Role of anti-angiopoietin therapy with trebananib for recurrent epithelial ovarian cancer

Sir,

Recurrent epithelial ovarian cancer (EOC) is a challenging tumor to manage with limited outcomes. It is estimated that about 85% of patients with EOC who attain a full remission with first-line treatment will develop recurrent disease.[1] The median survival for such patients varies from 12 to 24 months. Thus, the overall prognosis is very gloomy. In recent times, there have been developments in this field with a new drug, Trebananib shown to provide benefits in progression-free survival (PFS).

The selection of therapy for patients with recurrent EOC is primarily determined by response to first-line therapy. Recurrent EOC is categorized into either platinum-sensitive (progression-free interval [PFI] >6 months) or platinum-resistant (PFI ≤ 6 months) disease, with PFI predicting the expected response rate and duration of response.[2] Platinum-sensitive recurrent EOC is treated with a platinum agent alone or in combination with paclitaxel depending on the performance status of the patient. In OCEANS trial, the addition of bevacizumab with chemotherapy was found to improve PFS (12 months with bevacizumab vs. 8 months in the placebo group; hazard ratio [HR] =0.48; 95% confidence interval [CI]: 0.39-0.61).[3] However, the benefit came at the cost of higher rate of treatment discontinuation for adverse events (23% vs. 5%); the latter included higher rates of serious hypertension (17% vs. <1%), proteinuria > grade 3 (9% vs. 1%), and noncentral nervous system bleeding (6% vs. 1%).[3] Thus, there was a search for alternate drugs that can block the angiogenesis pathway without the significant adverse effects of bevacizumab.

Trebananib is a peptibody, an engineered protein with properties of both peptides and antibodies, that is an inhibitor of both angiopoietin-1 and 2 (Ang1 and Ang2), and also inhibit their interaction with the tyrosine kinase endothelial 2 (Tie2) receptor.[2] Ang1 and Ang2 each mediate different actions upon binding with Tie2.[4] Ang1 impacts vessel quality while Ang2 influences vessel quantity. Besides, Angs are also involved in lymphangiogenesis which plays a key role in tumor metastasis.[5] In a landmark study TRINOVA-1 by Monk *et al*., 919 patients were randomized to weekly intravenous paclitaxel (80 mg/m^2) plus either weekly masked intravenous placebo or trebananib (15 mg/kg).[6] Patient eligibility criteria included having been treated with three or fewer previous regimens, and a platinum-free interval of <12 months. The addition of trebananib to paclitaxel prolonged the time to disease progression or death by 52% compared with paclitaxel plus placebo ($P < 0.001$). Median PFS was significantly longer in the trebananib group than in the placebo group (7·2 months [5.8-7.4] vs. 5.4 months [95% CI: 4.3-5.5], respectively, HR: 0.66, 95% CI: 0.57-0.77, $P < 0.0001$).[6] An important finding being both subgroups with PFI <6 and 6-12 months were equally benefitted. Most importantly, the Incidence of grade 3 or higher adverse events was similar between treatment groups (54% in the placebo group vs. 56% patients in the trebananib group). Trebananib was associated with higher incidences of edema (64% patients had any-grade edema in the trebananib group vs. 28% patients in the placebo group). Grade 3 or higher adverse events included ascites (38% in the placebo group vs. 11% in the trebananib group), neutropenia (9% vs. 6%), and abdominal pain (5% in both the arms). There was a difference of 2% or less in class-specific adverse events associated with anti-vascular endothelial growth factor (VEGF) therapy (hypertension, proteinuria, wound-healing complications, thrombotic events, gastrointestinal perforations), except bleeding, which was more common in the placebo group than in the trebananib group (17% vs. 10%). Overall survival data are expected to mature by end of 2014; however, an interim analysis with 50% of deaths indicates a non-significant trend in favor of the trebananib arm (19.0 months vs. 17.3 months; HR: 0.86; $P = 0.19$). The agent is also being studied in two on-going phase III trials in combination with pegylated liposomal doxorubicin in recurrent EOC (TRINOVA-2) and in combination with first-line paclitaxel and carboplatin in newly diagnosed ovarian cancer (TRINOVA-3).

Inhibition of Ang1 and Ang2 with trebananib can provide significant improvement in PFS in patients of recurrent EOC without the typical anti-VEGF associated adverse effects.

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