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Fluoropyrimidine-Induced Cardiotoxicity: Manifestations, Mechanisms, and Management

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Abstract Fluoropyrimidines—5-fluorouracil (5-FU) and capecitabine—have been implicated as cardiotoxic chemotherapy agents. This rare, albeit potentially serious toxicity has been described in nearly four decades of case reports, case series, and in vitro modeling; however, there is a paucity in clinical trials and prospective analyses focused on cardioprotective strategies and cardiotoxic surveillance of these agents. While much attention has focused on the well-known cardiac toxicity of anthracyclines and monoclonal antibody agents such as trastuzumab, fluoropyrimidines remain one of the most common causes of chemotherapy-associated cardiotoxicity. The introduction of capecitabine, an oral prodrug of 5-FU, has made the treatment of solid tumors more convenient along with a subsequent rise in documented cardiotoxic cases. This review discusses the symptomatology, clinical manifestations, and proposed molecular mechanisms that attempt to describe the heterogeneous spectrum of fluoropyrimidine-induced cardiotoxicity. Four case examples showcasing the varied manifestations of cardiotoxicity are presented. Finally, several proposed management strategies for cardiotoxicity and post-hospital course precautions are discussed.

This article is part of the Topical Collection on *Cardio-oncology*

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Introduction

Fluoropyrimidine chemotherapy, including 5-fluorouracil (5-FU) and the oral prodrug, capecitabine, has remained the standard of care over four decades for many solid organ tumors [1, 2]. 5-FU is used in various adenocarcinomas of the gastrointestinal tract ranging from esophagus to anus, as well as other adenocarcinomas and squamous cell carcinomas of the bladder, breast, head, and neck. Colorectal cancer is the second leading cause of cancer-related deaths of men and women combined in the USA and is expected to cause 49,700 deaths during 2015 [3]. For those with stage III and greater colorectal carcinoma, fluoropyrimidine-based chemotherapy is considered the standard of care.

Common side effects of fluoropyrimidines, similar to that of other established chemotherapies, include nausea, emesis, diarrhea, mucositis, alopecia, and the more serious complications of myelosuppression and hand-foot syndrome (acral erythema). With the advent of the conveniently dosed oral prodrug capecitabine, cases of cardiotoxicity have become more commonly noted in the literature.

The History of Fluoropyrimidines

Heidelberger et al.'s research on 5-FU-induced tumor cell death in 1957 was a groundbreaking discovery for oncology [4]. Through the use of a bacterial model, it was found that (1) tumor cells utilized high rates of uracil, and (2) the fluorine-

substituted pyrimidine, 5-FU, possessed an unusual anti-tumor effect causing thymine-less cell death [5].

Since its introduction, 5-FU has become one of the most commonly used chemotherapy agents. Fluorouracil, a pyrimidine analogue, inhibits thymidylate synthase, an enzyme involved in the synthesis of thymidine and DNA replication [6]. Functioning as an S-phase anti-metabolite, 5-FU is used to treat numerous rapidly dividing solid tumors of glandular and squamous origin. A groundbreaking study found that in stage III colorectal cancer (regional lymph node invasion; disease is detected at a point where surgical cure is possible, but risk of recurrence remains high), the adjuvant use of 5-FU and levamisole following surgical resection had a staggering 41 % reduction in cancer recurrence over a 3-year period [7].

In 2005, capecitabine, the oral prodrug of 5-FU, received FDA approval for stage III colon cancer as a single-agent adjuvant therapy in those patients who had previous resection of the primary tumor. Approval was based on non-inferiority in disease-free survival compared to 5-FU plus leucovorin [8, 9]. As a prodrug, capecitabine is converted into 5-FU through a series of sequential steps. Initially, it is metabolized into 5′-deoxy-5-fluorocytidine in the liver; peripherally, 5′-deoxy-5-fluorocytidine is then converted to 5-FU in a two-enzyme series. These enzymes (cytidine deaminase and thymidine phosphorylase) are over-expressed in tumor cells, preferentially targeting the tumor over normally dividing tissue [10].

Case Examples of Fluoropyrimidine Cardiotoxicity

Case Example 1

A 48-year-old male with history of metastatic rectal adenocarcinoma, initiated on oral capecitabine 1500 mg twice daily 2 days prior to presentation, was admitted to the hospital for urgent incision and drainage of a perirectal abscess. The patient had no cardiac disease history. On post-operative day 1, the patient endorsed severe, substernal non-radiating chest tightness. Sublingual nitroglycerin offered only mild relief. An initial ECG was unrevealing for acute ischemia, but the first troponin I was elevated at 7.07 ng/mL. The patient received loading doses of aspirin 325 mg, clopidogrel 600 mg, and atorvastatin 80 mg and started on treatment doses of enoxaparin for non-ST elevation myocardial infarction (NSTEMI). The cardiac biomarkers reached a peak CK-MB of 109 ng/mL and troponin I of 67 ng/mL. Repeat ECG revealed ST elevations in leads II, III and aVF as well as tall R waves and upright T waves in V1–V2, consistent with inferoposterior STEMI (Fig. 1). The patient underwent cardiac catheterization, which showed no angiographic evidence for occlusive coronary artery disease (CAD) (Fig. 2). Transthoracic echocardiogram (TTE) showed normal left ventricular function with no wall motion abnormalities. Given the substantially negative workup, the patient's clinical presentation was thought to be secondary to cardiotoxicity from capecitabine. The patient's cardiac biomarkers eventually downtrended, and the patient had no further episodes of chest pain or anginal equivalent for the remainder of the hospitalization. Upon discharge, capecitabine was discontinued and switched to single-agent chemotherapy with oxaliplatin.

