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Inhibition of Angiogenesis – a single agent approach?

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Intense effort to identify anti-angiogenic agents of use in the treatment of cancer has now spanned a decade. There are currently more anti-angiogenic agents in clinical trial for cancer than those in any other mechanistic class and the next five years will witness a critical testing of the entire concept of anti-angiogenic therapy. Originally, effective anti-angiogenics were envisioned as agents to augment cytotoxic chemotherapy. However, it has now become clear that some single agent anti-angiogenics are able to induce vascular damage and tumour regression when given alone. Such agents either block the activity of an endothelial mainenance factor, for example, the tyrosine kinase inhibitors that block endothelial survival signalling by VEGF, or are naturally occurring inhibitors of angiogenesis such as endostatin that function by mechanisms as yet not known. Progess with single agents anti-angiogenics will be reviewed and the relevance of rodent tumour models to human cancer in the testing of anti-angiogenics critically assessed.

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PET and PK analysis of the humanized monoclonal anti-VEGF antibody HuMV833. An EORTC-Biological Treatment Development Group phase I study.

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We have performed the first PET study of an anti-angiogenic agent. HuMV833 is a humanized monoclonal anti-VEGF antibody in phase I clinical trial evaluation under the auspices of the EORTC-BTDG. I-124 labelled and unlabelled antibody were co-administered. Patients underwent PET scans 24 and 48 hours after the administration of HuMV833 at dose levels 1, 3 and 10 mg/kg. The intratumoral and intra-tissue concentration of antibody in the patients were compared with the plasma PK of the antibody. The PET data showed that the concentration of antibody was different in different tumor deposits within the same patient. While normal tissues cleared the antibody in a manner that paralleled the plasma pharmacokinetics, the clearance in the tumors was markedly heterogeneous. In conjunction with permeability measurements that also showed marked tumor heterogeneity these results suggest that future evaluation of cytostatic anti-angiogenic agents could include a cohort of patients who should undergo intra-patient dose escalation so that a dose response curve can be generated that takes into account the large variation in drug distribution and tumor response.

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Preclinical and Clinical Studies of Recombinant Human Endostatin

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Endostatin is C-terminal fragment of collagen XVIII with potent antiangiogenic activity. In preclinical studies, endostatin regressed established tumors to a state of dormancy defined by balanced tumor cell apoptosis and proliferation and a virtual complete blockade of angiogenesis. No toxicity or resistance to therapy was observed and prolonged therapy with endostatin induced self-sustained dormancy. Studies from several labs suggest that endostatin may have multiple mechanisms of action (i.e. induction of apoptosis of proliferating endothelial cells, inhibition of endothelial migration, interactions with endothelial integrins and tropomyosin, and inhibition of gelatinase A).

Recently, endostatin was evaluated in Phase I clinical trials at several centers in patients with refractory solid tumors. The University of Texas MD Anderson Cancer Center's endostatin trial included patient pharmacokinetic, safety and efficacy analyses and surrogate endpoints of tissue and radiological response were evaluated. Endostatin was administered to 26 patients at doses ranging from 15 – 600 mg/m^2. No significant toxic effects were observed and pharmacokinetics were linear. One patient with synovial cell sarcoma had evidence of anti-tumor activity and one with melanoma remained on study for over 1 year. Using $O^{15}H_2O$ and F^{18} FDG PET and dynamic CT, blood flow and metabolic changes were assessed. At days 28 and 56, blood flow and metabolism decreased as the endostatin dose was escalated. Analysis of biopsy specimens with laser scanning cytometry demonstrated an increase in endothelial and tumor cell apoptosis in some patients. We have currently initiated a Phase I trial of endostatin administered via continuous infusion and trials of endostatin in combination with other modalities are planned.

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In vivo observations on angiogenesis and vasodestruction in tumor window models.

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Vascular directed therapy is becoming a major field in cancer research. Tumor vessels, and other immature vessel types, exhibit features and specific markers which enable targeting of drugs to these vessels or to tumor tissue facilitating numerous possibilities to improve therapy. We demonstrated that TNF is capable of inducing vascular leakage at a relative high dose (in a so-called isolated perfusion setting), but also in a low dose setting, at which TNF is injected systemically. Next to targeting of pre-existing tumor vasculature the inhibition of tumor vascular network development, i.e. angiogenesis, seems to provide new targets for therapy. A tumor, just as any other type of tissue, is dependent on the supply of oxygen and nutrients. Tumor growth therefore is accompanied by extensive angiogenesis, and can be controlled when this process is blocked effectively. Targeting of the tumor vasculature, either by an effect on existing tumor vessels (e.g. vasculo-destruction, manipulation of vascular permeability) or anti-angiogenic therapy, seems to be very attractive and may be especially beneficial when combined with chemotherapy, facilitating a dual targeting approach.
Monitoring of anti-angiogenic or tumor vascular-directed therapie is therefore of utmost importance. In vivo (solid) tumor models have been developed which facilitate real-time monitoring of tumor vascular effect, of which the dorsal skinflap window model will be especially highlighted.