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REVIEW ARTICLE

Update on the Management of Advanced Ovarian Cancer: the Role of Anti-angiogenic Agents

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ABSTRACT

Ovarian cancer is often diagnosed in its later stages, leading to poor prognosis and high mortality rates. Chemotherapy with paclitaxel plus a platinum-based drug is the standard treatment for advanced ovarian carcinoma. Angiogenesis plays a key role in normal ovarian function, as well as in the development and progression of ovarian cancer. Anti-angiogenic agents can play a pivotal role in treatment. Bevacizumab is an anti-angiogenic agent with proven efficacy across multiple cancer types. The efficacy of bevacizumab, as a single agent and in combination regimens, has been demonstrated in patients with ovarian cancer. Bevacizumab significantly prolongs progression-free survival when used as first-line therapy for patients with residual disease after surgery, as well as for those with stage IV disease. Research data also support the use of bevacizumab as second-line treatment of patients with platinum-sensitive ovarian cancer. In bevacizumab-naïve patients with platinum-resistant recurrent ovarian cancer, bevacizumab in combination with standard chemotherapy provides significant and clinically meaningful improvements in progression-free survival and objective response rate compared with chemotherapy alone. Other oral anti-angiogenic agents being investigated for the treatment of patients with ovarian cancer include cediranib, sunitinib, pazopanib, sorafenib, nintedanib, and cabozantinib. Current and emerging data for bevacizumab and other anti-angiogenic agents in the management of ovarian cancer are presented in this paper.

Key Words: *Angiogenesis inhibitors; Bevacizumab; Ovarian neoplasms*

中文摘要

治療晚期卵巢癌的最新情況：抗血管新生藥物的角色

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卵巢癌患者在確診時往往已發展至晚期，所以預後較差，死亡率亦較高。化學治療以paclitaxel加上含鉑藥物是治療晚期卵巢癌的標準方法。血管新生的情況對於卵巢是否能正常運作，以及對其病情發展和會否惡化都相當重要，所以抗血管新生藥物成為治療關鍵。Bevacizumab是一種抗血管新生藥物，對於不同種類的癌症都證實有效。無論作為單一治療或合併藥物，bevacizumab都對卵巢癌有療效。對於術後有殘餘腫瘤和第四期卵巢癌的病人，作為一綫治療的bevacizumab可延長其無惡化生存期。至於那些對含鉑藥物有效的卵巢癌患者，研究結果亦顯示bevacizumab可作為二綫治療。對含鉑藥物有抗藥性的卵巢癌復發而未曾接受bevacizumab治療的患者，bevacizumab結合標準化療能顯著改善其無惡化生存期及客觀反應率，臨床上比只用化療的方法更為有效。其他正進行研究用作治療卵

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巢癌的口服抗血管新生藥物包括cediranib、sunitinib、pazopanib、sorafenib、nintedanib和cabozantinib。本文討論bevacizumab和其他抗血管新生藥物用作治療卵巢癌的最新資料。

INTRODUCTION

Ovarian cancer is known to be the most lethal of gynaecological cancers.[1] Despite aggressive primary therapy and promising initial response rates (RRs), most women with advanced ovarian carcinomas will relapse and develop drug-resistant disease.[2]

In Hong Kong, ovarian cancer is the seventh most common cancer in women, accounting for 3.7% of all new cancers affecting women in 2009.[3] In 2009, 449 new cases of ovarian cancer were diagnosed and the crude incidence rate was 12.2 per 100,000 female population. The age-standardised incidence rate was 9.0 per 100,000 standard population. Over the past two decades, there has been an upward trend in the age-standardised incidence rate.[3]

Ovarian cancer is the seventh leading cause of female cancer deaths in Hong Kong, and a total of 164 women died from this cancer in 2010.[3] Typically, signs and symptoms of ovarian cancer are absent early in the course of the disease and, if symptoms are present, these tend to be subtle and non-specific.[4] As a consequence, it is a disease difficult to be diagnosed until it advances to later stages.[5] About 70 to 80% of women with ovarian cancer already have disease spread beyond the ovaries at presentation.

Ovarian cancer is staged according to the International Federation of Gynaecology and Obstetrics (FIGO) staging system and staging includes information obtained after surgery. The management of ovarian cancer is based on the stage of the disease at diagnosis. In the majority of patients, the disease is fatal, but optimal multidisciplinary care, both initially and at relapse, has led to improvements in five-year overall survival (OS).

