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Editorial: Cardiotoxicity Induced by Fluoropyrimidine Drugs in the Treatment of Gastrointestinal Tumors

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

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Abstract

In this editorial, we review the article by Lam *et al* 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.

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]. However, unfortunately, a large number of patients experience varying degrees of cardiac damage during or after fluoropyrimidine chemotherapy, even leading to permanent damage. This not only severely affects the QOL of patients but also poses a threat to their lives [2]. Therefore, it is crucial to accurately assess the incidence of fluoropyrimidine-induced cardiac toxicity (FIC) and identify susceptible factors in order to determine the high-risk population for developing FIC and guide safe medication. However, due to the lack of universally recognized definition and diagnostic criteria for FIC, as well as the absence of precise data on the incidence and correlation with risk factors of FIC, FIC is often overestimated or underestimated.

SYMPTOMS, INCIDENCE, AND ECG MANIFESTATIONS

Recent studies have found that the clinical manifestations of cardiac toxicity associated with 5-fluorouracil (5-FU) and Capecitabine are similar [3-4]. The most common symptoms are chest pain or angina, with an incidence rate of about 2.27%, often accompanied by ischemic 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 ReZkala[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 [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.

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