Antiangiogenic Treatment in Ovarian Cancer in the Era of Evidenced-Based Medicine

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ABSTRACT

Angiogenesis plays a major role in tumor growth and metastatic spread of cancer, and therefore inhibition of angiogenesis seems a promising therapeutic strategy. In order to grow beyond microscopic size, tumors need a better delivery of nutrients and oxygen so neovascularization must occur. Vascular endothelial growth factor [VEGF] pathway is the most important factor in promoting angiogenesis. This pathway may be blocked by either extracellular interference with VEGF itself (bevacizumab [BEV] or aflibercept), or intracytoplasmonic inhibition of VEGF receptor (pazopanib, nintedanib, cediranib, sunitinib and sorafenib). Approximately 97% of ovarian tumors over express the VEGF ligand and this is correlated with early metastases, ascites formation and poor prognosis. The addition of antiangiogenic agents to standard chemotherapy in ovarian cancer is a rational therapeutic option for primary or recurrent ovarian carcinoma but it does not represent a new standard treatment until the subset of patients who benefit the most is identified.

Keywords: angiogenesis, VEGF, ovarian cancer

INTRODUCTION

Ovarian cancer is the fourth most common cause of cancer related death in women, but is the most lethal of the gynecological malignancies (1). This is part because about 75% of patients present at diagnosis with advanced disease and treatment options (surgery and platinum based chemotherapy) are only partially effective. Moreover, the 5-year survival ratio from ovarian cancer is less than 50% worldwide (2) and for advanced ovarian cancer 5-years overall survival rates remain at only 27% (3).

Current management of advanced stage disease includes surgical tumor debulking and chemotherapy with platinum and taxanes based chemotherapy (4,5). Intraperitoneal chemotherapy has been used in order to improve the prognosis of patients with ovarian cancer, but with increased toxicity (6,7).

The most important clinic-pathological features known to be prognostic in ovarian adenocarcinoma are stage (FIGO), histological grade, histological subtype, lymph node involvement,
residual tumor size after cytoreductive surgery, ascites and age (8). Angiogenesis seems to play a major role in the natural history of ovarian cancer, promoting tumor growth and progression in the form of ascites and metastatic spread (9,10). The main attention was focused on the VEGF family of growth factors and the receptor tyrosine-kinases that mediated their pro-angiogenic effects. This family includes VEGF-A, VEGF-B, VEGF-C and VEGF-D and placental growth factor (11). The major mediator of tumor angiogenesis is vascular endothelial growth factor A (VEGF-A) also call VEGF who signals through VEGF receptor 2 (VEGF-2). VEGF is expressed in most types of tumors and is associated with less favorable prognosis. The cause for increase in VEGF expression is environmental (epigenetic factors such as hypoxia, low pH, inflammatory cytokines, sex hormones, growth factors, and chemokines) or genetic (activation of numerous different oncogenes such as ras, src, EGFR, and erb-B2/HER2 or loss of inactivation of many tumor suppressor such as p53, PTEN). The binding of VEGF to VEGFR-2 leads to a cascade of different signaling pathways: first the dimerization of the receptor, followed by intracellular activation of PLCγ-PKC-RAF kinase-MEK-MAPK pathway and subsequent activation of DNA synthesis and cell growth; the other is the activation of phosphatidylinositol3-kinase (PI3K)-AKT pathways which leads to increase endothelial cell survival (11). Circulating VEGF and soluble form of VEGFR-2 have been used as surrogate markers of antiangiogenic therapy.

In recent years it was a continuous effort in order to identify targets for developing anti tumor activity. What we know in this moment is that antiangiogenic drugs, targeting VEGF or angiopoietin, are active in prolonging PFS (progression free survival) and OS (overall survival) in some subgroups of ovarian cancer. What we do not know are: when should an angiogenesis inhibitor be given (first-line, plat-in-sensitive, plat-in-resistant), how long, which angiogenesis inhibitor should be preferred in which group of ovarian cancer patients. Biomarkers for efficacy of antiangiogenesis are anyway urgently needed.

