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A NOVEL DRUG TIVOZANIB IS TREATMENT ON ADVANCED RENAL CELL CARCINOMA

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ABSTRACT

Tivozanib is a novel vascular endothelial growth factor receptor tyrosine kinase inhibitor (VEGF TKI) that inhibits phosphorylation of vascular endothelial growth Factor receptor (VEGFR). Tivozanib is a VEGF-TKI with high selectivity for VEGF receptors.[1–3] It has been evaluated in several clinical trials including a Phase I and Phase II and phase III trial demonstrating safety and efficacy for patients with advanced clear cell renal cell carcinoma (RCC). Multikinase inhibitors of the vascular endothelial growth factor receptor tyrosine kinases (VEGF-TKIs) comprise nearly all targeted therapies in renal cell carcinoma, having been prospectively tested through large, multi-institutional phase III trials. The results from Studies show that Tivozanib is generally well tolerated and safe to use in renal cell carcinoma patient. The aim of this review is to investigate, collect & reform the current knowledge in Suitable form about Tivozanib drug.

KEYWORDS: Tivozanib, Efficacy, Renal cell Carcinoma, vascular endothelial growth factor receptor tyrosine kinase, metastatic.

INTRODUCTION

Renal cell carcinoma (RCC) is the third most common type of urinary cancer in the people, and the sixth most common cancer type in Europe. About 403000 new cases and 175000

deaths were registered worldwide in 2018. Although maximum patients have localized disease at presentation, 20–40% experience either local or distant relapse, taking systemic treatment.[1-2]

RCC is the most common type of urinary cancer accounting for 90 to 95% of kidney tumors and it most commonly occurs between the ages of 60 and 70 years. At the time of diagnosis approximately 25 to 30% of cases have metastatic disease with a 10% chance of 5year survival. Surgical resection is most commonly used in localized disease and targeted therapies are most commonly suggested in metastatic disease.[3]

RCC is a cancer comprising different histological subtypes with distinctive inheritable and molecular alterations. The three major histologic Subtypes are clear cell renal carcinoma (CCRCC), which accounts for ~75% cases, papillary renal cell carcinoma (PRCC), which accounts for 15–20%, and chromophobe Renal cell carcinoma (CHRCC), representing ~5% of all RCC cases.[3] As per Scottish medicine consortium clinical experts advise the tyrosine kinase inhibitors, pazopanib and sunitinib, are now days the first line systemic treatment option for patients with advanced or metastatic RCC in Scotland.[4]

Drug description

Tivozanib, sold under the brand name **Fotivda**, is a medication used for the treatment of relapsed or refractory advanced renal cell carcinoma (RCC)

Name: Tivozanib (AV-951)

IUPAC Name: 1-[2-chloro-4-(6, 7-dimethoxyquinolin-4-yl)oxyphenyl]-3-(5-methyl-1,2-oxazol-3-yl)urea

Molecular formula: C22H19ClN4O5

Molecular weight: 454.9 g/mol

Solubility: Tivozanib (hydrate) is soluble in organic solvents such as DMSO and dimethyl formamide (DMF), which should be purged with an inert gas. The solubility of tivozanib (hydrate) in these solvents is approximately 25 and 30 mg/ml, respectively.

Dose: The recommended dosage of FOTIVDA is 1.34 mg taken orally once daily for 21 days on treatment followed by 7 days off treatment for a 28-day cycle.

Storage: Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F)

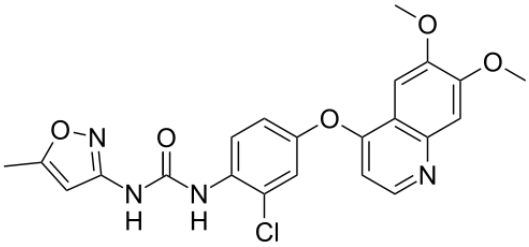

Fig. Chemical structure.

Pharmacokinetics

The recommended starting dose and schedule of administration may vary depending on the pharmacodynamic and pharmacokinetic properties of VEGFR-TKIs. For example, tivozanib can be administered at 1.5 mg once daily, while axitinib needs to be given twice daily at doses 3- to 6-fold higher than tivozanib. all VEGFR-TKIs are metabolized in the liver, the role of pre-systemic inactivation may depend on drug type.[5] Indeed, unchanged drug has been reported to be the main form of circulating tivozanib, while ~66% of axitinib is metabolised by CYP3A4. These differences may account for a longer elimination half-life and once vs. twice daily administration of tivozanib vs. axitinib. Tivozanib is tightly bound to plasma proteins, a pharmacokinetic property common to all VEGFR-TKIs used in RC.[3] Evidence regarding the central nervous system (CNS) activity by VEGFR-TKIs in RCC cases are not conclusive. However, anti-angiogenic effects of tivozanib were shown in patients with recurrent glioblastoma by dynamic contrast MRI and vessel architecture imaging, suggesting drug penetration across the blood–brain barrier (BBB). Such a peculiarity can be dependent on the ability of tivozanib to inhibit multidrug resistance mediated by ATP-binding cassette (ABC) transporters that, in turn, may favor CNS distribution. The capacity of cabozantinib to penetrate the CNS has also been suggested.[6-7]

