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Review Article

5-Fluorouracil-Associated Cardiovascular events: An Overview

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Abstract:

5-Fluorouracil (5-FU)–associated cardiotoxicity is a significant yet often underrecognized complication of chemotherapy, particularly in patients with gastrointestinal, breast, and head and neck cancers. It presents a range of cardiovascular manifestations—including coronary vasospasm, arrhythmias, myocardial infarction, myocarditis, and heart failure—that can necessitate treatment modification or discontinuation. This review outlines the incidence, clinical manifestations, pathophysiological mechanisms, and current management strategies for 5-FU-induced cardiotoxicity while highlighting future directions for improving risk stratification and therapeutic approaches.

Key words: 5-fluorouracil; fluoropyrimidines; cardiotoxicity; coronary vasospasm; chemotherapy

Introduction

Fluoropyrimidines (FPs), particularly 5-fluorouracil (5-FU) and its oral prodrug capecitabine, are widely used antimetabolite agents for treating gastrointestinal, breast, and head and neck cancers. 5-FU, a pyrimidine analog, inhibits thymidylate synthase, disrupting DNA synthesis in rapidly dividing tumor cells [1]. While 5-FU ranks as the third most commonly used chemotherapeutic for solid tumors, it is also the second most frequently associated with cardiotoxicity after anthracyclines [2]. Although 5-FU–based regimens significantly improve outcomes in both early-stage and advanced cancers, they may trigger a wide spectrum of cardiovascular toxicities [3, 4]. These toxicities range from asymptomatic ECG changes to angina, myocardial infarction, arrhythmias, heart failure, cardiogenic shock, and sudden death [5]. Proposed mechanisms include coronary vasospasm, endothelial dysfunction, oxidative stress, metabolic interference, and accumulation of toxic metabolites. This review discusses the incidence, risk factors, pathophysiology, clinical features, and management of 5-FU–induced cardiotoxicity. We also outline considerations for retreatment in selected patients through a multidisciplinary cardio-oncology approach.

Incidence and potential risk factors

Cardiovascular events (CVEs) related to 5-FU were first reported in the 1960s, with a reported incidence ranging from 1% to 20% [6-8]. While rare, 5-FU ranks second to anthracyclines among chemotherapeutic agents associated with cardiotoxicity. This wide variation in incidence may reflect differences in patient-related risk factors, dosing schedules, administration routes, concurrent chemoradiotherapy, and genetic predispositions. Reported mortality rates due to 5-FU–associated cardiotoxicity ranges from 2.2% to 13.3% [9-12].

The influence of preexisting cardiac disease remains controversial. Some studies, such as that by Labianca et al., found a significantly higher incidence of cardiotoxicity in patients with underlying cardiovascular disease (4.5% vs. 1.1%) [7, 13]. Comorbidities such as hypertension, diabetes, dyslipidemia, obesity, and smoking history may further elevate risk. However, 5-FU–induced cardiotoxicity can occur in individuals without prior cardiac history [9]. In a review of 377 cases, only 14% had known heart disease, and 37% had conventional cardiovascular risk factors [14]. Thus, current risk models are insufficient for accurate prediction or stratification. The mode of drug delivery significantly affects toxicity. Continuous infusion of 5-FU has consistently been linked with higher cardiotoxicity rates (2.0–18%) compared to bolus administration [6, 7, 9, 12, 14, 15]. The likely explanation for this variation is the short plasma half-life of 5-FU, approximately 15–20 minutes [16].

Genetic susceptibility and polymorphisms in enzymes responsible for 5-FU metabolism—particularly dihydropyrimidine dehydrogenase (DPD)—can significantly influence toxicity risk. Partial DPD deficiency, present in 3–8% of the general population, has been linked to increased rates of adverse effects, including cardiotoxicity [17, 18]. Additionally, co-administration with other cardiotoxic agents or exposure to left-sided chest radiation may further potentiate cardiovascular complications associated with 5-FU [11, 19, 20].

Clinical presentation

The clinical manifestations of 5-FU–associated cardiotoxicity are diverse, ranging from chest pain and typical angina to dyspnea, palpitations, dizziness, syncope, and presyncope. These events most commonly occur during the initial chemotherapy cycles [14, 21], though delayed

presentations during later cycles have also been reported [22]. In a review of 377 cases, cardiovascular symptoms typically emerged during or within 72 hours of the first cycle, with the majority occurring during continuous infusion protocols [14]. The likelihood of cardiotoxicity appears to be elevated when 5-FU is administered alongside other chemotherapeutic agents, particularly those with known cardiac effects, or in combination with chest radiotherapy [19, 20]. Table 1 summarizes the cardiac toxicities reported in association with 5-FU therapy.