**Antiangiogenic drugs targeting VEGF**

Vascular endothelial growth factor pathway may be blocked by either extracellular interference with VEGF itself (bevacizumab [BEV] or aflibercept), or intracytoplasmic inhibition of VEGF receptor (pazopanib, nintedanib, cediranib, sunitinib and sorafenib). An alternative approach is represented by trebananib, a fusion protein that prevents the interaction of angiopoietin [Ang]-1 and Ang-2 with Tie2 receptor on vascular endothelium (12).

**Bevacizumab** is a recombinant humanized monoclonal IgG1 antibody that targets vascular endothelial growth factors A and proved his efficacy in different cancer types (colon, lung, renal, glioblastoma, cervical, breast). This antibody binds to and neutralized all biologically active forms of VEGF-A, suppressing tumor growth, inhibits metastatic disease progression (13). First of all, VEGF blockade was showed to inhibit tumor progression in animal models, to inhibit ascites’ formation and to slow tumor growth. Another beneficial effect of bevacizumab was to normalize tumor vascularization and by that enhances the effect of chemotherapy (particularly paclitaxel), leading to decrease interstitial pressure, increase tumor oxygenation (14).

Recently, this drug has been approved in treatment of patients with ovarian adenocarcinoma either as monotherapy or in combination with different agents, but there are still many controversies around the benefit of this drug and the subpopulation of patients who benefit more.

First studies tested bevacizumab as a single agent in recurrent ovarian adenocarcinoma. The GOG 0170D study included 62 patients with persistent or recurrent ovarian carcinoma who received 15 mg/kg bevacizumab every three weeks. Overall response rate was a promising 21% and median PFS and OS were 4.7 and 17 months, respectively (15).

Next step was incorporating bevacizumab in the first line treatment of locally advanced and metastatic ovarian cancer. GOG 0218 phase III randomized trial published in 2011 assessed bevacizumab combined with carboplatin/paclitaxel compared to carboplatin/paclitaxel alone as primary treatment for stage III (incompletely resected) and IV ovarian cancer. One thousand eight hundred seventy three patients were randomized to receive chemotherapy alone, chemotherapy + bevacizumab (15 mg/kg every 3 weeks) from cycle 2 to 6 or chemotherapy+bevacizumab in cycle 2-22. The median PFS was significantly increased
(14.1 vs. 10.3 months, p < 0.001) in patients receiving prolonged bevacizumab (upfront and as maintenance therapy) when compared with chemotherapy alone. PFS was not significantly increased in patients who did not receive maintenance bevacizumab (upfront with placebo maintenance) versus chemotherapy alone (ie, bevacizumab/carboplatin/paclitaxel vs. carboplatin/paclitaxel) (16).

Another phase III randomized trial (ICON7) also assessed bevacizumab/carboplatin/paclitaxel in the upfront setting, but with a little different regimen. The trial compared bevacizumab (7.5 mg/kg) with paclitaxel and carboplatin every 3 weeks for 6 cycles followed by another 12 cycles of maintenance bevacizumab in 1528 patients with ovarian adenocarcinoma. The study confirmed a statistically significant increase of PFS (21.8 vs. 20.3 months HR=0.81; 95% confidence interval, 0.70 to 0.94; P = 0.004); in patients at high risk for progression, the benefit was greater with bevacizumab than without it, with progression-free survival at 42 months of 14.5 months with standard therapy alone and 18.1 months with bevacizumab added, with respective median overall survival of 28.8 and 36.6 months. Recently, the final overall survival analysis was published. The study concluded that overall there is no benefit in survival of adding bevacizumab to standard chemotherapy (45.5 vs. 44.6 months in favor of bevacizumab p=0.85) after a follow-up of 48.9 months. In predefined subgroup of patients with poor prognostic, high risk patients defined as FIGO stage IV disease or FIGO stage III disease and >1.0 cm of residual disease after debulking surgery, a significant difference in overall survival was noted between women who received bevacizumab plus chemotherapy and those who received chemotherapy alone (39.3 months with bevacizumab vs. 34.5 months with standard chemotherapy, log-rank p=0.03) (17). Bevacizumab continuation treatment seems to be associated with small, but clinically significant decrement in QoL compared with standard treatment for women with ovarian cancer (18).

