Characterization of Tumor Growth Supported by Novel Dihydrotestosterone Releasing Implants in a Subcutaneous Prostate Cancer Xenograft Model

Johanna Örling¹, Minna Auranen¹, Jukka P Rissanen⁰, Jussi M Halleen¹, Jenni Bernoulli¹, Tiina E Kähkönen¹

¹ Pharmatest Services, Turku, Finland ² PreclinApps, Raisio, Finland

E-mail correspondence to Tiina Kähkönen (tiina.kahkonen@pharmatest.com)

Introduction

Growth of prostate cancer is modeled by inoculation of human cancer cells to immunocompromised mice. LNCaP is an androgen sensitive human prostate cancer cell line which growth is reported to be dependent on external androgens in many mouse strains. Many androgen supplements are associated with inconsistent release rates and hormone levels in mice, leading to the need of new supplements with improved properties for more predictive modeling of tumor growth.

The aim of this study was to evaluate the growth of LNCaP cells in a subcutaneous model supplemented with two doses of dihydrotestosterone (DHT) using MedRod™, a novel substance delivery system.

Materials and Methods

DHT was dispersed in a polymer matrix and covered by a rate-controlling membrane where the compound was safely immobilized and steadily released. The drug diffusion was driven by concentration gradient. Animal experiments were approved by the National Committee for Animal Experiments of Southwest Finland. Altogether 30 NMRI male nude mice aged 8-10 weeks were used in the study (n=10 per group). Two groups of mice were implanted with 50 or 100 µg/day DHT-releasing MedRods™ under isoflurane anesthesia 4 days before cancer cell inoculation. 5x10⁶ LNCaP cells in Matrigel were inoculated subcutaneously to lower back of the mice, next to pelvic and lumbar region. The mice in control group received only cells and no hormone implant. Animal welfare was followed daily and the mice were weighed twice a week. The mice were housed in IVC cages 5 mice per cage. They had unlimited access to tap water and were fed an irradiated soy-free diet. Tumor growth was followed twice a week by caliper measurements. Tumor volume was calculated using the formula \( V = \frac{4}{3} \pi r^3 \) where \( r \) is the radius. The mice were sacrificed when the maximum tumor volume (1500 mm³) was achieved or if other sacrifice criteria were met. Statistical analyses were performed using fixed effects models and p-values were adjusted for multiple comparisons and the comparison groups is marked as COMP in the figures. Statistical significances are marked as *p<0.05*, **p<0.01**, and ***p<0.001***, NS = non-significant.

Conclusions

After the initial burst, DHT is steadily released from the MedRods™ for up to two months in vitro. 100 µg/day DHT releasing MedRods™ increased mouse body weight and the weight of androgen sensitive tissues indicating anabolic effects in mice.

LNCaP tumors grew in NMRI nude mice without DHT supplement, but 50 µg/day DHT releasing MedRods™ can be used to support tumor growth. DHT dose of 100 µg/day delayed tumor formation and the growth was slower compared to the group supplemented with 50 µg/day DHT in this model, demonstrating biphasic growth of LNCaP tumors.

Acknowledgements

Esa Ahloniemi and Ilmari Ahonen (Vincit, Finland) are acknowledged for assistance in performing statistical analyses.