A metanalysis on cabozantinib and bone metastases: True story or commercial gimmick?

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Abstract

Introduction: Is it true that cabozantinib should be the preferred option treating patients with bone metastases? Are there any reliable comparisons between this drug and other standard options in the population of interest? To address the issue, we performed a systematic review and a meta-analysis of randomized trials with cabozantinib, to assess its effectiveness, in terms of overall survival (OS), according to the presence of bone metastases, across all cancer types. **Methods:** Inclusion criteria were: (i) randomized controlled trials; (ii) patients with any solid tumors; (iii) use of cabozantinib in any therapeutic line; and (iv) the presence of data on overall survival according to site of disease (bone *vs* visceral metastases). Exclusion criteria: (i) insufficient data were available to estimate the outcome; (ii) hematological disease (iii) population of less than 10 patients/arm. **Results:** Cabozantinib improved OS both for the group with bone metastases, with risk of death decreased by 53% (HR=0.47; 95%CI, 0.26–0.87; p=0.02) and for the group without bone metastases, decreasing the risk of death by 44% (HR=0.56; 95%CI, 0.40–0.79; p=0.001) over the standard of care. The difference between the impact on OS was not significantly different between the two groups. **Conclusions:** Despite cabozantinib can be undoubtedly listed as good therapeutic option for cancer patients with bone metastases, it seems that its preclinical profile against bone remodeling does not translate into an actual clinical relevance, preventing from considering the presence of bone metastases as a principal criterion for the choice of this drug.

Keywords: cabozantinib; bone metastases; bone lesions; renal cell carcinoma; thyroid carcinoma; prostate cancer.

Introduction

Cabozantinib is an orally bioavailable inhibitor of tyrosine kinases including MET, vascular endothelial growth factor receptor 2 (VEGFR-2), and AXL. The hepatocyte growth factor (HGF)/MET pathway, which is targeted by cabozantinib, has been shown to affect expression in osteoblasts [1].

In preclinical studies, cabozantinib exerted potent effects on both tumor and tumor-induced bone matrix remodeling in prostate cancer mice models and resulted in changes to the bone microenvironment, including effects on osteoblast activity and inhibition of osteoclast production [2-6]. Cabozantinib-resistant prostate cancer mice models were used to test the effects of MET/VEGFR2 inhibition specifically in osteoblasts. Cabozantinib suppressed tumor growth in bone and reduced expression of RANKL and M-CSF and subsequent tumor-induced osteolysis [7]. Moreover, cabozantinib had significant effects on the bone microenvironment irrespective of the presence of the tumor, including reduced osteoclast and increased osteoblast numbers in healthy mice models [8].

It was demonstrated that cabozantinib inhibits osteoclast functions “directly” and “indirectly” reducing the RANKL/osteoprotegerin ratio in osteoblasts [9]. Such data suggest that beyond the direct anti-tumor activity of the drug, its ability to modulate osteoblast activity may contribute to the anti-tumor efficacy.

Cabozantinib was approved for the treatment of patients with metastatic renal cell carcinoma (mRCC) after previous antiangiogenic therapy, basing on significant improvements in progression-free survival (PFS), overall survival (OS), and objective response rate (ORR) when compared with everolimus in the METEOR phase III trial [10,11]. A post-hoc analysis of this trial was performed on patients with bone involvement, evaluating clinical outcomes, including SREs, and data on several serum bone biomarkers [12]. The results of such analysis were presented as potentially practice-changing, suggesting cabozantinib as the new standard of care for patients with advanced RCC and bone metastases. Considering the approval of the same drug also as first-line option to

treat intermediate/poor risk mRCC patients (and its more recent approval for the treatment of patients with hepatocellular carcinoma [13]), the deepening of the issue could be extremely useful. Is it true that cabozantinib should be the preferred option treating patients with bone metastases? Are there any reliable comparisons between this drug and other standard options in the population of interest?

To address the issue, we performed a systematic review and a meta-analysis of randomized trials with cabozantinib, to assess its effectiveness, in terms of OS, according to the presence of bone metastases across all cancer types (bone group and no-bone group).

