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CLINICAL VIGNETTE

Review of Angiogenesis in Ovarian Cancer

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Despite recent progress in diagnosis of ovarian cancer, more than 50% of women are diagnosed at advanced stages. In the past two decades, advances in surgical techniques and incorporation of taxanes in the adjuvant setting have improved the survival of women with advanced ovarian cancer. Despite this, mortality remains high, with only 10% of women with stage IV disease surviving for 5 years. As a result, there is a need for new approaches to treatment of this disease. The angiogenesis pathway is of paramount importance in ovarian cancer. Recent attempts targeting angiogenesis have had promising results in improvement of disease free survival for patients with advanced disease. Data delineating benefit of anti-angiogenic therapy will be briefly reviewed.

Several groups have reported that the Vascular Endothelial Growth Factor (VEGF) is over expressed in ovarian cancer cells[1,2] and there are increased circulating levels of VEGF in the serum and ascites in patients with ovarian cancer compared to those who are cancer free[3]. Specific settings, including hypoxia, acidosis or oxidative stress can result in increased production of VEGF, which can then exert its action through its associated receptors (VEGFR1-3). VEGFR-1 and VEGFR-2 have been implicated in angiogenesis while VEGFR-3 stimulation results in lymphangiogenesis and production of ascites[4]. VEGF exerts its actions via interaction with the VEGFR, initiating a complicated intra-cellular signaling cascade such as PI3/AKt protein Kinase B pathway, MAPK and Raf/MEK/Erk pathway, thereby resulting in endothelial cell proliferation, migration and survival, finally resulting in blood vessel formation[5]. Animal models of ovarian cancer show that VEGF inhibition drastically alters tumor vasculature, inhibits ascitic fluid accumulation and limits tumor growth[6]. VEGF may also promote tumor growth by direct action of the ligand on receptors on the ovarian tumor cells[7]. Furthermore, over-expression of VEGF is associated with poor survival in all stages of disease[8]. Pre-clinical data prompted various studies to look at the clinical benefit of targeting the angiogentic pathway in ovarian cancer patients. While numerous agents are actively being explored for anti-angiogenic properties in ovarian cancer, the greatest body of data to date is with bevacizumab (Avastin), a monoclonal antibody against the VEGFR.

Clinical Experience with Bevacizumab, Phase II trials

Interest in potential benefit of bevacizumab in ovarian cancer stemmed from the presentation and subsequent publication of a Phase II trial done by Gynecologic Oncology group GOG (United States) that examined bevacizumab as a single agent (15 mg/kg every 3 weeks) in recurrent ovarian cancer. The patients in this trial were allowed to have one or two prior cytotoxic regimens, and were required to have measurable disease. Recurrences within 12 months of prior cytotoxic agent were permitted in the study, and as a result this was a more favorable patient population as they included platinum sensitive patients. Of the 62 evaluable patients, 21% achieved objective response (two complete, 11 partial) to single agent bevacizumab[9]. Furthermore, 40% of the treated population remained free of progression for more than 6 months and had a median survival of 17 months. The most common reported side effect was hypertension.

A second Phase II trial of single agent bevacizumab was done in 44 patients who had more advanced disease. Approximately half of the patients had received at least three cytotoxic

agents. In this study, the objective response rate was 16% and the median overall survival was 10.7 months[10]. This trial however was associated with more significant adverse events, including a gastrointestinal perforation rate of 11% and three treatment-related deaths. The risk of perforation was greatest for patients with evidence of tumor involvement of the bowel.

A third Phase II trial explored combination of bevacizumab (10 mg/kg every two weeks) with low dose oral cyclophosphamide (50 mg/day). This was based on pre-clinical data that suggested that metronomic or continuous dosing of chemotherapy can have anti-angiogenic effect and can potentiate the blockade of angiogenesis[11-13]. In this trial, platinum free intervals of 12 months were permitted and measurable disease was required for entry in the study. The progression free survival (PFS) rate at 6 months was 56% and a partial response rate of 24% was seen. The median overall survival was 16.9 months[14].

Phase III trials of bevacizumab with combination chemotherapy in ovarian cancer.

