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Cardiotoxicity of the Antiproliferative Compound Fluorouracil

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Abstract

The antimetabolite fluorouracil (5-FU) is frequently administered for chemotherapy of various malignant neoplasms. The drug is well known for its adverse effects involving bone marrow, skin, mucous membranes, intestinal tract and central nervous system, whereas its cardiotoxicity is less familiar to clinicians.

The pathophysiology of fluorouracil-associated cardiac adverse events is controversial and conclusions are based on clinical studies and case reports more than on solid experimental evidence. While clinical and electrocardiographic features suggest myocardial ischaemia as a main aetiological factor, possibly induced by coronary vasospasm, histomorphological and biochemical studies indicate a more direct drug-mediated cytotoxic action. Estimates of the overall incidence of fluorouracil cardiotoxicity have varied widely from 1.2 to 18% of patients. Patients may present with angina-like chest pain, cardiac arrhythmias or myocardial infarction. There is no unequivocally effective prophylaxis or treatment in this syndrome. Once fluorouracil administration is discontinued symptoms are usually reversible, although fatal events have been described. The overall mortality rate has been estimated to be between 2.2 and 13.3%. There is a high risk of relapse when patients are re-exposed to this drug following previous cardiac incidents.

From the present data it is concluded that cardiotoxicity is a relevant but underestimated problem in fluorouracil treatment. Since the mechanisms of fluorouracil-associated cardiotoxicity are not yet fully understood, all patients undergoing this chemotherapy have to be carefully evaluated and monitored for cardiac risk factors and complaints. After cardiotoxic events, fluorouracil should definitely be withdrawn and replaced by an alternative antiproliferative regimen.

Cardiac complications in cancer patients may result from pre-existing heart disease, direct or secondary tumour involvement, irradiation to the chest, or adverse reaction to antineoplastic or supportive medication. Fluorouracil (5-FU), which was first introduced in the late 1950s,[1] has long been established as an antiproliferative compound in the treatment of various solid malignancies. This drug is a synthetic pyrimidine analogue and is degraded during its cellular metabolism to various nucleotide derivatives, which are cytotoxic at different intracellular targets. In particular, the nucleotide derivatives competitively inhibit thymidylate synthetase resulting in a thymine-depleted cellular state. In addition, they are incorporated into host DNA and RNA, leading to termination of nuclear transcription and ribosomal translation.[2-4] Although several sites of potential antitumour activity have been identified, their specific mode of action and the degree to which they contribute to fluorouracil-related cytotoxicity still need to be evaluated.

Fluorouracil serum half-life is brief after rapid intravenous bolus injection, lasting for 8 to 20 minutes.[3] Hepatic catabolism represents about 80% of fluorouracil clearance, with renal excretion accounting for 5 to 20% of its elimination.[3,4] Fluorouracil uptake into the myocardium has been demonstrated.[5,6]

Fluorouracil-associated cardiotoxic adverse events were first described in 1969 as part of a multiple chemotherapeutic regimen.[7] Angina related to exclusive application of fluorouracil was then first reported in 1975.[8,9] Up to the early 1990s a series of 135 published cases has been summarised from the literature.[4] Overall a variable incidence of 1.2 to 18% was observed by different sources.[4,10-25] Such epidemiological figures have to be assessed cautiously, since individual studies differed widely with regard to design, sample size, criteria of cardiotoxicity and mode of monitoring. Patients were often treated with additional cardiotoxic drugs, and they had rarely been investigated prospectively. Occurrence of fluorouracil-associated cardiotoxicity may also have been falsely attributed to pre-existing heart disease or progression of underlying malignancy due to unawareness of the potential role of fluorouracil.

For the present review a detailed computerised literature search was performed for data collection using the Medline database. Case reports, reviews, meta-analyses and bibliographies were scrutinised for original material and any relevant secondary referrals by independent reviewers. The different aspects of fluorouracil-associated cardiotoxicity were critically analysed to highlight corresponding and contradictory features, with personal experiences being included. Since prevailing concepts on this issue vary, especially with regard to the pathogenetic principles, particular attention was paid to deriving firm, data-based clinical conclusions and to giving reliable recommendations for the practical management of these patients.

1. Concepts in Aetiology and Pathogenesis

Mechanisms involved in fluorouracil-associated cardiotoxicity and their multiple interactions have not yet been identified exactly. Coronary vasospasm has been suggested to be a main pathogenetic factor in this syndrome[26-28] based on the characteristic clinical and electrocardiographic presentation of reversible ischaemic heart disease without gross vascular obstruction of the coronary arteries.[17,22,29-36] A direct, specific and dose-dependent arterial vasoconstriction has correspondingly been demonstrated in isolated rabbit aortic rings following fluorouracil administration.[37] This vasoconstriction typically lasted for a few minutes, and was abolished by nitroglycerin application. As a potential mediator of vasospasm *in vivo*, plasma levels of endothelin, a strong vasoconstrictor derived from endothelial cells, have been shown to be specifically elevated in cancer patients treated with fluorouracil, and particularly in those developing cardiotoxicity.[38]

It has further been demonstrated that fluorouracil toxicity may cause endothelial cell damage and consequent thrombus formation.[39,40] Such endothelial alterations proved to be partially reversible,[39] and they were more pronounced than those of contractile myocytes.[41] Fluorouracil-associated

effects on vascular endothelium reached their peak about 3 days from initiation of treatment,[40,41] which corresponds to the clinical course of fluorouracil-related cardiotoxicity.