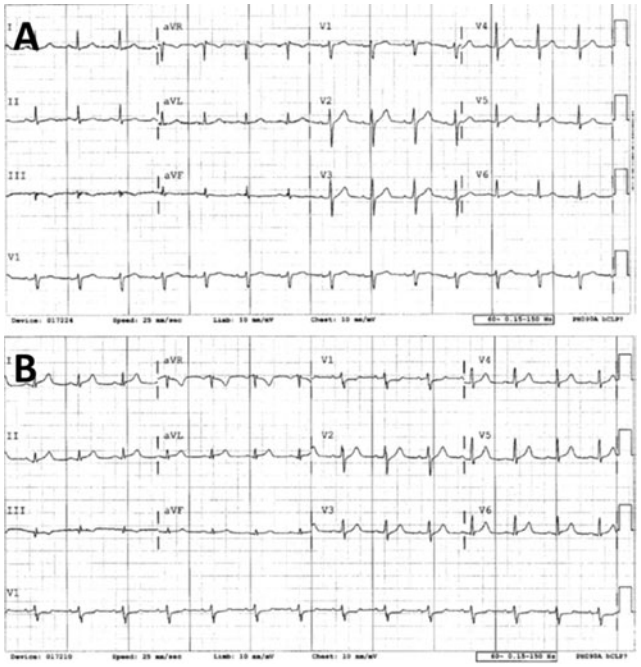


Fig. 1 Twelve-lead ECG of case example 1. **a** ECG on admission showing sinus rhythm with non-specific T wave flattening in leads III and aVF. **b** ECG during episode of chest pain showing ST segment elevations in the inferolateral limb leads. Prominent R waves with mild ST segment depressions with upright waves in leads V1–V3 are also seen, concerning for inferoposterolateral acute injury

Case Example 2

A 66-year-old male presented to the emergency department for worsening chest pain over a 2-day duration. He had a cardiac catheterization2 years prior for anginal chest pain that showed no evidence of CAD; microvascular CAD was a suspected etiology. His oncologic history was significant for poorly differentiated duodenal adenocarcinoma and was status-post pancreaticoduodenectomy (Whipple procedure). Recent abdominal imaging had revealed progression of disease, and the patient had subsequently been started on 5-FU. Forty-eight hours after the first infusion, he developed substernal chest pain not associated with exertion. In the emergency department, lab markers indicated a mildly elevated troponin I (0.14 ng/mL) and an ECG with T wave inversions in the inferolateral leads (Fig. 3). TTE showed normal wall motion and systolic function. Aspirin and sublingual nitroglycerin were administered to the patient with subsequent resolution of chest pain. Multidisciplinary discussions were held

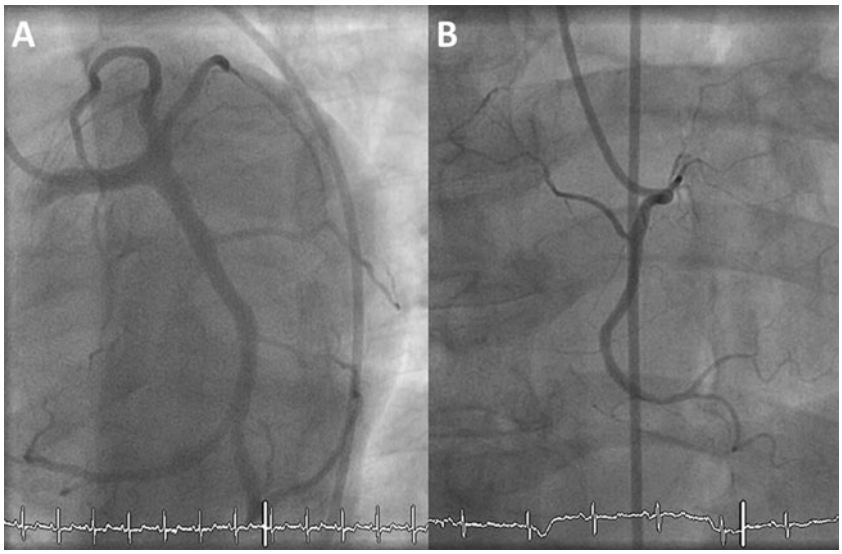


Fig. 2 Coronary angiography of case example 1 demonstrating no significant angiographic evidence of coronary artery disease. **a** Left anterior oblique caudal projection of the left coronary artery. **b** Right anterior oblique projection of the right coronary artery

between oncology and cardiology, and it was concluded that the patient's clinical presentation was likely consistent with coronary vasospasm due to 5-FU infusion. The patient remained stable with resolution of troponin elevation and ECG changes, and he was discharged the following day. The decision was made to not re-challenge the patient with 5-FU and was instead started on single-agent gemcitabine.

