**Name of Journal:** *World Journal of Gastrointestinal Oncology*

**Manuscript NO:** 88407

**Manuscript Type:** EDITORIAL

**Cardiotoxicity induced by fluoropyrimidine drugs in the treatment of gastrointestinal tumors**

Kong MW *et al.* Cardiotoxicity in treatment of gastrointestinal tumors

Mo-Wei Kong, Feng-Di Sun, Zhen-Ying Pei, Li Xu, Ze-Bi Wang, Yan Chen, Shu-Qing Tang, Ting-Fang Yang, Guo-Xiang He

**Mo-Wei Kong, Feng-Di Sun, Zhen-Ying Pei, Li Xu, Ze-Bi Wang, Yan Chen, Shu-Qing Tang, Guo-Xiang He,** Department of Cardiology, Guiqian International General Hospital, Guiyang 550018, Guizhou Province, China

**Ting-Fang Yang,** Department of Oncology, Guiqian International General Hospital, Guiyang 550018, Guizhou Province, China

**Author contributions:** He GX and Yang TF provided crucial suggestions and guidance for the writing; Kong MW wrote the manuscript; Chen Y, Sun FD, Pei ZY, Wang ZB and Tang SQ reviewed and revised the manuscript; all authors read and approved the final manuscript.

**Corresponding author: Ting-Fang Yang, MD, Doctor,** Department of Oncology, Guiqian International General Hospital, No. 1 Dongfeng Avenue, Wudang, Guiyang 550018, Guizhou Province, China. 672539517@qq.com

**Received:** September 23, 2023

**Revised:** December 28, 2023

**Accepted:** January 19, 2024

**Published online:**

**Abstract**

In this editorial, we review the article published in *World J Gastrointest Oncol* 2019, 11: 1031-1042. We specifically focus on the occurrence, clinical characteristics, and risk factors of fluoropyrimidine drug-related cardiotoxicity in patients with gastrointestinal tumors. Despite significant advancements in diagnostic and therapeutic techniques that have reduced mortality rates associated with digestive system tumors, the incidence and mortality rates of treatment-related cardiotoxicity have been increasing, severely impacting the survival and prognosis of cancer patients. Fluoropyrimidine drugs are widely used as antimetabolites in the treatment of malignant tumors, including gastrointestinal tumors, and they represent the second largest class of drugs associated with cardiotoxicity. However, there is often a lack of awareness or understanding regarding their cardiotoxic effects and associated risks.

**Key Words:** Cardiotoxicity; Gastrointestinal tumors; Risk factors; Fluoropyrimidine; Chest pain

Kong MW, Sun FD, Pei ZY, Xu L, Wang ZB, Chen Y, Tang SQ, Yang TF, He GX. Cardiotoxicity induced by fluoropyrimidine drugs in the treatment of gastrointestinal tumors. *World J Gastrointest Oncol* 2024; In press

**Core Tip:** This editorial focuses on the occurrence, clinical characteristics, and risk factors of fluoropyrimidine drug-related cardiotoxicity in patients with gastrointestinal tumors. Despite advancements in diagnostic and therapeutic techniques for digestive system tumors, treatment-related cardiotoxicity rates have been increasing, impacting the survival and prognosis of cancer patients. Fluoropyrimidine drugs, widely used in treating malignant tumors, including gastrointestinal tumors, are the second largest class of drugs associated with cardiotoxicity. However, there is often a lack of awareness or understanding regarding their cardiotoxic effects and associated risks.

**INTRODUCTION**

Chemotherapy based on fluoropyrimidine drugs can improve the quality of life (QOL) and survival time of patients with gastrointestinal tumors[1]. Regrettably, a substantial number of patients endure various levels of cardiac damage during or following fluoropyrimidine chemotherapy, occasionally resulting in permanent harm. This not only drastically impairs patients' QOL, but also places their lives at risk[2]. Hence, it is imperative to precisely gauge the prevalence of fluoropyrimidine-induced cardiac toxicity (FIC) and pinpoint predisposing factors. This will help identify the population at high risk of developing FIC and guide the safe administration of medication. However, due to the absence of a universally accepted definition and diagnostic criteria for FIC, coupled with imprecise data on its incidence and correlation with risk factors, the estimation of FIC is often either over or under-calculated. In this editorial, we review the article by Lam *et al*[3] published in *World J Gastrointest Oncol* 2019, 11: 1031-1042[3].

**Symptoms, Incidence, and electrocardiogram Manifestations**

Recent studies have found that the clinical manifestations of cardiac toxicity associated with 5-fluorouracil (5-FU) and Capecitabine are similar[4]. The most common symptoms are chest pain or angina, with an incidence rate of about 2.27%, often accompanied by ischemic electrocardiogram (ECG) changes[5]. Other relatively common symptoms include dyspnea (0.89%), palpitations (0.64%), and hypertension (0.04%)[6]. A small number of patients have experienced severe cardiac adverse events such as heart failure (0.39%), myocardial infarction, cardiogenic shock, cardiac arrest, and sudden death[7]. Fortunately, these severe cardiac events are not common, and deaths due to cardiac toxicity are rare.

