Title	Anti-tumor efficacy of recombinant human arginase in combination with chemotherapeutic agents in human hepatocellular carcinoma
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Supraventricular ectopic activity and new occurrence of atrial fibrillation

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Introduction: Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia encountered in clinical practice. Although patients often with symptoms including palpitation preceding the first-diagnosed AF, AF is often diagnosed when its complications such as ischaemic stroke occur. While various risk factors have been identified for increasing risk of AF, predicting occurrence of new AF remains challenging. Here, we tested the hypothesis whether a 24-hour ECG-derived parameter, excessive supraventricular ectopic activity (SVE), could be exploited to predict new-onset AF.

Methods and Results: From 2002 to 2004, 428 patients without pre-existing AF or structural heart disease undergoing 24-hour ECG monitoring for palpitation, dizziness, and syncope were recruited. Of these, 107 patients with SVE at the top quartile (ie >100 SVE/day) were defined to have excessive SVE. After a mean follow-up of 6.1±1.3 years, 31 (29%) patients with excessive SVE developed AF whereas only 29 (9%) patients with SVE ≤100 /day developed AF (P<0.01). Likewise, patients with excessive SVE were more likely to develop ischaemic stroke compared with those with SVE ≤100/day (P<0.01). Furthermore, Cox regression analysis revealed that excessive SVE was an independent predictor of new occurrence of AF (HR=3.32; 95% CI, 1.96-5.65; P<0.01).

Conclusion: Excessive SVE predicts subsequent development of AF.

Anti-tumour efficacy of recombinant human arginase in combination with chemotherapeutic agents in human hepatocellular carcinoma

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Introduction: Systemic chemotherapy of hepatocellular carcinoma (HCC) relies on few drugs and the response rates are low especially in patients with advanced HCC. HCC is considered as auxotrophic for arginine due to the lack of expression of argininosuccinate synthetase (ASS). Several recombinant human arginases were found to be effective in inhibiting liver, pancreatic and leukaemic cell proliferation. Recently, a new recombinant human arginase, BCT-100, has been synthesised to deprive arginine and inhibit arginine-dependent tumour growth. In this study, the efficacy of BCT-100 and the combined used of BCT-100 with cisplatin and fluorouracil on the inhibition of in-vitro cell proliferation of HCC cell lines and in-vivo tumour growth was studied.

Methods: The anti-tumour efficacy of BCT-100, cisplatin and fluorouracil, alone or in combination, on cell proliferation, cell cycle distribution and cellular apoptosis were determined in human hepatoma HepG2, Hep3B and PLC/PRF/5 cells. Protein phosphorylation and expression in the Wnt/β-catenin pathways, and expression of cyclin D1, eIF4E, survivin and XIAP, were also analysed by Western blotting. For in-vivo animal studies, subcutaneous tumours were established by subcutaneous injections of $1x10^6$ cells into nude mice. BCT-100 in combination with cisplatin or fluorouracil was administered. Mice were sacrificed at week 16 or when tumour sizes exceeded 30% of their body weight.

Results: Treatment with BCT-100 alone was found to inhibit cell proliferation and enhance cellular apoptosis. Additive effect of BCT-100 with cisplatin or fluorouracil was found in inhibiting cell proliferation and increasing apoptosis of HepG2, Hep3B and PLC/PRF/5 cells. Cell cycle arrest at G1/S phase was also observed with BCT-100 treatment. A significant reduction in β-catenin, cyclin D1, phosphorylated eIF4E, survivin and XIAP expression was observed. Furthermore, repeated sequential use of BCT-100 and chemotherapy with either cisplatin or fluorouracil demonstrated synergistic effect of inhibition of tumour growth compared with BCT-100 or chemotherapy alone.

Conclusion: These preclinical data suggested additive/synergistic effect of BCT-100 with other chemotherapeutic agents in HCC, which suggested the rationale of combining BCT-100 and chemotherapy in clinical treatment of HCC.