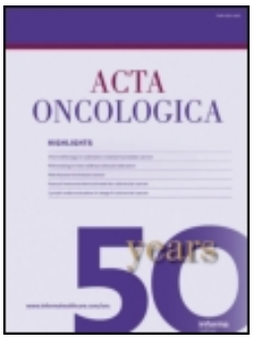

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LETTER TO THE EDITOR

Successful treatment with low-dose capecitabine for disseminated esophageal adenocarcinoma

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To the Editor

A 75-year-old man was diagnosed in 2004 with adenocarcinoma of the esophagus. At the time of diagnosis the disease was considered resectable and surgery was done in April 2004. Histological examination of the resected esophagus showed poorly differentiated adenocarcinoma with growth extending through all wall layers and metastases in all 20 resected lymph nodes however radically resected. Postoperative complications prolonged care in the intensive care unit and his clinical status was still poor (Karnofsky 60), when he came to see the oncologist 2 months after surgery. He was therefore considered too weak for adjuvant chemotherapy and was actively monitored with regular CT scanning and clinical examinations. During the first year of follow-up his clinical condition was improved and CT scan showed no signs of cancer. About one year after surgery, in March 2005, CT scan showed liver metastases. Since his clinical status and quality of life were good, active monitoring was continued. Over the next 6 months liver metastases were slowly progressing and new changes appeared in the lungs and there were enlarged para-aortic lymph nodes. By September 2005, he became symptomatic from his metastatic tumor, with difficulties eating, back and stomach pain, coughing, and breathing problems. Palliative treatment with Oxaliplatin- 5-Fluorouracil/ Leucovorin was initiated. This was administered for 2 months during which time symptoms diminished and partial regression (PR) of the tumor was seen on CT scan. However, treatment had to be interrupted due to severe nephrotoxicity arising from the combination of NSAIDs and x-ray contrast. During the following 6 months, while recovering from renal failure, no antitumor treatment was given. By June 2006 CT scan showed progressive disease in all locations and the patient suffered from pain and weight loss. At that time treatment was reinitiated with low-dose capecitabine at a continuous dose of 500 mg/day. There was a clinical response already after one month and by 2 months therapy, CT scan showed good tumor regression and the patient's clinical status had further improved, with weight gain, absence of pain, and good quality of life. On assessment after 4 months, CT scan showed further regression of changes in the lungs, liver, and lymph nodes. Some metastases were no longer measurable (Figure 1).

At the time his disease had progressed in June 2006, therapeutic options were highly limited because of the patient's age and compromised renal function, which included mild residual elevation of serum creatinine (S-creatinine 125 micro mol/l). One option would have been no treatment at all, but he wanted treatment if possible. Consequently, a relatively non-toxic treatment regimen was chosen in order to provide the best possible quality of life. To date in December 2006 his improvement has been sustained and his quality of life remains excellent.

Continuously administered low-dose chemotherapy with metronomic scheduling seems to be clinically effective for various types of tumors and is well tolerated, as supported by a range of clinical data. Two breast cancer studies have explored this approach. In one, low-dose oral cyclophosphamide added to Letrozole (n = 57) was compared to Letrozole alone (n = 57) as primary treatment of

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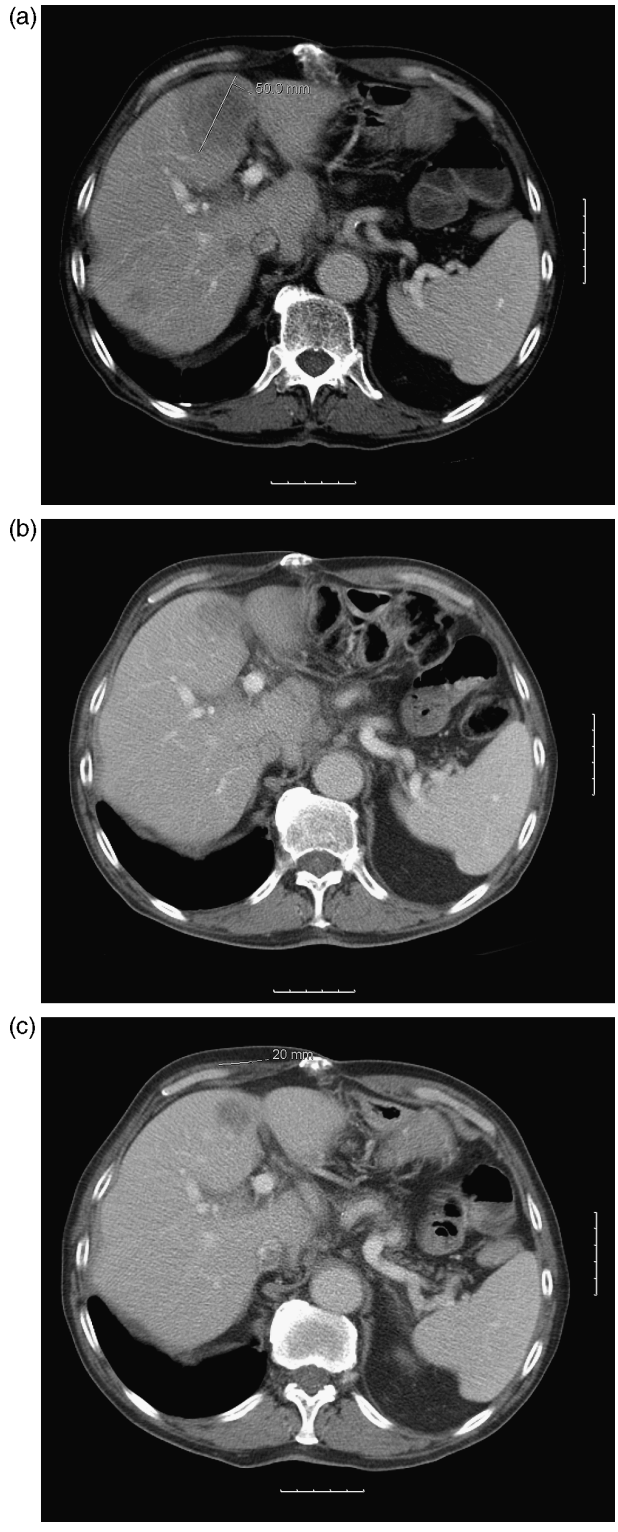