In patients who had experienced fluorouracil cardiotoxicity rechallenge with intravenous fluorouracil during cardiac catheterisation gave inconclusive results in that both coronary spasm was precipitated on angiography,[30] and such vasoconstriction could not be provoked by fluorouracil exposure.[42]

It has also been speculated that fluorouracil may provoke cardiac ischaemia by increasing myocardial oxygen demand. Such mechanisms would render patients, in particular those with pre-existing heart disease, prone to fluorouracil cardiotoxicity. In line with this, animal studies showed positive inotropic and chronotropic effects of fluorouracil,[43] and patients' peak heart rates were found to be significantly elevated during fluorouracil administration.[44] When investigated in the isolated perfused rat heart, fluorouracil pretreatment increased both oxygen consumption of the myocardium and coronary blood flow.[45]

In contrast, intravenous fluorouracil administration precipitated no significant changes in cardiac blood flow in guinea pigs,[46] and in humans intra-arterial hepatic fluorouracil infusion provoked no alterations in cardiopulmonary haemodynamics, and particularly no elevation of myocardial oxygen demand.[6]

It has also been suggested that fluorouracil might directly interfere with myocardial cell metabolism, leading to cellular hypoxia and thereby imitating ischaemic heart disease.[4,45] For example, it was shown that fluorouracil is hepatically metabolised into the cardiotoxic compound fluoroacetate,[47] which induces myocardial depletion of high-energy phosphates.[46,48] Furthermore, the fluorouracil metabolite fluorocitrate acts as a potent inhibitor of the tricarboxylic acid cycle.[17,22,46,49] Both mechanisms would account for diffuse cardiac hypoxia, although they may not explain why electrocardiographic changes are often pronounced in the distributive area of single coronary arteries or why extracardiac organs are not similarly involved.

Recently, dihydropyrimidine dehydrogenase (DPD) deficiency has been described in patients with fluorouracil-associated cardiotoxicity.[50-53] DPD is the initial and rate-limiting enzyme in uracil and thymidine catabolism, and is thereby also involved in the degradation of fluorouracil.[3] DPD levels in peripheral blood mononuclear cells were demonstrated to be inversely correlated to fluorouracil plasma concentrations.[54,55] DPD deficiency has consequently been incriminated in prolonged fluorouracil serum clearance and subsequent increased toxicity. However, quantification of DPD activity before fluorouracil treatment did not predict either development of fluorouracil-associated cardiotoxicity or the need for fluorouracil dose reduction,[56] suggesting that cardiac adverse events do not strictly relate to fluorouracil plasma levels, and that DPD deficiency may require additional co-factors to provoke fluorouracil-associated cardiotoxicity. Since other thymidylate synthase inhibitors were safely administered to patients previously experiencing fluorouracil-associated cardiotoxicity, this specific enzyme inhibition does not appear to essentially contribute to fluorouracil-related adverse cardiac effects.[57]

Histological studies investigating the effects of supratherapeutic oral doses of fluorouracil on myocardial morphology in rats demonstrated swelling, loss of striation and necrosis of myocytes, interstitial oedema with perivascular mononuclear infiltrates, and pericardial haemorrhage.[58,59] These alterations mainly affected the left ventricle, starting about 12 hours after fluorouracil ingestion, peaking at 4 to 5 days and persisting for about 2 weeks. They resulted in myocardial fibrosis in up to 40% of animals and, as a late sequela, left ventricular dilation developed. While these morphological changes were found to be specific for fluorouracil, they also affected various other extracardiac organs in these animals. In contrast, thrombosis or atherosclerosis of the coronary artery system were not observed in this model.[58,59]

Although such results may not safely be extrapolated to humans who are treated with therapeutic doses of fluorouracil intravenously, similar necropsy findings have been obtained in patients who died from fatal myocardial infarction[60] or in cardiogenic shock associated with fluorouracil administration.[61] Myocardial necrosis and mononuclear inflammation in these people were described as patchy, and did not correlate to the distribution of major coronary arteries, while there was no evidence of associated vasculitis.[61]

Histological findings corresponded to levocardiographic and echocardiographic observations in patients with fluorouracil-associated cardiotoxicity. The latter mostly demonstrated diffuse reduction of myocardial contractile function rather than segmental wall hypokinesia as would be suspected from the obstruction of a major coronary vascular supply.[32,62] Consequently, histomorphological and morphometric findings do not really support circumscribed ischaemia as the main aetiological factor in fluorouracil-associated cardiotoxicity, but instead suggest some primary drug-related cellular damage in this syndrome.

Other mechanisms previously proposed to be involved in the pathogenesis of fluorouracil-associated cardiotoxicity included the release of vasoactive compounds,[63] induction of autoimmune mechanisms,[64] coronary endarteritis,[29] increased serum thrombogenicity,[65] and toxic degradation products in commercially available fluorouracil preparations.[66,67]

Interestingly, the impact of pre-existing heart disease on fluorouracil-associated cardiotoxicity remains controversial, with some reports supporting its involvement[11,18,21,22,25,44,60,68,69] and others arguing against it.[13,16,17,24,27,61,63,70,71] While in earlier studies a 4-fold increased risk of fluorouracil-associated cardiotoxicity was reported for patients with pre-existing symptoms of coronary artery disease,[11,18] a recent meta-analysis found prevalence of cardiac pathology in patients with fluorouracil-associated cardiotoxicity not significantly different from age- and gender-matched unaffected patients.[4]

Previous or current radiation involving the heart has also been proposed as a risk factor for the development of fluorouracil-associated cardiotoxicity,[4,10,30] particularly since fluorouracil possesses radiosensitising properties.[15] Radiation may cause small-vessel thrombosis and myocardial fibrosis,[72] which could aggravate cardiac dysfunction potentially associated with fluorouracil application. Such concomitant radiotherapy has been reported in 12% of patients with fluorouracil-related angina.[4]

