against a tumor angiogenic factor would represent an effective anticancer drug, because it might cause inhibition of tumor neovascularization. A large number of natural stimulators of angiogenesis are now known, and not a single tumor angiogenic factor, and an equally large number of natural inhibitors of angiogenesis have been discovered. However, the interaction of different stimulators and inhibitors in the concert of angiogenesis is largely unknown even now. Ferrara et al. [6] identified a new heparin-binding endothelial-specific mitogen from bovine pituitary follicular cells in 1989, subsequently called VEGF. With the help of monoclonal neutralizing anti-VEGF antibodies, developed to investigate the significance of VEGF in vivo, scientists were able to demonstrate that anti-VEGF antibodies could reduce the growth of several human tumor cell lines in rodent experiments. The idea of using this approach in the treatment of cancer required the humanization of monoclonal anti-VEGF antibody, which was managed by Presta et al. in 1997 [7]. This antibody is now known as bevacizumab.

ADVANCED OVARIAN CANCER (FIGO STAGE IIB–IV)

Ovarian cancer has the highest mortality rate of all gynecological tumors. Patients present mostly at an advanced stage because early disease is asymptomatic or runs with nonspecific symptoms.

Despite sensitivity to taxane and platinum-containing chemotherapy, less than 50% of patients with Figo stage III or IV tumors are alive 5 years after the first diagnosis [8, 9].

Prognosis is primarily determined by the extent of tumor removal during surgery. Moreover, tumor stage, age and general health are significant prognostic parameters for survival in multivariate analyses [9]. At present, the only prognostic factor that can be changed is the extent of postoperative residual tumor. Therefore, the preferred treatment option for patients with advanced ovarian cancer is primary surgery to achieve maximum tumor reduction followed by standard chemotherapy. If primary surgery is unlikely to be successful, it is possible to use preoperative chemotherapy [10]. However, there are currently no validated predictive factors available to select patients who will not benefit from primary surgery.

The best data with respect to efficacy, side effects and route of administration are available for the combination of paclitaxel (175 mg/m^2 in 3 hours i.v.) and carboplatin (area under the curve [AUC] 5 or 6) [11, 12].

One of the important signal molecules for angiogenesis, VEGF, is overexpressed in ovarian cancer and is associated with ascites and worse prognosis [13–15]. Preclinical studies have shown that anti-VEGF therapy reduces tumor burden, inhibits the production of malignant ascites and acts synergistically with cytotoxic agents [16].

FIRST-LINE THERAPY IN ADVANCED OVARIAN CANCER

The combination of state-of-the-art surgery and state-of-the-art chemotherapy is crucial for long-term survival. Analyses by the Arbeitsgemeinschaft Gynäkologische Onkologie Studiengruppe Ovarialkarzinom (AGO-OVAR) in Germany showed that a large proportion of patients with ovarian cancer are treated suboptimally, and survival is significantly influenced therefrom [17].

It has not been possible to improve systemic conventional treatment with six cycles of paclitaxel and carboplatin for 10 years.

In a phase II study, 62 patients with newly diagnosed ovarian, primary peritoneal, or tubal cancer were treated with carboplatin (AUC 5), paclitaxel (175 mg/m^2) and bevacizumab (15 mg/kg) every 3 weeks for six to eight cycles followed by maintenance therapy with bevacizumab for up to 1 year. Seventy-five percent of patients showed a response (complete response [CR], 23%; partial response [PR], 52%; stable disease [SD], 25%) according to the response evaluation criteria in solid tumors (RECIST). Median progression-free survival (PFS) was 29.8 months at the time of reporting, whereas median overall survival (OS) had not been reached [18]. These data, in conjunction with other supportive hypothesis-generating data from phase II trials [18–21] (Table 1), supported the rationale for further investigations in this setting. Two large phase III, randomized studies (GOG-0218 and ICON 7/AGO-OVAR 11) were subsequently initiated to evaluate the benefit of combination therapy with paclitaxel, carboplatin and bevacizumab as first-line therapy in advanced, or early high-risk, ovarian, fallopian tube and peritoneal cancer.