Pharmacodynamic

Tivozanib is a selective VEGFR inhibitor that has recently been approved by regulatory agencies for the first-line treatment of patients with advanced RCC. Tivozanib is a quinoline-urea derivative structurally related to Lenvatinib with improved potency and selectivity for the VEGFR-1, 2 and 3 tyrosine kinases From the molecular point of view, tivozanib can be classified as a type II inhibitor, as it blocks the aspartate-phenylalanineglycine activation loop of VEGFR.[8] Tivozanib has also been reported to inhibit the phosphorylation of platelet-derived growth factor-ß (PDGFR-ß) and mast/stem cell growth factor receptor (KIT) at nanomolar levels, as well as of members of the Src family tyrosine kinases, such as ABL1,

FRK and FYN-A, and the serine/threonine kinase SLK, only at micromolar concentrations, thus making this drug very selective at clinically achievable concentrations.[9]

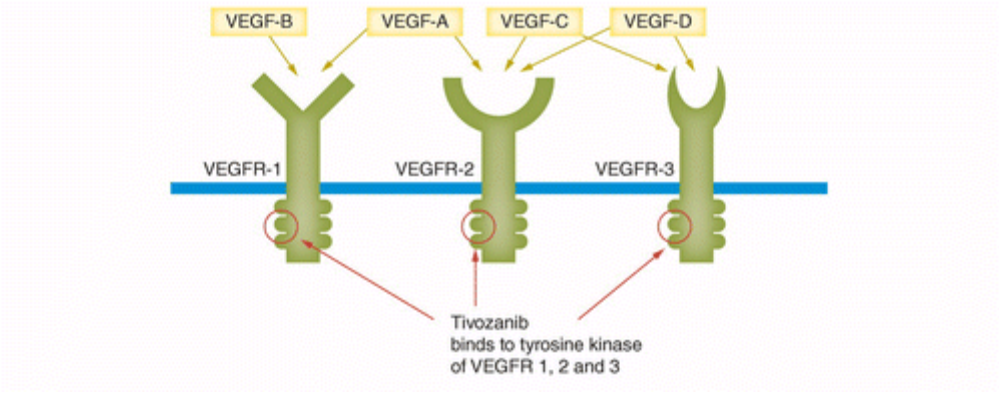

Fig. Mechanism of action.

The VEGF signaling pathway plays an important role in physiological and pathological conditions such as endothelial cell proliferation, migration, and survival and thus angiogenesis, which facilitates tumor growth and the formation of metastases. There are three VEGF receptors (1, 2, and 3) and five VEGF ligands (A, B, C, D, and placental growth factor). Each ligand exhibits distinct but overlapping binding profiles for the three receptors.[4] VEGFR-1 is critical for vessel morphogenesis and modulation of endothelial cell proliferation, whereas VEGFR-3 promotes vascular network formation and endothelial sprouting. The predominant receptor for endothelial cell proliferation and migration however is VEGFR-2. Most tumors produce VEGF, and in preclinical models, tumor growth was significantly reduced through inhibition of VEGF-induced angiogenesis. As each VEGFR plays an important and different role in cancer angiogenesis, it may be critical to block all three VEGFRs. Tivozanib is a TKI with the capacity to inhibit all three VEGFRs.[10-13]

Drug interaction

Tivozanib is a new medicine and is therefore still being tested in various clinical trials phase III. Thus, there is presently not much knowledge about the interactions between tivozanib and other drugs. Tivozanib study that was performed before phase 1 where the effect of tivozanib was tested in rats and dogs. This study gives the result that Concomitant use of Tivozanib with a strong CYP3A inducer decreases tivozanib exposure which may reduce Tivozanib antineoplastic activity.[14-15]

Tivozanib in other disease

Tivozanib may have potential for use in other cancers beyond RCC. Recent and ongoing trials have begun to investigate tivozanib in both hepatocellular carcinoma and ovarian cancer. The combination of tivozanib and durvalumab, an anti-PD-1 immunotherapy, is being studied in untreated, advanced hepatocellular carcinoma through a phase I/II dose-escalation and cohort expansion study. Tivozanib is also being studied in a single-arm phase II trial in the context of recurrent, platinum-resistant ovarian cancer, fallopian tube cancer, or primary peritoneal cancer.[16-19]

CONCLUSION

Tivozanib is an orally bioavailable VEGF TKI which has a long half-life and excellent potency and perticularly to the VEGF receptors. In particular, tivozanib has a higher bioavailability than other VEGFRTKIs and food has no effect on the overall AUC, indicating that tivozanib can be administered in both the fed and fasted states. Furthermore tivozanib has an extended plasma half-life, allowing daily drug administration that may facilitate patient compliance, and a favorable DDI profile that allows concomitant administration with CYP3A4 inhibitors, unlike other approved VEGFR-TKIs.[13] The most common AEs are manageable hypertension and hoarseness. Recently, the EMA has approved tivozanib for the treatment of previously untreated patients with RCC and for those patients who had disease progression during or after cytokine therapy. Thus, tivozanib has now become another treatment option for these patients. Because of the crowded and rapidly changing field of treatment options for patients with RCC, further research is ongoing to determine the role of tivozanib within this field. Special emphasis is currently put on the combination of TKIs such as tivozanib and other yet approved options for patients with RCC, in particular, anti-PD-(L)1-directed monoclonal antibodies.

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