Angina	Supraventricular tachycardia
Myocardial infarction	Prolonged QT interval
Congestive heart failure	Ventricular tachycardia
cardiomyopathy	Cardiogenic shock
Myopericarditis	Sudden death

Table 1: Cardiac toxicities reported with 5-FU

Angina

Angina is among the most frequently reported manifestations of 5-FU-associated cardiotoxicity. It typically presents as chest pain, which may be accompanied by palpitations, dyspnea, or pleuritic discomfort, and can occur at rest or during exertion. Electrocardiographic (EKG) evidence of ischemia, such as ST-segment or T-wave changes, is frequently observed, although not universally present.

In a review of 377 patients with 5-FU–induced cardiotoxicity, angina was reported in 45% of cases, EKG abnormalities in 65%, while only 12% exhibited elevated cardiac enzymes, highlighting the discrepancy between clinical symptoms, EKG changes, and biochemical markers [14].

Arrhythmia

Arrhythmias occur in approximately 15–20% of patients treated with 5-FU and represent a significant manifestation of cardiotoxicity [14, 23]. These can range from benign sinus bradycardia to life-threatening ventricular tachycardia (VT) and ventricular fibrillation (VF) [24-27]. In one study, Talapatra et al. documented transient bradycardia in six patients receiving continuous 5-FU infusion [26]. 5-FU has also been associated with QTc interval prolongation, predisposing patients to ventricular arrhythmias such as torsade de pointes. This was exemplified in a case report where QT prolongation during infusion led to Torsades de pointes [28]. Continuous EKG or Holter monitoring has proven useful in detecting these arrhythmias and dynamic ST-T wave abnormalities during therapy [10, 13].

Myocardial infarction and heart failure

Myocardial infarction (MI) and heart failure (HF) are also recognized consequences of 5-FU–associated cardiotoxicity. In a retrospective series of 377 patients, acute MI occurred in 22% and HF in 2% [14]. Turan et al. reported that 18.7% of patients experienced reduced systolic and diastolic function following just one cycle of 5-FU administration [29]. Additionally, in another series, 3.5% of patients developed acute decompensated HF during their initial chemotherapy cycle [19]. These findings underscore the potential for both ischemic and non-ischemic myocardial injury in patients receiving 5-FU.

Myocarditis, pericarditis, and others

Less common but serious cardiac complications of 5-FU include myocarditis, pericarditis, cardiomyopathy, and sudden cardiac death [30-32]. Although reported less frequently than angina or arrhythmias, these events may occur unpredictably and require high clinical suspicion for timely diagnosis.

Pathophysiology of cardiotoxicity

The mechanisms underlying 5-FU–associated cardiotoxicity remain incompletely understood but are believed to be multifactorial and interrelated. Proposed contributors include coronary vasospasm, direct myocardial injury, endothelial dysfunction, oxidative stress, prothrombotic effects, and toxic metabolites. These overlapping mechanisms may act synergistically to produce both ischemic and non-ischemic cardiac injury. A summary of proposed pathophysiological processes is provided in Table 2.

Coronary artery vasospasm
Direct myocardial injury
Accumulation of toxic metabolites
Oxidative stress
Endothelial damage
Thrombogenic effects
Activation of pro-inflammatory pathways

Table 2: Proposed mechanisms of 5-FU–associated cardiotoxicity

Coronary Vasospasm

Coronary vasospasm is the most widely accepted mechanism for 5-FU–induced myocardial ischemia. The first clinical evidence was described by Luwaert et al. in 1991, involving angiographic confirmation of coronary spasm in a patient receiving 5-FU [33]. Subsequent studies have demonstrated vasospasm not only in coronary arteries but also in peripheral vessels, such as the brachial artery, using ultrasound and angiography [34, 35]. Indirect evidence includes ECG findings mimicking acute coronary syndrome (e.g., ST-segment elevation) and troponin elevation in the absence of angiographic obstruction [36, 37]. Symptom relief following the administration of nitrates or calcium channel blockers (CCBs) further supports a vasospastic mechanism.