Phase III Approval Trials for Bevacizumab as First-line Therapy

Both phase III trials recruited patients over a similar time period: the Gynecologic Oncology Group (GOG) recruited patients in the USA, Canada, South Korea and Japan between October 2005 and June 2009 for the GOG-0218 trial and the Gynecologic Cancer InterGroup (GCIG)

Table 1 Phase II trials investigating bevacizumab in the treatment of ovarian cancer

	n	Previous therapies	Platinum sensitive	Platinum resistant	Study treatment	OR (% of patients)	SD (% of patients)	Median PFS (months)	Median OS (months)
First-line therapy									
Micha, 2007 [20]	20	0			Bev + CP	80	5	n.i.	n.i.
Penson, 2010 [18]	62	0			Bev + CP + maintenance	75	25	29.8	n.r.
Brown, 2010 [19]	20	0			Bev + CP	61.6	30.8	5.8	n.i.
Konner, 2011 [21]	41	0			Bev + (cisplatin + paclitaxel i.p.) + maintenance			28.6	
Recurrent disease									
Burger, 2007 [39]	62	≤2	x	x	Bev	21	52	4.7	17
Cannistra, 2007 [37]	44	2–3		x	Bev	16	25	4.4	
Chura, 2007 [40]	15	Median 8	x	x	Bev + cyclophosphamide	53.3	20.0	3.9	n.r.
Garcia, 2008 [38]	70	≤3	x	x	Bev + cyclophosphamide	24	63	7.2 (TTP)	16.9
Nimeiri, 2008 [41]	13	≤2		x	Bev + erlotinib	15	54	4.1	11.0
Smerdel, 2009 [42]	38	Median 5	x	x	Bev	30	–	5.9	8.6
Muggia, 2009 [44]	21	≤3		x	Bev + PLD	n.i.	n.i.	n.i.	n.i.
Kudoh, 2011 [43]	30	>1	x	x	Bev + PLD	33	40	6	n.i.
McGonigle, 2011 [45]	40	≤2		x	Bev + topotecan	25	35	7.8	16.6
Del Carmen, 2012 [46]	54	1	x		Bev + PLD	72.2	20.4	13.9	n.r.

Bev bevacizumab, *CP* carboplatin/paclitaxel, *n.i.* not indicated, *n.r.* not reached; *OR* overall response, *OS* overall survival, *PFS* progression-free survival, *PLD* pegylated liposomal doxorubicin, *SD* stable disease, *TTP* time to progression, *x* indicates the inclusion of the respective group of patients with recurrent ovarian cancer

recruited patients in Europe between December 2006 and February 2009 for the ICON 7/AGO-OVAR 11 trial.

GOG-0218

The GOG-0218 trial examined the efficacy and safety of standard chemotherapy with/without bevacizumab in patients with newly diagnosed ovarian, peritoneal or fallopian tube carcinoma. A total of 1,873 patients with FIGO stage III or IV disease and with macroscopic residual tumor after debulking surgery were randomly assigned (1:1:1) to six cycles of carboplatin (AUC 6) plus paclitaxel (175 mg/m^2) followed by placebo (arm I: n = 625), standard chemotherapy in combination with bevacizumab (15 mg/kg i.v.) followed by placebo (arm II: n = 625), or standard chemotherapy plus bevacizumab (15 mg/kg) followed by 16 cycles of bevacizumab (15 mg/kg) as maintenance therapy (arm III: n = 623). Patients were stratified according to performance status (GOG PS), tumor stage and size of residual tumor. The primary study endpoint was PFS and secondary endpoints were OS, safety and quality of life. The results from the study should be interpreted with caution for two reasons: first, the trial inclusion criteria were amended from the inclusion of patients with residual disease after surgery of greater than 1 cm to the inclusion of patients with macroscopic disease only, and second, the primary endpoint was changed from OS to PFS, leading to concerns about the impact of possible crossover.

