Preclinical Targeting of Established Prostate Cancer Lesions in Bone by Radium-223: Impact on Tumor Cells and the Microenvironment

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Background. Bone metastases are the initial site of progression and account for many complications experienced by men with metastatic prostate cancer (PCa), including therapy failure. PCa lodging/progression/propagation in bone recruits and modulates resident cell populations, that in turn support tumor cell proliferation and drug resistance. Radium-223 (Rad223) is a radioisotope with bone seeking properties that improves the duration and quality of life of advanced metastatic PCa patients. Rad223 targeting of the bone decreases alkaline phosphatase levels and, hence, bone remodelling, but does not proportionally affect PSA concentration in serum, suggesting differential effects on the tumor and non-malignant stromal cells.

Methods. We here dissect the effect of Rad223 on cancer cells and the bone compartment by combining mouse models for bone metastasis with intravital multiphoton microscopy (iMPM), bone histomorphometry and preclinical outcome analysis (x-ray) to longitudinally study PCa-stromal cell interactions and therapy response.
PC3 cells engineered to express luciferase were directly implanted into the tibia of nude mice and the dose-response to Rad223 treatment was monitored by macroscopic bioluminescence over time, selecting 385 KBeq/kg as working dose. Intravital-imaging experiments based on fluorescent PC3 cells were performed in a recently established mouse model amenable to longitudinal multiphoton microscopy that relies on an ectopic tissue-engineered bone construct established in the dermis.

Results. Mice bearing PC3 cells treated with Rad223 displayed a reduced number of osteolytic events, decreased number of osteoclasts and bone erosion. Intra-bone tumor growth and osteolysis dynamics caused by PC3 were three-dimensionally reconstructed by multi-parameter detection through a body window, including collagen and bone matrix (SHG), osteoclasts (cathepsin K), bone surface (THG), and PC3 cells (nuclear H2B/eGFP, cytoplasmatic DsRed2). These experiments showed a differential response of the tumor and adjacent bone stroma, including increased tumor cell apoptosis combined with reduced density and speed of osteoclasts.

Conclusions. Rad223 halted PC3 tumor cell growth and bone resorption function as monitored by macroscopic bioluminescence imaging, x-rays and intravital imaging. These results suggest that Rad223 differentially targets multiple cell subsets, reorganizing the tumor microenvironment to less permissive functions. These studies will be further extended to other PCa cell lines and PDXs and toward RNASeq to understand the molecular mediators of Rad223 function and the effect on the malignant and non-malignant compartment.

Conflicts of interest: None