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High dose folinic acid/etoposide/5-fluorouracil in advanced gastric cancer – a phase II study in elderly patients or patients with cardiac risk

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Summary

Thirty-four consecutive patients with measurable advanced gastric cancer were treated in a disease oriented Phase II study with high-dose folinic acid (HDFA) 300 mg/m^2 10 min. inf., followed immediately by etoposide 120 mg/m^2 50 min. inf., followed immediately by 5-fluorouracil (5-FU) 500 mg/m^2 10 min. inf., given on day 1,2,3 (ELF). Courses were repeated every 22–28 days. All patients who entered this study were older than 65 years or had underlying cardiac disease. Thirty-three patients were evaluable for response and toxicity (≥ 1 course). One patient was lost to follow up. The overall response rate was 48% (16/33) including 12% (4/33) complete remissions. Eight patients had minor responses or no change and 9 had progressive disease. Five of six patients with locally advanced and non-resectable disease had an objective response (1 CR, 4 PR's). The response rate in patients with metastatic disease was 41% (11/27). After a median observation time of 6.5 months, the median survival time was 10.5 months, with a median remission (CR + PR) duration of 8 months. Toxicity was manageable and included mild to moderate myelosuppression and gastrointestinal toxicities. One episode of life-threatening (Grade IV) leukopenia, and two episodes of severe diarrhea requiring hydration were noted. No treatment related death occurred.

ELF is an effective combination in advanced gastric cancer and can be safely administered to elderly patients and patients with cardiac risk.

Introduction

Chemotherapy is the treatment of choice in patients with advanced gastric cancer. The more frequently used combinations such as FAM (fluorouracil, doxorubicin, mitomycin), FAB (fluorouracil, doxorubicin, carmustine) or FAP (fluorouracil, doxorubicin, cisplatin) induce response rates of about 30%–40% but rarely complete remissions (<5%) [1,2]. The median survival time is approximately 7 months. Significantly higher response rates were achieved with EAP (etoposide, doxorubicin, cisplatin) in metastasized [3] and locally advanced gastric cancer [4].

More than 60% of patients with gastric cancer are older than 65 years [5] and additionally often suffer from diseases of the liver, kidney, lung and heart unrelated to the tumor [6–8]. For these reasons the subjective and objective toxicities of intensive chemotherapy regimens exclude most of the elderly patients from treatment with EAP, FAM, FAB and FAP. This is particularly true if they suffer from cardiac diseases and therefore cannot be treated with anthracyclines [9,10]. Most drugs

effective in gastric cancer have cumulative organ toxicities. These include cisplatin [11], anthracyclines [9,10], nitrosoureas [12,13] and mitomycin [13]. When used at conventional doses etoposide and 5-fluorouracil (5-FU) rarely induce severe objective and subjective side effects and are not associated with cumulative organ toxicities [14,15]. In previously untreated patients with advanced gastric cancer, objective responses of 20% were achieved with 5-FU [16] and etoposide [17], although the latter drug was given at less than 50% of the recommended dose for Phase II studies for pretreated patients. The administration of HDFA plus 5-FU in advanced gastric cancer has resulted in an overall response rate of 35% with acceptable toxicity but rarely in complete remissions (< 5%) [18,19]. Furthermore experimental data showed a synergism between 5-FU and etoposide *in vitro* [20] and *in vivo* [21] and a lack of cross resistance between 5-fluorouracil and etoposide [20]. Considering these clinical and experimental data, a disease oriented Phase II trial with HDFA/etoposide/5-FU (ELF) was conducted after a pilot dose finding study [22] in elderly patients and in patients with cardiac diseases preventing administration of anthracyclines.

Patients and methods

From June 1986 until October 1987, thirty-four consecutive patients with advanced gastric cancer entered this trial. Eligibility criteria included histologically proven gastric cancer, age > 65 years, age < 65 years plus cardiac disease, WHO performance status ≤ 2, measurable +/− evaluable disease, normal renal function (serum creatinine < 1.5 mg/dl, creatinine clearance ≥ 60 ml/min) normal liver function (serum bilirubin < 2 mg/dl) normal bone marrow function (leukocytes > 4×10^9/l, thrombocytes > 100×10^9/l), no clinical evidence of CNS metastases prior to chemotherapy, no prior chemo- or radiotherapy, no second malignancy and informed consent. Staging procedures were endoscopy, abdominal computed tomography, abdominal sonography, chest x-ray and bone scan. Explorative laparotomy was done in most of the patients as well as cytological confirmation of metastases. For evaluation of response after chemotherapy, the same diagnostic procedures were used. Blood counts were done weekly. Evaluation of liver and renal function and of measurable or evaluable disease were done prior to each chemotherapy course and 4 weeks after the last course. Follow up examinations were done monthly. Tumor response, response duration and toxicity were classified according to WHO criteria [23]. Median response duration, median progression-free interval and median survival time were calculated by the Kaplan-Meier method [24]. Survival was calculated from the first day of treatment.

