5-Fluorouracil cardiotoxicity: A critical review

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Summary. 5-Fluorouracil is a commonly administered chemotherapy agent that has infrequently been associated with cardiotoxicity. This review highlights the clinical features of this syndrome as described in reports from the medical literature. Clinical and laboratory evidence supporting proposed underlying mechanisms are reviewed.

Key words. 5-Fluorouracil, toxicity, angina, thrombosis, myocardial infarction, coronary spasm

Introduction

5-Fluorouracil (5-FU) is among the most commonly used chemotherapy drugs in clinical oncologic practice. It has become useful in the treatment of a variety of human malignancies including gastrointestinal cancer, breast cancer, and head and neck cancer. 5-FU has shown antitumor activity as single agent therapy and synergistically with other antitumor agents, and a multitude of studies are currently assessing the modulation of 5-FU with leucovorin and other biochemical agents [1]. In addition, 5-FU is commonly used as a radiosensitizing agent [2-4]. The common clinical toxicities of 5-FU affect rapidly dividing tissues such as the bone marrow hematopoietic cells and the gastrointestinal mucosal cells. The toxicity of 5-FU is fairly predictable based on dose, schedule, and route of administration (Table 1) [1].

<table>
<thead>
<tr>
<th>Route</th>
<th>Schedule</th>
<th>Dose (mg/m²/day)</th>
<th>Dose-limiting toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV</td>
<td>daily x 5, bolus</td>
<td>400-500</td>
<td>myelosuppression</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>diarrhea</td>
</tr>
<tr>
<td></td>
<td></td>
<td>450-500</td>
<td>myelosuppression</td>
</tr>
<tr>
<td></td>
<td>weekly bolus</td>
<td></td>
<td>mucositis</td>
</tr>
<tr>
<td>IV</td>
<td>daily x 5, CI</td>
<td>750-1100</td>
<td>diarrhea</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>mucositis</td>
</tr>
<tr>
<td>IV</td>
<td>protracted CI</td>
<td>200-400</td>
<td>mucositis</td>
</tr>
<tr>
<td>HAI</td>
<td>daily x 14-21, CI</td>
<td>750-1100</td>
<td>dermatitis (hand-foot)</td>
</tr>
<tr>
<td>IP</td>
<td>32-120 hours</td>
<td>5nM</td>
<td>mucositis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>diarrhea</td>
</tr>
</tbody>
</table>

Abbreviations:
HAI – hepatic artery infusion;
IP – intraperitoneal;
CI – continuous infusion.

Adapted from [1]

Table 2. Cardiac manifestations reported with 5-FU administration.

<table>
<thead>
<tr>
<th>Angina</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supraventricular tachycardia</td>
</tr>
<tr>
<td>Ventricular tachycardia</td>
</tr>
<tr>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>Reversible cardiomyopathy</td>
</tr>
<tr>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>Sudden death</td>
</tr>
</tbody>
</table>

Less frequently reported and evaluated is the possible association between 5-FU administration and the development of cardiac manifestations (Table 2). This review will highlight the clinical features of the syndrome and discuss the evidence supporting possible underlying mechanisms that have been proposed.

Scattered cases of cardiotoxicity associated with 5-FU administration have been reported (Table 3) [5-28]. The clinical manifestations that have been described include arrhythmias, silent myocardial ischemia, angina, congestive heart failure, myocardial infarction, cardiogenic shock, and sudden death. Unfortunately, most reports are based on observations in only a few patients. To further add to the problem, particularly in the earlier reports, few diagnostic tests were performed to evaluate cardiac function during or after 5-FU administration. More recently attempts have been initiated to prospectively assess cardiac function [29] and the coagulation system [30] with the goal of predicting which patients may be susceptible to 5-FU cardiotoxicity as well as to provide insight into the underlying mechanism that causes cardiotoxicity.

