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CLINICAL TRIAL REPORT

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Treatment of advanced gastric cancer with the combination fluorouracil, leucovorin, etoposide, and cisplatin: a phase II study of the ONCOPAZ cooperative group

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Abstract A phase II study was performed to assess the efficacy and toxicity of the combination of 5-fluorouracil (5-FU), leucovorin (LV), etoposide, and cisplatin (FLEP) in patients with advanced gastric carcinoma. A total of 46 consecutive, previously untreated patients with unresectable, measurable gastric carcinoma were treated with 300 mg/m^2 LV, 100 mg/m^2 etoposide, 500 mg/m^2 5-FU, and 30 mg/m^2 cisplatin on days 1–3 every 28 days. All courses were given on an outpatient basis. A total of 169 courses of treatment were given. In all, 18 of the 46 patients (39%) had an objective response [95% confidence interval (CI), 25%–54%] and 2 (4%) patients experienced a clinical complete response. The median duration of response was 5 months. The main side effects were hematological and gastrointestinal. Grade 3–4 toxicity was encountered as follows: leukopenia, in 9.5% of the courses; anemia, in 3%; thrombocytopenia, in 3%; nausea/vomiting, in 4%; and diarrhea, in 5%. Hospitalization due to fever and granulocytopenia was required in 5 patients, 3 of whom died of sepsis. In conclusion, FLEP shows moderate activity in patients with advanced gastric carcinoma, albeit at the cost of a high degree of toxicity. For this reason we do not recommend its use.

Key words Gastric cancer · Chemotherapy · Toxicity

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Introduction

Gastric cancer is the most chemosensitive adenocarcinoma among digestive neoplasms. Some agents show a response rate of at least 15% in monotherapy, including 5-fluorouracil (5-FU, F), mitomycin (M), semustine (Me), carmustine (B), cisplatin (P), Adriamycin (A), and epirubicin (E). These drugs have also been used in combinations such as FAM and its variants (FAB and FAMe), which obtain a response rate nearly 30% [1]. Other schemes try to take advantage of drug synergism and the modulation of 5-FU by several agents, for instance, FAMTX (where methotrexate modulates 5-FU) or PF, FAP, and FEP (synergism between 5-FU and cisplatin). Phase II trials using these regimens have shown a response rate of 40%–70% [1–4].

Experimental evidence suggests marked synergism between etoposide and cisplatin [5, 6], which has prompted the development of regimens based on this association. Elliot et al. [7] reported a 31% response rate in previously untreated patients using both drugs. Preusser et al. [8] obtained a global response rate of 64% and a 21% rate of complete responses with EAP (etoposide, Adriamycin, and cisplatin). Although some authors found similar response rates [9, 10], further studies showed lower efficacy and higher levels of toxicity [11, 12].

Finally, the modulation of 5-FU by leucovorin (LV) has also been studied in gastric cancer. The response rate has varied between 23% and 48%, depending on the schedule and the patients' characteristics [13–15]. These results suggested new possibilities such as the

addition of those drugs to FAM (FAM-CF) [16], or their association with etoposide (ELF) [17]. Another step in the search for more efficacious schemes consists of the combination of 5-FU modulated by LV, etoposide, and cisplatin (FLEP). Besides enhancing the cytotoxic activity of 5-FU through its modulation with LV, this combination should take advantage of the synergism among cisplatin, etoposide, and 5-FU [17]. Preliminary results were promising, involving a response rate of 57% and acceptable toxicity [17]. These encouraging results prompted us to assess the activity and toxicity of the FLEP combination in a phase II study including previously untreated patients with advanced gastric carcinoma.