Figure 1. (a) Liver metastases before treatment. (b) Liver metastases after 2 months therapy. (c) Liver metastases after 4 months therapy.

estrogen receptor-positive breast cancer in elderly women. Overall response was improved by 15.8% (87.7% vs. 71.9%) in the combination therapy group. There was also a significant difference in VEGF reduction [1]. Another study of metastatic breast cancer, using low-dose methotrexate and cyclophosphamide, demonstrated clinical benefit in 31.7% of patients and a significant drop in S-VEGF [2]. Patients with a variety of solid tumors were given low-dose daily oral cyclophosphamide, weekly vinblastine, and rofecoxib with the intention of inhibiting angiogenesis. Thirty percent of the patients achieved clinical benefit (CR, PR, SD) [3]. Since the 1970s data have supported the importance of vascularization and angiogenesis for tumor growth. Several studies show that VEGF is involved in angiogenesis and is secreted in response to a variety of stress factors, thereby stimulating angiogenesis.

High-dose chemotherapy has been in use for a long time. This approach requires scheduling of treatment-free intervals to allow for recovery of normal cells, e.g. hematopoietic cells. This strategy entails both a risk of drug resistance and tumour cell proliferation during treatment-free intervals. However, this problem does not seem to be relevant in slowly proliferating vascular endothelial cells. Since angiogenesis appears to be important for tumor growth, the theory that chemotherapeutic dosing might influence tumor growth was tested.

Preclinical studies support the theory that continuously administered low-dose chemotherapy may improve the therapeutic index and be better tolerated because of less toxicity. The antitumor effect of low-dose chemotherapy seems not to result from cytotoxicity only, but rather from a mechanism involving antiangiogenesis. This has been shown by Albertsson et al. for several cytotoxic agents [4]. Browder et al. studied the importance of chemotherapy scheduling on drug-resistant Lewis lung carcinoma and breast cancer cell lines. With a schedule for cyclophosphamide continuously at short intervals a significant improvement in long-term suppression of tumor growth, increased apoptosis of endothelial cells, and eradication tumours were seen [5]. Low-dose vinblastine affects functions involved in angiogenesis, such as proliferation, chemotaxis, spreading on fibronectin, and morphogenesis. Vascular proliferation was also affected [6]. Klement et al. studied protocols for low-dose vinblastine alone and a VEGF-receptor inhibitor, alone and in combination. This treatment was tested in immunodeficient mice inoculated with human neuroblastoma cell lines. Both treatments alone produced tumor regression and inhibition of angiogenesis. However the combination therapy yielded complete and sustained tumor regression without toxicity or development of drug resistance and this effect persisted throughout the course of treatment [7]. Tomoda et al. inoculated a cell line of highly metastasing osteosarcoma, into

rats and confirmed this finding. Low-dose methotrexate inhibited development of lung metastases and an inhibitory effect on endothelial cells was produced at lower concentrations than those required for affecting osteosarcoma cells directly [8]. According to Hanahan, low-dose metronomic schedules exert a non-cytotoxic effect on the tumor environment that might be related to angiogenesis and vasculogenesis [9].

Patients with metastatic esophageal carcinoma have few therapeutic options. Fluorouracil is one of the most widely used drugs, why capecitabine was chosen. Capecitabine is easy to administer and does not require hospital admission. In this situation, where the aim of treatment is to sustain good quality of life, it is important that the treatment is well tolerated and has minimal impact on daily life. We believe that this case presentation is an interesting example of successful palliative treatment in a setting where treatment options are highly limited and that this approach deserves further exploration.

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