Fruquintinib in Continuum of Care of Colorectal Cancer

Subjects: Oncology

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The management of patients with metastatic colorectal cancer (mCRC) has the continuum of care as the treatment paradigm. To date, trifluridine/tipiracil, a biochemically modulated fluoropyrimidine, and regorafenib, a multi-kinase inhibitor, remain the main options for the majority of patients who progressed to standard doublet- or triplet-based chemotherapies, although a tailored approach could be indicated in certain circumstances. Being highly selective for vascular endothelial growth factor receptor (VEGFR)-1, -2 and -3, fruquintinib demonstrated a strong anti-tumor activity in preclinical models and received approval from China's National Medical Products Administration (NMPA) in 2018 for the treatment of patients with chemo-refractory mCRC. The approval was based on the results of the phase III FRESCO trial. Then, in order to overcome geographic differences in clinical practice, the FRESCO-2 trial was conducted in the US, Europe, Japan, and Australia. In a heavily pretreated patient population, the study met its primary endpoint, demonstrating an advantage of fruquintinib over a placebo in overall survival (OS).

fruquintinib CRC VEGFR2 tyrosin kinase inhibitor

1. Introduction

Colorectal cancer (CRC) is the third most common tumor with approximately 1,931,590 cases annually, and the second leading cause of cancer-related death worldwide [1]. Nearly 15–30% of patients are diagnosed with advanced disease, while 20–50% of cases with resectable disease will develop metachronous metastases. The 5-year survival rate for the metastatic stage is approximately 14% [1][2].

The treatment paradigm for CRC is nowadays moving towards a tailored approach based on clinical and molecular characteristics. The combination of chemotherapy doublets or triplets with monoclonal antibodies (moAbs) remains the standard of treatment for the vast majority of patients with microsatellite stable (MSS) metastatic CRC (mCRC). The choice of the moAb lies between drugs directed against the epidermal growth factor receptor (EGFR) and the vascular endothelial growth factor receptor (VEGFR), according to the patient characteristics, tumor molecular profile, and primary tumor location [3][4][5][6][7][8]. In contrast, mismatch repair deficient (dMMR) CRC patients are a highly selected subgroup who have been shown to receive a remarkable benefit from immune checkpoint inhibitors as the chemo-free treatment strategy [9][10]. Being a key process for tumor growth and metastasis, angiogenesis has been considered a therapeutic target in the continuum of care of mCRC [11][12]. During rapid cell replication, hypoxic conditions trigger the activation of the hypoxia-inducible factor 1-alpha (HIF1A), which induces the

transcription of more than 60 genes, such as the pro-angiogenic factor VEGF (vascular endothelial growth factor), thus promoting oxygen delivery and cell survival [13]. The VEGF/VEGFR axis is composed of multiple ligands (i.e., VEGF-A, -B, -C, -D, -E, and placental growth factor) and tyrosine kinase receptors (VEGFR1, 2, and 3) with different binding affinities and functions [14].

Clinical studies have shown that anti-angiogenic drugs improve survival in patients with mCRC [15]. Bevacizumab, a moAb directed against the VEGF-A ligand, is the first anti-angiogenic drug approved in combination with cytotoxic chemotherapy as the first-line treatment in mCRC patients. From the results of the pivotal phase III AVF2107 trial [16], several other clinical trials investigated the effects of bevacizumab across various treatment lines, extending the indications for the second-line or beyond-progression therapy [17][18]. Among the resistance mechanisms to the anti-VEGF-A blockade, a decrease in VEGF-A and an increase in PDGF, VEGF-C, and VEGF-D levels after bevacizumab treatment has been reported by Hayashi et al. [19][20][21]. This suggestion paved the way for the development of other agents able to target multiple signaling pathways simultaneously. Displaying a high affinity to VEGF-A, VEGF-B, and placental growth factor, aflibercept showed a statistically significant overall survival (OS) improvement in the VELOUR study and in real-world datasets. The benefit has been observed both in bevacizumab-pretreated patients and in bevacizumab-naïve patients, thus making the drug an alternative second-line therapy [22][23].

In patients with mCRC who are refractory to these treatments, regorafenib, a multi-kinase inhibitor, and trifuridine/tipiracil, a biochemically modulated fluoropyrimidine, have been shown to improve OS in the randomized CORRECT and RECOURSE trials, respectively [24][25]. Regorafenib is an oral multi-kinase (anti-VEGFR1/3, PDGFR, and FGFR) and mutant oncogenic kinase (KIT, RET, and BRAF) inhibitor with antiangiogenic proprieties. Its efficacy in heavily pretreated patients may be due to the broad spectrum of anti-kinase activity, which conversely, may imply a higher incidence of adverse events (AE). However, a narrower range of targets might minimize off-target toxicities and improve the clinical outcome due to a higher drug exposure at the maximum tolerated dose (MTD) [26][27][28][29][30][31].