Data on the correlation of fluorouracil dosage to risk of cardiotoxicity are inconsistent. Studies in guinea pigs demonstrated ischaemic ECG changes to be dose dependent following intravenous bolus administration of fluorouracil.[46] Accordingly, high dose continuous fluorouracil infusion was suggested to be more cardiotoxic than conventional low dose bolus regimens.[17,18,21,24,57,69,73] In contrast, cumulative fluorouracil dosage reported in patients with manifestations of cardiotoxicity ranged widely from 0.5 to 61g,[24,74,75] and did not strictly correlate to the development of symptomatic angina.[4,16,25,71,74,75] Comparably, fluorouracil dose reduction only inconsistently relieved or prevented cardiac symptoms.[21]

With regard to the mode of application, fluorouracil-associated cardiotoxicity has been observed after intravenous, enteral[58,59,76] and topical[77] administration. In addition, no difference was found with regard to the incidence of cardiotoxicity between fluorouracil monotherapy, fluorouracil-containing multiple drug regimens, or fluorouracil therapy combined with folinic acid.[11,21,25,44] In one study,[25] concomitant administration of etoposide was reported to increase the risk of fluorouracil-associated cardiotoxicity. However, little is really known about the interference of any co-medication with the metabolism or cytotoxic action of fluorouracil.[3]

Although fluorouracil clearance was found to be significantly lower in women,[78] the incidence of fluorouracil cardiotoxicity does not appear to relate to gender. Likewise, there is no correlation with age or the type of underlying tum-

our.[11,19,22,25,42,63,70,73] Fluorouracil-related cardiac adverse events have been described in children.[69,79]

In summary, the wide spectrum of potential pathogenetic mechanisms and associated predisposing risk factors leaves some uncertainty about their individual roles in fluorouracil-related cardiotoxicity. It may be suggested that the different mechanisms would come into effect at different intervals during the time course of this syndrome. Overall, however, it appears most likely to assume a multifactorial aetiology of fluorouracil-associated cardiotoxicity that renders it nearly impossible so far to predict patients at particular risk.

2. Clinical Presentation

The most common presenting complaint of fluorouracil-induced cardiotoxicity is angina-like chest pain, which has been reported in up to 89% of patients.[4,12,13,17,19,21,75] Less frequent symptoms include cardiac arrhythmias,[12,13,17,21,31,80,81] congestive heart failure,[14,21,64,69] myocardial infarction,[12,20,21,23,29,60,63,65,70,73,81,82] (dilatative) cardiomyopathy,[31,34,80,83] cardiogenic shock,[32,35,61,70,81] cardiac arrest or sudden death syndrome.[4,13,15,17,23,30,34,44,75,84-86] The symptomatic course may occasionally be recurrent.[32]

Most incidents occur during or several hours after initial courses of fluorouracil treatment.[4,9,10,12,13,18,21,23-25,27,31-33,36,42,60,61,63,70,74,76,84,86-91]

In a prospective multicentre cohort study, fluorouracil-associated cardiotoxicity occurred in 3.4% of patients receiving their first course of treatment compared with 0.7% of patients during repeat courses of chemotherapy.[25] In a recent meta-analysis, clinical symptoms appeared within 72 hours from the start of fluorouracil administration in 52% of patients.[4] In other studies the mean time from initiation of fluorouracil medication to onset of cardiac symptoms was reported to range from few hours[11] to several days.[16,17] 'Silent' ischaemic ECG changes were documented as early as 20 hours after starting fluorouracil treatment.[44] Rarely, cardiotoxic episodes have been described after long term fluorouracil use.[29]

3. Diagnostic Features

Cardiac enzyme serum levels are usually normal during episodes of fluorouracil-related cardiotoxicity.[4,9,14,17,19,21,24,30-32,34,57,60,61,76,87]

ECG recordings revealed characteristic ischaemic changes in 68 to 88% of patients (fig. 1)[4,17] and arrhythmias in 38% of patients,[4,92] normal ECG recordings have also been described.[69,77,79,86] ECG alterations may vary during the course of fluorouracil cardiotoxicity and may be observed only intermittently in some patients,[91] with no close correlation to type and severity of clinical symptoms (fig. 1 a-c).

When continuous ambulatory ECG (Holter) monitoring was prospectively performed in patients undergoing fluorouracil chemotherapy, both incidence and duration of 'silent' reversible ST segment depression increased about 3-fold each compared with initial recordings, while only 4% of these patients eventually developed symptomatic angina. In contrast, no significant difference was detected in the overall incidence of ventricular ectopy in patients before and during fluorouracil therapy.[44] Noninvasive measurement of myocardial electrical stability by analysis of recovery time indices did not reveal any mechano-electrical disarrangement in these patients.[93]

Echocardiography revealed transient regional, or more often global, left ventricular dysfunction in 24 to 56% of patients,[4,12,14,17,89] lasting for up to 7 days and resembling postischaemic 'stunned myocardium' syndrome.[12,17,24,31,85,94] The prompt reversibility of systolic ventricular malfunction after discontinuation of fluorouracil therapy in patients experiencing cardiotoxicity might not represent the true extent of cardiac damage. Indeed, alterations of diastolic relaxation are more pronounced and may last for weeks.[62]

Chest x-ray may demonstrate consequences of left ventricular dysfunction such as cardiac enlargement or pulmonary congestion,[14,64,69,83] but it is often normal. Similarly, thallium scintigraphy was described to be regular in this syndrome.[36]