Epidemiology

The reported cases of 5-FU cardiotoxicity (Table 3) involve a very diverse group of patients with a variety of underlying malignant disorders. Breast carcinoma,
<table>
<thead>
<tr>
<th>Investigator [ref]</th>
<th>No. of patients</th>
<th>Cardiac risk factors</th>
<th>Concomitant chemotherapy</th>
<th>Concomitant radiation</th>
<th>Mode of administration</th>
<th>Clinical manifestation</th>
<th>Cardiac evaluation</th>
<th>Recurrence with rechallenge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dent, 1975 [5]</td>
<td>3</td>
<td>1/3</td>
<td>-</td>
<td>-</td>
<td>CI</td>
<td>a; b; f-1</td>
<td>-</td>
<td>2 patients</td>
</tr>
<tr>
<td>Roth, 1975 [6]</td>
<td>1</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>IVP</td>
<td>a; b</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Stevenson, 1977 [7]</td>
<td>1</td>
<td>0</td>
<td>-</td>
<td>CI</td>
<td>a; b; g</td>
<td>-</td>
<td>-</td>
<td>yes</td>
</tr>
<tr>
<td>Soukop, 1978 [8]</td>
<td>2</td>
<td>0</td>
<td>-</td>
<td>IVP</td>
<td>a-2; b-2; c-1; d-1; e-1; h-1</td>
<td>-</td>
<td>-</td>
<td>1 patient</td>
</tr>
<tr>
<td>Pottage, 1978 [9]</td>
<td>3</td>
<td>0</td>
<td>-</td>
<td>IVP</td>
<td>a-4; b-4; c-1; d-1</td>
<td>-</td>
<td>-</td>
<td>1 patient</td>
</tr>
<tr>
<td>Villani, 1979 [10]</td>
<td>2</td>
<td>0</td>
<td>thiotepa-1</td>
<td>IVP</td>
<td>a-2; b-2; c-1; e-1</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Sanani, 1981 [12]</td>
<td>2</td>
<td>1/2</td>
<td>-</td>
<td>CI</td>
<td>a-2; b-2</td>
<td>1-nl stress test</td>
<td>1-nl angiogram</td>
<td>V. tach, cardiac arrest</td>
</tr>
<tr>
<td>Labianca, 1982 [13]</td>
<td>17</td>
<td>6/17</td>
<td>CTX, VCR, BeNU, MeCCNU, MTX-10</td>
<td>IVP</td>
<td>a-16; b-12; c-1; d-1; e-1; f-3</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Vorobiof, 1982 [14]</td>
<td>1</td>
<td>0</td>
<td>VCR, CCNU</td>
<td>IVP</td>
<td>a; b</td>
<td>-</td>
<td>nl-stress test</td>
<td>-</td>
</tr>
<tr>
<td>Underwood, 1983 [15]</td>
<td>1</td>
<td>0</td>
<td>-</td>
<td>CI</td>
<td>a; b</td>
<td>-</td>
<td>nl-stress test</td>
<td>-</td>
</tr>
<tr>
<td>Leone, 1985 [16]</td>
<td>1</td>
<td>0</td>
<td>CCNU</td>
<td>IVP</td>
<td>a; b; d; f</td>
<td>-</td>
<td>angiogram - fusiform dilatations of coronary arteries</td>
<td>-</td>
</tr>
<tr>
<td>Baker, 1986 [17]</td>
<td>1</td>
<td>0</td>
<td>-</td>
<td>IVP</td>
<td>a; b; c</td>
<td>-</td>
<td>echocardiogram: E.F. - 30% repeated - E.F. 57% nl stress test; autopsy nl coronary arteries</td>
<td>yes</td>
</tr>
<tr>
<td>Blijham, 1985 [18]</td>
<td>2</td>
<td>0</td>
<td>vindesine-2</td>
<td>CI</td>
<td>a-2; b-2</td>
<td>-</td>
<td>echocardiogram - nl thallium scan - nl autopsy - nl coronaries</td>
<td>yes</td>
</tr>
<tr>
<td>Mancuso, 1986 [19]</td>
<td>1</td>
<td>0</td>
<td>-</td>
<td>CI</td>
<td>a; b</td>
<td>-</td>
<td>-</td>
<td>no</td>
</tr>
<tr>
<td>Burger, 1987 [20]</td>
<td>1</td>
<td>0</td>
<td>-</td>
<td>CI</td>
<td>a; b</td>
<td>ichocardiogram - nl thallium scan - nl autopsy - nl coronaries</td>
<td>yes</td>
<td></td>
</tr>
<tr>
<td>Raina, 1987 [21]</td>
<td>2</td>
<td>0</td>
<td>mitomycin C, doxorubicin-1</td>
<td>IVP</td>
<td>a-2; b-2; f-1</td>
<td>-</td>
<td>1-echocardiogram markedly enlarged LV</td>
<td>-</td>
</tr>
<tr>
<td>Collins, 1987 [22]</td>
<td>3</td>
<td>2/3</td>
<td>CDDP-3</td>
<td>CI</td>
<td>a-3; b-3; c-1; d-1</td>
<td>1-pyrophosphate scan Ml, EF - 27% angiogram, thallium scan ergonovine challenge - nl</td>
<td>yes</td>
<td></td>
</tr>
<tr>
<td>Thyss, 1987 [23]</td>
<td>1</td>
<td>0</td>
<td>CDDP</td>
<td>CI</td>
<td>a; b</td>
<td>-</td>
<td>angiogram, thallium scan ergonovine challenge - nl</td>
<td>-</td>
</tr>
<tr>
<td>Patel, 1987 [24]</td>
<td>7</td>
<td>6/7</td>
<td>CDDP-5</td>
<td>CI-7</td>
<td>a-9/13 cycles; b-12/13 cycles</td>
<td>1-echocardiogram - 5 patients LV wall abnormalities which resolved over time</td>
<td>-</td>
<td>yes</td>
</tr>
<tr>
<td>Coronel, 1987 [25]</td>
<td>1</td>
<td>yes</td>
<td>CDDP</td>
<td>CI</td>
<td>b; c</td>
<td>Echocardiogram - hypocontractile, dilated LV; reversible</td>
<td>-</td>
<td>no</td>
</tr>
<tr>
<td>Jakubowski, 1988 [26]</td>
<td>3</td>
<td>0</td>
<td>CDDP</td>
<td>CI</td>
<td>a; b-3; c-3; g-2</td>
<td>Echocardiogram - LV dysfunction</td>
<td>-</td>
<td>no</td>
</tr>
<tr>
<td>Freeman, 1988 [27]</td>
<td>1</td>
<td>yes</td>
<td>CDDP</td>
<td>CI</td>
<td>a; b</td>
<td>Angiogram - nl coronary arteries Ergonovine challenge - nl</td>
<td>-</td>
<td>yes</td>
</tr>
<tr>
<td>Gradishar, 1990 [28]</td>
<td>15</td>
<td>yes</td>
<td>CDDP, MTX</td>
<td>CI</td>
<td>a-3; b-4; d-1; h-10</td>
<td>None</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
gastrointestinal carcinoma, head and neck carcinoma, and lung carcinoma account for the majority of underlying cancers in affected patients since 5-FU alone or in combination regimens has demonstrated activity against these diseases. However, many of the affected patients, particularly those with lung cancer and head and neck cancer, have a long history of cigarette smoking and thus an increased risk of atherosclerotic coronary artery disease [31]. Similarly, many of these same patients have a history of alcohol abuse which can lead to the development of a dilated cardiomyopathy with the attendant risk of arrhythmias and thrombus formation [32]. Therefore, the difficulty of determining what role, if any, 5-FU plays in the development of cardiac events is easy to appreciate. Nevertheless, the reported cases provide a framework and data base for discussing this syndrome.