Two pathophysiological mechanisms have been proposed:

- **Endothelial-dependent vasospasm**, driven by endothelial dysfunction
- **Endothelial-independent vasospasm**, mediated by primary smooth muscle hyperreactivity

Endothelial dysfunction:

A central feature of 5-FU–associated cardiotoxicity is vascular endothelial dysfunction. The endothelium regulates vascular tone, platelet activity, and hemostasis; its disruption contributes significantly to vasospasm and thrombotic risk. 5-FU and its metabolite α-fluoro-β-alanine (FBAL) have been shown to inhibit endothelial cell proliferation, suppress DNA synthesis, and promote apoptosis in preclinical studies. This injury is associated with impaired nitric oxide production and elevated endothelin-1 levels, both of which promote vasoconstriction and inflammation [38-40]. Altieri et al. concluded that 5 FU causes

endothelial senescence and dysfunction, which may contribute to its cardiovascular side effects [41]. In another study, Focaccentti et al. examined the effects of 5-FU on primary cell cultures of human cardiomyocytes and endothelial cells and observed autophagic features at ultrastructural and molecular levels [42].

Primary smooth muscle dysfunction

Beyond endothelial effects, 5-FU may also exert direct action on vascular smooth muscle cells, contributing to endothelial-independent vasospasm. Experimental studies using isolated vascular rings in rats have demonstrated smooth muscle contraction in response to 5-FU, even without intact endothelium, supporting this mechanism [43].

Direct Myocardial Injury

Although coronary vasospasm is the most well-known mechanism of 5-FU–associated cardiotoxicity, increasing evidence highlights direct myocardial toxicity as a significant contributor to cardiac dysfunction. Oxidative stress, apoptosis, metabolic disruption, and inflammation are the key pathways leading to 5-FU-induced myocardial injury. Dyhl-Polk et al. conducted a prospective study demonstrating myocardial ischemia in patients receiving 5-FU. The study found a significant increase in the number of patients with myocardial ischemia on Holter recording during 5-FU infusion, along with elevated plasma copeptin levels, indicating myocardial stress [44]. De Forni et al. suggested the possibility of direct drug toxic actions on the myocardium, particularly given the evidence that there is global systolic dysfunction, which does not correspond to any individual coronary artery territory [9]. Research involving animal models revealed that 5-FU administration led to myocardial injury and increased oxidative stress and apoptosis in cardiac tissues [45].

Other Proposed Mechanisms

Additional mechanisms implicated in 5-FU–associated cardiotoxicity include oxidative stress, systemic inflammation, prothrombotic states, rheological changes, and hypersensitivity reactions. Reactive oxygen species (ROS) generated during 5-FU metabolism may induce lipid peroxidation, mitochondrial dysfunction, and apoptosis [46-48]. The physiological role of endothelium is not limited to modifying vascular tone but extends to regulating coagulation and thrombus formation. Inflammatory cytokine release may further damage endothelial and myocardial tissues. Indeed, studies of rabbit endothelium exposed to 5-FU have demonstrated platelet aggregation and fibrin formation [49, 50]. 5-FU also activates inflammatory pathways, including the nuclear factor kappa B (NF-kB) pathway, leading to increased production of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-β). This inflammation contributes to cardiomyocyte injury and apoptosis [51].

Moreover, metabolites like FBAL and fluoroacetate can impair oxidative phosphorylation, contributing to myocardial dysfunction [52]. Though rare, hypersensitivity reactions and coronary embolism have also been proposed as potential contributors [53, 54].

All these clinical studies provide strong evidence that 5-FU–associated cardiotoxicity is a complex, multifaceted phenomenon involving vascular, metabolic, inflammatory, and electrophysiological disturbance. Understanding these diverse mechanisms is crucial for developing effective risk stratification, monitoring strategies, and cardioprotective interventions in cancer patients receiving 5-FU therapy.

Management

Effective management of 5-FU–associated cardiotoxicity begins with early recognition of symptoms such as chest pain, palpitations, dyspnea, or syncope during or shortly after chemotherapy. Immediate discontinuation of 5-FU is critical upon suspicion of cardiotoxicity. Supportive therapy with nitrates and calcium channel blockers is often beneficial, particularly in patients with suspected coronary vasospasm [14, 55]. Although some studies and data showed limited efficacy of prophylactic coronary vasodilators, these medications are standard initial therapy [14, 56, 57].

The next step is determining whether the cardiac symptoms can be reasonably attributed to 5-FU. No definitive test can establish a causal link between 5-FU and cardiotoxicity; thus, clinical judgment is required. Diagnostic evaluation should include EKG, cardiac biomarkers (e.g., troponin, BNP), and echocardiography to assess for ischemia or myocardial dysfunction [13]. Ambulatory EKG or Holter monitoring may aid in detecting transient arrhythmias. However, its role in routine practice is still being defined in cases where symptoms are persistent or severe, advanced imaging such as coronary angiography or cardiac MRI may be warranted to rule out obstructive coronary artery disease or myocarditis. Early involvement of cardiology or cardio-oncology teams is strongly recommended to guide further care.

