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Review

Bevacizumab in ovarian cancer: Focus on clinical data and future perspectives

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ABSTRACT

The past five years have yielded substantial developments in the management of advanced ovarian cancer. Initial promise shown by anti-angiogenic agents has translated into positive phase III trials in the front-line and recurrent settings. Nevertheless, several questions remain unanswered, including the most appropriate timing for initiation of anti-angiogenic therapy and patient selection for the various treatment approaches. This review article summarises the key results (including final overall survival data), from five pivotal phase III trials of bevacizumab, highlights emerging data with new maintenance strategies and considers unanswered questions and ongoing research to address uncertainties in treatment duration, re-exposure to bevacizumab in bevacizumab-pretreated patients and the potential integration of anti-angiogenic therapy into neoadjuvant treatment regimens.

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1. Treatment landscape in ovarian cancer

The cornerstone of the management of ovarian cancer is primary cytoreductive surgery. After debulking surgery, patients receive front-line chemotherapy. For almost 15 years since the introduction of carboplatin–paclitaxel, most of the treatment strategies tested in the front-line setting yielded disappointing or controversial results. Substituting paclitaxel with other drugs in combination with carboplatin or adding a third drug to the carboplatin–paclitaxel regimen failed to improve outcomes (du Bois et al., 2006, 2010; Bolis et al., 2010; Pfisterer et al., 2006; Vasey et al., 2004; De Placido et al., 2004). Changes in the administration route (intraperitoneal application) or dose density (weekly paclitaxel) produced more encouraging results (Armstrong et al., 2006; Gadducci et al., 2000; Katsumata et al., 2009, 2013). Nevertheless, until relatively recently, there had been little improvement in progression-free survival (PFS) with standard front-line chemotherapy and it was generally accepted that the maximal efficacy with paclitaxel–carboplatin alone had been reached. Improvements in overall survival (OS) were generally attributable to the broadening range of active treatment options at the time of relapse, which typically occurs in 70% of patients who receive front-line therapy.

More recent research has explored the potential of novel targeted approaches to improve the outcomes in ovarian cancer (Banerjee and Kaye, 2011). In this article, we briefly discuss the rationale for one of the most advanced of these novel strategies, anti-angiogenesis, review the available phase III data with a particular focus on bevacizumab, and highlight some of the unanswered questions that are the focus of ongoing research.

2. Rationale for anti-angiogenic therapy in ovarian cancer

At the 2010 Consensus Conference on ovarian cancer, it was agreed that angiogenesis represents one of the most promising targets in ovarian cancer (Ledermann et al., 2011). One of the key mediators of angiogenesis is vascular endothelial growth factor (VEGF), a heparin-binding growth factor that selectively promotes proliferation and survival of vascular endothelial cells (Leung et al., 1989). VEGF also induces vascular permeability and angiogenesis in a variety of *in vivo* models (Ferrara, 2004). The VEGF gene family consists of VEGF-A, VEGF-B, VEGF-C, VEGF-D and placental growth factor. VEGF-A binds two closely related receptor tyrosine kinases, VEGFR-1 and VEGFR-2 (Kowanetz and Ferrara, 2006). VEGFR-2 is the major signalling receptor that mediates most of the biological activities of VEGF (Ferrara et al., 2003a; Chung et al., 2010). The role of VEGFR-1 is complex and varies according to the context (Shibuya, 2006). VEGFR-3 is a member of the same family of receptor tyrosine kinases (Pajusola et al., 1992) and binds VEGF-C and VEGF-D (Karkkainen et al., 2002), two molecules implicated in the regulation of lymphangiogenesis (Alitalo et al., 2005). In addition to these receptor tyrosine kinases, VEGF-A interacts with neuropilin-1, a cell surface protein that binds heparin-binding VEGF-A isoforms, resulting in potentiation of VEGFR-2 signalling (Neufeld et al., 2002).

