Adjuvant chemotherapy with 5-fluorouracil in a patient with colorectal cancer and Familial Mediterranean Fever

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Colorectal cancer is a common malignancy often requiring adjuvant chemotherapy. Familial Mediterranean Fever is a chronic hereditary disease which is relatively prevalent in the Middle East and is associated with recurrent episodes of serosal, synovial or cutaneous inflammations. The aim of this paper was to describe a patient with Familial Mediterranean Fever who received fluorouracil-based adjuvant chemotherapy for colorectal cancer. A 56-year-old man with Familial Mediterranean Fever and amyloidosis was referred for evaluation and treatment following surgery for colorectal cancer. In light of his relatively young age, good general state of health and apparently well-controlled Familial Mediterranean Fever, he was treated with chemotherapy consisting of four cycles of 5-fluorouracil and leucovorin. The patient's clinical course during chemotherapy was unremarkable except for one minor attack of Familial Mediterranean Fever. The patient's follow-up was notable for periodic fluctuations in serum carcinoembryonic antigen levels, up to 4-fold of normal. The Familial Mediterranean Fever remained stable. Although our patient showed a good tolerability of treatment, the administration of chemotherapy to patients with Familial Mediterranean Fever raises several concerns. These include a potential deterioration in the Familial Mediterranean Fever status owing to chemotherapy-induced stress, the potential effect of Familial Mediterranean Fever or its treatment on the tolerability of chemotherapy and an overlapping toxicity of the drugs used to treat the two diseases. An increase in serum carcinoembryonic antigen in this setting may be related to the underlying pathophysiologic mechanism of Familial Mediterranean Fever but does not necessarily indicate disease recurrence. Clinicians should be aware of these issues considering the recent worldwide increase in colorectal cancer. *Anti-Cancer Drugs* 18:733–735 © 2007 Lippincott Williams & Wilkins.

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Introduction

Globally, colorectal cancer (CRC) is the third most frequent cancer in men and second in women, with a similar mortality rate in both sexes. In 2002, the 5-year survival rate was 62% in the US for all patients diagnosed with the disease [1]. Prompted by findings that local or distant recurrences were common even after margin-free surgical resection, researchers developed adjuvant treatments in high-risk patients that have been shown to improve disease-free and overall survival [2]. At present, postoperative treatment with 5-fluorouracil (5FU) and folinic acid [leucovorin (LV)] is very common in patients with stage III and even stage II CRC [3].

Familial Mediterranean Fever (FMF) is a chronic hereditary disease characterized by recurrent episodes of fever with serosal, synovial or cutaneous inflammations. It may cause permanent joint disability as well as peritoneal adhesions leading to bowel obstruction [4]. In individuals, systemic amyloid A (AA) amyloidosis develops [5]. FMF is common in the Middle East, especially among Armenians, Arabs, Turks and non-Ashkenazi Jews (primarily from North Africa and Iraq). With the advent of genetic testing, higher rates have been documented also among Ashkenazi Jews and Italians [6].

We describe a patient with FMF who received adjuvant chemotherapy with 5FU and LV for CRC. His course and outcome were followed carefully, as no data were available regarding possible interactions between the two diseases and their therapies.

Case report

A 56-year-old man was admitted to our clinic after surgery for a moderately differentiated adenocarcinoma of the ascending colon. The tumor had penetrated the full thickness of the bowel wall and reached the pericolic adipose tissue. All 26 lymph nodes examined were negative for malignant cells. The patient's past medical history was significant for FMF and hypertension controlled by diuretics. The patient had also acquired AA amyloidosis, a late complication of FMF, leading to mild renal failure and proteinuria in the nephrotic range. For the last 20 years he had been treated with colchicine

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with good control of his disease: on average, he had 1–2 episodes of very mild peritonitis or arthritis yearly and his renal function was stable. Recently, he had also received treatment with fibrillex (NC 503) for the amyloidosis.

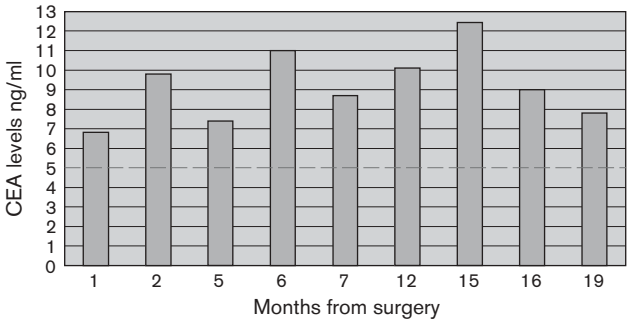
Findings on physical examination, routine blood tests (complete blood count, serum chemistry), measurements of the tumor markers carcinoembryonic antigen (CEA) and CA19-9, and chest and abdominal computerized tomography were all unremarkable. In light of the patient's relatively young age, good general state of health and apparently well-controlled FMF, we recommended that he receive standard adjuvant chemotherapy with four cycles of 5FU and LV, each cycle consisting of 6 weekly injections of 5FU/LV followed by a 2-week break.

