

5-FU CARDIOTOXICITY: CURRENT EVIDENCE AND CLINICAL IMPLICATIONS

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КАРДИОТОКСИЧНОСТ НА 5-FU: АКТУАЛНИ ДАННИ И КЛИНИЧНИ ПОСЛЕДСТВИЯ

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Abstract: Fluoropyrimidines, including 5-fluorouracil (5-FU) and its oral prodrug capecitabine, are widely used in the treatment of solid tumors. While generally well tolerated, these agents can cause cardiotoxicity, with reported incidence rates ranging from 0 to 35%. Cardiac manifestations include angina, acute coronary syndromes, hypotension, arrhythmias, myocarditis, and heart failure. The primary mechanism of toxicity is thought to involve coronary vasoconstriction and microvascular dysfunction, though direct myocardial and endothelial damage may also contribute. Risk factors remain poorly defined, and cardiotoxicity can occur even in patients without pre-existing heart disease. Diagnostic tools, including biomarkers such as NT-proBNP and troponin, as well as echocardiography and cardiac MRI, play a critical role in early detection. Management typically involves discontinuation of 5-FU and symptomatic treatment with vasodilators and beta-blockers. Prophylactic strategies remain controversial, and guideline-directed therapy is largely based on case reports and observational data. Rechallenge with 5-FU carries a high risk of recurrence and should be approached with caution. Multidisciplinary collaboration, involving cardio-oncology teams, is essential for optimizing patient outcomes and guiding individualized prevention, monitoring, and treatment strategies in patients receiving fluoropyrimidine therapy.

Key words: 5-fluorouracil, cardiotoxicity, chemotherapy, coronary vasospasm, fluoropyrimidine

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Резюме: Флуоропиримидините, включително 5-флуороурацил (5-FU) и неговият перорален пролекарствен препарат капецитабин, се използват широко за лечение на солидни тумори. Въпреки че като цяло се понасят добре, тези средства могат да причинят кардиотоксичност, като честотата на случаите варира от 0 до 35%. Сърдечните прояви включват ангина, остри коронарни синдроми, хипотония, аритмии, миокардит и сърдечна недостатъчност. Счита се, че основният механизъм на токсичност включва коронарна вазоконстрикция и микросъдова дисфункция, въпреки че директното увреждане на миокарда и ендотелиума също може да допринесе за това. Рисковите фактори остават слабо дефинирани, а кардиотоксичност може да възникне дори при пациенти без предварително съществуващо сърдечно заболяване. Диагностичните инструменти, вкл. биомаркери като NT-proBNP и тропонин, както и ехокардиография и сърдечна МРТ, играят решаваща роля в ранното откриване. Лечението обикновено включва преустановяване на 5-FU и симптоматично лечение с вазодилатори и бета-блокери. Профилактичните стратегии остават спорни, а терапията, базирана на препоръките, се основава до голяма степен на клинични случаи и наблюдателни данни. Повторното третиране с 5-FU носи висок риск от рецидив и трябва да се подхожда с повишено внимание. Мултидисциплинарното сътрудничество, включващо кардио-онкологични екипи, е от съществено значение за оптимизиране на резултатите и за изграждане на индивидуализирани стратегии за превенция, мониторинг и лечение при болните, получаващи терапия с флуоропиримидин.

Ключови думи: 5-флуороурацил, кардиотоксичност, химиотерапия, коронарен вазоспазм, флуоропиримидин

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INTRODUCTION

Fluoropyrimidines, which include 5-fluorouracil (5-FU) and capecitabine, are among the most commonly used chemotherapy drugs in the treatment of solid malignancies across the world. 5-FU acts primarily as an antimetabolite, which inhibits the synthesis of thymidine, a nucleotide required for DNA replication, leading to apoptotic cell death. Capecitabine is an oral pro-drug of 5-FU that is enzymatically converted to 5-FU in the tumor cells. The most common toxicities associated with fluoropyrimidine administration are hematologic (31% in patients with bolus administration and 4% in continuous infusion), hand-foot syndrome, diarrhea, nausea/vomiting and mucositis [1]. Reported rates of cardiotoxicity vary largely between studies (0 to 35%). The incidence of treatment-related sudden death ranges from 0 to 8% but is clustered around 0-0.5% [2]. Cardiac toxicity can manifest as atypical chest pain, exertional or rest angina, or acute coronary syndromes. Other, less common cardiac effects include atrial fibrillation and various arrhythmias, myocarditis and pericarditis and heart failure [3].

