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REVIEW ARTICLE

The Evolving Role of Anti-angiogenic Agents for Ovarian Cancer Therapy

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ABSTRACT

Angiogenesis, or the development of micro-vascular (blood and lymph) networks from established vasculature, is a process fundamental to proliferation, invasion and metastasis of ovarian cancer and other solid tumours. The initiation and maturation (remodelling) phases of angiogenesis are orchestrated by distinct growth factor–based signal transduction pathways operating in both sequential and parallel fashion. Therapeutic efficacy of anti-angiogenic agents in the treatment of ovarian cancer has been demonstrated in phase III trials of the anti–vascular endothelial growth factor (anti-VEGF) humanised monoclonal antibody bevacizumab, and in phase II trials (phase III trials in progress) of (a) multi-targeting inhibitors (e.g. BIBF 1120, pazopanib, and cediranib) of VEGF (plus platelet-derived growth factor and fibroblast growth factor) receptor tyrosine kinase domains, and (b) AMG386, a fusion protein blocking signalling of angiopoietin-2. This article focuses on evolving therapeutic considerations in the development and integration of anti-angiogenic therapy for patients with ovarian cancer, and in the process addresses some of the following quandaries. What might be the optimal duration of anti-VEGF therapy? How safe is anti-VEGF therapy in women with this disease? Should anti-angiogenic and cytotoxic agents be combined, or used in sequence? Is there any evidence that some tumours/patients may benefit from angiogenesis-targeted therapy more than others? What are the potential advantages versus disadvantages of multi-targeting over pure anti-VEGF inhibition? What are some of the newer agents under investigation?

Key Words: *Angiogenesis inhibitors; Bevacizumab; Endothelium, vascular; Ovarian neoplasms; Vascular endothelial growth factors*

中文摘要

針對治療卵巢癌的抗血管新生藥物的進程

RA Burger

血管新生，即指由現有脈管系統發展成一個微血管（包括血液和淋巴）網絡，是導致卵巢癌和其他腫瘤的細胞增殖、侵襲甚至轉移過程的根源。以生長因子為本的信號轉導途徑以串行和並行方式影響血管新生早期和成熟期（即改造期）的發展。針對治療卵巢癌的抗血管新生藥物，其治療成效可見於抗血管內皮細胞生長因子（即抗VEGF）擬人化單克隆抗體bevacizumab的第三階段試驗，以及（1）多定向VEGF〔包括血小板衍化生長因子和成纖維細胞生長因子〕受體酪氨酸激酶領域抑制劑（如BIBF 1120、pazopanib和cediranib）和（2）用作阻攔血管生成素-2發出信號指令的融合蛋白AMG 386的第二階段試驗（第三階段正進行中）。本文探討針對卵巢癌患者的抗血管新生治療發展和整合

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的進程，以及提出下列疑問：何時是進行抗VEGF療法的最佳時間？對卵巢癌患者來說，抗VEGF療法有多安全？抗血管新生藥可否結合化療藥物作合併使用，抑或須順序使用？有什麼證據支持部分癌症／患者可受惠於針對血管新生的療法？多定向與單一抗VEGF治療的潛在優勢和缺點是什麼？有什麼新藥正進行研究？

INTRODUCTION

Ovarian cancer is a major public health problem. In the United States for example, it ranked as the second most lethal cause of cancer in women in terms of the ratio of annual mortality to incidence.[1] The vast majority of ovarian cancers that contribute to the public health care problem are epithelial ovarian cancers, specifically the high-grade serous ovarian cancers.

Angiogenesis can be defined as the development of micro-vascular (blood and lymph) networks from established vasculature. This process is fundamental to proliferation, invasion, and metastasis of solid tumours and is orchestrated by a number of growth factors. Furthermore, the process is multi-step in nature and can be broadly divided into two phases. The initiation phase is characterised by immature, abnormally permeable vascular networks including endothelial cell proliferation, endothelial tube formation, and vessel sprouting. In the maturation phase, vascular networks re-model becomes supported by pericytes and smooth muscle cells, and is rendered more functional.[2] Vascular endothelial growth factor (VEGF) has been implicated as the most central promoter of the initiation phase of ovarian cancer angiogenesis.[3,4] It has been found that the expression of VEGF and hence the degree of angiogenesis in the tumours is directly related to the formation of malignant ascites and pleural effusions, the degree of malignant progression and poor prognosis, that often ensue independent of known prognostic factors.[5-8] Because of this biologic and prognostic relationship to ovarian cancer, angiogenesis and the VEGF pathway in particular are important therapeutic targets. Indeed, multiple agents targeting angiogenesis are under development. The most actively studied agents are those which block VEGF activity, by sequestering or neutralising the ligand of VEGF. The largest body of experience has been with the humanised monoclonal antibody, bevacizumab (BEV).