Patients and methods

During the period ranging from May 1989 to December 1992, 46 patients with histologically proven gastric cancer were entered into the present study. The criteria for entry included histological confirmation of adenocarcinoma of the stomach and advanced disease not potentially curable by other therapeutic modalities. All patients had a performance status of 3 or better according to Zubrod's scale (Eastern Cooperative Oncology Group, ECOG) [18]. They should have at least 3 weeks of recovery from any major surgical procedure involving resection or bypass or 2 weeks of recovery from exploration and biopsy only. No prior chemotherapy or radiation therapy was allowed. Patients were required to have a granulocyte count of 2×10^9/l or greater and a platelet count of $> 100 \times 10^9$/l; normal renal function as defined by a serum creatinine level of < 115 μmol/l and creatinine clearance of > 60 ml/min; and normal hepatic function, that is, a serum bilirubin level of < 35 μmol/l and serum glutamic oxalacetic transaminase (SGOT) and serum pyruvic transaminase (SGPT) levels of < 3 times the upper normal limit, unless these alterations were due to metastatic disease.

All patients had measurable disease that was defined as the presence of at least one lesion as clearly bidimensionally measured by computed tomography (CT) scan, X-ray, or ultrasound. Bone lesions were evaluated by bone scan and X-ray. In patients with locally advanced disease the primary tumor was evaluated by CT and endoscopy.

The drug doses and treatment schedules were identical to those used by the original investigators. Patients received LV given at 300 mg/m^2 per day in a 10-min infusion, followed by etoposide given at 100 mg/m^2 per day in 50 min, followed by 5-FU given at 500 mg/m^2 per day in 10–15 min, and, finally, cisplatin given at 30 mg/m^2 per day in a 1-h infusion, with treatment being given on days 1–3 every 28 days. All courses were given on an outpatient basis.

The toxicity for each course was recorded before the next treatment course and graded according to the WHO scale [19]. If the neutrophil count was $< 1.5 \times 10^9$/l or the platelet count was $< 100 \times 10^9$/l, treatment was postponed for a maximum of 2 weeks. After that time, if the neutrophils were $1–1.5 \times 10^9$/l or the platelets were $70–100 \times 10^9$/l, the doses of all drugs were reduced by 50%, and if lower values resulted, chemotherapy was discontinued. Treatment was also stopped if an elevated creatinine level had not returned to normal by the time of the next cycle. In the case of any grade 4 toxicity, the doses of all drugs were reduced by 25% in subsequent courses.

The response (WHO guidelines) [19] was evaluated after every three courses and included a medical history, a physical examination, measurement of lesions by the appropriate methods, and new laboratory studies. Reevaluation was undertaken sooner if there was clinical evidence of progression. Briefly, a complete response (CR) means the total disappearance of all tumors initially observed and no evidence of new lesions. A partial response (PR) is defined as a reduction of at least 50% (product of the longest perpendicular diameters) in the size of all measurable lesions and no increase in the size of any lesion or appearance of new metastases. Responses have to persist for a minimum of 1 month. A 25%–50% reduction in the size of the lesions or an increase of $< 25\%$ is considered as stable disease. Finally, progressive disease is defined as a 25% increase in the size of any measurable lesion, the appearance of new metastases, or a symptomatic deterioration in performance status.

Death due to disease progression or toxicity occurring before evaluation was considered as a therapeutic failure. The response of duration and the survival were calculated from the 1st day of chemotherapy by the Kaplan-Meier method. Complete or partial responders received additional cycles of chemotherapy until disease progression or unacceptable toxicity occurred, with the limit being nine courses.

Results

Table 1 shows the patients' characteristics. The median age was 55 years (range, 21–72 years). A total of 39 patients (85%) had an ECOG performance status of 2 or 3. Overall, 19 patients (35%) had lost $> 10\%$ of their usual weight before the beginning of therapy; of the 40 patients (87%) who presented with distant metastases at diagnosis, 8 (17%) also had local disease.

