Postprint of Meta-Analysis on Incidence and Risk of Fruquintinib Treatment-Related Cardiovascular Toxicity in Patients with Metastatic Colorectal Cancer

Authors: Wang Xiaolin, Li Qiuyue, Zhou Yanjun, Zhang Jinhui, Liang Tao, Liang Tao

Date: 2024-09-11T00:00:00+00:00

Abstract

Background 38.4% of colorectal cancer patients die from non-cancer causes, among which cardiovascular disease is the leading cause, accounting for 20.3% of total deaths. Cardiovascular toxicity associated with targeted therapy is not uncommon, with hypertension being the most prominent. Objective This study aims to investigate the incidence and risk of fruquintinib treatment-related cardiovascular toxicity in patients with metastatic colorectal cancer. Methods We systematically searched CNKI, Wanfang Data Knowledge Service Platform, Chinese Biomedical Literature Database, Web of Science, PubMed, Cochrane Library, and Embase databases for single-arm clinical trials and randomized controlled trials on fruquintinib treatment in patients with metastatic colorectal cancer, with the search period from database inception to May 2024. Two researchers independently conducted literature screening, data extraction, and quality assessment, and performed meta-analysis using R 4.3.3 software. Results A total of 8 articles were included, involving 6 single-arm clinical trials and 3 randomized controlled trials. Meta-analysis results showed: the incidence of all-grade hypertension and hemorrhage was 35% (95%CI=0.25~0.45) and 24% (95%CI=0.10~0.37), respectively. For high-grade events, the incidence of hypertension was 15% (95%CI=0.10~0.20), hemorrhage was 1% (95%CI=0.00~0.02), thromboembolism was 3% (95%CI=0.02~0.05), and cardiac disorders was 1% (95%CI=0.00~0.02). Fruquintinib was associated with an increased risk of all-grade hypertension, high-grade hypertension, and all-grade hemorrhage, with RRs of 3.93 (95%CI=2.95~5.24), 12.33 (95%CI=5.31~28.63), and 1.84 (95%CI=1.36~2.50), respectively, but was not associated with high-grade hemorrhage (RR=1.06, 95%CI=0.35~3.23), thromboembolic events (RR=3.35, 95%CI=0.89~12.55), or cardiac disorders

(RR=0.62, 95%CI=0.18~2.14). Conclusion Fruquintinib is significantly associated with increased incidence and risk of cardiovascular toxicity in patients with metastatic colorectal cancer, but primarily for low-grade events.

Full Text

Incidence and Risk of Cardiovascular Toxicity with Fruquintinib in Metastatic Colorectal Cancer: A Meta-analysis

WANG Xiaolin[1], LI Qiuyue[1], ZHOU Yanjun[2], ZHANG Jinhui[3], LIANG Tao[1]*

[1]School of Nursing, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing 100144, China
[2]Department of Nursing, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing 100045, China
[3]Department of Medical Oncology, Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing 100021, China

Corresponding author: LIANG Tao, Professor; E-mail: liangtao1@hotmail.com

Abstract

Background: 38.4% of patients with colorectal cancer die from non-cancer causes, with cardiovascular disease being the most important cause, accounting for 20.3% of total deaths. Cardiovascular toxicity associated with targeted therapy is not uncommon, most notably hypertension. **Objective:** This study aimed to determine the overall incidence and risk of cardiovascular toxicity associated with fruquintinib in metastatic colorectal cancer. **Methods:** We systematically searched CNKI, Wanfang Data, PubMed, Embase, Web of Science, and Cochrane Library databases for single-arm clinical trials and randomized controlled trials (RCTs) of fruquintinib therapy in patients with metastatic colorectal cancer from inception to May 2024. Two investigators independently performed literature screening, data extraction, and quality assessment. Meta-analysis was conducted using R 4.3.3 software. **Results:** Eight articles involving six single-arm clinical trials and three RCTs were included. Meta-analysis results showed that the incidence rates of all-grade hypertension and hemorrhage were 35% (95%CI=0.25-0.45) and 24% (95%CI=0.10-0.37), respectively. For high-grade events, the rates were 15% for hypertension (95%CI=0.10-0.20), 1% for hemorrhage (95%CI=0.00-0.02), 3% for embolic and thrombotic events (95%CI=0.02-0.05), and 1% for cardiac disease (95%CI=0.00-0.02). Fruquintinib was associated with increased risks for both all-grade and high-grade hypertension, as well as all-grade hemorrhage, with RRs of 3.93 (95%CI=2.95-5.24), 12.33 (95%CI=5.31-28.63), and 1.84 (95%CI=1.36-2.50), respectively, but not for high-grade hemorrhage (RR=1.06, 95%CI=0.35-3.23), embolic and thrombotic events (RR=3.35, 95%CI=0.89-12.55), or cardiac disease (RR=0.62,

