Cancer Chemother Pharmacol (1996) 38: 195–197

CLINICAL TRIAL REPORT

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5-Methyltetrahydrofolate or 5-formyltetrahydrofolic acid to modulate 5-fluorouracil's cytotoxic activity in vivo?

A phase II study in patients with advanced colon cancer

Received: 9 September 1995 / Accepted: 30 November 1995

Abstract The purpose of this study was to test the hypothesis that 5-methyltetrahydrofolate (Me-THF), a source of reduced folates alternative to leucovorin, could effectively modulate 5-fluorouracil's (5-FU) cytotoxic activity in patients with advanced colon cancer. A total of 23 patients were enrolled in a phase II trial; they received 5-FU as a 30-min infusion at a dose of 370 mg/m^2 following a rapid i.v. push of 200 mg/m^2 Me-THF, both drugs being given for 5 consecutive days. Cycles were repeated every 4 weeks until disease progression. No patient achieved a complete response. In all, 4 patients showed a partial response (17.4%), 7 developed stable disease (30.4%), and the remaining 12 (52.2%) progressed. Toxicity was acceptable and never exceeded WHO grade III intensity. According to our experience, the MeTHF/5-FU combination does not appear to be an effective treatment for advanced colon cancer. Despite its low toxic profile, in our opinion its wider use should be discouraged.

Key words 5-Methyltetrahydrofolate · 5-FU · Colon cancer · Biologic modulation · Advanced disease · Phase II trial

Introduction

5-Fluorouracil (5-FU) is the most active single agent used to treat gastrointestinal cancer patients, both in the advanced and in the adjuvant settings; however, this drug alone produces an objective response rate rarely exceeding 20–25% [8]. The antitumor activity of 5-FU can be ascribed at least to three different mechanisms: its incorporation into RNA or DNA as fluorouridine-5′-triphosphate (5-FUTP) and 5-fluoro-2′-deoxyuridine triphosphate (FdUTP), respectively, and its metabolic conversion to 5-fluorodeoxyuridine monophosphate (FdUMP), a selective inhibitor of thymidylate synthase (dTMP-s), an enzyme essential for DNA duplication [7]. Increased levels of reduced folates in the form of 5,10-methylene tetrahydrofolate (5,10-CH_3FH_4) have been shown to be necessary for a stronger bond between FdUMP and dTMP-s [1, 5], suggesting that they should potentiate 5-FU cytotoxic activity in vivo.

In a recent report, Bolli and co-workers [3] reported on a biochemical modulation of 5-FU activity alternative to the well-known combination of 5-FU with 5-formyltetrahydrofolic acid, i.e., leucovorin calcium (LV) [10]. In their phase II study on advanced pancreatic cancer patients, the Genoa group used 5-methyltetrahydrofolate (Me-THF) instead of LV as the source of reduced folates necessary to increase the stability of the ternary complex 5-FdUMP/dTMP-s/5,10-CH_3FH_4. Although the biological target of this combination was the same as that of 5-FU and LV, a possibility of greater selectivity in favor of the Me-THF/5-FU combination was postulated on the basis of the differences in the metabolic pathways responsible for the activation of Me-THF and LV to their active metabolite 5,10-CH_3FH_4 or its polyglutamylated derivatives [3]. Unfortunately, this attempt failed; indeed, this regimen yielded negligible results in pancreatic cancer patients despite its production of only modest toxic effects [3].

In this paper we report our negative experience with the Me-THF/5-FU regimen in the treatment of advanced colon cancer.

Patients and methods

Patients

Accrual criteria included histologically proven colon cancer; measurable metastatic disease; an ECOG performance status [9] of 2 or less; an age of 75 years; no previous therapy (including both adjuvant chemotherapy and treatment for metastases); and normal renal, hepatic, and bone marrow functions (serum creatinine <2 mg/dl; serum bilirubin <1.5 mg/dl; alkaline phosphatase, SGOT and SGPT levels

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Table 1 Patients' characteristics

Number of patients	23
M/F	15/8
Median age (range)	67.2 (40–75) years
WHO performance status:	
0	17
1	3
2	3
Sites of metastatic disease:	
Liver	12
Liver + peritoneum	5
Liver + lung	4
Pelvis	2

< 3 times the normal values; WBC ≥3,000/mm^3; platelets ≥100,000/mm^3). All patients gave their informed consent to protocol enrollment according to institutional requirements.

Treatment

5-FU (Fluorouracile Iketon, Iketon) was given as a 30-min infusion at a dose of 370 mg/m^2 for 5 consecutive days following a rapid i.v. push of 200 mg/m^2 Me-THF (Prefolic, Bioresearch). Cycles were repeated every 4 weeks until disease progression. No dose reduction was considered in the event of any grade III (severe) toxicity, whereas a 50% reduction in the 5-FU dose was scheduled for any patient developing grade IV (life-threatening) gastrointestinal or hematological toxicity.

