Angina Related to 5-Fluorouracil
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Treatment with 5-fluorouracil is common in oncological patients. Side effects on bone marrow, skin, and mucous membranes have been reported. Cardiotoxicity, which is less predictable, can be life-threatening. Manifestations include angina, arrhythmias, infarction, heart failure and cardiogenic shock. The toxic mechanisms that might be involved have been much discussed but have not yet been clearly established. Current evidence supports the possibility of a metabolic effect in common with the cascade secondary to ischemia due to coronary disease. Based on a case report, we discuss the usual clinical presentation, treatment and prognosis. Finally we make recommendations for managing patients being treated with 5-fluorouracil.

Key words: Unstable angina fluorouracil. Drug toxicity. Vasospasm.

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INTRODUCTION

5-fluorouracilo (5FU), an anti-neoplastic agent known since 1957, is a synthetic analogue of pyrimidine that degrades celluarily into various nucleotides that potently and competitively inhibit thymidilate synthesis, causing a depletion in thymidilate that capable of halting nuclear transcription and ribosome translocation. The cytotoxic effects are also mediated by the incorporation of fluorodexiuridine triphosphate into DNA and 5FU into RNA.

5FU has been used above all for the treatment of gastrointestinal adenocarcinoma, breast and prostate cancer, and squamous cell cancer of the head and neck in gynecological tumors.

The cardiotoxicity of some of the components used for treatment of patients with cancer is known: doxorubicin, with ultra structural changes related to accumulated doses; cyclophosphamide, which causes cardiac damage at high doses, and, infrequently, in cisplatin and radiation, but with possible synergy with other agents.

The cardiotoxicity of 5FU has been described as angina, with or without changes on electrocardiogram (ECG), acute myocardial infarction, induction or worsening of ventricular and supraventricular arrhythmias, and potentially reversible myocardial depression, analogous to that observed with anthracyclines. Nevertheless, its cardiac side-effects are less well known by clinicians than its effects on the mucous membranes, the skin, and the osseous medulla. We present a case in which the possible mechanisms of toxicity can be discussed, and practical conclusions reached.

CLINICAL CASE

The patient was a 69-year-old man whose only...
known significant clinical history was the diagnosis 3 months previously of stage IV sigma adenocarci-
oma, with infiltration of the bladder and retro perito-
neum, and metastases to the liver and upper right kid-
ney. Resection and permanent colostomy were
performed, and treatment with cisplatin and 5FU were
recommended by the oncology service. The patient
received an initial dose and another dose 6 days later.
Approximately 12 hours after receiving the latter
dose, the patient was taken to the emergency room
due to an episode of oppressive non-radiating chest
pain, suggestive of angina, with dyspnea and vegetati-
ve signs. On physical examination, neither murmurs
nor rubs were detected on cardiac auscultation, nor
were signs of ventricular dysfunction. There were no
significant changes on chest x-ray. On ECG a sinus
rhythm was observed, with greater than 1 mm depres-
sion of the ST segment in V5-V6 and less markedly I,
II, and V3-V4, and sharp symmetric T-waves in the
same locations (Figure 1).

The patient was treated with sublingual nitroglyceri-
ne, with instantaneous clinical improvement, normal-
ization of the ST segment, and complete inversion of
the T-waves in the same areas (Figure 2). The patient
later suffered a new episode of chest pain with the
same ECG changes that was completely controlled by
the administration of intravenous nitroglycerine. The
patient was admitted with a diagnosis of unstable angina,
and with the usual treatment regimen. Ordinary
analysis did not reveal significant changes on hemog-
gram, hydroelectric equilibrium tests, liver or kidney
function tests, or markers for myocardial lesion.

With the suspected diagnosis of vasospastic angina,
given the electrical changes and the patient’s behavior,
coronary angiography was performed, and revealed a
coronary tree without lesions, with normal volume and
segment contractility on ventriculography.

Under medical treatment with nitroglycerine and
calcium antagonists, the patient remained asymptoma-
tic. The ECG only showed persistent non-specific re-
polarization changes. 5FU therapy was discontinued,
and the patient received a new cisplatin dose days af-
fter the coronary angiography without incident. He
continued to be asymptomatic from a cardiological
point of view, until his death 7 months later secondary
to cancer.