Randomly assigned patients had a median age of 60 years, were predominantly Caucasian (83–84%) and were in good general health (GOG PS of 0 in 49–50% and PS of 1 in 43–44% of patients). Tumor characteristics were well balanced and representative of patients with advanced disease. Initial results from the study were presented at the American Society of Clinical Oncology Meeting in 2010. Final results were published in full in 2011 [22]. After a median follow-up of 17.4 months, 76.3% of all randomly assigned patients included were alive. Median PFS, assessed according to RECIST and CA-125, was 10.3, 11.2, and 14.1 months in the control group (arm I), the bevacizumab initiation group (arm II), and the bevacizumab maintenance therapy group (arm III), respectively. The hazard ratio (HR) for the PFS benefit in the maintenance therapy arm (arm III) compared with the chemotherapy-only arm (arm I) was 0.717 ($P < 0.0001$), and this was confirmed for all patient subgroups. No significant difference in PFS was noted between arm II and arm I (11.2 vs. 10.3 months; HR 0.908; $P = 0.16$). OS data were not mature and median OS was 39.3, 38.7, and 39.7 months for the control group (arm I), the bevacizumab initiation group (arm II), and the bevacizumab maintenance therapy group (arm III), respectively. Compared with the control group (arm I), the HR for death was 1.036 (95% CI 0.827–1.297; $P = 0.76$) for the bevacizumab initiation group (arm II) and 0.915 (95% CI 0.727–1.152; $P = 0.45$) for the bevacizumab maintenance therapy group (arm III), which did not change significantly even after a follow-up update. The most significant toxicity (common terminology criteria for adverse events [CTCAE] grade ≥2) in the study was hypertension, which occurred in 7.2% of patients in the chemotherapy-alone arm (arm I) and in 16.5% and 22.9% of patients in the bevacizumab initiation group (arm II) and bevacizumab maintenance arm (arm III), respectively. Gastrointestinal toxicities were also more common in the bevacizumab treatment arms (17 and 16 patients) compared with the chemotherapy-alone arm (seven patients), but this difference was not statistically significant [22].

ICON 7/AGO-OVAR 11

The International Collaborative Ovarian Neoplasm (ICON) 7 trial was a phase III,

international, prospective, randomized, open-label, two arm intergroup study designed to evaluate the efficacy of bevacizumab as first-line therapy in combination with chemotherapy and as maintenance therapy. A total of 1,528 patients with early, high-risk or advanced, histologically confirmed ovarian, peritoneal or fallopian tube carcinoma received six cycles of carboplatin (AUC 5 or 6) plus paclitaxel (175 mg/m^2) every 3 weeks or the same chemotherapy in combination with bevacizumab (7.5 mg/kg i.v.) followed by bevacizumab maintenance therapy every 3 weeks for a total of 18 cycles. The primary endpoint was PFS and secondary endpoints were OS, response rate and safety. The median age in both study arms was 57 years and the vast majority of patients (94%) were in good general health (ECOG PS 0–1). Ten percent of the patients had early-stage (FIGO stage I/II) high-risk cancer, and 69–71% had advanced disease (FIGO stage IIIC/IV). Postoperative residual tumor (≤1 cm) was present in 74% of patients; however, information regarding macroscopic complete resection (optimal debulking) was missing.