EVOLUTION OF OVARIAN CANCER TREATMENT OPTIONS

Cisplatin was the first chemotherapeutic agent used for the treatment of ovarian cancer. About a decade later, carboplatin was introduced, followed shortly by paclitaxel in the late 1980s. Chemotherapy with paclitaxel plus a platinum-based drug remains the standard treatment for advanced ovarian carcinoma. Clinical studies guide clinicians on the ways to optimise this treatment in day-to-day practice.

Attempts to improve patient survival by including other drugs have yielded disappointing results. Addition of a third cytotoxic agent (e.g. gemcitabine) provided no benefit in progression-free survival (PFS) or OS after optimal or suboptimal cytoreduction compared with standard paclitaxel and carboplatin.[6] Intraperitoneal administration of chemotherapy only conferred positive results with cisplatin 100 mg/m^2, and quality of life has been shown to be significantly worse for patients receiving intraperitoneal therapy than for those receiving intravenous therapy.[7]

The most promising data for first-line treatment in the context of conventional chemotherapy has incorporated the use of weekly paclitaxel.[8,9] Katsumata et al[8] compared a conventional regimen of paclitaxel and carboplatin with a dose-dense weekly regimen in women with advanced ovarian cancer. In this phase 3 open-label multicentre trial, Japanese patients were randomly assigned to receive six cycles of:

- paclitaxel 180 mg/m^2 plus carboplatin area under the curve (AUC) 6 mg/ml/min, given on day 1 of a 21-day cycle (conventional regimen; n = 320)
- dose-dense paclitaxel 80 mg/m^2 given on days 1, 8, and 15 plus carboplatin AUC 6 mg/mL/min given on day 1 of a 21-day cycle (dose-dense regimen; n = 317).

Remarkably, median PFS was significantly longer in the dose-dense treatment group (28.0 months) than in the conventional treatment group (17.2 months) [hazard ratio (HR) = 0.71; p = 0.0015). OS at 3 years was also higher in the dose-dense regimen group (72.1%) than in the conventional treatment group (65.1%) [HR = 0.75; p = 0.03].

For about 20 years, there have been few emerging novel treatments. It was only in recent years that bevacizumab became available for clinical assessment, and it now seems set to be added to the pharmaceutical armamentarium for the treatment of ovarian cancer.

ANGIOGENESIS AND OVARIAN CANCER

Angiogenesis is a fundamental process required for tumour growth and metastasis, mediated primarily through the interaction between vascular endothelial growth factor (VEGF) and VEGFR-2 (receptor tyrosine kinase of the VEGF receptor family).[10,11] Angiogenesis is a complex and highly regulated process by which tumours develop new vasculature.[11-13] In response to stimuli (such as oxidative and mechanical stresses) and acidosis, cytokines and proangiogenic growth factors (e.g. VEGF, fibroblast growth factor) are released.[14] These factors activate endothelial cells and endothelial progenitor cells to form new blood vessels.

VEGF plays a key role in both normal ovarian function and in the development and progression of ovarian cancer.[15] VEGF-related growth factors and receptors are primary signalling pathways in tumour angiogenesis and have been implicated as regulators of angiogenesis and disease progression in ovarian cancer.[16] High degrees of tumour angiogenesis and VEGF expression in ovarian carcinomas correlate with poor survival. Given the central role of angiogenesis in ovarian tumour development, anti-angiogenic agents can play a pivotal role in treatment.

BEVACIZUMAB IN THE TREATMENT OF OVARIAN CANCER

Bevacizumab directly inhibits VEGF extracellularly and may therefore cause angiogenesis inhibition without disrupting targets outside the VEGF pathway.[11,13,17,18] The efficacy of bevacizumab, as a single agent and in combination with other modalities, in ovarian cancer has been demonstrated.[19]

Single-agent Bevacizumab

Bevacizumab has more single-agent activity in epithelial ovarian cancer (EOC) than in any other epithelial cancer, apart from renal cancer, as the vascular biology is specifically relevant to this therapeutic approach.[20]

In a phase 2 trial, Burger et al[19] demonstrated that 21.0% of patients had clinical responses (2 complete, 11 partial; median response duration, 10 months), while 40.3% had PFS of at least 6 months. Median PFS and OS were 4.7 and 17.0 months, respectively. Bevacizumab seems to be well-tolerated and active in the second- and third-line treatment of patients with recurrent EOC/primary peritoneal cancer.

