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REVIEW ARTICLE

Emerging Novel Therapies in Recurrent Ovarian Cancer: Anti-angiogenesis

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ABSTRACT

Ovarian cancer is the leading cause of gynaecological cancer death in Hong Kong. It is often diagnosed late due to the absence of a means for routine screening. Up to 75% of patients relapse in spite of good initial response to platinum therapy. The patient response to chemotherapy in recurrent ovarian cancer can be predicted by the length of the platinum-free interval. Following relapse, chemotherapy is the standard of care, with response rates typically in the range of 17 to 31%; however, there have been few advances in chemotherapeutic agents in recent years. In comparison, an increasing number of anti-angiogenesis agents have been developed and investigated, based on the rationale that vascular endothelial growth factor (VEGF) — the driving force behind angiogenesis — is implicated in all stages of pathogenesis in ovarian cancer. Bevacizumab is a recombinant humanised monoclonal antibody of the immunoglobulin G1 isotype with high specificity and affinity for VEGF, resulting in potent VEGF-neutralising activity. It was the first anti-angiogenesis agent to be tested in ovarian cancer in phase III randomised clinical trials, both as first-line (GOG128 and ICON7) and second-line therapy (AURELIA and OCEANS). These trials demonstrated definitively the activity of bevacizumab in ovarian cancer, proving the concept that anti-angiogenesis is a viable and effective treatment option in ovarian cancer. Other classes of anti-angiogenesis agents currently under investigation that have shown early promise include the VEGF receptor / multi-target tyrosine kinase inhibitors and anti-angiopoietins.

Key Words: *Antiangiogenesis inhibitors; Molecular targeted therapy; Ovarian neoplasms; Vascular endothelial growth factor*

中文摘要

復發性卵巢癌的新興療法：抗血管生成

E Pujade-Lauraine

卵巢癌是香港婦科癌症死亡率最高的癌症。由於缺乏常規篩查，卵巢癌往往被遲診。儘管患者對鉑類治療有良好的初步反應，可是高達75%的患者仍會復發。復發性卵巢癌患者對化療的反應可以由「無鉑時段」的長短來預測。化療是復發性卵巢癌的治療標準，患者的反應率一般介乎17%至31%，可是近年化療藥物的進展有限。相對而言，越來越多的抗血管試劑已被開發和在研究中試驗，這些都是基於血管內皮生長因子（VEGF），即血管增生的驅動力，牽涉於卵巢癌各階段的發病機制中。貝伐單抗（bevacizumab）是免疫球蛋白G1同種型的重組人源化單克隆抗體，具有高特異性和VEGF親和力，從而能中和VEGF。貝伐單抗成為首個臨床試驗的抗血管試劑，在卵巢癌的III期隨

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機臨床試驗作為一線（GOG128和ICON7）和二線治療（AURELIA和OCEANS）。這些試驗明確顯示貝伐單抗在卵巢癌的效用，證明抗血管生成是卵巢癌的一種可行及有效的治療。目前經已初見成效的其他抗血管生成劑包括血管內皮生長因子受體／多靶點酪氨酸激酶抑製劑和抗血管生成素。

INTRODUCTION

Ovarian cancer is the most lethal gynaecological cancer in Hong Kong, accounting for 2.7% of all cancer deaths among local women and 3.7% of the total cancer incidence.[1] Most cases of ovarian cancer present late primarily owing to the fact that there is no means to routinely screen for ovarian cancer at present. The disease is characterised by multiple relapses; despite the initial good response to platinum therapy, up to 75% of cases will relapse. A number of treatment options exist following relapse. Ideally, any treatment plan should take into account factors such as the patient's age, frailty, treatment history, acceptance / tolerability of potential side-effects (such as hair loss), and her personal preferences.