According to these data, there is a major disagreement regarding the use of bevacizumab in up front treatment of stage III and IV ovarian cancer (category 3). If used, the best regimen to use is paclitaxel, carboplatin, bevacizumab followed by maintenance bevacizumab. Several phase III randomized clinical trials have recently assessed combination of chemotherapy with bevacizumab for recurrent ovarian cancer (AURELIA, OCEANS). These combinations proved safe and active (19). A randomized, multicenter, blinded, placebo-controlled phase III trial was OCEANS which tested the efficacy and safety of bevacizumab with gemcitabine and carboplatin compared with chemotherapy in 484 patients with platinum-sensitive recurrent ovarian, primary peritoneal, or fallopian tube cancer. Median PFS was 12.4 vs. 8.4 months, respectively HR of 0.484 (log-rank p=0.0001) (20).

Platinum resistant recurrent ovarian cancer (defined as progression less than 6 months after completing platinum based chemotherapy) is difficult to treat and single agent chemotherapy is the only option in these patients. A phase III randomized trial (AURELIA) included 361 patients to receive topotecan/ liposomal doxorubicin or weekly paclitaxel plus bevacizumab (10 mg/kg every 2 weeks or 15 mg/kg every 3 weeks) or placebo until progression, unacceptable toxicity, or consent withdrawal. Bevacizumab significantly improved response rate (27.3% vs. 11.8%) and PFS (3.4 vs. 6.7 months, HR = 0.48). There was a trend into improving overall survival rate, median OS was 16.6 months vs. 13.3 months, without reaching statistical significance (the OS HR was 0.85 (95% CI, 0.66 to 1.08; P=0.174 (21). Preclinical research indicated that tumor VEGF secretion was at least partially responsible for the development and maintenance of ascites, which may explain the control of ascites observed with bevacizumab therapy (21). Based on these studies, bevacizumab in combination with paclitaxel, topotecan, or pegylated liposomal doxorubicin is indicated for the treatment of adult patients with platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who received no more than two prior chemotherapy regimens and who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor targeted agents.

Adverse events of special interest associated with use of antiangiogenic treatment are hypertension (grade 3 or more in approximately 17% of patients), arterial and venous thromboembolic event (any grade approximately 3%), bleeding (7%), proteinuria, gastro-intestinal perforation (2.5%), wound-healing complication (3%) (22).
Another agent tested in maintenance in ovarian cancer after surgery and conventional chemotherapy is pazopanib, an oral multitargeted kinase inhibitor of VEGFR 1, 2, 3, PDGFR α and β and c-kit. The study AGO-OVAR 16 enrolled 940 patients who were randomized to receive pazopanib 800 mg once daily. Pazopanib maintenance therapy improved PFS (17.9 vs. 12.3 months) HR=0.77, but failed to show any survival benefit between the two groups and was associated with severe toxicity which lead to treatment discontinuation in 33% of the patients in treatment arm (23).

Nintedanib (BIBF 1120) is a potent triple angiokinase inhibitor, inhibiting 3 groups of receptors engaged in the regeneration and stabilization of vessels: VEGFR, PDGFR, FGFR. Nintedanib at the dose of 200 mg twice daily has been evaluated in a randomized phase III trial of first-line treatment (AGO-OVAR 12). One thousand and three hundred-sixty six women with FIGO stage IIB–IV disease were randomized in a ratio 2:1 to receive paclitaxel (175 mg/m²) + carboplatin (AUC 5 or 6) plus either nintedanib or placebo for six cycles, and those who had not progressed at the end of chemotherapy were maintained on daily nintedanib or placebo for a maximum of 120 weeks. Nintedanib arm experienced better PFS (HR = 0.84, p = 0.0239), whereas OS data were not yet mature. Grade ≥3 adverse events were more common with nintedanib, and included diarrhea, hepatotoxicity, hypertension, and fatigue (24).