Follow-up procedures

Complete serum biochemistry, including hemochrome, renal, and hepatic function tests, was performed before each treatment cycle, and standard chest X-ray examinations (two projections) and abdominal computerized tomography (CT) were performed every two cycles or more often, if clinically appropriate, to assess the tumor status and eventual response to treatment. Abdominal CT was preferred over ultrasound due to the low reliability of the latter technique for monitoring the response to treatment of liver metastases [6].

Response was assessed only if patients completed at least two treatment cycles; a complete response (CR) required the disappearance of all perceptible tumor; a partial response (PR) was defined as a 50% reduction in the product of the largest perpendicular diameters of the most clearly measurable known malignant disease with no increase in the size of other measurable disease and no appearance of new lesions. The duration of response was calculated from the time the response began until progression; 8 weeks was required as a minimal response duration. Stable disease (SD) required no change in the size of the measurable lesions or a decrease in tumor size of <50% or an increase of <25% with no appearance of new lesions; SD also required a minimum of 8 weeks' duration. Progression (P) was defined as the appearance of any new lesion and/or growth of any existing lesion by ≥25% from the start of treatment. Toxicity was evaluated according to standard WHO criteria [13].

Results

Patients

Accrual started in December 1990 and ended in April 1991; in that period, 23 consecutive patients, 15 men and 8 women aged a median of 67.2 (range 40–75) years entered this study. The patients were in good general condition; the ECOG performance status was 0 in 17 patients, 1 in 3 subjects, and 2 in 3 patients. Metastatic sites were the liver only in 12 patients, the liver and peritoneum in 5 subjects, and the liver and lung in 4 patients; the remaining 2 patients had neoplastic pelvic masses. The patients' characteristics are summarized in Table 1. All enrolled patients were assessable for both response and toxicity.

Efficacy

Treatment with 5-FU and Me-THF resulted in no CR, 4 PRs (17.4%; 95% confidence interval 1.6–33.2%), and 7 cases of SD (30.4%); the remaining 12 patients (52.2%) progressed (P) despite treatment. The average duration of the PRs was 5.75 (range 4–8) months; PRs were obtained after an average of three cycles. The median time to disease progression for all treated patients, calculated from the treatment start until the first instrumental confirmation of progression, according to the above-mentioned criteria, was 4.08 months. The overall median survival time was not calculated since the majority of these patients were enrolled at progression in a second-line protocol.

Toxicity

Toxicity was acceptable, never exceeding WHO grade III intensity; indeed, only 3 patients experienced grade III leukopenia (13%), 6 patients each complained of grade III nausea/vomiting and diarrhea (26%), and 7 patients had grade III stomatitis (34.7%). Neither signs of cardiac toxicity nor toxic deaths were recorded. Since no case of grade IV toxicity was observed, no dose reduction was performed.

Discussion

Colorectal cancer represents a dramatic threat to public health in the Western world; in 1995 an estimated 138,200 new cases will be diagnosed, and 55,300 more patients will ultimately die of this cancer solely in the United States [12]. 5-FU is undoubtedly the most active single agent used to treat colorectal cancer. As far as the advanced setting is concerned, although modulation of 5-FU activity by means of LV has produced response rates higher than those obtained with 5-FU alone, it has not improved patients' overall survival, as has clearly been demonstrated in a recent meta-analysis [10]. Bolli et al. [3] have postulated that another source of reduced folates, Me-THF, could be of greater efficacy than LV. Both their attempt in advanced pancreatic cancer and our experience in colon cancer produced unsatisfactory results.

Indeed, we did not observe CRs, which are the most important indicator of chemotherapeutic efficacy and the prerequisite for cure [4]. Furthermore, the overall response rate observed in our study appears to be lower than both the average response rate reported in the literature for the 5-FU/LV combination in advanced colon cancer, i.e., 23% [10], and the figures obtained by our own group using 5-FU and racemic LV [2] and, more recently, 5-FU and the pure l-stereoisomer of LV [11]. For these reasons, despite the small sample size of our study, yielding a large confidence interval, we decided not to evaluate this protocol further.

With regard to side effects, in both our investigation and the Genoa study [3], the MeTHF/5-FU combination produced acceptable toxicity, which never exceeded WHO grade III intensity; as suggested by Bolli et al. [3], different and tissue-specific metabolic pathways responsible for the activation of MeTHF and LV to 5,10-CH_3FH_4 may account for the lower toxicity of the MeTHF/5-FU combination as compared with the well-known and more severe toxicologic profile of 5-FU and LV [2, 10].

In conclusion, the MeTHF/5-FU combination does not appear to be superior to the classic 5-FU/LV regimen despite their common intracellular target; the antineoplastic activity of the former is probably lower, and its lower toxic profile does not compensate for such low activity in vivo. Taking into account both the similar mechanism of action and the results of the present phase II study, in our opinion, MeTHF should not be considered an alternative to LV for the modulation of 5-FU activity, and there is no need for a randomized trial aimed at comparing 5-FU and LV with 5-FU and MeTHF.

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