95%CI=0.18-2.14). **Conclusion:** Fruquintinib use is associated with a significantly increased incidence and risk of cardiovascular toxicity in patients with metastatic colorectal cancer, primarily for lower-grade events.

Keywords: Metastatic colorectal cancer; Fruquintinib; Cardiovascular toxicity; Meta-analysis

1. Materials and Methods

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and was registered with PROSPERO (registration number: CRD42024512891).

1.1 Search Strategy

We systematically searched CNKI, Wanfang Data, Chinese Biomedical Literature Database, Web of Science, PubMed, Cochrane Library, and Embase databases from inception to May 2024. The search combined subject headings and free-text terms. Chinese search terms included "结直肠肿瘤" (colorectal tumor), "结肠直肠癌" (colorectal cancer), "直肠癌" (rectal cancer), and "呋喹替尼" (fruquintinib). English search terms included "Colorectal Neoplasms," "Colorectal Cancers," "Colorectal Tumors," and "Fruquintinib." Chinese databases were limited to core journals. The specific search strategy for PubMed is provided in .

1.2 Literature Screening

Inclusion criteria: (1) Study design: single-arm clinical trials or RCTs; (2) Study population: patients with metastatic colorectal cancer; (3) Interventions: for RCTs, fruquintinib plus best supportive care (BSC) in the intervention group versus placebo plus BSC in the control group; for single-arm trials, fruquintinib monotherapy or combination therapy; (4) Outcome measures: reporting at least one clinical outcome of hypertension, hemorrhage, thromboembolism, or cardiac disease, with adverse events assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE).

Exclusion criteria: (1) Cellular or animal studies; (2) Letters to editors, conference abstracts, case reports, retrospective studies, commentaries, or other meta-analyses.

Two investigators independently screened literature according to the inclusion and exclusion criteria, with disagreements resolved through discussion with a third investigator. Extracted information included first author, publication year, trial phase, treatment regimen, sample size, follow-up duration, age, NCI-CTCAE version, and relevant data on hypertension, hemorrhage, thromboembolism, and cardiac disease. For multiple publications from the same popula-

tion, we included the most comprehensive data. Missing or unclear data were supplemented using details from https://ClinicalTrials.gov.

1.3 Quality Assessment

We used the revised Cochrane risk-of-bias tool for randomized trials (RoB 2) to assess RCTs and the Methodological Index for Non-Randomized Studies (MINORS) for single-arm clinical trials.

1.4 Statistical Methods

All statistical analyses were performed using R 4.3.3 and RStudio software. For RCTs, we calculated relative risk (RR) with 95% confidence intervals (CI) to assess differences between groups. The I^2 statistic evaluated heterogeneity, with $P<0.05$ and $I^2>50\%$ indicating significant heterogeneity. A random-effects model was used when $I^2>50\%$; otherwise, a fixed-effects model was applied. Sensitivity analysis was conducted by sequentially removing each study to assess result stability. Egger's test evaluated publication bias, with $P<0.05$ considered statistically significant.

---

2. Results

2.1 Literature Screening Process and Results

The search yielded 625 records: PubMed (n=90), Cochrane Library (n=59), Web of Science (n=159), Embase (n=257), CNKI (n=8), Wanfang (n=27), and Chinese Biomedical Literature Database (n=25). After removing 284 duplicates, 341 records remained. Following title and abstract screening, 333 records were excluded for being irrelevant (n=64), reviews/meta-analyses/protocols (n=156), unavailable full text (n=60), duplicate publications (n=30), or non-clinical trials (n=23). Eight articles were ultimately included, comprising six single-arm clinical trials and three RCTs [Figure 1: see original paper].