Methods

We searched Pubmed, EMBASE, and the Cochrane Library up to February 2019 using the terms: "*cabozantinib"* and *"bone metastases"* and *"randomized*". We also reviewed reference lists for additional citations. We applied no language restriction. Two reviewers (FP and MB) independently assessed titles and abstracts and full-text articles of potentially relevant citations for inclusion. Disagreements were resolved by consensus. Trials published only in abstract form (e.g., a conference proceeding) were not included. The studies were identified according to the following inclusion criteria: (i) randomized controlled trials; (ii) patients with any solid tumors; (iii) use of cabozantinib in any therapeutic line; and (iv) the presence of data on overall survival (OS) according to site of disease (bone *vs* visceral metastases). The following exclusion criteria were used: (i) insufficient data were available to estimate the outcome; (ii) hematological disease (iii) population of less than 10 patients/arm.

Data extraction and assessment were made independently by two different authors (MB and FP), and disagreements were resolved by discussion with a third author (SB). The primary survival outcome was OS. Hazard ratios for OS were extracted from each randomized trial. Author, year of publication, experimental arm, and number of patients were also reported for each trial.

Hazard ratios (HRs) and 95% confidence intervals (CIs) were used to estimate the impact of cabozantinib on OS. A combined HR >1 implied worse survival, and it was considered statistically significant if 95% CI for the combined HR did not overlap 1. We calculated the pooled HRs for OS, estimating pooled RRs and 95% confidence intervals using a fixed-effect model (Mantel–Haenszel method) or a random-effect model (DerSimonian–Laird method) depending on the absence or presence of heterogeneity (I^2) [14-15]. Statistical heterogeneity was assessed by calculating the percent of the total variance due to between-study variability (I2 statistic). Higher I2 values (>50%) indicate greater between-study heterogeneity. Relative risks and confidence intervals were calculated using comprehensive meta-analysis software.

The study selection is summarized by **Fig.1**.

Results

Table 1 summarizes the characteristics of the 4 trials finally included [10-12, 16-20]. The results of our metanalysis (**Fig. 2**) demonstrated that cabozantinib improved OS both for the group with bone metastases, with risk of death decreased by 53% (HR=0.47; 95%CI, 0.26–0.87; p=0.02) and for the group without bone metastases, decreasing the risk of death by 44% (HR=0.56; 95%CI, 0.40–0.79; p=0.001) over the standard of care. The difference between the impact on OS was not significantly different between the two groups, confirming the efficacy of cabozantinib irrespective of the presence of bone metastases.

Discussion

Considering the promising preclinical rationale supporting the “bone-activity” of cabozantinib, the investigators of clinical trials with this drug often reported the outcomes related to bone metastases, including explorative endpoints such as bone scan response (BSR), skeletal-related events (SREs), bone pain palliation and biomarkers for bone turnover.

In clinical studies in prostate cancer, cabozantinib treatment was associated with an increase in BSR, a reduced incidence of SREs and decreases in biomarkers for bone turnover [19-23]. In a phase II randomized discontinuation trial, cabozantinib resulted in partial resolution of bone lesions in 56% of prostate cancer patients and complete resolution in 19% of the patients [23]. In another dose finding phase II trial, the dose of 40 mg (capsules) was found to be associated with a high rate of BSR with better tolerability compared to the 100 mg dose [20]. The reported effects of cabozantinib on the cell microenvironment of bone seemed to be consistent with its effectiveness in reducing lesions from prostate cancer metastases. Nevertheless, the subsequent phase III studies on prostate cancer did not fully confirm the clinical relevance of such effectiveness. In the COMET-1 trial in metastatic castration resistant prostate cancer (mCRPC) patients, cabozantinib improved PFS and BSR, but no OS improvement was observed compared to the control arm with standard therapy [20]. In the COMET-2 trial, investigating cabozantinib versus mitoxantrone in men with mCRPC, the primary endpoint of bone pain palliation was not met [24].

Interestingly, cabozantinib has been reported as effective therapy for primary skeletal tumors, such as the giant cell tumor of the bone [25].

