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Weekly chronomodulated 48 h infusion of high-dose 5-fluorouracil modulated by methotrexate and (6*S*)-leucovorin in advanced colorectal cancer: a phase IB study

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In this phase IB study, 24 patients with advanced colorectal cancer were treated with escalating doses of weekly chronomodulated 48 h infusions of 5-fluorouracil (5-FU) biochemically modulated by methotrexate 40 mg/m^2 and (6*S*)-leucovorin 8 × 45 mg orally. Two daily peak delivery periods (PDP), during which 65% of the daily dose was administered, were investigated: from 18.00 to 0.30 h and from 0.00 to 06.30 h. The maximal tolerated dose of 5-FU was 2800 mg/m^2/48 h, with a PDP from 18.00 to 0.30 h.

Key words: Biochemical modulation, chemotherapy, chronomodulation, colorectal cancer, 5-fluorouracil, phase I study.

Introduction

A steep dose relationship has been demonstrated for the antitumor efficacy of 5-fluorouracil (5-FU) in colorectal cancer.[1] Infusional administration of 5-FU allows a higher dose intensity compared with bolus administration. Several clinical trials in patients with colorectal cancer have shown the superiority of infusional versus bolus delivery of 5-FU in terms of response rate, quality of life and cost-effectiveness; however, a survival benefit has never been demonstrated.[2–4]

Circadian mechanisms relevant to the treatment of cancer have been identified in rodents and humans. These include 24 h changes in the activities of several enzymes involved in 5-FU metabolism, the pharmacokinetics of 5-FU infusion, and the proliferative activity of bone marrow and intestinal mucosa.[5–10] Based on these data it has been hypothesized that circadian timing of drug delivery may permit a further increase in dose intensity compared with delivery at a flat rate and this has been demonstrated in several clinical trials.[11–17] In a randomized trial involving 92 colorectal cancer patients, the delivery of chronomodulated oxaliplatin, 5-FU and leucovorin (LV) was shown to be significantly superior in terms of dose intensity of 5-FU, toxicity, response rate and survival compared to the same schedule but given at a flat infusion rate.[18] In this study a 5-FU peak delivery period (PDP) with a maximum occurring at 03.00–04.00 h was used. Others have shown that a PDP of 5-FU with a maximum at 21.00–22.00 h may allow a further 20% increase in the daily 5-FU dose.[19] We performed a phase I study in patients with colorectal cancer with a schedule of weekly chronomodulated 48 h infusion of high-dose 5FU biochemically modulated by methotrexate (MTX) and LV. The objectives of our study were to determine the maximal tolerated dose (MTD) and the optimal PDP of 5-FU at this schedule.

Patients and methods

Patients

Inclusion criteria were histologically proven adenocarcinoma of the colon or rectum, measurable metastatic or advanced disease with a minimum diameter of the largest lesion of 2 cm, disease not amenable to curative surgery, WHO performance status ≤ 2, age 18–75 years, normal values for serum creatinine and bilirubin, WBC ≥ 3.0×10^9/l, platelets ≥ 100×10^9/l, and written informed consent. Exclusion criteria were previous radiotherapy on all disease parameters, clinical signs of CNS involvement, evidence of significant ascites or pleural fluid, previous second malignancy with the exception of adequately treated *in situ* carcinoma of the cervix or

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basal/squamous cell carcinoma of the skin, serious active infections or other concomitant serious non-malignant disease and pregnancy or lactation. Institutional board review was obtained.

