The effects of capecitabine in Raynaud’s disease: a case report

5-Fluorouracil (5-FU) is one of a number of chemotherapeutic agents associated with cardiovascular toxicities, with an incidence ranging from 2% to 10% [1–3]. Side-effects including angina, arrhythmias, ventricular dysfunction and myocardial infarction, along with the induction and exacerbation of Raynaud’s disease, are well documented. With the increasing use of the oral 5-FU prodrug capecitabine, recent reports suggest that its cardiotoxic incidence is similar to that of 5-FU at ~ 3% [4]. However, at present there is no clear documentation relating to its effects on peripheral vasospasm. This case report is based on a patient who experienced profound deterioration of Raynaud’s disease whilst receiving capecitabine chemotherapy.

In March 2003, an 86-year-old man with a long-standing history of Raynaud’s disease was diagnosed with Dukes’ B (pT2 pN0) adenocarcinoma of the rectum. He proceeded to an anterior resection, but at follow-up in January 2004 his CEA had risen to 40. A subsequent staging computed tomography scan demonstrated liver metastases with no additional visceral disease. He was commenced on oral capecitabine 2000 mg/m² daily on days 1–14 every 3 weeks. After the first cycle the patient felt that his symptoms relating to digital Raynaud’s were gradually deteriorating. On examination, all distal phalanges were hyperaemic and desquamating, but there were no signs of digital infarction or palmar–plantar erythema. Although the chemotherapy dose was reduced to 1500 mg/m² daily for the second cycle, there was no amelioration of his symptoms. At this point his erythrocyte sedimentation rate was 12 and the autoantibody screen was negative. In view of the reported connection between exacerbations of Raynaud’s and fluoropyrimidine therapy [5], the capecitabine was discontinued. The patient promptly received vasodilator treatment with a prostaglandin infusion, which led to a moderate improvement in the pulp desquamation. Following 1 week of treatment rest the patient was commenced on raltitrexed. Although the EDTA was 63 ml/min, in view of his general frailty this was initiated at a reduced dose of 1.5 mg/m² intravenously every 4 weeks. After receiving four cycles the patient’s symptoms continued to improve significantly and he experienced no major toxicity relating to the alternative chemotherapy. Unfortunately, in September 2004 this gentleman’s liver metastases have progressed and he is currently receiving irinotecan with no further exacerbations in his digital Raynaud’s.

This case highlights that a degree of caution should be adopted in initiating capecitabine in patients with a history of peripheral vasospasm. Although there are a variety of postulates on the pathophysiology of fluoropyrimidine-related vascular toxicity, it is still poorly understood. Most hypotheses focus on the induction of coronary vasospasm [6–9] via activated protein kinase C [9] and direct vascular endothelial damage [10] from 5-FU or 5-FU metabolites as being the main factors responsible for its cardiotoxicity. It has also been suggested that the final step of capecitabine’s conversion to 5-FU by thymidine phosphorylase (TP) in the myocardium may also contribute to cardiovascular problems [11]. There are fewer published articles on the effects of 5-FU with Raynaud’s, and these also suggest that mechanisms involving changes in endothelium, hyperviscosity and platelet activity may be responsible for the peripheral vasospasm associated with this drug [7–9]. However, there are no published reports relating to Raynaud’s disease being exacerbated by capecitabine. Since our patient’s diagnosis, this gentleman has required annual prostaglandin infusions to alleviate his symptoms. Capecitabine clearly affected the control of his disease and the symptoms subsided when the treatment was discontinued. As with coronary vasospasm, it is reasonable to assume that capecitabine induces its effects on Raynaud’s via mechanisms similar to 5-FU. Significantly, TP levels appear to be elevated in hypoxic environments [12]. Hence it is feasible that the deleterious side-effects of capecitabine witnessed in this disease could be potentiated by digital ischaemia itself. Although the improvement can mainly be attributed to the vasodilatory therapy, no recurrence was evident with raltitrexed, a thymidine synthase inhibitor with no documented cardiac side-effects.

Even though the cardiotoxicity attributable to both 5-FU and capecitabine is well recognised, it is important for practitioners to be aware that potential vascular toxicity can occur with all fluoropyrimidines. Additionally, this case highlights the validity in using raltitrexed for all patients who experience significant vascular problems with capecitabine.

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References
Liver does not care about age

Because elderly patients have associated diseases, old age has been regarded as an adverse factor for liver resection (LR) [1]. Consequently, resectable hepatic metastasis from colorectal cancer (HMCC) in the elderly are still more frequently treated by chemotherapy. On the other hand, recent series showed that after major LR in aged people, liver function is preserved, with acceptable morbidity [2]. However, the impact on long-term survival is not clear, because aged patients often die of another pathology. Thus, data on 185 patients who had undergone a major LR (removing at least four Couinaud’s segments) between January 1990 and December 2002 were retrieved from an ongoing database. Medical charts of patients initially operated on for colorectal cancer were studied by two independent observers, and 47% and 15% (P < 0.05), respectively. The median survival for groups 1 and 2 was 22 and 12 months, respectively (P = 0.03).

Our series indicated that exclusive major LR for HMCC in elderly patient can be safe and can improve survival. Patient age is a useful prognostic factor for prediction of postoperative liver failure. Thus, surgeons use less aggressive procedures because of higher comorbidity rates [3]. As a result, we found that postoperative complications and operative mortality rates after major LR did not differ from those in younger patients [4]. Surgical resection of HMCC improved survival because the benefit of major LR was not offset by high postoperative mortality. In fact, patients >70 years old who were eligible for surgery but who are treated exclusively by chemotherapy had a reduced life expectancy. Surgical eligibility is classically determined by number and location of tumors, as for younger patients [5]. In our experience, selected elderly patients with HMCC benefited from resection as much as young patients, and age alone may not be a contraindication to surgery. Association with thermoablation by radiofrequency could raise the limits of management of multitemastatic liver in the elderly.


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