Incidence

The incidence of clinically apparent 5-FU cardiotoxicity is less than 10% in patients receiving the drug. Labianca et al. reported an incidence of 1.6% in a retrospective review of 1083 patients who received 5-FU alone or in combination with other agents [13]. Increasing age or treatment with multiple chemotherapy agents did not increase the risk of cardiotoxicity; however, a previous history of ischemic heart disease was associated with an increased risk of developing cardiac complications. Similarly, Pottage et al. determined that 5-FU cardiotoxicity occurred in 4 of 140 patients (2.9%) that were retrospectively reviewed [9]. The clinical manifestations in the four cases were chest pain and new EKG abnormalities. More recently, Kuwabara et al. reported that 5-FU cardiotoxicity occurred in 4 of 140 patients (2.9%) that were retrospectively reviewed [33]. In our own experience at the University of Chicago, we reported on 15 patients out of a total of 277 (5.4%) who developed cardiac toxicity (e.g., EKG abnormalities, chest pain, myocardial infarction, sudden death) while receiving high-dose (>800 mg/m²/day), continuous infusion 5-FU [28]. These are all anecdotal reports based on retrospective review and the cardiac evaluation in most cases was minimal.

Etiology

The underlying mechanism of 5-FU cardiotoxicity remains undefined; however, speculation has focused on a direct cardiac effect of 5-FU or an indirect effect by perturbation of the coagulation system.