Treatment

Treatment was ambulatory, and consisted of MTX 40 mg/m^2 i.v. bolus on day 1, followed 20–24 h later by LV (Isovorin$^{(R)}$; Cyanamid, Hoofddorp, The Netherlands) 45 mg/dose orally every 6 h for eight doses and 5-FU infusion on day 2. 5-FU was administered as a continuous infusion for 48 h through a s.c. implanted venous port system (Port-A-Cath; Pharmacia, Woerden, The Netherlands) by a programmable in-time pump (Deltec Cadd-Plus; Pharmacia or Verifuse; NPBI, Amsterdam, The Netherlands). Patients were evaluated every cycle for toxicity and every 2 months for response. Toxicity and response were evaluated according to WHO criteria. The dose of 5-FU was increased in cohorts of three patients. In case of grade ≥ 3 toxicity, a total of six patients were treated at that particular 5-FU dose level. Dose-limiting toxicity was defined as grade ≥ 3 toxicity in two or more of six patients during the first four evaluable weekly cycles. The MTD was defined as the 5-FU dose at which one or less of six patients experienced reversible, tolerable and manageable grade 3 toxicity, which was immediately below a 5-FU dose that produced grade ≥ 3 toxicity in two or more of six patients. The starting dose of 5-FU was 2400 mg/m^2/48 h and this was increased in steps of 200 mg/m^2/48 h in subsequent cohorts of patients. The initial PDP of 5-FU was 0.00–06.30 h. During this period 65% of the daily 5-FU dose was delivered. After reaching the MTD of 5-FU, subsequent cohorts of three to six patients were treated at MTD but with a PDP from 18.00–0.30 h and 5-FU dose was increased according to the abovementioned schedule. Treatment cycles were administered every week for four consecutive weeks and once every 2 weeks thereafter until the occurrence of disease progression or unacceptable toxicity.

In case of grade ≥ 3 toxicity treatment was withheld until values had returned to the normal range and/or symptoms had disappeared. In case of recovery within this period, the dose of 5-FU was reduced to 75%. Doses of MTX and LV were not reduced. In case of 5-FU dose reduction due to toxicity occurring during the first four weekly cycles, and in the absence of grade ≥ 2 toxicity during subsequent two weekly cycles, it was recommended to increase the 5-FU dose again to 100%.

Results

Twenty four patients entered the study, 14 male and 10 female. Median age was 61 years (range 43–71), median WHO performance status was 1 (0–2), median serum LDH value was 770 U/l (range 161–2883, normal values <330 U/l) and median WBC was 8.6 $\times$ 10^9/l (range 5.0–12.2). One patient was excluded from the analysis because of disease progression after one cycle. Ten patients (43%) had failed on previous systemic chemotherapy; most of them had been treated with a 5-FU bolus schedule.

Toxicity

The 5-FU dose levels with corresponding PDP administered to 23 patients is shown in Table 1. At a PDP of 0.00–6.30 h the MTD of 5-FU was 2600 mg/m^2/48 h, since of the three patients treated at 2800 mg/m^2/48 h, one patient experienced grade 3 stomatitis and diarrhea, and one patient grade 3 vomiting and grade 4 diarrhea. The PDP was then changed to 18.00–0.30 h and at this PDP dose-limiting toxicity occurred at 3000 mg/m^2/48 h with all three patients experiencing grade 3/4 toxicities (one patient grade 3 stomatitis and diarrhea, and two patients grade 3 and grade 4 stomatitis, respectively). A 5-FU dose of 2800 mg/m^2/48 h with a PDP of 18.00–0.30 h could safely be administered. In order to assure feasibility, 10 patients were eventually treated at this 5-FU dose level and PDP, and grade 3 vomiting and diarrhea occurred in only one patient, and grade 2 stomatitis and diarrhea in nine and one patients, respectively. After the fourth cycle, when cycles were administered once every 2 weeks, a further 5-FU dose escalation was performed in four patients to 3500 mg/m^2/48 h and this was possible without an increase in toxicity.

Table 1. Patients and occurrence of toxicity at the different 5-FU dose levels

5-FU dose (mg/m^2/48 h)	PDP (h)	Total no. of patients/ patients with grade 3/4 toxicity
2400	0.00–6.30	3/0
2600	0.00–6.30	4/0
2800	0.00–6.30	3/2
2800	18.00–0.30	10/1
3000	18.00–0.30	3/3

Tumor response

One patient was not evaluable for response due to withdrawal from the study after three cycles because of toxicity. Therefore, 22 patients were evaluable for response. One previously untreated patient achieved a partial response of 9 months duration, the remaining 21 patients had stable disease for a median duration of 8 (range 3–20+) months. With a median follow-up of 10 months, the median overall survival for all patients has not been reached.