Although the process of growth and maturation of new blood vessels is highly complex and requires sequential activation of a series of signalling pathways, VEGF signalling often represents a rate-limiting step (Chung et al., 2010; Ferrara et al., 1996; Carmeliet et al., 1996). A key function of VEGF in adults is the regulation of the cyclical angiogenesis that takes place in the female reproductive tract. Expression of VEGF mRNA is temporally and spatially related to blood vessel growth in the ovaries (Phillips et al., 1990; Fraser and Lunn, 2000; Ferrara et al., 2003b). VEGF inhibition results in suppression of *corpus luteum* and uterine angiogenesis in rodents and primates (Ferrara et al., 1998; Fraser et al., 2000; Ryan et al., 1999).

Many tumour cell lines secrete VEGF *in vitro*, suggesting that VEGF may be a mediator of tumour angiogenesis. *In situ* hybridisation studies have shown that VEGF mRNA is up-regulated in the majority of human tumours, including lung, kidney, bladder, ovary, cervix and endometrium carcinomas, as well as several intracranial tumours (reviewed in Ferrara, 2004). Approximately 97% of ovarian tumours overexpress the VEGF ligand (Yamamoto et al., 1997), and this expression correlates with ascites formation, poor prognosis and reduced survival (Yamamoto et al., 1997; Mesiano et al., 1998; Li et al., 2004; Byrne et al., 2003).

2.1. Preclinical studies of bevacizumab

Subcutaneous and orthotopic models were used to test the effects of bevacizumab or its murine precursor, A4.6.1, on the growth of a variety of tumour cell lines. Collectively, these studies demonstrated reduction in tumour vessel density and suppression of primary tumour growth, even with single-agent treatment (Kim et al., 1993; Gerber and Ferrara, 2005). In addition, bevacizumab or A4.6.1 demonstrated inhibitory effects on metastasis (Warren et al., 1995; Rowe et al., 2000) and was shown to abrogate ascites formation (Hu et al., 2002). Additive and/or synergistic effects between bevacizumab and several commonly used chemotherapeutic agents, including paclitaxel, were observed in a variety of human tumour xenografts (Gerber and Ferrara, 2005; Hu et al., 2002; Fujita et al., 2007). The mechanism of the additive or synergistic interactions between VEGF inhibitors and cytotoxic agents is highly debated. As these therapeutic modalities have different mechanisms of action, the additivity may result from targeting both tumour and endothelial compartments (Klement et al., 2000). Another possibility is that bevacizumab or other anti-angiogenic agents 'normalise' the abnormal and leaky tumour vessels, which typically result in increased interstitial fluid pressure, impaired flow and hypoxia (Jain, 2005). The resulting improvement in flow would enhance delivery of chemotherapy to tumour cells.

3. Clinical evaluation of bevacizumab

These preclinical properties, together with the proven efficacy of bevacizumab in a range of other solid tumour types and the known poor prognosis of patients with ovarian cancer overexpressing VEGF, led to clinical evaluation of bevacizumab in patients with recurrent ovarian cancer. The Gynecologic Oncology Group (GOG) carried out a series of phase II studies evaluating targeted agents, including bevacizumab, in patients with ovarian cancer. The activity demonstrated by bevacizumab in GOG 170D in terms of objective response rate (ORR) and 6-month PFS rate was substantially higher than that of all the other compounds evaluated in the GOG series of similarly designed phase II trials testing new agents (Burger et al., 2007) and was supported in subsequent phase II studies in more heavily pretreated populations in the recurrent setting (Cannistra et al., 2007; Smerdel et al., 2010). These encouraging results triggered evaluation of bevacizumab as a component of front-line therapy. Two prospective randomised phase III trials, GOG-0218 and ICON7, were initiated to investigate the role of bevacizumab administered in combination with front-line chemotherapy and continued as single-agent maintenance therapy.

4. Bevacizumab as front-line treatment for ovarian cancer

4.1. GOG-0218

The double-blind, placebo-controlled randomised phase III GOG-0218 trial included 1873 patients with stage III (incompletely