The METEOR phase III trial, investigating cabozantinib *versus* everolimus in mRCC patients, did not include bone-related endpoints. Nevertheless, a duplicate publication basing on subgroup analysis of the trial, even suggested that cabozantinib could be a new standard of care for mRCC patients with bone metastases [12]. This statement was motivated by the authors by the evidence that the benefit from the drug was the same irrespective of the presence of bone lesions, which is known as a poor prognostic factor. Effectively, the performance of cabozantinib was not inferior in such poor prognostic subgroup, confirming its efficacy also in mRCC patients with bone metastases.

Nevertheless, we wonder if the benefit from cabozantinib could be at least partially due (or not) to the bone remodeling, maybe contributing to its positive outcome in terms of ORR and PFS, or instead if it is totally independent from an alleged bone-activity of the drug.

The present analysis suggests that the benefit from cabozantinib across clinical studies is independent from bone metastases. Furthermore, in our opinion, also the results of the METEOR trial were already supporting this simple interpretation, more than allowing conclusions about a particular efficacy of the drug for patients with bone metastases.

To further explore if the favorable effect of cabozantinib could be due to its activity on bone lesions in the case of mRCC, we compared the curves for the overall study population and for the patient population with bone metastases from the METEOR trial. Ideally overlapping the curves (showed in **Fig. 3**) it clearly emerges that cabozantinib has similar efficacy in terms of OS and PFS in both groups, whilst everolimus demonstrates lower efficacy in the subgroup of patients with bone metastases, enhancing the gap between the curve of cabozantinib and that of the control arm in this subgroup of patients. Finally, it seems that the difference can be made by the comparator, suggesting discouraging the use of everolimus for mRCC patients with bone metastases rather than indicating cabozantinib as the preferred option in this subgroup.

Indeed, we currently have at our disposal other available therapeutic alternatives in this setting, including the immune checkpoint inhibitor nivolumab that, similarly to cabozantinib, demonstrated to improve survival across all subgroups, including that of patients with bone metastases (without reckless conclusions about such point from the CheckMate-025 investigators) [26].

In conclusion, despite cabozantinib can undoubtedly be listed as a good therapeutic option for cancer patients with bone metastases, it seems that its preclinical profile against bone remodeling does not translate into an actual clinical relevance, preventing from considering the presence of bone metastases as a substantial criterion for the choice of this drug over the others (obviously except for everolimus!).

Compliance with Ethical Standards:

Funding: Not applicable (no funding).

Conflict of Interest: M. Bersanelli received honoraria for advisory role and as speaker at scientific events from Bristol-Myers Squibb (BMS), Novartis and Pfizer, and research funding from Seqirus, Novartis, BMS, Sanofi and Pfizer. S. Buti received honoraria for advisory role and as speaker at scientific events from Pfizer, BMS, IPSEN, Pierre-Fabre, Merck Sharp & Dohme (MSD), AstraZeneca and research funding from Novartis. M. Tiseo received honoraria from BMS, BI, MSD, Takeda, AstraZeneca and research funding by AstraZeneca. None to declare for A. Ghidini and F. Petrelli.

Ethical approval: This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent: not applicable.

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Tables

Table 1. Characteristics of the studies included in the meta-analysis.

Figure Legend

Figure 1. PRISMA flow-diagram of the study selection.

Figure 2. Forest plots with Hazard Ratios for overall survival in the patient population according to the presence or not of bone metastases, demonstrating the superiority of cabozantinib over the standard of care irrespective of the presence of bone lesions.

Figure 3. Progression free survival (PFS) [A] and overall survival (OS) [B] curves from the METEOR trial, respectively overlapped, for the overall study population (dark-blue line for cabozantinib and green line for everolimus) and for the patient population with bone metastases (light-blue line for cabozantinib and yellow line for everolimus). It emerges that cabozantinib has a similar efficacy in both groups (the blue curves are almost completely overlapped, for both PFS and OS), whilst everolimus demonstrates lower efficacy in the subgroup of patients with bone metastases (the yellow curves are clearly below the green ones). [*Modified from Choueiri TK et al,* 10-11].