Understanding 5-FU cardiotoxicity is crucial for balancing the benefits of cancer treatment with the potential for cardiac harm. By recognizing the risk factors, mechanisms, and clinical manifestations of this complication, healthcare professionals can optimize patient outcomes and improve the overall quality of cancer care.

We searched PubMed (MEDLINE) for studies related to fluoropyrimidine-associated cardiotoxicity from January 1, 1980 through July 31, 2025. We selected this window to capture early mechanistic/experimental work and to extend to modern meta-analyses and clinical guidelines. We combined fluoropyrimidine exposure terms (fluorouracil/5-FU/capecitabine) with cardiotoxicity outcomes (cardiotoxic*, vasospasm/angina/ACS, ischem*, arrhythm*, myocardit*) using Boolean logic and right-hand truncation to retrieve word variants. Field tags were applied to focus on Title/Abstract where appropriate and MeSH terms were used to increase precision. In total 54 records were screened and 39 were taken for full-text assessment.

MECHANISM OF ACTION

5-fluorouracil (5-FU) and its oral prodrug, capecitabine, act as antimetabolites by mimicking the structure of natural metabolites essential for DNA and RNA synthesis. 5-FU is an analogue of uracil – one of the four nucleotide bases in the structure of RNA, in which a fluorine atom replaces the hydrogen at the C-5 position. It enters cells rapidly facilitated via the same transport mechanism as uracil. Inside the cell, 5-FU

is metabolized into several active forms: fluorodeoxyuridine monophosphate (FdUMP), fluorodeoxyuridine triphosphate (FdUTP), and fluorouridine triphosphate (FUTP). 5-FU has multiple mechanisms of action. One of the key metabolite of 5-FU, FdUMP, crucially inhibits thymidylate synthase (TS) by competitive binding and disrupting cell growth [4]. Its cytotoxic effects are due to the incorporation of fluorodeoxyuridine triphosphate (FdUTP) into DNA, and fluorouridine-5'-triphosphate (FUTP) and 5-fluorocytosine into RNA. Misincorporation into DNA and RNA of these metabolites has an effect on calcium channel-dependent membrane functions, disrupts mitochondrial phosphate metabolism, alters contractile proteins, induces oxidative damage, releases vasoactive substances such as histamine and catecholamines, and triggers autoimmune mechanisms, leading to cell death [4, 5]. Important part of 5-FU mechanism of action is the rate-limiting enzyme in 5-FU catabolism – dihydropyrimidine dehydrogenase (DPD), which converts 5-FU to dihydrofluorouracil (DHFU). Normally more than 80% of the administered 5-FU is catabolized in the liver, where DPD is abundantly expressed. A deficiency in DPD significantly increases the risk of severe toxicity from fluoropyrimidines. Partial DPD deficiency affects approximately 3-8% of the Caucasian population, while complete deficiency - occurring in about 0.3% – can lead to life-threatening toxicity [6].

CARDIOTOXICITY

Animal studies and research on cultured myocardial and endothelial cells have established a relationship between 5-FU dosage and changes in myocardial tissue [7]. In rabbits, a single high intravenous dose led to hemorrhagic infarction of the ventricle walls, proximal coronary artery spasms, and death within one day of application of 5-FU. Conversely, repeated lower doses caused left ventricular hypertrophy due to interstitial fibrosis and edema, as well as concentric fibrous thickening of the small distal coronary arteries' intima [8]. In guinea pigs, studies of myocardial metabolism revealed that 5-FU decreased myocardial high-energy phosphate levels and increased citrate accumulation, indicating enhanced anaerobic metabolism. These metabolic alterations were associated with ECG changes indicative of myocardial ischemia and occurred about 3 hours after administration of 5-FU [9].