Fluorouracil can also affect the conduction of cardiac signals, leading to significant prolongation of the PR interval, P wave duration, and QT interval, resulting in various arrhythmias[8]. Common arrhythmias include atrial fibrillation, ventricular fibrillation, premature ventricular contractions, and atrioventricular block[9]. Although these ECG manifestations are often detected when symptoms occur during fluorouracil treatment, other causes need to be ruled out, such as pre-existing or current atherosclerotic heart disease, hypertensive heart disease, and rheumatic heart disease, various myocarditis, endocarditis, myocardial or pericardial tumor infiltration, past or current radiation therapy, and other drugs and biological agents with cardiac toxicity[10]. Therefore, only ECG abnormalities that occur during fluorouracil treatment and are new, and other causes have been ruled out, can be considered as ECG abnormalities induced by fluorouracil.

**Incidence and Monitoring**

It must be noted that during chemotherapy based on fluorouracil, some patients only show transient ECG abnormalities and may be asymptomatic. In the study by Südhoff *et al*[11], these asymptomatic ECG abnormalities occurred in 6.45% of single ECG collections. Dynamic ECG monitoring by Rezkalla *et al*[12] found that asymptomatic ST-segment elevation could reach 64%. FIC or ECG abnormalities usually occur within the first 72 h of initial treatment with fluoropyrimidine drugs, but a few patients may experience FIC at any time thereafter. In addition, research by Kosmas *et al*[13] showed that most patients with newly occurring symptomatic FIC will have ischemic ECG changes, which disappear with the disappearance of symptoms. Talapatra *et al*[14] reported transient asymptomatic bradycardia during continuous infusion of 5-FU. This suggests that we should closely monitor patients' ECG changes, especially dynamic ECG monitoring can detect more FIC, even subclinical FIC, otherwise the incidence of FIC may be underestimated, because some patients will have transient cardiac toxicity (including symptoms and/or ECG abnormalities).

For patients with gastrointestinal tumors, the incidence of cardiac toxicity related to fluoropyrimidine drugs is about 4.28%, the incidence of severe cardiac adverse events is about 0.45%, and the mortality rate related to cardiac toxicity is about 0.39%[15,16]. The most common symptom of cardiac toxicity is chest pain/angina, followed by dyspnea, palpitations, hypertension, *etc.* The incidence of new ECG abnormalities is about 3.12%, and the incidence of ECG abnormalities in symptomatic patients is about 2.49%[15]. Some patients may experience transient FIC and/or asymptomatic FIC. Arrhythmias and ischemic changes are the most common ECG changes.

**CONCLUSION**

We hope that this editorial can raise awareness of the cardiac toxicity associated with fluoropyrimidine drugs and its harm, identify high-risk groups prone to FIC, and ensure the safe use of drugs in patients with gastrointestinal tumors.

**REFERENCES**

1 **Fedorinov DS**, Lyadov VK, Sychev DA. Genotype-based chemotherapy for patients with gastrointestinal tumors: focus on oxaliplatin, irinotecan, and fluoropyrimidines. *Drug Metab Pers Ther* 2022; **37**: 223-228 [PMID: 36100443 DOI: 10.1515/dmpt-2021-0162]

2 **Sobrero A**, Lenz HJ, Eng C, Scheithauer W, Middleton G, Chen W, Esser R, Nippgen J, Burris H. Extended RAS Analysis of the Phase III EPIC Trial: Irinotecan + Cetuximab Versus Irinotecan as Second-Line Treatment for Patients with Metastatic Colorectal Cancer. *Oncologist* 2021; **26**: e261-e269 [PMID: 33191588 DOI: 10.1002/onco.13591]

3 **Lam KO**, Fu MC, Lau KS, Lam KM, Choi CW, Chiu WH, Yuen CM, Kwok LH, Tam FK, Chan WL, Chan SY, Ho PY, Leung TW, Lee HF. Revisiting oral fluoropyrimidine with cetuximab in metastatic colorectal cancer: Real-world data in Chinese population. *World J Gastrointest Oncol* 2019; **11**: 1031-1042 [PMID: 31798783 DOI: 10.4251/wjgo.v11.i11.1031]

4 **Visacri MB**, Duarte NC, Lima TM, de Souza RN, Cobaxo TS, Teixeira JC, Barbosa CR, Dias LP, Tavares MG, Pincinato EC, Lima CS, Moriel P. Adverse reactions and adherence to capecitabine: A prospective study in patients with gastrointestinal cancer. *J Oncol Pharm Pract* 2022; **28**: 326-336 [PMID: 33470162 DOI: 10.1177/1078155221989420]