Subsequent coronary angiography[17,22,29-36,57] or necropsy[27,60,61,89] did not reveal major coronary

atherosclerosis in patients with fluorouracil-associated cardiotoxicity, although aneurysmatic coronary artery malformation[29] or intimal hyperplasia[27] have been anecdotally described in these patients. In addition, endomyocardial biopsies obtained in patients recovered from fluorouracil-related cardiotoxicity were grossly unremarkable.[31,32]

4. Therapeutic Options

Once fluorouracil-associated cardiotoxicity occurs there is a need for intensive monitoring because of the risk of life-threatening low cardiac output syndrome and malignant arrhythmias. Treatment is mainly symptomatic, and directed to the complaints of the patient. Overall response rate of symptomatic fluorouracil-associated cardiotoxicity to any form of treatment was reported to reach 87%.[4] Among therapeutic options, nitrates were described to be both effective[27,30,32,33,37,42,64,76,77,84,87] and less effective or ineffective.[12,21,25,36,82,85,86] Similarly, calcium antagonists were considered both to be the treatment of choice[28] and to lack therapeutic efficacy.[12,25,27,36,85,86] Considering the limited spectrum of treatment options, a trial of both nitrates and calcium antagonists perhaps accompanied by effective heparinisation, may be worthwhile in this syndrome. Severe anginal symptoms may require supportive opiate analgesia.

To our knowledge, there are no published data investigating the use of other cardiotropic drugs, such as molsidomine, β-blockers or ACE inhibitors, in fluorouracil-associated cardiotoxicity. However, from all published uncontrolled observations, it may well be expected that a considerable number of patients will experience spontaneous improvement after discontinuation of fluorouracil administration alone.

Intravenous uridine has been proposed for treatment of acute fluorouracil intoxication, since this compound competes with fluorouracil for its binding sites in DNA or RNA synthesis. While haemodialysis was not found to reduce fluorouracil plasma concentrations effectively, charcoal haemoperfusion could be demonstrated to substantially increase fluorouracil clearance.[90]

5. Prognostic Considerations

Prognosis of fluorouracil-associated cardiotoxicity is usually good, with most clinical symptoms, laboratory changes and electrocardiographic or echocardiographic alterations being promptly and fully reversible. The mean resolution time of symptoms was reported to range from 20 minutes to 2 days.[17,19] Once recovered, there appear to be no late sequelae after most incidents.[4,12,17,24,44,69] However, fatal events have been described,[82,86] resulting in an overall mortality rate of 2.2 to 13.3%.[4,17,18,74]

Repeated exposure to fluorouracil carries a high risk of relapse,[9,10,12,17,18,20,21,24,26,30,33,42,57, 64,70,76,81,82,86-89] being reported in 82 to 100% of cases.[4,73,74,85] Not uncommonly, such relapse may present with a clinical picture different to that during initial episodes of this syndrome.[69]

6. Conclusions and Recommendations

When using fluorouracil, particular care should be taken to check for cardiotoxicity, since no reliable criteria are established to identify specific patients at risk.[4,15,17,63,85] It remains controversial if patients with pre-existing heart disease should be assessed differently from those without concomitant cardiac pathology, since there are not many hard data on these patients.[4] Given the malignant underlying disease and the high antiproliferative potential of the drug, there appears to be no absolute contraindication for fluorouracil administration, although patients with recent myocardial infarction, unstable angina refractory to treatment, malignant arrhythmias or severe heart failure should probably be excluded from this therapy.

As a routine cardiac workup before fluorouracil administration in asymptomatic patients, an electrocardiogram should be performed. Once cardiomyopathy or coronary artery disease is suspected, cardiac enzymes should be checked, and a baseline echocardiogram should be done. Routine echocardiographic monitoring as advocated by others[62] appears to be too extensive, both in view of the large number of patients currently receiving fluorouracil chemotherapy, and particularly due to the

lack of therapeutic consequences on the basis of the present data.

Prophylactic anti-anginal medication has been advised in selected patients,[20,42,64,88,92] but beneficial effects have not been established.[4,21,25,36,57,74,85]

