CBT profiles of cabozantinib approved for advanced renal cell carcinomas

Xiangdong Wang

Received: 28 June 2016 / Accepted: 30 June 2016 / Published online: 6 July 2016
© Springer Science+Business Media Dordrecht 2016

Cabozantinib (CABOMETYX, Exelixis, Inc.) was recently approved by the US Food and Drug Administration (FDA) for the treatment of advanced renal cell carcinoma in patients who have received prior anti-angiogenic therapy. The approval was based on a randomized study in which patients with advanced renal cell carcinoma, who had received a prior anti-angiogenic therapy, received either cabozantinib (60 mg orally once daily; $N=330$) or everolimus (10 mg orally once daily; $N=328$) [Approved drugs 2016]. There is increasing evidence that cabozantinib alone or in combination with other medications will be used to treat other cancers and has shown potency and efficacy in clinical preliminary trials. The more potential cabozantinib has, the greater our understanding of cabozantinib-associated cell biology and toxicology profiles should be.

Cell biology and toxicology (CBT) profiles mainly include drug efficacy-driven or associated molecular interactions, mechanisms, or adverse effects on cells (Gu and Wang 2016). Cabozantinib as a small molecule receptor tyrosine kinase inhibitor, primarily targets ret proto-oncogene (RET)-encoded receptor tyrosine kinase (RTK), mesenchymal epithelial transition factor (MET), and the vascular endothelial cell growth factor receptor 2 (VEGFR2), of which VEGFR2 is more sensitive. Approximately 60 RTK proteins act as high-affinity cell surface

receptors for many polypeptide growth factors, cytokines, hormones, and as key regulators of physiological and pathophysiological cellular processes, through the trans-membrane and/or non-transmembrane domains (Kano et al. 2016; Li and Hristova 2010). One of the most important factors to influence CBT profiles of cabozantinib is the specificity and affinity of RTK binding types and efficacies in various conditions. In addition to bind RET, MET, and VEGFR2, cabozantinib can also inhibit KIT, VEGFR3, TRKB, VEGFR1, AXL, TIE2, and FLT3, in order of the efficacy according to IC_{50} values.

RTK is also known as tyrosine receptor kinase or tyrosine kinase receptor depending on the permutation and has about 17 classes/families involved in major biological function and signaling through the cell membrane. Treatment with cabozantinib decreased tumor and endothelial cell proliferation and growth and increased apoptosis in a number of cancers though the inhibition of MET and VEGFR2 phosphorylation (Yakes et al. 2011). It is also reasonable to postulate the inhibitory effects of cabozantinib on tumor growth through targeting multi-RTKs, of which some may be unexpected. The binding specificity of cabozantinib as the critical part of biological function not only alters drug efficacy and efficiency but also drug side effects and toxicity, in tissues and systems or drug resistance to protein kinase inhibitors. The development of uncontrolled adverse effects and drug resistance of cabozantinib is a potential risk and challenge for clinicians to pay special attention to during application, due to the complex interplay of cabozantinib with multi-RTKs, even though clinical trials have demonstrated

X. Wang (✉)
Zhongshan Hospital Clinical Science Institute of Fudan
University, Shanghai Institute of Clinical Bioinformatics,
Shanghai, China
e-mail: xiangdong.wang@clintransmed.org

that cabozantinib is a promising drug to inhibit tumor angiogenesis and metastasis. It is important to investigate the multifactorial genetics and epigenetics on tissues and systems in response to cabozantinib.

Decisive molecules and biological biomarkers for binding specificities of cabozantinib should be considered as an important issue to monitor the efficacy and toxicity of the drug in clinical practice, which can be measured by the integration of molecular simulations and computational alanine scanning with network-based approaches (Tse and Verkhivker 2015). It is helpful to understand the interaction network of RTK inhibitors with ligands, the tension between bindings, and elements within networks, since each RTK inhibitor has its own regulatory residues, energetic hot spots, and residue interaction network constructions. We believe that cabozantinib may have residue interaction networks and network-bridging effects with a special stability and conformational equilibrium between inactive and active states, although further evidence to determine the reality and accuracy of such a theoretical framework between ligand binding and inhibitor-mediated changes within residue interaction networks (Tse and Verkhivker 2015). Small molecule kinase inhibitors approved by the FDA are classified on the basis of binding mechanisms and common structural features. It is easier and more powerful to use selective small molecule inhibitors of protein kinases to understand kinase biological functions, while it is more challenging and difficult to develop kinase inhibitors as drugs to target dysfunctional cells, organs, and diseases, due to the broad binding and weak specificity as previously described (Wang and Gray 2015).

The preclinical and clinical profiles of toxicology and adverse effects of cabozantinib have been carefully investigated and a number of toxicology profiles have been found to be correlated with the doses applied, including gastrointestinal, immunological, systemic, renal, hepatotoxic, endocrine tissue, or reproductive and developmental toxicology. Furthermore, the molecular toxicology of cabozantinib should be seriously considered in its development and application. Structure and binding domains of kinase inhibitors can be varied according to different challenges and microenvironments, e.g., intracellular calcium ions, Golgi apparatus, intravesicular acidification, or transportation of proteins between organelles (Oh-hashii et al. 2014). It is an ongoing progression to develop RTK inhibitors as new small molecular drugs and increasing evidence to show biological and pharmacological efficacies even in stem

cells (Kim et al. 2016). Inhibition of kinases may influence the formation of abnormal mitotic spindles, the improper alignment of segregating chromosomes, and reduced phosphorylation of the target, probably resulting in cell reprogramming, epigenetic remodeling, or chromosome reconstruction. Cabozantinib as the RTK inhibitor has been found to have therapeutic effects on many categories and locations of cancers probably through the regulation between RTKs or negative feedback of kinase-dominated biological loops. For example, it is unpredictable or unexpected that the activation of feedback loops following inhibition of PI3K/AKT, BRAF, and MEK/ERK can lead to the development of drug resistance associated with upregulation of RTKs, due to the heterogeneity of inter- or intra-cancers. Recent studies have suggested to increase the therapeutic effects and prevent drug resistance by combining inhibitors of multi-RTKs, e.g., the combination of PI3K and BET inhibitions prevented the feedback activation of the PI3K pathway and the PI3K signal in many types of cancers (Stratikopoulos et al. 2015).