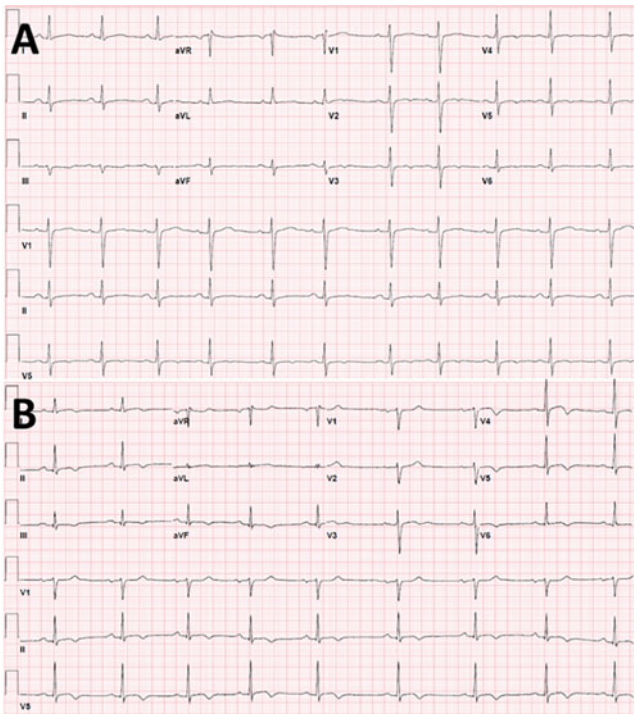


Fig. 3 Serial 12-lead ECGs during hospital course of case example 2. **a** Baseline ECG prior to presentation, showing sinus rhythm with non-specific T wave flattening noted in inferolateral leads. **b** Twelve-lead ECG at time of presentation with dynamic T wave inversions in leads I, II, III, aVF, and V3–V6

Case Example 3

A 60-year-old male with a history of paroxysmal atrial fibrillation and recently diagnosed metastatic colorectal cancer status-post hemicolectomy presented to the emergency room with worsening heart palpitations and epigastric pain for a 3-day duration. He had recently started oxaliplatin and oral capecitabine at 2220 mg twice daily (1000 mg/m^2) 7 days prior to presentation. The patient normally was able to jog short distances but began noticing worsening episodes of epigastric pain with exertion following the start of capecitabine. On the day of admission, while at rest, the patient felt symptoms consistent with atrial fibrillation and severe epigastric pain. Emergency medical services were called, and a 12-lead prehospital ECG showed atrial fibrillation with inferolateral ST elevations (Fig. 4). Nitroglycerin in the emergency room provided mild relief, and the patient was taken immediately to the cardiac catheterization lab. Coronary angiography findings revealed no significant CAD (Fig. 5) with noted normal left ventricular systolic function on angiography. Left ventricular end diastolic pressure was unremarkable at 10 mm Hg. Serial troponin I biomarkers during the patient's hospital course were negative. The patient's ECG findings gradually resolved, and the patient was discharged without symptoms. The patient's capecitabine was subsequently discontinued, and the patient was continued on oxaliplatin and initiated on irinotecan without further symptoms of cardiotoxicity.

Case Example 4

A 65-year-old male with a history of hypertension, peripheral arterial disease, and newly diagnosed metastatic gastric cancer complicated by pulmonary embolism was admitted for palliative chemotherapy with a FOLFOX

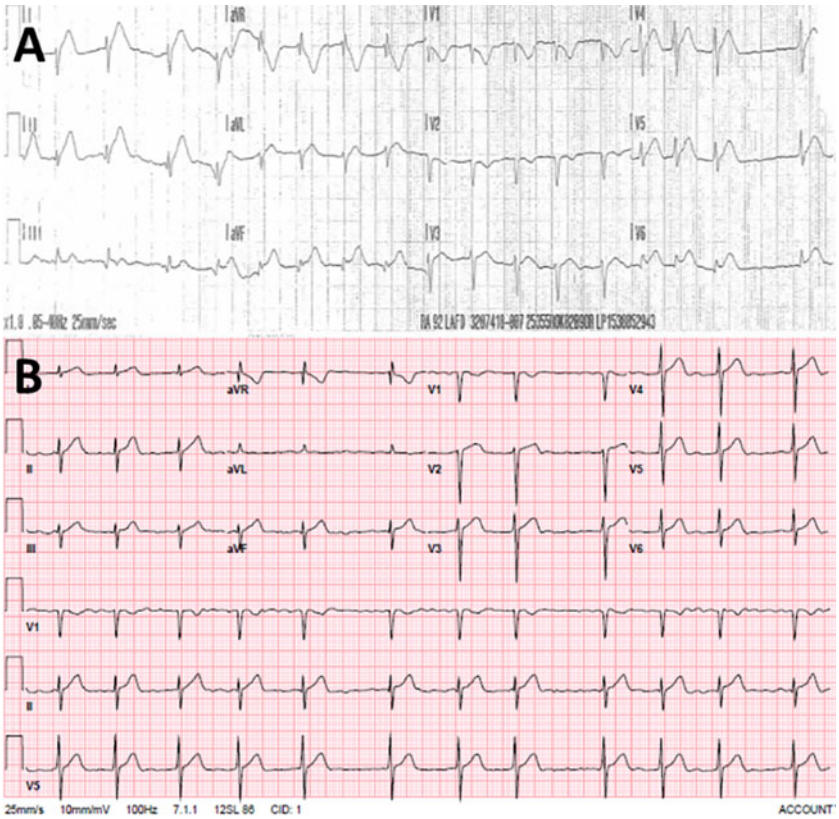


Fig. 4 Serial 12-lead ECGs during hospital course of case example 3. **a** Pre-hospital ECG demonstrating atrial fibrillation with rapid ventricular response at 104 bpm. Right-axis deviation is noted with ST segment elevations in the inferolateral leads. **b** ECG prior to hospital discharge demonstrating atrial fibrillation and early repolarization pattern, with resolution of the convex appearing ST segment elevations noted on the prior ECG

