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Research papers

A randomized trial of two schedules of trimetrexate versus 5-fluorouracil in advanced colorectal cancer: a Southwest Oncology Group Study

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Trimetrexate (TMQ), a non-classical folate antagonist, was studied in a randomized controlled trial in patients with advanced colorectal cancer and without prior chemotherapy. Patients were randomly assigned to one of three treatments: TMQ at 200 mg/m^2 i.v. q 2 weeks, TMQ at 12 mg/m^2 i.v. daily × 5 or 5-fluorouracil (5-FU) at 15 mg/kg i.v. weekly. Overall response rates were: 6% (four partial responses in 71 patients, 95% CI of 2–14%) for q 2 week TMQ, 0% (zero of 29, 95% CI of 0–29%) for daily × 5 TMQ and 18% (two complete and nine partial responses in 62 patients, 95% CI of 9–30%) for 5-FU. Median survival estimates were 10.3 months for the q 2 week TMQ schedule, 8.7 months for the daily × 5 TMQ schedule and 13.6 months for the 5-FU schedule. Grade ≤ 3 toxicities were significantly more common with TMQ. TMQ does not appear to have significant antitumor activity against colorectal cancer.

Key words: Advanced colorectal cancer, 5-fluorouracil, phase II–III trial, trimetrexate

Introduction

Trimetrexate (TMQ) is a non-classical diaminoquinazoline folate antagonist originally synthesized in an attempt to develop new antimalarial agents.[1] This compound is a potent inhibitor of dihydrofolate reductase and demonstrates a broader range of preclinical antitumor activity than methotrexate.[2] TMQ appears to enter cells independent of the methotrexate carrier system and does not undergo intracellular polyglutamation. The preclinical data for this compound suggested marked schedule dependency with murine models showing most activity with frequently repeated doses.[3] The phase I clinical investigations of TMQ revealed myelosuppression to be dose limiting on all schedules tested, with the drug having a terminal half-life in man of approximately 12 h.[4–6] Of note during the phase I trials was preliminary evidence for antitumor activity, in particular against colon cancer. The suggestion of schedule dependency with repetitive dosing led to choosing the daily × 5 bolus schedule for investigation at the phase II level. In an attempt to test the predictive ability of the murine model regarding schedule dependency, both the daily × 5 bolus schedule and the q 2 week bolus schedule were studied in colon cancer. Due to preliminary evidence of TMQ activity against colon cancer and to allow for survival comparison, a weekly i.v. bolus 5-fluorouracil (5-FU) arm was included. Therefore, this phase II–III study consisted of a randomization amongst three arms: (i) TMQ given as an i.v. bolus daily × 5, (ii) TMQ given by an i.v. bolus every 2 weeks and (iii) 5-FU given as an i.v. bolus weekly. The schedule of 5-FU administration utilized in this trial was chosen for convenience of administration, with reported response and survival data for this schedule being comparable to that for other schedules of 5-FU.[7,8]

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Materials and methods

Eligibility criteria

Eligibility criteria included: a pathologically verified diagnosis of advanced adenocarcinoma arising from the colon or rectum; bidimensionally measurable disease; SWOG performance status of 0–2; no prior chemotherapy; prior radiotherapy limited to < 25% of bone marrow volume; adequate organ function with WBC $\geq$ 4000/μl, Hgb $\geq$ gm/dl, platelets $\geq$ 100 000/μl, creatinine $\leq$ 2.0 mg%; and total bilirubin $\leq$ 2.0 mg/dl. Institutional review board approval and written informed consent in accordance with institutional and FDA guidelines.

Treatment

Patients were randomized to receive TMQ i.v. bolus every 2 weeks (arm I), TMQ i.v. bolus daily × 5 every 3 weeks (arm II) or 5-FU i.v. bolus weekly. Patients not previously treated with radiotherapy received a starting dose of 200 mg/m^2 on arm I and 12 mg/m^2 on arm II. Patients having received prior radiotherapy received a starting dose of 150 mg/m^2 on arm I and 8 mg/m^2 on arm II. Patients on arm III received a starting dose of 5-FU of 15 mg/kg i.v. up to a maximum dose of 1 g. All TMQ doses were administered in 100 ml D_5W over 30 min on arm I and over 10 min on arm II. All 5-FU doses were administered undiluted as an i.v. push over 3–5 min.

