Two studies were carried out to determine the activity and evaluate the toxicity of oral chemotherapy with uracil and tegafur in a 4:1 molar ratio (UFT) plus or minus calcium folinate in elderly patients with advanced colorectal cancer.

Introduction

An intravenous, modulated, bolus 5-fluorouracil (5-FU)-based regimen is the standard treatment for colorectal cancer. According to a meta-analysis, overall response rates are 19% to 23%, and median survival is 10.7 to 11.5 months.[1,2] According to our experience, overall response rates are 19.2% to 25.7%, and median survival is 10.6 to 14.3 months.[3,4] Several studies suggest that the alternative therapy of continuous-infusion 5-FU increases response rate,[5] possibly due to a higher dose intensity and longer exposure of tumor cells to this drug, which has a short half-life (≤ 11 minutes) when administered as a bolus infusion. Continuous-infusion 5-FU also has a better toxicity profile than bolus infusion, and a recently published meta-analysis has shown a small but significant improvement in survival with this regimen.[5] Nevertheless, continuous infusion necessitates a subcutaneous port, a portable infusion pump, frequent hospital visits, weekly complete blood cell counts, and toxicity and treatment costs that are not negligible.

These limitations are especially important in the elderly. Elderly patients do not tolerate chemotherapy as well as younger patients, and concomitant medical conditions may preclude certain treatments. Furthermore, patients 70 years of age or older are often insufficiently staged and treated.[6] By the year 2000, it is estimated that 70% of cancer cases will occur in patients over 65 years old,[7] making it desirable to identify a more tolerable and nontoxic chemotherapy that exhibits at least comparable activity to continuous-infusion 5-FU.

Several studies carried out in Japan have proved the activity of the oral fluoropyrimidine agent, uracil and tegafur (in a molar ratio of 4:1 [UFT]), in colorectal cancer.[8-10] In Europe, Malik et al.[11] demonstrated a response rate of 16.6% using UFT alone. Recently, in the United States and Europe, calcium folinate modulation of UFT yielded improved results, producing response rates of 42% and 39%.[12-14] The continuous oral administration of UFT pharmacokinetically simulates delivery of protracted 5-FU by continuous intravenous infusion, making this oral therapy a possible substitute for intravenous chemotherapy. Based on these data, the Gastrointestinal Tumor Therapy (TTD) Spanish Cooperative Group initiated a study (study 1) of UFT plus calcium folinate modulation. Because the results suggested that modulation is not necessary when 5-FU is administered as a continuous infusion at the maximum tolerated dose,[15-18] a second study (study 2) with UFT alone was organized.

Patients and Methods

Enrollment Criteria

From September 1994 to September 1998, the Gastrointestinal Tumor Therapy Spanish Cooperative Group performed two consecutive studies involving elderly patients with advanced colorectal cancer. The final results of study 1 (N = 106) and preliminary results from study 2 (N = 95) are hereby presented. Eligibility criteria were similar in the two trials: age ≥ 72 years, confirmed colorectal adenocarcinoma, no resectable or metastatic tumor, measurable disease (at least one lesion with...
dimensions of 2 × 2 cm at the longest diameter), a Karnofsky performance status of ≥ 60%, and no other malignancies except skin basocellular carcinoma or in situ carcinoma of the cervix. Patients could not have received prior systemic chemotherapy for metastatic disease. Patients who had received adjuvant therapy were eligible providing the therapy was completed at least 6 months before enrollment in this study. Laboratory criteria included an absolute granulocyte count of ≥ 1,500 µL, a platelet count of ≥ 100,000/µL, serum bilirubin levels of ≤ 1.5 mg/dL, and a serum creatinine level of ≤ 1.5 mg/dL. Informed consent was required.

**Treatment Regimen**

**Study 1**—A fixed dose of UFT 400 mg/day was administered in two daily doses every 12 hours continuously, plus calcium folinate 45 mg/day in three divided doses administered every 8 hours indefinitely.

