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Fluoropyrimidine-induced cardiotoxicity

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Abstract

Cardio-oncology is a discipline based on early screening, monitoring, and treating chemotherapy-induced cardiotoxicity. There are many chemotherapeutics known for their cardiac toxic effects, including fluoropyrimidines. Fluoropyrimidine represents the cornerstone of many types of cancer and each year almost two million cancer patients undergo this treatment. Fluoropyrimidine-induced cardiotoxicity can be manifested in several forms, from angina pectoris to sudden death. This paper is a review of how the cardiotoxicity of fluoropyrimidines is presented, the mechanisms of its occurrence, its diagnosis, and management.

Key Words: Fluoropyrimidines; Cancer treatments; Cardiotoxicity; Rechallenge; Prevention; Antidote

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Core Tip: There are several reviews and cases which showed fluoropyrimidine-induced cardiotoxicity. However, this mini-review includes useful information on clinical manifestations, pathophysiological mechanisms, diagnosis, and management of fluoropyrimidine-induced cardiotoxicity.

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INTRODUCTION

Fluoropyrimidine-based treatments are one of the most frequently used methods of chemotherapy worldwide. The fluoropyrimidine drugs include 5-fluorouracil (5-FU), Capecitabine, Tegafur, S-1, and TAS-102. Fluoropyrimidines are useful in the treatment of head and neck cancer, breast cancer, esophageal cancer, gastric cancer, pancreatic cancer, and colorectal cancer, and it is estimated that more than 2 million patients are being treated with fluoropyrimidines^[1,2]. The toxicity associated with fluoropyrimidine chemotherapy affects almost 30% of patients with more than 10% severe toxicity (CTC-AE grade ≥ 3) requiring hospitalization, and in 0.5%-1% of cases, the toxicity is lethal^[3,4].

The most known cause of fluoropyrimidine toxicity is the deficiency of dihydropyrimidine dehydrogenase (DPD), a crucial enzyme in fluorouracil metabolism, which is encoded by the *DPYD* gene^[4]. DPD levels show an important intra- and inter-individual variability which influences the patient's response to fluoropyrimidine in terms of efficacy, resistance, and toxicity^[5]. Deleterious polymorphism of *DPYD* represents the main cause of DPD deficiency. The most common *DPYD* variants associated with toxicity during treatment with fluoropyrimidine are *DPYD*2A* (IVS14+1G>A, c.1905+1G>A), *DPYD*9B* (c.2846A>T), *DPYD*13* (c.1679T>G), and *HapB3* (c.1129-5923C>G)^[6-9].

Fluoropyrimidine toxicity can be manifested through hematological non-cumulative toxicity most common in bolus infusion (anemia, neutropenia, thrombocytopenia), immediate digestive toxicity (nausea, vomiting, diarrhea, stomatitis, ileitis), alopecia in the case of continuous perfusion, thrombophlebitis and photosensitivity along the vein pathway, neurological toxicity if in high doses (cerebellar ataxia), ophthalmological toxicity through tear excretion (conjunctivitis, tear hypersecretion), skin toxicity usually aggravated by sun exposure (hand-foot syndrome, hyperpigmentation, hives, rash), and reversible cardiac toxicity following continuous perfusion (angina pectoris, unstable angina pectoris, arrhythmias, myocardial infarction, heart failure, myocardial necrosis)^[10].