Dose modifications

Retreatment with TMQ required a granulocyte count $\geq$ 1500/μl or platelet count $\geq$ 100 000/μl, with doses held on a weekly basis until these levels were met. TMQ doses were modified according to the nadir granulocyte and platelet counts during the preceding course. For SWOG grade 3 or 4 granulocytopenia or thrombocytopenia TMQ doses were reduced by 50 or 75%, respectively. For other toxicities of SWOG grade $\geq$ 2 TMQ doses were reduced by 50%, following resolution of toxicity. TMQ doses were held for serum creatinine levels > 2.0 mg%. In the absence of hematologic toxicity or grade > 1 non-hematologic toxicity, TMQ doses were increased by 25%.

Retreatment with 5-FU required a WBC $\geq$ 3000/μl and no evidence of stomatitis or diarrhea, with doses held on a weekly basis until these levels were met. 5-FU doses were modified on a weekly basis according to interval toxicities. For SWOG grade 3 or 4 leukopenia doses were reduced by 33 or 66% respectively. For other toxicities of SWOG grade $\geq$ 2 5-FU doses were reduced by 33%, following resolution of toxicity. In the absence of hematologic or non-hematologic toxicity, 5-FU doses were increased by 33%.

Disease assessment

Measurable disease was followed at least every 4–6 weeks for patients on arms I and II. Measurable disease was followed every month for patients on arm III. Patients failing to achieve a complete response, partial response or stable disease after two courses were removed from study. Responses were classified by the standard SWOG definitions.[9]

Statistical considerations

The biologic activity of each schedule of TMQ was to be assessed through an evaluation of tumor response rates, while the clinical efficacy was to be assessed through a comparison of toxicity and survival relative to that for patients receiving a 5-FU control regimen. Early termination of accrual to a given schedule of TMQ was to be considered after 25 and after 50 patients had been entered if the response rate on the schedule was inconsistent at the α = 0.01 level with a true response rate of 30%, i.e. if fewer than three responses in the first 25 patients or fewer than eight responses in the first 50 patients were observed. Furthermore, if 50 patients were accrued to each TMQ schedule and response rates differed at the α = 0.01 level, termination of accrual to the inferior regimen was considered.

If both schedules of TMQ passed the phase II screen, the two regression rates were to be compared at study completion. A two-sided 0.05 Pearson χ^2 statistic would have 90% power to detect a 10 versus 30% difference in response rates with 90 patients per arm. A TMQ versus 5-FU survival comparison was performed for each schedule of TMQ, using the two-sided 0.05 level log rank statistic which would have 90% power to detect a 6 month increase (8 versus 14 months) in survival duration.

Results

Patient characteristics

One hundred and sixty-three patients from 44 SWOG institutions were entered on this study.

Seventy-two patients were entered on the q 2 week TMQ schedule, with 71 patients eligible; 29 patients were entered on the daily × 5 TMQ schedule (arm II), with all patients eligible; 62 patients were entered on the 5-FU schedule, with all patients eligible. All eligible patients were evaluable for toxicity and response. Patient characteristics are shown in Table 1.

Antitumor activity

Based on the above described early stopping criteria, the TMQ daily × 5 schedule (arm II) was closed to accrual after the first interim analysis and the TMQ q 2 week schedule (arm I) was closed to accrual after the second interim analysis. On the TMQ daily × 5 schedule there were no complete or partial responses. The overall response rate for this arm was therefore 0% (zero of 29) with an exact 95% confidence interval of 0–12%. On the TMQ q 2 week schedule there were no complete responses and four partial responses (durations of 4, 5, 9 and 23+ months), for an overall response rate of 6% (four of 71) with a 95% exact confidence interval of 2–14%. On the 5-FU arm, there were two complete responses (durations of 4 and 15+ months) and nine partial responses (durations of 2, 4, 4, 7, 8, 8, 11, 15+ and 20 months). The overall estimated response rate was therefore 18% (11 of 62) with a 95% exact confidence interval of 9–30%. The two-sided χ^2 statistic testing the difference in response rates between the q 2 week TMQ schedule and the 5-FU schedule was $p = 0.051$. Median survival estimates were 10.3 months for the TMQ q 2 week schedule, 8.7 months for the TMQ daily × 5 schedule and 13.6 months for the 5-FU schedule.