regimen (leucovorin, 5-FU, oxaliplatin). 5-FU was started at a 400 mg/m^2 intravenous bolus followed by 600 mg/m^2 as a 22-h continuous infusion. Within 15–20 min of the infusion, the patient developed central chest pressure with diaphoresis and dyspnea. An ECG showed sinus tachycardia with non-specific T wave flattening in the lateral precordial leads. The infusion was stopped, and he received sublingual nitroglycerin with subsequent resolution of chest pain 3 h later. Serial troponin I biomarkers peaked at 16.08 ng/mL. TTE was notable for a newly depressed left ventricular ejection fraction of 30–35 %, with wall motion abnormalities in the distribution of the left anterior descending artery. This was new compared to a prior unremarkable echocardiogram performed 1 month earlier. In multidisciplinary discussions between cardiology and oncology, the patient had a poor prognosis of approximately less than 3 months given the nature of his advanced metastatic disease, and the decision was made to cease 5-FU therapy and medically manage the patient's presumed NSTEMI in lieu of invasive angiography. The patient

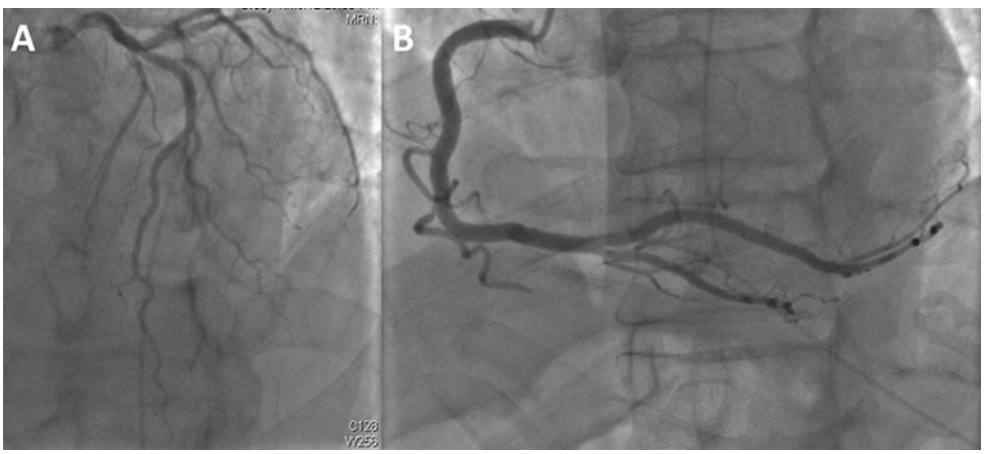


Fig. 5 Coronary angiography of case example 3 demonstrating no significant angiographic evidence of coronary artery disease. **a** Left anterior oblique cranial projection of the left coronary artery. **b** Left anterior oblique projection of the right coronary artery

remained chest pain free and was discharged to follow-up with oncology for consideration of alternative palliative options.

Epidemiology of Fluoropyrimidine Cardiotoxicity

Four decades of clinical use has provided sufficient data on the multitude of fluoropyrimidine toxicities. Most are generally manageable and reversible with reduced dosing or temporary discontinuation [11, 12]. Cardiotoxicity, although rare, is a potentially lethal complication of fluoropyrimidine use. While less commonly discussed in the literature, fluoropyrimidines, along with anthracyclines, are considered one of the chemotherapeutic agents with the most cardiotoxic potential [13, 14]. The incidence of fluoropyrimidine-induced cardiotoxicity ranges widely from 1 to 19 % with a 0–13 % mortality rate [15, 16, 17••, 18]. The majority of cases present with anginal chest pain, which comprises 40–60 % of all initial cardiotoxic presentations [8, 19–22]. A systematic review of fluoropyrimidine-induced cardiotoxicity by Polk et al. found that, in larger studies, the incidence of 5-FU cardiotoxicity may be lower (1.2–4.3 %) than capecitabine-induced cardiotoxicity (3–35 %) [17••]. However, other reports, including a large meta-analysis on breast and colorectal cancer patients receiving 5-FU or capecitabine, have revealed similar low rates of cardiotoxicity with either agent [8].

Risk Factors for Fluoropyrimidine Cardiotoxicity

The wide incidence range of cardiotoxicity reported in the literature may be related to the frequency of administration, concomitant polychemotherapy, radiotherapy exposure, and coronary risk factors that may predispose individuals to cardiac symptoms. Identifying these potential risk factors prior to initiating chemotherapy is important, as controlling for these may decrease the risk of cardiotoxicity.

Frequency of Administration

The incidence of 5-FU cardiotoxicity appears to differ significantly between bolus versus continuous infusion. Continuous infusion over 4 to 5 days has traditionally been the preferred delivery method given its increased efficacy and lower toxicity rates. Recent studies have demonstrated an increased incidence of cardiotoxicity with continuous 5-FU infusion compared to bolus infusion, suggesting that prolonged exposure of 5-FU is a cardiotoxic risk factor [18, 21, 23–25]. A bolus regimen, termed de Gramont's regimen, is a combination of high-dose leucovorin and 5-FU with biweekly bolus infusions. It has been associated with a lower incidence of cardiotoxicity compared to more prolonged infusion regimens [18]. However, this finding has not been reproduced. Of 102 patients receiving either 5-FU bolus or continuous infusion, Wacker et al. noted a trend toward increased anginal symptoms in the bolus versus continuous infusion group; of note, this study was not powered to study this difference as a primary endpoint with only 20 % of the patient population receiving a bolus infusion [15]. Oztop et al. noted prolonged QTc with this regimen, but a control group was not used in this study and the clinical implications of these findings are unclear [26].