**Study 2**—UFT 400 mg/m²/day was administered in two daily doses every 12 hours indefinitely.

In both studies, treatment was continued until toxicity or disease progression. If grade 3 or grade 4 toxicity appeared, treatment was stopped until recovery, wherein patients resumed treatment at the same doses.

**Baseline Data**

Patient characteristics are listed in Table 1. Of the 106 patients entered in study 1, 80 (75%) had only one site of metastasis, and 26 (25%) had two or more sites. The predominant sites of metastasis were the liver (56%), local and peritoneum (27%), and lymph node (21%). In study 2, 63 (66%) of the 95 patients had only one metastatic site, and 32 (34%) had two or more sites. In this study, 68% of patients had liver metastasis.

Response and toxicity were evaluated using standard criteria.[19] Toxicity was evaluated monthly, and response to treatment was evaluated every 2 months by computed tomography scan (chest radiography for lung metastasis was permitted). Only responses lasting 2 months were considered objective responses. The Kaplan-Meier method was used to calculate the actuarial median survival.

**Results**

**Study 1**

The median treatment time for these 106 patients was 4 months (range, 1 to 23 months) and minimum follow-up was 5 months to a maximum of 24 months. Toxicity, calculated as the maximum grade for the patient, was evaluable in 98 patients (Table 2). Six patients were lost to follow-up, and two patients had protocol violations. One patient (1%) had grade 3 or grade 4 thrombocytopenia, six patients (6%) experienced grade 3 nausea/vomiting, 11 patients (11%) had grade 3 or grade 4 diarrhea, and one patient (1%) had grade 3 mucositis. Other toxicities included one case of grade 1 lacrimation and five cases of grade 1 alopecia. Toxicity resulted in delayed chemotherapy in 20 patients (20%) for a median 10-day delay per patient over the treatment period (range, 1 to 48 days).

The median UFT dose intensity was 400 mg/day. Response to treatment was evaluable in 96 patients. Two additional patients refused treatment before they completed 2 months of therapy. Responses included five complete responses (CR) and 12 partial responses (PR), for an overall response rate of 17.7% (95% confidence interval [CI], 10% to 27%). Stable disease (SD) was noted in 24 patients (25%). The total number of patients with nonprogressive disease (objective response plus SD) was 41 (43%); 55 patients (57%) had progressive disease (Table 3). Median survival for the entire group was 13.7 months (Figure 1), with no differences observed among responders and stable patients. The difference between patients with nonprogressive disease (CR + PR + SD) and patients with progressive disease was significant (P < .01) (Figure 2).

**Study 2**

This preliminary data analysis includes 95 patients (of the 117 patients who entered the study [to date, 81% of patients have been analyzed]), including 80 patients evaluable for toxicity and 62 patients evaluable for response. The median treatment time was 14 months, with a minimum follow-up of 0.3 months and a maximum follow-up of 20.3 months. No patient experienced grades 3-4 hematologic toxicity; 7% of patients had grades 3-4 diarrhea; and 2% of patients had grades 3-4 nausea/vomiting. Grades 1-2 toxicity included nausea/vomiting, occurring in 24% of patients (Table 2). Chemotherapy delay due to toxicity occurred in 11% of patients.

Treatment response was evaluated in 62 patients. There were five complete responses (8%) and eight partial responses (13%), for an overall response rate of 21% (95% CI, 13% to 30%). Twenty-five patients had stable disease (40%), and 24 patients had progressive disease (39%). The total number of patients with nonprogressive disease (objective response plus SD) was 38 (61%) (Table 3). At this
time, the data are not mature enough for an overall survival analysis.

Discussion

In advanced colorectal carcinoma, the standard chemotherapy regimen in the United States is the Mayo Clinic schedule combining bolus 5-FU with low doses of calcium folinate (20 mg). According to a meta-analysis, this regimen yields an overall response rate of 19% to 23% and a median survival rate of 10.7 to 11.5 months.[1,2] In Europe, continuous infusion of 5-FU is considered superior to bolus 5-FU, and a recent meta-analysis[5] has shown some small but significant improvement in survival favoring continuous infusion.