In another phase 2 study, partial responses were observed in 16% of patients.[21] Median PFS was 4.4 months (95% confidence interval [CI], 3.1-5.5 months) and the median survival duration was 10.7 months at study termination. Bevacizumab-associated grade 3 to 4 events included hypertension (9.1%), proteinuria (15.9%), bleeding (2.3%), and wound healing complications (2.3%). This study was terminated early due to an 11% incidence of bowel perforations.

Efficacy and Safety of First-line Bevacizumab in Combination with Chemotherapy

There are two phase 3 clinical trials (Gynecologic Oncology Group [GOG]-0218[22] and ICON-7[23]) that have firmly defined the role of bevacizumab in combination with chemotherapy as first-line treatment.

Gynecologic Oncology Group–0218

GOG-0218[22] is a double-blind, placebo-controlled, phase 3 trial involving 1873 patients with newly diagnosed stage 3 (incompletely resectable) or stage 4 EOC who had undergone debulking surgery to receive one of the following three treatments:

- bevacizumab throughout: paclitaxel 175 mg/m^2 3-weekly plus carboplatin AUC 6 mg/ml/minute for cycles 1 to 6 plus bevacizumab 15 mg/kg 3-weekly for cycles 2 to 22;
- bevacizumab initiation: paclitaxel 175 mg/m^2 3-weekly plus carboplatin AUC 6 mg/ml/minute for cycles 1 to 6 plus bevacizumab 15 mg/kg 3-weekly for cycles 2 to 6 then placebo for cycles 7 to 22; and
- control: paclitaxel 175 mg/m^2 3-weekly plus carboplatin AUC 6 mg/ml/minute for cycles 1 to 6 plus placebo 3-weekly for cycles 2 to 22.

The primary endpoint was PFS.

The median PFS was 14.1 months in the bevacizumab-throughout group, 11.2 months in the bevacizumab-initiation group, and 10.3 months in the control group. In a subgroup analysis (required for regulatory purposes), patients who discontinued treatment due to elevated levels of cancer antigen-125 (CA-125) were excluded (CA-125–censored group). In the CA-125–censored patient group, there was a significant difference in PFS between the bevacizumab-throughout and the control groups (18.2 vs. 12.0 months, respectively; $p < 0.0001$).

Relative to control treatment, the HR for progression or death was 0.908 ($p = 0.16$) with bevacizumab initiation and 0.717 ($p < 0.001$) with bevacizumab throughout. At the time of analysis, 76.3% of patients were alive, with

no significant differences in OS among the three groups. The use of bevacizumab during and up to 10 months after standard carboplatin and paclitaxel chemotherapy prolonged the median PFS by about four months in patients with advanced EOC.

ICON-7

ICON-7[23] was a multicentre phase 3 study of 1528 women with ovarian cancer who were randomised to receive one of the following two treatments:

- standard therapy: carboplatin AUC 5 or 6 mg/ml/minute plus paclitaxel 175 mg/m^2 3-weekly for 6 cycles; or
- standard therapy plus bevacizumab: carboplatin AUC 5 or 6 mg/ml/minute plus paclitaxel 175 mg/m^2 3-weekly for 6 cycles plus bevacizumab 7.5 mg/kg 3-weekly for 5 or 6 cycles, and continued for 12 additional cycles or until progression of disease.

Outcome measures included PFS and interim OS.

PFS was 16.9 months with standard therapy compared with 19.3 months with standard therapy plus bevacizumab (HR for progression or death with bevacizumab added, 0.86; p = 0.0185). Non-proportional hazards were detected (i.e. the treatment effect was not consistent over time on the hazard function scale) [p < 0.001], with a maximum effect at 12 months, coinciding with the end of planned bevacizumab treatment, and diminishing by 24 months.

In patients at high risk for progression (patients with FIGO stage 3 [suboptimal debulking] and stage 4 disease), the benefit was greater with bevacizumab than without it, with median PFS of 10.5 months with standard therapy alone and 15.9 months with bevacizumab added, and respective median OS of 28.8 and 36.6 months, respectively. These results show a significant improvement in OS in this high-risk subgroup of ICON-7, probably due to the lack of availability of bevacizumab at progression in this patient population.

Bevacizumab improved PFS in women with ovarian cancer. The benefits with respect to both PFS and OS were greater among those at high risk for disease progression.