CURRENT TREATMENT OF RECURRENT OVARIAN CANCER

Treatment of recurrent ovarian cancer primarily involves palliation to control disease-related symptoms (while limiting treatment-related toxicity), maintain or improve quality of life, delay the time to progression and, ultimately, prolong survival.[2] Platinum is the cornerstone first-line treatment in ovarian cancer. One of the most important and reliable predictors of response following initial treatment is the patient's platinum-free interval (PFI).[3]

Platinum-free interval is defined as the interval from the date of the last platinum dose to the first date of disease progression. According to the response to platinum therapy (i.e., the length of PFI), the expected platinum sensitivity of ovarian cancer can be divided into one of the four categories: platinum-refractory, if there is progression or stable disease during or within 1 month of first-line therapy; platinum-resistant, if there is a response during therapy and relapse within 6 months; platinum-sensitive, if there is a relapse after 12 months post-therapy; and platinum partially sensitive, if there is relapse within 6 to 12 months, demonstrating intermediate sensitivity to platinum. Simply put, the longer the PFI, the better the outcome. In the course of ovarian cancer, each patient will likely transition through and experience more than one category of platinum sensitivity, and the PFI gets shorter with each relapse. Moreover, clinically, the length of PFI is strongly predictive of overall survival (OS), progression-free survival (PFS), and response rate.[3]

Rationale for Anti-angiogenesis in Recurrent Ovarian Cancer

In the setting of recurrence, chemotherapeutic agents are the mainstay of treatment; however, there have been few advances in chemotherapy in recent years. In contrast, the field of biologic therapy has grown substantially and, taking into account the number of targeted agents currently being investigated in preclinical and clinical trials, it is valid to say that ovarian cancer management has entered the era of biologic therapy.

Vascular endothelial growth factor (VEGF) is the major driving force behind tumour angiogenesis, also evident in ovarian cancer, such that its inhibition represents an attractive therapeutic target. In ovarian cancer, VEGF plays a central role in all stages of pathogenesis, including the critical initiation phase. The over-expression of VEGF in ovarian cancer is strongly correlated with the formation of malignant ascites, poor prognosis, worse outcomes, and reduced survival.[4-7]

BEVACIZUMAB IN THE TREATMENT OF OVARIAN CANCER

Bevacizumab (BEV) is a recombinant humanised monoclonal antibody of the immunoglobulin G1 isotype, which binds to all isoforms of VEGF with high specificity and affinity, resulting in potent VEGF-neutralising activity.[8-11] It was the first biologic therapy to be investigated in ovarian cancer in four phase III randomised controlled trials, two in the front-line setting (GOG218 and ICON7) and two in the recurrent setting (AURELIA and OCEANS).[12-15] All four trials showed efficacy of BEV, thereby proving the concept that anti-angiogenesis targeting VEGF is an active and viable therapeutic option in ovarian cancer.[16] Based on the data from these clinical trials, BEV was approved as first- and second-line therapy in platinum-sensitive recurrent ovarian cancer in Hong Kong and the European Union.

Platinum-resistant Disease

In platinum-resistant disease (relapse <6 months), the standard strategy prior to the availability of BEV was treatment with a non-platinum single agent such as

pegylated liposomal doxorubicin (PLD), topotecan, or paclitaxel. These single agents exhibited similar activity in clinical trials, and were associated with response rates of 17 to 31%, median PFS of 3 to 4 months, and median OS of 8 to 12 months.[17]

In comparison, three early phase II trials of BEV as a single agent in heavily pre-treated ovarian cancer patients also showed activity, with overall response rates of 16 to 30%, median PFS of up to 5.9 months, and median OS of up to 10.7 months.[10,18,19] Although one of these trials revealed an early safety warning of increased risk of bowel perforation,[18] greater experience with BEV has since shown that this risk can be avoided with careful and strict patient selection among those with platinum-resistant disease or who have been heavily pre-treated. Specifically, bowel perforation is correlated with the number of previous lines of therapy, a history of bowel occlusive disease, and signs of tumour bowel involvement (clinical sign of bowel obstruction; subocclusive or occlusive disease; or radiological sign of malignant bowel infiltration). By excluding these patients from BEV therapy, the risk of bowel perforation can be avoided.

