

Cell and gene therapy to improve cancer treatment

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Although approved for the treatment of pancreatic cancer, the chemotherapeutic agent ifosfamide is not an effective therapy for this type of tumour. Ifosfamide must be activated by cytochrome P450 (P450) enzymes in the liver, initially to a short lived intermediate and then to toxic metabolites that are subsequently distributed by the circulatory system. Particularly for pancreatic cancer, this liver mediated conversion results in relatively high systemic toxicities and poor therapeutic concentrations at the liver distant tumour site.

Activation of ifosfamide at the site of the tumour may allow lower doses to be used, while increasing the therapeutic index due to the resultant active concentrations generated locally. A cell based therapy has been conceived where encapsulated, 293 derived, cells genetically modified to overexpress a cytochrome P450 enzyme, are implanted near solid tumours. The cells are encapsulated in polymers of cellulose sulphate in order to provide a means immunoprotection *in vivo* as well as to physically constrain them in the vicinity of the tumour. A major advantage of this strategy is that it allows one standard cell line to be applied to all patients and this approach can be extended to the treatment of other tumour types.

After proof of principle studies in animal models, a phase I/II clinical trial was initiated in patients with stage III/IV nonresectable pancreatic cancer. Encapsulated cells were angiographically placed into the tumour vasculature of 14 patients and followed by systemic low dose ifosfamide treatment. Angiographic delivery of encapsulated cells proved feasible in all but one patient, and was well tolerated with no capsule or ifosfamide treatment related adverse events. Four of the treated patients showed tumour regression after capsule delivery and ifosfamide treatment in computer-tomography scans. The other 10 patients showed no further tumour growth (i.e. stable disease) during a 20 week observation period. The median life expectancy of the patient collective was extended two fold as compared to age and status matched historical controls, with a 3 fold improvement in one year survival being attained. Evidence for a clinical benefit of the treatment was also obtained on the basis of standard parameters for quality of life.

This approach has been evaluated by the European Medicines Evaluation Agency (EMA) and orphan drug status has been granted. A pivotal clinical trial is now being planned with the help of the EMA.

The usefulness of this approach for the treatment of other tumour types has been demonstrated in a second trial involving dog patients with spontaneously occurring mammary adenocarcinomas. In this study the encapsulated cells were delivered by direct injection around the mammary tumour, followed by administration of cyclophosphamide, another chemotherapeutic agent requiring cytochrome P450 mediated activation and a drug that is a component of standard chemotherapy for human breast cancer. Dogs enrolled in the study were assessed for a number of clinical parameters as well as for reduction in tumour size. The treatment was well tolerated with no evidence of adverse reactions or side effects being associated with administration of the encapsulated cells. Reductions in tumour size of more than 50% were observed for 6 of the 10 tumours analysed, with an additional tumour showing 48% reduction and three tumours showing minor responses i.e. stable disease. In contrast, tumours that received cyclophosphamide alone showed only stable disease. On day 57, post capsule implantation, the tumours were surgically resected and analysed. Two tumours treated with encapsulated cells followed by cyclophosphamide showed a less malignant histology after treatment as compared to before treatment.

Taken together, the data from these two clinical trials suggest that encapsulated cytochrome P450 expressing cells combined with chemotherapy may be useful for the local treatment of a number of solid tumours and support the performance of further clinical studies of this new treatment.