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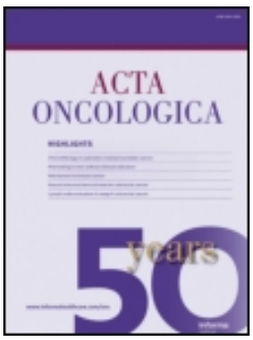

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The study was closed after the enrollment of the first eight patients. There were four males and four females with ages between 40 and 79. Performance status was ECOG 0 in three patients, ECOG 1 in four patients, and ECOG 2 in one patient. Two patients received previous chemotherapy only and six patients received both chemotherapy and irradiation, including prophylactic brain irradiation in three patients. Six patients were evaluable for response. Two patients were removed from the study, the first one due to allergy to filgrastim and the second one due to refusal to continue on therapy after the first cycle. Of the six evaluable patients, four patients had stable disease and two had progressive disease. Only one patient was able to complete six cycles of chemotherapy. The most common grade 3 or 4 toxicity was neutropenia, occurring in five patients. Other severe toxicities included thrombocytopenia in three patients, anemia in one patient, dehydration in two patients, fatigue in two patients, and malaise in one patient. The lack of responses, poor accrual, and increased toxicity leading to early withdrawal of therapy in three of the four patients with ongoing stable disease resulted in the premature closure of the study for patient safety. It is unclear why this treatment was so toxic and ineffective in our population. The treatment was administered with the lower doses and identical sequence to the regimen previously tested by Tkaczuk et al. [5]. The only difference was the administration of docetaxel on day 4 in the even cycles of the phase I study. The lack of responses in the first patients may be attributed at least in part to the significant toxicity leading to dose delay and early discontinuation from the study. The combination of topotecan and docetaxel at the doses utilized in our study cannot be recommended as a second-line therapy for patients with chemotherapy-sensitive relapsed SCLC.

Conflict of interest

The authors have no conflict of interest to report.

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To the Editor

Established systemic treatment choices for metastatic neuroendocrine tumours (NETs) are somatostatin analogues and alpha interferons (IFN-alpha) both reducing the secretory activity of the tumour. IFN-alpha also has an anti-proliferative effect, inhibiting angiogenesis, blocking the cell cycle, and stimulating apoptosis [1]. Chemotherapy has limited value, used in NETs with a high-proliferative index.

Angiogenesis has raised interest as a new target in NETs. This interest is fuelled by the fact that NETs are highly vascularised and vascular endothelial growth factor (VEGF) and its receptors are present [2]. We performed a study with IFN-alpha, 5-fluorouracil (5-FU) and leucovorin in patients with metastatic NETs because of the suggested synergistic effects between 5-FU and IFN-alpha, and promising results of this combination obtained by others [3]. In this feasibility study, approved by the Medical Ethical Committee, patients were treated with IFN-alpha-2b (2.5 million U/day subcutaneously), and after 2 weeks, intravenous 5-FU 750 mg/m^2 (day 2) and oral leucovorin 180 mg/day (day 1 and 2) was added as a 2 weekly cycle.

The primary endpoint was toxicity, the secondary endpoints included radiological and biochemical response. In addition, serum was prospectively stored for serum VEGF level measurements.

This study was prematurely closed after nine patients because of side effects. After one cycle, three patients had to stop, because of grade 3 fatigue (n = 2) and heart failure (n = 1). Three additional patients discontinued after respectively two, three and four cycles because of arthritis and polyneuropathy (n = 1) and grade 3-4 diarrhoea and fatigue (n = 2). The remaining three patients completed 10, 19 and 20 cycles. Median survival was 22 months; two patients are still alive after 144 months. All three radiological evaluable patients experienced stable disease lasting 5–84 + months.

Serum VEGF levels (R&D Systems, Minneapolis, USA) decreased in seven of eight evaluable patients, from a median level of 352 pg/ml (range 41–1 276 pg/ml) to 219 pg/ml (range 18–938 pg/ml), a median reduction of 40% in 88 days (median) (range 34–462 days). This suggests an antiangiogenic effect of the combination IFN-alpha and 5-FU. One study showed that IFN-alpha alone did not reduce serum VEGF levels in patients with carcinoid tumours, although it did in another study (median reduction 33%) also decreasing VEGF mRNA expression in liver metastases [1,4].