5 **Sahashi Y**, Nawa T. Incessant Atrial Tachycardia Following Combination Chemotherapy with Cetuximab, Cisplatin and 5-Fluorouracil for Hypopharyngeal Cancer. *Cardiovasc Toxicol* 2021; **21**: 494-497 [PMID: 33830451 DOI: 10.1007/s12012-021-09648-z]

6 **Dyhl-Polk A**, Schou M, Vistisen KK, Sillesen AS, Serup-Hansen E, Faber J, Klausen TW, Bojesen SE, Vaage-Nilsen M, Nielsen DL. Myocardial Ischemia Induced by 5-Fluorouracil: A Prospective Electrocardiographic and Cardiac Biomarker Study. *Oncologist* 2021; **26**: e403-e413 [PMID: 32959474 DOI: 10.1002/onco.13536]

7 **Li Y**, Zhang Y, Zhou X, Lei X, Li X, Wei L. Dynamic observation of 5-fluorouracil-induced myocardial injury and mitochondrial autophagy in aging rats. *Exp Ther Med* 2021; **22**: 1451 [PMID: 34721693 DOI: 10.3892/etm.2021.10886]

8 **George TJ**, Ali A, Wang Y, Lee JH, Ivey AM, DeRemer D, Daily KC, Allegra CJ, Hughes SJ, Fan ZH, Cameron ME, Judge AR, Trevino JG. Phase II Study of 5-Fluorouracil, Oxaliplatin plus Dasatinib (FOLFOX-D) in First-Line Metastatic Pancreatic Adenocarcinoma. *Oncologist* 2021; **26**: 825-e1674 [PMID: 34101295 DOI: 10.1002/onco.13853]

9 **Bellyei S**, Boronkai Á, Pozsgai E, Fodor D, Mangel L. Effective chemotherapy and targeted therapy supplemented with stereotactic radiotherapy of a patient with metastatic colon cancer following renal transplantation: a case report. *J Med Case Rep* 2021; **15**: 125 [PMID: 33741057 DOI: 10.1186/s13256-021-02702-y]

10 **More LA**, Lane S, Asnani A. 5-FU Cardiotoxicity: Vasospasm, Myocarditis, and Sudden Death. *Curr Cardiol Rep* 2021; **23**: 17 [PMID: 33537861 DOI: 10.1007/s11886-021-01441-2]

11 **Südhoff T**, Enderle MD, Pahlke M, Petz C, Teschendorf C, Graeven U, Schmiegel W. 5-Fluorouracil induces arterial vasocontractions. *Ann Oncol* 2004; **15**: 661-664 [PMID: 15033676 DOI: 10.1093/annonc/mdh150]

12 **Rezkalla S**, Kloner RA, Ensley J, al-Sarraf M, Revels S, Olivenstein A, Bhasin S, Kerpel-Fronious S, Turi ZG. Continuous ambulatory ECG monitoring during fluorouracil therapy: a prospective study. *J Clin Oncol* 1989; **7**: 509-514 [PMID: 2466960 DOI: 10.1200/JCO.1989.7.4.509]

13 **Kosmas C**, Kallistratos MS, Kopterides P, Syrios J, Skopelitis H, Mylonakis N, Karabelis A, Tsavaris N. Cardiotoxicity of fluoropyrimidines in different schedules of administration: a prospective study. *J Cancer Res Clin Oncol* 2008; **134**: 75-82 [PMID: 17636329 DOI: 10.1007/s00432-007-0250-9]

14 **Talapatra K**, Rajesh I, Rajesh B, Selvamani B, Subhashini J. Transient asymptomatic bradycardia in patients on infusional 5-fluorouracil. *J Cancer Res Ther* 2007; **3**: 169-171 [PMID: 18079582 DOI: 10.4103/0973-1482.37412]

15 **Tian Y**, Wang Q, Wang J, Qiao XY, Zhang J, Lin YC, Li Y, Fan LQ, Yang PG, Zhao Q. [Neoadjuvant chemoradiotherapy combined with surgery *vs* direct surgery in the treatment of Siewert type II and III adenocarcinomas of the esophagogastric junction: long-term prognostic analysis of a prospective randomized controlled trial]. *Zhonghua Wei Chang Wai Ke Za Zhi* 2021; **24**: 128-137 [PMID: 33508918 DOI: 10.3760/cma.j.cn.441530-20201019-00565]

16 **Abdel-Rahman O**, Wu C, Easaw J. Risk of arterial and venous thromboembolic events among patients with colorectal carcinoma: a real-world, population-based study. *Future Oncol* 2021; **17**: 3977-3986 [PMID: 34342490 DOI: 10.2217/fon-2021-0252]

**Footnotes**

**Conflict-of-interest statement:** All the authors report no relevant conflicts of interest for this article.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review started:** September 23, 2023

**First decision:** December 26, 2023

**Article in press:**

**Specialty type:** Oncology

**Country/Territory of origin:** China

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): B

Grade C (Good): 0

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Thongon N, Thailand **S-Editor:** Li L **L-Editor:** A **P-Editor:** Li L