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Short communication

Etoposide, folinic acid, and 5-fluorouracil in carboplatin-pretreated patients with advanced gastric cancer

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Summary. A group of 20 patients with gastric cancer, refractory to or with no change after two or three cycles of carboplatin were treated with etoposide/folinic acid/5-fluorouracil (ELF). An objective remission rate of 45% (9/20), a median remission duration of 8 months and a median survival time of 11 months were achieved. Toxicities were mild to moderate only. These results are comparable to those being achieved with ELF in previously untreated gastric cancer patients and confirm its efficacy and good tolerability.

Introduction

Carboplatin, a second-generation platin analogue with a molecular mode of action comparable to cisplatin has been investigated in advanced gastric cancer by our group using a fractionated day-1,3,5 schedule [4]. Patients with early tumour progression or no sign of tumour regression after 2(3) cycles of carboplatin were taken off study and received etoposide/folinic acid/5-fluorouracil (ELF) as second-line treatment. ELF was chosen because of its activity in untreated gastric cancer patients [5, 6] and lack of cross-resistance between carboplatin, etoposide, and 5-fluorouracil in vitro and in vivo.

Materials and methods

Eligibility criteria included histologically confirmed irresectable or metastasized adenocarcinoma of the stomach, measurable disease, performance status <2 according to WHO scale, adequate bone marrow, liver and renal function, no severe comorbidities, and informed consent.

Tumour measurements were done by physical examination, endoscopy, X-ray, abdominal computed tomography (CT) and ultrasound, and chest CT if indicated. Liver and renal function were monitored prior to each cycle and blood counts weekly during treatment.

Tumour response and side-effects were assessed prior to each chemotherapy cycle, 4 weeks after the last one and then every 3 months.

The evaluation of tumour response and documentation of side-effects were done according to WHO criteria [2]. Median remission duration and median survival time were calculated using the Kaplan-Meier method.

Out of 24 patients treated with carboplatin, 20 have been entered into this trial. All patients had at least one measurable lesion and histologically confirmed gastric cancer. The median age was 63 years (49–70), the median WHO performance status 1 (0–2). Two patients had only locally advanced disease and 18 patients had distant metastases (liver with or without other sites except for peritoneal carcinosis 13, lymph nodes 2, peritoneal carcinosis + other sites 3). According to the Lauren classification 13 patients had intestinal-type and 7 diffuse-type gastric cancer. Twelve patients had progressive disease during carboplatin treatment and 8 patients had no change when entering the trial.

Chemotherapy consisted of folinic acid 300 mg/m^2 10 min i.v. followed by etoposide 120 mg/m^2 50 min i.v. followed by 5-fluorouracil 500 mg/m^2 10 min i.v. on days 1–3, every 22 days. Patients without tumour progression during ELF treatment received up to 6 cycles depending on side-effects.

Results

All 20 patients were evaluable for response, toxicity and survival. A total of 91 cycles [median 5 (1–6)] were administered; 9 (45%) partial remissions were achieved, 6 (30%) patients had no change and 5 (25%) had progressive disease. Both patients with locally advanced disease

Table 1. Treatment results (n = 20)

Condition of patients	PR[a]	(%)
All patients	9/20	(45)
Locally advanced disease	2/2	
Metastasized disease	7/18	(39)
Prior progression with carboplatin	4/12	(33)
Previously no change with carboplatin	5/8	(63)
Diffuse type	2/7	(29)
Intestinal type	7/13	(54)

[a] Partial remission

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Table 2. Maximum toxicity per patient during whole treatment ($n = 20$)

Toxicity	Percentage patients with WHO grade			
	1	2	3	4
Leucocytes	30	40	30	0
Thrombocytes	25	20	0	0
Nausea/vomiting	40	10	0	0
Mucositis/stomat.	15	5	5	0
Diarrhoea	10	5	0	0
Alopecia	0	30	70	0

and 7 out of 18 (39%) patients with distant metastases responded to ELF. Four out of 12 (33%, all with distant metastases) patients with progressive disease and 5/8 patients with no change during carboplatin had a partial remission. Table 1 summarizes these data.

ELF was well tolerated. Side-effects such as myelosuppression, mucositis/stomatitis or nausea/vomiting were mild to moderate only and of short duration (Table 2). No life-threatening toxicities were observed.

The median remission duration was 8 months (range 6–10) and the median survival time for responders 12 months (range 10–15). The survival for all patients was 11 months (range 1–19).

Discussion

Because of the recent successes being achieved with newer chemotherapy protocols such as etoposide/Adriamycin/cisplatin, 5-fluorouracil/Adriamycin/methotrexate and ELF, gastric cancer has to be regarded as a chemosensitive tumour [1, 3, 6].

With ELF an overall remission rate of 52%, a median remission duration of 8.5 months and a median survival time of 11.5 months were achieved in a former phase-II trial in previously untreated patients.

This trial confirms the efficacy of ELF. In spite of the pretreatment with carboplatin, the partial remission rate of 45%, the median remission duration of 8 months and the median survival time of 11 months are comparable to the results of ELF in untreated patients.

The good tolerability of ELF could also be confirmed. No WHO grade 4 toxicity occurred and the observed side-effects were mild to moderate only, of short duration, and never led to treatment discontinuation.

This trial also showed that there is no clinically relevant cross-resistance between carboplatin, etoposide and 5-fluorouracil. Objective remissions were observed with ELF in 33% of patients refractory to carboplatin.

Therefore, the clinical investigation of single-agent activity of new drugs is also justified in chemosensitive tumours if an effective and rationally based second-line treatment is available. In such a situation, the early change from first-line treatment to salvage chemotherapy in the case of progression or no change after 2 or 3 cycles might be of importance.

References

1. Klein HO, Wickramanyake PD, Farrkh GR (1986) 5-Fluorouracil (5-FU), Adriamycin (ADM), and methotrexate (MTX) – a combination protocol (FAMTX) for treatment of metastasized stomach cancer (abstract). Proc 22nd ASCO Meeting, Los Angeles, May 4–6, p 84
2. Miller AB, Hoogstraten B, Staquet M, Winkler A (1981) Reporting results of cancer treatment. Cancer 47: 207–214
3. Preusser P, Wilke H, Achterrath W, Fink U, Lenaz L, Heinicke A, Meyer J, Meyer HJ, Buente H (1989) Phase II study with the combination etoposide, doxorubicin, and cisplatin in advanced and measurable gastric cancer. J Clin Oncol 9: 1310–1317
4. Preusser P, Wilke H, Achterrath W, Lenaz L, Stahl M, Casper J, Meyer HJ, Meyer J, Blum M, Schmoll HJ (1990) Phase II study of carboplatin in untreated inoperable advanced stomach cancer. Eur J Cancer 10: 1108–1109
5. Wilke H, Preusser P, Fink U, Achterrath W, Lenaz L, Stahl M, Schöber C, Link H, Meyer HJ, Lücke B, Schmoll HJ (1990) High dose folinic acid/etoposide/5-fluorouracil in advanced gastric cancer – a phase II study in elderly patients or patients with cardiac risk. Invest New Drugs 8: 65–70
6. Wilke H, Preusser P, Fink U, Achterrath W, Meyer HJ, Stahl M, Lenaz L, Meyer J, Siewert JR, Geerlings H, Köhne-Wömpner CH, Harstrick A, Schmoll HJ (1990) New developments in the treatment of gastric cancer. Semin Oncol 1 [Suppl 2]: 61–70