Short Communication

Prophylactic options in patients with 5-fluorouracil-associated cardiotoxicity

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At present, the various mechanisms involved in 5-fluorouracil (5-FU)-correlated cardiotoxicity remain to be elucidated and a universally accepted prophylaxis or treatment for this specific toxicity is not available. Although it may improve time to progression, survival and clinical benefit, a 5-FU-based regimen usually has to be discontinued if a patient experiences cardiotoxicity. Here, we describe our experience with three cases of 5-FU-associated cardiotoxicity. The angina-like pain that appeared approximately 95 h after beginning 5-FU therapy was apparently independent of the drug’s administration modality. In the two patients receiving 5-FU 12-h flat continuous infusion from 22.00 to 10.00 h (5-FU 12-h c.i.) in combination with other drugs, the dose of 5-FU was reduced by 10–20% and patients received prophylactic transepidermal nitroglycerin. In the third patient, 5-FU administration modality was changed and prophylactic therapy was not given. By taking these precautions, the patients no longer complained of anginal pain and none of them discontinued chemotherapy.

Keywords: prophylaxis; cardiotoxicity; 5-fluorouracil

PATIENTS AND METHODS

Case 1

A 57-year-old male, with positive family history for acute myocardial infarction (AMI) but with no history of cardiovascular disease, came to our observation after undergoing an anterior resection of the rectum for a stage III rectal–sigmoid adenocarcinoma (RSA) (Table 1). Physical examination, chest X-rays, blood pressure and EKG were all within normal limits. The patient received four cycles of adjuvant chemotherapy with 5-FU (370 mg m⁻² day⁻¹) and folic acid (FA) (50 mg tot⁻¹) i.v. for 5 days, every 3 weeks. During adjuvant chemotherapy, disease progressed with liver metastasis and the patient's therapy was changed to irinotecan (180 mg m⁻²) day 1 and 5-FU 12-h flat continuous infusion from 22.00 to 10.00 h (5-FU 12-h c.i.) (900 mg m⁻² day⁻¹) for 4 days, every 2 weeks. Approximately 93 h after starting the first cycle of the second 5-FU regimen, the patient presented angina-like pain that lasted a few minutes and disappeared with oral nitroglycerin. The blood pressure was 160/115 mmHg and the heart rate was 105 beats min⁻¹. During the anginal attack, EKG recordings showed ST-T wave changes, ventricular dysfunction and cardiogenic shock.

The overall incidence of 5-FU cardiotoxicity varies from 1.2 to 18% of patients and is usually underestimated, since silent EKG alterations often occur (Klaus Becker et al, 1999). The different mechanisms involved in 5-FU-associated cardiotoxicity are not yet fully understood and no unequivocally effective prophylaxis or treatment for this specific toxicity exists. Here, we describe three cases of 5-FU-associated cardiotoxicity, its clinical management and the prophylactic treatment used.

Case 2

A 65-year-old male with high blood pressure (HBP), diabetes and gastritis came to our attention with abdominal lymphatic and pulmonary metastases from an ampulla of Vater adenocarcinoma...
(Table 1). He received one cycle of induction chemotherapy containing cisplatin (CDDP) (100 mg m⁻² day⁻¹) day 1 and 5-FU 12-h.c.i. (1000 mg m⁻² day⁻¹) for 5 days, every 3 weeks. Approximately 95 h after beginning the first cycle of 5-FU infusion, the patient referred several episodes of anginal pain, associated with sweating, that disappeared with oral nitroglycerin. On day 5 of cycle I, the blood pressure was 130/80 mmHg, the heart rate was 104 b.p.m. and the EKG recorded shortly after pain remission showed ischaemic alterations. The patient was admitted to the hospital and immediately subjected to an echocardiogram that revealed a reduction in inferior and posterolateral contractility and an altered left ventricle diastolic release with an ejection fraction of 56%. The EKG recorded the following day showed a T-alteration in the lateral leads, likely due to an AMI with inferior leads. At 4 days after the pain episode, the EKG showed a T-alteration in the anterolateral leads and a nonspecific ST segment elevation in the inferior leads. The patient was subjected to CT-scan for restaging of disease. This showed a 50% reduction of pulmonary metastases and disappearance of abdominal lymphatic metastasis. For this reason, the same chemotherapy infusion schedule was continued, but the dose of 5-FU was reduced to 800 mg m⁻² day⁻¹. Transepidermal nitroglycerin administration was administered during 5-FU infusion and chemotherapy was administered while the patient recovered at the hospital. The dose of 5-FU for the cycles thereafter was increased to 900 mg m⁻² day⁻¹ with trans-epidermal nitroglycerin administration during 5-FU infusion. The patient received a further four cycles of this treatment, in an outpatient setting, and no longer complained of anginal pain.

