symposium article

Antiangiogenic agents should be integrated into the standard treatment for patients with ovarian cancer

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Tumor angiogenesis is a fundamental process driving the progression of epithelial ovarian cancer and related malignancies. The question is whether agents targeting tumor angiogenesis should at this time be integrated into standard treatment. In this article, the pro side of this question is presented. Multiple phase II trials have demonstrated efficacy for antiangiogenic agents in the treatment of women with recurrent ovarian cancer. Results of three phase III trials evaluating the antivascular endothelial growth factor antibody bevacizumab have been presented, all demonstrating significant increases in progression-free survival when combined with standard cytotoxic chemotherapy and continued beyond chemotherapy, with acceptable toxicity. Several other angiogenesis-targeted agents are undergoing phase III evaluation. Based on these data, it is concluded that antiangiogenic therapy, at least with bevacizumab, should be integrated into the standard clinical management of patients with this disease. Further investigation is needed to determine optimal utilization.

Key words: angiogenesis, bevacizumab, fallopian tube cancer, ovarian cancer, primary peritoneal cancer, vascular endothelial growth factor

introduction

Despite advances in cytotoxic therapy and surgical management, the vast majority of women with epithelial ovarian cancer and related Mullerian duct adenocarcinomas (denoted ‘ovarian cancer’) still die of the disease. Strategies to target the fundamental mechanisms of disease progression are critical to decreasing morbidity and potentially extending survival.

For ovarian cancer and other solid tumors, the process of angiogenesis is fundamental to disease progression. Angiogenesis is a multistep process orchestrated by tumor-generated growth factors that operate along several convergent and divergent pathways, and can be divided into an initiation phase and a maturation phase [1]. The initiation phase is orchestrated by cytokines released by tumors, such as vascular endothelial growth factor (VEGF), and is characterized by the development of immature, abnormally permeable, microvascular networks from existing blood and lymphatic vessels with microvascular permeability. In the maturation phase, the vascular networks become functional. The end result is the promotion of tumor proliferation, invasion and metastasis by the tumor microenvironment.

VEGF has been characterized as a central promoter of the activation phase of angiogenesis [1]. This phase is characterized by the degradation of the perivascular basement membrane and the migration of endothelial cells into the extracellular space, proliferation of the endothelial cells, and the formation of capillary sprouts. VEGF expression and indices of angiogenesis in primary tumors have correlated directly with the extent of disease and inversely with progression-free survival (PFS) [2–5] or overall survival (OS) [3, 4, 6–11], often independent of known prognostic factors [2–8, 10, 11]. It is also the growth factor thought to be primarily responsible for the development of malignant ascites and pleural effusions characteristic of advanced ovarian cancer, by virtue of the increased microvascular permeability characteristic of the activation phase of angiogenesis [1].

VEGF-inhibitory agents

As shown in Table 1, multiple VEGF inhibitory agents are under investigation in the treatment of ovarian cancer. These can be subclassified as those neutralizing VEGF itself, such as the humanized monoclonal antibody bevacizumab, and those blocking signal transduction of the receptors for VEGF and other angiogenic growth factors.

bevacizumab in first and second line

Unlike the case for most nongynecologic tumors, bevacizumab has demonstrated single-agent activity in two phase II trials in women with recurrent ovarian cancer, both in terms of objective response rates (21% in a mixed population; 15% in a population with platinum-resistant disease) and PFS (40% without progression at 6 months in a mixed population; 28% in a population with platinum-resistant disease) [12, 13]. This agent is currently listed by the USA National Comprehensive
Table 1. Anti-VEGF agents under investigation for ovarian cancer

<table>
<thead>
<tr>
<th>Target</th>
<th>Class</th>
<th>Agent</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>VEGF-A</td>
<td>MoAb</td>
<td>Bevacizumab</td>
<td>III (some data available)</td>
</tr>
<tr>
<td>VEGF</td>
<td>Soluble decoy receptor</td>
<td>VEGF Trap</td>
<td>II/III</td>
</tr>
<tr>
<td>VEGFR2</td>
<td>MoAb</td>
<td>Ramucirumab</td>
<td>II</td>
</tr>
<tr>
<td>VEGFR</td>
<td>TKI</td>
<td>Sunitinib</td>
<td>II</td>
</tr>
<tr>
<td>VEGFR</td>
<td>PDGFR, Raf</td>
<td>Sorafenib</td>
<td>II</td>
</tr>
<tr>
<td>VEGFR</td>
<td>PDGFR, Ret</td>
<td>Motesanib</td>
<td>II</td>
</tr>
<tr>
<td>VEGFR</td>
<td>EGFR, Ret</td>
<td>Vandetanib</td>
<td>II</td>
</tr>
<tr>
<td>VEGFR</td>
<td>PDGFR</td>
<td>Pazopanib</td>
<td>II</td>
</tr>
<tr>
<td>VEGFR</td>
<td>PDGFR + FGFR</td>
<td>Cediranib</td>
<td>III (ongoing)</td>
</tr>
<tr>
<td>VEGFR</td>
<td>PDGFR + FGFR</td>
<td>BIBF-1120</td>
<td>III (ongoing)</td>
</tr>
</tbody>
</table>

MoAb, monoclonal antibody; PDGFR, platelet-derived growth factor receptor; EGFR, epidermal growth factor receptor; FGFR, fibroblast growth factor receptor; TKI, tyrosine kinase inhibitor.

