Commentary

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Bone Metastases in Metastatic Renal Cell Carcinoma: Now We Know That Cabozantinib Targets Bone Microenvironment

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Commentary

The multiple tyrosine kinases inhibitor cabozantinib has shown improvements in progression-free survival (PFS), overall survival (OS) and objective response rate (ORR) in comparison to everolimus in patients with metastatic renal cell carcinoma (mRCC) in the METEOR trial, a phase III, randomized, open-label trial [1,2], leading to its approval in mRCC patients previously treated with antiangiogenic agents.

Escudier and colleagues in their recent paper [3] presented the subgroup analysis of patients with bone involvement treated within the METEOR trial. This analysis underlined the impressive activity of cabozantinib also in patients with bone metastases in all the efficacy endpoints. For patients with bone metastases, median PFS was 7.4 months in the cabozantinib group and 2.7 months in the everolimus group; cabozantinib showed its superiority in patients with bone metastases who also had visceral metastases (median PFS was 5.6 months for the cabozantinib group and 1.9 months for the everolimus group, HR 0.26, 95% CI 0.16-0.43). Patients with bone metastases treated with cabozantinib had also an improved ORR in comparison to everolimus: objective responses per independent radiology committee were observed in 17% of patients treated with cabozantinib with bone metastases and in 20% of patients with both bone and visceral metastases, while no responses were observed in patients with bone metastases treated with everolimus. Median OS for patients with bone metastases was 20.1 months in the cabozantinib group and 12.1 months in the everolimus group (HR 0.54, 95% CI 0.34-0.84). The superiority of cabozantinib in terms of OS was clear also in patients with bone and visceral metastases (20.1 *vs.* 10.7 months, HR 0.45, 95% CI 0.28-0.72). Also bone turnover markers bone-specific alkaline phosphatase (BSAP), N-terminal propeptide of type 1 collagen (P1NP) and C-terminal cross-linked telopeptides of type 1 collagen (CTx) were evaluated during treatment at specific timepoints (at day 1 before the first dose, at week 5 and at week 9) in both patients with and without bone metastases. In patients treated with cabozantinib a greater decrease in P1NP and CTx levels was observed in comparison to patients treated with everolimus; these changes were observed also in patients without bone metastases, suggesting that may be related to a potential effect of cabozantinib on bone microenvironment.

The analysis is of course of primary importance, since bone is not an uncommon site of metastatization: bone metastases (BMs) occur in almost 35% of patients with advanced RCC and have a negative impact on clinical outcomes [4]. Tyrosine kinase inhibitors (TKIs) have improved survival of patients with mRCC, but they have a limited impact and fewer efficacies on outcomes of patients with BMs in comparison to patients without bone involvement [5].

The strong evidence of the clinical efficacy of cabozantinib on outcomes of patients with BMs is strength and a promising aspect of this drug.

So, which could be the biological mechanisms at the basis of the “osteotropism” of cabozantinib?

First of all, the inhibition of the receptor tyrosine kinase c-MET. Patients with tumors expressing high levels of c-MET had significantly shorter PFS and OS than patients with low c-Met levels [6].

The MET and VEGF signaling pathways play a significant role in bone metastatization and regulate the tightly balanced coupling between osteoblasts and osteoclasts, as both these cells express target receptors and are therefore potentially affected by cabozantinib [7]. Osteoblasts and osteoclasts also secrete Hepatocyte Growth Factor (HGF), which is a ligand for c-MET, indicating that the HGF/MET signalling axis regulates growth, activity and survival of these cells through autocrine and paracrine mechanisms.

Secondly, cabozantinib could have a direct effect on bone microenvironment [8]: non-cytotoxic doses of cabozantinib significantly inhibit osteoclast differentiation and bone resorption activity and also induce a significant decrease in the expression of receptor activator of nuclear factor kappa-B ligand

(RANKL) and a concomitant up-regulation of osteoprotegerin levels in mature osteoblasts. Furthermore, c-MET mRNA levels significantly increase in the early stages of osteoclast differentiation, while VEGFR2 is more expressed in mature osteoclasts and both c-MET and VEGFR2 mRNA levels remain unchanged during the osteoblast maturation process. Moreover, when osteoblasts are pre-treated with cabozantinib, they are potentially able to inhibit the osteoclasts differentiation and function.

Finally, the "osteotropism" of cabozantinib has been pointed out by recent data, showing that cabozantinib reduces cell proliferation and migration of four different osteosarcoma cell lines [9].

In conclusion, considering the molecular mechanisms at the basis of bone metastatization, the preclinical and clinical data regarding the bone action of cabozantinib corroborate the theory according to which cabozantinib might be the therapeutic option of choice for mRCC patients and bone involvement.

Conflict of Interest Statement

Giuseppe Procopio reports receiving fees for serving on advisory boards from Astellas, Bayer, Bristol-Myers Squibb, Ipsen, Janssen, Novartis and Pfizer.

Elena Verzoni reports receiving fees for serving on advisory boards from Ipsen, Janssen, Novartis and Pfizer.

The remaining authors have nothing to disclose.

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