2. Pharmacodynamic Properties

Fruquintinib (6-[6,7-dimethoxyquinazolin-4-yloxy]-N, 2-dimethylbenzofuran-3-carboxamide) is a new generation potent tyrosine kinase inhibitor of VEGFR1, 2, and 3 [30] (**Figure 1**). This bond prevents VEGFR conformational change and dimerization and consequently, the phosphorylation of the intracellular kinase domain, which would trigger downstream signaling cascades, such as the PI3K/AKT, PKC, RAF/RAS, and ERK pathways [32][33]. VEGFR2 is a crucial member of the VEGFR family, being deeply involved in pro-angiogenic processes, whereas VEGFR1 seems to act as a negative regulator of the R2 signaling [32][34]. VEGFR3 is only expressed on lymphatic vessels and endothelial cells, thereby, promoting lymphangiogenesis and lymph node metastasis [35][36].

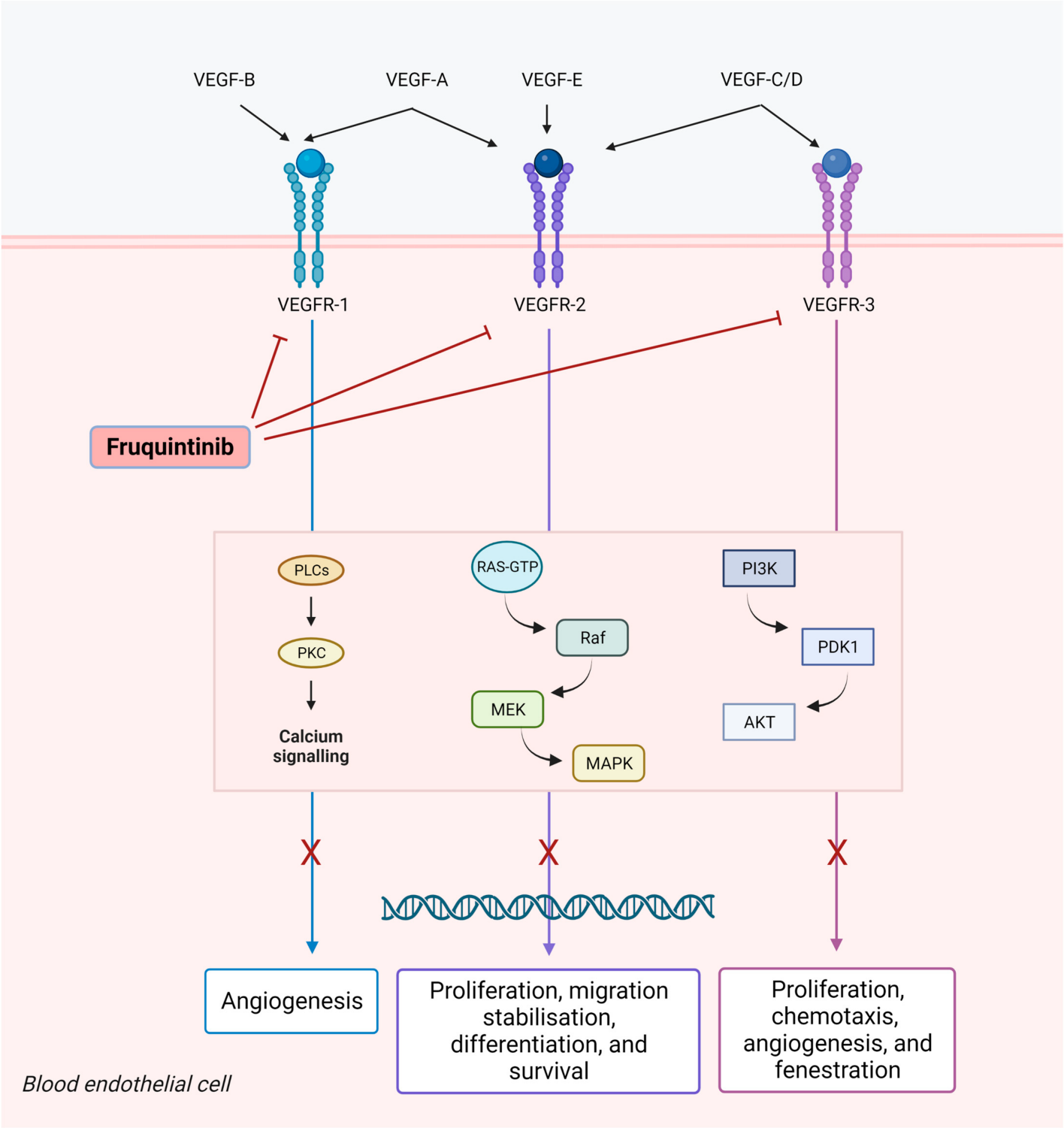

Figure 1. Fruquintinib inhibits vascular endothelial growth factor (VEGF)-induced phosphorylation of VEGF receptors 1, 2, and 3 and related signaling pathways. This may result in the inhibition of migration, proliferation, and survival of endothelial cells, micro-vessel formation, the inhibition of tumor cell proliferation, and tumor cell death.