The most frequently cited cardiotoxic mechanism of 5-FU is vasoconstriction. Two studies found that patients experienced brachial artery vasoconstriction immediately after 5-FU infusion. This vasoconstriction was transient, recurred with subsequent 5-FU doses, and was alleviated by glycerol nitrate in 100% of the cases [10, 11]. Salepci et al. demonstrated that after

the infusion there was no change in the level of angiotensin II and troponin [10]. Another study investigated 5-FU-induced vasoconstriction in vitro using isolated aorta rings from rabbits. The occurrence of vasoconstriction correlated with the molar concentration of 5-FU, and the extent of constriction was proportional to the concentration, regardless of the endothelium's condition. Nitroglycerin was effective in mitigating the vasoconstriction, and the relaxation induced by acetylcholine was unaffected by 5-FU treatment, implying that the vasoconstriction is not due to the impairment of endothelial relaxation pathways. There was no evidence indicating that 5-FU-induced vasoconstriction was modulated by membrane receptor blockers or activators of the cyclooxygenase pathway; treatments with calcium antagonists such as verapamil and diltiazem also did not show any effects [12]. The elevated plasma levels of endothelin-1 reported in patients treated with 5-FU, particularly in those experiencing 5-FU-induced cardiotoxicity, may lend support to the hypothesis of 5-FU-induced vasoconstriction, although this trend was not restricted to those who developed vasoconstriction [13]. In addition Parr-Ukena et. al. discovered increased activity of protein kinase C in human coronary smooth muscle cells 10 minutes after exposure to 5-FU chemotherapy with levels similar to controls after one hour [14].

There have been some inconsistencies with the theory of vasospasm and 5-FU administration. Coro-

nary vasospasm has not been consistently demonstrated at angiography during symptomatic episodes. Furthermore in one study of patients who reported angina in response to a 5-FU challenge and who had ECG changes suggestive of ischemia, those who underwent concurrent echocardiography were shown to have global akinesia, incompatible with a characteristic territorial distribution of a major coronary artery [15]. Despite the systemic distribution of 5-FU, multivessel coronary vasospasm is uncommon in patients receiving 5-FU [16]. The discordance between echocardiographic and angiographic findings could undermine the epicardial vessel vasospasm theory in patients receiving 5-FU, though does not preclude microvascular vasospasm. Endothelial-dependent and -independent dysfunction also affects the coronary microvasculature, often without involvement of the epicardial vessels where it leads to diffuse as opposed to segmental ischemia. Since the coronary microvasculature cannot be directly visualized, its function is best assessed with pharmacologic provocation at angiography [17].

CLINICAL MANIFESTATIONS

The clinical presentation of 5-fluorouracil (5-FU) induced cardiotoxicity is highly variable, ranging from mild chest discomfort to life-threatening cardiac events (Figure 1). Chest pain is the most frequently reported