Based on these promising phase II results, BEV was investigated in the randomised phase III AURELIA trial of recurrent platinum-resistant ovarian cancer.[15,20] However, unlike the phase II studies that previously investigated single-agent BEV, AURELIA compared standard chemotherapy with the combination of BEV plus chemotherapy. Patients were included in AURELIA if they had ovarian cancer that progressed within 6 months of completing at least four cycles of platinum-based therapy and no history of bowel complications. Chemotherapy was selected by the investigator based on patients' prior drug exposure, and options included PLD, topotecan, or weekly paclitaxel. Patients were randomised to receive chemotherapy alone or in combination with BEV 15 mg/kg every 3 weeks or 10 mg/kg every 2 weeks until disease progression or unacceptable toxicity. Those in the chemotherapy arm were permitted to cross over to BEV monotherapy upon disease progression. At median follow-up (13.9 months in the standard chemotherapy group, 13 months in the BEV group), the median PFS was 3.4 months in patients receiving standard chemotherapy alone versus 6.7 months in those receiving BEV and chemotherapy ($p < 0.001$). Furthermore, subgroup analysis indicated that the addition of BEV to standard chemotherapy improved PFS regardless of age, relapse-free interval, extent of disease, presence of ascites, or type of chemotherapy administered.

Evaluation by the Response Evaluation Criteria In Solid Tumors (RECIST) criteria and CA-125 levels found that the response rate was significantly greater with BEV and chemotherapy versus standard chemotherapy (30.9% vs. 12.6%; $p < 0.001$). There were also improvements in the patient global health status / quality-of-life score, as measured by the European Organization for Research and Treatment of Cancer QLQ-C30 questionnaire, and in the specific domains of physical function, role function, and social function of this questionnaire. The safety profile of BEV in AURELIA was consistent with previous clinical experience; hypertension and proteinuria (≥ grade 2) were more frequent in the BEV group than in the chemotherapy alone group, but the incidence of fatigue, abdominal pain, vomiting, and dyspnoea was less frequent than in the chemotherapy alone group.

Thus, AURELIA was the first randomised phase III trial to demonstrate benefit with a biologic therapy, within a combination regimen, in patients with platinum-resistant ovarian cancer. As such, the researchers suggested that BEV combined with chemotherapy should be considered a new standard of care in platinum-resistant disease.

Platinum-sensitive Disease

The efficacy and safety of adding BEV to combination regimen with gemcitabine-carboplatin (GC) was evaluated in the setting of recurrent measurable platinum-sensitive ovarian cancer, in the phase III randomised, multicentre, blinded, placebo-controlled OCEANS trial.[14] Patients were randomised to receive GC plus either BEV 15 mg/kg every 3 weeks or placebo for 6 to 10 cycles, after which BEV or placebo, respectively, was continued until disease progression. The primary endpoint was PFS by RECIST, and secondary endpoints were objective response rate, duration of response, OS, and safety. Patients receiving BEV plus GC showed a significantly higher objective response rate (78.5% vs. 57.4%; $p < 0.0001$), and longer median PFS (12.4 months vs. 8.4 months; hazard ratio [HR] = 0.484; 95% confidence interval [CI], 0.388-0.605; $p < 0.0001$) compared with the GC-placebo group. There were no new safety concerns with BEV; grade 3 or higher hypertension (17.4% vs. 1%) and proteinuria (8.5% vs. 1%) occurred more frequently in the BEV arm. Preliminary data on OS (median, 33

months) failed to show any significant difference in OS between the two treatments. One explanation for this result may be the crossover design of the trial, which may have been a confounding factor; approximately 40% of patients in the standard chemotherapy arm were subsequently allowed to receive BEV. Nevertheless, given the highly significant improvement in PFS, BEV plus GC represents another possible therapeutic option in recurrent platinum-sensitive disease.

When to Re-introduce Bevacizumab Following Relapse?

Although the current evidence from phase III clinical trials indicates an effective role for BEV in both first- and second-line treatment of ovarian cancer, it is unclear as to whether BEV should be re-introduced after relapse in the second-line setting if it was originally used in front-line treatment. To answer this critical question, the MITO-16/MaNGO OV-2 trial was initiated and is currently ongoing. It aims to randomise patients with platinum-sensitive disease (relapse at ≥6 months), who were initially treated with chemotherapy plus BEV, to receive either standard chemotherapy or standard chemotherapy plus BEV. Thus, this trial should help determine the efficacy of repeat BEV treatment in patients who have already been exposed to anti-VEGF therapy; all previous BEV trials in recurrent ovarian cancer were conducted in BEV-naive patients.