Fruquintinib has shown optimal antitumor activity, both in vitro and in vivo, in pre-clinical models [37]. In vitro studies were conducted on human umbilical vein (HUVEC) and lymphatic endothelial cells (HLEC) to evaluate both the

angiogenic VEGFR2 and the lymphangiogenic VEGFR3 pathways, towards which fruquintinib demonstrated an equal inhibitory potential. In vitro, fruquintinib displayed anti-angiogenetic properties, suppressing endothelial cell proliferation and tubule sprouting in a dose-dependent fashion. Its kinase selectivity was tested against a panel of 253 kinases. A potent inhibition of VEGFR1, 2, and 3 was shown, with IC50s of 33 nmol/L, 35 nmol/L, and 0.5 nmol/L, respectively. A weak activity (IC50 values of 128–458 nmol/L) against RET, FGFR1, and c-KIT kinases has also been reported. The potent in vitro activity against VEGFR was then confirmed in vivo following administration in multiple human tumor xenograft murine models of colon, renal, gastric, and lung cancer. A near complete (>85%) inhibition of the VEGFR2 was obtained for at least 8 h after a single oral dose of fruquintinib at 2.5 mg/kg. Furthermore, the association with chemotherapeutic agents has been investigated. Enhanced antitumor activities were observed when fruquintinib was administered in combination with docetaxel and oxaliplatin in gastric cancer and colon cancer patient-derived xenograft (PDX) models, respectively, resulting in approximately a 30% decrease in tumor growth inhibition (TGI) rate. Other drug combinations in xenograft models have been evaluated due to the fact that certain cell lines (i.e., renal cancer models) showed scarce TGIs with fruquintinib monotherapy [30]. Interestingly, the coadministration of fruquintinib and the c-MET inhibitor savolitinib or the tyrosine kinase inhibitor geftitinib produced a marked reduction in tumor growth in preclinical models [38]. Furthermore, the influence of anti-VEGF therapy on the tumor immune microenvironment was examined on CRC allograft tumor models. Interestingly, low doses of fruquintinib combined with sintilimab, an anti-programmed death-1 (PD-1), seemed capable of reprogramming the immune response. A reduced angiogenesis, together with enhanced infiltration of CD8+T cells and reduced ratios of immunosuppressive cells, such as myeloid-derived suppressor cells (MDSCs) and macrophages, was described. Of note, the combination of anti-PD-1 and anti-VEGF achieved effective responses in patients with refractory MSS mCRC, suggesting a relevant synergistic effect [39].

3. Clinical Development

3.1. Phase 1–2

Recommended phase II dose (5 mg once daily for 3 weeks on and 1 week off) was determined from a Phase I trial, involving 40 Chinese patients with different tumor types (i.e., CRC, lung cancer, breast cancer, gastric cancer, melanoma). The study design included several dose cohorts: 1–6 mg on the continuous regimen and 5–6 mg for 3 weeks on and 1 week off regimen. Two patients experienced grade (G) 3 hand–foot skin (HFS) reaction as dose-limiting toxicity leading to treatment discontinuation in the 6-mg cohort. In the 5-mg cohort, after the enrolment of an additional three patients, one G3 symptomatic thrombocytopenia and one G3 HFS reaction were observed. Therefore, 4 mg was determined as the MTD for the continuous regimen. After the expansion of the 4-mg cohort, no other DLT was reported. Considering the AE time to onset, the dose level of 5 mg for the 3 weeks on and 1 week off regimen was selected. None of the first eight patients included in this cohort had a DLT. In contrast, at the 6-mg dose level, one patient experienced G3 fatigue. Overall, HFS reaction, hypertension, and thrombocytopenia were the most commonly reported AEs. Serious AEs were observed in 7.5% of cases. Among all G AEs, an HFS reaction was observed in 77.5%, hypertension in 42.5%, proteinuria in 47.5%, and a G1 TSH increase in 67.5%. Among the patients evaluated for response, the overall response rate (ORR) was 41.1%, and disease control was

obtained in 82.3%. Three patients with mCRC obtained a partial response (PR) and two young women with chemo-refractory lung cancer and breast cancer had a long-term PR (PR duration of 12 months and 13.2 months, respectively). Pharmacokinetic analyses revealed a high plasma exposure after oral administration and long half-life that supported the 3 weeks on and 1 week off regimen. In fact, the steady state was reached after two weeks of treatment and maintained in the third week. A gradual decrease until complete elimination was observed in the treatment-free week [40].