CARDIOTOXICITY GENERALITIES

Chemotherapy-related cardiac dysfunction is one of the chemotherapy side effects that can appear even 20 years after treatment with an incidence of 10%^[11]. Chemotherapy-related cardiotoxicity can be due to the direct effect of chemotherapeutic agents on the entire cardiovascular system or indirectly through thrombogenic status or alteration of hemodynamic flow during treatment^[12]. The European Society of Cardiology (ESC) defines cardiotoxicity as the decrease in left ventricular ejection fraction with more than 10% of the normal value or a decrease of more than 15% of the overall longitudinal deformation of the cord while preserving the ejection fraction^[13]. Two types of cardiotoxicity have been described: (1) Type I, irreversible, dose-related, and caused by free radical formation, oxidative stress and myocyte fiber rearrangements, and mitochondrial dysfunction, *e.g.*, anthracycline-induced toxicity; and (2) Type II, reversible, not dose-related and is not associated with structural changes and can be induced by biological therapy, *e.g.*, Trastuzumab^[12-15]. Cardiotoxicity manifests itself in the form of hypertension, arrhythmias, myocardial dysfunction, coronary artery disease, sinus node dysfunction, atrioventricular block, thromboembolic disease, peripheral vascular disease and stroke, pulmonary hypertension, pericardial complications, and heart failure^[12,13].

FLUOROPYRIMIDINE-INDUCED CARDIOTOXICITY

Fluoropyrimidines produce type II, reversible cardiotoxicity. The incidence of fluoropyrimidine-induced cardiotoxicity ranges from 1% to 18%^[16,17]. The most common symptom of fluoropyrimidine cardiotoxicity is chest pain^[16,17]. Other symptoms that may occur are palpitations, dyspnea, hypertension, or hypotension, while less common manifestations include myocardial infarction, reversible

cardiomyopathy, myopericarditis, congestive heart failure, tachyarrhythmias, coronary dissection, cardiogenic shock, and sudden death^[18]. Another manifestation of cardiotoxicity is the development of silent cardiac ischemia. Prospective and retrospective studies have reported electrocardiography (ECG) changes of silent ischemia ranging from 4% to 88%^[18].

Among the proposed risk factors for fluoropyrimidine cardiotoxicity are older age, concurrent radiotherapy or history of chest radiotherapy, concurrent administration of cardiotoxic drugs, history of cardiovascular diseases or the presence of cardiovascular risk factors such as hypertension, dyslipidemia, diabetes mellitus, and smoking^[17]. Studies have shown that the continuous infusion of 5-FU compared with bolus administration is associated with a higher incidence for cardiac adverse events^[17,19]. Kosmas *et al*^[19] also demonstrated that the addition of Leucovorin (LV), a potentiator of 5-FU activity in 24 h continuous infusion and five days of 5-FU, may increase the incidence of cardiac adverse events (13%) compared with the same schedule of 5-FU administration but without LV addition (5%). Furthermore, de Forni *et al*^[28] examined 367 patients receiving a continuous infusion of 5-FU at doses between 600-1000 mg/m²/day and showed higher toxicity at doses more than 800 mg/m²/day. Symptoms usually appear in the first 72 h during the first cycle of 5-FU, but they can develop any time during the course of treatment and even a couple of days after the end of treatment^[20].

MECHANISM OF CARDIOTOXICITY

The pathogenesis of fluoropyrimidine-induced cardiotoxicity has not been fully elucidated. Several hypotheses have been proposed, such as vasoconstriction, direct myocardial toxicity, endothelial dysfunction, and a hypercoagulable status leading to thrombosis, all of them leading to cardiac damage (Figure 1)^[16].

The coronary vasospasm and the ischemic events it produces are probably the most studied cardiac adverse events of fluoropyrimidines. Patients usually present symptoms and signs of acute coronary syndrome, possibly increased troponin in blood levels, and often ST segment changes on ECG^[16,21]. ST-T wave changes are seen in 65% of cases and elevated cardiac enzymes only in 7%^[21]. Luwaert *et al*^[22] in one of the first reports of coronary vasospasm associated with fluoropyrimidine cardiotoxicity, performed angiography during the 5-FU infusion and observed vasospasm of the left circumflex artery, which was resolved by an intracoronary injection of isosorbide dinitrate. Despite this, coronary angiography was often normal without any evidence of a thrombotic event^[23]. Mosseri *et al*^[24] showed that the activation of protein kinase C (PK-C), a subcellular mediator of vascular smooth muscle tone, can also be a mediator of 5-FU-induced vasoconstriction and 5-FU causes direct endothelium-independent vasoconstriction of vascular smooth muscle *in vitro*. In other studies, Thyss *et al*^[25] and Porta *et al*^[26] found high levels of endothelin-1, a regulatory vasoconstrictor, in patients with 5-FU-induced cardiotoxicity. The vasodilator therapy included non-dihydropyridine calcium channel blockers such as Verapamil or Diltiazem, and nitrates have been shown to be effective in resolving symptoms and ECG changes^[27].