A total of 169 cycles of FLEP were given to 46 patients (median, 3 courses/patient; range, 1–6). The mean weekly doses were 20.2 mg/m^2 for cisplatin, 60 mg/m^2 for etoposide, and 318 mg/m^2 for 5-FU. Three patients died in the 1st month: one of a stroke and two of sepsis and neutropenia. Two patients died after the 1st month but before the time of evaluation: one of sepsis and neutropenia and the other due to tumor progression. One patient decided to discontinue therapy after the first course.

In all, 2 patients (4%) achieved a complete remission and 16 (35%) attained a partial response, for an overall response rate of 39% (95% confidence interval, 25%–54%; Table 2). The median duration of response was 5 months. Altogether, 55% of the patients with an ECOG performance status of 0–1 responded, in contrast to only 35% of those with an ECOG performance status of 2–3 (difference nonsignificant). In the six patients with locally advanced disease there were two complete and two partial responses. When the site of metastasis was considered, the response rate was 40% for the liver, 46% for lymphadenopathies, 27% for the peritoneum, and 0 for the lungs. Those patients with local disease in addition to distant metastases achieved a response rate of 50% for the local disease. No difference was detected with regard to the number of metastatic locations (1 versus 2–3). The median overall survival for all patients was 7 months.

The toxicites encountered per cycle are delineated in Table 3. Hematological toxicity predominated. Grade 3–4 leukopenia, thrombocytopenia, and anemia appeared in 10 (22%), 3 (6.5%), and 4 (8.7%) patients,

Table 1 Patients' characteristics

Number of patients	46
Median age in years (range)	55 (21–72)
M/F	24/22
Pretreatment ECOG performance status:	
0–1	7
2	32
3	7
Percentage of weight loss:	
None	12
0–10%	15
> 10%	19
Locoregional/metastatic disease	6/40
Sites of metastatic disease:	
Distant lymph nodes	15
Liver	20
Lung	4
Peritoneum	11
Others	11
Number of metastatic locations:	
0	6
1	28
2	8
3	4

Table 2 Therapeutic results

Complete response	2 (4%)
Partial response	16 (35%)
Stable disease	13 (28%)
Progression	15 (33%)

Table 3 Toxicity encountered in 169 courses

	WHO grade	
Toxicity	1–2	3–4
Nausea/vomiting	44 (26%)	8 (4%)
Diarrhea	8 (4%)	6 (3.5%)
Mucositis	6 (3.5%)	2 (1%)
Thrombocytopenia	7 (4%)	5 (3%)
Anemia	6 (3.5%)	5 (3%)
Leukopenia	19 (11%)	16 (9.5%)
Neurotoxicity	3 (1.7%)	
Nephrotoxicity	2 (1%)	

respectively. Five patients required hospitalization because of fever and granulocytopenia, and three of them died of sepsis. Grade 3–4 nausea vomiting or diarrhea was present in three patients each, and grade 3 mucositis developed in one patient. Patchy alopecia was frequently observed. Two patients developed symptoms or signs of mild peripheral neuropathy.

Discussion

This phase II study was undertaken to confirm the promising results obtained by Preusser et al. [17] using the FLEP regimen in patients with advanced gastric cancer. In 1989, these authors reported a 57% response rate in a series of 14 patients [17]. However, 1 year later they increased their series to 29 patients and observed a response rate of 38% along with a high degree of hematological toxicity and 1 toxic death [20]. After the publication of these results, we questioned whether we should close the study before recruiting the scheduled number of patients, but a preliminary analysis of our first 16 patients revealed high efficacy (50% response rate) and manageable toxicity. Thus, we decided to continue the trial to define further the therapeutic potential of the scheme. It should be noted that some characteristics of our patients, such as the performance status (2–3 in 85%) or the presence of distant metastases (87%) are unfavorable prognostic factors for response and survival [21]. However, as our population came from different geographical areas, we think that they truly represent the general features of patients with advanced gastric cancer in our environment. Anyway, our final results are similar to those obtained by Preusser et al. [20]: FLEP is moderately efficacious but produces important hematological toxicity.