2.2 Characteristics and Quality Assessment of Included Studies

Baseline characteristics and MINORS scores for single-arm trials are presented in . Quality assessment results for RCTs using RoB 2 are shown in . All three RCTs [2,4,9] had "some concerns" regarding bias arising from the randomization process.

2.3 All-Grade Hypertension

Eight trials [2-4,9-13] reported all-grade hypertension incidence. Significant heterogeneity existed among studies ($I^2=97\%$, $P<0.01$), so a random-effects model was used. The pooled incidence of all-grade hypertension with fruquintinib was 35% (95%CI=0.25-0.45) [Figure 2: see original paper].

Three RCTs [2,4,9] showed low heterogeneity (I^2=0%, P=0.87) for all-grade hypertension risk. Fixed-effects meta-analysis revealed a significantly higher risk in the fruquintinib group versus control (RR=3.93, 95%CI=2.95-5.24, P<0.05) [Figure 3: see original paper].

2.4 High-Grade Hypertension

Nine trials [2-4,9-13] reported high-grade hypertension incidence. Significant heterogeneity was observed (I^2=88%, P<0.01), and random-effects analysis showed a pooled incidence of 15% (95%CI=0.10-0.20) [Figure 4: see original paper].

Three RCTs [2,4,9] demonstrated low heterogeneity (I^2=0%, P=0.86). Fixed-effects analysis indicated a significantly increased risk in the fruquintinib group (RR=12.33, 95%CI=5.31-28.63, P<0.05) [Figure 5: see original paper].

2.5 All-Grade Hemorrhage

Three trials [2,4,10] reported all-grade hemorrhage events. Significant heterogeneity existed (I^2=95%, P<0.01). Random-effects meta-analysis showed a pooled incidence of 24% (95%CI=0.10-0.37) [Figure 6: see original paper].

Two RCTs [2,4] had low heterogeneity (I^2=34%, P=0.22). Fixed-effects analysis revealed a significantly higher risk in the fruquintinib group (RR=1.84, 95%CI=1.36-2.50) [Figure 7: see original paper].

2.6 High-Grade Hemorrhage

Three trials [2,4,10] reported high-grade hemorrhage events. Heterogeneity was moderate (I^2=55%, P=0.11). Random-effects analysis showed a pooled incidence of 1% (95%CI=0.00-0.02) [Figure 8: see original paper].

Two RCTs [2,4] showed low heterogeneity (I^2=0%, P=0.83). Fixed-effects analysis found no significant difference between groups (RR=1.06, 95%CI=0.35-3.23) [Figure 9: see original paper].

2.7 High-Grade Thromboembolism

Two RCTs [4,9] reported high-grade thromboembolic events with low heterogeneity (I^2=0%, P=0.70). Fixed-effects analysis showed a pooled incidence of 3% (95%CI=0.02-0.05) [Figure 10: see original paper]. No significant risk difference was found between groups (RR=3.35, 95%CI=0.89-12.55) [Figure 11: see original paper].

2.8 High-Grade Cardiac Disease

Two RCTs [4,9] reported high-grade cardiac disease with low heterogeneity (I^2=0%, P=0.41). Fixed-effects analysis showed a pooled incidence of 1%

(95%CI=0.00-0.02) [Figure 12: see original paper]. No significant risk difference was observed (RR=0.62, 95%CI=0.18-2.14) [Figure 13: see original paper].

2.9 Sensitivity Analysis and Publication Bias

Sensitivity analysis by sequentially excluding each study did not affect the pooled effect estimates, indicating robust results. Egger's test revealed publication bias for high-grade hypertension incidence (t=2.86, P=0.02); after trim-and-fill correction, the pooled estimate was 8% (95%CI=0.02-0.15). Funnel plots for other outcomes were symmetrical, and Egger's tests (P>0.05) indicated no significant publication bias.