Chemotherapy consisted of HDFA 300 mg/m^2 given as a 10 minute infusion, followed immediately by etoposide 120 mg/m^2 50 minutes infusion, followed immediately by 5-FU 500 mg/m^2 10 minute infusion on days 1,2 and 3. The dose of 5-FU as reduced by 10% in case of stomatitis, mucositis and diarrhea ≥ WHO grade 2, and in case of thrombocytopenia ≥ WHO grade 3, and/or leucopenia of WHO grade 4. Courses were repeated every 22–28 days. Chemotherapy was administered on an outpatient basis.

If a complete remission was achieved in patients with metastatic disease, two further courses of HDFA/etoposide/5-FU were given for consolidation. Patients with PR/MR/NC received up to 6 courses, depending on tolerance. Second look surgery (SLO) was planned in case of an objective response in patients with locally advanced and non resectable (staged by laparotomy) gastric cancer in order to remove residual disease if possible. All patients who received at least 1 course were evaluable for toxicity. Patients were considered evaluable for response after receiving 2 courses of chemotherapy, although patients with progressive disease after the first course are included in the response analysis. Patient characteristics are listed in Table 1.

Results

Thirty-four patients were entered into this trial. Thirty-three were evaluable for response and toxicity. One patient was lost to follow up and not included in this analysis. A total of one hundred and thirty-nine [mean 4,2 per patient (1–8)] chemotherapy courses have been administered to date. The overall response rate (CR + PR) was 48%

Table 1. Patient characteristics (n = 33)

Male/female	22/11
Age	66 years (48–75)
– > 65 yrs.	22
– < 65 yrs. + cardiac risk	11
– myocardial infarction	4
– congestive cardiomyopathy	6
– arrythmias	1
Performance status (WHO)	
– 0	1
– 1	13
– 2	19
Locally advanced disease	6
Metastatic disease	27
– with local tumor	14/27
– without local tumor	13/27

Table 2. Treatment results (n = 33)

CR	4 (12%)
CR + PR	16 (48%)
MR/NC	8 (24%)
PD	9 (27%)
Locally advanced disease	
– CR	1/6
– CR + PR	5/6
Metastatic disease	
CR	3/27
CR + PR	11/27 (41%)
– with local tumor	
CR	1/14
CR + PR	6.14 (43%)
– without local tumor	
CR	1/13
CR + PR	5/13 (38%)
Age > 65 years	10/23 (45%)
Age < 65 years + cardiac risk	6/11 (55%)

(16/33) with a 95% confidence limit of 31%–65%. Four of 33 patients (12%) achieved a complete response. Eight patients had minor response or no change and 9 patients had progressive disease. Five of 6 patients with locally advanced gastric cancer had an objective response (1 CR and 4 PR). One of these patients underwent SLO within resection of residual disease, and a PR was pathologically confirmed. Two patients refused SLO and 2 were inoperable due to medical reasons. Forty-one percent (11/27) of the patients with metastases achieved objective responses (3 CR – 1 pathologically confirmed by second look operation, and 8 PR). Response rate in patients with both local tumor and distant metastases was 43% (6/14), while in patients with only distant metastases it was 38% (5/13). There was no significant difference between response rates of patients older or younger than 65 years. Treatment results are summarized in Table 2. An analysis of response by tumor site revealed a low response rate (9%) only in patients with peritoneal carcinosis (Table 3).

After a median observation time of 6.5 months (1.5–17.5), the median response duration is 8 (3+ –13+) months. Median progression-free interval for MR/NC is 6.5 months (2.5–11.5). Median survival time for all patients is 10.5 months (1.5–17.5+). Patients with objective response (CR/PR) or MR/NC have a median survival time of 12 months (4+ –13+) and 10.5 months (4+ –18+), respectively. The median survival time for patients with progressive disease is 4 months (Fig. 1).

Myelosuppression was usually mild to moderate. Leukopenia and thrombocytopenia of WHO grade 3 only occurred in 9% and 3% of the patients respectively. One patient had a WHO grade 4 leukopenia. Mean leukocyte nadir was 2.6 × 10^9/l (0.8–4.2), that of platelets 106 × 10^9/l (34–260). Lowest leukocyte and thrombocyte counts were measured between day 12–21 (mean day 15) and 13–21 (mean day 15), respectively. Peripheral blood counts recovered on day 17–24 (mean day 20). Nausea/vomiting of WHO grade 1 and 2 occurred in 33% (11/33) and 15% (5/33) of the patients. Two patients had diarrhea of WHO grade 3, requiring hospitalization. The dose of 5-FU was reduced in one patient with leucopenia of WHO grade 4 plus thrombocytopenia of WHO grade 3, and in 5 patients with diarrhea and mucositis of ≥ WHO grade 2. Delays in treatment were not necessary. No other severe toxicities were observed. Toxicity data are listed in Table 4.