Animal studies

Few laboratory or animal studies have been done that contribute to our understanding of 5-FU's effect on the heart or vascular endothelium. Levillain, using a rat model, was able to demonstrate edema of myocardial fibers and loss of striation within 12 hours of exposure to 5-FU [34]. Liss and Chadwick demonstrated that radiolabeled 5-FU (C14) injected into mice localized within the myocardium and retained radioactivity for 96 hours which was longer than most organ systems [35]. Other investigators have concluded that 5-FU's effect on the myocardium is due to disruption of the tricarboxylic acid cycle within the myocytes. Matsubara et al. [36] and Tamatsu et al. [37] have reported animal data that supports the theory that 5-FU depletes high-energy phosphate compounds in the myocardium resulting in metabolic dysfunction of the myocardium. Satoh et al. demonstrated that 5-FU infused into a canine sinoatrial node and atrial preparation caused positive inotropic and chronotropic effects [38]. Similarly, Mosseri et al. recently reported that 5-FU induced arterial vasospasm in isolated aortic rings obtained from rabbits [39]. Vasospasm occurred with increasing frequency as the concentration of 5-FU was increased. Whether these effects occur in humans is unknown; however, if these metabolic and hemodynamic changes do occur during 5-FU administration, particularly in patients with underlying coronary artery disease, cardiac function may be compromised.

Observations in human subjects

Rezkalla et al. at Wayne State University recently reported a prospective study that confirmed a high incidence of cardiac ischemia during 5-FU infusions [29]. Employing continuous EKG monitoring during continuous infusion of 5-FU, 6 of 25 patients (24%) were found to have ischemic ST-segment changes immediately before the 5-FU infusion (placebo) versus 12 of

<table>
<thead>
<tr>
<th>Table 3 (Continued).</th>
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</thead>
</table>

**Abbreviations:**
- CI - continuous infusion
- IVP - bolus administration
- CTX - cyclophosphamide
- VCR - vincristine
- MTX - methotrexate
- BeNU, MeCCNU - nitrosoureas
- nl - normal
- E.F. - ejection fraction

**Legend:**
- a - angina
- b - EKG abnormality
- c - hypotension
- d - myocardial infarct
- e - cardiogenic shock
- f - elevated cardiac enzymes
- g - congestive heart failure
- h - death
25 patients (68%) who were observed to have ischemic ST-segment changes during the 5-FU infusion. All EKG changes were clinically asymptomatic, except for one patient, and the majority of EKG changes occurred in patients with underlying coronary artery disease. Two patients who developed asymptomatic EKG changes died suddenly shortly after the 5-FU infusion was discontinued. At autopsy both patients were found to have extensive coronary artery disease without signs of newly infarcted myocardium. The Wayne State study highlights the potential risk of infusing 5-FU in patients with underlying coronary artery disease. Other investigators have determined that silent ischemia is associated with reduced coronary artery blood flow [40, 41]. Furthermore, silent ischemia in patients with coronary artery disease is similar to symptomatic episodes of ischemia (e.g. angina) in its ability to predict infarction and death [42].

Few other investigators have studied patients experiencing cardiac manifestations with a careful diagnostic evaluation adequate to explain why the clinical event occurred. Patel et al. recently reported 7 patients who developed 5-FU cardiotoxicity with a wide range of clinical manifestations (e.g., hypotension, angina, ventricular tachycardia, cardiogenic shock) [24]. As part of the evaluation 5 patients received echocardiograms demonstrating global or regional left ventricular wall motion abnormalities. Three patients received repeat echocardiograms 8–15 days following the initial study which showed interval improvement in left ventricular wall motion abnormalities. All three patients who demonstrated left ventricular dysfunction had one or more cardiac risk factors suggesting that some episodes of 5-FU cardiotoxicity may be superimposed on underlying coronary artery disease. Other investigators have reported similar cases of reversible left ventricular dysfunction [17, 25].

Another frequently advanced theory to explain the mechanism of 5-FU cardiotoxicity is coronary artery spasm. Many of the reported cases describe the clinical course and EKG findings that are consistent with coronary artery spasm; however, few patients have undergone cardiac catheterization while receiving an infusion of 5-FU as a means of demonstrating coronary artery spasm. Freeman et al. attempted to induce coronary artery spasm by administering an ergonovine challenge [27]. No spasm was detected, nor was vasospasm or angina noted when an intravenous infusion of 5-FU was administered at the same concentration and rate of infusion previously received. Prophylactically administering coronary vasodilators (e.g., nitrates or calcium channel blockers) in an effort to prevent coronary artery spasm has met with mixed success [7, 12, 15, 22, 24, 27]. Some patients are able to receive subsequent courses of 5-FU treatment without incident and others experience a recurrence of symptoms. Furthermore, some patients who experience cardiac toxicity during a 5-FU administration may have no cardiac complications during subsequent treatments with 5-FU even though no vasodilators were administered prophylactically [43].

The relationship between the route of 5-FU administration (e.g., bolus or continuous infusion) and the development of cardiotoxicity is not clear although the majority of patients received continuous infusion 5-FU. Furthermore, higher doses of 5-FU (>800 mg/m²) seem to increase the risk of cardiac events. In our own study there were 9 patients with sudden death who were treated with high-dose, continuous infusion 5-FU [28].