Polychemotherapy

Numerous other chemotherapy agents are often administered with 5-FU. These include—but are not limited to—leucovirin, anthracyclines, oxaliplatin, cisplatin, cyclophosphamide, mitomycin, etoposide, interferon, paclitaxel, methotrexate, vincristine, gemcitabine, and irinotecan. Polychemotherapy is thought to be a potential risk factor for fluoropyrimidine-induced cardiotoxicity [27]. It is most commonly reported with platinum-based compounds (e.g., cisplatin, carboplatin). This association has been noted in various chemotherapy regimens for gastrointestinal, breast, head, and neck cancers and described with both 5-FU and capecitabine [23, 28–32]. Moreover, case reports have reported cardiotoxic side effects from cisplatin monotherapy, suggesting a potential multiplicative effect of giving both therapies [33–35].

Radiation Therapy

Chest wall radiation and the risk of cardiac disease are a known association, which has been mostly studied in pediatric cancer survivors of Hodgkin's lymphoma and early-stage breast cancer patients with prior radiation exposure. High-risk features for developing cardiac disease are doses greater than 30–35 Gy, early age of exposure, and modifiable coronary risk factors including diabetes, hypertension, hyperlipidemia, obesity, and smoking [36]. Radiation therapy in association with anthracyclines is also a known risk factor for accelerated manifestations of cardiovascular disease [37]. However, there is limited prospective data for those patients receiving fluoropyrimidine treatment and concomitant radiation therapy to the chest wall/mediastinum. One such study by Meyer et al. demonstrated no increased cardiac risk in those patients who had a history of chest wall irradiation [27]. More recent studies, however, have revealed that prior or concurrent chest wall radiation is a significant risk factor for cardiotoxicity seen with both 5-FU and capecitabine [23, 38]. Thus, the clinician should be aware of the possible increased risk of cardiotoxic manifestations in patients undergoing fluoropyrimidine therapy with a history of prior/active chest radiotherapy.

Cardiac Disease and Associated Risk Factors

It has been proposed that underlying cardiac disease is a risk factor for cardiotoxicity in those receiving fluoropyrimidine treatment. This relationship was described over three decades ago with Labianca et al. reporting a 4-fold increase (4.5 to 1.1 %, $n = 1083$) in cardiac events (chiefly anginal chest pain and ACS) following 5-FU exposure in patients with a cardiac history compared to those without a known cardiac history [39]. A similar study also reported a 4-fold increase (1.6 to 7.6 %, $n = 367$) of cardiac events following 5-FU exposure in underlying heart disease patients [22]. Smoking—in association with fluoropyrimidine exposure—appears to be a potential risk factor whereas a family history of heart disease, hypertension, and underlying diabetes mellitus does not [17••, 21, 27, 29]. Meyer et al. reported a 6.8-fold increased relative risk for cardiotoxicity in ischemic heart disease patients whereas no associated toxicity was seen in patients with preexisting cardiomyopathy or congestive heart failure [27]. Similar outcomes have been described in patients with structural heart disease, along with an increased incidence of silent ischemic ECG changes during 5-FU infusion [20, 40, 41]. These correlations have not been supported in all studies, however [23, 27, 28]. Outcome discrepancies may be related to confounders such as age, smoking history, and other cardiac risk factors, along with low event rates resulting in subgroup analysis of limited value. Some studies did not include objective evidence of ischemia in their criteria, which also poses potential for inconsistent results. Careful and precise delineation of clinical presentations with objective findings (i.e., cardiac biomarkers, ECG findings, non-invasive/invasive diagnostic findings) in association with fluoropyrimidine administration is warranted for future studies.

Manifestations of Cardiotoxicity

The most common fluoropyrimidine-induced cardiotoxic manifestation is anginal chest pain [15, 17••, 18–20, 27]. Other commonly reported symptoms attributed to cardiotoxicity include heart palpitations, dyspnea, blood pressure variations (hypertension or hypotension), and malaise [17••, 42, 43], while less common, myocardial infarction, myopericarditis, congestive heart failure, and reversible cardiomyopathy have been reported. Severe manifestations of fluoropyrimidine-induced cardiotoxicity have been reported in case reports, including tachyarrhythmias (both supraventricular and ventricular), coronary dissection, cardiogenic shock requiring intra-aortic balloon pump and extracorporeal membrane oxygenation (ECMO) support, and sudden cardiac death [44–46]. Polk et al.'s systematic review of fluoropyrimidine toxicities reported an incidence of chest pain up to 18 % while severe clinical event rates occurred only 0–2 % of the time [17••]. Of note, the incidence of cardiotoxicity is similar between capecitabine and 5-FU, suggesting a common downstream toxic pathway, which is further discussed below [8, 38].