Discussion

A schedule of weekly flat-rate 5-FU infusion at 60 mg/kg/48 h (equivalent to 2400 mg/m^2/48 h) has been described by Shah *et al.*[20] Subsequently this schedule has been used in several clinical studies.[21–25] The MTD of chronomodulated 5-FU biochemically modulated by MTX and LV in our study was 2800 mg/m^2/48 h. The MTD of double modulated flat-rate 5-FU infusion given over 48 h has never been investigated. For comparison, the MTD of weekly 48 h flat-rate 5-FU infusion without modulation was 3500 mg/m^2,[26] and of weekly 24 h 5-FU infusion modulated by LV was 2600 mg/m^2.[27] Based on these data, it seems likely that a 5-FU dose of 2800 mg/m^2/48 h given at a flat rate will be too toxic in combination with both MTX and LV, since double modulation is likely to result in an increase in toxicity compared with single or no modulation. Although our study did not have the appropriate design to allow a direct comparison with a flat-rate infusion schedule, our results appear to confirm earlier observations that chronomodulated delivery of 5-FU allows a high 5-FU dose intensity. These data also suggest that a 5-FU dose of 2400 mg/m^2/48 h which has been used in a recent randomized study was suboptimal, as was also evidenced by the very low incidence of grade 3/4 toxicity in this study.[21] Furthermore, in this last study the same schedule of four weekly cycles followed by one cycle every 2 weeks was used, and although this was not the primary objective in our study, we could increase the 5-FU dose of the two-weekly cycles in four patients up to 3500 mg/m^2/48 h without any increase in toxicity.

We found that a PDP of 18.00–0.30 h allowed a higher 5-FU dose intensity compared with a PDP of 0.00–6.30 h, but this difference was small (200 mg/m^2/cycle). Bjarnason *et al.*[19] also found in a schedule of low-dose 14 day infusion of 5-FU that a peak infusion around 21.00–22.00 h was superior to a peak infusion around 03.00–04.00 h.

LV and MTX are the only biochemical modulators of 5-FU to date that have shown activity in randomized clinical trials.[28,29] Furthermore, MTX effectively modulates 5-FU when given as a continuous infusion.[21] Very few data exist on clinical trials in which MTX and LV are both administered as biochemical modulators of 5-FU. Two small randomized trials have failed to show a significant difference between treatment with 5-Fu/MTX/LV and 5-FU/LV.[30,31] In most trials in which 5-FU is combined with both MTX and LV, the latter is used as a rescue for MTX administration.[29] From this meta-analysis, the authors could not exclude the possibility that the clinical benefit of MTX modulation was due to the LV rescue. In preclinical models the results of double modulation of 5-FU by MTX and LV are conflicting, although most studies failed to show an advantage for double over single modulation.[32–34] Trimetrexate, a dihydrofolate reductase inhibitor which does not compete with LV for cellular uptake and metabolism, might therefore be a more suitable modulator of 5-FU in combination with LV.[33] Early results of clinical trials with this combination have been promising.[35,36]

We had one partial response in 12 patients previously not treated with chemotherapy and no response in 10 pretreated patients. Although this result is disappointing, it should be noted that patients remained stable for a substantial period of time (median of 8 months). Graf *et al.*[37] have shown that in metastatic colorectal cancer patients treated with chemotherapy stabilization of disease is meaningful to the patients, since they found only a small difference (i.e. 2 months) in median survival between patients with disease stabilization and those who achieved a partial remission. The median survival in excess of 10 months in our patients of whom 43% were pretreated with another 5-FU regimen may support this.

In conclusion, we showed that weekly chronomodulated 48 h infusion of 5-FU biochemically modulated by MTX and LV is feasible, and that the MTD of 5-FU in this schedule is 2800 mg/m^2. With this schedule a PDP of 18.00–0.30 h is modestly superior to a PDP of 0.00–06.30 h. Based on our results as well as the results of recent clinical trials, the use of double modulation of 5-FU by LV and MTX cannot be advocated.

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