Safety

In the GOG-0218 study,[22] the rate of hypertension requiring medical therapy was higher in the bevacizumab-initiation group (16.5%) and the bevacizumab-throughout group (22.9%) than in the control group (7.2%). Gastrointestinal wall disruption requiring medical intervention occurred in 1.2%, 2.8%, and 2.6% of patients in the control, bevacizumab-initiation, and bevacizumab-throughout groups, respectively. These rates were similar to those observed in trials of bevacizumab in other cancers.

In the ICON-7 study,[23] bevacizumab was associated with more toxic effects (most often hypertension of grade 2 or higher; 18% vs. 2% with chemotherapy alone). There appeared to be no differences in key side-effects between patients treated with either 7.5 mg/kg or 15 mg/kg of bevacizumab.

Summary

Based on these studies, bevacizumab is shown to be effective when used in combination with standard chemotherapy as first-line treatment for ovarian cancer. A key issue is whether a subgroup of patients treated at first-line could be identified as most likely to benefit from this agent. In this context, exploratory analysis of three prospective randomised trials (Arbeitsgemeinschaft Gynaekologische Onkologie Studiengrappe Ovarialkarzinom [AGO-OVAR] 3, 5, and 7) investigating platinum-taxane–based chemotherapy regimens in advanced ovarian cancer conducted between 1995 and 2002 showed improved PFS and OS in patients with complete resection (p < 0.0001).[24] The goal of primary surgery is complete resection. If this is not achieved, the outcome is less favourable and for these patients (i.e. those with stage 4 ovarian cancer or residual disease following primary debulking surgery), bevacizumab could be recommended in addition to standard platinum-taxane–based chemotherapy. On the other hand, for those patients with a favourable outlook (i.e. with no residual disease after primary surgery), bevacizumab could be withheld for later line treatment (e.g. sensitive relapse).

Even though the ICON-7 study shows that 7.5 mg/kg may be a sufficiently efficacious dose, the approved dose of bevacizumab for the treatment of ovarian cancer is 15 mg/kg. Bevacizumab treatment should be continued for 15 months based on PFS benefits shown in the GOG-0218 study. Bevacizumab could potentially have OS benefits in patients with high-risk FIGO stage 3 and 4 ovarian cancer, as shown by the ICON-7 study.

Efficacy and Safety of Second-line Bevacizumab in Combination with Chemotherapy

For patients with platinum-sensitive recurrent ovarian cancer, bevacizumab has also been shown to be effective. The recently published OCEANS trial is a randomised multicentre blinded placebo-controlled phase 3 trial conducted to test the efficacy and safety of bevacizumab (15 mg/kg 3-weekly) with gemcitabine and carboplatin (GC) compared with GC alone in 484 patients with platinum-sensitive recurrent ovarian, primary peritoneal, or fallopian tube cancer.[25] Patients with platinum-sensitive cancers (recurrence ≥6 months after first-line platinum-based therapy) and measurable disease were randomly assigned to either bevacizumab + GC or GC + placebo for 6 to 10 cycles. Bevacizumab or placebo, respectively, was then continued until disease progression. The primary endpoint was PFS by Response Evaluation Criteria In Solid Tumors (RECIST) criteria. Secondary endpoints were objective response rates (ORR), duration of response, OS, and safety.

PFS for the bevacizumab group was superior to that for the control group (HR = 0.484; $p < 0.0001$). Median PFS was 12.4 versus 8.4 months, respectively. ORR (78.5% vs. 57.4%; $p < 0.0001$) and duration of response (10.4 vs. 7.4 months; HR = 0.534) were significantly improved with the addition of bevacizumab. No new safety concerns were noted.

Grade 3 or higher hypertension (17.4% vs. <1%) and proteinuria (8.5% vs. <1%) occurred more frequently in the bevacizumab group. The rates of neutropaenia and febrile neutropaenia were similar in both groups. Only two patients in the bevacizumab group experienced gastrointestinal perforation after study treatment discontinuation.

In summary, OCEANS showed that second-line treatment with GC plus bevacizumab at the dose of 15 mg/kg 3-weekly followed by bevacizumab until progression resulted in a statistically significant improvement in PFS compared with GC treatment alone in patients with platinum-sensitive recurrent ovarian, primary peritoneal, or fallopian tube cancers.

