Promoting advanced prostate cancer drug development by clinically predictive models enhanced with novel patient-derived xenografts (PDX)

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Introduction

Despite the recent progress in the treatment of advanced prostate cancer, resistance to therapy often develops and new treatments are in high demand. Therefore, preclinical models are urgently needed to foster prostate cancer drug development with focus on prevention and treatment of bone metastases.

Aim of the Study

The aim of our study is to establish a clinically predictive platform, in which efficacy and safety of drug candidates can be reliably examined and proven prior to clinical trials.

Materials and Methods

The prostate cancer cell lines PC-3, LNCaP and VCaP (ATCC, USA) were first used in in vitro studies. Two known cytotoxic drugs, an anthracycline antibiotic doxorubicin (Sigma-Aldrich) and a nucleoside analog gemcitabine (Eli Lilly), were tested as reference compounds. As an efficacy assessment, in vitro proliferation was measured using a commercial WST-1 kit (Roche Diagnostics). PC-3, LNCaP and VCaP cells were inoculated intratibially and orthotopically into male NOD-Scid and Balb/c nude mice, supplemented with DHT-pellets. Treatment was started on the following day and continued until end of the study. Mice were sacrificed 28 days after inoculation, followed by x-ray analysis and histopathological analyses of primary tumours and metastases. PSA and the bone biomarkers (TRACP 5b and PINP) were measured using commercial ELISA kits (IDS Ltd, UK).

Clinical prostate tumour specimens were collected from robotic assisted laparoscopic radical prostatectomy operations in Turku University Hospital (Turku, Finland). The patient-derived tissues were cut into small pieces and cultured in vitro for 5 days. Test compounds (fibroblast growth factor receptor inhibitors dovitinib and AZD4547) and reference compounds (androgens) were administered into the tissue culture medium. In PDX (patient-derived xenograft) models, tissue slices were either implanted subcutaneously into testosterone pellet-bearing immunodeficient mice, or digested and then inoculated intratibially or under renal capsule.

Efficacy assessment in vitro and patient-derived tissue culture

In vitro studies: determining EC50 values in vitro and effects on morphology using tissue culture

Conclusions

Strategy for identifying effective prostate cancer drug candidates for clinical studies:
1) In vitro studies: determining EC50 values in vitro and effects on morphology using tissue culture
2) Xenograft studies: to test efficacy in orthotopic and metastasis models.
3) Patient-derived xenografts for confirming the results in an appropriate tumor microenvironment
4) Personalised medicine

References