SINGLE-AGENT ANTI-TUMOUR ACTIVITY

The VEGF neutralising agents have demonstrated single-agent activity, which is a distinct observation when considering experience with most solid tumours. Two phase II studies with the monoclonal antibody BEV in patients with recurrent ovarian cancer demonstrated single-agent anti-tumour activity in terms of both response rate by response evaluation criteria in solid tumours (RECIST) imaging criteria and progression-free survival (PFS).[9,10] For example, in the Gynecologic Oncology Group trial of patients on second- or third-line therapy, 40% of patients with recurrent, measurable disease had no evidence of tumour progression for at least 6 months.[10]

FRONT-LINE THERAPY IN OVARIAN CANCER

Based on the phase II studies, there are now three phase III studies of BEV reported for ovarian cancer, two in front-line therapy.

The GOG-0218 study[11] was a three-arm, placebo-controlled, double-blinded trial that examined three different treatments in 1873 patients, all with stage III and IV ovarian cancer. The control regimen was chemotherapy (paclitaxel and carboplatin) alone, the second entailed concomitant BEV during the chemotherapy phase, and the third entailed extension of BEV beyond the chemotherapy phase, up to a total maximum treatment time of 10 months beyond the completion of the chemotherapy and BEV. The primary endpoint was PFS. In this trial, all the prognostic factors were balanced across the treatment arms. Notably, two-thirds of the patients were considered to have poor prognosis with either suboptimally debulked stage III or stage IV cancers. In this trial, the assessment of disease progression was based not only on diagnostic imaging using the RECIST criteria, but also using cancer antigen 125–based progression criteria from the Gynecologic Oncology InterGroup.

The ICON7 study was an open-label phase III international trial performed in Europe in 1528 women with ovarian cancer, and evaluated standard chemotherapy versus chemotherapy with BEV followed

by continued BEV for a maximum of seven months beyond completion of chemotherapy.[12] It utilised half the dose of that administered in the GOG-0218 trial, with the same primary endpoint of PFS. This study involved a broader range of patients that included those with advanced disease as well as subjects with high-risk early stage disease. Two-thirds of the patients actually had less advanced disease than in GOG-0218, and only one-third had either sub-optimally debulked stage III or stage IV cancers.

In the GOG-0218 trial,[11] we investigated the impact of BEV administered only in combination with chemotherapy versus chemotherapy alone. The PFS plot comparing these two groups demonstrated a slight separation of the two PFS curves favouring BEV, however, the difference was not statistically significant. Extension of BEV therapy beyond completion of chemotherapy for up to 10 additional months or 16 additional cycles demonstrated a statistically significant improvement in PFS, with the hazard ratio (HR) of 0.717 ($p<0.0001$), or about 28% reduction in the risk of progression over time. In the ICON7 trial,[12] a similar relationship was observed with respect to the impact on the PFS. Though there was a more modest effect (HR = 0.87, $p=0.039$), with ICON7 having enrolled a broader range of patients, many of whom had a lower risk for progressive disease over time.

Regulatory agencies required an overall survival (OS) analysis for both trials at the time of the primary PFS analyses. Mature data for the OS analysis are not yet available for the GOG-0218 study, but so far there is no statistically significant difference between the treatment groups. In the ICON7 study, there was a slight separation of the OS curves in favour of the BEV cohort, which was not statistically significant. One of the issues that may account for this separation of the OS curves not seen in the GOG trial was that majority of patients enrolled into the GOG trial would have had access to BEV for the treatment of progressive or recurrent disease, while in the ICON7 study, the majority of patients did not have access to VEGF inhibitors outside of clinical trials.

Whether patients with more aggressive or more advanced disease might have tumours that were more angiogenic and therefore more amenable to benefit from a VEGF inhibitor was another compelling question. An exploratory analysis of the high-risk subset of 465 patients in ICON7 (about one-third of the study population), who had either suboptimally debulked stage III or stage IV cancers, demonstrated a significant difference in OS (HR = 0.64, $p=0.0022$) in favour of women who had received BEV.[13] This suggests that women with poor prognosis disease may benefit not only in terms of PFS but also in terms of OS.