Aside from symptomatic cardiotoxicity, some patients may develop silent cardiac ischemia. Rezkalla et al. was the first to prospectively identify an association between 5-FU infusion and ischemic ECG changes in otherwise asymptomatic patients who underwent ambulatory rhythm monitoring [41]. This report raised the possibility of a clinically silent but cardiotoxic effect (especially more common in those patients with CAD), making some providers more cautious during regimented 5-FU infusions. Other prospective and retrospective analyses have reported silent ischemic ECG changes ranging from 4 to 88 % during 5-FU infusions [22, 32, 47]. The wide range suggests that other predisposing factors such as CAD—as reported by Rezkalla et al.—may increase the risk of silent ischemia. Along with ischemic ECG changes, arrhythmias, QTc and PR prolongation, and less commonly torsades de pointes have been described [15, 17••, 41]. Both silent and symptomatic ECG changes have also been described in patients receiving capecitabine [38, 48•, 49–51].

Proposed Mechanisms of Fluoropyrimidine-Induced Cardiotoxicity

Although not well understood, there are several proposed mechanisms for fluoropyrimidine-induced cardiotoxicity. These mechanisms have been elucidated through a compilation of in vitro analyses, animal modeling, and small clinical studies. It should be noted that the active metabolites of capecitabine, including 5-FU, are probably responsible for similar toxic mechanisms.

Coronary artery vasospasm is thought to be the predominant manifestation of 5-FU-related myocardial ischemia. This has been observed on coronary angiography [43, 52]. Mosseri et al. demonstrated endothelium-independent vasoconstriction with incremental doses of 5-FU on rabbit aortic rings. Furthermore, they found that protein kinase C, a subcellular mediator of vascular smooth muscle tone, was directly responsible for 5-FU-induced coronary vasospasm [53]. These findings suggest that in vitro 5-FU can directly cause vasospasm, independent of a toxic effect on the endothelium.

Fluoropyrimidines also appear to have a direct cellular toxicity. As reported by Eskilsson et al., the use of a prophylactic calcium channel blockers to prevent vasospasm has not been successful [54]. This has led to the development of other non-vasospasm-mediated mechanisms including a direct toxic effect of 5-FU on the coronary endothelium [55–57]. Endothelial injury may cause microthrombotic occlusions undetectable by coronary

angiography. This has been confirmed by scanning electron microscopy, and experimental evidence suggests that the use of anti-coagulation products may partially mitigate this toxic mechanism [58, 59]. Another mechanism of causing cytotoxic endothelial dysfunction is thought to be mediated by free oxygen radicals [60••]. An in vitro study of probucol, an anti-hyperlipidemic drug and antioxidant, has shown that the toxic effect of 5-FU, as demonstrated on scanning electron microscopy, can partially protect endothelial cells from damage [61].

The degradative pathway of 5-FU appears to have a potential toxic mechanism. Muneoka et al. reported a patient with a history of 5-FU-induced cardiotoxicity who was successfully treated with the prodrug S-1, an oral fluoropyrimidine that lacks alpha-fluoro-beta-alanine (FBAL) as a metabolite [62]. The patient experienced no recurrence of cardiac symptomatology while receiving the prodrug suggesting a possible role for FBAL in cardiotoxicity. A downstream metabolite of FBAL, known as fluoroacetate, is a degradation compound created from prolonged storage of 5-FU in alkaline conditions and has been shown to be directly toxic to cardiomyocytes [63].

Histopathological studies of fluoropyrimidine-induced cardiotoxicity in humans are lacking likely owing to the difficulty of obtaining human myocardial biopsies. Instead, animal models have shed light on histologic changes following a cardiotoxic event. A study involving rat hearts demonstrated multifocal interstitial hemorrhages and myofiber necrosis with inflammatory reactions including perivascular involvement, pericarditis, and valvular inflammation. Vascular abnormalities were also seen, which included vessel dilation, ruptured vascular walls, and microthrombosis. In a rabbit study, high intravenous dosing also resulted in ventricular hemorrhagic infarction and proximal coronary vasospasm; lower doses given repeatedly caused the development of left ventricular hypertrophy from reticular interstitial fibrosis with edema, fibrous concentric thickening of the intima of small distal coronary arteries, and disseminated foci of necrotic myocardial cells. However, it is unknown whether these differences were species specific and/or dose related [64••].