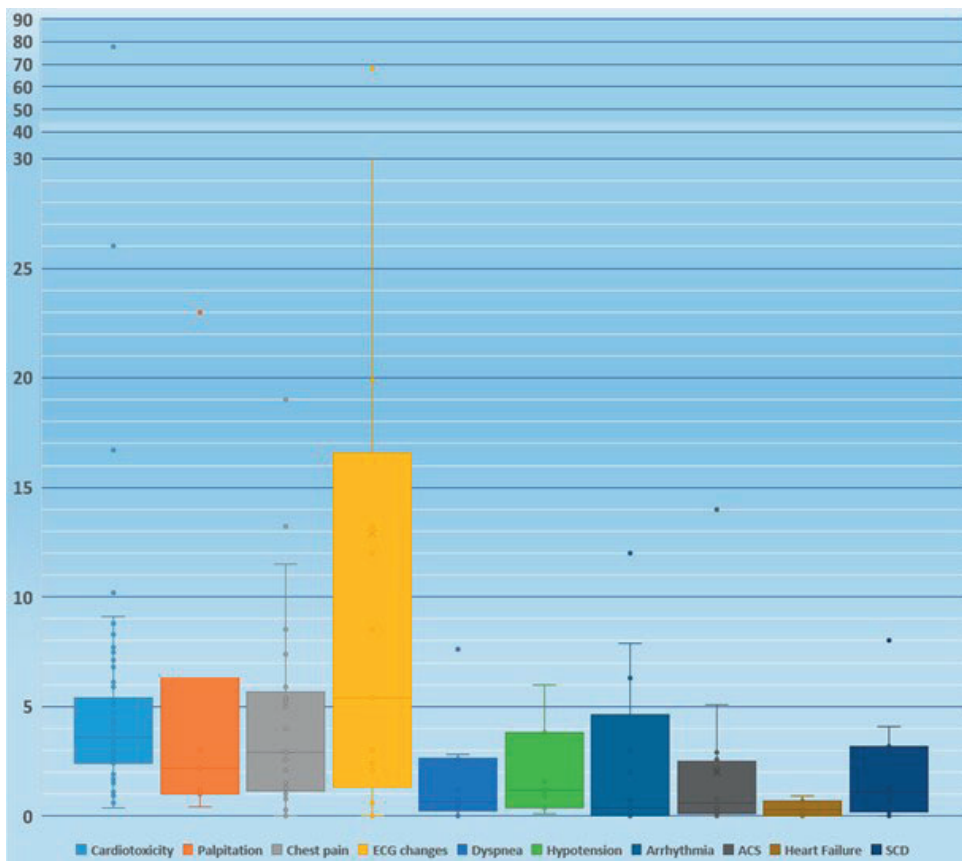


Fig. 1. Distribution of reported 5-FU cardiotoxicity (ACS – Acute Coronary Syndrome; SCD – Sudden Cardiac Death)

symptom (0-18.6%), often with concomitant ischemic changes in the electrocardiogram. Palpitations (0-23.1%), dyspnoea (0-7.6%) and hypotension (0-6%) are also frequent symptoms, while development of symptomatic heart failure (0-0.7%), events as myocardial infarction, cardiogenic shock and cardiac arrest (0-2%) are rare [2]. In a retrospective analysis of capecitabine-related cardiotoxicity the most frequently observed cardiac event was myocardial ischaemia (2.9%), followed by arrhythmias (2.0%, including atrial fibrillation), chest pain (0.8%) and heart failure (0.4%) [18].

New ECG changes are frequently reported (0-68%, with a mean of 12.9%), most commonly including ST-segment deviation and QT interval prolongation. Arrhythmias were present in 0-21% of the cases and included sinus tachycardia, atrial fibrillation, sinus bradycardia and ventricular fibrillation [2, 19]. Continuous electrocardiographic (Holter) monitoring in patients treated with 5-FU demonstrated increased number and complexity of ventricular premature complexes and 22% of the patients had at least one episode of complex ventricular arrhythmia [20]. Myocarditis is infrequently cited in the literature as a manifestation of 5-FU cardiotoxicity. Many cases are diagnosed based on ECG changes, troponin elevation, angina, and symptomatic heart failure, which can coincide with vasospasm or endothelial dysfunction [21]. As cardiac magnetic resonance becomes more integrated into the diagnostic process for cardiovascular diseases, it may reveal the true incidence of 5-FU-induced myocarditis. Sudden cardiac death has been reported in up to 8% of cases in one study [19], although most studies report an incidence ranging from 0.2% to 1.3%.

RISK FACTORS

Risk factors for cardiotoxicity in patients treated with 5-FU or capecitabine are incompletely defined. Many patient- and treatment-related factors have emerged as potential targets for reducing cardiotoxicity, but the results are conflicting. The most well-recognized risk factor is underlying ischaemic or structural heart disease [22]. Of note is the fact that in most studies cases of cardiotoxicity occur in patients who do not have pre-existing cardiovascular disease. In a retrospective analysis, Saif et al. found that among 377 patients diagnosed with fluoropyrimidine-induced cardiotoxicity, only 14% had a prior history of cardiac disease [3]. In another series involving colorectal cancer patients treated with 5-FU infusions, 9 out of 106 developed cardiotoxicity, despite only one having significant pre-existing cardiovascular disease. Conversely, none of the 7 patients with significant cardiovascular disease experienced cardiotoxicity [24]. Although the SCORE2 scale has been proposed as a tool for identifying pa-

tients at risk of developing fluoropyrimidine-induced cardiotoxicity [25], traditional risk factors for ischemic heart disease – such as hypertension, dyslipidemia, diabetes, smoking, and family history – have not shown a discernible correlation with the occurrence of 5-FU cardiotoxicity [19, 20, 21]. Further research is warranted to better understand the risk factors underlying 5-FU-induced cardiotoxicity and to assess their clinical relevance.