Another mechanism of fluoropyrimidine cardiotoxicity is represented by direct myocardial injury highlighted by global systolic dysfunction^[28]. Following a ventricular biopsy, Kuropkat *et al*^[29] reported the role of sarcoplasmic reticulum dilatation in cardiotoxicity, a mechanism similar to the cardiotoxicity of anthracyclines.

The accumulation of alpha-fluoro-beta-alanine (FbAL), a metabolite of 5-FU metabolism, which is converted to fluoroacetate and then to fluorocitrate, can cause an impairment in the Krebs cycle leading to citrate accumulation and downstream depletion of ATP resulting in ischemia^[30,33]. FbAL involvement as a direct mediator of cardiotoxicity was demonstrated by Muneoka *et al*^[30] who showed elevated levels of FbAL in a patient suffering from a myocardial infarction after administration of 5-FU. The same patient was later treated with S-1, a combination of ftorafur (FT), oxonic acid and gimeracil at a molar ratio of 1:0.4:1, and did not experience any associated cardiac adverse effects^[30,31]. Kwakman *et al*^[32] demonstrated in a series of seven patients that the rechallenge with S-1 after Capecitabine-induced cardiotoxicity was without recurrent cardiac side effects. An explanation for the lack of associated cardiotoxicity of S1 is due to gimeracil, a DPD-inhibitor, which increases the concentration of 5-FU, leading to a lower concentration of FbAL^[33,34].

The dysfunction of vascular endothelium followed by thrombosis, independent of vasoconstriction, seems to be a possible mechanism associated with fluoropyrimidine-

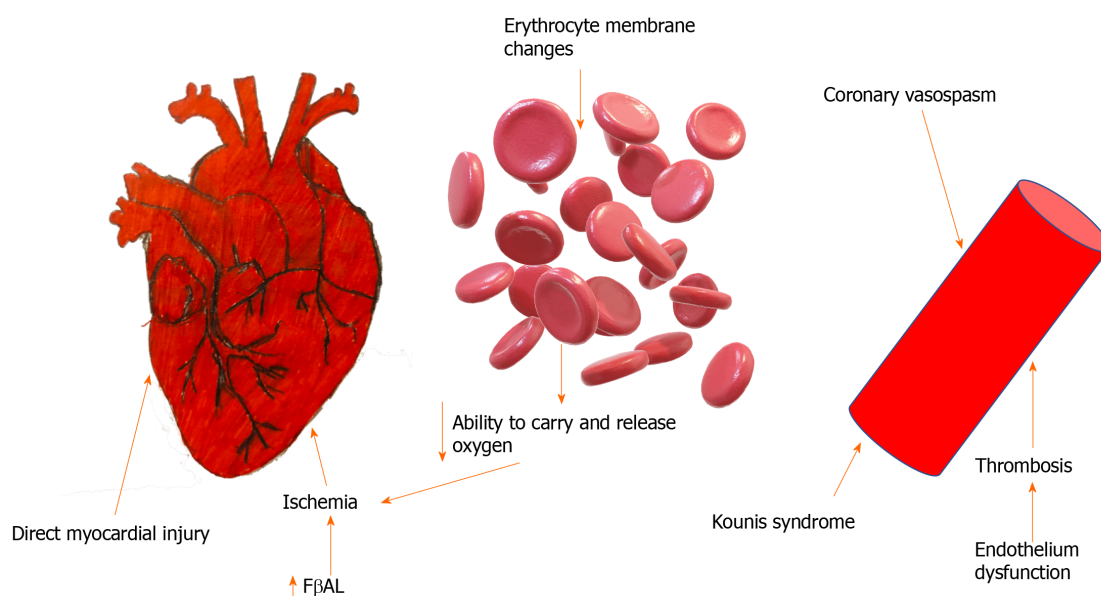


Figure 1 Proposed mechanism of fluoropyrimidine-induced cardiotoxicity.