The patient's clinical course during chemotherapy was unremarkable, except for one minor FMF attack manifesting as mild abdominal pain for several days. This single attack was not significantly different from the patient's prior attacks. Otherwise, he tolerated therapy very well, without any complications. The follow-up to date, over 2 years after the diagnosis of CRC and 1.5 years after the completion of chemotherapy, has been notable only for periodic fluctuations in the serum levels of CEA, up to nearly four times the upper limit of normal (Fig. 1). This abnormality was eventually assessed to be unrelated to the CRC, on account of its fluctuating pattern, and the negative findings for recurrent disease on repeated physical examinations, blood tests and imaging studies, including computed tomography and ultrasound. The clinical course of the FMF remains stable, with the same frequency and severity of attacks as before the diagnosis of CRC.

Discussion

To the best of our knowledge, this is the first reported case of a patient with FMF receiving adjuvant chemotherapy for CRC and the second report of a patient with FMF receiving chemotherapy at all [7]. Although our patient's clinical course was generally uneventful, his clinical management was associated with significant concerns, some of which are discussed below.

Fig. 1



Patient's serum carcinoembryonic antigen (CEA) levels at different time intervals following surgery (broken line delineates upper normal limit of CEA).

The first concern was the potential risk of a deteriorating effect of chemotherapy on the clinical course of FMF. The precise trigger for FMF attacks is currently unclear. As the attacks are largely unpredictable, some patients have been able to relate them to physical exertion, emotional stress or menses [3]. Chemotherapy is clearly a major stressful event, but data on its impact on FMF are almost absent. Whereas in our case the clinical course of FMF was not influenced by chemotherapy, the only other patient described in the literature experienced an exacerbation of FMF during chemotherapy [7]. It is possible that the different effects were related to the different agents used. For example, in contrast to 5FU, the drug administered in the earlier case, cisplatin, is reportedly involved in the production of inflammatory cytokines, an important element in FMF flare-ups [8].

The opposite effect, i.e. the potential influence of FMF or its medications on the efficacy and tolerability of chemotherapy, was of much concern as well. Frequent attacks of a disease such as FMF limit the effective administration of any therapy, including chemotherapy. Specifically, a peritoneum subject to recurrent episodes of inflammation may theoretically respond in an exaggerated manner to the gastrointestinal toxicity induced by chemotherapy. Another aspect of this issue is a possible interaction of the chemotherapy agents with the anti-FMF drugs. Although we did not observe any evidence of such interaction in our patient, it may well have a theoretical basis. Colchicine, the most commonly used drug in the treatment of FMF, acts by arresting dividing cells at the metaphase [9]. As such, it may interfere with the recovery of gastrointestinal and hematological stem cells following exposure to chemotherapy. Accordingly, the drug's most common adverse effects of nausea, vomiting and diarrhea [10] are also the most common chemotherapy-associated side effects. Furthermore, another possible adverse effect of colchicine, myelosuppresion [11], is indeed the dose-limiting toxicity of many chemotherapeutic agents. To summarize, despite its absence in the present case, increased chemotherapy-induced toxicity may be expected in patients receiving colchicine, considering the drug's overlapping toxicity with many chemotherapeutic agents, including 5FU.

An additional observation in our case which may be of clinical relevance is the unusually high amplitude of fluctuations in CEA levels. It is possible that the underlying pathophysiological mechanism of FMF, which involves repeated irritation of mesothelial membranes, including the peritoneum, can by itself cause an elevation

of this marker in the serum. It is important that clinicians be aware that elevated CEA levels in patients with FMF do not necessarily indicate a recurrence.

Finally, FMF is not a rare condition, especially in the Mediterranean basin, and the increase in incidence of CRC globally, and more so in this part of the world [12], will eventually lead to an increased number of patients with FMF who will require chemotherapy for CRC. In this report, we described such a patient, and at least in his case, adjuvant chemotherapy with 5FU and LV was well tolerated.

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