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S9511: A Southwest Oncology Group Phase II Study of Trimetrexate, 5FU, and Leucovorin in Unresectable or Metastatic Adenocarcinoma of the Stomach

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Abstract

Objective—The primary objective of this trial was to evaluate the response rate for trimetrexate (TMTX) in conjunction with 5FU and leucovorin (LV) (=TFL) in the treatment of advanced gastric cancer in a phase II, cooperative group setting.

Methods—Patients with locally advanced, unresectable, or metastatic adenocarcinoma of the stomach received TMTX 110 mg/m² IV over 60 minutes day 1, followed by 5-FU 500 mg/m² IV bolus and LV 200 mg/m² IV over 60 minutes day 2, followed by oral LV 15 mg every 6 hours × 7 doses, all weekly for 6 weeks followed by 2 weeks of rest, continued until progression.

Results—Characteristics for 37 eligible patients: median age 63 (range 23 to 83); male/female: 69%/31%; performance status 0/1/2 15/20/1. The confirmed response rate was 19%, and median overall survival was 6 months. Two patients died as a result of therapy, one due to infection without significant neutropenia, and one due to perforation of a responding gastric lesion. 72% experienced Grades 3 and 4 toxicity, most commonly diarrhea, fatigue, and lymphopenia.

Conclusions—This regimen achieves response rates comparable to other 5FU-based regimens, when used in treatment of incurable gastric cancer. Toxicity appears manageable.

Keywords

trimetrexate; chemotherapy; gastric neoplasms

INTRODUCTION

In 2008, there will be an estimated 21,500 new cases of cancer gastric cancer in the United States, with 10,880 deaths from this disease.¹ Most patients present with locally advanced, unresectable disease, or distant metastases. Median survival for those with distant metastases is 6-9 months, and five-year survival for all stages is only 22%. Drug therapy does offer a survival benefit in patients with incurable disease, versus best supportive care alone.² 5-fluorouracil (5-FU) based regimens, with or without cisplatin, have been the mainstay of chemotherapy for gastric cancer in the United States, conferring response rates approaching 25%.^{3,4}

Methotrexate (MTX) potentiates the cytotoxicity of 5-FU-both in vitro and in vivo in pre-clinical models^{5,6}. MTX impedes tumor cell purine metabolism, leading to an accumulation of phosphoribosyl-pyrophosphate (PRPP). Increased levels of PRPP drive the formation of inhibitory 5-FU metabolites. MTX has single-agent activity in treatment of gastric cancer, and it can effectively be combined with 5FU-based regimens.⁷

Trimetrexate glucuronate (TMTX), like MTX, is a dihydrofolate reductase inhibitor. Unlike MTX, TMTX is lipophilic and appears to enter cells via simple diffusion. TMTX does not require activation by the enzyme folylpolyglutamyl synthetase, and it does not use the reduced folate transport system to enter neoplastic cells. Unlike MTX, TMTX thus avoids competition for uptake when administered with LV.⁸⁻¹⁰ Though the combination of MTX, 5FU, and LV is not more effective *in vitro* than 5FU and LV alone, adding TMTX to 5FU and LV clearly enhances cytotoxicity, in a CCRF-CEM cell model.¹¹

Preclinical studies suggested TMTX should be administered before the 5FU and LV, to maximize PRPP accumulation.¹²⁻¹⁴ Phase I trials were carried out using a variety of TMTX schedules, with antitumor effects seen in colorectal, breast, lung, head and neck, renal, pancreatic, and esophageal cancers, as well as melanoma.¹⁵⁻¹⁸ One of the most promising phase I trials used TMTX, high dose LV, and 5FU, administered sequentially, in patients with gastrointestinal carcinomas. TMTX was given weekly, followed by LV 500 mg/m² iv and 5FU500 mg/m², both started 24 hours later, followed by oral LV rescue beginning 6 hours after the IV 5FU/LV.¹⁹ This study showed tolerable toxicity even at the highest TMTX dose (110 mg/m²). 20% of colon cancer patients demonstrated partial responses, despite having been heavily pre-treated. Phase II studies of the sequential triple-drug regimen showed response rates of 36-50% in untreated advanced colorectal cancer patients.^{20,21}

Based on the activity of MTX-5FU regimens in advanced gastric cancer, as well as the theoretic advantages for TMTX, the Southwest Oncology Group initiated a phase II trial of TMTX, 5FU, and LV (=TFL) in patients with unresectable, or metastatic adenocarcinoma of the stomach or gastroesophageal junction (S9511). The primary endpoint was the rate of confirmed complete or partial response, with secondary endpoints of overall survival, time to treatment failure, and toxicity.