induced cardiotoxicity. Many studies on animals have analyzed the effect of 5-FU on vascular endothelial cells and showed direct endothelial dysfunction and platelet and fibrin accumulation^[34]. Kuzel *et al*^[35] reported an increase in fibrinopeptide A and a decrease in protein C in the presence of 5-FU, which together confer a more susceptible environment for thrombus formation.

In another study, Spasojević *et al*^[36] demonstrated that 5-FU can cause changes in the shape of the erythrocyte membrane and lead to increased blood viscosity and decreased ability to carry and release oxygen, thus causing myocardial ischemia. Focaccetti *et al*^[37] demonstrated increased reactive oxygen species (ROS) in cardiomyocytes and endothelial cells, leading to 5-FU induced apoptosis. In guinea pig hearts treated with 5-FU, decreased levels of superoxide dismutase and glutathione peroxidase have been observed, supporting the theory of oxidative stress^[38]. Eskandari *et al*^[39] support the same theory in their study and demonstrated that fluoropyrimidine cardiotoxicity was associated with the formation of ROS, depletion of glutathione and lipid peroxidation, resulting in an increase in oxidative stress, which correlated with mitochondrial dysfunction that triggers caspase-3 and activates apoptosis or necrosis.

Another mechanism suggested by Karabay *et al*^[40] is Kounis syndrome, an acute coronary syndrome caused by an allergic reaction which can precipitate the release of inflammatory mediators that can break the atherosclerotic plaques caused by 5-FU exposure, causing coronary vasospasm which partially responds to antihistamine and corticosteroid therapy.

DIAGNOSIS OF FLUOROPYRIMIDINE-INDUCED CARDIOTOXICITY

There is no specific test for the diagnosis of fluoropyrimidine-induced cardiotoxicity, and it is usually guided by anamnesis of cardiovascular risk factors and diseases followed by a cardiologic examination, electrocardiography, cardiac enzymes, and echocardiography.

In cancer patients with previous coronary artery disease and indications of fluoropyrimidine-based chemotherapy, additional attention must be paid to risk factors such as smoking, hypertension, diabetes mellitus, and dyslipidemia followed by pharmacological treatment, before starting treatment with fluoropyrimidines^[13].

Cardiac 12-lead ECG monitoring is the most feasible method for early detection of cardiac adverse events during the course of 5-FU chemotherapy^[41]. ECG is recommended for all patients before and during chemotherapy. The most common findings on ECG are ST elevation, ST depression, QT prolongation and inverted T waves^[41]. Holter monitoring represents a method with a higher sensitivity, but no recommendations have been made for this technique. ECG changes may occur early during the continuous infusion of 5-FU or in the first days of Capecitabine

administration^[42,43].

The brain natriuretic peptide (BNP), troponin I and T (TnI and TnT) and creatine phosphokinases (CK and CK-MB) are well known markers for the diagnosis and prognosis of heart diseases. TnI is a protein specific to the myocardial tissue and a component of the troponin protein complex; an increase in serum TnI level is an early and specific sign of myocardial injury, but no significant changes have been found in patients with fluoropyrimidine-induced cardiotoxicity^[42]. The European Society of Medical Oncology (ESMO), in their clinical practice guidelines regarding fluoropyrimidine cardiotoxicity, recommends monitoring of TnI and brain natriuretic peptide (BNP) in patients with symptoms or signs of cardiac ischemia as a grade C III/IV level of evidence^[44]. Holubec *et al*^[45] determined BNP and TnI before and after 5-FU chemotherapy and showed increased levels of TnI in 57% of cases and BNP in 57% of cases, but no correlations have been made with clinical signs of cardiotoxicity. Data on the clinical relevance of cardiac biomarkers are very controversial; several studies have shown that BNP and troponins remain unchanged despite the occurrence of cardiac adverse events^[42,45]. In only one study, out of 26 patients who experienced cardiac adverse events, seven had an increase in CK-MB level; the remaining studies did not show changes in CK-MB in patients with cardiotoxicity^[19,46].