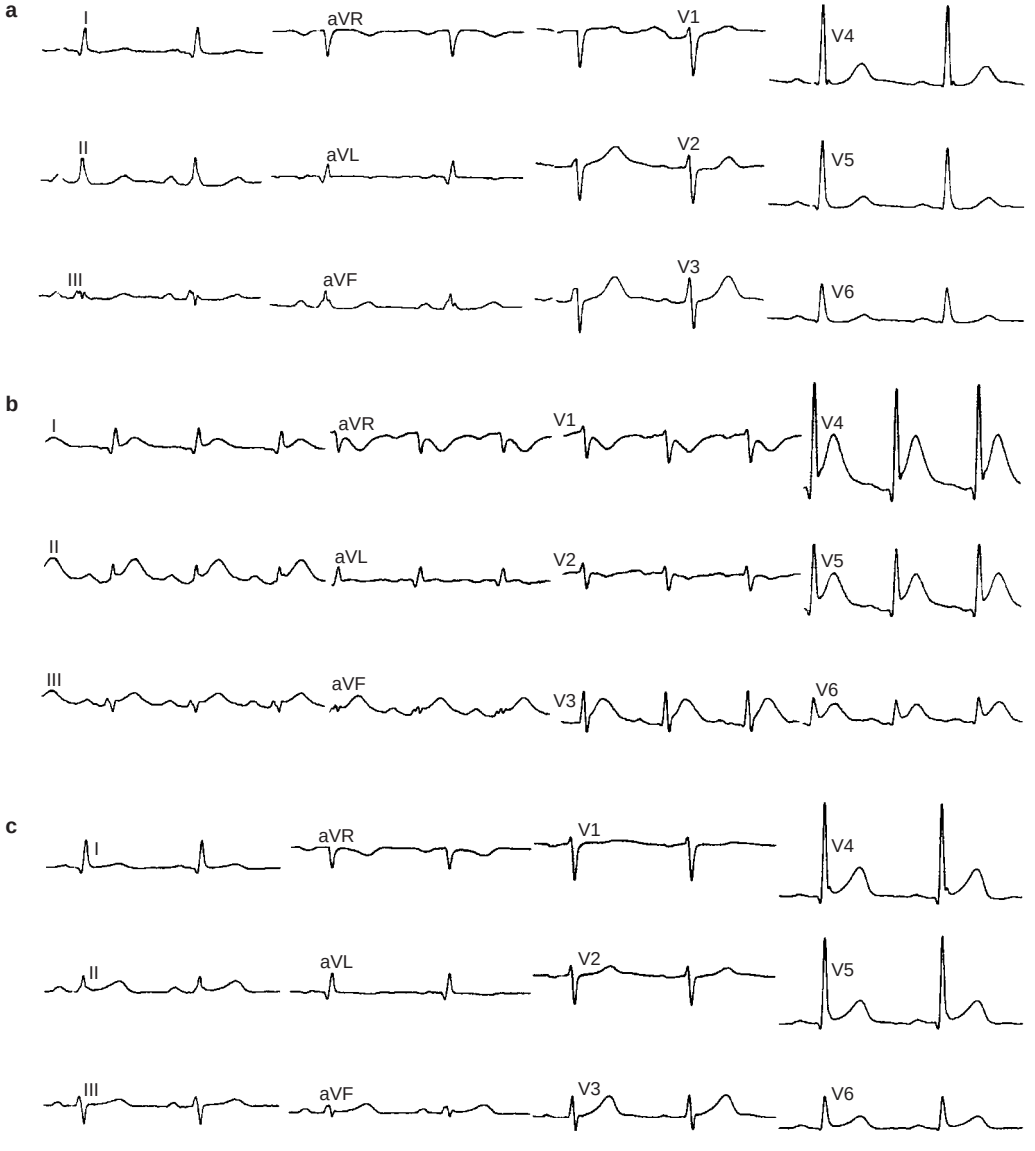

Fig. 1. Follow-up electrocardiography in fluorouracil-associated cardiotoxicity. A patient with metastatic colonic carcinoma experienced angina-like chest pain during his second course of palliative high dose intravenous fluorouracil treatment. (**a**) Initial tracings during this episode revealed no abnormalities, despite the patient being in severe distress. (**b**) During follow-up, multiple ST segment elevations were demonstrated. (**c**) Four hours later, while under intravenous treatment with nitrates, diltiazem and heparin, symptoms and electrocardiographic changes had resolved. **aVF, aVL, aVR** = Goldberger extremity leads; **V1-V6** = Wilson chest leads; **I, II, III** = Einthoven extremity leads.

Therefore, it should not be recommended routinely. It has been sporadically suggested that DPD activity be screened in peripheral blood mononuclear cells of cancer patients prior to fluorouracil chemotherapy.[90,95] However, adjustment of fluorouracil dosage according to this parameter in order to reduce the risk of fluorouracil-associated cardiotoxicity appears doubtful.[53,55,56]

Ambulatory patients should be advised to seek medical attention without delay when symptoms or signs of cardiotoxicity arise. Fluorouracil should immediately be discontinued when cardiac complaints occur, and it should no longer be used in patients who have previously had adverse cardiac effects with this compound.[11,21] For relief of cardiac symptoms, a trial of nitrates and/or calcium antagonists is warranted. ACE inhibitors may also be helpful. The most appropriate alternative chemotherapy after fluorouracil-associated cardiotoxicity is a matter of debate and should be decided individually. Raltitrexed, another specific thymidylate synthase inhibitor, has recently been successfully used in 2 patients with colon cancer and severe fluorouracil-associated cardiotoxicity.[57]

Increasing awareness of the potential cardiotoxicity of fluorouracil is expected to increase the reported incidence of cardiac complications with this antiproliferative compound. However, it will continue to be an indispensable and relatively safe drug in oncology.

