

Tumour profile directed therapy in castrate resistant prostate cancer

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Summary

Prostate cancer (PC) represents a growing health burden worldwide. Its treatment remains controversial. Accepting the risk of over-diagnosis and over-treatment for some patients with PC, individuals with aggressive disease, particularly those with metastatic and/or castrate resistant disease, have very limited treatment options. Even with the recent exciting development of second line androgen ablation therapy and taxane based chemotherapy, the survival benefit remains modest and survival advantage following their use was limited to only weeks.

Targeted therapy for high risk and castrate resistant PC holds important promise to improved outcome. A major obstacle to the application and assessment of targeted therapy in the context of personalised medicine is our current inability to define clinically relevant tumour groupings in a robust manner for PC. Such an approach is much better developed in breast cancer and other haematologic malignancies. Based on data from in vitro, preclinical in vivo and clinical studies from ours and others' laboratories (Ahmad et al, 2011; Carver et al, 2011), we propose a strategy to develop robust methodologies to profile prostate tumours using selected biomarkers.

In this training project, the CRF will carry out relevant optimisation and validation study focusing on patients with castrate resistant tumours, followed by a proof of principle clinical study using targeted therapy guided by the tumour profiles. Individual tumour profiles will be based on the key status of the signaling molecules including AR, pAKT, PTEN, HER2/3 and Sprouty2 expression, as assessed by immunohistochemistry. Selective and targeted therapy scheme will incorporate novel anti-androgen as well as inhibitors against AKT, mTOR and PI3K.

Using a combination in vivo transgenic mouse prostate cancer models and clinical prostate cancer patients and focusing on 1-2 selected tumour profiles to guide specific (1-2) sets of targeted therapy scheme, the CRF will perform pre-clinical evaluation experiments followed by proof of principle clinical study.

In conjunction with the above strategy for targeted therapy, the CRF will also carry out 'real time' monitoring of tumour response using molecular marker (including circulating DNA) and functional imaging of the tumours. Based on reported unique mutational sequences from the cancer genome project and prostate cancer integrated genome study (Taylor et al, 2010), a panel of DNA sequences will be used as surrogate markers to track tumour response. In addition, selected tumours will also be studied by next generation sequencing method to identify novel sequence to look for in the circulating DNA.

Hence, this project will provide timely translational training in personalized medicine using tumour profile to guide specific scheme of targeted therapy and will be of interest to any clinician with an interest in translational research in oncology.