Cediranib. The ICON6 trial tested cediranib (a potent oral tyrosine kinase inhibitor of all three VEGF receptors VEGFR 1, 2, 3 and c-kit plus standard chemotherapy at the time of first relapse in patients with platinum-sensitive disease. One hundred and fifty-six women were to receive: (i) 3-weekly platinum-based chemotherapy (taxane + carboplatin; gemcitabine + carboplatin, single-agent carboplatin) + daily placebo for 6 cycles followed by daily placebo for 18 months from randomization; (ii) the same chemotherapy + cediranib 20 mg daily during chemotherapy followed by daily placebo for 18 months; or (iii) the same chemotherapy + cediranib 20 mg daily during chemotherapy and after chemotherapy for 18 months. The patients enrolled in cediranib-maintenance arm experienced longer PFS (HR = 0.57, p = 0.024) and longer OS (HR = 0.70, p = 0.042) when compared with those treated with chemotherapy alone (25). Another interesting trial added cediranib to a PARP inhibitor olaparib in platinum sensitive relapse patients with ovarian cancer and found an impressive 80% response rate for the combination and an increased in PFS from 9 to 17.7 months (26).

Afibercept was tested in two phase II trials in patients with relapsed ovarian cancer, and the end point was “time to repeat paracentesis”. Afibercept proved a better control of malignant ascites with less paracentesis needed at a longer interval, but no overall survival advantages could be demonstrated (27,28).

Sunitinib and sorafenib are oral multitargeted tyrosine kinase inhibitors targeting VEGFR and PDGFR, KIT, and FMS-like tyrosine kinase-3 (FTL3) who failed to demonstrate sustained response rates or a benefit regarding progression free survival, so no phase III trial were started (29,30,31).

Antiangiogenic drugs targeting angiopoietin

Trebananib inhibits angiopoietin 1 and 2 connection to Tie 2 receptor and so finally angiogenesis in a different mechanism. Compared to bevacizumab different adverse events were reported: no hypertension, no bowel perforations, no wound healing problems, but more ascites, pleural effusions, edema - were observed. Beyond bevacizumab: an outlook to new anti-angiogenics for the treatment of ovarian cancer (32). The combination of trebananib plus paclitaxel for recurrent epithelial ovarian cancer has been further investigated in a phase III study (TRINOVA-1). Nine hundred and nineteen women were randomly allocated to receive paclitaxel (80 mg/m² on days 1, 8 and 15 every 4 weeks) plus either weekly trebananib (15 mg/kg) or masked i.v. placebo. Median PFS was significantly longer in the trebananib group (HR = 0.66, p < 0.0001). The interim overall survival analysis failed to show any significant difference between groups (17.3 months in the placebo group vs. 19.0 months in the trebananib arm (HR = 0.86, p = 0.19) (33).

The identification of a predictive marker for response to antiangiogenic treatment is mandatory. VEGF expression failed to identify a subgroup of patients who would benefit of antiangiogenic treatment. Recently, molecular signature The Cancer Genome Atlas [TCGA] project has assessed messenger RNA (mRNA) expression, microRNA (mi-RNA) expression, pro-
CONCLUSION

The role of antiangiogenic agents in ovarian cancer is still debated. Due to present inconclusive data, further randomized clinical trials and study of molecular background are needed.

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REFERENCES

19. O’Mallely DM, Richardson DL, Rheume PS, et al. – Addition of bevacizumab to weekly paclitaxel significantly improves progression-free


34. Winterhoff BJN, Kommoss S, Oberg AL, et al. – Bevacizumab and improvement of progression-free survival (PFS) for patients with the mesenchymal molecular subtype of ovarian cancer. J Clin Oncol 2014;32(5s):Abstr. 5509.