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Clinical trial report

Etoposide, leucovorin, 5-fluorouracil and interferon alpha-2b in elderly gastric cancer patients: a pilot study

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Abstract. A total of 23 advanced gastric cancer patients older than 65 years received 500 mg/m^2 5-fluorouracil i.v. on days 2–4, 120 mg/m^2 vepesid i.v. on days 2–4, 150 mg/m^2 6S-leucovorin on days 2–4, and 5 MU/m^2 interferon alpha-2b on days 1–5, with cycles being repeated every 3 weeks. Toxicity was severe at an interferon (IFN) dose of 5 MU/m^2; only one patient tolerated this dose. In 18 patients an IFN dose of 3 MU/m^2 and in 3 other patients a dose of 4 MU/m^2 could be given without producing toxicity. At an IFN dose of 5 MU/m^2 the most common toxicities encountered were stomatitis (grade 4 in 1 patient and grade 3 in 12 patients), leukopenia (grade 4 in 1 patient and grade 3 in 5 patients), and thrombocytopenia (grade 3 in 3 patients). Two patients achieved a complete response and eight showed a partial response, resulting in an overall response rate of 45% [95% confidence interval (CI), 25%–64%]. The median survival was 7 months for all patients and 9 months for responding patients. In conclusion, without substantially increasing the toxicity, IFN can be added to the etoposide/leucovorin/5-fluorouracil combination, at a dose of 3 MU/m^2. To verify the possible enhancement by IFN of the activity of this combination, a randomized trial is under way.

Introduction

About 60% of patients with advanced gastric cancer are older than 65 years [1]. These patients often cannot take advantage of cytostatic treatment because of underlying diseases that are common in the elderly and may complicate or even hinder cytotatic treatments. Furthermore, except for etoposide (VP16) and 5-fluorouracil (5FU), most drugs that are effective in gastric cancer produce cumulative organ toxicity [2, 3].

On the basis of preclinical data, a new combination of 5FU, VP16 and leucovorin (LV); (ELF regimen) was developed and investigated by Wilke et al. [4]. Preliminary data showed the interesting activity and safety of this combination [4, 5]. Recently, experimental data suggested the possibility of enhancing the cytotoxicity of 5FU and VP16 by the addition of interferon (IFN) [6, 7].

With the aim of evaluating in a randomized study the possible enhancement by IFN of the activity of this regimen, a pilot clinical trial was initiated at our institution to determine the feasibility and safety of combining IFN with the ELF regimen.

Patients and methods

A total of 23 patients with histologically proven metastatic gastric adenocarcinoma were included in this study. Admission criteria included an age of >65 years; an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, the presence of measurable disease, the absence of concomitant disease, and a life expectancy of >3 months. Informed consent was obtained from all patients.

The treatment schedule consisted of 150 mg/m^2 6S-LV followed by 120 mg/m^2 etoposide given as a 50-min infusion and then by 500 mg/m^2 5FU given as a 15-min infusion on days 1–3. IFN alpha-2b was injected i.m. at a dose of 5 MU/m^2 daily for 5 days beginning on the day before chemotherapy. Cycles were repeated every 3 weeks. If patients developed any toxicity of grade 3 (WHO) apart from alopecia, the daily dose of IFN was reduced to 4 MU/m^2, and in cases of further severe toxicity it was decreased to 3 MU/m^2. Patients presenting with grade 4 toxicity were withdrawn from the study. Complete blood counts and liver [total and direct bilirubin, SGOT, SGPT, lactic dehydrogenase (LDH), alkaline phosphatase, serum electrophoresis] and kidney [blood urea nitrogen (BUN), creatinine clearance] function tests were required before each course of therapy. Furthermore, hemograms were repeated every week to record hematologic toxicity. Response and toxicity were assessed according to standard WHO criteria [8]. All patients who received at least one cycle were evaluable for toxicity. Patients were considered evaluable for response after receiving two cycles of chemotherapy.

Results

Of the 23 patients included in this study, 22 were evaluable for response and toxicity. One patient refused further

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Table 1. Patients' characteristics

Age (years):	
Median	72
Range	65–78
Sex:	
M/F	16/7
Performance status (ECOG):	
0	8
1	10
2	5
Prior surgery:	
None	4
Curative	10
Palliative	9
Sites of primary tumors:	
Gastroesophageal junction	1
Proximal stomach	5
Body	6
Distal stomach	11
Histologic type:	
Well-differentiated	3
Moderately differentiated	13
Poorly differentiated	7
Sites of metastases:	
Liver	9
Abdomen/peritoneum	7
Lymph nodes	4
Lung	3
Bone	2
Prior chemotherapy:	
Yes	16
No	7