Uridine triacetate is an FDA-approved antidote for 5-FU and capecitabine overdose or early-onset severe toxicity. It competes with fluorinated metabolites to restore intracellular pyrimidine pools, mitigating cytotoxic effects. Although its role in treating cardiotoxicity remains unclear, its use may be considered in select life-threatening cases where 5-FU-induced injury is suspected [58].

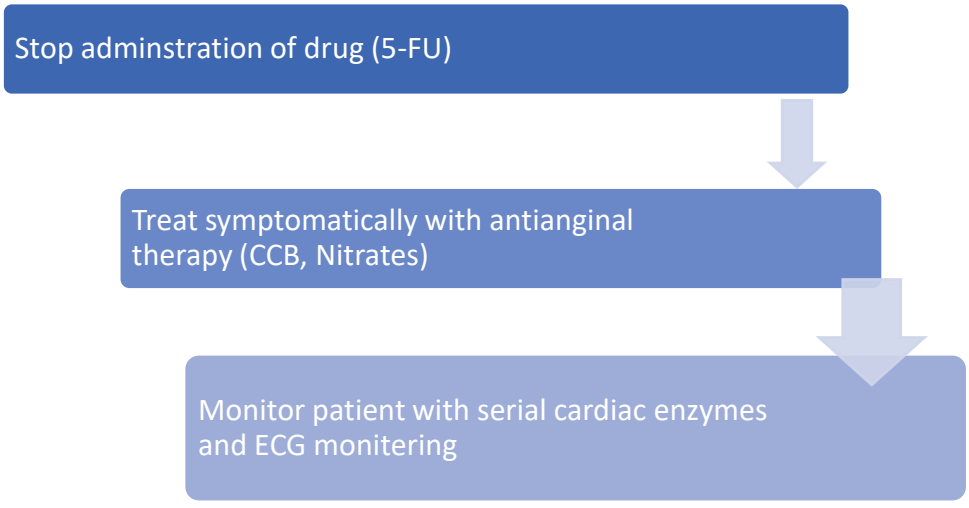

Figure 1: Management of 5-FU–associated cardiotoxicity

5-FU, 5-fluorouracil; CCB, Calcium channel blocker; ECG, Electrocardiogram

Reintroduction of 5-FU

Reintroduction of 5-FU following a cardiotoxic event remains controversial due to the high recurrence rate and associated mortality. In one series, recurrence of cardiotoxicity was observed in 82% of rechallenged patients [9, 14, 59], and the associated fatality rate was as high as 13% [14]. Therefore, rechallenge should generally be avoided unless no effective alternative exists. In cases where 5-FU is deemed essential, strategies such as switching to bolus dosing, premedication with calcium channel blockers or nitrates, and continuous cardiac monitoring may be employed [12, 60]. These decisions should be individualized and guided by a multidisciplinary cardio-oncology team.

Alternative fluoropyrimidines may be considered for patients with previous 5-FU–associated cardiotoxicity, particularly when continuation of fluoropyrimidine therapy is necessary. Options include TAS-102 (trifluridine/tipiracil), raltitrexed, and S1, an oral formulation designed to reduce systemic exposure and toxicity [61, 62]. These agents may offer safer therapeutic alternatives, although experience remains limited. Figure 2 summarizes the steps for reintroducing 5-FU.