RECURRENT OVARIAN CANCER

We have a greater deal of experience in the treatment of recurrent ovarian cancer with BEV, because of the original phase II studies that demonstrated single-agent activity of BEV given alone in patients with one to two prior regimens. On that basis, the US National Comprehensive Cancer Network (NCCN) adopted BEV as a preferred agent for management of recurrent disease and it has been listed as such in the NCCN Practice Guidelines for many years, including those during which the GOG-0218 trial was active. Of the several active regimens listed, BEV is the only drug targeting the process of tumour angiogenesis.[14]

The first randomised phase III trial that investigated BEV in recurrent disease was the placebo-controlled, double-blinded OCEANS trial[15] in platinum-sensitive recurrent ovarian cancer at first relapse. This trial utilised the approved chemotherapy regimen of carboplatin and gemcitabine and examined BEV in conjunction with chemotherapy followed by BEV extended beyond completion of chemotherapy until disease progression versus chemotherapy alone, with PFS as the primary endpoint. This design was quite different from that of the front-line studies, which evaluated continuation of BEV for a pre-determined maximum number of treatment cycles. OCEANS demonstrated more robust impact on PFS, with an HR of 0.484 ($p<0.0001$). The interim analysis of OS presented in the 2011 ASCO (American Society of Clinical Oncology) Meeting was immature, and though the difference in OS between the study groups was not statistically significant, there was a trend for improvement in OS favouring BEV. What accounted for this greater magnitude of effect on PFS compared with the front-line trials?

TREATMENT DURATION

Treatment duration may be an important issue with respect to anti-angiogenic agents. When you look at the trials integrating BEV into front-line therapy, again, the maximum duration of treatment with BEV was arbitrarily pre-defined with discontinuation regardless of whether or not patients had developed progression disease. Furthermore, the effects on PFS were maximal

at approximately the maximal extent of active treatment.

In GOG-0218, the maximal effect in terms of the separation of the PFS curves occurred at about 15 months. The same relationship was also evident in the ICON7 trial, in which the maximal degree of separation of curves occurs at about 12 months. In GOG-0218, 24% of patients received all 22 cycles of therapy in the extended BEV group and did not progress, and 19% of patients were still on treatment in that group; therefore, up to 43% of the patients in the extended BEV cohort could have continued treatment beyond the pre-defined number of cycles, until disease progression. In ICON7, 62% in the BEV group had completed all cycles of therapy and could have continued treatment beyond that point until disease progression. One could speculate that if these front-line trials had been designed so that BEV was administered until disease progression, perhaps the effect of BEV would have been more dramatic, as was noted in OCEANS trial.

TREATMENT BEYOND DISEASE PROGRESSION

What about treatment with an angiogenesis inhibitor beyond disease progression? The pattern of disease progression in patients benefiting from an anti-angiogenic agent may be quite different from that in patients progressing while on cytotoxic therapy, where local proliferation was demonstrated, but invasion and metastasis may still have been inhibited. A hypothesis generated from our studies of ovarian cancer was based on this principle. In the GOG 170-D phase II BEV monotherapy trial,[16] quantitative immunohistochemistry for CD31 expression as a surrogate of micro-vessel density was performed on tumour tissue at baseline. OS was significantly worse for patients with highly angiogenic tumours. However, the PFS curves for these two groups were relatively compressed, and differences were not statistically significant. This finding suggested that patients with more highly angiogenic, aggressive tumours potentially derived greater benefit while on treatment with BEV, but rapidly progressed at discontinuation of therapy and led to worse OS. Hypothetically, continuation of BEV beyond disease progression could have provided continued benefit. Clinical evidence for potential benefit beyond disease progression comes from the BRiTE (Bevacizumab Regimens: Investigation of Treatment Effects and Safety) colorectal cancer registry study. The latter retrospectively evaluated patients with metastatic colorectal cancer who received BEV in the context of front-line cytotoxic therapy. Thus, OS was markedly improved in patients who received BEV at the time of disease progression in combination with second-line chemotherapy, in contrast to those receiving chemotherapy alone.[17]

A randomised trial addressing this question[18] is now in progress in patients with metastatic colorectal cancer receiving first-line therapy with standard chemotherapy plus BEV followed by BEV until evidence of progressive disease. At the time of progression, patients are randomised to continue BEV with second-line cytotoxic chemotherapy or discontinue BEV and use chemotherapy alone, until disease progression, with the primary endpoint being OS. The results of this trial will have ramifications as to how we use anti-angiogenic therapy for multiple solid tumours such as ovarian cancer.