MATERIALS AND METHODS

Eligible patients had histologically confirmed, bidimensionally measurable adenocarcinoma of the stomach or gastroesophageal junction, with locally advanced, unresectable, or metastatic disease. Prior chemotherapy given adjuvantly or as a radiation sensitizer was allowed, but patients with prior chemotherapy for advanced metastatic gastric cancer were not eligible. Prior radiation therapy and prior surgery were allowed. Adequate hematologic, renal and hepatic function were required. Patients with known brain metastases or known AIDS or HIV associated syndrome were not eligible. Patients with weight loss of greater than 10% within 2 months prior to registration were required to have an albumin level of 3.5 g/dl. Patients with

weight loss greater than 15% within 2 months prior to registration were ineligible. No prior malignancies were allowed other than adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, adequately treated stage I or II cancer from which the patient was in complete remission, or any other cancer from which the patient had been disease free for at least 5 years. Patients were required to be at least 18 years of age. All patients were informed of the investigational nature of this study and signed a written informed consent in accordance with local institutional review board and federal guidelines.

Each eight-week cycle consisted of 6 weeks of treatment followed by two weeks of rest. Patients received weekly TMTX 110 mg/m² IV over 60 minutes on day 1, 5FU 500 mg/m² via IV bolus and LV 200 mg/m² IV over 60 minutes on day 2, followed by LV 15 mg P.O. every 6 hours $\times$ 7 doses. Patients were treated indefinitely, until disease progression or unacceptable toxicity. Complete blood counts were done weekly and other serum chemistries were done at the beginning and midway through each cycle.

The primary objective of S9511 was to estimate the response rate of the TFL regimen using a two-stage design. Assuming that the regimen would be of no further interest if the true response rate were 10% or less, at least one confirmed response among the first 20 eligible patients accrued was required to continue with the accrual of an additional 15 patients for a total of 35. Eight confirmed responses out of 35 would be sufficient to reject the null hypothesis of a 10% response rate, indicating that the regimen would be of further interest in advanced gastric cancer. This design had a significance level (probability of falsely declaring a regimen with a 10% response rate worthy of further study) of .02, and a power (probability of correctly declaring that the regimen warranted further study) of .87.

Disease was reassessed every 8 weeks during treatment, and all patients were followed until death. Response was determined using standard SWOG response criteria for bidimensionally measurable disease.²¹ A confirmed complete or partial response was recorded only after two consecutive statuses of complete or partial response were observed, at least four weeks apart. Time to treatment failure was defined to be from the date of registration to the date of first observation of progressive disease, death due to any cause, or early discontinuation of treatment. Time to death was defined to be from the date of registration to the date of death due to any cause.

Toxicity was reported using NCI common toxicity criteria version 2.0.²³

RESULTS

This study was activated in January 1997 and closed to patient accrual in November 1998. Of forty patients entered, two were ineligible due to baseline scans that were outside of the required time frame, and one was ineligible with an esophageal cancer. Another patient was unable to receive any protocol treatment due to dyspnea and pleural effusion, which developed shortly after study registration. Thirty-six patients were thus eligible and evaluable for survival and toxicity. Thirty-four had adequate response assessments. Baseline characteristics are shown in Table 1.

Five patients discontinued treatment early, due to toxicity. Six patients discontinued early for other reasons, including patient choice after general decline (3), development of an intracranial cyst (1), bowel obstruction (1), mistaken removal from treatment by the treating institution, and other major protocol deviation (1). One patient died while on treatment, due to a perforated stomach following an unconfirmed complete response. The remaining 24 patients were on treatment until progression. All but five patients received at least one cycle of treatment. The median time on treatment was 13 weeks (range 2 days to 55 weeks).

Table 2 lists major toxicities for this study. Eighteen patients (50%) experienced at least one grade 3 event, and eight patients (22%) experienced at least one grade 4 event. Hematologic toxicities consisted mostly of anemia (5 cases grade 3) and lymphopenia (7 cases grade 3). Neutropenia occurred in two cases (one grade 3 and one grade 4). The most common severe gastrointestinal toxicities were nausea (7 cases grade 3) and diarrhea (eight cases grade 3, two cases grade 4). Vomiting was generally mild. Two patients (5%) suffered fatal toxicities. One patient died of infection. The other, in his fifth week of chemotherapy, sustained an acute gastric perforation in the setting of a major tumor response, as previously discussed.

In the first stage of accrual, five (5) confirmed responses were documented in 21 patients. The study closed permanently with 36 eligible patients and a total of seven responses: one complete response (3%) and six partial responses (17%). The overall response rate was 19% (95% confidence interval 8% - 36%). Nine patients (25%) had progressive disease while on treatment, and two patients (6%) were not assessable for response, due to failure to adequately follow measurable lesions.