Table 1. Characteristics of eligible patients

	I (TMQ q 2 weeks)	II (TMQ q d × 5)	III (5-FU)
Patients	71	29	62
Sex			
female	35	7	19
male	36	22	43
Age (median)	65	61	64
Performance status (median)	1	1	1
Prior radiotherapy	11	6	11

Toxicity

The toxicities observed on each arm are as shown in Table 2. On both TMQ arms the most common toxicities were granulocytopenia, leukopenia, nausea/vomiting/anorexia, anemia, mucositis and dermatitis. On the 5-FU arm the most common toxicities were nausea/vomiting/anorexia, diarrhea, granulocytopenia and dermatitis. Toxicities of grade ≥ 3 were as shown in Table 3. On both TMQ arms the most common severe toxicities were granulocytopenia and mucositis. On the 5-FU arm severe toxicities consisted primarily of myelosuppression and diarrhea. The incidence of SWOG grade ≥ 3 toxicities on the TMQ arms was significantly greater than on the 5-FU arm ($p \leq 0.001$). On the TMQ q 2 week arm, nine patients discontinued treatment due to toxicity (six due to dermatitis/mucositis/myelosuppression and two due to allergic reactions); there were five treatment associated deaths (four due to sepsis and one episode of sudden death). On the TMQ daily × 5 arm, two patients discontinued treatment due to toxicity (dermatitis) and there were no treatment associated deaths. On the 5-FU arm, two patients discontinued treatment due to toxicity (one due to neurotoxicity and one due to diarrhea) and there was one treatment associated death due to fungal sepsis.

Discussion

Based on results of this trial TMQ does not have significant antitumor activity against advanced colorectal carcinoma and it appears inferior to single agent 5-FU. There was no significant difference in survival between the three treatment arms. The results of this trial do not support schedule dependency of TMQ as initially interpreted in preclinical models. The inactivity of TMQ in colorectal cancer impedes observation of schedule dependent characteristics of this drug. It has been suggested that the initial interpretations of the preclinical murine data did not take into account the relatively long terminal half-life of TMQ in man.[4] Specifically, the murine preclinical models showed maximal drug exposure (largest AUC) when TMQ was administered at close intervals (e.g. with a q 3 h on days 1,5 and 9). Whereas pharmacokinetic modeling in humans suggests a much larger AUC with less frequent dosing due to the relatively long terminal half-life of TMQ in man. This evaluation assumes that schedule dependent antitumor effects are primarily a function of drug exposure.

Table 2. Toxicities observed in eligible patients

Toxicity	No. of patients with toxicity		
	I (TMQ q 2 weeks)	II (TMQ q d × 5)	III (5-FU)
Granulocytopenia	50	13	16
Nausea/vomiting/anorexia	41	17	34
Anemia	36	8	13
Allergy/dermatitis	33	8	15
Mucositis	33	10	9
Thrombocytopenia	24	8	6
Diarrhea	15	8	27
Alopecia	11	4	0
Fever/rigors	5	0	1
Dizziness/hot flashes	3	1	0
Hepatic	3	0	1
Ileus	2	0	0
Renal	2	0	0
Phlebitis	2	0	0

Table 3. Toxicities of SWOG grade ≥ 3 observed in eligible patients

Toxicity	No. of patients with toxicity		
	I (TMQ q 2 weeks)	II (TMQ q d × 5)	III (5-FU)
Granulocytopenia	19	4	2
Mucositis	18	6	0
Thrombocytopenia	9	3	1
Nausea/vomiting/anorexia	9	3	1
Allergy/dermatitis	4	1	0
Diarrhea	3	1	3
Anemia	1	0	0
Hepatic	1	0	1
Infection	1	0	0
Renal	1	0	0

The TMQ regimens utilized in this study were associated with significant toxicity, with the q 2 week schedule appearing most toxic. These regimens were significantly more toxic than the 5-FU regimen. Early in the development of TMQ, marked interpatient variability was noted with respect to the maximally tolerated dose. Impaired hepatic function, as assessed by pre-treatment hypoalbuminemia, has been correlated with reduced total body clearance of TMQ and also with the occurrence of dose-limiting toxicity.[10,11] Similarly low serum total protein and presence of liver metastases have been correlated with occurrence of dose limiting toxicity.[12] On this trial, of the 40 patients having SWOG grade ≥ 3 toxicities (myelosuppression, mucositis, dermatitis) with TMQ treatment, serum albumin data were available for 13 patients. Nine of these patients had serum albumin levels ≥ 3.5 gm/dl, without prior radiotherapy and without evidence of effusions. However, eight of these nine patients had liver predominant disease.

Given that patients on the TMQ arms were treated to greater toxicity as compared with the 5-FU arm, the relative antitumor activity of 5-FU may have been underestimated. It should be noted that the antitumor activity observed on the 5-FU arm was consistent with the established response rate of 5-FU in colorectal carcinoma.[13] Based on this negative trial and the disappointing preliminary results with TMQ–5-FU combination therapy, TMQ does not appear to be effective in colorectal cancer.[14] Due to the toxicity observed on the q 2 week schedule of TMQ, it is recommended that future studies with this schedule use a starting dose of TMQ of 150 mg/m^2 with subsequent intrapatient dose escalation as toxicity allows.

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