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A phase II study of sequential methotrexate and fluorouracil in advanced colorectal cancer

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Summary. Twenty-nine patients with advanced colorectal cancer were treated with methotrexate (MTX) 200 mg/m^2 followed 1 h later by fluorouracil (FU) (1000 mg/m^2) and 24 h later by oral leucovorin 20 mg every 6 h for six doses. The cycle was repeated every 2 weeks. Among the 25 evaluable patients there were 2 complete responses (confirmed by liver scan) and 5 partial responses. Although hematological toxicity was mild, there were four episodes of nonfatal sepsis. The majority of patients developed an erythematous scaly rash on the palms and soles plus eye irritation after six courses of chemotherapy. In addition, the sequential MTX-FU had to be discontinued in 6 of the 7 responders because of (a) severe chills, (b) severe hyperpigmentation, or (c) neurologic complications (ataxic gait or disorientation).

These results indicate that this sequential MTX-FU has modest activity in colorectal cancer but is associated with moderately severe toxicity. Only randomized trials of FU alone versus sequential MTX-FU can determine whether sequential MTX-FU has a therapeutic advantage over FU alone in the treatment of advanced colorectal cancer.

Introduction

The standard chemotherapeutic agent for the treatment of advanced colorectal cancer is fluorouracil (FU). It has been shown that FU produces objective responses of measurable disease in approximately 20% of patients with advanced colorectal cancer [8]. However, there is little evidence that this agent has improved overall survival.

More recently, FU in combination with methyl-CCNU and vincristine has produced objective tumor regression in up to 40% of patients with advanced colorectal cancer [4, 9]. However, the median survival of responders was not significantly improved over that in nonresponders [7].

Bertino et al. demonstrated schedule-dependent antitumor effects of methotrexate (MTX) and FU in the sarcoma 180 mouse model. Treatment with MTX prior to FU resulted in a significantly higher response rate than simultaneous administration of both drugs [2]. In addition, Benz and Cadman demonstrated maximal in vitro inhibition of clonal growth of the human colon adenocarcinoma cell line, HCT-8, when FU was added for the last 6 h of a 24-h MTX incubation period. This increased FU cytotoxicity correlated with total intracellular accumlation of FU and incorporation into cellular RNA [1].

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We initially treated six patients with MTX (200 mg/m^2) IV, followed 1 h later by FU (600 mg/m^2) and 24 h later by leucovorin (20 mg) PO every 6 h for six doses. This chemotherapy was repeated every 2 weeks. There was no serious toxicity with this dose and schedule. The dose of FU was gradually increased to 1000 mg/m^2 with acceptable myelotoxicity [10]. The dose of FU was increased to a maximally tolerated dose to allow for maximal expression of the proposed increased FU intracellular accumulation. There is only one other report of a 1-hour sequential MTX-FU combination with high-dose FU (1500 mg/m^2) administered to patients with metastatic colorectal cancer. In that study two of seven patients responded to the treatment [11]. We report a phase II investigation of with the same schedule as outlined above but with our higher FU dose in patients with advanced colorectal cancer.

Materials and methods

Twenty-nine patients with advanced colorectal carcinoma were entered on this study. They had an initial Eastern Cooperative Oncology Group (ECOG) performance status ≤ 3, serum creatinine ≤ 1.5 mg/dl, WBC count ≥ 4000 cells/mm^3, and platelets ≥ 150000/mm^3, and had received no prior FU chemotherapy. Four patients were not evaluable (2 patients did not have measurable disease, 1 patient died after receiving only one course of chemotherapy, and 1 patient refused further chemotherapy and radiographic examinations after two courses). Of the 25 evaluable patients (mean age, 62 years; mean ECOG performance status, 1.0), 2 had received previous chemotherapy (spirogermanium only in both cases). The sites of measurable disease were liver (18 patients), lung (4 patients), and other (3 patients). All patients who received at least two courses of chemotherapy were considered evaluable for response (mean number of courses, 6.4). Partial response was defined as a decrease of $\geq 50\%$ in the sum of the products of the two largest perpendicular diameters of measurable lesions. Complete response was defined as complete disappearance of disease as measured by radionucleotide liver scans and liver function studies. Serial CEA determinations were performed in all patients and correlated with response to chemotherapy. Survival time was calculated from the initiation of chemotherapy.

