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A phase 1b, open-label study of trebananib in combination with paclitaxel and carboplatin in patients with ovarian cancer receiving interval or primary debulking surgery ☆

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Abstract ***Aim:*** To evaluate the tolerability, pharmacokinetics and tumour response of first-line trebananib plus paclitaxel and carboplatin followed by trebananib maintenance in high-risk or advanced ovarian cancer.
Methods: In this open-label phase 1b study, patients received intravenous (IV) trebananib 15 mg/kg administered weekly (QW) plus paclitaxel 175 mg/m^2 once every 3 weeks (Q3W) and carboplatin 6 mg/mL·min Q3W followed by trebananib 15 mg/kg QW monotherapy for 18 months. End-points were dose-limiting toxicities (DLTs; primary); treatment-emergent

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adverse events (AEs), anti-trebananib antibodies, pharmacokinetics and tumour response (secondary).

Results: Twenty seven patients (interval debulking surgery [IDS], $n = 13$) were enrolled. No DLTs occurred. During the combination therapy phase, AEs (>50%) in patients with IDS were nausea, diarrhoea, fatigue, decreased appetite and thrombocytopenia. In patients with primary debulking surgery (PDS), they were nausea, diarrhoea, fatigue and localised oedema. Grade 4 AEs were neutropenia (IDS, PDS; all $n = 3$) and thrombocytopenia (IDS, PDS; all $n = 1$). No deaths occurred. Toxicity results pertaining to trebananib maintenance were immature. The treatment combination did not markedly affect the pharmacokinetics across agents. In patients with IDS ($n = 14$ after one patient was reassigned from PDS to IDS), 12 patients had a partial response (PR), two patients had stable disease. In patients with PDS ($n = 4$), three patients had a complete response, one patient had a PR.

Conclusions: In women with ovarian cancer receiving IDS or PDS, IV trebananib 15 mg/kg QW plus paclitaxel and carboplatin appears tolerable. Results suggest that the treatment combination followed by trebananib 15 mg/kg monotherapy is associated with antitumour activity.

1. Introduction

Primary debulking surgery (PDS) plus carboplatin and paclitaxel is the standard first-line treatment option for patients with advanced ovarian cancer [1]. For patients who may not be able to tolerate PDS, interval debulking surgery (IDS) is recommended [2,3]. Despite their clinical benefits, both approaches have only limited success [2,3]. Therefore, to further improve efficacy, research has focused on combining antiangiogenic agents with chemotherapy and debulking surgery. Results suggest clinical efficacy of this approach in patients with PDS [4,5]. However, only limited information is available on treatment with angiogenic pathway inhibitors in patients receiving IDS [6,7]. Angiogenesis drives tumour development and metastasis and plays an important role in disease progression and prognosis for ovarian cancer [8,9]. It is a complex biological process regulated by numerous endogenous factors, including the vascular endothelial growth factor (VEGF) protein family and its receptors [10]. VEGF pathway inhibitors provide limited clinical benefits in this disease setting due to the development of toxicities or treatment resistance [4,5,11,12]. Antiangiogenic agents targeting different pathways may circumvent those limitations.

The angiopoietin axis is critical for angiogenesis and distinct from the VEGF pathway [13–17]. Angiopoietin-1 and -2 (Ang1 and Ang2) are endogenous ligands binding to the tyrosine kinase receptor Tie2 [15,18]. Ang1 promotes normal vessel structure and function; Ang2 prevents the stabilising action of Ang1 on blood vessel development and increases tumour vascularity [18,19]. Some preclinical research suggests that simultaneous blocking of Ang1 and Ang2 provides greater inhibition of tumour angiogenesis than blocking either ligand in isolation [15,20].

Trebananib is an investigational recombinant peptide-Fc fusion protein (peptibody) that suppresses tumour angiogenesis by binding to Ang1 and Ang2, which prevents their interaction with Tie2 [21]. In a randomised double-blind phase 3 study (TRINOVA-1), intravenous (IV) trebananib 15 mg/kg administered weekly (QW) plus paclitaxel relative to IV placebo QW plus paclitaxel significantly improved progression-free survival in patients with recurrent ovarian cancer [22]. Toxicities were distinct to the treatment regimens. Trebananib plus paclitaxel and carboplatin as first-line treatment for advanced disease is currently being evaluated in a phase 3 study (TRINOVA-3).

The objectives of this study were to evaluate the tolerability, pharmacokinetics (PK) and tumour response of first-line treatment with trebananib combined with the standard chemotherapy backbone of paclitaxel and carboplatin followed by trebananib maintenance monotherapy in patients with high-risk stage I and stages II–IV ovarian cancer.

2. Patients and methods

2.1. Eligibility criteria

Patients were women (>18 years old) with newly diagnosed high-risk Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) stage I (grade 3, or aneuploid grade 1 or 2) or stages II–IV epithelial ovarian, primary peritoneal or fallopian tube cancer; a Gynecologic Oncology Group (GOG) performance status of $\leqslant 1$; adequate bone marrow, renal and hepatic function; completion of PDS 4–12 weeks prior to enrolment or, for patients with stage IIIC or IV disease who have not had PDS, planned IDS following three study treatment cycles. Patients were excluded if they had a diagnosis of pseudomyxoma, mesothelioma, adenocarcinoma of unknown primary tumour, sarcoma or neuroendocrine histology; or had a higher than average risk of bowel perforation. Additional exclusion criteria were a history of