Development of Bone Metastases in Men With Prostate Cancer

Explore the Causes

Understand the Consequences
• Many prostate tumors may become castrate-resistant and metastasize to bone\textsuperscript{1}
Many Men With Castrate-Resistant Prostate Cancer (CRPC) Develop Bone Metastases

- Over 80% of men with CRPC will develop bone metastases\textsuperscript{2-5}

- Nearly half of men with CRPC developed at least one bone metastasis within 2 years\textsuperscript{6}

- There are currently no FDA approved treatments to delay time to bone metastases in men with CRPC\textsuperscript{7}

The Prevention of Bone Metastases for Men With CRPC Represents an Area of Unmet Medical Need
Identification of Men at Risk for Bone Metastases Is Important

- In men with prostate cancer and rising PSA despite ADT, the risk of bone metastases is increased with: \(^7\)–\(^{10}\)
  - High absolute PSA levels (>10 ng/mL)
  - Rapidly rising PSA levels or short PSA doubling time

A retrospective analysis of 201 patients with nonmetastatic prostate cancer and PSA progression despite ADT showed a statistically significant correlation of baseline PSA levels and increasing PSA velocity with shorter time to bone metastases. Baseline PSA level greater than 10 ng/mL (relative risk, 3.18, 95% CI, 1.74–5.80; \(P<0.001\)) and PSA velocity (relative risk, 4.34 for each 0.01 increase in PSA velocity; 95% CI, 2.30–8.21; \(P<0.001\)) independently predicted shorter time to first bone metastasis in the reduced multivariate Cox regression model.
Bone Metastases Are Associated With Important Clinical Consequences

- Consequences of bone metastases in men with prostate cancer:

  - **Increased mortality**\(^{11}\)
    In men with bone metastases from prostate cancer and no skeletal-related events, the one-year mortality rate was 4.7 times higher than in men with no bone metastases

  - **Debilitating bone pain**\(^{12}\)
    Patients with bone metastases often experienced debilitating bone pain

  - **Physical and functional impairment**\(^{13,14}\)
    Physical and functional impairment was seen in patients who experienced a skeletal-related event such as radiation to bone or pathologic fracture

  - **Reduced quality of life**\(^{14}\)
    A reduced quality of life was reported in men who experienced a skeletal-related event such as radiation to bone

  - **Increased medical costs**\(^{15}\)
    Healthcare costs were significantly higher for men with prostate cancer and bone metastases compared with those without bone metastases
The Development of Bone Metastases Depends on Complex Interactions Between Prostate Cancer Cells and the Bone Microenvironment

• Multiple factors influence interactions between the tumor cells, the seed, and the bone microenvironment, the soil, to promote the development of bone metastases\textsuperscript{16,17}

Development of Bone Metastases

1. Prostate cancer cells shed from the primary tumor enter the circulation, and release growth factors, cytokines, and other proteins which promote adhesion and proliferation to the bone\textsuperscript{18}

2. Circulating prostate cancer cells initially adhere to cells lining blood vessels in bone marrow\textsuperscript{19}

3. Tumor cells are actively recruited to the bone microenvironment by multiple factors and preferentially adhere to areas of increased bone turnover\textsuperscript{18-23}
ADT increases bone resorption and subsequently releases multiple factors in the bone microenvironment which may create more fertile conditions for the development of bone metastases\textsuperscript{26-31}

**Development of Bone Metastases in Men With Prostate Cancer**

- Tumor cells that have invaded bone secrete multiple factors that stimulate osteoblasts to overproduce growth factors\textsuperscript{24,25}
- Increased levels of growth factors drive excessive osteoclast activity and bone resorption resulting in destruction of the bone matrix\textsuperscript{24,25}
- Increased bone resorption releases growth factors from the bone matrix, which may further stimulate tumor growth and bone destruction leading to the further development of bone metastases\textsuperscript{24,25}
Development of Bone Metastases in Men With Prostate Cancer

- The prevention of bone metastases for men with CRPC represents an area of unmet medical need
- Over 80% of men with CRPC will develop bone metastases which can lead to important clinical consequences, such as debilitating bone pain, physical and functional impairment, and increased mortality
- In men with prostate cancer and rising PSA despite ADT, the risk of bone metastases is increased with PSA levels >10 ng/mL, rapidly rising PSA levels or short PSA doubling time
- There are currently no FDA approved treatments to delay time to bone metastases in men with CRPC
- The development of bone metastases depends on complex interactions between prostate cancer cells and the bone microenvironment