---

3. Discussion

Evidence indicates that the small-molecule tyrosine kinase inhibitor (TKI) regorafenib increases hypertension risk in metastatic colorectal cancer patients [14]. Two previous meta-analyses reached similar conclusions regarding common cardiovascular toxicities—hypertension, hemorrhage, thromboembolism, and cardiac disease—demonstrating associations with small-molecule TKI use [5-6]. These adverse events not only complicate treatment but may also cause treatment discontinuation, significantly increasing mortality [15]. Therefore, this meta-analysis was necessary to determine the incidence and risk of fruquintinib-related cardiovascular toxicities to guide clinical practice.

A meta-analysis of 72 RCTs found that solid tumor patients receiving small-molecule TKIs had an all-grade hypertension incidence of 23.0% (95%CI=20.1-26.0) and high-grade incidence of 4.4% (95%CI=3.7-5.0), with RRs of 3.85 (95%CI=3.37-4.40) and 4.60 (95%CI=3.92-5.40), respectively [16]. A network meta-analysis of nine FDA-approved small-molecule TKIs found that lenvatinib carried the highest risk for all-grade hypertension, followed by vandetanib, while regorafenib and nintedanib had relatively lower risks; high-grade hypertension risks may be similar across these agents [17]. Previous meta-analyses also showed that cancer patients receiving small-molecule TKIs had significantly increased all-grade hemorrhage risk (9.1%, 95%CI=6.8-12.1), but not high-grade hemorrhage, thromboembolism, or cardiac disease [5,18]. Notably, two meta-analyses demonstrated significantly increased all-grade cardiac disease risk with small-molecule TKIs, though all-grade thromboembolism risk was not significantly altered [5-6]. However, another meta-analysis found that small-molecule TKIs did not significantly increase all-grade venous thromboembolism risk but did increase all-grade arterial thromboembolism risk [19].

Our findings indicate that fruquintinib is associated with significantly increased hypertension incidence and risk, which appears slightly higher than other small-molecule TKIs [10], possibly related to tumor type. Colorectal cancer itself has multiple hypertension risk factors, such as high BMI and sedentary lifestyle,

making these patients more susceptible. Studies have shown that metastatic colorectal cancer patients have significantly increased all-grade hypertension risk (RR=4.05, 95%CI=3.16-5.20) [16]. Additionally, regorafenib, another small-molecule TKI for metastatic colorectal cancer, has similar hypertension incidence and risk profiles [20-22], supporting this hypothesis. Consistent with previous meta-analyses [18], fruquintinib significantly increased all-grade hemorrhage risk (24% incidence), which is slightly higher than other small-molecule TKIs. However, high-grade hemorrhage risk was not significantly increased, suggesting relative safety. Similar to prior research [5], fruquintinib did not increase high-grade thromboembolism or cardiac disease risks, with incidence rates below 5%. Due to limited included studies, we could not comprehensively assess all-grade thromboembolism and cardiac disease risks.

This study has several limitations. First, data scarcity prevented pooling of all-grade thromboembolism and cardiac disease incidence and risk. Second, the limited number of included studies precluded subgroup analysis. Third, except for FRESCO-2—a phase III trial conducted across North America, Europe, Asia, and Australia [4]—most trials enrolled only Chinese patients. Finally, all included patients had colorectal cancer, though recent trials have investigated fruquintinib in other malignancies. Future research should explore racial and tumor-type differences.

---

4. Conclusion

Fruquintinib is associated with increased cardiovascular toxicity risk in metastatic colorectal cancer patients, including all-grade and high-grade hypertension and all-grade hemorrhage. No associations were found with high-grade hemorrhage, thromboembolism, or cardiac disease. Clinicians should remain vigilant for and manage high-grade cardiovascular toxicities in patients receiving fruquintinib.

Author Contributions: All authors contributed to study conception and design. WANG Xiaolin performed literature search and screening and drafted the manuscript. LI Qiuyue and ZHOU Yanjun extracted and analyzed data. ZHANG Jinhui and LIANG Tao critically revised the manuscript.

Conflict of Interest: The authors declare no conflict of interest.

References

[1] SUNG H, FERLAY J, SIEGEL RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries[J]. CA Cancer J Clin, 2021, 71(3): 209-249. DOI: 10.3322/caac.21660.