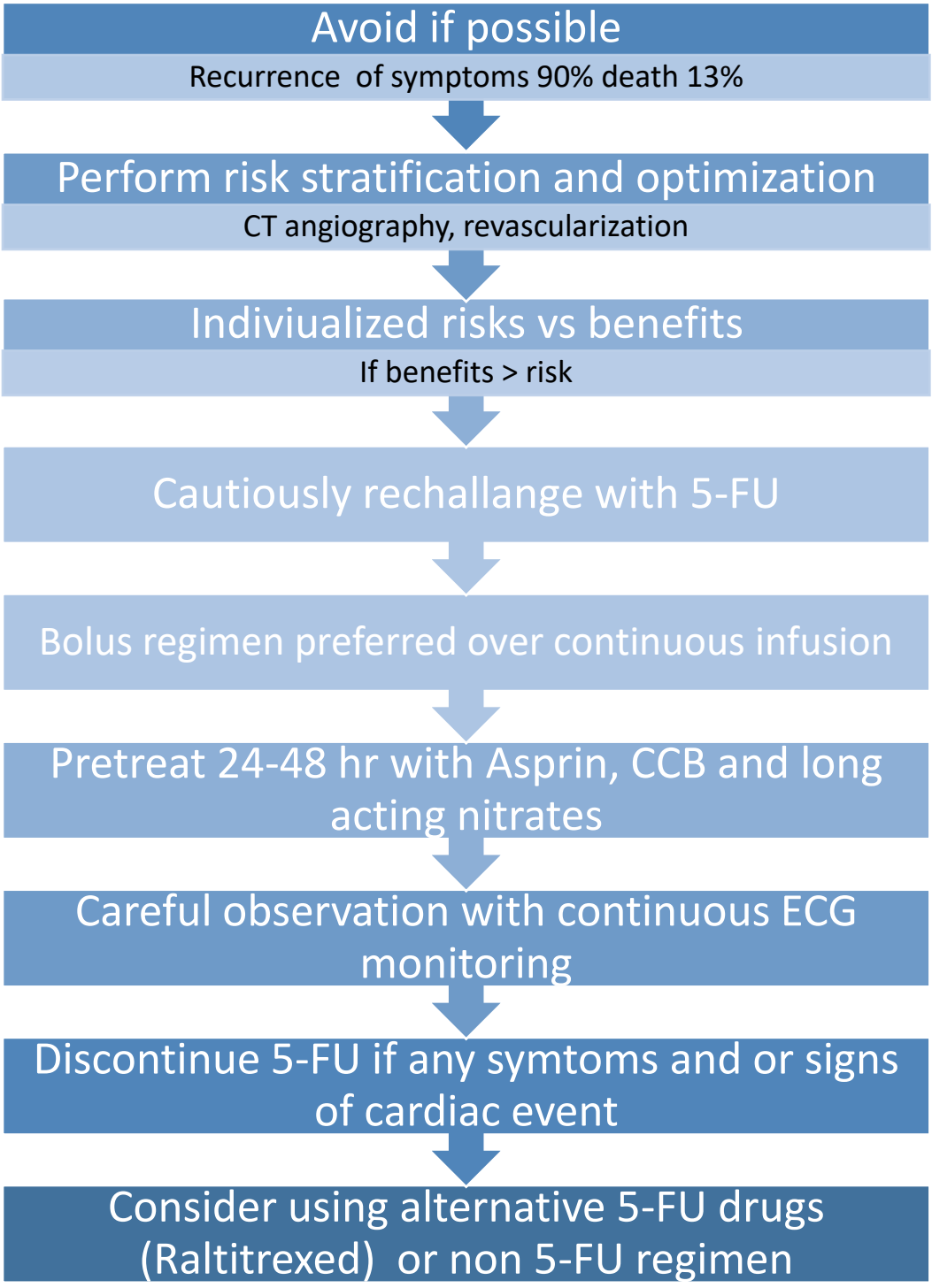

Figure 1: Reintroducing patients with 5-FU

Future Directions

Predicting 5-FU–associated cardiotoxicity remains a major clinical challenge, as no validated risk stratification models exist. Future research should aim to identify reliable biomarkers, imaging techniques, and clinical predictors that can help stratify patient risk and guide prophylactic strategies. Preliminary studies have suggested that heart-type fatty acid binding protein (h-FABP) and the myocardial performance index (MPI or Tei index) may serve as early indicators of cardiotoxicity [29].

Studies suggest that genetic polymorphisms in DPYD, TYMS, MTHFR, and OPRT may increase the risk of serious toxicity. Determining polymorphisms in xenobiotic metabolizing enzymes through genetic profiling before 5-FU administration might suggest new and individualized strategies for safely optimizing chemotherapy [63]. There is also the possibility of treatment of FP-related cardiovascular toxicity with GLP-1 analogs and GLP-1 degradation inhibitors in the future [41]. Prospective validation of these markers—alongside advanced modalities such as cardiac MRI, serum biomarker panels, and EKG-based risk scores—could support the development of integrated predictive tools. Large-scale studies are essential to confirm their clinical utility and potentially transform how 5-FU cardiotoxicity is managed.

Conclusion

5-FU–associated cardiotoxicity represents a serious but frequently underrecognized complication of cancer therapy. Clinical manifestations span from asymptomatic ECG changes to acute coronary syndromes, heart failure, and life-threatening arrhythmias. A high index of suspicion is warranted, particularly in high-risk individuals and those receiving continuous infusion.

Timely recognition, cessation of the offending agent, and appropriate supportive therapy are essential to minimize morbidity. As the use of fluoropyrimidines continues across various malignancies, future efforts should focus on elucidating underlying mechanisms, validating predictive biomarkers, and establishing evidence-based strategies for prevention and management. A multidisciplinary cardio-oncology approach remains central to optimizing care in affected patients.