Most of the studies exploring different schedules of administration indicate that infusional regimens are associated with greater risk compared to bolus application [26, 28]. Patients receiving continuous infusion 5-FU therapy had a reported incidence of cardiotoxicity from 6 to 18%. In contrast, the rate of cardiotoxicity was 2%-5% among patients receiving 5-FU in bolus form [28]. In a prospective study evaluating different administration schedules, cardiotoxicity was more common in patients receiving continuous 5-FU infusion (13 out of 205; 6.3%) compared to those on bolus regimens or oral capecitabine (7 out of 317; 2.2%) [26]. 5-FU has a half life of 15-20 min and the data suggests that continuous infusions would allow for drug accumulation or continual exposure with a greater propensity for cardiotoxicity that might not occur with bolus administration [17, 29]. No strong correlation was found between the development of cardiotoxicity and the amount of 5-FU administered [22]. Studies have shown that plasma concentrations of 5-FU in patients experiencing cardiotoxicity following administration do not significantly differ from those observed in patients without adverse events [30].

Although many drugs used in combination with 5-FU have cardiotoxic effects, there is relatively limited data indicating a higher risk of developing cardiotoxicity with combination regimens. An increase in cardiotoxicity cases has been reported when 5-FU is combined with leucovorin, docetaxel, cisplatin and radiotherapy [26, 27, 29, 31].

DIAGNOSTIC TOOLS

With the emergence of cardio-oncology as a dedicated field, much of the current research has focused on identifying diagnostic markers capable of detecting early cardiac involvement and distinguishing it from other causes of chest pain in oncology patients. A study by Jensen et al. investigated the changes in N-terminal pro b-type natriuretic peptide (NT-proBNP), troponin and lactic acid in patients receiving the FOLFOX4 regimen (infusional 5-FU, folinic acid and oxaliplatin) for colorectal cancer. It reported a significant increase in NT-proBNP levels from baseline and during 5-FU therapy. Furthermore patients experiencing cardiotoxicity had notably higher NT-proBNP levels

compared to those without cardiotoxicity. The increase in NT-proBNP induced by FU therapy was significantly more pronounced in female patients. NT-proBNP levels were lower in patients with bolus application of FU. Plasma lactic acid levels also showed a significant rise from base levels during therapy. NT-proBNP levels returned to normal ranges after treatment in both patients groups (patients with developed cardiotoxicity and asymptomatic patients) [24].

In the context of 5-FU cardiotoxicity, troponin measurements can serve as an important tool for detecting subclinical cardiac effects and evaluating acute cardiac events. In a study using troponin as a marker of cardiotoxicity, a slight elevation of troponin was detected in 57% of the patients when the cut-off value was 0,04 µg and in 14% when it was 0,3 µg. All of the patients who had elevated troponin levels also had at least one episode of chest pain or palpitations [32].

Cardiac imaging, including echocardiography, is essential for detecting, characterizing, and monitoring cardiotoxicity associated with 5-FU and capecitabine [33]. In the 2022 ESC Guidelines on cardio-oncology, a baseline transthoracic echocardiography is recommended for patients with a history of symptomatic cardiovascular disease to assess for pre-existing regional wall motion abnormalities or left ventricular dysfunction. This approach is particularly relevant for patients with pre-existing cardiac conditions undergoing 5-FU therapy [25]. Several case series have reported patients developing severe, diffuse left ventricular hypokinesia during symptomatic episodes associated with fluoropyrimidine therapy. In most cases where significant coronary artery disease (CAD) was not evident on angiography, left ventricular ejection fraction returned to normal within three months [34, 35, 36]. Right-ventricular dysfunction is rarely reported as a complication of fluorouracil therapy. In a prospective cohort of 23 patients, Bilir et al.

found no significant pre- to post-treatment change in RV wall thickness, tricuspid annular plane systolic excursion (TAPSE), or the RV Tei index [37].

In specific clinical scenarios involving suspected 5-FU cardiotoxicity, cardiac magnetic resonance imaging (CMR) can provide valuable insights, even though it's less readily available than echocardiography. CMR can detect myocardial edema, potentially indicating 5-FU-induced myocarditis, and late gadolinium enhancement can distinguish between ischemic and non-ischemic causes of cardiac injury. Beyond these diagnostic clues, CMR enables detailed assessment of pericardial disease and precise measurement of left ventricular function (left ventricular systolic function, volumes, and mass) as well as detection of subtle regional wall motion abnormalities, assisting in the differential diagnosis of ischemia, myocarditis, and cardiomyopathy [38].