Diagnosis and Management of Fluoropyrimidine Cardiotoxicity

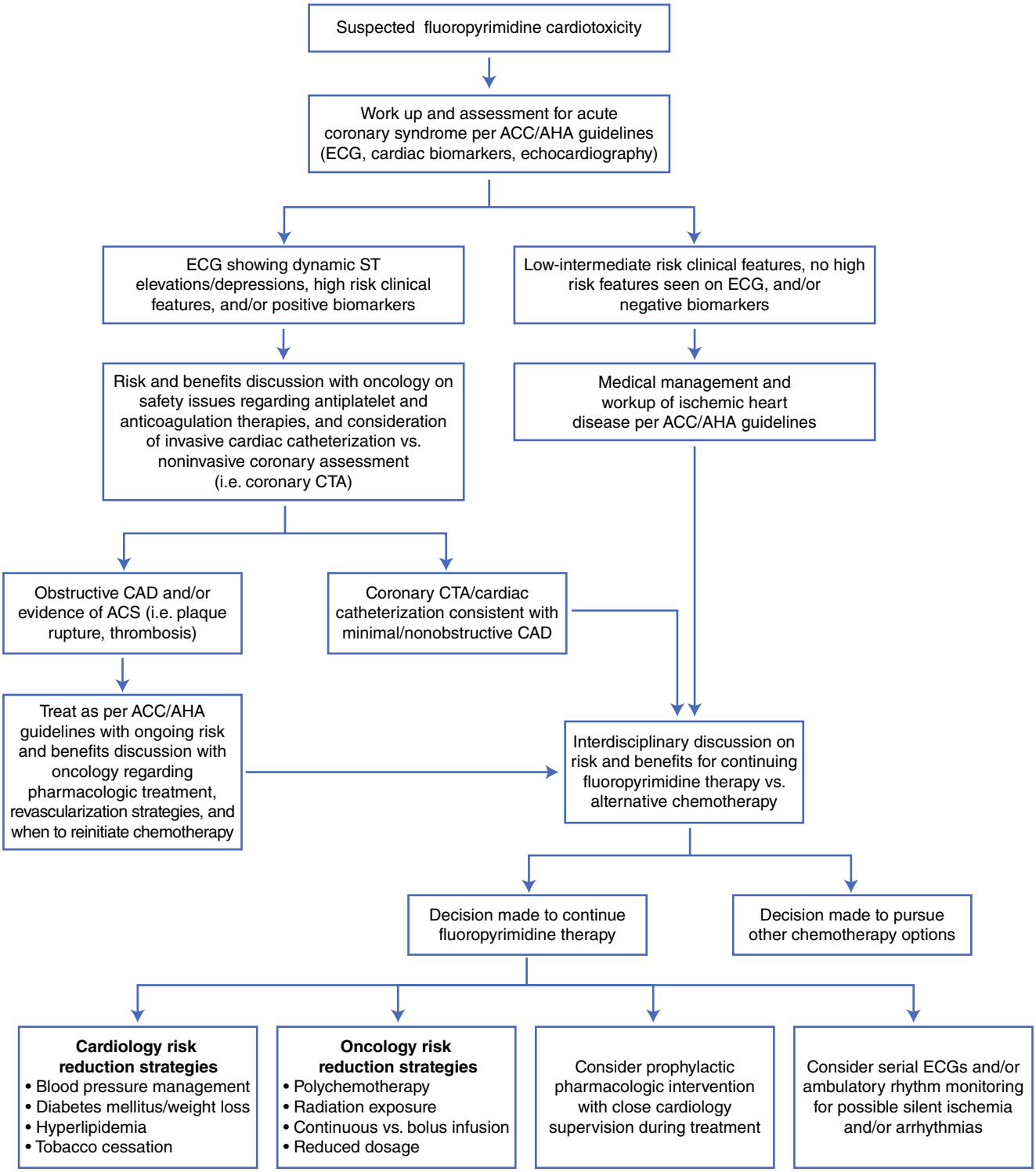
The widespread use of both intravenous and oral fluoropyrimidines translates to a likely underreported rate of cardiotoxic events [15]. In those patients suspected of developing symptomatic cardiotoxicity, early recognition is crucial to prevent progression of toxicity to rare—albeit lethal—complications. The most common presentation of fluoropyrimidine cardiotoxicity is chest pain. Chest pain symptoms with 5-FU typically develop within 2–5 days after administration but may occur as early as 3 h after administration [22, 27, 32, 41, 65]. The median duration to first occurrence with capecitabine is 4 days from the start of treatment (range of 2–15 days); this delay may be related to the three-step intracellular activation process of capecitabine into 5-FU [25].

In any chest pain presentation concerning for fluoropyrimidine cardiotoxicity, a thorough history including an assessment of coronary risk factors and a focused cardiopulmonary physical exam are warranted. Obtaining a chemotherapy history is prudent as dosage, route of administration, and the date of last chemotherapy administered prior to the onset of symptoms are all potential risk factors in identifying fluoropyrimidine cardiotoxicity. A prompt ECG should be acquired to assess for ischemic ST changes, conduction abnormalities, and arrhythmias.

Echocardiography can help identify segmental wall motion abnormalities, a manifestation observed in 56 % of 5-FU cardiotoxic patients in one study [22]. Chest pain associated with new ECG changes prompts immediate transfer to the emergency department or inpatient cardiology service. Although serial assessment of cardiac enzymes is required in ACS rule out, cardiac enzymes may be undetectable in many cardiotoxic cases, suggesting that insult to the myocardium is usually not severe enough to cause significant necrosis [26, 49, 51, 52, 66, 67]. However, some reports have seen substantial troponin elevation, demonstrating the heterogeneity of this cardiotoxic effect [48•, 68, 69].

The prognostic role of cardiac biomarkers, including troponin and brain natriuretic peptide (BNP), remains undetermined. Holubec et al. reported that 57 % of patients being monitored for cardiotoxicity while receiving 5-FU had elevations in troponin above normal and recommended those who received 5-FU to undergo monitoring of cardiac biomarkers throughout their chemotherapy course; however, this study did not evaluate for cardiovascular events or other clinical outcomes [70]. Regardless, the monitoring of serial biomarkers during 5-FU treatment is recommended, albeit with a Class III/IV recommendation, by the European Society of Medical Oncology 2012 Clinical Practice Guidelines in patients with history of cardiovascular disease [36, 71].

Urgent coronary angiography should be performed in high-risk patients according to American College of Cardiology/American Heart Association (ACC/AHA) guidelines if there is suspicion of ACS or to definitively exclude ACS. A proposed management strategy for suspected fluoropyrimidine cardiotoxicity has been outlined by the authors (Fig. 6). Such cases of cardiotoxicity are usually a diagnosis of exclusion, as active coronary vasospasm may not always be present on angiography, and preexisting non-obstructive CAD may be present. Withdrawal of the offending agent usually results in symptom relief within hours, although it can take several days for chest pain to resolve entirely [22, 32, 51, 72, 73].



