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Probable Cure of Two Patients With Advanced Gastric Carcinoma by Chemotherapy Only: Long-term Follow-up of a Phase I Trial With a Weekly Carboplatin and Epirubicin Regimen

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Abstract: A dose escalation study of carboplatin in combination with 5FU and epirubicin in surgically incurable gastric cancer. Carboplatin was combined with a fixed dose epirubicin 35 mg/m^2, leucovorin 250 mg/m^2 and 5 FU 500 mg/m^2 (CELF). The starting dose of carboplatin was 100 mg/m^2 which was escalated to 150 mg/m^2. This CELF regimen was repeated every week, for a maximum of 14 cycles. Primary prophylaxis against leucopenia with filgastrim was given. Twelve chemotherapy naive patients were enrolled, 9 with metastatic disease and 3 with locally advanced surgically irresectable disease. The major toxicities of the CELF regimen were uncomplicated leucopenia and thrombopenia. Nausea and mucositis were the most common non-hematological toxicities. The dose-limiting toxicity was grade 3 leucopenia, observed at a dose of 150 mg/m^2/week. The objective response rate was 58% (95% CI 31%-85%). From the three patients with localized but surgically incurable disease two remain alive without disease progression and without symptoms after 6 and 9 years after chemotherapy without any other treatment.

Key words: Stomach neoplasms, metastatic, chemotherapy, gastric, long-term survival

INTRODUCTION

At the end of the last decade of the twentieth century a multitude of chemotherapy regimens were investigated for the treatment of surgically incurable gastric cancer (Wagner *et al.*, 2006). Differences between regimens were especially at the level of toxicity rarther than the antitumor activity was concerned. Cascinu reported in 1997 on an active intensive weekly with a high response rate (Cascinu *et al.*, 1997). Essentially the compounds used in this regimen were by that time emerging to become the standard of care for incurable gastric cancer. In the previous years 5-fluorouracil (5-FU) had been the mainstay of treatment as it had demonstrated that its use improved overall survival and quality of life compared to best supportive care (BSC) in several randomized trials (Murad *et al.*, 1993a; Pyrhonen *et al.*, 1995; Glimelius *et al.*, 1997). Subsequently, from all drugs added to 5FU especially cisplatin and epirubicen or adriamycin seemed to improve on the results of 5FU alone. The 3 weekly regimens were most commonly used in these comparisons till today, but it was not yet standard when the current weekly regimen was tested. Based on those data we performed a study of Cascinu regimen with a modification of the platinum compound in order to improve the feasibility and tolerability of this intensive weekly regimen. Triggered by the long term clinical results we report on the mature data.

MATERIALS AND METHODS

In august 1998, we initiated this phase I, dose finding study in chemotherapy naive patients with metastatic and/ or non-resectable locally advanced gastric carcinoma.in the university hospital in Groningen, the Netherlands.

Eligibility criteria: All patients had to have histologically proven, measurable gastric carcinoma, either surgically non-curable, locally advanced disease or metastatic disease. Age was 18 – 60 years, with an ambulatory performance status of 0-1 on the Eastern Cooperative Oncology Group (ECOG) scale and a life expectancy of > 3 months. Laboratory acceptance parameters included a white blood cell count ≥ 4.0 x 10 *9* /L, platelet count ≥ 150 x 10^9 /L, serum bilirubin ≤ 1,5 x upper limit of normal, and calculated creatinine clearance of ≥ 80 ml/min .

Additional eligibility criteria included the absence of clinical signs of myocardial ischemia, no serious active infections requiring antibiotics, no clinical signs of brain metastasis no concurrent radiotherapy and no previous chemotherapy. Pregnant or lactating women were not eligible as were patients with previous or current malignancy at other sites with the exception of squamous cell carcinoma of the skin or in situ carcinoma of the cervix uteri. All patients gave written informed consent before entering this study. The study protocol was approved by the institutional review board.

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Study design: Before study entrance, patients underwent a complete history and physical examination, including performance status and weight. Base line imaging studies were obtained to define the extent of the disease. Laboratory tests included a complete blood cell count with differential and platelet count, blood chemistry studies and urinalysis.

