

Bone Directed Approaches and Imaging Biomarkers

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BONE TROPISM CAN BE LEVERAGED IN METASTATIC PROSTATE CANCER

Metastatic prostate cancer (MPC) is a uniquely bone tropic disease, causing some of the most severe complications of cancer, including death. After localizing to the bone marrow, the prostate cancer engages in a complex set of interactions with osteoclasts and osteoblasts, leading to dysregulation of normal bone metabolism. The biology of bone metabolism and the pathways that regulate the interactions between the cancer cells and those cells integral to bone metabolism have been leveraged to achieve such benefits as delaying the onset of skeletal-related events (SRE). Altered bone metabolism has also been utilized for imaging purposes and is the basis of standard Tc-99 bone scintigraphy and newer methods such as sodium fluoride (NaF) PET imaging [1].

Bone-seeking radiopharmaceuticals are taken up in sites of copious bone deposition that characterize sites of MPC. Older agents such as strontium (Sr-89) and samarium (Sm-153) emit beta particles, but they differ in the degree to which the radiation penetrates tissue and in the amount of radiation delivered. Because these agents deliver radiation to a depth that often penetrates to the bone marrow, they can be associated with significant hematologic toxicities [2]. While these agents have been used for palliation, they have not been shown to prolong survival in prospectively adequately powered studies. Radium-223 (Ra-223), a new bone-seeking alpha-emitting agent, has changed the landscape of radiopharmaceuticals, because it has been shown to prolong survival with a highly favorable side effect profile.

RADIUM-223 DELIVERS HIGH ENERGY WITH LESS RADIATION EXPOSURE

Radium-223 emits high-energy alpha particles that deposit energy over a short track length (<100 μm) while delivering sufficient energy to initiate a double-stranded DNA break. Because it penetrates the bone marrow to a lesser degree than older agents, Ra-223 spares the bone marrow from significant toxicity. Phase 1 studies have shown that Ra-223 collects in the

tumor, where it remains for up to 2 weeks. Elimination of Ra-223 begins within minutes of injection, via the small bowel and is subsequently eliminated with bowel passage [3]. Because it leaves the blood pool relatively quickly, the amount of circulating radiation is minimized. The ALSYMPCA phase III study compared Ra-223 plus best standard of care with placebo plus best standard of care in patients with prostate cancer without visceral metastases who had been treated with prior chemotherapy or who were not deemed suitable for chemotherapy [4]. The results showed that Ra-223 conferred an overall survival benefit (30% reduction in risk of death) and delayed time to first SRE [4]. Relative to other radiotherapies, Ra-223 has a more favorable side effect profile than beta-emitting radiopharmaceuticals, with low rates of hematologic toxicities in particular.

Although the ALSYMPCA trial results demonstrate that Ra-223 is clinically beneficial, important questions remain to be answered. The optimal dose and duration of treatment need to be determined. The impact of treatment on pain and identification of pain endpoints and the durability of effects need to be examined. It is not clear how to identify patients who are responders to the drug versus those who will progress, and prostate-specific antigen (PSA) may not be helpful. Bone markers may be helpful as indicators of treatment effect, but it is not known if or how they correlate to survival. The study did not include imaging studies so it is not known how the treatment impacts imaging results or how imaging differs in responders and nonresponders. Finally, further research is needed to understand how to effectively combine Ra-223 with other therapies in the armamentarium and when in the disease course it should be introduced.

TARGETING CANCER CELLS, RATHER THAN BONE, COULD IMPROVE TREATMENT AND DIAGNOSTICS

Targeting cancer cells, rather than bone, could realize the maximum therapeutic benefits of radiopharmaceuticals, both as treatment and as imaging biomarkers. This approach could potentially increase tumor cell kill, minimize

toxicity to normal organs, and enhance detection of disease before it alters surrounding bone or host organs. Potential targets that are being investigated include the androgen receptor (AR), prostate-specific membrane antigen (PSMA), the prostate stem cell antigen (PSCA) for which no imaging agent is yet available, the Kallikrein family (e.g., PSA), and others.

The prostate-specific membrane antigen is one of the most mature targets right now. It is a transmembrane protein that is expressed in primary and metastatic disease, and expression appears to increase with downregulation of AR. PSMA-directed PET imaging using Zr-89 J591 antibody targets cancer cells, thereby allowing imaging of the disease itself rather than the reactive bone that is induced by the disease. This approach appears to provide superior detection of bone lesions than routine Tc-99 bone imaging. Though it is not currently clear what the clinical correlates are, the information could potentially be used to inform clinical decisions [5].

From a therapeutic perspective, J591 radioligands with such radiometals as Lu-177 have been shown to reduce PSA levels and induce regression of soft tissue disease; however, such compounds are also associated with dose-limiting hematologic toxicities.

Moving forward, tumor-directed radiopharmaceuticals may allow both superior imaging techniques and treatment opportunities than those offered today. The field of theranostics leverages the ability of these agents to both image and treat patients. The imaging component is used to assess disease distribution and dose calculation, so that treatment is as personalized as possible, with each patient receiving a dose tailored to minimize normal organ exposure and maximize cancer exposure to the therapy.

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