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Ovarian Cancer and Gene Therapy - Modelling, Angiogenesis and Targeting Vascular Supply

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ABSTRACT

Ovarian cancer is the most lethal of all gynaecological malignancies. Despite current treatment approaches, surgery and chemotherapy, the prognosis still remains poor. Therefore, new therapies are required to improve outcome in this disease. Solid tumours need a vascular supply to grow and metastasise. The aim of this study was to evaluate the treatment effects of adenoviral gene therapy with antiangiogenic and antilymphangiogenic genes in a human ovarian cancer xenograft model. This new and highly reproducible animal model resembled the disease of clinical patients with intraperitoneal tumours and ascites. Finally, we explored the circulating levels of angiopoietin-1 (Ang-1) and angiopoietin-2 (Ang-2) in patients with benign, borderline or malignant ovarian neoplasms and correlated them with prognosis of patients with epithelial ovarian cancer.

Human SKOV-3m ovarian carcinoma cells produced intraperitoneal tumours in nude mice within three weeks after tumour cell injection. Magnetic resonance imaging (MRI) was used to confirm the existing tumours before gene therapy. Soluble vascular endothelial growth factor (VEGF) receptors sVEGFR-1, -2 and -3 and their combinations as well as soluble angiopoietin receptors sTie1 and sTie2 were used as treatment genes. Gene transfer was done intravenously via the tail vein. It was shown that antiangiogenic and antilymphangiogenic gene therapy significantly reduced tumour growth, tumour vascularity and ascites formation, as assessed by weekly MRI, histology and immunohistochemistry. Spesifically, combined gene therapy with sVEGFR-1, -2 and -3 or combination of sVEGFR-1 and -3 and sTie2 had the most powerful antitumour effects.

In the clinical setting we found that Ang-1 and Ang-2 levels in the serum of patients with epithelial ovarian carcinoma were elevated compared with patients with benign or borderline ovarian tumour or compared with healthy women. Moreover, high levels of Ang-2 predicted poor overall survival and recurrence free survival in patients with epithelial ovarian carcinoma. In clinic, Ang-2 may serve as an angiogenic marker of decreased patient survival in ovarian cancer.

In conclusion, the established ovarian cancer animal model was suitable for *in vivo* gene therapy studies. Antiangiogenic and antilymphangiogenic gene therapy appeared to have significant potential in treatment of ovarian cancer. These results warrant further studies to define the most efficient and safe dose and schedule for such a treatment, and suggest that this approach could be used clinically along with other anticancer therapies.