Table 3. Response by tumor sites (all localizations in 33 patients)

Sites	Number of	CR	CR + PR	MR/NC	PD
Local tumor	20	2 (10%)	11 (55%)	5 (25%)	4 (20%)
Liver	17	2 (12%)	8 (47%)	4 (24%)	5 (29%)
Intraabdom. lymphnodes	17	3 (18%)	8 (47%)	5 (29%)	4 (24%)
Extraabdom. lymphnodes	2	0	2	0	0
Peritoneal carcinosis	11	0	1 (9%)	6 (55%)	4 (36%)
Lung	1	1	1	0	0

Table 4. Toxicity (WHO grade (n = 33))

	1	2	3	4
Leukopenia	9 (27%)	13 (39%)	3 (9%)	1 (3%)
Thrombocytopenia	9 (27%)	2 (6%)	1 (3%)	0
Nausea & vomiting	11 (33%)	5 (15%)	0	0
Mucositis	6 (18%)	3 (9%)	0	0
Diarrhea	4 (12%)	3 (9%)	2 (6%)	0
Alopecia	5 (15%)	16 (48%)	10 (30%)	0
Infection	1 (3%)	0	1 (3%)	0
Neurotoxicity	0	0	0	0
Cardiotoxicity	0	0	0	0

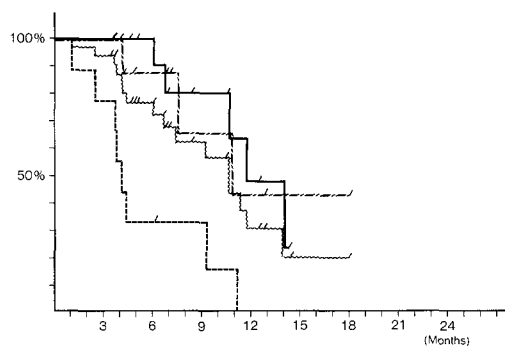

Fig. 1. Duration of survival:
– Patients achieving CR and PR (—). Number of patients: 16; median survival: 12 months; MR and NC (– · – · –). Number of patients: 8, median survival: 10.5 months; all patients (〰): Number of patients: 33, median survival: 10.5 months. Progressive disease (– – –); number of patients: 9, median survival: 4 months. Vertical tick marks represent patients last follow-up.

Discussion

Treatment of gastric cancer remains a challenge. Patients with gastric cancer often have a poor performance status. The majority is older than 65 years and often underlying diseases (cardiovascular system, liver, kidney, lung) [6–8] may complicate or prevent cytostatic treatment more often than in young patients. Thus the development of safe treatment programs with a higher therapeutic index are warranted, especially for palliative treatment.

In this study ELF induced an objective response rate of 48%, a median remission duration of 8 months and a median survival time of 10.5 months in patients with significant risk factors (advanced age, cardiac disease, measurable disease). These treatment results seem to be at least equivalent to those being reported with FAM and FAM-modifications [1,2]. The small difference between survival of patients with CR/PR or MR/NC (Fig. 2)

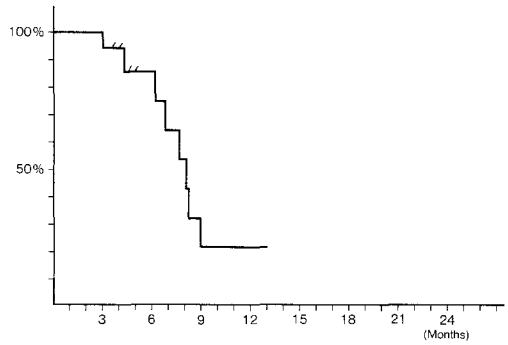

Fig. 2. Duration of response for patients achieving CR and PR (—). Number of patients: 16; median duration of response, 8 months. Vertical tick marks represent patients last follow-up.

reflects the long lasting stable disease obtained with ELF.

This chemotherapy regimen was better tolerated considering both subjective and objective side effects, than FAM and FAM-modification. Myelotoxicity was moderate. Only one episode of leukopenia WHO grade 4 occurred. Nausea and vomiting as well as mucositis and stomatitis were usually mild. However two severe episodes of diarrhea requiring hydration were observed.

Summarizing these first experiences with High-Dose Folinic Acid/etoposide/5-FU we conclude:

- This combination can be safely administered to elderly patients and to patients with cardiac risks.
- Response rates, remission duration and survival times demonstrate the efficacy of this protocol.
- Because of these results, and the synergism between cisplatin, etoposide and fluorouracil, a study combining these drugs and HDFA in patients with good prognostic factors is currently being considered.

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