Cancer Network as a preferred agent for the management of recurrent disease [14].

Furthermore, in 2010, two positive international cooperative group phase III studies of bevacizumab in front-line therapy were reported: GOG 0218 (double blind, placebo controlled) [15–17] and ICON7 (open label) [18, 19]. Both trials demonstrated that, in comparison to women treated with carboplatin and paclitaxel alone, those treated with chemotherapy in combination with bevacizumab followed by bevacizumab continued up to a pre-specified number of cycles had a statistically significant prolongation of PFS, the primary end point. The experimental regimens were well tolerated, with adverse events similar to previous phase III trials for metastatic nongynecologic malignancies. For ICON7, the results of an exploratory subanalysis of patients with stage III disease who had undergone suboptimal cytoreductive surgery or those with stage IV disease demonstrated a more robust impact for bevacizumab on PFS than the intent to treat population.

At the time the primary results of the two front-line phase III trials were presented, OS data had yet to mature and at that point no statistically significant differences in OS had been demonstrated among the treatment groups. Unfortunately, the validity of the OS analysis for the GOG trial may be compromised, as patients were informed of their treatment assignment at the time of disease progression, and bevacizumab has been commonly utilized in the treatment of recurrent ovarian cancer, in part as a result of National Comprehensive Cancer Network guidelines [14].

The validity of PFS as the preferred primary end point in front-line ovarian cancer trials is supported in a 2010 consensus statement by the Gynecologic Cancer InterGroup based on the influence of subsequent, uncontrolled regimens [20]. In addition, based on an analysis of 50 000 simulated trials, Broglio et al. [21] concluded, ‘For clinical trials with a PFS benefit, lack of statistical significance in OS does not imply lack of improvement in OS, especially for diseases with long median survival post-progression.’ A reduction in the risk of progression for patients with advanced ovarian cancer assuming an acceptable level of risk is in itself important, since most recur and die of the disease. Lastly, the magnitudes of PFS benefit in terms of hazard ratios for GOG 0218 and ICON7 are consistent with PFS hazard ratios reported in previous ovarian cancer phase III trials of chemotherapeutic agents, for which statistically significant improvements in OS were observed [22–24]. Importantly, the OS analyses of these three trials were not vulnerable to a potential cross-over effect, as is the case for GOG 0218.

The USA National Cancer Institute appears to accept antiangiogenic therapy as standard in front-line therapy, since bevacizumab is incorporated in all three arms of GOG 0252, a phase III trial evaluating intraperitoneal versus intravenous platinum-taxane combination chemotherapy. Also, in the GOG 0262 phase III trial evaluating dose-dense paclitaxel, selection of bevacizumab by patients/investigators is allowed and is a stratification factor prior to randomization.

Two phase III trials have investigated bevacizumab in second-line therapy for patients with platinum-sensitive recurrent ovarian cancer. The results of one of these have been reported in a placebo-controlled double-blind trial of carboplatin/gemcitabine followed by bevacizumab until disease progression. This trial met its primary end point of PFS in favor of the experimental regimen, with no new safety signals [25].

other antiangiogenic agents

Several other classes of antiangiogenic agents are under active investigation in phase II and phase III studies. It is theorized that such agents may act on compensatory pathways that may be simultaneously up-regulated in tumors and may even result from VEGF blockade [26, 27]. These agents include oral tyrosine kinase inhibitors, which simultaneously target receptor signal transduction for VEGF as well as a number of other growth factors, such as platelet-derived growth factor (PDGF). Adverse effects overlap those of pure anti-VEGF agents, but in addition in some cases may cause rash and diarrhea. PDGF is thought to be involved in both the activation and maturation phases of angiogenesis, the latter involving the reconstitution of the basement membrane along with a recruitment of pericytes and smooth muscle cells, which provide vessel wall integrity [28]. Phase II studies have demonstrated single-agent activity for BIBF-1120 [29], pazopanib [30] and cediranib.
[31, 32], and all three agents have entered phase III testing in first-line (BIBF-1120 and pazopanib) and second-line (cediranib) settings.

Newer agents targeting nonclassical pathways of tumor angiogenesis are being explored. For example, recently, AMG-386, a recombinant peptide-FC fusion protein that binds to and inactivates angiopoietin 2 was found to prolong PFS in a phase II randomized trial [33]. Adverse effects were manageable and distinct from those of VEGF inhibitors. Two phase III studies are in progress – TRINOVA-1 and TRINOVA-2.

**Conclusions**

There is a strong rationale for the integration of angiogenesis inhibitors in the standard management of patients with newly diagnosed and recurrent ovarian cancer, based on tumor biology and the results of both phase II and phase III trials presented within the last few years. Refinements of the use of antiangiogenic agents in clinical practice, e.g. with respect to the duration of therapy, sequencing versus combinations of antiangiogenic agents with nonoverlapping mechanisms of action and the selection of patients based on biologic characteristics of the tumor or host, will require additional investigation.

**Disclosures**

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**References**