The promising data from the phase II trials led to the design of two large randomized Phase III trials in ovarian or primary peritoneal cancers. The first trial, the GOG 218 was reported in the meeting of American Society of Clinical Oncology in June of 2010. GOG 218 was a double-blinded randomized placebo controlled trial for the first line treatment of ovarian or primary peritoneal cancers. The study was a three arm study, comparing carboplatin and paclitaxel for six cycles to carboplatin, paclitaxel and bevacizumab at dose of 5 mg/kg/week for six cycles and a third arm which consisted of carboplatin, Paclitaxel, and bevacizumab for six cycles and maintenance bevacizumab for a total of 15 months. This trial was limited to patients with stage III disease with optimal or suboptimal cytoreducton or patients with Stage IV disease. Patients were stratified based on performance status and stage at presentation. The primary endpoint was progression free survival with secondary endpoint of overall survival and toxicity assessment. A total of 1800 patients were enrolled and randomized to one of the three arms. The initial report of the trial was notable for a statistically improved progression free survival in the carboplatin, Paclitaxel, bevacizumab with maintenance bevacizumab arm (14.1 months versus 10.3 for control arm $p < 0.0001$) ; however, at the initial presentation the overall survival did not reach statistical significance (39.7 months versus 39.3 months for control). Toxicity profile was similar to other bevacizumab containing trials demonstrating an increase in hypertension, proteinuria. Interestingly there was no significant increase in the rate of venous or arterial thrombotic events and the bleeding rate was 2.!% for bevacizumab arm compared to control arm at 0.8%[15].

A second large phase III trial, ICON 7 was reported in Europe later in 2010. This was an open label two-arm trial, comparing carboplatin and Paclitaxel to Carboplatin, Paclitaxel, and bevacizumab for 12 months in patients with fallopian, primary peritoneal or ovarian cancer. This trial differed from the GOG218 in that it included not only stage III and IV patients, but also high-risk stage I-IIB patients, defined as patients with either clear cell histology or high nuclear grade. Over 1500 patients were randomized to one of the two arms with the primary end point of study being disease free survival and secondary endpoint of overall survival and toxicity. There was a statistically significant benefit for addition of bevacizumab in terms of disease free survival (18.3 months versus 16.0 months $p < 0.0010$). The overall survival data has not been reported at this time. Again, similar to other bevacizumab trials, there was increased rate of hypertension, thrombocytopenia, and bleeding. It is also important to note that unlike the GOG 218 trial, the dose of bevacizumab was lower at 2.5 mg/kg/week in ICON 7 trial[16].

The two large trials above give additional support for the benefit of bevacizumab, at least in regards to improvement of progression-free survival in the first line treatment of ovarian cancer. Whether this benefit translates to meaningful improvement in overall survival remains to be seen. Two other large trials, OCEANS and GOG 213 are currently exploring the role of bevacizumab in recurrent, platinum

sensitive ovarian cancer. OCEANS trial is exploring the benefit of bevacizumab in this patient population on a backbone of carboplatin and Gemcitabine, in bevacizumab naïve patient population, while GOG213 is exploring the benefit of bevacizumab on backbone of carboplatin and paclitaxel in the second line setting, allowing of bevacizumab use in the first line.

The collective phase II and phase III trials of bevacizumab in ovarian cancer have provided clinical support for the benefit of targeting angiogenesis in this disease model and provide proof for the pre-clinical model. Whether the larger phase III trials culminate in actual survival benefit remains to be seen and the future of this drug in ovarian cancer is unclear especially given the recent reversal of approval of bevacizumab in breast cancer by the Food and Drug Agency in United States. In addition, a recently published meta-analysis of all bevacizumab trials suggests that an adverse increase of 1%[17] in mortality is seen with incorporation of bevacizumab in management of solid tumors and this needs to be factored in decision of treating patients at least with this particular agent. Clearly, there are patients who gain meaningful benefit from bevacizumab; however, in absence of valid biomarkers, identification of this patient population remains elusive and the clinician needs to exercise judgment in deciding whether a specific patient may benefit from addition of bevacizumab to their chemotherapy regimen. Results of on-going trials and additional data should provide the much-needed support for benefit of targeting angiogenesis in this disease.

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