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The development and use of vascular targeted therapy in ovarian cancer

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HIGHLIGHTS

- Combining antiangiogenic and vascular disrupting agents may result in enhanced efficacy.
- Vascular disrupting agents appear to be particularly effective in treating large tumors.
- A phase II/III study is underway to evaluate combined vascular targeted therapies.

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ABSTRACT

Combination vascular-targeted therapies (VTTs) represent a promising approach for patients with platinum-resistant recurrent ovarian cancer (OC). VTTs include two mechanistically distinct classes of agents: anti-angiogenic agents (AAs) and vascular-disrupting agents (VDAs). AAs suppress growth of new tumor vasculature through inhibition of vascular endothelial growth factor (VEGF) and other pro-angiogenic molecules. Bevacizumab, a monoclonal antibody that binds to VEGF, has improved progression-free survival (PFS) when given with chemotherapy in patients with advanced OC. VDAs target the established tumor vascular network, inducing vessel occlusion, shutdown of circulation, and widespread necrosis within the tumor interior – a region often resistant to conventional chemotherapy and radiation. Tubulin-binding VDAs such as BNC105P, ombrabulin, and combretastatin A4-phosphate (CA4P) have been studied for the treatment of OC. These agents act by binding tubulin in the endothelial cells of tumor vessels, triggering cytoskeletal disruption, altering cellular shape, and destabilizing cell–cell junctions, which lead to increased vascular leakage and, ultimately, to disruption of blood flow. Fundamental differences between the vascular networks of tumors and those of normal tissues allow these agents to selectively reduce tumor circulation while having little effect on non-malignant tissues. Animal studies and clinical trials show enhanced efficacy when VDAs are combined with chemotherapy as well as AAs. The latter combination allows targeting of different aspects of the tumor vasculature, a strong rationale for combining these two drug classes into a single regimen. CA4P is the only VDA in active development for OC. In a phase II trial of patients with recurrent OC, CA4P added to bevacizumab improved PFS compared with bevacizumab alone. The phase II, placebo-controlled PAZOFOS trial (NCT02055690) is evaluating the effects of CA4P plus the anti-angiogenic agent pazopanib in recurrent OC. FOCUS, a phase II/III, placebo-controlled trial (NCT02641639), is currently evaluating CA4P plus bevacizumab and chemotherapy in platinum-resistant OC.

1. Introduction

While >50% of women with advanced ovarian cancer (OC) achieve a complete remission with first-line therapy [1], most of these patients relapse and eventually succumb to the disease [1]. Treatment decisions for recurrent OC are guided in part by a patient's platinum-free interval, which is defined as the length of time between completion of platinum-based chemotherapy and detection of disease recurrence. Patients with a platinum-free interval of >6 months are considered platinum-sensitive, and another platinum-based regimen is recommended after recurrence [2]. Patients with a platinum-free interval of <6 months are considered platinum-resistant, and those who progress during chemotherapy or within 4 weeks after its completion are considered platinum-refractory [1,2]. These latter two groups are treated with non-platinum, single or doublet therapy with a cytotoxic agent, such as a taxane, topotecan, or pegylated liposomal doxorubicin, with or without bevacizumab [1,2].

Second-line, platinum-based therapy can result in median progression-free survival (PFS) of ≤14 months and median overall survival

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(OS) of ≤42 months in patients with platinum-sensitive disease [3]. With successive lines of chemotherapy, however, most tumors eventually become platinum-resistant or platinum-refractory. Treatment outcomes in patients with platinum-resistant or platinum-refractory disease are poor, with response rates of 20% to 25%, median PFS of 3 to 6 months, and survival usually ≤16 months [2]. With no curative therapies available, the overall goals of managing recurrent OC are palliation of symptoms, prevention of complications, such as ascites or bowel obstruction, and preservation of quality of life (QOL) [1]. Unfortunately, the chemotherapy agents often utilized to treat recurrent OC can compromise QOL due to toxicities, including progressive neuropathy, cumulative thrombocytopenia, hand–foot syndrome, alopecia, and fatigue [1].

Poor prognosis and limited treatment options have prompted a search for new approaches to treating recurrent OC, such as combination vascular-targeted therapy (VTT) regimens. VTTs include two mechanistically distinct classes of therapies: anti-angiogenic agents (AAs) and vascular-disrupting agents (VDAs) [4]. This review discusses the complementary mechanisms of action of AAs and VDAs, the rationale for incorporating these therapies into the treatment of OC, efforts to optimize these therapies, and the current status of clinical trials.

2. Systematic literature searches

Since recent reviews on the role of AAs in the treatment of OC are available [5–7], these studies will not be reviewed in detail in this article. Studies evaluating VDAs alone or in combination therapy were identified by searching the US clinical trials database (clinicaltrials.gov) for all studies on VDAs in any tumor type (Table 1). For VDAs still in development, publications were identified via PubMed searches using the name of each agent (all variations) in the [Title field]. The ASCO annual meeting abstract database was searched in a similar manner. Company websites and Google were searched to identify congress presentations not occurring at ASCO. The resulting outputs were reviewed to eliminate duplicates. Specifically, if results were presented at a congress and later published in a peer-reviewed journal, only the latter reference was retained.