MTX (200 mg/m^2) was administered IV 1 h prior to FU (1000 mg/m^2) IV. Both drugs were administered by bo-

lus injection in less than 5 min. Starting 24 h after MTX administration, 20 mg leucovorin was given PO every 6 h for a total of six doses. The drugs were recycled every 2 weeks. If, on the day of treatment, the WBC count was 3000–3499/mm^3 and/or the platelet count was 75000–99999/mm^3, half the dose of MTX and FU was given. If on the day of treatment, the WBC count was <3000/mm^3 and/or the platelet count $<75\,000$/mm^3, treatment was delayed by 1 week. Patients who experienced a nadir WBC <1500/mm^3 or treatment delay secondary to myelosuppression received ten doses of leucovorin with subsequent cycles of chemotherapy.

Results

Twenty-eight percent of the patients (7 of 25) responded to sequential MTX-FU chemotherapy (95% confidence limits 12%–48%). There were two complete responses, confirmed by normalization of liver scans, and five partial responses (4 with measurable liver disease and 1 with measurable disease in a surgical scar). The five responders with an initial CEA value ≥ 20 ng/ml had 72%–95% reductions in their CEA values at the time of maximum response. Only one nonresponder with locally recurrent rectal cancer demonstrated a decrease (75%) in the pretreatment CEA. The CEA value rose by at least 50% in the nine nonresponders, who had serial values and pretreatment CEA values ≥ 10 ng/ml. The median duration of response is 6 months (2, 4, 5, 6, 6, 10+, and 12). Six responding patients stopped MTX-FU chemotherapy because of toxicity as outlined below. The median survival of the seven responding patients is at least 15 months (10, 13+, 15, 15+, 21+, 28+, and 39+). The median survival of nonresponding patients was 8 months.

A total of 160 courses of chemotherapy was given. Sequential MTX-FU chemotherapy was generally well tolerated for the first two to three courses. Nausea and/or mild vomiting occurred in approximately 25% of the patients. Nadir WBC count <2000/mm^3 and/or nadir platelet count $<100\,000$/mm^3 occurred with 13 courses of chemotherapy. There were four episodes of nonfatal sepsis in three patients. Mild (ECOG grade 1) mucositis occurred in approximately 25% of the patients. Two episodes of severe (ECOG grade 3) mucositis occurred. There was one episode of mild reversible renal failure (creatinine, 3.6 mg/dl). However, after several (≥ 6) courses of chemotherapy there were disturbing side effects, including (a) erythema and scaling of the skin of the palms and soles in 50% of the patients and (b) eye irritation in 80% of the patients.

Sequential MTX-FU was discontinued in six of seven responding patients after a total of 6–18 courses. Two patients developed severe chills 30 min after MTX administration on four separate occasions after 8 and 16 courses, respectively. Two patients developed severe hyperpigmentation of their skin plus the previously described palmar skin reactions necessitating cessation of chemotherapy. Two patients developed severe neurologic complications (disorientation in 1 patient and an ataxic gait in 1 patient) on repeated occasions necessitating cessation of sequential chemotherapy. Only the neurologic complications developed with the initial courses of chemotherapy. Five of six responding patients were treated with FU alone after cessation of sequential MTX-FU chemotherapy. Three of these five patients in whom the MTX-FU chemotherapy was stopped relapsed within 2 months.

Discussion

The response rate of 28% with sequential MTX-FU is not significantly different from that previously reported with FU alone. However, the survival is better in responding than in nonresponding patients. Five of the seven responding patients had a pretreatment alkaline phosphatase greater than 4 times the normal value. A previous study has demonstrated that an initial alkaline phosphatase greater than twice normal correlates with a poor survival (median survival, 3 months) [6]. This suggests that our responding patients may have benefited from chemotherapy. However, this sequential MTX-FU chemotherapy was very highly toxic and only one patient tolerated more than 18 courses of chemotherapy.

A more recent study with a 24-h delay between conventional dose MTX and FU yielded a 32% response rate with less toxicity. As suggested in this report, the response rate of sequential MTX-FU may be higher wehn the interval between drugs is 3 h or greater [5]. Browman has recently reviewed the possible biochemical mechanisms responsible for the synergistic activity of sequential MTX-FU in rodent tumor studies. However, he cautioned that it could be very difficult to extrapolate these results to the complicated clinical situation [3].

Although sequential MTX-FU is an active regimen against colon cancer, routine use is not warranted on the basis of this study. Furthermore, it appears that increasing the dose of FU in 1-h sequential MTX-FU therapy results in significant toxicity and a response rate similar to the better response rates reported with FU alone. A randomized prospective trial of optimal FU therapy alone vs optimal sequential MTX-FU in advanced colorectal cancer would be of value in establishing whether sequential MTX-FU is more effective than FU alone.

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