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Phase II Study with High-Dose N^{5-10}-Methyltetrahydrofolate and 5-Fluorouracil in Advanced Colorectal Cancer

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Abstract—*Thirty-eight patients with advanced colorectal adenocarcinoma were treated with the following regimen:* N^{5-10}*-methyltetrahydrofolate (MTHF)* (200 mg/m²/day) *and 5-fluorouracil (5-FU)* (375 mg/m²/day) *given concomitantly, consecutively for* 5 days, *every* 4 weeks, *in order to evaluate the potential advantage derived from the biochemical enhancement of cytotoxic activity of 5-FU by high-dose reduced folates. Of* 33 *evaluable patients (six of whom had received prior 5-FU chemotherapy) three untreated patients achieved a partial response* (9.1%) *lasting* 84, 281 *and* 401 days; 24 *patients* (72.7%) *had stable disease lasting a median of* 150 days (*range* 60-304 days). *The overall toxicity was acceptable: two patients had severe cardiac symptoms. Pharmacokinetics and biochemical studies seem necessary to determine the optimal dosage and timing of 5-FU and folates.*

INTRODUCTION

EXPERIMENTAL studies have shown that physiological concentrations of intracellular folates are unable to allow the optimal cytotoxicity of 5-FU [1, 2]; significant growth inhibition of tumor cell lines after combination of 5-FU with folinic acid or N^{5-10}-methyl-THF acid has been reported [3]. In advanced colorectal and gastric adenocarcinoma treated with 5-FU and high-dose folinic acid given concomitantly, Machover *et al.* reported 56 and 21% response rates in previously untreated and previously 5-FU-treated patients, respectively [4]. We report the results of a phase II trial of 5-FU and 5-methyltetrahydrofolate (MTHF) in advanced colorectal cancer. MTHF, the main active folate coenzyme in man, is the predominant folate form in serum and tissues; data are reported on pharmacokinetics of MTHF tested in serum either microbiologically [5] or by liquid chromatographic monitoring [6, 7].

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MATERIALS AND METHODS

Thirty-eight consecutive patients with advanced progressive metastatic colorectal carcinoma were entered into the study. The median age was 61 yr (range 41-77 yr), with a median ECOG performance status of 1 (range 0-2). Twenty patients were male and 18 female. All patients had measurable metastatic tumor documented by physical examination and by oriented tests such as chest X-ray, liver echography, and thoracic and abdominal computerized tomography. The predominant sites of secondary involvement were liver (22 patients) and lung (ten patients); other areas involved were peritoneum and pelvis. Fifteen patients had involvement of at least two anatomical sites. Most of the patients had not received any prior chemotherapy; seven patients failed prior 5-FU treatment. No patient had prior radiotherapy for metastatic disease. The treatment consisted of 200 mg/m² of MTHF (Prefolic, Bioresearch), i.v. bolus, followed by a 15-min infusion with 5-FU 375 mg/m², for five consecutive days. Treatment was repeated every 4

weeks and at least two courses were considered necessary for response evaluation.

In cases of myelotoxicity treatment was delayed until recovery to normal values; no dose reduction was performed. Patients were classified for objective response, duration of response and toxicity according to WHO criteria [8].

RESULTS

Thirty-three of 38 patients entered in the study were evaluated for response. Five patients were not evaluated: three because of rapid increase of tumor masses (pelvic localizations with peritoneal dissemination) and rapid deterioration of performance status following the first course of therapy; and two because of cardiac symptoms during the first course of therapy.