### Table 1 Clinical and pathological features of patients

|                      | Case 1 | Case 2 | Case 3 |
|----------------------|--------|--------|--------|
| Familiarity          | AMI    | —      | —      |
| Age                  | 57     | 65     | 70     |
| Clinical history     | —      | HBP, diabetes, gastritis | HBP |
| Tumour size          | RSA    | RSA    | RSA    |
| Phase                | Metastatic | Metastatic | Adjuvant |
| Adjuvant therapy     | No     | No     | Yes    |
| Type                 | —      | —      | 5-FU   |
| Procedure            | —      | —      | Bolus  |
| Advanced therapy     | Yes    | Yes    | No     |
| Type                 | CPT11/5-FU | CDDP/5-FU | —      |
| Procedure            | Bolus/continuous infusion | Bolus/continuous infusion | —      |
| Symptom              | Chest pain | Chest pain | Chest pain |
| Duration             | Few minutes | 5 min | Few minutes |
| Cycle                | 1°     | 1°     | 3°     |
| Day                  | 4°     | 4°     | 4°     |
| Therapy              | Yes    | Yes    | Yes    |
| Type                 | Nitroglycerin | Nitroglycerin | Nitroglycerin |
| Examinations         | Yes    | Yes    | Yes    |
| EKG                  | Negative | Ischaemic alteration | Negative |
| EchoCG               | No     | Reduction of contractility | No |
| Enzymes              | Negative | Not done | Negative |
| Effort-EKG           | No     | Ventricular extrasystole | Negative |
| Other symptoms       | Yes    | Yes    | Yes    |
| Number               | 5      | 6      | 3      |
| Procedure            | Bolus/continuous infusion | Bolus/continuous infusion | Bolus |
| Therapy              | Nitroglycerin/dose reduction of 5-FU | Nitroglycerin/dose reduction of 5-FU | Weekly therapy |
| Other symptoms       | No     | No     | No     |
| Other chemotherapy   | Yes    | No     | No     |
| Type                 | OXP/5-FU | —      | —      |
| Procedure            | Bolus/continuous infusion | —      | —      |
| Symptoms             | No     | No     | No     |
| Other symptoms       | No     | No     | No     |
| Number               | 6      | —      | —      |
| Procedure            | Bolus/continuous infusion | —      | —      |
| Therapy              | Nitroglycerin | —      | —      |

AMI = acute myocardial infarction; CPT11 = irinotecan; EKG = electrocardiogram; EchoCG = echocardiogram; CDDP = cisplatin; OXP = oxaliplatin; 5-FU = 5-fluorouracil; HBP = high blood pressure; RSA = rectal–sigmoid adenocarcinoma.

### DISCUSSION

Relatively S-phase specific, 5-FU is a synthetic pyrimidine antimetabolite drug that has been used as a cytostatic agent in the treatment of various solid malignant tumours (adenocarcinomas, squamous cell cancer). The antitumour activity of 5-FU is...
fluorouridine-5'-monophosphate; FUDP ¼ 5-fluorouridine-diphosphate; FUTP ¼ fluorouridine-triphosphate; dU ¼ deoxyuridine; 1 ¼ uridine phosphorylase; 2 ¼ uridine kinase; 3 ¼ orotate phosphoribosyltransferase; 4 ¼ thymidine phosphorylase; 5 ¼ thymidine kinase; 6 ¼ thymidylate synthetase.

Figure 1  Fluorouracil metabolism: FUR ¼ fluorouridine; FUMP ¼ fluorouridine-monophosphate; FUDP ¼ fluorouridine-diphosphate; FUTP ¼ fluorouridine-triphosphate; dU ¼ deoxyuridine; 1 ¼ uridine phosphorylase; 2 ¼ uridine kinase; 3 ¼ orotate phosphoribosyltransferase; 4 ¼ thymidine phosphorylase; 5 ¼ thymidine kinase; 6 ¼ thymidylate synthetase.

exerted through several mechanisms of action and its dose, route of administration and administration schedule may play a critical role in its mechanism of action. Initially, 5-FU is inactive and is converted, within cells, into various active nucleotide forms (Rose et al., 2002): 5-fluoro-2'-deoxyuridine-5'-monophosphate (FdUMP), 5-fluorouracil (5-FU), and 5-fluorouridine-5'-diphosphate; FUTP is one of the critical nucleotide metabolites generated in tumour cells and other sensitive tissues (Figure 1).

FdUMP potently inhibits thymidylate synthetase by competitive binding, resulting in a thymine-depleted state (‘thymine-less death’). This is enhanced by folate cofactors. Cytotoxic effects are also mediated through the incorporation of fluorodeoxyuridine triphosphate into DNA (seen in continuous 5-FU infusion), and of fluorouridines-5'-triphosphate (FUTP) and 5-fluorocytosine into RNA (seen in bolus 5-FU). Furthermore, these metabolites are also thought to alter membrane function (calcium channels), interfere with mitochondrial metabolism (energy failure phosphate balance), inhibit ribosomal RNA, alter macromolecule characteristics (contractile elements), cause oxidative damage (pyrimidines are thought to play a role in favism) and release of vasoactive substances (histamine and catecholamines are known to cause ultrastructural changes similar to doxorubicin toxicity) and induce autoimmune activity (complexes between 5-FU cells or exposure of immunogenic native compounds after cell damage) (Norwood et al., 1993).

