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

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Received date: January 27, 2018; Accepted date: February 08, 2018; Published date: February 16, 2018


Keywords: Bone metastases; Bone turnover markers; Cabozantinib; Meteor trial; Renal carcinoma

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 

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.

References