

Targeting FGFR Disrupts the Reciprocal Interplay Between Prostate Cancer and Bone

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BACKGROUND

Bone metastases remain a major clinical challenge in castration-resistant prostate cancer (CRPC), for which curative treatment options are lacking. Fibroblast Growth Factor Receptor (FGFR) signalling contributes to bone homeostasis and has been associated with cancer stemness and therapeutic resistance. Our previous work showed that Dovitinib, a multi-tyrosine kinase inhibitor, has clinical activity, supporting FGFR as a therapeutic target and suggesting an effect on tumor-bone crosstalk. In this study, we investigated the effects of Erdafitinib, a selective pan-FGFR inhibitor approved for metastatic urothelial carcinoma, on prostate cancer (PCa) and the bone metastatic microenvironment.

METHODS

The effects of Erdafitinib on PCa stem-like properties and viability were evaluated using spheroid formation, including measurements of area, circularity, solidity, and Feret's diameter, together with cell viability assays in multiple PCa cell lines, including PC3 cells overexpressing *FGFR1* isoforms α and β . Its effects on bone cells were assessed using the osteoblast progenitor MC3T3 and *shFGFR1*-MC3T3 cells. Tumor-free mice and mice bearing intrafemoral PCa patient-derived xenografts (MDA-PCa-PDX 118b and 183) received Erdafitinib (12.5 mg/kg, BID for 21 days). Tumor progression was monitored by MRI. Femurs were evaluated by μ CT and bone histomorphometry. Additionally, a pilot clinical study assessed Erdafitinib activity in patients with CRPC bone metastases (NCT04754425).

RESULTS

Erdafitinib altered the stem-like morphology of PCa spheroids and cell line viability with varied magnitude of response across cell models. Overexpression of *FGFR1* isoforms α and β attenuated sensitivity to Erdafitinib in PCa cells, while the pre-osteoblastic MC3T3 cells were the most sensitive to Erdafitinib, regardless of *FGFR1* modulation. *In vivo*, Erdafitinib altered bone architecture, resulting in decreased bone volume, increased bone surface, and changes in trabecular number, thickness, separation and shape in tumor-free mice. Conversely, treatment reduced bone mineral density and bone volume in both contralateral tumor-free femurs and *FGFR1*-low PDX-bearing femurs. *FGFR1*-high tumors exhibited a 40% reduction in tumor volume, indicative of tumor-bone interaction targeting. In the clinical study, 20% of patients responded to Erdafitinib, showing decreased alkaline phosphatase levels despite unchanged PSA, supporting an effect on the bone microenvironment.

CONCLUSION

These findings demonstrate that Erdafitinib exerts distinct effects on PCa cells and the bone compartment, with responses varying according to tumor characteristics. Beyond its effects on PCa stem-like phenotypes and viability, Erdafitinib modifies bone architecture and may therefore influence tumor-bone crosstalk. By simultaneously affecting tumor stemness and the bone microenvironment, Erdafitinib may generate a tissue context less permissive to metastatic progression. Future studies will further dissect its effects on reciprocal tumor-bone interactions.

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CONFLICTS OF INTEREST DISCLOSURE STATEMENT

Authors declare no conflicts of interest.