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References

1. Heidelberger C, Chaudhuri NK, Danneberg P, et al. Fluorinated pyrimidines, a new class of tumour-inhibitory compounds. Nature 1957; 179: 663-6
2. Friedman MA, Sadée W. The fluoropyrimidines: biochemical mechanisms and design of clinical trials. Cancer Chemother Pharmacol 1978; 1: 77-82
3. Diasio RB, Harris BE. Clinical pharmacology of 5-fluorouracil. Clin Pharmacokinet 1989; 16: 215-37
4. Robben NC, Pippas AW, Moore JO. The syndrome of 5-fluorouracil cardiotoxicity: an elusive cardiopathy. Cancer 1993; 71: 493-509
5. Liss RH, Chadwick M. Correlation of 5-fluorouracil (NSC-19893) distribution in rodents with toxicity and chemotherapy in man. Cancer Chemother Rep 1974; 58: 777-86
6. Andersson M, Domellöf L, Häggmark S, et al. Cardiopulmonary hemodynamics and pharmacokinetics after hepatic intra-arterial infusion of 5-fluorouracil (5-FU). Cancer Chemother Pharmacol 1988; 22: 251-5
7. Gaveau T, Banzet P, Marneffe H, et al. Troubles cardio-vasculaires au cours d'infusions d'anti-mitotiques a fortes doses. 30 observations cliniques. Anesth Anal Réan 1969; 26: 311-27
8. Dent RG, McColl I. 5-Fluorouracil and angina. Lancet 1975; I: 347-8
9. Roth A, Kolaric K, Popovic S. Cardiotoxicity of 5-fluorouracil (NSC-19893). Cancer Chemother Rep 1975; 59: 1051-2
10. Pottage A, Holt S, Ludgate S, et al. Fluorouracil cardiotoxicity. BMJ 1978; i: 547
11. Labianca R, Beretta G, Clerici M, et al. Cardiac toxicity of 5-fluorouracil: a study on 1083 patients. Tumori 1982; 68: 505-10
12. Patel B, Kloner RA, Ensley J, et al. 5-Fluorouracil cardiotoxicity: left ventricular dysfunction and effect of coronary vasodilators. Am J Med Sci 1987; 294: 238-43
13. Eskilsson J, Albertsson M, Mercke C. Adverse effects during induction chemotherapy treatment with cis-platin and 5-fluorouracil. Radiother Oncol 1988; 13: 41-6
14. Jakubowski AA, Kemeny N. Hypotension as a manifestation of cardiotoxicity in three patients receiving cisplatin and 5-fluorouracil. Cancer 1988; 62: 266-9
15. Gradishar WJ, Vokes EE. 5-Fluorouracil cardiotoxicity: a critical review. Ann Oncol 1990; 1: 409-14
16. May D, Wandl U, Becher R, et al. Cardiotoxicity of 5-fluorouracil. Dtsch Med Wschr 1990; 115: 618-21
17. de Forni M, Malet-Martino MC, Jaillais P, et al. Cardiotoxicity of high-dose continuous infusion fluorouracil: a prospective clinical study. J Clin Oncol 1992; 10: 1795-801
18. Sorbette F, Simon I, Bonneterre J, et al. Etude prospective multicentrique des accidents cardiaques survenus au cours de traîtements comportant du 5-FU. Thérapie 1992; 47: 371-3
19. Akhtar SS, Salim KP, Bano ZA. Symptomatic cardiotoxicity with high-dose 5-fluorouracil infusion: a prospective study. Oncology 1993; 50: 441-4
20. Anderson NR, Lokich JJ, Moore C. The syndrome of 5-fluorouracil cardiotoxicity: an elusive cardiopathy. Cancer 1993; 72: 2287-8
21. Schöber C, Papageorgiou E, Harstrick A, et al. Cardiotoxicity of 5-fluorouracil in combination with folinic acid in patients with gastrointestinal cancer. Cancer 1993; 72: 2242-7
22. Anand AJ. Fluorouracil cardiotoxicity. Ann Pharmacother 1994; 28: 374-8
23. McLachlan SA, Millward MJ, Toner GC, et al. The spectrum of 5-fluorouracil cardiotoxicity. Med J Aust 1994; 161: 207-9
24. Weidmann B, Jansen W, Heider A, et al. 5-Fluorouracil cardiotoxicity with left ventricular dysfunction under different dosing regimens. Am J Cardiol 1995; 75: 194-5
25. Meyer CC, Calis KA, Burke LB, et al. Symptomatic cardiotoxicity associated with 5-fluorouracil. Pharmacother 1997; 17: 729-36