ACC: American College of Cardiology, AHA: American Heart Association, ECG: electrocardiogram
CTA: computed tomography angiography, CAD: coronary artery disease, ACS: acute coronary syndrome

Fig. 6 A proposed algorithm for diagnosis and management of suspected fluoropyrimidine cardiotoxicity. *ACC* American College of Cardiology, *AHA* American Heart Association, *ECG* electrocardiogram, *CTA* computed tomography angiography, *CAD* coronary artery disease, *ACS* acute coronary syndrome

Managing cancer patients with a suspected history of fluoropyrimidine cardiotoxicity involves ongoing multidisciplinary discussions between oncology and cardiology. Ensuring that symptoms have completely

resolved is the first step before attempting further chemotherapy. Important considerations before restarting chemotherapy are if the agent in question provides the best chances for survival with cancer treatment. If this is the case, then further risk stratification and treatment per ACC/AHA guidelines should be undertaken prior to restarting therapy. Risk stratification including obtaining lipids and other cardiovascular disease-related biomarkers may help guide therapy. Some authors have even suggested mandating coronary angiography following fluoropyrimidine cardiotoxicity if chemotherapy extends life expectancy [43]. As preexisting CAD may be a risk factor for cardiotoxicity, reducing other risk factors through smoking cessation, lowering blood pressure, statin use, and aggressive diabetes control should be implemented. Once coronary evaluation has been completed and the patient has been medically optimized (including prophylactic agents, discussed below), fluoropyrimidine reintroduction can be considered if it is deemed the most efficacious choice per multidisciplinary discussion with care providers and the patient on the risks and benefits of resuming therapy.

The role for pharmacologic prophylaxis continues to be unclear, due to limited data and studies showing questionable benefit of various agents. Studies are small and mostly involve examination of anti-anginal and coronary vasodilator agents. Specifically, calcium channel blockers, long-acting nitrates, and beta-blockers have all been used with variable success [17••, 20, 74, 75]. The largest study to date by Eskilsson et al. detected no difference in ischemic symptoms for 58 patients receiving prophylactic verapamil [54]. A placebo arm was not included in this study, however, and ischemic events were instead compared to a previously studied control group who did not receive prophylaxis. Moreover, patients receiving verapamil had reduced arrhythmia rates compared to the control group (0 versus 8 %). Many other case reports have shown individual patient benefit with any combination of these medications [43, 72, 73, 76]. More recently, Jensen et al. reported significantly decreased cardiotoxic rates in 9 out of 12 patients receiving both dose-reduced 5-FU as well as prophylaxis with either a calcium channel blocker, long-acting nitrate, or beta-blocker [25]. Another agent of interest that may provide anti-ischemic effects in chemotherapy-induced toxicity is ranolazine, a piperazine derivative used to treat refractory angina, which is currently under investigation by Minotti et al. in the INTERACT trial [77]. At this time, screening to identify patients who may benefit from such interventions requires further study, and in the setting of needing to continue fluoropyrimidine chemotherapy, consultation with a cardiologist is advised. Suggested cardioprotective prophylactic agents are listed in Table 1.

Monitoring for anatomic, vascular, and electrophysiologic toxicity remains a topic of ongoing evaluation. Serial ECGs and/or outpatient ambulatory rhythm monitoring to evaluate for silent ischemia and arrhythmias should be performed once therapy is reintroduced [41, 78]. For patients who may be at prohibitive risk for invasive coronary angiography, coronary computed tomography may offer a non-invasive method to further risk stratify those that may respond poorly to reintroduction of fluoropyrimidine chemotherapy if CAD is detected. The role of cardiac MRI is a largely unexplored imaging modality in this patient population and may offer another method to evaluate for subclinical cardiotoxicity [79]. Lastly, toxic risk may be mitigated at a reduced dosing pending a discussion on the risks and benefits on administering suboptimal doses of potentially lifesaving treatment for the patient's malignancy [11].

Table 1 A list of pharmacologic agents investigated in the medical literature to potentially treat and/or reduce the risk of cardiotoxicity

Beta-blockers
Calcium channel blockers
Long-acting nitrates
Ranolazine (under investigation)
Anti-oxidants (Probucol) [61]

Conclusion

Fluoropyrimidine chemotherapy, including 5-FU and capecitabine, possesses rare but potentially significant cardiotoxic properties. Cardiotoxicity likely occurs through several mechanisms including coronary vasospasm and direct cytotoxicity, which may explain the heterogeneity of clinical presentations. In patients who have experienced fluoropyrimidine-induced cardiotoxicity, multidisciplinary discussions between oncology and cardiology are warranted if fluoropyrimidine chemotherapy is to be continued along with consideration of implementing cardioprotective therapy to minimize further cardiotoxic sequelae. Further investigation is warranted in evaluating the efficacy of pharmacologic prophylactic agents, cardiac event risk reduction strategies, and alternative dosing, which potentially may may help mitigate the risk of recurrent cardiotoxicity.

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Compliance with Ethical Standards

Conflict of Interest Michael E. Layoun, Chanaka D. Wickramasinghe, Maria V. Peralta, and Eric H. Yang declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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