Abstract

From the 33,000 men in the U.S. who die from prostate cancer each year, the majority of these patients exhibit metastatic disease with bone being the most common site of metastasis. Prostate cancer bone metastases are commonly blastic, exhibiting new growth of unhealthy sclerotic bone, which can cause painful skeletal related events. Patient’s current care entails androgen deprivation therapy, anti-resorptive agents, radiation and chemotherapy to help control the spread of the cancer but little intervention is available to treat blastic bone disease. The transforming growth factor beta (TGFβ) and bone morphogenetic protein (BMP) pathways are known to regulate bone growth and resorption of destructive lytic bone lesions, yet the role of TGFβ/BMP signaling in prostate cancer blastic bone lesions are not fully understood. We hypothesized that in order to target the BMP/TGFβ pathway a useful biomarker of bone lytic or blastic pathology would have a superior response.

Methods

- We used clinical archived FFPE decalcified bone samples to detect differences in lytic or blastic pathologies using IHC staining.
- BMPs exhibit distinct effects on bone homeostasis, so to examine the effect of BMP inhibition on these phenomena, we used the BMP receptor small molecule antagonist dorsomorphin homolog 1 (DMH1).
- We next sought to use the BMP inhibitor DMH1 to treat bone metastasis seeded by a caudal artery injection of the lytic human prostate cell line PC3 in immunodeficient mice. (Nagatava K, et al. A Reliable murine model of bone metastasis by injecting cancer cells through caudal arteries. Nat Commun 9, 2981 (2018)) We next proceeded to test BMP inhibition in an injury model of bone metastasis via intratibial injection of the MYC.CaP mouse prostate cell line into FVB syngeneic mice.
- Data collection was performed using the following imaging modalities: DXA (Faxitron) was used for multiple data points to measure BMC and BMD during the studies, pCT (1276 SkyScan) was used to quantitate trabecular and cortical bone measurements (data not shown) and total radiance detection using RediJect2-DeoxyGlucose (DG) 750 (Perkin Elmer) using the IVIS Spectrum (Perkin Elmer).
- Peripheral blood was analyzed. Venipuncture via submandibular blood collection analyzed by performing a standard CBC using a HemaTrue (Heska) instrument.

Human Metastatic Prostate Cancer in Bone

- C57Bl6, NSG, FVB
- PC3 Cells, MYC.CaP Cells, DMH1 or DMSO
- No Tumor Cells, DMH1 or DMSO

Future Directions

Using our current animal models and organoid model, we would like to enhance the model translational:

- Add chemotherapies (Docetaxel) for treatment.
- Add ADT (Abiraterone/Enzalutamide).
- Add targeted radiation therapy (RT) with ablative/fractionated doses.
- Increased resolution to detect cancer cells which extravasate to the bone (i.e. IVIS probes) for TIBO.
- Target blastic models with BMP/TGFβ inhibitors.

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