Targeting fibroblast growth factor receptor (FGFR) pathway in renal cell carcinoma

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Abstract

Fibroblast growth factor receptor (FGFR) pathway is involved in driving vascular endothelial growth factor (VEGF)-independent tumor angiogenesis, as a compensatory mechanism to escape VEGF-targeted therapies. Therefore, targeting FGF/FGFR axis seems to be a promising strategy in order to inhibit tumor angiogenesis and reduce resistance to VEGF receptor-tyrosine kinase inhibitors. This editorial is focused on the role of FGF/FGFR pathway in renal cell carcinoma and on the ongoing trials of emerging agents targeting this axis.

Keywords

fibroblast growth factor receptor, kidney, personalized medicine, precision medicine, renal cell carcinoma, targeted therapy, vascular endothelial growth factor receptor

Introduction

Angiogenesis is the hallmark of kidney cancer development and progression. Therefore, the crucial drivers of metastatic renal cell carcinoma (mRCC) – VEGF and mTOR signaling pathways – represent fundamental targets of the current approved therapies. Certainly, VEGF receptor-tyrosine kinase inhibitors (VEGFR-TKIs) (sunitinib, sorafenib, pazopanib and axitinib)

Massari, F., Ciccarese, C., Santoni, M., Lopez-Beltran, A., Scarpelli, M., Montironi, R., & Cheng, L. (2015). Targeting fibroblast growth factor receptor (FGFR) pathway in renal cell carcinoma. Expert Review of Anticancer Therapy, 15(12), 1367–1369. http://doi.org/10.1586/14737140.2015.1110488

and mTOR-inhibitors (everolimus and temsirolimus) have dramatically revolutionized the treatment algorithm and the prognosis of mRCC patients [1]; however, almost all patients invariably develop tumor progression through primarily (intrinsic) or acquired resistance mechanisms.[2]

Determinants of VEGF-targeted therapies response and the molecular bases underlying the antiangiogenic escape are far from being entirely understood.[3,4] This presents a substantial barrier to the achievement of complete durable responses to anticancer treatments.

The inhibition of the major regulator of angiogenesis, VEGF, results in vascular regression and consequent tumor response to treatment. However, the creation of intratumoral hypoxic regions triggers the hyperexpression of other proangiogenic factors responsible for mediating angiogenesis reactivation and therefore tumor treatment's resistance and progression. Several growth factors (PIGF, FGF, angiopoietin-1, IL8, Ephrin-A1), which are upregulated in the tumor microenvironment during VEGFR2-blocking treatments, may stimulate tumor angiogenesis to overcome acquired resistance to VEGFR inhibition.[5–7] In particular, activation of the proangiogenic fibroblast growth factor (FGF) pathway seems to play a key role in driving VEGF-independent tumor angiogenesis as a compensatory mechanism to elude VEGF-targetedz therapies.[7]

FGF/fibroblast growth factor receptor (FGFR) signaling promotes vascularization (vessel assembly, sprouting and branching), lymphangiogenesis and cellular growth in several human malignancies,[8–10] including RCC.[11] Interestingly, increased basic-FGF plasma concentrations correlate with high tumor grade and stage,[12] metastatic spreading [13] and poor prognosis [14] in kidney cancer patients. Moreover, FGF serum levels significantly increase in mRCC patients with disease progression while receiving sunitinib therapy, supporting the

potential FGF-pathway role as a potent mediator of endothelial cell resistance to VEGFR inhibitors.[15,16]

Emerging FGF/FGFR inhibitors

Targeting antiangiogenic escape via FGF-pathway blockade is a promising strategy after progression on VEGF-inhibitors therapy. Several molecules capable of simultaneously inhibiting both VEGF and FGF have been developed.

Dovitinib, a TKI that targets FGFR, PDGRF and VEGFR,[17] failed in demonstrating a progression-free survival (PFS) and overall survival advantage over sorafenib in the third-line setting after progression to VEGFR and mTOR inhibitors, not corroborating the strong preclinical rational of targeting the FGF pathway critical for antiangiogenic escape.[18] The main criticism of this phase 3 study (the GOLD trial) lies in the inappropriate timing of FGF inhibition (immediately after failure of an mTOR inhibitor).[19] During mTOR inhibition treatment, in fact, cancer cells could restore a VEGF-driven angiogenesis (rather than FGF), given the temporary effects of VEGF-inhibitor resistance.[20] The wrong timing, and probably not the wrong target, compromised the clinical approval of dovitinib, at least at the moment. A phase 2 study (DILIGENCE-1) is ongoing, evaluating the first-line activity of dovitinib in RCC, with a preplanned exploratory tumor gene status analysis aimed at identifying possible ways in which the tumor becomes resistant to dovitinib (NCT01791387).

