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Short report

Phase II trial of continuous oral trofosfamide in patients with advanced colorectal cancer refractory to 5-fluorouracil

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Fourteen patients with 5-fluorouracil (5-FU) refractory, progressive colorectal cancer metastatic to liver and/or lung were treated with continuous oral trofosfamide, an alkylating agent structurally related to cyclophosphamide and ifosfamide. Trofosfamide was given daily at 200 mg/day. No objective partial or complete responses were seen in 14 evaluable patients. There were four patients with stable disease or minor responses; the median duration of stable disease during trofosfamide treatment was 14 weeks, with of range of 12–36 weeks. Mild to moderate side effects were reported in seven patients including grade 1–2 nausea in four patients, grade 1 leukopenia in two patients and grade 1 anemia in one patient. Trofosfamide in this dose and schedule shows minor activity in 5-FU refractory colorectal cancer. Because of very little side effects, dose escalations appear to be possible.

Key words: Colorectal cancer, 5-FU resistance, phase II, trofosfamide.

Introduction

Colorectal cancer is one of the most common neoplastic diseases in western countries with an incidence of about 40–50/100 000 annually. Approximately 50% of the patients will eventually develop metastasis or recurrent disease. If not amenable to locoregional therapy, these patients will require systemic chemotherapy.[1]

Among the numerous drugs tested for antineoplastic activity in colorectal cancer, 5-fluorouracil (5-FU) remains the most active single agent with an objective response rate of 11–20%.[1] Biochemical modulation of 5-FU by folinic acid produced higher response rates than 5-FU alone, but there has been no evidence of improved patient survival with a median time to progression of 5–8 months.[1,2]

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At present, there is no established chemotherapeutic treatment for patients with 5-FU-resistant colorectal cancer. Second line therapy usually consisting of mitomycin C or methyl-CCNU yields objective remission rates of less than 10%.[1,3] Both compounds are alkylating agents and therefore this class of drugs seems to exhibit some chemotherapeutic efficacy in the treatment of colorectal cancer.

Trofosfamide belongs to the class of oxazaphosphorines, and is a congener of cyclophosphamide and ifosfamide. Trofosfamide is available only in oral formulation; one of the main metabolites of trofosfamide being ifosfamide.[4,5] Trofosfamide produces little toxicity when given as continuous low-dose treatment.[6,7] It has previously shown activity in the treatment of non-Hodgkin lymphoma and chronic lymphocytic leukemia,[7–9] breast cancer,[10,11] testicular seminoma,[7–9] and soft-tissue sarcoma.[12,13]

This trial was initiated to determine the activity and toxicity of oral trofosfamide in the treatment of patients with 5-FU refractory advanced colorectal cancer.

Patients and methods

Patients

A total of 14 patients with progressive colorectal cancer with measurable liver and/or lung metastasis, who were not amenable to surgical management, were treated between December 1994 and May 1996. All patients included in this study had progressive disease while receiving therapy with high dose 5-FU (2600 mg/m^2 24 h infusion weekly) either in combination with folinic acid (nine patients) or interferon-α (five patients) (Köhne-Wömpner *et al.*,

Proc. ASCO 1996, abstr 445). The median duration of 5-FU first line treatment was 12.5 months, with a range of 4–27 months. Additional inclusion criteria were: measurable or evaluable lesions, age ≤ 75 years, WHO performance status ≤ 2, and adequate renal, liver and bone marrow function. All patients gave their informed consent.

The patients' characteristics are summarized in Table 1.

Staging and follow-up

Prior to treatment, all patients underwent complete medical history and physical examination, ECG, determination and measurement of study parameters by chest X-ray, computer tomography (CT) scan and/or ultrasound. During treatment, patients had weekly full hematological blood counts, determination of liver and renal functions, and assessment of non-hematological toxicities. Response to treatment was assessed every fourth week. The standard WHO criteria were used for evaluation of toxicities and response.

Treatment schedule

Trofosfamide was given as a continuous oral treatment with a daily dose of 200 mg, because in previous studies[13] a continuous low-dose regimen with trofosfamide 200 mg/day corresponded to the maximum tolerated dose (MTD) in the majority of patients. The dose was decreased by 50 mg daily if the leukocyte count decreased below 4.0×10^9/l, if the platelets decreased below 100×10^9/l or in case of nausea/vomiting. In case of leukopenia greater than WHO grade 2 or thrombocytopenia greater than WHO grade 1 treatment was discontinued until hematologic recovery. A minimum treatment of 4 weeks was required in order for the patient to be evaluable for response. For stable disease, a minimum period of 8 weeks without progression was required. Treatment was continued until disease progression or unacceptable toxicity. The study was approved by the local ethics committee.

Results

A total of 14 patients entered the study between December 1994 and May of 1996. All patients were fully evaluable for response and toxicity. The characteristics of the patients are listed in the table. All but one patient had a WHO performance status ≤ 1.

There were four patients with a stable disease; the median duration of stable disease during trofosfamide treatment was 14 weeks (range 12–36 weeks). All other patients progressed at least 8 weeks after the start of trofosfamide treatment. One patient died on day 12 after initiation of trofosfamide treatment, most likely due to disease progression.

The side effects were mild (Table 1). Only seven patients had signs of toxicity; hematologic toxicity was acceptable with grade 1 leukopenia in two patients and grade 1 anemia in one patient. The only non-hematologic toxicity was nausea grade ≤ 2 in four patients, which was well controlled by oral metoclopramide treatment.

Discussion

Trofosfamide is an oral oxazaphosphorine, which is structurally related to cyclophosphamide and ifosfamide. It is well absorbed when given by the oral route and is well tolerated when given on a continuous low-dose daily regimen (150–300 mg/day).[4–7] In our study a continuous 200 mg/day regimen was associated with mild side effects in only 50% of the patients. On this schedule, no responses were observed in 14 evaluable patients with 5-FU refractory advanced colorectal cancer.

Table 1. Patient characteristics (14 evaluable patients)

Patient characteristics	No. of patients
Eligible patients	14
Male/female	8/6
Age	
median	55
range	43–73
Performance status (WHO)	
0	6
1	7
2	1
Site(s) of metastasis	
liver only	9
lung only	2
liver and lung	3
Response	
CR/PR	0
stable	4
progression	10
Toxicity	
anemia (WHO 1)	1
leukopenia (WHO 1)	2
nausea/Vomiting (WHO 1/2)	4

However, patients presented tumor progression during high dose 5-FU treatment and in this very unfavorable patient population, four of the 14 patients achieved stable disease with a median time to progression of 14 weeks. These results may indicate some antitumor activity of trofosfamide in colorectal cancer and the drug might be considered as a nontoxic therapeutic approach in selected patients with 5-FU refractory colorectal cancer. Furthermore, because of the very limited toxicity encountered in this dose of trofosfamide, further dose escalation might be attempted.

Conclusion

Oral trofosfamide administered in a continuous 200 mg/day regimen demonstrated no responses in 14 evaluable patients with 5-FU refractory advanced colorectal carcinoma. Four of the 14 patients presented stable disease. Because of the very mild toxicity it cannot be excluded that higher doses would have yielded better results.

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