Another way to assess fluoropyrimidine cardiotoxicity is by echocardiography and imaging techniques. Fluoropyrimidine-induced cardiotoxicity can affect ventricular systolic and diastolic kinetics by reducing left ventricular ejection fraction^[47]. Evidence of the role of echocardiography is also controversial; some authors failed to detect changes in diastolic and systolic function, while others such as Turan *et al*^[48] and Wacker *et al*^[49] found a significant correlation between a decrease in diastolic and systolic function and fluoropyrimidine cardiotoxicity in 18.7% of patients after the first cycle and in 10.5% of patients three months after chemotherapy^[42,46].

MANAGEMENT

In cases of acute fluoropyrimidine cardiotoxicity, the first step should be to stop the treatment immediately and treat the symptoms with antianginal drugs such as nitrates, calcium channel blockers, and antiplatelets^[50]. Symptom cessation has been shown in 69% of cases^[50]. For high-risk patients with suspected acute coronary syndrome, the American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommend an urgent coronarography with revascularization, and for low risk patients with persistent minor or mild symptoms, it is suggested to consider a stress test or coronary computed tomography angiography^[17,51].

Rechallenging a patient with fluoropyrimidine may cause a recurrence of cardiac symptoms in 45%-90% of patients and a death rate of 18%^[52,53]. Clavel *et al*^[54] reported 4 cases of myocardial necrosis and 4 cases of cardiogenic shock in a series of 28 rechallenged patients. Given all the existing scientific evidence, several strategies have been proposed depending on what other therapeutic options exist and the need to keep fluoropyrimidines in patient treatment. If the patient still needs fluoropyrimidine-based chemotherapy, the following strategies should be considered: (1) Switch from continuous infusion to 5-FU bolus administration; (2) Dose reduction along with antianginal drug prophylaxis; and (3) Other oral fluoropyrimidines such as uracil-tegafur or S-1, both drugs contain either uracil which competes with 5-FU for DPD and therefore reduces the degradation of 5-FU into FbAL, or gimeracil which as we have seen before is a DPD inhibitor and also prevents FbAL formation^[52]. Even if we know about the possible benefit of those two prodrugs, we still need more studies to prove the lower cardiotoxicity and trials of equalization with 5-FU and Capecitabine. Another option is TAS-102, the combination of trifluridine (TFD) and tipiracil, the last fluoropyrimidine approved in chemorefractory colorectal cancer. TFD exhibits two anti-tumor mechanisms: Inhibition of TS and the creation of single-strand DNA breaks by incorporating the triphosphate form into DNA in the place of thymidine^[55,56]. The addition of tipiracil inhibits trifluridine degradation and increases bioavailability^[56]. The fact that TAS-102 is not metabolized by DPD explains the lack of cardiac adverse events^[56].

Clasen *et al*^[57] in a case series of 11 patients with previous fluoropyrimidine cardiotoxicity, successfully rechallenged with the same drug, and based on their experience, they made the following recommendations: (1) Switch from continuous administration to bolus; (2) Pretreatment with isosorbide mononitrate for 3 to 4 h and extended-release nifedipine before 5-FU administration; (3) Treatment with short-

acting diltiazem and sublingual nitroglycerin during the treatment with 5-FU; (4) Posttreatment with nifedipine and isosorbide mononitrate 12 h after the first dose of antianginal pretreatment; and (5) Posttreatment with nifedipine 24 h after the first dose.