The expression levels of a large number of kinase genes were either increased or decreased in circulating leukocytes harvested from patients with chronic lung inflammation (Wu et al. 2014) or in lung tissues from patients with lung cancer (Bao et al. 2016; Wang et al. 2015). It indicates that multi-kinases are involved in the pathogenesis of diseases, e.g., cancer or inflammation. Cyclin-dependent kinases play a critical role in cell proliferation and apoptosis and can be regulated by many factors, which can be directly or indirectly inhibited by anti-cancer agents (Wong et al. 2014). We should try to understand whether cabozantinib can interact with other kinases, especially cyclin-dependent kinases. Another influencing factor of cabozantinib CBT profiles is the mutation and heterogeneity of kinase genes among cancer foci, locations, and cells (Wang 2016a, b). The epidermal growth factor receptor (EGFR) mutations can alter sensitivity to EGFR tyrosine kinase inhibitors and cause the development of drug resistance in 50–60 % patients after starting treatment. The mutant specificity of kinase inhibitors has been suggested as critical in the design of a new generation of small molecular kinase inhibitors and in the discovery of gene mutation-based and specific therapies in precision medicine (Wang 2016b; Politi et al. 2015). For example, the new-generation mutant-selective EGFR inhibitors are proposed as potential therapeutics to inhibit EGFR T790M-positive tumors.

With an increase in our understanding of the CBT profiles of cabozantinib, new strategies for cabozantinib use will be discovered and developed for various categories of cancers, including its combination with other inhibitors or therapies, kinase-mutant specific inhibitions, and sensitivity-selected applications. Cabozantinib as a new therapy has been started for multi-cancer therapies and can be a new candidate for precision medicine. Thus, with a better understanding of cabozantinib CBT profiles, a more successful and efficient therapy could be possible.

References

- Approved drugs: cabozantinib (CABOMETYX). <http://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm497483.htm>
- Bao L, Zhang Y, Wang J, Wang H, Dong N, Su X, Xu M, Wang XD. Variations of chromosome 2 gene expressions among patients with lung cancer or non-cancer. *Cell Biol Toxicol* 160607.
- Gu J, Wang XD. New future of cell biology and toxicology: thinking deeper. *Cell Biol Toxicol*. 2016;32(1):1–3.
- Kano Y, Cook JD, Lee JE, Ohh M. New structural and functional insight into the regulation of Ras. *Semin Cell Dev Biol*. 2016.
- Kim WH, Shen H, Jung DW, Williams DR. Some leopards can change their spots: potential repositioning of stem cell reprogramming compounds as anti-cancer agents. *Cell Biol Toxicol*. 2016;32(3):157–68.
- Li E, Hristova K. Receptor tyrosine kinase transmembrane domains: function, dimer structure and dimerization energetics. *Cell Adh Migr*. 2010;4(2):249–54.
- Oh-hashii K, Kanamori Y, Hirata Y, Kiuchi K. Characterization of V-ATPase inhibitor-induced secretion of cysteine-rich with EGF-like domains 2. *Cell Biol Toxicol*. 2014;30(3):127–36.
- Politi K, Ayeni D, Lynch T. The next wave of EGFR tyrosine kinase inhibitors enter the clinic. *Cancer Cell*. 2015;27(6):751–3.
- Stratikopoulos EE, Dendy M, et al. Kinase and BET inhibitors together clamp inhibition of PI3K signaling and overcome resistance to therapy. *Cancer Cell*. 2015;27(6):837–51.
- Tse A, Verkhivker GM. Molecular determinants underlying binding specificities of the ABL kinase inhibitors: combining alanine scanning of binding hot spots with network analysis of residue interactions and coevolution. *PLoS One*. 2015;10(6):e0130203.
- Wang J, Gray NS. SnapShot: kinase inhibitors I. 2015; 58(4):708–708.e1, SnapShot: Kinase Inhibitors II. 710–710.e1.
- Wang XD, Zhang Y, et al. Association of chromosome 19 to lung cancer genotypes and phenotypes. *Cancer Metastasis Rev*. 2015;34(2):217–26.
- Wang XD. Cancer Moonshot 2020: a new march of clinical and translational medicine. *Clin Transl Med*. 2016a;5:11.
- Wang XD. Gene mutation-based and specific therapies in precision medicine. *J Cell Mol Med*. 2016b;20(4):577–80.
- Wong HC, Wong CC, Sagineedu SR, Loke SC, Lajis NH, Stanislas J. SRJ23, a new semisynthetic andrographolide derivative: in vitro growth inhibition and mechanisms of cell cycle arrest and apoptosis in prostate cancer cells. *Cell Biol Toxicol*. 2014;30(5):269–88.
- Wu X, Sun X, Chen C, Bai C, Wang XD. Dynamic gene expressions of peripheral blood mononuclear cells in patients with acute exacerbation of chronic obstructive pulmonary disease: a preliminary study. *Crit Care*. 2014;18(6):508.
- Yakes FM, Chen J, Tan J, et al. Cabozantinib (XL184), a novel MET and VEGFR2 inhibitor, simultaneously suppresses metastasis, angiogenesis, and tumor growth. *Mol Cancer Ther*. 2011;10(12):2298–308.