Contributing factors

Another confounding factor complicating the assessment of this syndrome is that many patients were treated with chemotherapy agents in addition to 5-FU (Table 3). The cytotoxic agents strongly associated with cardiotoxicity are anthracyclines, cyclophosphamide, and mitomycin C [44–46]. Acutely, anthracyclines such as doxorubicin and daunorubicin may cause arrhythmias and transient left ventricular failure, whereas irreversible left ventricular failure can occur once a cumulative dose of drug is surpassed (450–500 mg/m²) [44–46]. Acute myocardial necrosis has been described with the use of high dose cyclophosphamide particularly in the transplant setting. Reports have also described a myocarditis, similar to radiation-induced myocarditis, following prolonged use of mitomycin C [47]. Although cisplatin does not directly affect the heart, the preparative hydration regimen administered prior to cisplatin may result in acute volume overload precipitating left ventricular dysfunction. Furthermore, renal losses of magnesium, calcium, and potassium caused by cisplatin may precipitate arrhythmias. Since many of these drugs were used in combination with 5-FU, their contribution to cardiotoxicity cannot be discounted. A few patients have been reported who received mediastinal radiation prior to the exposure of 5-FU [12, 27]. Since mediastinal radiation may cause small vessel thrombosis (i.e., coronary arteries), the additional toxicity caused by 5-FU in these patient is difficult to access [48].

Abnormalities in the coagulation system

Abnormalities of the coagulation system have also been demonstrated during chemotherapy administration which suggests that coronary artery thrombosis may be the underlying cause of the clinical manifestations associated with 5-FU administration. Ruiz et al. reported on the changes detected in coagulation and fibrinolysis parameters in 40 patients with inoperable stage III and IV lung cancer [49]. Blood was sampled prior to and 48 hours after receiving chemotherapy. A significant increase in fibrinopeptide A (FPA) levels and a decrease in the level of functional tissue plasminogen activator were observed following the administration of chemotherapy. These findings suggest that chemotherapy may
decrease fibrinolytic activity resulting in an enhanced tendency to develop thrombosis.

Kuzel et al. recently reported on the results of a prospective study assessing the thrombogenicity of 5-FU [30]. Ten patients, six with head and neck cancer and four with gastrointestinal cancer, received continuous infusion 5-FU for 4 or 5 days. The six patients with head and neck cancer also received cisplatin on day 1. Blood samples were assayed for FPA, protein C activity, and protein C and protein S antigen. Samples were obtained prior to, during, and following the 5-FU infusion. A significant increase in FPA levels were observed during the infusion of 5-FU which returned to baseline at the end of the 5-day infusion. In addition, following the 5-FU infusion protein C activity was significantly lower than protein C antigen levels. During activation of the coagulation system, thrombin cleaves fibrinopeptides A and B from fibrinogen, forming fibrin monomers which self-assemble into the matrix of a clot. FPA is a specific biochemical marker of fibrin formation, and increased levels have been observed in patients with pulmonary embolism and venous thrombosis [50]. Protein C is one of the vitamin K-dependent plasma proteins which exerts an anticoagulant effect by enzymatic cleavage of factor Va and factor VIIIa. Patients with protein C deficiency are at increased risk for recurrent venous thrombosis, arterial thrombosis, and stroke [51–54]. Although no cardiac toxicity was observed by Kuzel et al., these findings suggest that coagulation is activated by 5-FU which may promote a hypercoagulable state (e.g., coronary artery thrombosis).

The observations of many investigators suggest that 5-FU cardiotoxicity is a real phenomenon. Patients with certain malignancies are best treated with 5-FU containing chemotherapy regimes. Unfortunately our present understanding of the syndrome does not reliably predict which patients will develop cardiotoxicity. As a result, the clinician must be vigilant for signs and symptoms which suggest a cardiac event. This is particularly important in patients with known underlying coronary artery disease. The frequency of silent ischemia detected in the study by Rezkalla et al. [29] supports this concern.

The underlying mechanism of 5-FU cardiotoxicity has not been clearly defined. The effect of the drug on the heart may be multifactorial as suggested by animal studies and coagulation studies. Further understanding of this syndrome will be gained through prospective clinical studies that carefully stratify patients according to cardiac risk factors. A prospective assessment of cardiac function and coagulation parameters (i.e., protein C, protein S, tissue plasminogen activator, antithrombin III, fibrinopeptide A, etc.) throughout the 5-FU infusion will also be necessary.

Acknowledgement

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