In the present study toxicity was considerable. Next to the synergistic effect of this regime, IFN-alpha also can potentiate the toxicity of 5-FU. Four different dosages of 5-FU and IFN-alpha were previously studied in patients with NETs, only the regimen in a study of Andreyev and colleagues was well tolerated in which 5-FU was given continuously [3].

Bevacizumab, a monoclonal antibody against VEGF was found to prolong progression free survival compared to IFN-alpha in carcinoids while sunitinib, a tyrosine kinase inhibitor, induced stable disease in NETs [5,6]. Recently Zhang et al. showed that bevacizumab inhibited tumour growth in carcinoid xenograft, but at the same time up regulation of VEGF transcription occurred as a possible resistance mechanism [2]. During sunitinib therapy elevated baseline serum VEGF also increased, possibly due to resistance [7].

We conclude that this combination of 5-FU and IFN-alpha is not feasible due to side effects. However taken our observation of decreased VEGF levels, less toxic modifications, e.g. 5-FU given continuously or IFN-alpha combined with capecitabine, an oral fluoropyrimidine prodrug, in combination with one of the new antiangiogenic drugs can be envisioned. Such a regime might potentiate the effect of angiogenesis inhibitors.

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Fatal tumor lysis syndrome after irinotecan/5-FU/folinic acid/bevacizumab-containing therapy in a patient heavily pretreated for metastatic colon cancer

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To the Editor

Tumor Lysis Syndrome (TLS) is a metabolic complication usually arising from treatment of rapidly proliferating and drug-sensitive neoplasms. It comprises a number of metabolic abnormalities such as hyperkalemia, hyperuricemia, hypocalcemia and precipitation of calcium phosphate or urate that occur as a result of spontaneous or treatment-related cell death. Commonly described in hematopoietic malignancies, it occurs rarely in solid tumors [1].

We report on a patient with a ten-year history of metastatic colon cancer who developed TLS after having received 5th line irinotecan/5-FU/folinic acid/bevacizumab-containing chemotherapy.

In March 1996 a 62-year old man was diagnosed with colon cancer metastasized to the right lung. From May 1996 to August 1997 he received 12 courses of 5-FU/folinic-acid (FA) based chemotherapy (Mayo regimen) followed by surgical excision of the remaining lung metastases. Recurrent lung metastases were excised in June 1999 (1st relapse) and June 2000 (2nd relapse). Tumor tissue was negative for expression of epidermal growth factor receptor (EGFR). From May 2002 to April 2003 eight courses of capecitabine were administered for recurrent disease involving lungs and thyroid. A transient partial remission was achieved. However, lung metastases increased in size again and proved unresponsive to two courses of 3rd line chemotherapy with oxaliplatin and infusional 5-FU/FA (FOLFOX) given from May–July 2003. Treatment was changed to irinotecan/infusional 5-FU/FA in August 2003 with only one course being applied because the patient experienced severe diarrhea refractory to appropriate supportive therapy. He was thus followed by observation from November 2003 to January 2005. As lung metastases increased in size again another cycle FOLFIRI was administered. However, severe diarrhea resulted in early termination of chemotherapy. Since the patient experienced progressive lung disease FOLFIRI was restarted under intensive supportive medication in August 2005. After having responded to two courses of FOLFIRI the patient requested termination of chemotherapy. Radiation was administered for newly diagnosed bone metastases in November 2005. The patient received monthly bisphosphonates but refused any further chemotherapy.

More than ten years after primary diagnosis of metastatic colon cancer the patient presented with progressive bone and lung metastases, the latter involving almost the entire lung. Serum lactatdehydrogenase (LDH), uric acid and creatinine were elevated at 493 U/l, 9.7 mg/dl and 1.4 mg/dl, respectively. The patient received bevacizumab 5 mg/kg i.v. (day 1) in combination with irinotecan (50 mg/m^2

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