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Clinical report

Weekly 24-h infusion of high-dose 5-flurouracil and leucovorin in patients with advanced gastric cancer

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The effect of biochemical modulation of weekly high-dose 5-fluorouracil (5-FU) 24 h infusion by leucovorin (LV) in the treatment of 39 consecutive patients with advanced gastric cancer without prior chemotherapy from October 1996 to August 1997 was examined. There were 21 male and 18 female patients with a median age of 56 years. The regimen consisted of 5-FU 2600 mg/m^2 and LV 150 mg administered by 24 h infusion weekly for 6 weeks followed by a 2 week break. The treatment was repeated every 8 weeks until disease progression, patient refusal or unacceptable toxicity. Placement of a central vascular device and a portable external infusion pump was required in all patients and was used for outpatient treatment. The response to treatment was evaluated every 8 weeks. A total of 395 chemotherapy treatments were given with a mean of 10 (2–24). This response rate was: 33% (12 of 36) partial response (PR) rate, 33% (12 of 36) stable disease (SD) and 33% (12 of 36) progressive disease (PD). In general, the toxicity was mild but two toxic deaths occurred, one due to neutropenic sepsis and the other due to hyperammonemia. The median time to progression was 4 months. The overall median survival was 7 months. The survivals of the PR, SD and PD were 12, 8 and 5 months, respectively. This regimen showed a modest activity against gastric cancer with acceptable toxicity. Weekly 24 h infusion of high-dose 5-FU with LV in an outpatient setting for patients with gastric cancer is feasible and deserves further study as a basis for combination therapy. []

Key words: High-dose 5-fluorouracil, gastric cancer, infusion pump, leucovorin.

Introduction

Gastric cancer is one of the leading causes of cancer-related death worldwide, with a current 5-year survival rate of less than 20%.[1,2] About 25% of patients with gastric cancer are associated with disseminated disease at presentation and more than half of patients with localized disease recur within 5 years.[3–6] Systemic chemotherapy is widely used in patients with advanced or metastatic gastric cancer since it is relatively sensitive to chemotherapy. The 5-fluorouracil (5-FU)-based regimens, used either alone or in combination with other drugs, are commonly used in general clinical practice. The response rate yields only 20–50% with very few complete responses.[6–11]

Several pre-clinical studies have suggested that the biochemical modulation of 5-FU by leucovorin (LV) can enhance the anti-tumor activity. Clinical controlled trials have confirmed the increase in objective response rates on patients with metastatic colorectal cancer treated with 5-FU/LV combination compared with those treated with 5-FU alone.[12] However, the optimal dose schedule of 5-FU/LV combination remains elusive. Ardalan *et al.* reported a regimen consisting of a weekly 24 h infusion of high-dose 5-FU (2600 mg/m^2) and LV (500 mg/m^2) for patients with metastatic colorectal cancer in 1991.[13] Their study differed from the other 5-FU/LV-based trials in the following respects: (i) the maximum-tolerated dose of 5-FU as a single agent was not compromised when a modulator was co-administered, (ii) unlike other 5-FU/LV studies, toxicity was minimal and acceptable, (iii) responses were seen in patients who had failed to 5-FU/LV administrated by other methods, and (iv) survival of chemotherapy-naive patients greater than 22 months was reported.

Vanhoefer *et al.* used Ardalan's regimen on patients with refractory gastric cancer and showed a response

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rate of 18% in 1994.[14] In addition, a retrospective study by Hsu *et al.* has shown a response rate of 48% with acceptable toxicity on chemotherapy-naive patients with gastric cancer by the similar regimen in 1997.[15] Since 5-FU remains the most commonly agent for patients with gastric cancer, we suggest that Ardalan's regimen is worthy to explore on patients with gastric cancer. However, one disadvantage of this regimen which was reported by Ardalan and our pilot study experience is that many implanted central venous catheters were blocked by 'calcium-LV stones' when 5-FU and high-dose LV (500 mg/m^2) were infused in the same bag. In addition, the optimal dose for LV as a bio-modulator of 5-FU has not been determined, therefore we decided to conduct a prospective trial using a regimen similar to that of Ardalan but reducing the dosage of LV on patients with gastric cancer without prior chemotherapy. Here, we present the results of this phase II trial.

Materials and methods

All patients were required to have a known primary gastric cancer beyond the hope of cure, i.e. histologic proof of residual primary, recurrent or metastatic disease. The tumors were required to be radiologically measurable or evaluable. Patients should have no prior chemotherapy, a Karnofsky performance status $\geqslant 30$, absolute granulocyte count $\geqslant 1500/\mu l$, platelet count $\geqslant 100\,000/\mu l$, serum creatinine concentration $\leqslant 2$ mg/dl and serum bilirubin $\leqslant 3.0$ mg/dl.