[2] LI J, QIN SK, XU RH, et al. Effect of fruquintinib vs placebo on overall survival in patients with previously treated metastatic colorectal cancer: the FRESCO randomized clinical trial[J]. JAMA, 2018, 319(24): 2486-2496. DOI: 10.1001/jama.2018.7855.

[3] LI J, WANG ZQ, ZHONG HJ, et al. A phase IV study to evaluate the safety of fruquintinib in Chinese patients in real-world clinical practice[J]. Oncologist, 2024, 29(8): e1012-1019. DOI: 10.1093/oncolo/oyae073.

[4] DASARI A, LONARDI S, GARCIA-CARBONERO R, et al. Fruquintinib versus placebo in patients with refractory metastatic colorectal cancer (FRESCO-2): an international, multicentre, randomized, double-blind, phase 3 study[J]. Lancet, 2023, 402(10395): 41-53. DOI: 10.1016/S0140-6736(23)00772-9.

[5] LI J, GU J. Cardiovascular toxicities with vascular endothelial growth factor receptor tyrosine kinase inhibitors in cancer patients: a meta-analysis of 77 randomized controlled trials[J]. Clin Drug Investig, 2018, 38(12): 1109-1123. DOI: 10.1007/s40261-018-0709-5.

[6] TOTZECK M, MINCU RI, MROTZEK S, et al. Cardiovascular diseases in patients receiving small molecules with anti-vascular endothelial growth factor activity: a meta-analysis of approximately 29,000 cancer patients[J]. Eur J Prev Cardiol, 2018, 25(5): 482-494. DOI: 10.1177/2047487318755193.

[7] GALVANO A, GUARINI A, IACONO F, et al. An update on the conquests and perspectives of cardio-oncology in the field of tumor angiogenesis-targeting TKI-based therapy[J]. Expert Opin Drug Saf, 2019, 18(6): 485-496. DOI: 10.1080/14740338.2019.1613371.

[8] HUEDO-MEDINA TB, SÁNCHEZ-MECA J, MARÍN-MARTÍNEZ F, et al. Assessing heterogeneity in meta-analysis: Q statistic or I^2 index?[J]. Psychol Methods, 2006, 11(2): 193-206. DOI: 10.1037/1082-989X.11.2.193.

[9] XU RH, LI J, BAI YX, et al. Safety and efficacy of fruquintinib in patients with previously treated metastatic colorectal cancer: a phase Ib study and a randomized double-blind phase II study[J]. J Hematol Oncol, 2017, 10(1): 22. DOI: 10.1186/s13045-016-0388-8.

[10] TAN SR, ZHANG SY, ZHOU N, et al. Efficacy and safety of fruquintinib dose-escalation strategy for elderly patients with refractory metastatic colorectal cancer: a single-arm, multicenter, phase II study[J]. Cancer Med, 2023, 12(24): 22038-22046. DOI: 10.1002/cam4.6786.

[11] ZHAO W, LEI J, KE S, et al. Fecal microbiota transplantation plus tislelizumab and fruquintinib in refractory microsatellite stable metastatic colorectal cancer: an open-label, single-arm, phase II trial (RENMIN-215)[J]. EClinicalMedicine, 2023, 66: 102315. DOI: 10.1016/j.eclinm.2023.102315.

[12] MA SC, CHEN R, DUAN L, et al. Efficacy and safety of toripalimab with fruquintinib in the third-line treatment of refractory advanced metastatic col-

orectal cancer: results of a single-arm, single-center, prospective, phase II clinical study[J]. J Gastrointest Oncol, 2023, 14(2): 1052-1063. DOI: 10.21037/jgo-23-108.

[13] GUO Y, ZHANG WJ, YING JE, et al. Phase 1b/2 trial of fruquintinib plus sintilimab in treating advanced solid tumours: the dose-escalation and metastatic colorectal cancer cohort in the dose-expansion phases[J]. Eur J Cancer, 2023, 181: 26-37. DOI: 10.1016/j.ejca.2022.12.004.

[14] WANG ZX, XU J, NIE WW, et al. Risk of hypertension with regorafenib in cancer patients: a systematic review and meta-analysis[J]. Eur J Clin Pharmacol, 2014, 70(2): 225-231. DOI: 10.1007/s00228-013-1598-1.