The first interim results were presented at the European Society of Medical Oncology and International Gynecologic Cancer Society meetings in 2010, and final results were published in 2011 [23]. After a median follow-up of 19.4 months, 759 patients had progressive disease and 241 patients had died. Median PFS was 17.3 months in the standard therapy group and 19.0 months in the bevacizumab group, with an estimated HR for progression or death in the bevacizumab group of 0.81 (95% CI 0.70–0.94; $P = 0.004$). All patients in the bevacizumab arm had a benefit on the treatment that was shown in subgroup analyses. Patients with FIGO stage IIIC/IV disease experienced the greatest benefit with bevazicumab in terms of PFS of 5.4 months (15.9 vs 10.5 months; HR 0.68; $P < 0.001$). Due to nonproportional effects of bevacizumab over time the PFS advantage was greatest after 12 months, resulting in an advantage of 15.1% (95% CI 10.7–19.5) compared with standard therapy. This was the point at which bevacizumab maintenance therapy was stopped according to protocol requirements. A second analysis was conducted after a median follow-up of 28 months, during which 934 PFS events and 378 deaths were reported. In this analysis median PFS was 19.8 months for patients treated with bevacizumab compared with 17.4 months for patients treated with chemotherapy alone (HR 0.87; $P = 0.039$) and although median OS had not been reached there was a trend toward a benefit in the bevacizumab group (HR 0.84; $P = 0.099$). However, in patients with FIGO stage IV disease or with large postoperative residual tumor (>1 cm), statistical significance in favor of the bevacizumab arm was reached for median OS (36.6 vs. 28.8 months; HR 0.64; $P = 0.002$).

The safety profile of bevacizumab in this trial was similar to that reported in the first bevacizumab approval trials. Hypertension and bleeding complications (all common terminology criteria grades) were reported in 25.9% and 39.6% of patients, respectively, in the bevacizumab arm compared with 6.2% and 11.6% of patients, respectively, in the chemotherapy-only arm. However, severe toxicities (≥ grade 2 CTCAE) were reported to be different for hypertension 18.3% with bevacizumab versus 2.1%, thromboembolic events 7% with bevacizumab versus 3% with standard therapy, and gastrointestinal perforations occurring in 10 patients (1.3%) in the bevacizumab group versus three patients (0.4%) in the standard therapy group [23].

Differences Between GOG-0218 and ICON 7/AGO-OVAR 11

Although both the GOG-0218 study and the ICON 7/AGO-OVAR 11 study evaluated the efficacy

of bevacizumab in combination with standard chemotherapy in the first-line setting [22, 23], the two trials differed somewhat with respect to study design, inclusion criteria and methods. GOG-0218 was a three-arm, double-blind, placebo-controlled trial, whereas ICON 7/AGO-OVAR 11 included two treatment arms and was open and nonblinded. The second arm in GOG-0218 evaluated the addition of bevacizumab to chemotherapy without bevacizumab maintenance therapy, but failed to demonstrate a significant benefit in terms of PFS compared with the control group comprising chemotherapy alone (HR 0.908; 95% CI 0.795–1.040; $P = 0.16$).

Evaluation of disease progression was conducted slightly differently in the two studies. In ICON 7/AGO-OVAR 11, disease progression was defined according to the RECIST guidelines on the basis of radiologic, clinical, or symptomatic indicators of progression, and did not include isolated asymptomatic progression on the basis of CA-125 levels for primary analyses. In GOG 0218 PFS was defined as progression as shown on radiography, according to RECIST and an increase in the CA-125 level in patients who had completed chemotherapy. Another difference between the studies was the duration of therapy and dosage of bevacizumab. In GOG-0218 maintenance bevacizumab was administered at a dose of 15 mg/kg for 15 months, based on the dosage used for the treatment of metastatic breast cancer. In ICON 7/AGO-OVAR 11, maintenance bevacizumab was administered for 12 months at a dosage of 7.5 mg/kg, a dosage adapted from that used in therapy regimens for colorectal cancer. In addition to the fact that the treatment interval was 3 months shorter in ICON 7/AGO-OVAR 11, fewer patients were treated until disease progression in the study due to the inclusion of patients with a better prognosis.

As a result of the differences in design, dosing and other factors, it is difficult to conclude that both trials are supportive of each other. The fact that there was an OS benefit for high-risk patients in a subgroup analysis in the ICON 7/AGO-OVAR 11 trial, but no OS differences in GOG 0218, in which high-risk patients were included exclusively is one of the most striking peculiarities. However, OS data from these studies are still immature.

