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 After cardiotoxic events, fluorouracil should definitely be withdrawn and replaced by an alternative antiproliferative regimen.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