In the 33 evaluated patients no complete responses were recorded. Three partial responses (9.1%, with a 95% confidence interval of 2.3-25%) were observed, lasting 84, 281 and 401 days respectively, all in previously untreated patients. The first patient had pulmonary and hepatic metastases; after two courses of treatment chest X-ray and computerized tomography (CAT) revealed disappearance of hepatic nodules and a partial response of lung metastases, but the patient developed multiple brain metastases and died 4 months after the start of treatment. The second patient had multiple lung metastases which no longer showed up on chest X-ray after four courses of treatment: bronchoscopy was performed and provided histological confirmation of residual disease; progression of disease occurred 9 months after the start of treatment, but the patient is still alive. The third patient experienced a partial response of liver metastases, lasting more than 12 months. No change was observed in the majority of the patients (24 patients; 72.7%, with a 95% confidence interval of 54.2-90.4%); 7/24 patients had a tumor mass reduction below 50%. Stable disease lasted a median of 150 days (range 60-304 days). The remaining six patients experienced progressive disease. The overall median survival was 200 days; responders survived 133, 553 and 693+ days. Median survival was 267 days (range 70-543 days) for stable disease and 81 days (range 45-207 days) for patients with progressive disease.

A total of 167 courses of therapy were performed; the mean number of courses per patient was five (range 2-11). The following toxicity was observed: nausea grade 1-2 in eight patients (30/61 courses); vomiting grade 2 in only one patient; and diarrhoea grade 1-2 in eight patients (17/42 courses). Oral mucositis occurred in seven patients: grade 3 in three patients (9/19 courses) and grade 1 in four patients (8/12 courses). Hair loss grade 1 was infrequent. Haemoglobin reduction grade 1 occurred in two patients, leukopenia grade 1 in four patients; no platelets reduction was observed. Two patients had petechiae, without any laboratory alteration. Two patients who were not considered for response had severe cardiac symptoms. One patient suffered a reversible severe angina-like pain during the first MTHF bolus and one patient developed an acute pericarditis on the first day of treatment. Treatment was interrupted in both patients even if drug-related toxicity could not be clearly established.

DISCUSSION

The phase II study reported here does not confirm the previous data by Machover *et al.* [4]; these authors reported 56 and 21% response rates, complete plus partial, in previously untreated and previously treated patients respectively. We did not observe any complete response; only an overall 9.1% partial response rate was recorded, and of the previously untreated patients only 11.1% responded.

The unique difference with the Machover therapeutic regimen consists in the use of folinic acid in the Machover study and MTHF in our study. This difference is probably not important according to present knowledge: folinic acid must be converted into MTHF, the principal active folate coenzyme in man; MTHF must be then converted to methylene-THF, the active folate cofactor involved in the formation of the ternary complex with 5-FdUMP and thymidylate synthetase. However, differences in percentages in plasma protein binding, storage tissues and enterohepatic cycle [5] could account for a different biochemical activity and finally for a different therapeutic outcome.

REFERENCES

1. Waxman S, Bruckner H. The enhancement of 5-fluorouracil antimetabolic activity by leucovorin, menadione and alfatocopherol. *Eur J Cancer Clin Oncol* 1982, **18**, 685-692.
2. Donaldson KO, Keresztsy JC. Naturally occurring forms of folic acid. II Enzymatic conversion of methylenetetrahydrofolic acid to prefolic A-methyleetrahydrofolate. *J Biol Chem* 1962, **237**, 1298-1309.

3. Evans RM, Laskin JD, Hakale MT. Effect of excess folates and deoxyinosine on the activity and site of action of 5-fluorouracil. *Cancer Res* 1981, **41**, 3288-3295.
4. Machover D, Schwarzenberg L, Goldschmidt E *et al.* Treatment of advanced colorectal and gastric adenocarcinoma with 5-FU combined with high-dose folinic acid: a pilot study. *Cancer Treat Rep* 1982, **66**, 1803-1807.
5. Periti P, Ciuffi M, Coronello M, Mazzei T, Mini E. Pharmakinetics of 5-methyltetrahydrofolate in normal adults. *Chemioterapia* 1983, **II**, 83-87.
6. Cortellaro M, Boschetti C, Di Padova F *et al.* Methotrexate with N^5-methyltetrahydrofolic acid in the treatment of non-Hodgkin's lymphomas and acute leukemias. *Haematologica* 1983, **68**, 74-86.
7. Giulidori P, Galli-Kienle M, Stramentinoli G. Liquid chromotographic monitoring of 5-methyltetrahydrofolate in plasma. *Clin Chem* 1981, **27**, 2041-2043.
8. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer* 1981, **47**, 207-214.