Summary and Perspective on Bevacizumab as First-line Treatment

Both approval trials, GOG-0218 and ICON 7/AGO-OVAR 11, evaluating the addition of bevacizumab to standard chemotherapy followed by maintenance therapy with bevacizumab demonstrated significant prolongation of PFS, the primary endpoint of both studies [22, 23]. On this basis, the European Medicines Agency (EMEA) approved bevacizumab 15 mg/kg in combination with standard chemotherapy for the treatment of advanced (FIGO stage IIIB/IV) ovarian, Müllerian tube and primary peritoneal carcinoma for 15 months. However, neither trial offers clarity to physicians and their patients regarding the dose or duration of treatment.

The toxicity profile of bevacizumab in the two studies was acceptable; however, the main toxicity, hypertension, occurs in approximately 20% of all patients and requires medical treatment. Based on earlier observations for bevacizumab in other malignancies, the toxicity seems to be dose dependent. For example, if hypertension (≥2 common terminology criteria grade) is compared between the GOG-0218 and ICON 7/AGO-OVAR 11 trials, 18.0% of patients treated with bevacizumab 7.5 mg/kg and 22.9% treated with bevacizumab 15 mg/kg developed hypertension. Whether the higher dosage is more clinically effective is unknown. Due to changing effects of bevacizumab over time in ICON 7/AGO-OVAR 11, the PFS advantage was greatest after 12 months, the time at which bevacizumab maintenance

treatment was stopped. In GOG 0218 many patients were treated until disease progression, on the assumption that treatment duration is of importance and that a longer treatment period potentially prolongs PFS. This issue of treatment duration is currently under investigation in the prospective, randomized, two-arm AGO-OVAR 17 intergroup trial. In that trial, which started in 2011, patients with primary ovarian, Müllerian tube or peritoneal carcinoma are treated with carboplatin (AUC 5), paclitaxel (175 mg/m^2) and bevacizumab 15 mg/kg followed by bevacizumab maintenance for an overall treatment duration of 15 months analog to the GOG regimes in the standard arm. In the experimental arm patients are treated with the same chemotherapy and concurrent bevacizumab followed by bevacizumab maintenance up to 30 months [24]. Whether treatment with bevacizumab as first-line therapy prolongs OS significantly remains speculative, until the final overall results have been published.

THERAPY OF RECURRENT OVARIAN CANCER

Recurrent disease is diagnosed in approximately two thirds of patients with advanced ovarian cancer within 5 years despite optimal primary therapy [9]. Maintaining quality of life is the main goal in these patients, together with symptom control and, if possible, prolongation of life. Surgery for recurrent ovarian cancer is a reasonable option in selected patients [25]; the value of such an approach is currently under investigation in two studies, the international DESKTOP III AGO study group trial [26] and the GOG 213 trial [27]. Regardless of whether surgery is performed, systemic therapy is indicated for the majority of patients with recurrent disease.

Recurrent ovarian cancer is classified as platinum-sensitive or platinum-resistant as a function of time. Platinum-resistant recurrence is defined by a platinum treatment-free interval of up to 6 months. This definition includes the subgroup of patients with platinum refractory disease, who experience a recurrence during first-line therapy [28]. For these patients, nonplatinum-based mono chemotherapy is recommended.

Topotecan [29], pegliposomal doxorubicin and gemcitabine [30, 31], in addition to paclitaxel (in patients who have not received previous taxane therapy) [32] have demonstrated confirmed activity in randomized studies including patients with recurrent ovarian cancer. In platinum-sensitive disease, platinum-based combination chemotherapy is beneficial, as shown in several prospectively randomized trials [33–35]. This indication for such a combination therapy was approved by the Ovarian Cancer Consensus Conference GCIG 2010 and has been included in national therapy guidelines [36].

Inhibition of angiogenesis with bevacizumab in recurrent disease appears promising, as the results from several phase II trials suggest that bevacizumab is active as monotherapy in both platinum-sensitive and platinum-resistant disease (Table 1) [27–46]. Moreover, two phase III trials with bevacizumab have shown activity in patients with platinum-sensitive disease previously treated with carboplatin and gemcitabine [47] and in patients with platinum-resistant disease [48].