26. Escudier B, Alexandre JB, Leclercq B, et al. Cardiotoxicité du 5 fluorouracil: caractéristiques, mécanisme, conduite pratique. Presse Med 1986; 15: 1819-21
27. Burger AJ, Mannino S. 5-Fluorouracil-induced coronary vasospasm. Am Heart J 1987; 114: 433-6
28. Oleksowicz L, Bruckner HW. Prophylaxis of 5-fluorouracil-induced coronary vasospasm with calcium channel blockers. Am J Med 1988; 85: 750-1
29. Leone B, Rabinovich M, Ferrari CR, et al. Cardiotoxicity as a result of 5-fluorouracil therapy. Tumori 1985; 71: 55-7
30. Sanani S, Spaulding MB, Masud ARZ, et al. 5-FU cardiotoxicity. Cancer Treat Rep 1981; 65: 1123-5
31. Chaudary S, Song SYT, Jaski BE. Profound, yet reversible, heart failure secondary to 5-fluorouracil. Am J Med 1988; 85: 454-6
32. McKendall GR, Shurman A, Anamur M, et al. Toxic cardiogenic shock associated with infusion of 5-fluorouracil. Am Heart J 1989; 118: 184-6
33. Luwaert RJ, Descamps O, Majois F, et al. Coronary artery spasm induced by 5-fluorouracil. Eur Heart J 1991; 12: 468-70
34. Unverdorben M, Birkenhake S, Kunkel B, et al. Reversible global left ventricular dysfunction in patent coronary arteries following continuous infusion of 5-fluorouracil (5-FU). Strahlenther Onkol 1994; 170: 461-6
35. Misset B, Escudier B, Leclercq B, et al. Acute myocardiotoxicity during 5-fluorouracil therapy. Intensive Care Med 1990; 16: 210-1
36. Thyss A, Falewee MN, Leborgne L, et al. Cardiotoxicite du 5 fluoro-uracile: spasme ou toxicite myocardique directe? Bull Cancer 1987; 74: 381-5
37. Mosseri M, Fingert HJ, Varticovski L, et al. In vitro evidence that myocardial ischemia resulting from 5-fluorouracil chemotherapy is due to protein kinase C-mediated vasoconstriction of vascular smooth muscle. Cancer Res 1993; 53: 3028-33
38. Thyss A, Gaspard MH, Marsault R, et al. Very high endothelin plasma levels in patients with 5-FU cardiotoxicity [letter]. Ann Oncol 1992; 3: 88
39. Cwikiel M, Zhang B, Eskilsson J, et al. The influence of 5-fluorouracil on the endothelium in small arteries: an electron microscopic study in rabbits. Scanning Microsc 1995; 9: 561-76
40. Cwikiel M, Eskilsson J, Albertsson M, et al. The influence of 5-fluorouracil and methotrexate on vascular endothelium: an experimental study using endothelial cells in the culture. Ann Oncol 1996; 7: 731-7
41. Wenzel DG, Cosma GN. A model system for measuring comparative toxicities of cardiotoxic drugs for cultured rat heart myocytes, endothelial cells and fibroblasts: II. Doxorubicin, 5-fluorouracil and cyclophosphamide. Toxicology 1984; 33: 117-28
42. Freeman NJ, Costanza ME. 5-Fluorouracil-associated cardiotoxicity. Cancer 1988; 61: 36-45
43. Satoh H, Hashimoto K. Effects of ftorafur and 5-fluorouracil on the canine sinoatrial node. Jpn J Pharmacol 1983; 33: 357-62
44. Rezkalla S, Kloner RA, Ensley J, et al. Continuous ambulatory ECG monitoring during fluorouracil therapy: a prospective study. J Clin Oncol 1989; 7: 509-14
45. Millart H, Brabant L, Lorenzato M, et al. The effects of 5-fluorouracil on contractility and oxygen uptake of the isolated perfused rat heart. Anticancer Res 1992; 12: 571-6
46. Matsubara I, Kamiya J, Imai S. Cardiotoxic effects of 5-fluorouracil in the guinea pig. Jpn J Pharmacol 1980; 30: 871-9
47. Arellano M, Malet-Martino M, Martino R, et al. The anti-cancer drug 5-fluorouracil is metabolized by the isolated perfused rat liver and in rats into highly toxic fluoroacetate. Br J Cancer 1998; 77: 79-86
48. Tamatsu H, Nakazawa M, Imai S, et al. ^{31}P-topical nuclear magnetic resonance (^{31}P-TMR) studies of cardiotoxic effects of 5-fluorouracil (5-FU) and 5'-deoxy-5-fluorouridine (5'-DFUR). Jpn J Pharmacol 1984; 34: 375-9
49. Koenig H, Patel A. Biochemical basis for fluorouracil neurotoxicity: the role of Krebs cycle inhibition by fluoroacetate. Arch Neurol 1970; 23: 155-60
50. Tuchman M, Stoeckeler JS, Kiang DT, et al. Familial pyrimidinemia and pyrimidinuria associated with severe fluorouracil toxicity. N Engl J Med 1985; 313: 245-9
51. Diasio RB, Beavers TL, Carpenter JT. Familial deficiency of dihydropyrimidine dehydrogenase: biochemical basis for familial pyrimidinemia and severe 5 fluorouracil-induced toxicity. J Clin Invest 1988; 81: 47-51
52. Harris BE, Carpenter JT, Diasio RB. Severe 5-fluorouracil toxicity secondary to dihydropyrimidine dehydrogenase deficiency: a potentially more common pharmacogenetic syndrome. Cancer 1991; 68: 499-501
53. Milano G, Etienne MC. Potential importance of dihydropyrimidine dehydrogenase (DPD) in cancer chemotherapy. Pharmacogenetics 1994; 4: 301-6
54. Petit E, Milano G, Lévi F, et al. Circadian rhythm-varying plasma concentration of 5-fluorouracil during a five-day continuous venous infusion at a constant rate in cancer patients. Cancer Res 1988; 48: 1676-9
55. Harris BE, Song R, Soong SJ, et al. Relationship between dihydropyrimidine dehydrogenase activity and plasma 5-fluorouracil levels with evidence for circadian variation of enzyme activity and plasma drug levels in cancer patients receiving 5-fluorouracil by protracted continuous infusion. Cancer Res 1990; 50: 197-201
56. Etienne MC, Lagrange JL, Dassonville O, et al. Population study of dihydropyrimidine dehydrogenase in cancer patients. J Clin Oncol 1994; 12: 2248-53
57. Köhne CH, Thuss-Patience P, Friedrich M, et al. Raltitrexed (Tomudex): an alternative drug for patients with colorectal cancer and 5-fluorouracil associated cardiotoxicity. Br J Cancer 1998; 77: 973-7
58. Levillain R. Lésions cardiaques observées en microscopie optique chez le rat Wistar après ingestion de 5-fluoro-uracile. J Méd Besançon 1972; 8: 37-44
59. Levillain R. Myocardite expérimentale; étude anatomique de 210 coeurs de rats ayant ingéré du 5 fluoro-uracile. C R Soc Biol 1972; 2-3: 340-2
60. Maurer U, Härle M, Jungius KP. 5-Fluorouracil: cause of a fatal myocardial infarction during combined radiochemotherapy. Strahlenther Onkol 1996; 172: 257-9
61. Sasson Z, Morgan CD, Wang B, et al. 5-Fluorouracil related toxic myocarditis: case reports and pathological confirmation. Can J Cardiol 1994; 10: 861-4
62. Grandi AM, Pinotti G, Morandi E, et al. Noninvasive evaluation of cardiotoxicity of 5-fluorouracil and low doses of folinic acid: a one-year follow-up study. Ann Oncol 1997; 8: 705-8
63. Villani F, Guindani A, Pagnoni A. 5-Fluorouracil cardiotoxicity. Tumori 1979; 65: 487-95
64. Lang Stevenson D, Mikhailidis DP, Gillett DS. Cardiotoxicity of 5-fluorouracil. Lancet 1977; II: 406-7
65. Kuzel T, Esparaz B, Green D, et al. Thrombogenicity of intravenous 5-fluorouracil alone or in combination with cisplatin. Cancer 1990; 65: 885-9