DISCUSSION

The bibliography includes reviews of clinical cases
that have been collected, as well as the few prospecti-
ve studies designed to study this type of cardio-
toxicity. Its incidence varies, according to the
various series, from 1.2% to 18%. Little is known about the individual variability in the
pharmacokinetics of 5FU in host and tumor cells.
Eighty percent of the degradation is hepatic and 20%
is eliminated by the kidneys. Gastrointestinal mucous
membranes, the skin, the cerebellum, and the myocardium capture it selectively. The predominant side-
effects are diarrhea, stomatitis, nausea and vomiting.
leukopenia, alopecia, and cerebellar ataxia.

Clinical signs appear in the great majority of cases within the first 72 hours, and usually not later than within the first 3 cycles, which excludes the need for an accumulated dose. They tend to consist of angina with ischemic changes on ECG; they also appear with a normal ECG, and with less frequency as an infarct, arrhythmia, cardiac insufficiency, or cardiogenic shock. The symptoms are highly reproducible if treatment is stopped. In general, myocardial enzymes are unchanged. When echocardiography is performed, overall, or at times regional, dysfunction of the left ventricle can be detected that resolves in approximately 1 week, as does the myocardial daze. Coronary angiography and endomyocardial biopsy tend to be normal.

The physiopathology has yet to be unequivocally determined, if indeed a single cause exists. The temporal relationship and the clinical presentation strongly suggest an ischemic component or a common method of action with ischemia. The absence of coronary epicardial disease supports the hypothesis of vasospasm, and, in fact, aortic ring vasoconstriction in rabbits has been demonstrated after the administration of 5FU that is reversible with nitroglycerine administration. Nevertheless, there are no conclusive results with regard to the occurrence of vasospasm when 5FU is administered during coronary angiography in patients with cardiotoxicity. There has been discussion regarding damage of the endothelial cells with maximum effect during the first 3 days of treatment, coinciding with the clinical course, and of the added potential formation of a reversible thrombus. An ischemic toxic effect on cell metabolism has been suggested, mediated by the entrance into the Krebs cycle of its derivate, fluoroacetate. Metabolic changes have been described, with a decline in ATP values and citrate accumulation, in Guinea pigs with ischemia and electrocardiographic changes, without changes in the myocardial flow. In fact, there may be characteristics in common with fluoroacetate intoxication. Nevertheless, this does not explain the non-diffuse damage and the lack of effect on the non-cardiac organs. The 5FU dose, individual differences in metabolism, and myocardial susceptibility also may intervene in the process.

It seems clear that vasospasm by itself would not explain all the possible changes, or the histopathological findings of patchy or diffuse damage observed in patients who die of cardiogenic shock. There must be cell failure (mitochondrial, nucleic acid metabolism, structural proteins, ionic channels) that causes myocardial dysfunction, without evidence of necrosis and similar to a post-ischemic myocardial daze.

In some series a greater rate of cardiotoxicity has been noted in patients with a history of heart disease, but these results are controversial. The incidence of heart disease in the review of 134 cases compiled by Robvben el al is not greater than that of the general population in the same age group, and does not offer conclusive data showing that a history of heart disease increases the risk of cardiotoxicity. No differences have been found between the incidence of cardiotoxicity in 5FU monotherapy and 5FU poly-therapy. As in the case we present, angina and nonspecific ECG changes have been described, as well as supraventricular arrhythmias with 5FU and cisplatin, but the latter alone is rarely associated with cardiotoxicity. A synergic effect cannot be excluded, nor can the possibility that cisplatin is associated with a greater volume over-

Fig. 2. Electrocardiogram of the same patient after treatment.
load or electrolytic changes.

In summary, the existence of distinct mechanisms and possible predisposing factors make it very difficult to identify those patients at greater risk for developing these side-effects. Broader studies are needed to identify these risk factors.

Usually, there is good response to treatment with nitroglycerine and calcium antagonists, but these have not been proven to be effective prophylactically. Nevertheless, this toxicity is a potentially lethal complication, with a mortality rate described as 2.2%, generally by acute myocardial infarction or cardiogenic shock.

Given the widespread use of 5FU, it would seem prudent to recommend that a baseline ECG be performed, as well as echocardiography in patients with a history of heart disease. Initiating treatment in patients with a recent infarct, unstable angina, malignant arrhythmias, or severe cardiac insufficiency is not recommended. It is fundamental to note the appearance of cardiac symptoms or ECG changes, so that treatment can be interrupted immediately, thus avoiding more severe complications. In the case of cardiotoxicity, treatment is basically symptomatic, with nitroglycerine, calcium antagonists, and even ECA inhibitors. 5FU must not be restarted as it is highly probable that the symptoms will recur; treatment with raltitrexed is recommended instead.

REFERENCES