The trials were then separated into those evaluating VDAs in OC and those in other tumor types. Publicly available data from phase II studies of agents currently in development for non-OC indications are provided in Table 2. Although one phase III study is ongoing in this group, data are not yet available. Data from all studies in OC are provided in Table 3.

3. Tumor vasculature in OC

OC spreads by local extension, seeding of the peritoneal cavity, and invasion through lymphatic channels [24]. As it grows, the spreading malignancy relies on its own endogenously developed vascular network for a supply of oxygen and nutrients. Numerous studies have documented how the tumor vascular network, its development, and its unique characteristics influence the course of disease in patients with OC [25–27]. A systematic review of nine studies encompassing 529 patients treated for OC found that high circulating serum levels of vascular endothelial growth factor (VEGF), a key promotor of angiogenesis, correlated with a higher risk of death and tumor recurrence [25]. A separate study investigated the prognostic significance of microvessel density (MVD) in resected tumor tissue. MVD was quantified through immunohistochemical staining of CD105, a protein marker of actively proliferating vascular endothelial cells and newly developing vessels. Among 106 women with advanced, previously untreated OC, a high MVD was correlated with an increased risk of disease progression (hazard ratio [HR], 1.873; 95% confidence interval [CI], 1.102–3.184; $p = 0.020$) [27]. This finding was supported by another study, in which MVD was quantified by staining of CD31, a marker of both proliferating and quiescent vascular endothelial cells. Median OS was significantly shorter among patients with high tumor MVD compared with those with low tumor MVD (10.4 vs 23.5 months; HR, 2.2; 95%CI, 1.067–4.467) [26]. Taken together, these results suggest that a high density of both developing vessels and established vessels contribute to the poor prognosis in patients with OC.

Starting in the 1990s, efforts were made to develop novel therapies targeting tumor vasculature; namely, AAs, which inhibit the formation of new vessels, and VDAs, which disrupt established tumor vasculature (Fig. 1).

4. AAs: mechanism of action

In tumors, new vessel development is dependent on a balance of biochemical signals and receptors in a variety of cell types required for the formation of these new vessels [28]. This process, angiogenesis, is necessary for tumors to grow beyond 1–2 mm in diameter [32]. VEGF is a major driver of many angiogenic processes in solid tumors [28]. By binding to the VEGF receptor-1 or -2 (VEGFR-1/VEGFR-2) on target cells, VEGF initiates a cascade of signaling through intracellular tyrosine kinases. VEGF prompts the recruitment of circulating endothelial progenitor cells from bone marrow and promotes the survival, differentiation, and proliferation of endothelial cells during vessel development. The complex process of vessel formation by endothelial cells, pericytes, vascular smooth muscle cells, and other cell types is further coordinated by other growth factors, including platelet-derived growth factor (PDGF), basic fibroblast growth factor (bFGF), and angiopoietin-1 and -2 [28]. These factors bind to different receptors, each transmitting their intracellular signals through a distinct set of tyrosine kinases [28]. A number of AAs have been developed to block these signaling pathways at different points. These include (1) humanized monoclonal anti-VEGF antibodies, such as bevacizumab, which prevent VEGF from binding to its receptor; (2) soluble VEGFRs, such as aflibercept, which also prevent VEGF from binding to cell-surface receptors; (3) peptide/antibody fusion proteins, or "peptibodies," such as trebananib, which binds angiopoietin-1 and -2 to neutralize their interaction with receptors; and (4) small molecule tyrosine kinase inhibitors (TKIs), which inhibit intracellular signaling by a range of different receptors, including those for VEGF, PDGF, bFGF, and other growth factors. TKIs, such as cediranib, pazopanib, sorafenib, sunitinib, and nintedanib, generally inhibit more than one tyrosine kinase, thereby impeding the downstream signaling of more than one receptor; the kinase inhibition profile is distinct for each agent [28].

Bevacizumab is the only AA currently approved by the US Food and Drug Administration (FDA) for treatment of OC—specifically, for recurrent platinum-resistant OC in combination with paclitaxel, topotecan, or pegylated liposomal doxorubicin and recurrent platinum-sensitive OC in combination with carboplatin and paclitaxel or in combination with carboplatin and gemcitabine, followed by bevacizumab as a single agent. A number of other AAs, including aflibercept, sorafenib, pazopanib, and sunitinib, are FDA-approved for other malignancies and have also been evaluated in clinical trials of OC.

5. VDAs: mechanism of action

It is well known that the neovasculature of tumors differs in many respects from that found in normal tissues [30,33]. Vascular networks of tumors are chaotic, irregular, and tortuous, with inconsistent diameters and frequent blind ends [29,30]. Tumor vasculature lacks the hierarchical organization of normal vessel networks, without functionally distinct arrangements of inflowing arterioles, capillaries, and outflowing venules. Individual vessels within tumors are also aberrant, with irregular endothelial cells that form poor junctions with one another, poor connections between endothelial cells and pericytes, an abnormal basement membrane, and poor investiture of vascular smooth muscle cells [29,30,33]. Circulation is inefficient within the vascular beds of tumors, and because vessels are leaky, interstitial fluid pressure is high [29,30].

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