Indirect evidence of greater efficacy by blocking FGFR immediately after the occurrence of VEGFR-TKIs resistance comes from the impressive results of another FGFR inhibitor, lenvatinib. Lenvatinib is a potent oral TKI of VEGF- and FGF-driven angiogenesis, which showed an acceptable safety profile and an encouraging antitumor activity in preclinical models

[21] and in patients with multiple solid tumors, including mRCC in phase 1 studies.[22,23] A phase 1b clinical trial of lenvatinib plus everolimus in mRCC revealed a manageable safety profile with no unexpected toxic manifestations, and a promising antitumor activity,[24] highlighting the solid rational of concurrently blocking critical signaling pathways activated in RCC–VEGF, FGF and mTOR pathways.[25] At the 2015 ASCO Annual Meeting Motzer and colleagues presented the impressive results of a randomized phase 2 study comparing lenvatinib ± everolimus, versus everolimus alone in 153 mRCC patients who progressed on one prior VEGF-targeted therapy.[26] Lenvatinib improved response rate (highest response rate and duration with combination treatment than with lenvatinib alone) and PFS over everolimus both alone and in combination with everolimus (mPFS 5.5 vs 7.4 vs 14.6 months), while a significant survival benefit was observed only with the combination regimen (Hazard ratio [HR]: 0.51; 95% CI: 0.30–0.88; p = 0.024), at the price of greater toxicity. A phase 3 randomized trial of the combination in mRCC is planned to confirm these promising results.

Several novel emerging TKI molecules that recognize FGFR as a target are currently under study for the treatment of RCC, with conflicting data. Among them, brivanib, a dual VEGFR-2 and FGFR-1 TKI, demonstrated promising antiangiogenic and antitumor activity with manageable toxicity in advanced solid tumor patients.[27] We are awaiting the results of a phase 2, open-label trial conducted to assess the activity of brivanib in refractory mRCC patients (NCT01253668).

As for regorafenib (BAY 73-4506), a multikinase inhibitor targeting VEGFR, c-kit, RET, FGFR, platelet-derived growth factor receptor (PDGFR), RAF and p38MAPK, it was tested in a single-arm phase 2 trial (NCT00664326) conducted in 49 previously untreated advanced RCC patients,

showing antitumor activity as first-line treatment (27% PR and 42% SD), with a significant toxicity (35% of drug-related serious adverse events).[28]

In addition XL999, a small molecule inhibitor of multiple kinases including VEGFR, PDGFR, FGFR, FLT-3, and Src, was evaluated in a phase 2 study enrolling mRCC patients after failure of one anti-VEGF therapy (NCT00277316). The study was stopped due to the cardiac toxicities, impeding further development of this drug.

Furthermore, a phase 1 study (NCT02275910) is recruiting subjects with advanced solid tumors for testing the safety and tolerability of E7090, especially in patients with malignancies characterized by genetic abnormalities in FGF/FGFR pathway. On the other hand, the small molecule TKI PD173074, a potent reversible inhibitor of FGFR tyrosine kinase activity,[29] seems to inhibit FGF2-mediated resistance to sunitinib in preclinical models.[16]

Conclusion

A multidisciplinary integrated approach is needed for deeper understanding of tumor biology of RCC. An increasing number of molecules are emerging in the treatment landscape of this tumor. Recently, the multikinase inhibitor, cabozantinib, and the anti-PD1, nivolumab, join the list of active therapies, demonstrating significant overall survival benefit.[30,31] A major issue which remains is the selection of the best drug available for each specific patient. Only an in-depth study of the carcinogenesis biological bases and of the mechanisms underlying treatment resistance could enable radically changes of the cancer patient’s prognosis with the development of true personalized therapy.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Acknowledgements

We thank Francesca Tartari for her assistance.

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