Phase II Trials in Recurrent Disease

Bevacizumab was administered as monotherapy in a phase II trial that included patients with refractory or resistant ovarian or peritoneal carcinoma [39]. A total of 62 patients (median age 57 years) and a GOG PS score of 0–1 received bevacizumab 15 mg/kg every 3 weeks. One third (33.9%) of the eligible patients had received one previous chemotherapy regimen and

two thirds (66.1%) had received two; 67.7% of patients had received one platinum-based and 32.3% two platinum-based therapies. More than half (58.1%) of the patients had experienced a platinum-resistant recurrence, whereas 41.9% were platinum sensitive. Two patients achieved CR, 11 patients PR (overall response rate [ORR] 21%) and 32 patients (51.6%) had SD. After 6 months, 40.3% of patients had no sign of recurrent disease. Median PFS was 4.7 months and median OS was 16.9 months.

In a second phase II study, patients with platinum-resistant ovarian or peritoneal cancer and progressive disease during or within 3 months of stopping second-line therapy with topotecan or liposomal doxorubicin received bevacizumab 15 mg/kg every 3 weeks [37]. Following the inclusion of 44 heavily pretreated patients who had received at least one cycle of bevacizumab, the study was closed due to a high incidence of gastrointestinal perforations (n = 5; 11.4%). A PR was observed in seven patients (15.9%), with a response duration of 4.2 months. A total of 27 patients (61.4%) had SD and this lasted for at least 12 weeks in 11 patients (25%). Median PFS was 4.4 months and median OS was 10.7 months.

In a third phase II study, 70 patients were treated with oral cyclophosphamide 50 mg/day and bevacizumab 10 mg/kg every 2 weeks. Eligible included patients had received a median of two previous chemotherapy regimens and 40 patients (57.1%) had platinum-resistant disease. A PR was achieved in 17 patients (24%). After a median follow-up of 23.2 months, median time to progression and survival were 7.2 and 16.9 months, respectively [38].

Phase III Study: OCEANS

A total of 484 patients with platinum-sensitive ovarian cancer were randomly assigned in the phase III placebo-controlled OCEANS study to receive second-line therapy comprising carboplatin (AUC 4) plus gemcitabine (1,000 mg/m^2, days 1 and 8) combined with bevacizumab (15 mg/kg, day 1) or placebo every 3 weeks, followed by bevacizumab or placebo as maintenance therapy until disease progression [47]. The median age was 60–61 years and more than a third of the patients were older than 64 years. The platinum-free interval ranged from 6 to 12 months in approximately 40% of the patients and in 10% of patients cytoreductive surgery had been used without success. All randomly assigned patients had to have evidence of measurable disease. Patients in both study arms received a median of six chemotherapy cycles. The ORR was 78.5% in the bevacizumab arm and 57.4% in the control arm (HR 0.534; $P < 0.0001$) and CR was observed in 17% and 9% of patients, respectively. The median duration of response was 10.4 versus 7.4 months (bevacizumab vs. control). After a median follow-up of 24 months, median PFS was significantly prolonged by 4 months with the addition of bevacizumab (12.4 vs. 8.4 months) $P < 0.0001$) [47]. OS data are not sufficiently mature to draw clear conclusions.

Phase III Study: AURELIA

Patients with platinum-resistant ovarian cancer (n = 361), who had received two or fewer previous anticancer regimens and who had no history of bowel obstruction, or clinical/radiological evidence of rectosigmoid involvement were included in the AURELIA study. They were scheduled to receive chemotherapy comprising paclitaxel, topotecan or peg-liposomal doxorubicin or the same chemotherapy in combination with bevacizumab (15 mg/kg, day 1) every 3 weeks until progression or unacceptable toxicity. The median patient age was 61 years and patient characteristics were well balanced at baseline. Approximately one third of the patients

had a PFS of less than 3 months and 54% were treated with chemotherapy alone and 69% with additional bevacizumab were in good general condition (ECOG PS 0). However, patients treated with chemotherapy plus bevacizumab had previously received more chemotherapy cycles.