All patients received a central vascular device through the subclavian vein for outpatient infusion therapy. The chemotherapy consisted of 5-FU 2600 mg/m^2 with LV 150 mg, which was infused simultaneously through a portable pump for 24 h. It was administered every week for 6 weeks with a 2 week break. However, if grade 3 hematological or gastrointestinal toxicity according to the WHO Toxicity Guidelines was observed, the dose of 5-FU was reduced to 2000 mg/m^2. The chemotherapy was repeated every 8 weeks with a 2 week break until disease progression, unacceptable toxicity or patient refusal.

Prior to the therapy, all patients were evaluated by a complete history review, physical examination, complete blood counts, biochemistry profile, serum tumor marker, chest roentgenogram and abdominal computerized scan (CT scan). Patients were re-assessed after 8 weeks by the same procedures. In instances of clinical suspicion of progress disease (PD) during treatment, the evaluation was performed immediately. Complete response (CR) was defined as disappearance of all measurable disease based on the image studies. Partial response (PR) was defined as 50% or greater decrease in the sum of the products of the largest perpendicular diameters of the all the measurable lesions or decrease at least 50% of the one dimension of the evaluable lesions for at least 4 weeks without the appearance of the new lesions. Stable disease (SD) was defined as a decrease of the lesions for at least 4 weeks, which did not reach the criteria of PR or a less than 25% increase of lesions. PD was defined as a 25% or greater increase in the size of one or more evaluable lesions or the appearance of new lesions. The presence of ascites was not considered to be a criterion of measuring response; however, the new appearance of ascites was considered to be a progression.

The time to progression was measured from the start of the therapy to the date of progression. The survival time was calculated from the start of the therapy to the date of death and survival time was established by the Kaplan-Meier method. The differences in survival among several factors were determined by log-rank test and $p < 0.05$ was considered to be statistically significant.

Results

From October 1996 to September 1997, 39 consecutive patients were registered to this study. The patient characteristics are summarized in Table 1. There were 21 males and 18 females patients, with a median age of 56 years (range: 24–70 years). The mean Karnofsky performance was 67% (range: 30–100). The sites of diseases included stomach (17), peritoneum (16), intra-abdominal lymph nodes (11) and liver (6). Seven patients (18%) had ascites prior to treatment. Three patients initially presented with intestinal obstruction that required nasogastric tube drainage and parenteral nutrition. Twenty-five patients (64%) had problems with oral feeding and weight loss before treatment.

A total of 395 chemotherapy treatments were given (range: 2–24) with a mean of 10. Dose reduction was required for seven patients (17.9%) due to side effects of chemotherapy. All were reduced by one level of the dosage. The majority of the chemotherapy was given at outpatient clinics.

Except for one patient who was lost to follow-up after completing the first six doses of chemotherapy and two toxic deaths early in the course, the remaining 36 patients were assessable for response. The overall response rate was 33% (12 of 36) (95% confidence interval: 18–50%) without any complete response. Twelve patients (33%) were SD, while 12 patients (33%) developed PD.

The overall median time to progression was 4 months. The overall median survival was 7 months. Among the patients with PR, the median survival was 12 months. The median survival of the SD was 8.0 months. The median survival was only 5 months in patients with PD. There was no survival difference in terms of sex, age, performance status and number of disease sites by the log-rank test.

The toxicity profiles are summarized in Table 2. One patient (3%) developed neutropenic sepsis, four patients (10%) developed grade III mucositis and two patients (6%) exhibited grade III or IV neurotoxicity due to hyperammonemia. There were two treatment-related deaths. One patient died of grade IV neutropenic sepsis after the second chemotherapy. Another patient was associated with gastric outlet obstruction and a Karnofsky performance score of 30. Her consciousness changed immediately after the third dose of chemotherapy, at which time a serum ammonia level of 430 mg/dl was found. She died a few hours later due to asphyxia and her death was considered to be a treatment-related death. Fatigue, which occurred in over 90% of the patients, was the most common side effect, but patients were able to continue their usual daily activity. No patients had more than grade III nausea/vomiting, diarrhea and hand-foot syndrome. No catheter obstruction due to calcium-LV stones was identified.[13]

Table 1. The characteristics of patients (n=39)

Characteristics	No. of patients
Sex	
male	21
female	18
Median age	56 (range: 24–70)
Performance status (Karnofsky)	67 (mean; range: 30–100)
100%	1
80–90%	12
60–70%	20
40–50%	5
⩽30%	1
Tumor site	
loco-regional	17
peritoneum	16
lymph nodes	11
ascites	7
liver	6
abdominal wall	3
other site	4