Conflict of interest: None declared

References:

1. Longley, D.B., D.P. Harkin, and P.G. Johnston. (2003). 5-fluorouracil: mechanisms of action and clinical strategies. *Nature reviews cancer*, 3(5): p. 330-338.
2. Sara, J.D., et al. (2018). 5-fluorouracil and cardiotoxicity: a review. *Ther Adv Med Oncol,* 10: p. 1758835918780140.
3. Akazawa, H. (2017). Cardiotoxicity of cancer chemotherapy-mechanisms and therapeutic approach. *Gan to kagaku ryoho. Cancer & chemotherapy*, 44(13): p. 2058-2063.
4. Jain, D. and W. Aronow. (2019). Cardiotoxicity of cancer chemotherapy in clinical practice. Hospital practice, 47(1): p. 6-15.
5. Eskilsson, J., M. Albertsson, and C. Mercke. (1988). Adverse cardiac effects during induction chemotherapy treatment with cis-platin and 5-fluorouracil. *Radiotherapy and Oncology*, 13(1): p. 41-46.
6. Anand, A.J. (1994). Fluorouracil cardiotoxicity. Annals of Pharmacotherapy, 28(3): p. 374-378.
7. Labianca, R., et al. (1982). Cardiac toxicity of 5-fluorouracil: a study on 1083 patients. *Tumori Journal*, 68(6): p. 505-510.
8. Lestuzzi, C., et al. (2014). Effort myocardial ischemia during chemotherapy with 5-fluorouracil: an underestimated risk. Annals of oncology, 25(5): p. 1059-1064.
9. De Forni, M., et al. (1992). Cardiotoxicity of high-dose continuous infusion fluorouracil: a prospective clinical study. Journal of Clinical Oncology, 10(11): p. 1795-1801.
10. Wacker, A., et al. (2003). High Incidence of Angina pectoris in Patients Treated with 5-FluorouracilA Planned Sur veillance Study with 102 Patients. *Oncology*, 65(2): p. 108-112.
11. Robben, N.C., A.W. Pippas, and J.O. Moore. (1993). The syndrome of 5-fluorouracil cardiotoxicity. An elusive cardiopathy. Cancer, 71(2): p. 493-509.
12. Kosmas, C., et al. (2008). Cardiotoxicity of fluoropyrimidines in different schedules of administration: a prospective study. *Journal of cancer research and clinical oncology*, 134: p. 75-82.
13. Rezkalla, S., et al., (1989). Continuous ambulatory ECG monitoring during fluorouracil therapy: a prospective study. *Journal of Clinical Oncology*, 7(4): p. 509-514.
14. Saif, M.W., M.M. Shah, and A.R. Shah. (2009). Fluoropyrimidine-associated cardiotoxicity: revisited. *Expert opinion on drug safety*, 8(2): p. 191-202.
15. Meydan, N., et al. (2005). Cardiotoxicity of de Gramont's regimen: incidence, clinical characteristics and long-term follow-up. *Japanese journal of clinical oncology*, 35(5): p. 265-270.
16. Sara, J.D., et al. (2018). 5-fluorouracil and cardiotoxicity: a review. *Therapeutic advances in medical oncology*, 10: p. 1758835918780140.
17. Milano, G., et al. (1999). Dihydropyrimidine dehydrogenase deficiency and fluorouracil-related toxicity. *British journal of cancer*, 79(3): p. 627-630.
18. Ma, W.W., et al. (2019). Emergency use of uridine triacetate for the prevention and treatment of life-threatening 5-fluorouracil and capecitabine toxicity. *Cancer*, 123(2): p. 345-356.
19. Meyer, C.C., et al., (1997). Symptomatic cardiotoxicity associated with 5-fluorouracil. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy, 17(4): p. 729-736.
20. Bovelli, D., et al., (2010). Cardiotoxicity of chemotherapeutic agents and radiotherapy-related heart disease: ESMO Clinical Practice Guidelines. *Annals of oncology*, 21: p. v277-v282.
21. Ng, M., D. Cunningham, and A.R. (2005). Norman, The frequency and pattern of cardiotoxicity observed with capecitabine used in conjunction with oxaliplatin in patients treated for advanced colorectal cancer (CRC). *European journal of cancer*, 41(11): p. 1542-1546.
22. Jensen, S.A., et al., (2010). Fluorouracil induces myocardial ischemia with increases of plasma brain natriuretic peptide and lactic acid but without dysfunction of left ventricle. *Journal of clinical oncology,* 28(36): p. 5280-5286.
23. Khan, M.A., et al., (2012). A retrospective study of cardiotoxicities induced by 5-fluouracil (5-FU) and 5-FU based chemotherapy regimens in Pakistani adult cancer patients at Shaukat Khanum Memorial Cancer Hospital & Research Center. *JPMA-Journal of the Pakistan Medical Association*, 62(5): p. 430.
24. Lai, S., J.L. Marshall, and R.L. Morrissey. (2015). Rechallenging 5-fluorouracil in a patient with capecitabine-