[15] TOUYZ RM, HERRMANN SMS, HERRMANN J. Vascular toxicities with VEGF inhibitor therapies-focus on hypertension and arterial thrombotic events[J]. J Am Soc Hypertens, 2018, 12(6): 409-425. DOI: 10.1016/j.jash.2018.03.008.

[16] LIU B, DING FX, LIU Y, et al. Incidence and risk of hypertension associated with vascular endothelial growth factor receptor tyrosine kinase inhibitors in cancer patients: a comprehensive network meta-analysis of 72 randomized controlled trials involving 30013 patients[J]. Oncotarget, 2016, 7(41): 67661-67673. DOI: 10.18632/oncotarget.11813.

[17] HOU WT, DING MF, LI XH, et al. Comparative evaluation of cardiovascular risks among nine FDA-approved VEGFR-TKIs in patients with solid tumors: a Bayesian network analysis of randomized controlled trials[J]. J Cancer Res Clin Oncol, 2021, 147(8): 2407-2420. DOI: 10.1007/s00432-021-03521-w.

[18] QI WX, TANG LN, SUN YJ, et al. Incidence and risk of hemorrhagic events with vascular endothelial growth factor receptor tyrosine-kinase inhibitors: an up-to-date meta-analysis of 27 randomized controlled trials[J]. Ann Oncol, 2013, 24(12): 2943-2952. DOI: 10.1093/annonc/mdt292.

[19] LIU B, DING FX, ZHANG DY, et al. Risk of venous and arterial thromboembolic events associated with VEGFR-TKIs: a meta-analysis[J]. Cancer Chemother Pharmacol, 2017, 80(3): 487-495. DOI: 10.1007/s00280-017-3386-6.

[20] WU YY, FAN YW, DONG DF, et al. Efficacy and safety of regorafenib as beyond second-line therapy in patients with metastatic colorectal cancer: an adjusted indirect meta-analysis and systematic review[J]. Ther Adv Med Oncol, 2020, 12: 1758835920940932. DOI: 10.1177/1758835920940932.

[21] ZHU J, ZHOU R, ZHANG BL. A comparison of regorafenib and fruquintinib for metastatic colorectal cancer: a systematic review and network meta-analysis[J]. J Cancer Res Clin Oncol, 2019, 145(9): 2313-2323. DOI: 10.1007/s00432-019-02964-6.

[22] MERCIER J, VOUTSADAKIS IA. A systematic review and meta-analysis of retrospective series of regorafenib for treatment of metastatic colorectal

cancer[J]. Anticancer Res, 2017, 37(11): 5925-5934. DOI: 10.21873/anticanres.12039.

[23] CHEN JY, ZHENG YQ, WANG HH, et al. Cause of death among patients with colorectal cancer: a population-based study in the United States[J]. Aging, 2020, 12(22): 22927-22948. DOI: 10.18632/aging.104022.

[24] STURGEON KM, DENG L, BLUETHMANN SM, et al. A population-based study of cardiovascular disease mortality risk in US cancer patients[J]. Eur Heart J, 2019, 40(48): 3889-3897. DOI: 10.1093/eurheartj/ehz766.

[25] SUNDARARAJAN S, KUMAR A, POONGKUNRAN M, et al. Cardiovascular adverse effects of targeted antiangiogenic drugs: mechanisms and management[J]. Future Oncol, 2016, 12(8): 1067-1080. DOI: 10.2217/fon.16.4.

[26] ZHANG X, GAO YQ, YANG BY, et al. The mechanism and treatment of targeted anti-tumour drugs induced cardiotoxicity[J]. Int Immunopharmacol, 2023, 117: 109895. DOI: 10.1016/j.intimp.2023.109895.

[27] PANTAZI D, TSELEPIS AD. Cardiovascular toxic effects of antitumor agents: Pathogenetic mechanisms[J]. Thromb Res, 2022, 213(Suppl 1): S95-S102. DOI: 10.1016/j.thromres.2021.12.017.

(Received: 2024-04-19; Revised: 2024-08-06)
(Editor: JIA Mengmeng)

Note: Figure translations are in progress. See original paper for figures.