New challenges in kidney cancer therapy: bevacizumab

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Bevacizumab (Avastin®) is a recombinant humanized monoclonal antibody able to recognize and bind to circulating VEGF (Vascular Endothelial Growth Factor). Neutralizing VEGF prevents the binding to the receptor of VEGF (VEGFR) and so far the activation of the signal transduction pathway. In preclinical models, bevacizumab and its parental murine antibody have inhibited the growth of primary tumours and metastatic spread and have increased survival in the majority of tumour types. Vascular changes have been seen under bevacizumab with reduction of amounts of endothelial cells and decreased vascular permeability. It has a long terminal half-life of 19–20 days, justifying administration of the drug every 2 or 3 weeks. In the phase I trial conducted as a monotherapy, the dose was escalated to 10 mg/kg every week with no dose-limiting toxicity.

Three major studies have been or are being conducted in metastatic renal cell carcinoma.

The NCI initiated a randomised, double blind, phase II trial comparing bevacizumab at 3 and 10 mg/kg every 2 weeks to placebo [1]. Patients had a clear cell type of renal cell carcinoma, having previously received interleukin-2 based therapy. The study was stopped earlier at the interim analysis owing to positive results after the inclusion of 116 patients. In the placebo arm, the progression of the disease was rapid with a median time to progression of 2.5 months, while a trend of improvement was observed with bevacizumab at the dose of 3 mg/kg (3 months), although the dose of 10 mg/kg significantly increased the median time to progression to 4.8 months ($P < 0.001$). The response rate, which was limited to partial responses, was low at 10% with the higher dose of bevacizumab. No gain in overall survival was observed with early discontinuation and the cross-over from placebo to bevacizumab. The main toxicities were hypertension and proteinuria.

The two other randomised phase III studies in a first-line setting are comparing the association of interferon alpha and bevacizumab to interferon alpha (CALGB) or to interferon alpha plus placebo (AVOREN) with the objective of a gain in overall survival. Press release of the AVOREN study indicated a significant gain in disease-free survival and a trend in overall survival in favour of the association. The results should be presented at ASCO 2007. If these findings are confirmed, these results will challenge the place of sunitinib as first-line treatment in metastatic renal cell carcinoma.

references