In view of these results, it seems useful to reexamine the rationale for the FLEP regimen. 5-FU remains the mainstay of the systemic therapy for gastric carcinoma [22]. The 20% response rate obtained in monotherapy may be increased to 48% when 5-FU is modulated with LV [13]. As different authors have reported such good results for 5-FU plus LV [14, 23], the role for the addition of etoposide and cisplatin should be questioned. When used in monotherapy, etoposide achieves a response rate of 6% [1], but it acts synergistically with 5-FU and there is no cross-resistance between these two drugs [24]. For the scheme ELF (similar to FLEP but without cisplatin) a 53% response rate with very low toxicity has been reported [21], which suggests some synergism between etoposide and 5-FU. With regard to cisplatin, the results obtained with ELF and the FLEP combination indicate that its efficacy, if any, is very low and that it mainly contributes by increasing the toxicity.

On the other hand, the doses of 5-FU and LV used in FLEP are different from those given in schemes involving only these two drugs which raises questions about their suitability. However, the best schedule for the use of LV to modulate 5-FU has not yet been defined. Besides, the activity of thymidylate synthase in untreated human tumors varies widely [25] such that the optimal dose of LV may depend on the characteristics of the tumor. Recent results indicate that the level of expression of tumoral thymidylate synthase, as determined by the polymerase chain reaction, would allow one to predict the response to chemotherapy in patients treated with cisplatin and 5-FU modulated with LV [26]. From these observations it seems that some gastric carcinomas express high levels of the thymidylate synthase gene. In these cases, therapy with fluorinated

pyrimidines is ineffective; therefore, other drugs should be used. Unfortunately, most centers cannot determine the levels of that enzyme.

As long as more active drugs and techniques to predict chemosensitivity are developed, we need to look into new combinations to improve further the results achieved with the current cytostatics. The data presently available on the FLEP combination, indicating moderate activity and high toxicity, do not allow us to recommend its use for the treatment of gastric carcinoma.