Our group[4] has recently performed a randomized phase III trial comparing the Mayo Clinic 5-FU oral calcium folinate regimen to continuous infusion of 5-FU at doses of 3.5 g/m² in 48 hours weekly. The response rate was higher with the continuous-infusion regimen than the modulated regimen. There was, however, no significant difference in survival, time to progression between regimens, or grade 3-4 toxicity. Calcium folinate was omitted based on previous phase II data indicating that biochemical modulation is not necessary and that it is more toxic than high-dose 5-FU therapy.[15-18] Nevertheless, both bolus and continuous-infusion 5-FU produce considerable toxicity. In the case of 5-FU plus calcium folinate, the incidence of severe stomatitis is 14% to 28%; diarrhea, 12% to 18%; and leukopenia, 20% to 29%, [12,13] with 15% to 21% of patients requiring hospitalization. In our regimen of weekly continuous infusion of 5-FU, the most important grade 3-4 toxicities were mucositis (9%), diarrhea (9%), and hand-foot syndrome (4%).[4] It is important, therefore, to find a regimen that offers the same activity with less toxicity, no toxicity requiring hospitalization, and no need for weekly complete blood cell counts. These statements are especially important for the elderly. Furthermore, oral chemotherapy would be more suitable in this population.

In both Gastrointestinal Tumor Therapy group studies of UFT plus calcium folinate or UFT alone, toxicity was mild and produced only a median of 10 days’ treatment delay. Toxicity was equivalent in the modulated study (study 1). The toxicity rate observed in our studies falls in the range of published trials (Table 4).[12-14,20] Activity was similar in both Gastrointestinal Tumor Therapy studies, with a 17.7% response rate in study 1 and a 21% response rate in study 2. These results fall in the range (19% to 23%) reported in the meta-analysis of randomized trials using either 5-FU modulated by calcium folinate[1] or 5-FU modulated by methotrexate[2] (Table 5) and continuous-infusion 5-FU.[5]

Our results indicate worse response rates than those reported by Pazdur[12,13] and Gonzalez Baron,[14] but clinical benefit (objective responses + SD) and overall survival were similar. It should be noted that the studies used different inclusion criteria and dose intensities. It is also important to note that our multicenter trials produced response rates that are known to be inferior to response rates of single-center studies. On the other hand, only two studies included elderly patients—our study and a study by Feliu et al.[20] However, the patient number in the study by Feliu was low (N = 38), with a response rate of 29%. The same group obtained a response rate of 39% in patients younger than 72 years.[14]

Table 6 compares the results of several studies evaluating UFT in advanced colorectal cancer. Our studies differ from those of Pazdur,[12,13] primarily in the distribution of metastases. Interestingly, liver metastasis is related to a higher response rate in most of the studies. However, only 55% of our patients in study 1 had liver metastasis, which is lower than in the above-mentioned studies; and 42% of patients had local and peritoneal metastasis, which is a less responsive site. Moreover, the locoregional and peritoneal masses presented fibrous and irregular areas that make their evaluation difficult by computed tomography scan, thereby increasing the number of patients with stable disease. If we include patients with nonprogressive disease (CR + PR + SD), we reach a response rate of 43% for study 1 and 61% for study 2.

Stable disease exists in a sizable number of colorectal cancer cases and is associated with a time to progression and survival equivalent to patients with objective response. In study 1, there are no differences in survival between these two groups. The median overall survival of 13.7 months is similar to that obtained by our group using the Mayo Clinic regimen of 5-FU plus calcium folinate, or the regimens with continuous-infusion 5-FU.[4] On the other hand, this overall survival rate falls in the range of other UFT studies (Pazdur,[12,13] 15.8 months; Gonzalez Baron,[14] 13.5 months; Feliu, 12.5 months[20]).

Conclusion

In summary, oral UFT with or without calcium folinate modulation is a tolerable, nontoxic
chemotherapy regimen for elderly patients with advanced colorectal cancer. This treatment simulates continuous-infusion 5-FU—a treatment that induces a degree of toxicity unacceptable for patients over 72 years of age. For these reasons, the authors believe that UFT is a good choice for treating advanced colorectal cancer in the elderly.

References:


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