Efficacy and Safety of Bevacizumab in Combination with Chemotherapy for Patients with Platinum-resistant Recurrent Ovarian Cancer

AURELIA is the fourth phase 3 study in ovarian cancer to show that adding bevacizumab to chemotherapy significantly increased PFS.[26] AURELIA is a multicentre randomised open-label 2-arm phase 3 study of 361 women with platinum-resistant recurrent EOC, primary peritoneal, or fallopian tube cancer (measurable by RECIST 1.0 or assessable) who had received no more than two anticancer regimens prior to enrolment in the trial and had progressed ≤six months after ≥four cycles of platinum-based therapy. The trial was designed to evaluate bevacizumab (10 mg/kg every 2 weeks or 15 mg/kg every 3 weeks) in combination with standard chemotherapy (either weekly paclitaxel or topotecan or pegylated liposomal doxorubicin) compared with standard chemotherapy alone. The primary endpoint of the study was PFS. The secondary endpoints of the study included OS, ORR, quality of life, safety, and tolerability.

Women who received bevacizumab in combination with chemotherapy had a median PFS of 6.7 months compared with 3.4 months for women who received chemotherapy alone ($p < 0.001$). In a subgroup analysis, PFS benefits were most evident in patients who were concurrently receiving paclitaxel chemotherapy. In addition, these patients had a significantly higher ORR than women who received chemotherapy alone (30.9% vs. 12.6%, respectively; $p = 0.001$). Select adverse events (grades 2–5) that occurred more often in the bevacizumab group compared with the chemotherapy alone group were high blood pressure (20% vs. 7%) and proteinuria (11% vs. 1%). Gastrointestinal perforations and fistulas occurred in 2% of women in the bevacizumab group, while none of those in the chemotherapy-only group experienced these effects. Indeed, the adverse event data indicated that patients receiving concurrent bevacizumab had fewer (disease-related) symptoms, including nausea and fatigue.

Summary

In platinum-resistant ovarian cancer, bevacizumab used in combination with standard chemotherapy provides statistically significant and clinically meaningful improvements in PFS and ORR compared with chemotherapy alone. Strict screening can minimise the incidence of bevacizumab adverse events, particularly the incidence of gastrointestinal perforations. OS data from the AURELIA study are expected by 2013.

Other Ongoing Trials with Bevacizumab

AGO-OVAR17 is a prospective randomised phase 3 trial to evaluate optimal treatment duration of first-line bevacizumab in combination with carboplatin and paclitaxel in patients with primary EOC, fallopian tube, or peritoneal cancers.

Currently recruiting, the BOOST trial (NCT1462890) seeks to determine whether the early and continuous addition of bevacizumab to standard chemotherapy for up to 30 months is more effective than the early and continuous addition of bevacizumab for up to 15 months.

ROSIA (NCT01239732) is an open-label non-comparative multicentre study to assess the safety and efficacy of bevacizumab when added to carboplatin and paclitaxel therapy in patients with EOC, fallopian tube, or primary peritoneal carcinoma. Patients will receive bevacizumab 15 mg/kg on day 1 of every cycle for up to 36 cycles of 3 weeks each, carboplatin AUC 5-6 mg/ml/minute on day 1 every 3 weeks for a maximum of 8 cycles, and paclitaxel 175 mg/m^2 on day 1 every 3 weeks or 80 mg/m^2 every week for a maximum of 8 cycles. The anticipated time on the study drug will be 108 weeks or until disease progression or unacceptable toxicity.

GOG-213 (NCT00565851) is a randomised phase 3 trial investigating the efficacy of carboplatin plus paclitaxel with or without bevacizumab after surgery in patients with recurrent platinum-sensitive EOC, primary peritoneal cavity cancer, or fallopian tube cancer. Currently, patient recruitment for this study has been completed.

OCTAVIA is a single-arm study evaluating first-line bevacizumab plus weekly paclitaxel plus 3-weekly carboplatin in the treatment of patients with ovarian cancer. Patients received 6 to 8 cycles of bevacizumab 7.5 mg/kg on day 1 plus weekly paclitaxel 80 mg/m^2 on days 1, 8, and 15 plus carboplatin AUC 6 mg/ml/minute intravenously 3-weekly on day 1, with bevacizumab 3-weekly continued alone for up to 17 cycles as first-line therapy. The primary endpoint was PFS. Secondary endpoints included RR, duration of response, OS, biological progression-free interval, and safety. Safety data from the study were presented at ASCO 2012.[27]

A trial is currently being planned to evaluate the efficacy and safety of bevacizumab plus chemotherapy in patients with recurrent ovarian cancer after the repeat or continuous use of bevacizumab at progression.