Another alternative to fluoropyrimidine is represented by Raltitrexed (Tomudex), a quinazoline folate analogue, which inhibits thymidylate synthase (TS), thereby blocking DNA synthesis^[58]. The results of two prospective studies proposed Raltitrexed as an option for colorectal cancer patients with cardiovascular risk factors or fluoropyrimidine cardiotoxicity. Ransom *et al*^[59] published the final results of the Australasian Gastrointestinal Trials Group ARTIC study and reported no cardiac adverse effects attributed to Raltitrexed in 42 patients who previously experienced fluoropyrimidine cardiotoxicity. In the second study, Raltitrexed was used in 111 colorectal cancer patients who presented fluoropyrimidine cardiotoxicity and important cardiovascular risk factors^[60]. The study reported five patients who experienced cardiac adverse events during treatment with Raltitrexed^[60]. Both of these studies indicate that Raltitrexed can be a safe alternative in patients after cardiac adverse events.

In the desire to counterbalance the severe side effects or fluoropyrimidine overdose, uridine triacetate (UT, Vistogard) was approved by the FDA in 2015 as an antidote based on two open-label, single-arm trials which demonstrated a survival benefit in 96% of cases^[61,62]. Uridine triacetate is an oral pyrimidine analogue of uridine, which competes with fluorouridine-triphosphate incorporation into RNA and this way improves fluoropyrimidine toxicity^[17,61]. Uridine triacetate can be used in the first 96 h after the last dose of 5-FU or Capecitabine for early-onset, severe or life-threatening toxicity such as severe neutropenia, gastrointestinal toxicity or cardiotoxicity unresponsive to drug cessation and antianginal therapy (Table 1)^[62,63].

Phenotyping and genotyping DPD activity before starting the treatment with fluoropyrimidine can be useful to detect the patients who are already more predisposed to experiencing severe adverse events. In a case report, Saif *et al*^[64] showed the presence of both *DPYD* and *TYMS* gene mutations in a patient who developed a severe Takotsubo cardiomyopathy after receiving fluoropyrimidine treatment. We need more studies to evaluate the possible correlation between DDP deficiency and cardiotoxicity.

CONCLUSION

Fluoropyrimidine cardiotoxicity may be more common than is currently diagnosed due to the multiple indications of this class. Despite the fact that 5-FU and Capecitabine cardiotoxicity is not very common, it can be unpredictable and sometimes fatal. Even if some of the fluoropyrimidine cardiotoxicity mechanisms are known, we still need more studies to discover new mechanisms or to explore the mechanisms already known and the possible relationship with *DPYD* mutation or other genes involved in the metabolism of fluoropyrimidines. There is currently no consensus on the treatment and prophylaxis of these adverse events, the only certainty is the need for immediate discontinuation of fluoropyrimidine chemotherapy and treatment of symptoms. Rechallenging the patient with 5-FU or Capecitabine is feasible, but it comes with certain risks such as the recurrence of cardiac toxicity or more severe forms of it. If a decision is made to continue this treatment, antianginal therapy may prevent ischemic events. In such a scenario, dose reduction is also recommended. We still need more studies and tools to identify the patients who will develop cardiotoxicity due to fluoropyrimidine-based chemotherapy and to determine how we can prevent it.

Table 1 Management of fluoropyrimidine-induced cardiotoxicity and rechallenge

Management of acute cardiotoxicity	Rechallenge with fluoropyrimidine	Antidote
Stop fluoropyrimidine chemotherapy	Switch from continuous infusion to bolus administration	Uridine triacetate
Administration of antianginal drugs and antiplatelets	Dose reduction with antianginal drugs administration: (1) Preatreatment 3 to 4 h before fluoropyrimidine; (2) Administration during the treatment with 5-FU; (3) Posttreatment 12 or 24 h after fluoropyrimidine	
Monitor patient's cardiac enzymes, ECG	Use of alternative fluoropyrimidine agents (S1, TAS-102)	
Coronarography with revascularization if acute coronary syndrome is suspected	Use of alternative non-fluoropyrimidine agents	
Stress test or coronary CT angiography in patient's with persistent minor or mild symptoms		

ECG: Electrocardiography; CT: Computed tomography; 5-FU: 5-fluorouracil.

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