The postulated causative mechanisms involved in 5-FU cardiotoxicity are the following: an autoimmune response to damaged cells; an increased oxygen demand in patients receiving 5-FU; a coronary spasm caused by protein kinase C-mediated vasoconstriction; dihydropyrimidine dehydrogenase deficiency (Milano et al., 1999) and the 5-FU contaminant fluoroaacetic acid. Inhibition of DNA synthesis, due to 5-FU incorporation into myocardial cells, was suggested to be the first step of cardiotoxicity and myocardial depression has been explained by inhibition of mitochondrial DNA synthesis due to 5-FU (Kohne et al., 1998). Furthermore, it has been demonstrated that 5-FU may cause damage to endothelial cells with consequent thrombus formation. In our experience, 5-FU-associated effects on vascular endothelium reached their peak about 3 days from initiation of treatment, which corresponds to the clinical course of 5-FU cardiotoxicity (Cwikiel et al., 1995, 1996).

According to the analysis of 114 case reports, cardiotoxicity was experienced in 61 ¼ 33% of patients who received 5-FU 12-h c.i. or bolus 5-FU, respectively; 20% of the patients for whom data were available had a history of coronary artery disease or some other heart disease (Norbertus et al., 1993). Data do not support the conclusion that dose and mode of administration of 5-FU therapy may be an important factor in the development of cardiac toxicity (Norwood et al., 1993). Data do not support the conclusion that a history of cardiac disease increases the risks of 5-FU-induced cardiotoxicity (Norbertus et al., 1993). CDDP frequently is combined with 5-FU, and although a synergistic effect of CDDP or carboplatin with 5-FU cannot be excluded, 5-FU therapy alone could completely explain the toxicity observed. After the chest pain appears, 5-FU treatment is usually discontinued and the response to supportive treatment with nitrates or calcium-channel blockers is good (Norbertus et al., 1993).

Many authors suggest that prophylaxis with cardioprotective agents, after development of 5-FU-associated coronary ischaemia, permits protracted 5-FU administration, where clinically indicated (Olekszowicz and Bruckner, 1988; Norwood et al., 1993).

According to our experience, the average age of patients was 64 years, none had a history of cardiac disease, but two patients had HBP. Two patients were treated with combination therapy regimens. Apparently, 5-FU administration modality did not influence the angina-like pain presentation that appeared approximately 95 h after starting 5-FU therapy. The angina-like syndrome disappeared with oral nitroglycerin and by stopping infusion.

Since it was deemed necessary, 5-FU treatment was not discontinued in our patients. For the two patients (Cases 1 and 2) receiving nocturnal 5-FU infusion in combination therapy, the dose of 5-FU was reduced by 10–20% and patients were given transesophageal nitroglycerin prophylaxis. 5-Fluorouracil administration modality was changed in the third patient (Case 3): the bolus schedule (5-FU 370 mg m⁻² day⁻¹ plus FA 50 mg tot⁻¹ day⁻¹ for 5 days every 3 weeks) was modified to a weekly schedule (5-FU 450 mg m⁻² week⁻¹ and FA 100 mg tot⁻¹ week⁻¹), without prophylactic therapy.

By taking the above-mentioned precautions, patients continued therapy and no longer complained of acute angina-like pain.

REFERENCES

Cwikiel M, Eskilsson J, Albertsson M, Starenow L (1996) The influence of the 5-fluorouracil and methotrexate on vascular endothelium: an experimental study using endothelial cells in the culture. Ann Oncol 7: 731–737

Cwikiel M, Zhang B, Eskilsson J, Wieslander JB, Albertsson M (1995) The influence of 5-fluorouracil on the endothelium in small arteries: an electron microscopic study in rabbits. Scanning Microsc 9: 561–576

Klaus Becker F, Erkenbrecht J, Haussinger D, Frieling T (1999) Cardiotoxicity of the antiproliferative compound fluorouracil. Drugs 57 (4): 475–484

Kohne C-H, Thuss-Patience P, Friedrich M, Daniel PT, Kretzschmar A, Benter T, Bauer B, Dietz R, Dorken B (1998) Raltitrexed (Tomudex®): an alternative drug for patients with colorectal cancer and 5-fluorouracil associated cardiotoxicity. Br J Cancer 77 (6): 973–977

Milano G, Etienne MG, Pierrefite V, Barbieri-Heyob M, Deportee-Fety R, Reneé N. (1999) Dihydropyrimidine dehydrogenase deficiency and fluorouracil-related toxicity. Br J Cancer 79 (3–4): 627–630

Norbertus CR, Pippas AW, Moore JO (1993) The syndrome of 5-fluorouracil cardiotoxicity: an elusive cardiopathy. Cancer 71 (2): 493–509

Norwood RA, Lokich JJ, Moore C (1993) The syndrome of 5-fluorouracil cardiotoxicity: an elusive cardiopathy. Cancer 72: 2287–2288

Olekszowicz L, Bruckner HW (1988) Prophylaxis of 5-fluorouracil-induced coronary vasospasm with calcium channel blockers. Am J Med 85: 750–751

Rose MG, Farrell MP, Schmitz JC (2002) Thymidylate synthase: a critical target for cancer chemotherapy. Clin Colorectal Cancer 1 (4): 220–229