Conclusions of Bevacizumab Treatment

Bevacizumab significantly prolongs PFS when used as first-line treatment for patients with residual disease after surgery, as well as those with stage 4 disease, and its use for these patients, concurrently with chemotherapy and as maintenance treatment, is recommended. However, bevacizumab could be reserved for use for first relapse in the best prognosis group (i.e. those with optimal surgery [no resistant disease] and first-line treatment). Once approved, the data also support the use of bevacizumab, together with GC, as second-line treatment for patients with platinum-sensitive ovarian cancer.

In bevacizumab-naïve patients with platinum-resistant recurrent ovarian cancer, bevacizumab in combination with standard chemotherapy provides significant and clinically meaningful improvements in PFS and ORR compared with chemotherapy alone.

OTHER ANTI-ANGIOGENIC AGENTS FOR THE TREATMENT OF PATIENTS WITH OVARIAN CANCER

There are currently six oral anti-angiogenic agents being investigated for the treatment of patients with ovarian cancer. These are cediranib, sunitinib, pazopanib, sorafenib, nintedanib (BIBF1120), and cabozantinib (XL184).

Cediranib is a tyrosine kinase inhibitor. ICON-6 is a phase 3 study comparing chemotherapy alone with chemotherapy plus cediranib for relapsed ovarian cancer. The trial will be completed in 2014.

Single-agent sunitinib has modest activity in recurrent platinum-sensitive ovarian cancer, but only at the 50 mg intermittent dose schedule.[28]

An open-label phase 2 study showed that pazopanib monotherapy was relatively well-tolerated with toxicity similar to other small-molecule oral angiogenesis inhibitors, and demonstrated promising single-agent activity in patients with recurrent ovarian cancer. A first-line treatment trial evaluating the potential role of pazopanib as maintenance therapy in patients with ovarian cancer is ongoing.[29]

Sorafenib is a multikinase inhibitor that was investigated in an open-label multicentre phase 2 study involving patients with persistent or recurrent ovarian cancer. This study showed that sorafenib has modest anti-tumour activity in patients with recurrent ovarian cancer, but the activity was at the expense of substantial toxicity.[30]

The LUME-Ovar 1 study (NCT 01015118) will

evaluate whether nintedanib in combination with paclitaxel and carboplatin is more effective than placebo in combination with paclitaxel and carboplatin in first-line treatment of patients with advanced ovarian cancer.

Cabozantinib was investigated in patients with EOC with progressive measurable disease. Patients were administered cabozantinib 100 mg daily over a 12-week lead-in stage. Up to two prior regimens were allowed for platinum-resistant patients and up to three prior regimens for platinum-sensitive patients. The primary endpoints were ORR in the lead-in stage and PFS in the randomised period. The study showed that cabozantinib exhibits clinical activity in ovarian cancer patients with advanced disease, regardless of prior platinum status.[31]

AMG 386 is an anti-angiopoietin peptibody that targets the angiopoietin axis by blocking the interactions between angiopoietins-1 and -2 (Ang1 and Ang2) and their receptor Tie2. Ang1 and Ang2 each play a significant role in the growth and stabilisation of neovascular vessels. The TRINOVA-1 study (NCT01204749) is being conducted to determine whether treatment with paclitaxel plus AMG 386 is superior to paclitaxel plus placebo in women with recurrent partially platinum sensitive or resistant EOC, primary peritoneal cancer, or fallopian tube cancer.

TARGETING ANGIOGENESIS IN OVARIAN CANCER: LOOKING TO THE FUTURE

Multiple approaches for anti-angiogenic therapies in ovarian cancer are currently being studied. Future studies will hopefully shed light on the role of various new agents and also examine the potential for rational combinations or sequential therapy. A better understanding of both horizontal and vertical signalling pathways, identification of predictive markers to better identify a targeted subpopulation of patients that will respond, and an improved appreciation of the underlying mechanisms of resistance to anti-angiogenic therapy, should all contribute to improved treatment for this disease. Only then can we truly make informed decisions on personalised targeted therapy for our patients with ovarian cancer. At this stage, data with bevacizumab have clearly demonstrated that anti-angiogenesis is a major step forward for the treatment of ovarian cancer.

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