induced ventricular fibrillation. *Clinical Colorectal Cancer*, 14(3): p. 198-201.
25. Hrovatin, E., et al., (2006). Severe ventricular dysrhythmias and silent ischemia during infusion of the antimetabolite 5-fluorouracil and cis-platin. *Journal of Cardiovascular Medicine*, 7(8): p. 637-640.
26. Talapatra, K., et al., (2007). Transient asymptomatic bradycardia in patients on infusional 5-fluorouracil. *Journal of cancer research and therapeutics,* 3(3): p. 169-171.
27. Moriyama, S., et al., (2009). Atrial fibrillation observed in a patient with esophageal cancer treated with fluorouracil. *Journal of Cardiology Cases*, 20(5): p. 183-186.
28. Stewart, T., N. Pavlakis, and M. Ward. (2010). Cardiotoxicity with 5-fluorouracil and capecitabine: more than just vasospastic angina. *Internal medicine journal,* 40(4): p. 303-307.
29. Turan, T., et al., 92017). Usefulness of Heart-Type Fatty Acid-Binding Protein and Myocardial Performance Index for Early Detection of 5-Fluorouracil Cardiotoxicity. *Angiology,* 68(1): p. 52-58.
30. Killu, A., et al., (2011). 5-Fluorouracil induced pericarditis. *BMJ Case Reports,* p. bcr0220113883.
31. More, L.A., S. Lane, and A. Asnani. (2011). 5-FU Cardiotoxicity: Vasospasm, Myocarditis, and Sudden Death. *Current Cardiology Reports,* 23(3): p. 17.
32. Lasica, R., et al. (2022). Case report: Acute toxic myocardial damage caused by 5-fluorouracil—from enigma to success. *Frontiers in Cardiovascular Medicine*, 9.
33. Luwaert, R.J., et al. (1991). Coronary artery spasm induced by 5-fluorouracil. *Eur Heart J*, 12(3): p. 468-70.
34. Südhoff, T., et al. (2004). 5-Fluorouracil induces arterial vasocontractions. *Annals of Oncology,* 15(4): p. 661-664.
35. Salepci, T., et al. (2010). 5-Fluorouracil induces arterial vasoconstrictions but does not increase angiotensin II levels. *Medical Oncology*, 27: p. 416-420.
36. Tajik, R., et al. (2010). Angina induced by 5-fluorouracil infusion in a patient with normal coronaries. *The American Heart Hospital Journal,* 8(2): p. E111-E112.
37. Alter, P., et al. (2006). Cardiotoxicity of 5-fluorouracil. Cardiovascular & Hematological Agents in Medicinal Chemistry *(Formerly Current Medicinal Chemistry-Cardiovascular & Hematological Agents),* 4(1): p. 1-5.
38. Cwikiel, M., et al. (1996). The influence of 5-fluorouracil and methotrexate on vascular endothelium. An experimental study using endothelial cells in the culture. *Annals of Oncology,* 7(7): p. 731-737.
39. Cwikiel, M., et al. (1995). The influence of 5-fluorouracil on the endothelium in small arteries. An electron microscopic study in rabbits. *Scanning microscopy,* 9(2): p. 23.
40. Thyss, A., et al. (1992). Very high endothelin plasma levels in patients with 5-FU cardiotoxicity. *Ann Oncol,* 3(1): p. 88.
41. Altieri, P., et al. (2017). 5-fluorouracil causes endothelial cell senescence: potential protective role of glucagon-like peptide 1. *Br J Pharmacol,* 174(21): p. 3713-3726.
42. Focaccetti, C., et al. (2015). Effects of 5-fluorouracil on morphology, cell cycle, proliferation, apoptosis, autophagy and ROS production in endothelial cells and cardiomyocytes. *PLoS One*, 10(2): p. e0115686.
43. Mosseri, M., et al. (1993). In vitro evidence that myocardial ischemia resulting from 5-fluorouracil chemotherapy is due to protein kinase C-mediated vasoconstriction of vascular smooth muscle. *Cancer research*, 53(13): p. 3028-3033.
44. Dyhl-Polk, A., et al. (2021). Myocardial Ischemia Induced by 5-Fluorouracil: A Prospective Electrocardiographic and Cardiac Biomarker Study. *Oncologist*, 26(3): p. e403-e413.
45. Lamberti, M., et al. (2014). A mechanistic study on the cardiotoxicity of 5-fluorouracil in vitro and clinical and occupational perspectives. *Toxicol Lett,* 227(3): p. 151-156.