OTHER BIOLOGIC AGENTS TARGETING ANGIOGENESIS

Angiogenesis is a complex process that involves not only VEGF, but other angiogenic growth factors such as platelet-derived growth factor (PDGF) and fibroblast growth factor (FGF). There is also heterogeneity in the secretion of angiogenic factors by tumour cells, which increases the number of potential therapeutic targets and the complexity of treatment. Furthermore, the inhibition of VEGF can result in compensatory upregulation of FGF, PDGF and other growth factors, which may lead to reactivation of angiogenesis and resistance to VEGF-targeted agents.[21] Thus, there is a rationale for the development of novel anti-angiogenesis agents that target more than one growth factor.

In ovarian cancer, nintedanib, pazopanib, and cediranib are novel small molecules that have shown the most promise in anti-angiogenesis and are most studied in phase III clinical trials. Pazopanib is an oral tyrosine kinase inhibitor of the VEGF receptor-1, -2 and -3, PDGF receptor-α and -β, and c-Kit.[22] In a phase II study of pazopanib, 11 (31%) of 36 patients had a CA-125 response, with median time to response of 29 days and median response duration of 113 days. The overall response rate was 18% in patients with measurable disease at baseline. The most common adverse events leading to study drug discontinuation were grade 3 elevation of alanine aminotransferase and aspartate aminotransferase; in total, 19% of patients discontinued pazopanib due to toxicity.[23]

Subsequently, the phase III double-blind, multicentre, randomised AGO OVAR 16 study was conducted to investigate the efficacy of pazopanib versus placebo, following first-line chemotherapy, in patients with ovarian, fallopian tube or primary peritoneal cancer, for up to 24 months.[24] The recently reported results showed that median PFS was significantly prolonged with pazopanib maintenance treatment versus placebo (17.9 months vs. 12.3 months; HR = 0.766; 95% CI, 0.643-0.911; p = 0.0021); OS data were immature at this first interim analysis. The most frequent adverse events with pazopanib were hypertension (≥ grade 2), diarrhoea, liver toxicity, and neutropenia. In total, 58% of patients in the treatment arm required dose reduction compared with 14% in the placebo arm. Furthermore, Asian women had a lower tolerance to pazopanib, with 75% requiring dose reduction compared with 53% of non-Asian patients. The mean daily dose of pazopanib associated with the median PFS benefit was 585 mg; however, most Asian women required dose reduction and their mean daily dose of pazopanib was 344 mg. Whether pazopanib remains active in Asian women at these substantially lowered doses is unknown and needs to be studied further.

Another class of agents currently in development that has sparked considerable interest is the anti-angiopoietins, which interrupt the angiopoietin/Tie2 axis involved in vessel stabilisation during angiogenesis.[25] Trebananib, a recombinant peptide-Fx fusion protein (peptibody) that inhibits the interaction of the endothelial cell-selective Tie2 receptor with its ligands, angiopoietin 1 and 2, may inhibit angiogenesis, eventually leading to an inhibition of tumour cell proliferation.[25,26] The phase III, randomised, double-blind TRINOVA-1 study was designed to determine whether treatment with paclitaxel plus trebananib was superior to paclitaxel plus placebo in women with recurrent, partially platinum sensitive or resistant epithelial ovarian cancer, primary peritoneal cancer or fallopian tube cancer.[27] It was recently reported that there was a statistically significant difference in PFS

between the trebananib and placebo arms (7.2 months vs. 5.4 months; $p < 0.001$). The risk of disease progression or death was reduced by 34% reduction with trebananib compared with placebo (HR = 0.66; 95% CI, 0.57-0.77; $p < 0.001$). A formal publication of these study results is awaited.

CONCLUSION

For the first time, phase II and III clinical trials of BEV have provided solid evidence that anti-angiogenesis therapy targeting VEGF is an active and rational option for ovarian cancer. In the future, a clear advance in BEV therapy would be the ability to predict response. Although there is considerable research in this area, a reliable, reproducible biomarker or imaging technique that would help to better identify patients most likely responding to, and benefiting from, BEV is yet to emerge. Building on the foundation set by BEV, a number of novel oral VEGF-receptor / multi-target tyrosine kinases and anti-angiopoietin agents which show promising activities are currently in development or being studied in clinical trials; some of these may become available in the future for the treatment of ovarian cancer. Given that almost 10,000 patients to date have been included in anti-angiogenesis trials of ovarian cancer, this truly heralds a new era in the treatment of ovarian cancer with the use of biologic agents.

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