MANAGEMENT STRATEGIES

Cardiotoxicity associated with 5-fluorouracil (5-FU) can be potentially fatal, thus, the standard clinical approach upon symptom onset is immediate discontinuation of the drug. This recommendation is supported by current guidelines and reflects the available clinical evidence [25]. Symptomatic management commonly involves the use of nitroglycerin, calcium channel blockers, and beta-blockers, with reported effectiveness in approximately 69% of cases [3, 22]. However, most of the evidence stems from case reports and small case series, leading to variability in reported efficacy. In a review of 134 cases of chemotherapy-induced cardiotoxicity, 33 patients (25%) exhibited severe left ventricular dysfunction, 28 of whom had no underlying coronary artery disease. Among these, treatment with nitroglycerin and calcium channel blockers resulted in clinical

Table 1. Proposed strategy for monitoring cardiovascular toxicity in patients receiving 5-FU

	Baseline	Before every cycle	At 3 months	At 6 months	At 12 months	At the onset of symptoms
ECG	+	+	+	+	+	+
Blood pressure	+	+	+	+	+	+
Echocardiography	+	-	+ (in high risk population)	+	+	+
SCORE2	+	-	-	-	-	-
Lipid profile/HbA1c	+	-	-	+	+	-
Troponin	+	-	+ (in high risk population)	+	+	+
Natriuretic peptide	+ (in high risk population)	-	-	+	+	+
CAD screening	+/- (in high risk population)	-	-	-	-	+
CMR	-	-	-	-	-	+ (if CAD screen is negative)

improvement in 90% of cases [39]. Jensen et al. report sublingual nitroglycerin as an effective treatment for anginal symptoms following 5-FU infusion in 88% of the patients [28].

Prophylactic strategies with using nitrates, calcium channel blockers and ACE inhibitors before initiating 5-FU therapy have been studied [10, 40]. In a prospective study of 58 patients, it was reported that ECG signs of ischemia occurred as frequently in patients receiving calcium channel blockers during 5-FU therapy as in a control group that did not receive calcium channel blockers [40]. The use of nitroglycerin also had no discernable effect in preventing symptomatic cardiotoxicity. Currently prophylactic use of antiplatelet agents, nitroglycerin, or calcium-channel blockers are not recommended by standard guidelines [25]. Initiating ACE inhibitor/angiotensin receptor blocker, statin and beta-blocker depends on the baseline cardiovascular toxicity risk assessment and the underlying cardio-vascular risk factors of the patient [32].

In earlier studies rechallenge with fluoropyrimidines after initial cardiovascular side effects was usually discouraged. Data suggests that the possibility of recurrence of the symptoms is 80% with a death rate of 13% [3, 15]. If alternative regimens are inadequate and continuation of 5-FU is advisable clinicians and patients should undergo a detailed and informed discussion about the potential risks and benefits of such a strategy. Newer studies suggest that with appropriate precautions, including treating the patients with cardioprotective medication such as calcium channel blockers and nitrates as well as careful cardiac monitoring could help mitigate the risk [17, 35]. Additionally using a bolus regimen has consistently been proven to be safer than a continuous infusion and should be the method of choice [17, 29, 34].

Before any change in therapy a cardio-oncology team should define a suitable prevention and surveillance plan for early identification and appropriate management of further 5-FU cardiotoxicity [33]. Improved monitoring through remote devices and long-term surveillance programs will aid in early detection [41]. Fostering collaboration among multidisciplinary teams and promoting educational initiatives are essential for enhancing awareness and optimizing patient care in the context of 5-FU cardiotoxicity.

CONCLUSION

5-FU and capecitabine, while crucial antineoplastic agents, are associated with a risk of cardiotoxicity that can significantly impact patient outcomes. The mechanisms underlying 5-FU cardiotoxicity are complex and multifactorial, involving vasoconstriction, endothelial dysfunction, and direct myocardial damage. While the

incidence of cardiotoxicity varies, early recognition, careful monitoring, and prompt management are essential to minimize adverse cardiac events. Cardiac biomarkers and imaging techniques play a vital role in risk stratification and detection of cardiac dysfunction. Current management strategies primarily involve discontinuation of 5-FU and symptomatic treatment with vasodilators and beta-blockers. Continuing promoting and fostering multidisciplinary collaboration are essential to enhance awareness and optimize patient care in the context of 5-FU cardiotoxicity.

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