66. Lemaire L, Malet-Martino MC, Longo S, et al. Fluoroacetaldehyde as cardiotoxic impurity in fluorouracil [letter]. Lancet 1991; 337: 560
67. Lemaire L, Malet-Martino MC, de Forni M, et al. Cardiotoxicity of commercial 5-fluorouracil vials stems from the alkaline hydrolysis of this drug. Br J Cancer 1992; 66: 119-27
68. Praga C, Beretta G, Labianca R. Cardiac toxicity from antitumor therapy. Oncology 1980; 37: 51-8
69. Lieutaud T, Brain E, Golgran-Toledano D, et al. 5-Fluorouracil cardiotoxicity: a unique mechanism for ischaemic cardiopathy and cardiac failure? Eur J Cancer 1996; 32A: 368-9
70. Clavel M, Siméone P, Grivet B. Toxicité cardiaque du 5-fluorouracile: revue de la littérature, cinq nouveaux cas. Presse Méd 1988; 17: 1675-8
71. Thyss A, Milano G, Schneider M, et al. Circulating drug levels in patients presenting cardiotoxicity to 5-FU. Eur J Cancer Clin Oncol 1988; 24: 1675-6
72. Fajardo LF, Stewart JR. Pathogenesis of radiation-induced myocardial fibrosis. Lab Invest 1973; 29: 244-57
73. Collins C, Weiden PL. Cardiotoxicity of 5-fluorouracil. Cancer Treat Rep 1987; 71: 733-6
74. Escudier B, Conscience G, Nkam M, et al. Cardiotoxicité du 5 fluoro-uracile: a propos d'un nouveau cas. Arch Mal Coeur Vaiss 1985; 10: 1579-81
75. Gradishar W, Vokes E, Schilsky R, et al. Vascular events in patients receiving high-dose infusional 5-fluorouracil-based chemotherapy: the University of Chicago experience. Med Pediatr Oncol 1991; 19: 8-15
76. Vorobiof DA. Cardiotoxicity of 5-fluorouracil. S Afr Med J 1982; 61: 634-5
77. Rozenman Y, Gurewich J, Gotsman MS. Myocardial ischemia induced by topical use of 5-fluorouracil. Int J Cardiol 1995; 49: 282-3
78. Milano G, Etienne MC, Cassuto-Viguier E, et al. Influence of sex and age on fluorouracil clearance. J Clin Oncol 1992; 10: 1171-5
79. Blütters-Sawatzki R, Grathwohl J, Mertens R, et al. Severe cardiotoxicity of high-dose 5-fluorouracil in combination with folinic acid, cisplatin and methotrexate in a 14-year-old boy with nasopharyngeal carcinoma (Schmincke Tumor). Oncol 1995; 52: 291-4
80. Raina A, Ferrante F, Bisol A, et al. Cardiotoxicity during chemotherapy for advanced gastroenteric tumors. Tumori 1987; 73: 359-61
81. Ferrari E, Taillan B, Tibi T, et al. Toxicité cardiaque du fluorouracile: aspects typiques et atypiques. A propos de 8 observations. Ann Cardiol Angéiol 1992; 41: 191-5
82. Soukop M, McVie JG, Calman KC. Flourouracil cardiotoxicity [letter]. BMJ 1978; i: 1422
83. Coronel B, Madonna O, Mercatello A, et al. Myocardiotoxicity of 5 fluorouracil. Intensive Care Med 1988; 14: 429-30
84. Millward MJ, Ganju V, Buck M. Cardiac arrest: a manifestation of 5-fluorouracil cardiotoxicity. Aust NZ J Med 1988; 18: 693-5
85. Ensley JF, Patel B, Kloner R, et al. The clinical syndrome of 5-fluorouracil cardiotoxicity. Invest New Drugs 1989; 7: 101-9
86. Davidson JA. Prevention of 5 fluorouracil associated cardiotoxicity. Aust NZ J Med 1994; 24: 321
87. Gamucci T, Zampa G. Cardiotoxicity of 5-fluorouracil. Tumori 1980; 66: 635-6
88. Beretta G, Labianca R, Montinari F, et al. Antitumor chemotherapy after fluorouracil angina. J Cancer Res Clin Oncol 1982; 104: 321-2
89. Baker WP, Dainer P, Lester WM, et al. Ischemic chest pain after 5-fluorouracil therapy for cancer. Am J Cardiol 1986; 57: 497-8
90. Fleming RA, Milano GA, Gaspard MH, et al. Dihydropyrimidine dehydrogenase activity in cancer patients. Eur J Cancer 1993; 29A: 740-4
91. Farooqi IS, Aronson JK. Iatrogenic chest pain: a case of 5-fluorouracil cardiotoxicity. Q J Med 1996; 89: 953-5
92. Kleiman NS, Lehane DE, Geyer CE, et al. Prinzmetal's angina during 5-fluorouracil chemotherapy. Am J Med 1987; 82: 566-8
93. Orditura M, de Vita F, Sarubbi B, et al. Analysis of recovery time indexes in 5-fluorouracil-treated cancer patients. Oncol Rep 1998; 5: 645-7
94. Braunwald E, Kloner RA. The stunned myocardium syndrome: prolonged postischemic ventricular dysfunction. Circulation 1982; 66: 429-38
95. Lu Z, Zhang R, Diasio RB. Dihydropyrimidine dehydrogenase activity in human peripheral blood mononuclear cells and liver: population characteristics, newly identified deficient patients, and clinical implication in 5-fluorouracil chemotherapy. Cancer Res 1993; 53: 5433-82

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