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Perspective

Not all Bone Metastases are the Same: Treatment Resistance in Renal Cell Carcinoma Revisited

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ABSTRACT

Renal Cell Carcinoma (RCC) is the most frequent malignancy of the kidney, accounting for 80–90% of all renal neoplasms and having a five-year overall survival rate of around 74%. Bone is the second most common location of metastasis. RCC Bone Metastases (RCCBM) treatment failure is becoming more common as patients live longer because to new RCC targeted medicines and immunotherapy. In RCC, the occurrence of bone metastases indicates a more aggressive illness with a worse prognosis. Identification of essential pathways underlying RCCBM-induced anabolic impairment could provide needed insight on how to enhance treatment results for patients with RCCBM, with the goals of limiting progression and enhancing survival.

Keywords: RCC bone metastases, metastasis, Renal cell carcinoma, immunotherapy

INTRODUCTION

Renal Cell Carcinoma (RCC) is the most frequent malignancy of the kidney, accounting for 80–90% of all renal neoplasms and having a five-year Overal Survival (OS) rate of about 74%. One-third of patients will have locally progressed or metastatic disease at the time of nephrectomy, and another one-third will acquire metastatic disease after the procedure. Bone is the second most common location of metastasis, after the lung. Involvement of the skeleton is reported in 20–39% of cases. RCC Bone Metastases (RCCBM) are becoming increasingly common as patients live longer thanks to targeted therapies and immunotherapy. Bone metastasis is a key contribution to morbidity and mortality and is an independent risk factor for poor survival. The International Kidney Cancer Working Group (IKCWG) has determined that the presence of either bone or liver metastases is associated with significantly lower Overall Survival (OS) when compared to other metastatic sites. Despite advancements in medical and surgical treatment for primary RCC, individuals who develop RCCBM have a 19.7-month overall survival rate [1].

The pelvis, sacrum, spine, and proximal extremities are the most prevalent sites for RCCBM. The predominance of bone resorption over anabolic activity drives the majority of osteolytic lesions (79 percent osteolytic, 7% osteoblastic, and 13% mixed). Over 70% of patients with bone metastases have several sites of involvement, putting the majority of patients at risk for SREs and related morbidities. Treatment resistance with RCCBM is a conundrum for improving RCC prognosis. Because bone focused medication like bisphosphonates and denosumab has such a low response rate, additional measures for palliation (rather than cure) are sometimes the sole available choice. These nonspecific treatments fail to target important steps in RCCBM progression in the bone. By suppressing osteoblast development and causing osteocyte apoptosis, invading RCC tumour cells disrupt bone regulation. This results in a pro-osteolytic environment that is unique to RCCBM and is resistant to antiresorptive drugs since it does not rely on osteoclast amplification at first. The weakening of bone anabolic response by RCCBM represents a separate mechanism for progression in the osteogenic niche.

In addition to anti-resorptive therapies, preclinical research suggests treating patients with RCCBM with bone anabolic medicines such cabozantinib. We also discuss current RCCBM treatment options and compare them to treatments for prostate, breast, and lung cancer bone metastasis. Although all of these tumour forms respond to the bone microenvironment, we believe that innate distinctions in cancer cells make each one a unique metastatic illness that requires a therapeutic strategy tailored to the individual. The title of this article is based on this concept. Osteolysis produces bone-derived growth factors and cytokines, which promote cancer cell proliferation and tumour growth even more, resulting in a vicious cycle that manifests clinically as SRE. Transforming Growth Factor– (TGF-), Platelet Derived Growth Factor (PDGF),Fibroblast Growth Factor (FGF), insulin-like growth factors, and Bone Morphogenic Protein (BMP) are some of the factors released. Antiresorptive bone targeted drugs, such as bisphosphonates and denosumab, are now used to treat RCCBM. Bisphosphonates work by preventing osteoclasts from adhering

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to the mineral surface of the bone. In individuals with RCCBM, bipshosphonates have been demonstrated to inhibit both the start and progression of SRE. There have also been instances of seemingly contradicting findings in RCC patients when it comes to SRE. Osteolytic BCa bone metastasis (BCaBM) is the most common type of BCa bone metastasis [2]. The pathologic processes generated by bone invasion, colonisation, progression, and further dissemination have been widely studied, and they can be used to compare malignancies. When tumour cells either arrive in bone or are awakened from dormancy, the 'vicious cycle' feedback-loop that creates BCaBM is established. BCa cells proliferate in the osteogenic niche, expanding locally and stimulating osteoblasts and osteoclasts through reciprocal stimulation.

Patients with lung cancer who have spread to their bones continue to have the worst prognosis, with an even poorer overall survival rate than RCC patients. The decline in OS (as a percentage of 5-year OS) with the onset of distant illness is similar to that seen in RCC patients. Tumor dissemination happens early in lung cancer (LCa) and has little to do with the initial tumor's size [3]. Osteoblasts use the stromal derived factor-1 (SDF-1) and annexin II (Anxa2) receptors to attract cancer cells. Physical variables within the bone, such as hypoxia, acidic pH, and extracellular calcium, also stimulate the expression of osteoblast stimulatory factors including BMPs, VEGF, and ET-1 in the tumour.

CONCLUSION

RCC patients with bone metastases have a more aggressive disease and a worse prognosis than those with many other solid tumours that metastasis to bone. RCCBM patients not only have a worse overall survival rate and a higher rate of surgical intervention, but they also have severe morbidity in the form of pathologic fractures and SRE. Treatment resistance is becoming more common in late-stage RCCBM, which is due to specific cellular and molecular interactions in the bone microenvironment that promote development. To better understand the particular RCC-bone interactions that lead to pathologic osteolysis and SRE, more research is urgently needed.

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