References

1. Findlay M, Cunningham D (1993) Chemotherapy of carcinoma of the stomach. Cancer Treat Rev 19: 29–44
2. Wils JA, Klein HO, Wagener DJT, et al (1991) Sequential high-dose methotrexate and fluorouracil combined with doxorubicin—a step ahead in the treatment of advanced gastric cancer: a trial of the EORTC Gastrointestinal Tract Cooperative Group. J Clin Oncol 9: 827–831
3. Lacave AJ, Barón FJ, Antón LM, et al (1991) Combination chemotherapy with cisplatin and 5-fluorouracil 5-day infusion in the therapy of advanced gastric cancer: a phase II trial. Ann Oncol 2: 751–754
4. Moertel CG, Rubin J, O'Connell MJ, et al (1986) A phase II study of combined 5-fluorouracil, doxorubicin, and cisplatin in the treatment of advanced upper gastrointestinal adenocarcinomas. J Clin Oncol 4: 1053–1057
5. Mabel JA, Little AD (1979) Therapeutic synergism in murine tumors for combinations of *cis*-dichlorodiammineplatinum with VP-16-213 or BCNU (abstract). Proc Am Assoc Cancer Res 20: 230
6. Schabel FM, Trader MW, Laster WR, et al (1979) *cis*-Diamminedichloroplatinum(II): combination chemotherapy and cross-resistance studies with tumors in mice. Cancer Treat Rep 63: 1459–1473
7. Elliot TE, Moertel CG, Wieand HS, et al (1990) A phase II study of the combination of etoposide and cisplatin in the therapy of advanced gastric cancer. Cancer 65: 1491–1494
8. Preusser P, Wilke H, Achterrath W, et al (1989) Phase II study with the combination etoposide, doxorubicin, and cisplatin in advanced measurable gastric cancer. J Clin Oncol 9: 1310–1317
9. Katz A, Gansi R, Simon S, et al (1989) Phase II trial of VP-16, Adriamycin, and cisplatinum in patients with advanced gastric cancer (abstract 378). Proc Am Soc Clin Oncol 8: 98
10. Taguchi T (1989) Combination chemotherapy with etoposide, Adriamycin, and cisplatinum (EAP) for advanced gastric cancer (abstract 420). Proc Am Soc Clin Oncol 8: 108
11. Lerner A, Gonin R, Steele GD, Mayer RJ (1992) Etoposide, doxorubicin and cisplatin chemotherapy for advanced gastric adenocarcinoma: results of a phase II trial. J Clin Oncol 10: 536–540
12. Kelsen D, Atiq OT, Saltz L, et al (1992) FAMTX versus etoposide, doxorubicin and cisplatin: a random assignment trial in gastric cancer. J Clin Oncol 10: 541–548
13. Machover D, Goldschmidt E, Chollet P, et al (1986) Treatment of advanced colorectal and gastric adenocarcinomas with 5-fluorouracil and high-dose folinic acid. J Clin Oncol 4: 685–696
14. Louvet C, Gramont A de, Demuynck B, et al (1991) High-dose folinic acid, 5-fluorouracil bolus and continuous infusion in poor-prognosis patients with advanced measurable gastric cancer. Ann Oncol 2: 229–230
15. Berenberg JL, Goodman PJ, Olshi N, et al (1989) 5-Fluorouracil and folinic acid for the treatment of metastatic gastric cancer (abstract 392). Proc Am Soc Clin Oncol 8: 101
16. Arbuck SG, Silk Y, Douglass HO, Nava H, Rustum YM (1990) A phase II trial of 5-fluorouracil, doxorubicin, mitomycin C, and Iv in advanced gastric carcinoma. Cancer 65: 2442–2445
17. Wilke H, Preusser P, Stahl M, et al (1989) Folinic acid/5-fluorouracil alone or in combination with other cytostatic drugs in the treatment of advanced gastric carcinoma. Proceedings, NCI-EORTC symposium on new drugs in cancer therapy, Amsterdam, pp 20–22
18. Zubrod C, Schneidernman M, Frei I, et al (1960) Appraisal of methods for the study of chemotherapy of cancer in man: comparative therapeutic trial of nitrogen mustard and thiethylene thiophosphoramide. J Chronic Dis 11: 7–33
19. Miller AB, Hoogstraten B, Staquet M, Winkler A (1981) Reporting results of cancer treatment. Cancer 42: 207–214
20. Preusser P, Wilkke H, Meyer JJ, et al (1990) Phase II trial with leucovorin, etoposide, 5-FU and cisplatin in advanced gastric cancer (abstract). Proc Am Soc Clin Oncol 31: 1246
21. Wilke H, Preusser P, Fink U, et al (1990) New developments in the treatment of gastric carcinoma. Semin Oncol 17: 61–70
22. Muggia FM (1993) How to improve survival after diagnosis of gastric cancer? It's back to the drawing board. J Clin Oncol 11: 1437–1438
23. Colucci G, Maiello E, Lacatema M, et al (1991) Folinic acid + FU alone or with 4-epidoxorubicin in advanced gastric carcinoma. Ann Oncol [Suppl] 1: 45
24. Osswaldt H, Kunz W (1987) Therapeutic synergism of etoposide and 5-fluorouracil combined sequentially in advanced leukemia L1210 (abstract). J Cancer Res Clin Oncol 115: 53
25. Peters GJ, Groeningen CJ van, Wilt van der, et al (1992) Time course of inhibition of thymidylate synthase in patients treated with fluorouracil and leucovorin. Semin Oncol [Suppl] 19: 26–35
26. Lenz HJ, Leichman C, Danemberg P, et al (1993) Thymidylate synthase gene expression predicts response of primary gastric cancer to 5-fluorouracil-leucovorin-cisplatin (abstract 585). Proc Am Soc Clin Oncol 12: 199