ADVERSE EVENTS

Adverse events reported in GOG-0218 and ICON7 were similar in spectrum and severity to those reported in front-line studies of metastatic non-gynaecologic malignancies for which BEV has been approved by regulatory agencies. In GOG-0218, while the gastrointestinal perforation and fistula rate in the two BEV cohorts was almost double that noted in the chemotherapy alone group, this complication occurred in less than 3% of the patients overall. Hypertension deemed to require treatment was observed in up to 23%, and as expected, was significantly more common in BEV-treated patients; however, few patients discontinued BEV due to hypertension or hypertension-related problems. Apparently, there was no significant difference in the rates of other adverse events, including febrile neutropenia, thromboembolic events, or wound healing complications.[11] A very similar pattern was observed in the ICON7 study.[12]

Most of the adverse events in these studies were reported during the cytotoxic chemotherapy phase of treatment rather than during the continued BEV phase. For example, in GOG-0218, in each arm all but one gastrointestinal perforation or fistula occurred during the cytotoxic phase. This suggests that such events are not cumulative in nature. However, in the group receiving chemotherapy plus BEV followed by continued BEV, the frequency of hypertension, proteinuria and pain were higher during the maintenance phase. This observation was expected for both hypertension and proteinuria, which are known to be cumulative effects

of BEV that warrant continuous monitoring. While myalgia and arthralgia have been reported with BEV, the distinction between treatment and disease-related pain in clinical trials is often unclear, and results are often biased. In GOG-0218, adverse event reporting was required only within 30 days of the last treatment date, so pain events related to disease would more likely have been underreported for patients in the control group, for whom BEV was discontinued earlier because of disease progression.

RATIONALE FOR COMBINATION OF ANTI-ANGIOGENIC AGENT AND CYTOTOXIC REGIMENS

Why have randomised trials typically combined anti-angiogenic agents with cytotoxic chemotherapy and then continued anti-angiogenic agents beyond the completion of chemotherapy, rather than utilising anti-angiogenic agents solely following completion of chemotherapy as a maintenance approach? The rationale initially stemmed from preclinical studies leading to the model published by Jain.[19] One of the initial effects observed for VEGF inhibitors was a transient reduction in tumour microvascular permeability and interstitial pressure. Arguably therefore, concomitant administration of a cytotoxic drug with an angiogenesis inhibitor could improve tumour access to chemotherapeutics, thereby enhancing chemo-sensitivity. It remains to be seen whether this concept is clinically relevant. GOG-0218[11] is the only trial in which there was a treatment arm where the anti-angiogenic agent was utilised only in combination with cytotoxic therapy. A statistically non-significant difference in PFS was observed between this arm and the arm receiving cytotoxic therapy alone. Though one could speculate that BEV added minimally to therapeutic benefit when initiated with chemotherapy, this conclusion may be erroneous in the context of this trial, since a regimen with chemotherapy followed by BEV only during the maintenance phase was omitted. While still unable to answer this question, the concept of an angiogenesis inhibitor utilised solely in sequence with cytotoxic therapy is currently under investigation. This investigation involves the drug pazopanib, a kinase inhibitor that blocks signal transduction of VEGF, administered immediately following front-line chemotherapy.[20] Patients with advanced disease received front-line chemotherapy for six cycles, and if they had not progressed, were randomly assigned to treatment with either pazopanib or placebo, and treated for up to 24 months. This trial has completed accrual, but the data have yet to be analysed.

PREDICTORS OF THERAPEUTIC BENEFIT

A major challenge has been the identification of clinical, pathological, and/or biological factors specific to patients or their tumours that can predict benefit or non-benefit for angiogenesis inhibitors. A multivariate analysis in the GOG 170-D phase II study demonstrated that neither performance status, platinum sensitivity, age or number of prior regimens were predictive of PFS in patients receiving BEV in the management of recurrent disease.[10] Similarly, in GOG-0218, a subset analysis of the combination of stage and debulking level, histologic cell type, tumour grade, performance status, and age demonstrated remarkably consistent results across the strata; again, none of which were predictive of PFS in patients receiving BEV in front-line therapy.[11] In ICON7, an exploratory analysis showed that the patients with suboptimally debulked stage III and stage IV cancers seemed to benefit more than patients with high-risk early stage or completely resected advanced disease.[12] As indicated by laboratory results from the GOG 170-D phase II monotherapy trial,[16] the angiogenesis index may be predictive of benefit, and, while not conclusive, it may explain the relatively impressive clinical benefit for BEV in ICON7.

