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Review

The search for biomarkers to direct antiangiogenic treatment in epithelial ovarian cancer

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HIGHLIGHTS

- Prognostic biomarkers for clinical outcomes in women with EOC have not proven predictive for the efficacy of antiangiogenic treatment.
- Plasma biomarkers currently under investigation include VEGF-A and its receptors, VEGFR-2, VEGFR-3, VEGF-D, FGF, PDGF, Ang-2, SDF-1, OPN, and IL-6.
- Biomarkers are needed for promising antiangiogenic agents in EOC.

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ABSTRACT

Antiangiogenic agents have demonstrated improved progression-free survival in women with primary and recurrent epithelial ovarian cancer (EOC). Biomarkers that predict outcomes in patients treated with antiangiogenic agents are being investigated to rationally direct therapy for women most likely to benefit from these agents. Among the most promising plasma-based biomarkers are vascular endothelial growth factor (VEGF)-A, fibroblast growth factor, platelet-derived growth factor, angiopoietin-2, and VEGF receptor-2. While these biomarkers have been correlated with prognosis, they have not been shown to predict benefit, specifically from anti-VEGF therapy, highlighting the need for alternative biomarkers, including molecular and clinical factors, which may be predictive of outcome in women with ovarian cancer treated with antiangiogenic agents. Biomarkers are currently being investigated as secondary outcomes in several ongoing phase II and phase III clinical trials of antiangiogenic agents in patients with EOC. Molecular techniques, such as microarray analyses, and imaging techniques, such as dynamic contrast-enhanced magnetic resonance imaging, positron emission tomography, and single photon emission computed tomography, are also being explored in this field. In this review, we provide a comprehensive overview of current biomarker research, with an emphasis on angiogenic biomarkers associated with EOC.

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Introduction

Many biomarkers currently under evaluation are involved in the regulation of angiogenesis, a complex process that involves multiple pathways, genes, and epigenetic mechanisms. Angiogenesis is regulated by both pro- and antiangiogenic factors and is promoted during tumor development when an imbalance in these factors favors a proangiogenic milieu [1]. While proangiogenic factors such as vascular endothelial growth factor (VEGF) are often overexpressed by cancer cells, including epithelial ovarian cancers (EOCs) [2], receptors for these proangiogenic factors are mostly expressed by tumor endothelial cells and not tumor epithelial cells (Fig. 1A) [3]. Therefore, antiangiogenic agents such as bevacizumab are thought to suppress EOC by targeting the tumor blood supply. Recent randomized clinical trials have demonstrated that combination treatment with chemotherapy and bevacizumab followed by maintenance bevacizumab therapy significantly improved progression-free survival (PFS), and in select cases improved overall survival (OS), compared with chemotherapy alone in women with EOC [4–7].

A variety of antiangiogenic agents targeting molecular biomarkers in solid tumors, including EOC, are currently being evaluated. For example, phase III clinical trials have evaluated small molecule tyrosine kinase inhibitors (TKIs; nintedanib, cediranib, and pazopanib) and a fusion peptibody (trebananib) in patients with ovarian cancer (OC) [1,8–11]. Despite improvements in PFS, some patients may experience significant toxicities, including diarrhea, nausea, fatigue, and hypertension [1]. Molecular and clinical biomarkers that identify patients most likely to benefit from antiangiogenic therapies may maximize patient survival while minimizing unnecessary toxicity and cost. In this review, we provide an overview of current biomarker research, with an emphasis on angiogenic biomarkers in EOC (Fig. 1B).

Plasma- and tissue-based biomarkers

Vascular endothelial growth factor

VEGF is one of the most potent pro-angiogenic factors identified to date. VEGF is commonly overexpressed in a number of cancer cell types, including EOC [2]. Increased expression of VEGF has also been found in tumor tissue samples from patients with colorectal cancer, breast, prostate, oropharyngeal, and bladder cancers [12].

VEGF expression is higher in OC than in benign ovarian neoplasms, and increased VEGF expression in tumor or plasma has been associated with more advanced tumor stage and poorer survival outcomes [13–15]. In patients with early-stage disease, elevated VEGF expression in plasma and tumor tissue has been associated with a greater risk of disease recurrence and poorer disease-free and OS [16]. A study evaluating 9 primary OCs on tissue microarrays found that high tumor VEGF levels correlated with poorer survival and were an independent prognostic factor in a multivariate analysis [17]. A study in 61 patients with EOC or primary peritoneal cancer treated with bevacizumab found that high baseline plasma VEGF levels were associated with a shorter median survival and an increased risk of death [18].

Of the 7 members of the VEGF family of ligands, VEGF-A is the most well characterized and plays a dominant role in angiogenesis [1]. A recent meta-analysis of 1816 patients with colorectal cancer (CRC), non-small cell lung cancer (NSCLC), and renal cell carcinoma (RCC) participating in phase III trials of bevacizumab found that pre-treatment plasma VEGF-A levels were prognostic for patient outcome but were not predictive of response to bevacizumab [19]. Studies included in the meta-analysis used an older version of the VEGF assay that was not selective for any specific VEGF isoform and was thought to predominantly bind VEGF165 due to its higher concentration. A novel enzyme-linked immunosorbent assay (ELISA), with a preference for short VEGF-A isoforms (VEGF110 and VEGF121), found that baseline plasma VEGF was predictive of response to bevacizumab in patients with pancreatic, gastric, and breast cancers, but not in patients with CRC, NSCLC, or RCC [20].

VEGFR-2 is the most important receptor for VEGF-A-mediated angiogenesis [21]. Increased genetic or tissue expression of VEGFR-2 has demonstrated potential prognostic value in pancreatic and breast cancers [22,23]. Plasma VEGFR-2 was not predictive of clinical outcome for women with EOC treated in the randomized GOG-0218 trial that evaluated chemotherapy alone or with bevacizumab, with or without maintenance bevacizumab [24].

The other members of the VEGF family include VEGF-B, -C, -D, and -E, as well as placental growth factors 1 and 2 (PLGF-1 and -2). VEGF isoforms bind preferentially to certain cell surface tyrosine kinase receptors, with VEGF-A binding preferentially to VEGFR-1 and VEGFR-2, VEGF-B to VEGFR-1, VEGF-C and -D to VEGFR-3, and VEGF-E, produced only in viruses, to VEGFR-2 [25]. VEGFR-3 mediates lymphangiogenesis induced by VEGF-C and VEGF-D, and is involved in lymphatic metastases [12,26,27]. Importantly, processed VEGF-C and VEGF-D can also bind to and activate VEGFR-2, which is involved in ascites formation [28].

Low levels of tissue-based VEGF-C, delta-like ligand-4, and neuropilin protein expression in women with metastatic breast cancer were associated with a trend toward improved PFS with bevacizumab in a retrospective subset analysis from the AVF2119g trial [29].

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