46. Cwikiel, M., et al. (1996). The appearance of endothelium in small arteries after treatment with 5-fluorouracil. An electron microscopic study of late effects in rabbits. *Scanning Microsc*, 10(3): p. 805-18; discussion 819.
47. Kinhult, S., et al. (2001). Antithrombotic treatment in protection against thrombogenic effects of 5-fluorouracil on vascular endothelium: a scanning microscopy evaluation. *Scanning,* 23(1): p. 1-8.
48. Kinhult, S., et al. (2003). Effects of probucol on endothelial damage by 5-fluorouracil. Acta Oncologica, 42(4): p. 304-308.
49. Jensen, S.A. and J.B. (2012). Sørensen, 5-Fluorouracil-based therapy induces endovascular injury having potential significance to development of clinically overt cardiotoxicity. *Cancer Chemotherapy and Pharmacology*, 69(1): p. 57-64.
50. Yudkin, J.S., et al. (1999). C-reactive protein in healthy subjects: associations with obesity, insulin resistance, and endothelial dysfunction: a potential role for cytokines originating from adipose tissue? *Arteriosclerosis, thrombosis, and vascular biology*, 19(4): p. 972-978.
51. Lokman, M.S., et al. (2023). Protective effect of quercetin against 5-fluorouracil-induced cardiac impairments through activating Nrf2 and inhibiting NF-κB and caspase-3 activities. *Environ Sci Pollut Res Int,* 30(7): p. 17657-17669.
52. Arellano, M., et al. (1998). The anti-cancer drug 5-fluorouracil is metabolized by the isolated perfused rat liver and in rats into highly toxic fluoroacetate. *British journal of cancer*, 77(1): p. 79-86.
53. Baerlocher, G., et al. (1997). The anti-neoplastic drug 5-fluorouracil produces echinocytosis and affects blood rheology. *British journal of haematology*, 99(2): p. 426-432.
54. Spasojević, I., et al. (2005). Effects of 5-fluorouracil on erythrocytes in relation to its cardiotoxicity: membrane structure and functioning. *Journal of chemical information and modeling,* 45(6): p. 1680-1685.
55. Thalambedu, N. and Y. Khan. (2019). Fluorouracil (5-FU)-induced cardiomyopathy. *Cureus,* 11(7).
56. Patel, B., et al. (1987). 5-Fluorouracil cardiotoxicity: left ventricular dysfunction and effect of coronary vasodilators. The *American journal of the medical sciences*, 294(4): p. 238-243.
57. Eskilsson, J. and M. and Albertsson. (1990). Failure of Preventing 5-Fluorouracil Cardiotoxicity by Prophylactic Treatment with Verapamil. *Acta Oncologica,* 29(8): p. 1001-1003.
58. Ison, G., et al. (2016). FDA approval: uridine triacetate for the treatment of patients following fluorouracil or capecitabine overdose or exhibiting early-onset severe toxicities following

administration of these drugs. *Clinical cancer research,* 22(18): p. 4545-4549.

59. Saif, M.W., et al. (2008). Capecitabine-related cardiotoxicity: recognition and management. *The journal of supportive oncology*, 6(1): p. 41-48.
60. Anderson, J.L., et al. (2013). ACCF/AHA focused update incorporated into the ACCF/AHA 2007 guidelines for the management of patients with unstable angina/non–ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Journal of the American College of Cardiology,* 61(23): p. e179-e347.
61. Petrelli, F., et al. (2016). TAS-102, the first "cardio-gentle" fluoropyrimidine in the colorectal cancer landscape? *BMC cancer,* 2016. 16: p. 1-4.
62. Kelly, C., et al. (2013). Use of raltitrexed as an alternative to 5-fluorouracil and capecitabine in cancer patients with cardiac history. *European Journal of Cancer,* 49(10): p. 2303-2310.
63. Matsusaka, S. and H.J. Lenz. (2015). Pharmacogenomics of fluorouracil -based chemotherapy toxicity. *Expert Opin Drug Metab Toxicol*, 11(5): p. 811-21.

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