Fluorouracil cardiotoxicity

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Summary and conclusions

Out of 140 patients treated with intravenous 5-fluorouracil, four developed ischaemic chest pain within 18 hours of either the second or third dose. In three of these patients the pain recurred after subsequent doses. Predose electrocardiograms in two cases were normal. None of the four patients had a history of ischaemic heart disease, although all had received left ventricular irradiation.

Although cardiotoxicity is a rare complication of fluorouracil treatment, it merits wider recognition.

Introduction

Chest pain after the administration of 5-fluorouracil is rare, and only five cases have been reported.[1-3] In four the pain was associated with changes in the electrocardiogram (ECG) or cardiac enzyme concentrations. Four patients developed further chest pain after subsequent doses, which in three responded to glyceryl trinitrate. We describe four similar cases of chest pain occurring after fluorouracil treatment.

Present series

One hundred and forty patients with carcinoma received 919 doses of fluorouracil. All had undergone radiotherapy, and in 70 the irradiated area included the left ventricle. Four patients developed chest pain. None had a history of myocardial infarction, angina, or hypertension, but all had received irradiation to the left ventricle.

Case 1—A 41-year-old woman with breast carcinoma received monthly bolus injections of fluorouracil 1000 mg intravenously. A pretreatment ECG was normal. Eighteen hours after the second injection she developed severe crushing central chest pain and was admitted to a coronary care unit. ECGs showed T-wave inversion in all anterior leads, but cardiac enzyme concentrations remained normal. One month later a further dose produced mild retrosternal discomfort but had no effect on the ECG abnormalities from the first episode; these partially resolved over four months.

Case 2—A 69-year-old woman with breast carcinoma received monthly bolus injections of fluorouracil 1250 mg intravenously. Three hours after the third dose she developed severe central chest pain which lasted for 48 hours and only partially responded to diamorphine. No further doses of fluorouracil were given.

Case 3—A 62-year-old man with gastric carcinoma received one dose of vincristine 2 mg intravenously, then daily bolus injections of fluorouracil 150 mg intravenously. Three hours after the third dose he developed crushing central chest pain, which radiated down the left arm. An ECG showed S-T elevation (leads V3-6) and tall, peaked T waves (leads V2-4). His serum lactate dehydrogenase concentration rose to 557 IU/l, confirming subendocardial infarction. The ECG abnormalities resolved in four days. Five days later a further dose of fluorouracil produced similar though less severe chest pain, which responded to glyceryl trinitrate.

Case 4—A 45-year-old woman with breast carcinoma received monthly bolus injections of fluorouracil 1350 mg intravenously. A pretreatment ECG was normal. Twelve hours after the second dose she developed mild chest tightness and breathlessness, which lasted for one hour. An ECG taken before the third dose was again normal. Three hours after the dose she experienced severe chest tightness and breathlessness lasting for 30 minutes and coinciding with the appearance on the monitoring ECG of tall, peaked T waves, which persisted for 20 hours. Serum aspartate transaminase and lactate dehydrogenase concentrations did not change.

Discussion

Chest pain after fluorouracil treatment, though rare, may cause considerable distress. Its severity ranges from mild angina to crushing chest pain indistinguishable from that of myocardial infarction, and it often recurs with subsequent doses of fluorouracil. Prediction of this complication is difficult: two of our patients had normal predose ECGs, and none had a history of myocardial ischaemia or hypertension.

The aetiology of fluorouracil cardiotoxicity is unknown, though several mechanisms have been proposed, including a direct toxic effect on myocardial cells and an autoimmune reaction.[3] These seem unlikely, however, as pain is uncommon in cardiomyopathy and myocarditis[4] and has occurred after only one dose of fluorouracil. The description of the pain and the response of milder episodes to glyceryl trinitrate strongly suggest cardiac ischaemia. It may be important that all our patients with pain had received myocardial irradiation, which is known to induce small vessel thrombosis. Irradiation was not a factor, however, in previous cases. Coronary artery spasm may be the cause of pain after the administration of fluorouracil but confirmation by angiography is hardly justifiable. Further studies are in progress to assess the number of patients who have altered ECG appearances but no pain while receiving fluorouracil.

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