Discussion

The present study revealed a 33% response rate against gastric cancer and occurred in less than 10% of patients that had grade III or IV toxicity. This response rate of the present study falls within the confidence interval of other FU/LV combination trials on patients with gastric cancer.[14–18] The Southwest Oncology Group compared bolus versus continuous infusion of 5-FU and LV combination, and found only 20 and 8% response rate, respectively, among patients with gastric cancer. Thirty-six percent of the patients in the continuous arm developed grade 3 or 4 mucositis and 28% of the patients in the bolus arm developed grade 3 or 4 hematological toxicity. The median survival of both arms was only 5 months.[16] Rubin *et al.*[17] reported a 22% response rate among patients with gastric cancer using a conventional 5 day continuous infusion of 5-FU/LV, but with a nearly 20% incidence of grade 4 leukopenia and stomatitis. In contrast, Vanhoefer *et al.*[14] used weekly high-dose 5-FU/LV 24 h infusion as a salvage treatment in patients with refractory advanced gastric cancer and reported an 18% response rate with only two patients developing grade 3 or 4 diarrhea. In a retrospective study, Hsu *et al.*[15] reported a response rate of 48% among patients with gastric cancer using similar regimen, with only 2.9% of patients developing grade 3 or 4 leukopenia and minimal non-hematological toxicity. Their progression-free survival and median survival were almost the same as in the present series. Because the toxicity of the 24 h FU/LV regimen is mild and its anti-tumor activity is promising, this regimen appears well suited to elderly patients and patients with poor performance. It is worthy of further study to compare

Table 2. Maximal toxicity grade (WHO) (n=39)

Grade	0	1	2	3	4
Leukocytes	33 (84%)	3 (8%)	2 (5%)	0	1 (3%)
Mucositis	25 (64%)	8 (21%)	2 (5%)	4 (10%)	0
Nausea/vomiting	25 (64%)	4 (10%)	10 (26%)	0	0
Diarrhea	34 (87%)	5 (13%)	0	0	0
Neurotoxicity	37 (94%)	0	0	1 (3%)	1 (3%)
Hand–foot syndrome	36 (92%)	3 (8%)	0	0	0

with conventional bolus or continuous infusion of 5-FU and LV regimens in patients with advanced gastric cancer.

The regimen in this study used a relatively low-dose continuous infusion of LV compared to the series of Ardalan *et al.* They found that a combination of high-dose LV and 5-FU may result in the development of 'calcium -LV stones' which subsequently block the central venous catheter.[13] To resolve the problem, they administered 5-FU and LV in separate pumps. However, the use of two separate pumps is inconvenient to both patients and nurses. An alternative method to avoid this is to administer the infusion of LV 500 mg/m^2 at 1-2 h prior to infusion of 5-FU infusion. Houghtton *et al.*[19] reported a significantly higher tumoral concentration of 5,10-meththyenetetrahydrofolate when LV was infused over 24 h compared to 4 h or bolus. Also, Houghtton *et al.*[20] and Boarman *et al.*[21] suggested that prolonged LV exposure, rather than a high dose, may result in a more pronounced thymidylated synthase inhibition by 5-FU. In addition, Jolivet[22] suggested that prolonged cellular exposures (over 24 h) to relative low LV concentrations simultaneously with prolonged 5-FU administration is the optimal method to enhance 5-FU efficacy. We consider that continuous infusion and the relative low dose of LV may be more potent than bolus and high-dose LV in bio-modulating the anti-tumor effect of 5-FU. The present series did not find any 'calcium-LV stones', suggesting that this dosage is feasible for continuous infusion of LV.

We had two neurologic complications from hyperammonemia. It has been reported that hyperammonemia may occur in patients receiving 5-FU, particularly in patients with dehydration, infection or malnutrition.[23,24] The mechanism of hyperammonemia is unclear. Yeh[24] had reported a 5% incidence of hyperammonemia in patients receiving weekly high-dose 5-FU/LV chemotherapy, but all cases were transient and the patients recovered spontaneously after chemotherapy. A reduction of the dosage may prevent its recurrence. We suggest that patients should have adequate hydration and nutrition prior to initiating weekly high-dose 5-FU/LV.

We did not observe complete response in this series and the median survival was the same as other 5-FU-based chemotherapies. Adding other agents such as cisplatin or mitomycin into this regimen may improve the response rate and survival. A combination of paclitaxel and weekly high-dose 5-FU/LV has been reported. However, the response rate was 22% and the toxicity was higher than with weekly high-dose 5-FU/LV alone.[25] However, whether the low toxicity of this weekly high-dose schedule allows more intensive combinations to achieve higher response rates and longer response duration remains interesting. A phase II trial of weekly high-dose 5-FU and LV with cisplatin has been recently initiated in our institute.

In conclusion, we present an active dose schedule and low toxicity of weekly high-dose 5-FU/LV 24 h infusion for patients with advanced gastric cancer. Thus, this schedule may have great potential for use as part of the combination regimen for future clinical trials.

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