Median time to treatment failure was 3.0 months (95% C.I. 1.9-3.5 months). Median overall survival was 6.4 months (95% C.I. 4.6-9.0 months) (Figure 1). The six month survival rate was 54%. One patient, who had a partial response while on protocol treatment and later received 5-FU, LV, and VP-16 is still alive without evidence of disease, with follow-up of 74 months.

DISCUSSION

Chemotherapy for advanced gastric cancer has changed significantly over the last several years. FAMTX, a MTX-containing regimen also containing 5FU and adriamycin, looked quite promising in phase II studies, but was inferior to ECF (epirubicin, cisplatin, and 5FU) in phase III testing (response rate 46%, with median survival 8.7 months for the latter).²⁴ ECF is now standard of care therapy for advanced gastric cancer patients treated in much of Europe and Canada, though it is less popular in the United States. Oxaliplatin has been substituted for cisplatin, and capecitabine for 5FU, in the EOX regimen; a randomized trial comparing these drugs as alternatives to cisplatin and fluorouracil demonstrated improved overall survival.²⁵ Cisplatin has also been combined with 5FU alone (ORR = 23%; median survival 8.5 months) and with irinotecan (ORR = 58%; median survival = 9 months).^{3,26,27} Taxanes have demonstrated activity as single agents and in combination therapy. Docetaxel, administered with cisplatin and 5FU, demonstrated improved time-to-progression (5.6 months) and overall survival (9.2 months) versus cisplatin/5FU alone in a large phase III study, but at a cost of markedly higher grade 3/4 toxicity rates (69%).⁴

TMTX, administered with 5FU and LV has strong rationale in treatment of gastric cancer. MTX-based regimens are effective, and TMTX offers both theoretic and pre-clinically proven advantages over MTX. In treatment of advanced colon cancer, TFL regimens demonstrated high response rates in phase II studies, but they were no more effective than 5FU/LV in phase III comparisons.^{28,29} Trimetrexate and the TFL regimen are no longer in clinical development in large bowel malignancy.

On this study, TFL had a 19% response rate and median survival of 6.4 months. This response rate did not meet the postulated 23% that would have been sufficient to statistically rule out the possibility of a true 10% rate. Although the response rate and survival outcomes achieved in this trial are acceptable for patients with advanced gastric cancer, they are not clearly superior to those achieved with 5FU/LV alone. In addition, there is certainly no evidence that this combination would improve upon results using platinum-based chemotherapy.

The toxicity profile of this regimen was equal to or slightly better than that expected from other modern regimens used in advanced disease. On this study, 28% had grade 3/4 diarrhea (mostly

3), 6% severe or life-threatening neutropenia, and 72% any grade 3/4. Cisplatin/CPT-11 has a grade 3/4 diarrhea rate of 22% and a grade 3/4 neutropenia rate of 27%.²⁶ The triple-drug, docetaxel-containing regimen previously discussed had an overall grade 3/4 adverse event rate of 69%.⁴ However, TFL is not sufficiently safer nor better as to warrant further study.

Future trials in advanced gastric cancer may focus more on molecularly targeted therapies. Though trials of the biologic agents gefitinib, erlotinib, and lapatinib have been negative in gastric cancer,³⁰⁻³² the Southwest Oncology Group will continue to try to identify a better target in this disease.

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Figure 1.
Overall Survival

Patient Characteristics

Table 1

AGE		PRIOR RADIATION THERAPY	
Median	63	Yes	2 6%
Minimum	23	No	34 94%
Maximum	83		
SEX		PRIOR CHEMOTHERAPY	
Males	25 69%	Yes	1 3%
Females	11 31%	No	35 97%
RACE		PERFORMANCE STATUS	
White	25 69%	Zero	15 42%
Black	5 14%	One	20 56%
Asian/Pacific Islander	6 17%	Two	1 2%

Table 2

Grade 3-5 Toxicities

Toxicity	Grade 3	Grade 4	Grade 5
Gastrointestinal			
Diarrhea	8 (22%)	2 (6%)	0
Nausea	7 (19%)	0	0
Vomiting	2 (6%)	1 (3%)	0
Gastric Perforation	0	0	1 (3%)
Stomatitis/Pharyngitis	2 (6%)	0	0
Circulatory			
Thrombosis/Embolism	1 (3%)	2 (5%)	0
Hematologic/Infections			
Anemia	5 (14%)	0	0
Neutropenia	1 (3%)	1 (3%)	0
Lymphopenia	7 (19%)	0	0
Infection w/o neutropenia	1 (3%)	0	1 (3%)
Pulmonary			
Dyspnea	1 (3%)	2 (6%)	0
Constitutional/Pain			
Fatigue/Malaise/Lethargy	6 (17%)	2 (6%)	0
Abdominal Pain	4 (11%)	2 (6%)	0
Metabolic			
Hypokalemia	1 (3%)	1 (3%)	0
Maximum Grade Any Toxicity	18 (50%)	8 (22%)	2 (6%)