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Carboplatin in Patients with Advanced Colorectal Cancer Pretreated with Fluoropyrimidines

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The activity of carboplatin (CBDCA) was tested in 21 consecutive patients with advanced colorectal cancer that had progressed during fluoropyrimidine therapy. CBDCA was chosen in view of the favourable results obtained in previous phase II studies. We were unable to find any activity of the agent which was given every 21 days at a dose of 400 mg/m². The main toxicity was haematological. CBDCA is not recommended in pretreated patients with colorectal cancer.

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INTRODUCTION

FLUOROURACIL (FU) is considered one of the most active chemotherapeutic agents in gastrointestinal cancer, standard doses and modalities leading to an objective response rate of 10–20% [1]. Randomised clinical trials have shown that leucovorin increases the therapeutic index of FU [2].

In clinical practice, it is not uncommon to observe progressive disease during or after FU therapy in patients with a good performance status and a limited extent of disease. At present, there is no standard second-line chemotherapy, and efforts are needed to test new potentially active drugs [3].

Cisplatin is a major drug in the therapy of a variety of malignancies, but its role in colorectal cancer is controversial [4–6]. Carboplatin (CBDCA) is a second-generation platinum analog designed to maintain or improve the antineoplastic activity of the parent drug while producing less toxicity [7, 8]. In recent phase II trials, CBDCA has demonstrated therapeutic efficacy in untreated patients with colorectal cancer [9–12].

The present study was undertaken to assess the activity of this agent in patients with advanced or metastatic colorectal carcinoma pretreated with fluoropyrimidine-containing chemotherapies.

PATIENTS AND METHODS

Patients were considered eligible if they had a proven metastatic adenocarcinoma of the colon or rectum with measurable bidimensional disease and if they had been previously treated with fluoropyrimidine-containing therapy. Pretreatment studies included a medical history, physical examination, routine haematological and serum chemistry tests, including liver and kidney function and carcinoembryonic antigen (CEA). All patients underwent electrocardiogram and, where relevant, computed tomography scans and X-rays.

CBDCA was given on an outpatient basis intravenously at a dose of 400 mg/m² every 21 days. There was no prehydration or mannitol diuresis. Antiemetic prophylaxis with ondansetron was given on a regular basis. Dose modifications and/or delays were based on haematological and gastrointestinal toxicity scores made at the time scheduled for next treatment and nadir blood counts. Responses and toxicity grades were defined using UICC/WHO criteria [13].

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RESULTS

From May 1991, 21 consecutive patients were enrolled at Milan's Istituto Nazionale Tumori; all of them were considered evaluable for response and toxicity. Their characteristics are summarised in Table 1.

The ECOG performance status of the patients (12 men and 9 women; median age 57 years, range 38–76) was 0 in 5, 1 in 11, and 2 in 5. All of the patients had received at least one type of chemotherapy; 4 had had previous prior pelvic irradiation. Metastatic sites were liver in 17 cases, lung in 6, nodes in 5, local relapse in 3 and peritoneal carcinosis in 1. Pretreatment serum CEA levels were altered in all cases.

A total of 66 cycles was given with a median of three per patient (range two to eight). No case of tumour regression was observed. 19 patients rapidly progressed (3 of whom were treated with only one cycle) and 2 experienced stable disease lasting 4 and 5 months, respectively.

The observed side-effects are shown in Table 2 (nausea and/or vomiting occurred in 8 patients; haematologic toxicity was

Table 1. Patients' characteristics

No. of evaluable patients	21
Median age in years (range)	57 (38–76)
Males/females	12/9
Performance status	
0–1	16
2	5
Primary tumour	
colon/rectum	18/3
No. disease site/s	
1	9
≥2	12
Disease sites	
Liver	17
Lung	6
Local recurrence	4
Nodes	5
Other	5
No. of previous treatments	
1	12
2	9

Table 2. Side-effects in 21 evaluable patients

Side-effect	WHO grade 1	2	3	4
Leucopenia	2	2	0	0
Thrombocytopenia	1	3	0	0
Anaemia	0	1	0	0
Nausea/vomiting	2	5	1	0
Fever	0	1	0	0

moderate). Myelosuppression delayed 10/66 cycles (15%) but there was no WHO grade 3–4 toxicity. The other toxic events were limited.

CONCLUSION

There is no active medical treatment for advanced colorectal cancers refractory to fluoropyrimidines, although published phase II studies report the therapeutic efficacy of CBDCA in previously untreated patients [9–12].

The present study evaluated the role of CBDCA as a single drug in pretreated cases, and the results demonstrate its inefficacy in this subset of patients; the most important toxicity was myelosuppression.

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Feature Articles

Black (Air-cured) and Blond (Flue-cured) Tobacco and Cancer Risk V: Oral Cavity Cancer

Paolo Boffetta

INTRODUCTION

BLACK TOBACCO has traditionally been used in Latin American and Mediterranean European countries. A stronger carcinogenic effect of black tobacco as compared with blond tobacco has been shown on four sites: larynx, lung, oesophagus and urinary bladder. They are the object of other reviews in the same series [1–4]. The difference in effect has been related to higher levels of *N*-nitrosamines and of aromatic amines in black tobacco smoke [5, 6].

Tobacco smoking is probably the most important risk factor for cancer of the oral cavity [7, 8]. Some aspects of tobacco smoking, such as average consumption, duration of exposure, quitting smoking, use of filter cigarettes and smoking of cigar and pipe, have been studied in detail with respect to risk of oral cancer [8]. In general, the association between various aspects of cigarette smoking and cancer risk closely resembles that found for other cancer sites, such as larynx and lung, although the relative risks are somewhat lower for oral cancer than for low respiratory tract. Cigar and pipe smoking, on the other hand, seem to exert a stronger carcinogenic effect in the oral cavity than in other sites [8]. Furthermore, a synergistic effect in the causation of oral cancer has been shown between tobacco smoking and alcohol drinking [8, 9].

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