Table 2. Toxic effects encountered according to IFN dose levels

Toxic effect	WHO grade	Number of patients with toxicity		
		3 MU/m²	4 MU/m²	5 MU/m²
Leukopenia	1–2	4	3	6
	3–4	–	5	6
Thrombocytopenia	1–2	2	1	3
	3–4	–	1	3
Anemia	1–2	–	1	2
	3–4	–	–	–
Diarrhea	1–2	–	–	3
	3–4	–	–	–
Stomatitis	1–2	3	4	3
	3–4	–	10	13

treatment after having experienced grade 3 mucositis during the first cycle. The patients' characteristics are summarized in Table 1. Four patients had not received prior surgery and ten had undergone palliative surgery alone. None of the patients had only locoregional disease. The toxicities encountered are outlined in Table 2. A total of 18 patients experienced severe toxicity at IFN doses of 5 and 4 MU/m², tolerating only a dose of 3 MU/m². In three patients an IFN dose of 4 MU/m² could be given without producing toxicity, and only one patient tolerated a dose of 5 MU/m². The side effects most commonly observed at an IFN dose of 5 MU/m² were stomatitis (grade 4 in 1 patient and grade 3 in 12 patients), leukopenia (grade 4 in 1 patient and grade 3 in 5 patients), and thrombocytopenia (grade 3 in 3 patients). Systemic side effects secondary to IFN treatment were seen in all patients treated at 4–5 MU/m² but not in those given 3 MU/m².

The overall response rate was 45% [95% confidence interval (CI), 25%–64%]. Two patients achieved a complete remission and eight achieved a partial remission; six had stable disease and six progressed on therapy. In all, 6 of the 8 partial responses (40%) occurred in the 15 evaluable patients who had previously been treated with a combination of weekly low doses of cisplatin, epidoxorubicin, and 5FU. The median duration of response was (range, 2–8) months. The overall median survival was 7 months, and the median survival of responding patients was 9 months.

Discussion

A combination of 5FU, etoposide and LV has recently been investigated by Wilke et al. [4] in elderly gastric cancer patients. These drugs rarely induce severe subjective or objective side effects when given at conventional doses. Furthermore, experimental data have indicated synergy between etoposide and 5FU as well as the lack of cross-resistance between the two drugs [3, 9]. Finally, LV has been shown to be capable of enhancing the activity of 5FU in gastric cancer [10].

Preliminary trials confirmed the interesting activity (overall response rate, 50%) and low toxicity of this regimen, making it very appealing for elderly gastric cancer patients [4, 5]. Preclinical and clinical data have suggested that IFN is capable of enhancing the activity of 5FU and VP16 [6, 7]. Moreover, clinical trials have indicated that both LV and IFN modulation appear to be acting in concert to enhance the inhibition of the critical target enzyme thymidylate synthase. However, because IFN can also increase the toxicity of cytotoxic drugs, we performed the present pilot study to evaluate the feasibility and toxicity of a combination of IFN with the ELF regimen as proposed by Wilke et al. [4].

We did not follow the design of a classic phase I study, whereby the IFN dose is increased in cohorts of patients to determine the maximum tolerated dose, because a cyclic intermediate dose of IFN has been reported to be the optimal schedule [11]. In fact, preclinical evidence suggests that IFN should be given concurrently with cytotoxic drugs for optimal potentiation [6]. Another reason for cyclic IFN administration is the capability of IFN to arrest cells in the G_0/G_1 phase, thus rendering tumor cells insensitive to 5FU, an S-phase-specific agent [12].

An intermediate dose of IFN (5 MU/m²) seemed to be more effective in the biochemical and pharmacokinetic modulation of 5FU than did low (3 MU/m²) or high doses (10 MU/m²) as demonstrated by Grem et al. [11] and Wadler et al. [13]. In spite of these data, we were capable of giving the planned IFN dose of 5 MU/m² only to one patient because of the presence of severe gastrointestinal and

hematologic toxicity. However, even at this lower IFN dose we observed interesting activity, obtaining an objective response rate of 45%. Indeed, these data are similar to those obtained by Wilke et al. [4, 5] without IFN, although more than two-thirds of our patients had previously been treated with a regimen including cisplatin, epidoxorubicin, and 5FU. Another study employing a low IFN dose (3 MU given twice a week) has shown the feasibility of this combination [14]. However, for the reasons mentioned above, we think that cyclic rather than continuous administration of IFN is the optimal schedule.

In conclusion, considering the strong preclinical rationale, the safety of adding IFN at a low dose of the ELF regimen, and the interesting activity of this combination, even in previously treated patients, we designed a random-assignment trial comparing ELFI with the ELF regimen so as to evaluate definitively the contribution of IFN in terms of response and survival.

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