An open-label, single-arm phase Ib trial was conducted in two hospitals in China (NCT01975077), between December 2012 and January 2014. The study included patients with mCRC who progressed after at least two previous treatment lines, including fluoropyrimidine, oxaliplatin, or irinotecan-based regimens. In the extension stage of the study, the regimen that was chosen for further development was fruquintinib 5 mg daily for 3 weeks on and 1 week off. The primary endpoint was progression-free survival (PFS). Forty-two patients aged between 33 and 70, and with good ECOG performance status (0–1), were enrolled. The vast majority of patients (88.1%) received more than three previous treatment lines. The median PFS was 5.8 months (95% CI 4.01–7.60). Median OS was 8.9 months (95% CI 7.53–15.53). ORR and disease control rate (DCR) were 9.5% and 76.2%, respectively. Although all the patients included in the study developed treatment-emergent AEs, toxicities that led to permanent discontinuation in 5 patients were chest pain, pancreatitis, hemoptysis, proteinuria, and skin toxicity. The most commonly reported G3-4 treatment-emergent AEs were hypertension in 21.4%, diarrhea in 9.5%, HFS reaction in 9.5%, and serum sodium decrease in 7.1%. About half of the patients (47.6%) required a dose reduction or interruption. One toxic death due to hemoptysis was reported [41][42].

3.2. Phase 3

The phase III FRESCO (Fruquintinib Efficacy and Safety in 3+ Line Colorectal Cancer Patients) trial was a randomized, double-blind, placebo-controlled, multicenter study (28 hospitals in China). From December 2014 to June 2017, 416 patients were randomized (2:1) to receive fruquintinib plus BSC or placebo plus BSC. The study population included patients who had mCRC and experienced progressive disease (PD) after two standard lines of treatment containing fluoropyrimidine, irinotecan, and oxaliplatin, an anti-VEGF therapy and, if wild-type RAS, an anti-EGFR moAb. Patients who received VEGFR inhibitors (e.g., regorafenib, ramucirumab, or apatinib) were excluded. Anti-VEGF therapy and KRAS mutational status were stratification factors. Disease characteristics were well balanced in both treatment arms, with a high proportion of patients having multi-organ metastasis (95.3% in the fruquintinib arm and 97.1% in the placebo arm) and the left colon as the primary tumor location (77.0% and 83.3%, respectively). Among patients in the fruquintinib arm, 30.2% previously received bevacizumab and/or aflibercept, and 14.4% received cetuximab. Fruquintinib 5 mg per os, administered with the 3 weeks on and 1 week off scheme, significantly improved median OS compared with placebo meeting the primary endpoint (median OS: 9.3 months [95% CI: 8.2–10.5] vs. 6.6 months [95% CI: 5.9–8.1]; HR 0.65; 95% CI: 0.51–0.83; $p < 0.001$). The OS benefit was observed across nearly all subgroups, including patients who previously received more than three treatment lines. Among the key secondary endpoints, median PFS was also significantly longer in the fruquintinib arm compared with the placebo arm (3.71 months vs. 1.84; HR 0.26; 95% CI, 0.21–0.34; $p < 0.001$); ORR (4.7% vs. 0%, respectively) and DCR (62.2% vs. 12.3%, respectively) were also higher in the experimental arm. At the

time of PD, 45.2% of patients received subsequent treatments (42.4% in the fruquintinib arm and 50.7% in the placebo arm). G3-4 AEs were experienced by 61.2% of patients receiving fruquintinib, including hypertension in 21.2%, HFS reaction in 10.8%, and proteinuria in 3.2%. Serious AEs were reported in 15.5% of cases receiving fruquintinib. Eleven patients reported G5 AEs (nine in the fruquintinib arm and two in the placebo arm), including cases of gastrointestinal hemorrhage, stroke, and hemoptysis. Dose discontinuation was reported in 15.1% in the fruquintinib arm, and treatment interruption or dose reduction in 47.1%.

4. Summary

The management of patients with mCRC has the continuum of care as its paradigm. As early as 2004, Grothey and colleagues showed that mCRC patients benefited from receiving all available active agents for which they were candidates. At that time, only 5FU, irinotecan, and oxaliplatin were available agents, and patient survival was closely related to the possibility of receiving all three drugs (p = 0.0008) [43]. The concept of the continuum of care was then confirmed over the years. The introduction of moAbs, multi-kinase inhibitors, and new fluoropyrimidines has led to a median survival of over two years. [24][25][44][45] To date, a comprehensive treatment strategy with the integration of sequential chemotherapies, biological agents, surgery, local treatments, off-treatment periods, and best supportive care is a prerequisite to obtaining excellent outcomes in selected patients.

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