The best ORR (RECIST) was significantly improved in patients treated with bevacizumab (11.8 vs. 27.3%; $P < 0.001$). After a median follow-up of 13.9 months in the chemotherapy-alone arm and 13.0 months in the bevacizumab arm, PFS was significantly prolonged in patients treated with bevacizumab (3.4 vs. 6.7 months; HR 0.48; 95% CI 0.38–0.60; $P < 0.001$). OS data have not been reported to date. Hypertension (CTCAE grade ≥2) and proteinuria was observed in 6.6% and 0.6% of patients treated with chemotherapy alone versus 20.1% and 10.6% of patients treated with additional bevacizumab, respectively. Gastrointestinal perforation and arterial thromboembolic events occurred in seven (3.9%) and four patients (2.2%), respectively, all treated with bevacizumab. In conclusion, this phase III trial was the first to show a benefit with a combination regimen versus monotherapy in patients with platinum-resistant ovarian cancer [48].

Summary: Recurrent Therapy

Bevacizumab is active in the treatment of recurrent platinum-sensitive and platinum-resistant ovarian cancer, as mono or combination therapy [18, 37, 39]. The phase III OCEANS study showed a clinically relevant benefit for the combination of bevacizumab with carboplatin plus gemcitabine followed by bevacizumab until progression in recurrent, platinum-sensitive disease. In addition, treatment with bevacizumab in combination with chemotherapy prolonged PFS in patients with platinum-resistant ovarian cancer, as shown in the phase III AURELIA trial.

TOXICITY OF BEVACIZUMAB

The known toxicity profile of bevacizumab in the treatment of ovarian cancer includes hypertension as well as arterial thromboembolic events and minor bleeding. However, particular attention must be paid to the severe, albeit rare, gastrointestinal complications (e.g., perforations) of bevacizumab-treated patients with different cancer types. One phase II trial conducted by Cannistra et al. [37] demonstrated a significant increase in the incidence of gastrointestinal perforations with bevacizumab monotherapy, which led to the premature termination of the study. Of the five patients who experienced gastrointestinal perforations in that study, all had radiological evidence of bowel involvement before study entry and had received three previous chemotherapy regimens.

In the ICON 7/AGO-OVAR 11 [23] and GOG-0218 [22] trials, 2012 and 1389 patients were treated in the bevacizumab and standard treatment arms, respectively, and 43 (2.1%) and 10 (0.7%) cases of gastrointestinal complications (including perforations) occurred. Although the increased incidence of gastrointestinal complications with bevacizumab was not statistically significant in either trial, there appears to be a numerical increase in these, sometimes fatal, complications among patients treated with bevacizumab and therefore caution must be exercised.

CRITICAL ASPECTS OF THERAPY WITH BEVACIZUMAB IN OVARIAN CANCER

There is a general consensus among study groups worldwide that PFS is the preferred primary endpoint in trials of first-line therapy in patients with ovarian cancer [36]. However, the price for the modest, but significant

improvement in PFS of 1.7 months in the ICON 7/AGO-OVAR 11 study and 3.8 months in the GOG-0218 study is not negligible. Treatment has to be administered every 3 weeks for at least 1 year, or even until disease progression, nearly one quarter of the patients develop hypertension and approximately 2.5% of all patients will experience major complications (e.g., gastrointestinal perforation or major bleeding) [49]. Moreover, the financial cost is high. A cost-effectiveness analysis based on patients treated with bevacizumab maintenance therapy in the GOG-0218 study, and including the cost of bowel perforation, calculated a cost per progression-free life-year gained of US$401,088 [50]. However, because bevacizumab as first-line therapy prolongs PFS in patients with ovarian cancer, this treatment strategy should be discussed with eligible patients.

CONCLUSION

The antiangiogenic drug bevacizumab is active as first-line therapy for advanced ovarian cancer, as well as in the treatment of recurrent disease. Therefore, it represents a new option in therapy and extends the armamentarium of standard therapy.

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