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Letter to the Editor

Phase II Study of a 21-day Continuous Infusion Schedule with Epirubicin in Metastatic Colorectal Cancer

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EPIRUBICIN (EPI) is an isomer of doxorubicin, with a more favourable therapeutic index than its parent compound. Phase II trials with bolus injections have shown an antitumour effect in metastatic colorectal carcinoma with an overall response rate of 16% [1]. In a phase I study with continuous infusion of EPI during 21 days, we found an optimal dose for phase II studies of 6 mg/m^2/day [2].

In this study we evaluated the efficacy of EPI given in a continuous infusion schedule, in 14 patients with metastatic colorectal cancer who were not pretreated with anthracycline containing regimens. Criteria for entry to the trial were: progressive, histologically proven, measurable metastatic colorectal carcinoma; age 18–75 years; normal renal and bone marrow function (creatinine < 130 μmol/l, leukocytes > 3000/mm^3, platelets $> 100{,}000$/mm^3; serum bilirubin < 35 mmol/l); Karnofsky performance score > 60; and normal cardiac function including normal ECG and no history of overt cardiac disease defined as cardiac angina or cardiac decompensation.

EPI was given in a continuous infusion schedule over 21 days in a dose of 6 mg/m^2/day. Courses were repeated every 6 weeks if no unacceptable toxicity (grade III/IV according to the WHO criteria [3]) occurred and no progression of tumour growth was recorded. The drug was administered via a totally implantable venous access port (Infuse-A-Port®) and a portable syringe driver (Graseby Medical MS 16A®). Patients prepared their own cytostatic solutions every 48 h and changed the syringes themselves.

Details of the 14 patients studied are shown in Table 1. All patients completed at least one cycle of 6 weeks and were evaluable for response and toxicity. A total of 32 cycles were administered. There were no complete or partial remissions. Stable disease was observed in 11 patients, with a median duration of 12 weeks (range 6–24 weeks). Tumour progression during the first cycle occurred in three patients.

Therapy was well accepted and toxicity was infrequent. Thrombocytopenia was not seen. One patient experienced grade III leukocytopenia at the end of his third administration period. Two patients needed antiemetic treatment for nausea and vomiting (grade III) in the last week of the 21 day infusion period during their last cycle. Grade I/II nausea and vomiting during the last period of the infusion were observed in five patients during five cycles. All patients except one experienced hair loss starting after the first infusion period. Complete hair loss occurred in three patients, all had extensive liver metastases. Mucositis (grade I/II) was seen in two patients. Although two patients received a total cumulative dose of 504 mg/m^2, no clinical signs of cardiotoxicity were seen.

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Table 1. Patient characteristics

	No. of patients
No. of patients entered	14
Age in years:	
mean 50	
range 26–70	
Sex: male/female ratio	8/6
Site of primary tumour:	
colon	3
rectum/sigmoid	11
Site of measurable disease:	
lung	2
liver	13
pelvis	1
Prior therapy:	
none	3
surgical resection of the primary tumour	10
chemotherapy	1
radiotherapy on pelvic tumour	2
Number of cycles:	
1 cycle	3
2 cycles	6
3 cycles	3
4 cycles	2
Response:	
complete/partial	0
stable disease (>6 weeks)	11
disease progression	3
Toxicity:	
Hematologic: leukocytopenia	
grade I	2
grade II	0
grade III	1
Non-haematologic:	
nausea and vomiting	
grade I/II	5
grade III	2
hair loss	
grade I/II	10
grade III	3
musositis	
grade I/II	2
Cardiac toxicity	0

Complications due to the implanted venous access port (VAP) consisted of temporary catheter occlusion in one patient at the beginning of a cycle. No signs of subclavian and/or superior caval vein thrombosis were seen. No needle dislocation, drug extravasation or infectious complications due to the VAP and needle were seen. Pump malfunctioning did not occur.

Although continuous infusion of EPI in a dose of 126 mg/m^2 over 3 weeks might have resulted in a higher response rate, we observed no complete or partial responses in this study. This is in accordance with a recent study with bolus injection of EPI in patients with metastatic colorectal cancer [4]. Compared to phase II studies with bolus injection of EPI every 3 weeks, we saw less myelotoxicity in this study with continuous infusion of EPI.

We conclude that EPI given in a continuous infusion schedule is well tolerated and causes minimal toxicity, but cannot be recommended for the treatment of patients with metastatic colorectal cancer.

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