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GYNECOLOGICAL CANCER

True progress in ovarian cancer or just the tip of the iceberg?

Development of malignant ascites is common in patients with ovarian cancer, and few therapeutic options exist for women with ascites whose tumors become resistant to chemotherapy. Furthermore, in such patients symptom palliation options are limited, and the few available treatments are unpleasant and can result in the need for paracentesis. The pathophysiology of ascites suggests a key role of VEGF in malignant ascites formation. Moreover, early clinical studies indicate that blockade of VEGF can suppress the formation of ascites.

Against this background, Walter Gotlieb and his team conducted a phase II double-blind, randomized, placebo-controlled study to evaluate the efficacy and safety of aflibercept, a potent inhibitor of both VEGF and placental growth factor, for the treatment of patients with malignant ascites. In total, 58 patients from 23 centers in seven countries were enrolled into the study. Patients had advanced-stage chemoresistant ovarian cancer and recurrent symptomatic malignant ascites, with most patients having undergone previous debulking surgery and all were heavily pretreated with a median of four previous lines of chemotherapy.

Gotlieb summarizes the key findings of the study: "our study demonstrates the effectiveness of VEGF blockage in the reduction of malignant ascites but confirms the significant clinical risk of bowel perforation in this patient population with very advanced cancer. These results mandate caution in the use of VEGF blockers in patients with advanced ovarian cancer-related ascites." There was no notable difference in overall survival or progression-free survival between the aflibercept and placebo groups. However, the mean time to repeat paracentesis was significantly longer for aflibercept-treated patients compared with those receiving placebo (55.1 days versus 23.3 days). In addition, the paracentesis-free survival time was also significantly improved in aflibercept-treated patients, with some not requiring a repeat paracentesis during the 6 months of treatment.

Preliminary studies carried out before this trial had raised concerns that there might be an association between VEGF inhibition and bowel perforation. As has been observed with the VEGF inhibitor, bevacizumab, the frequency of grade 3 or 4 gastrointestinal perforations was higher with aflibercept.

Hence, there is a trade-off between efficacy and serious adverse events with aflibercept in patients with advanced-stage chemorefractory ovarian cancer and malignant ascites. As Gotlieb cautions, "to provide a more favorable benefit–risk balance for this therapeutic intervention, additional prospective and larger clinical studies are required to identify those patients that may safely benefit from VEGF-blockade in this setting. Until then, anti-VEGF therapy should be used with caution in advanced ovarian cancer with abdominal carcinomatosis, and the benefit–risk balance should be discussed individually with each patient." Although aflibercept showed promising clinical activity and symptom improvement from ascites was reported by patients treated with the drug, the researchers conclude the following, "this study offers an important message to clinicians because the recorded bowel perforations, including fatalities, point to an unfavorable benefit–risk balance for this therapeutic anti-VEGF intervention in heavily pretreated patients with ovarian cancer." For now, until we know more than the tip of the iceberg, caution should be applied when using anti-VEGF treatments.

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Original article Gotlieb, W. H. *et al*. Intravenous aflibercept for treatment of recurrent symptomatic malignant ascites in patients with advanced ovarian cancer: a phase 2, randomised, double-blind, placebo-controlled study. *Lancet Oncol*. doi:10.1016/S1470-2045(11)70338-2