Contribution ID: **79** Type: **not specified**

Therapeutic efficacy and dosimetry of targeted alpha therapy using 225Ac-PSMA-617 in a murine model of prostate cancer

Background and Objective. Targeted alpha therapy shows promise as a treatment in metastatic castration-resistant prostate cancer (mCRPC), owing to the high dose deposition and short range characteristics of alpha particle radiation. Ac-225 decays via multiple alpha particles –each capable of inducing irreparable DNA double-strand breaks in cell nuclei. PSMA-617 is a targeting ligand with specific affinity for prostate-specific membrane antigen (PSMA), a protein that is overexpressed in mCRPC but has low expression in normal tissues. Coupled with the lethal effects of alpha radiation, 225Ac-PSMA-617 is potentially highly cytotoxic to mCRPC while sparing normal tissues. The objective of this study was to evaluate the efficacy of alpha-particle radioligand therapy in a mouse model of mCRPC. Radiation dosimetry analysis was carried out to determine tumor dose as well as dose-limiting organs.

Methods. NSG mice bearing subcutaneous PSMA-expressing C4-2 tumors were injected with escalating activities of 225Ac-PSMA-617: 20, 40, and 100 kBq/mouse (n=8/group). The tumor volumes were assessed over time by weekly low-dose microCT and compared with an untreated control group. In parallel, twenty-five NSG mice were used in a biodistribution study at five time points –1, 4, 24, 48, and 168 hours post-administration of 40 kBq of the radiopharmaceutical. After sacrifice, percent tumor and organ radioactivity uptake was measured using gamma spectroscopy. Biexponential curve-fitting was used to fit the time-activity curves for the tumor and each organ, and integrated according to standard medical internal radiation dose methods to estimate the tumor and organ doses.

Results. Significant tumor growth retardation was observed in all treatment groups compared with the untreated group. Mice treated with 100 kBq exhibited some weight loss, while the mice treated with lower activities experienced only transient weight loss. There was a significant survival benefit conferred on tumor-bearing mice treated with 225Ac-PSMA-617. The biodistribution over five time points showed high uptake and slow tumor activity clearance, and low uptake with fast clearance in non-target organs. The salivary glands, a dose-limiting organ in humans, did not show high uptake in mice, possibly due to lower PSMA expression. Estimates of the absorbed dose to the tumor and organs are reported.

Conclusion. An administered activity of 40 kBq per mouse of the peptidomimetic 225Ac-PSMA-617 is well-tolerated and results in significant tumor growth retardation and improved survival. This work provides a preclinical foundation for further studies towards a more effective treatment option for advanced castration-resistant prostate cancer.

Email Address

cameyer@mednet.ucla.edu

Presentation Type

Poster

Primary author: MEYER, Catherine (Physics & Biology in Medicine Interdepartmental Graduate Program, David Geffen School of Medicine, UCLA.)

Co-authors: STUPARU, Andreea (Department of Molecular & Medical Pharmacology, David Geffen School of Medicine, UCLA.); RADU, Caius (Department of Molecular & Medical Pharmacology, David Geffen School of Medicine, UCLA.); CAPRI, Joe (Department of Molecular & Medical Pharmacology, David Geffen School of Medicine, UCLA.); CZERNIN, Johannes (Department of Molecular & Medical Pharmacology, David Geffen School of Medicine, UCLA.); WEI, Liu (Department of Molecular & Medical Pharmacology, David Geffen School of Medicine, UCLA.); DAHLBOM, Magnus (Physics & Biology in Medicine Interdepartmental Graduate Program, David Geffen School of Medicine, UCLA.); SLAVIK, Roger (Department of Molecular & Medical Pharmacology,

David Geffen School of Medicine, UCLA.); LE, Thuc (Department of Molecular & Medical Pharmacology, David Geffen School of Medicine, UCLA.)

Presenter: MEYER, Catherine (Physics & Biology in Medicine Interdepartmental Graduate Program, David Geffen School of Medicine, UCLA.)