Laboratory studies on tumour tissue and peripheral samples are in progress for GOG-0218 and ICON7 testing multiple factors hypothetically predictive of benefit. Notably, in a genomic analysis of a consecutive series of over 360 advanced, previously untreated epithelial ovarian cancers at a single institution in Scotland, Gourley et al[21] identified a subgroup associated with up-regulation of angiogenesis-related genes. A validation study examining the predictive value of this genomic 'signature' would be valuable and could be performed in tumour tissue samples from GOG-0218 and ICON7.

MULTIPLE GROWTH FACTOR TARGETING

It has been hypothesised that targeting multiple angiogenic growth factor pathways simultaneously might be a more effective approach than targeting VEGF alone. Other angiogenic promoters, such as platelet-derived growth factor (PDGF) and fibroblast growth factor (FGF), may be important. For example, PDGF stimulates angiogenesis not only via endothelial cell activation, but also through recruitment of pericytes and maturation of newly developed micro-vessels of the tumours. Pre-clinical studies have demonstrated up-

regulation or activation of PDGF and PDGF receptors, respectively, following treatment with pure VEGF inhibitors.[22-29] There is a series of tyrosine kinase inhibitors (TKIs) blocking signal transduction of receptors for VEGF, PDGF, and FGF. The rationale for developing these multiple growth factor–targeted agents include the potential for more effective blockade of tumour angiogenesis than isolated VEGF inhibition, reduced likelihood of resistance due to activity of compensatory pathways,[30,31] and the convenience of oral administration. On the contrary, use of multi-targeted TKIs has been associated with a wider spectrum of symptomatic adverse effects than pure VEGF inhibitors; these effects include skin rash, diarrhoea and mucositis. Also, in women with advanced ovarian cancer, oral administration can be problematic due to the impact of the disease on gut motility and absorption. This can lead to highly variable bio-distribution of orally administered agents. Nevertheless, there have been several positive phase II trials reported for TKIs which have led to several phase III trials. For example, the AGO-OVAR12 trial[32] of BIBF1120 is now evaluating patients with advanced disease in the front-line setting; this study is similar to ICON7 but is placebo-controlled, and anti-angiogenic therapy is extended up to 24 months from enrolment. As discussed previously, the AGO-OVAR 16 trial[33] is examining pazopanib in the maintenance setting only. Finally, the ICON6 trial[34] is investigating the drug cediranib in a population similar to that of the OCEANS trial, with a design identical to GOG-0218, but with a primary endpoint of OS.

INHIBITORS OF MICRO-VASCULAR REMODELLING AND MATURATION

Selective antagonists of micro-vessel remodelling and maturation are under investigation, including angiopoietin inhibitors. Angiopoietins interact with the Tie2 receptor, which mediates vascular remodelling independently of typical angiogenic growth factors, and is also up-regulated in ovarian cancer. AMG 386 is a novel peptide-Fc fusion protein that inhibits the maturation phase of angiogenesis by preventing the interaction of angiopoietins with the Tie2 receptor. AMG 386 demonstrated a PFS advantage when used in combination with weekly low dose of paclitaxel in a phase II randomised trial.[35] There are now two phase III trials evaluating this agent in patients with recurrent ovarian cancer.[36,37]

CONCLUSION

There is a biological rationale to pursue anti-angiogenic therapy in the management of ovarian and related cancers. Individualised integration of angiogenesis inhibitors in the management of newly diagnosed and recurrent disease can already be justified based on the activity for pure anti-VEGF and multi-targeted agents. This was demonstrated in phase II trials and positive phase III trials for PFS using BEV in front-line and second-line settings. Moreover the adverse effects for BEV had been generally tolerable and manageable, similar to what had been reported in phase III trials of metastatic non-gynaecologic cancers for which this agent is approved by regulatory agencies. Optimisation of anti-angiogenic therapy (e.g. duration and timing, use alone or in combination with cytotoxic chemotherapy, refinements in patient selection with respect to safety and efficacy, and integration of multi-targeted and remodelling/maturation inhibitors) will require further investigation.

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