In order to define the maximum tolerated dose (MTD) of carboplatin in combination with epirubicin, 5-FU and leucovorin, escalating doses of carboplatin were added to fixed doses of epirubicin, 5-FU and leucovorin. The starting dose of carboplatin was 100 mg/m^2/week in the first four patients. In the absence of toxicity exceeding WHO grade 2 on leucocytes and platelets in the first three weeks of treatment, the next cohort of four patients were planned to receive carboplatin 150 mg/m^2/ week. In case of no hematological toxicity exceeding WHO grade 2 in this cohort, the next dose level was 200 mg/m^2/week. In case of toxicity WHO grade 3 or 4 on leucocytes and or platelets during the first three weeks of treatment, this was considered dose limiting toxicity. In case of 2 patients with dose-limiting toxicity on a given dose level the level below this level was considered to be the maximum tolerated dose. The carboplatin dose was de-escalated to the prior dose level for the following courses. Planned doses of chemotherapy were given if white blood cell count ^{3} 4.0 x 10^9 /L and platelets $\geq$ 100 x 10^9 /L otherwise treatment was delayed for one week until full recovery. In the case of grade 2 or 3 mucositis or diarrhea treatment was also delayed for one week until recovery.

The outpatient chemotherapeutic regimen consisted of a 1-day per week (day 1) administration of Carboplatin as a 30-min i.v. infusion; epirubicin 35 mg/m^2 as an i.v. bolus infusion; leucovorin 250 mg/m^2 as a 60 min split i.v. infusion before and after 5-FU; 5 FU 500 mg/m^2 as a 15 min i.v. infusion. From day 2 till day 6 patients received G-CSF 5 µg/kg s.c.. As anti-emetic therapy patients received ondansetron before and after chemotherapy administration. After 8 weeks of treatment tumor re-evaluation was performed and patients with a tumor response or stable disease, according to WHO criteria were planned to have a further 6 weeks of treatment. Treatment was stopped in case of progression or any grade 4 non-hematological toxicity. Toxicity was evaluated according to the National Cancer Institute Common Toxicity Criteria (NCI CTC), version 2.0.

Statistical analysis: The analysis of this phase 1 study is primarily descriptive. Values are presented as median with ranges unless stated otherwise. Pearsons correlation was used to calculate the relation between carboplatin dose and toxicity.

RESULTS

Patient characteristics: During the study period a total of 12 patients, 8 men and 4 females, with a median age of 55 years (range 32-62) were enrolled. Nine patients had stage IV disease and three had locally advanced surgically incurable disease. (Table 1)

Table 1: Patient and tumor characteristics

	total	(%)
Number entered	12	
Median age in years	55	
Range	32-62	
Sex		
Male	8	(67)
Female	4	(33)
WHO performance status		
0	3	(25)
1	9	(75)
Gastric cancer stage (AJCC)		
IIIb	3	(25)
IV	9	(75)
Histology		
Diffuse	3	(25)
Intestinal	9	(75)
Differention grade		
Well differentiated	3	(25)
Moderately differentiated	4	(33)
Poorly differentiated	5	(42)

Treatment characteristics: The first four patients were treated at the 100 mg/m^2 carboplatin level, without dose-limiting toxicity during the first three cycles. Subsequently the next four patients were treated at the 150 mg/m^2 carboplatin dose level. In this dose level, one patient had grade 3 leucopenia in the third cycle and one grade 4 with septicemia in the fifth cycle. As defined by protocol the following patients were treated at a dose of 100 mg/m^2 carboplatin. 108 treatment cycles were applied in this study. The median number of cycles administered was 10 per patient (range 4-14). Dose reductions and delayed administration of cycles resulted in a dose intensity of respectively 81% in the 100 mg/m^2 carboplatin dose level. At the 150 mg/m^2 carboplatin dose level the dose intensity was 67 %, and 85% of this reduced intensity was due to delayed administration. Since we expected that frequent dosing, dose density, is one of the features to increase the therapeutic index, the frequent delays and even a delay of 3 weeks in the 150 mg/m^2 carboplatin dose level, combined with a complicated grade IV leukopenia in the fifth cycle, led to the conclusion that 100 mg/m^2 carboplatin was the MTD.

Toxicity: All patients were assessable for toxicity (Table 2). Hematological toxicity, diarrhea and nausea were the major toxic effects of CELF chemotherapy. One patient with evidence of response based on reduction of a supra-clavicular lymph node, had a gastric perforation, possibly due to the tumor response. This was considered grade IV toxicity so treatment was stopped, and the patient died 5 months later. The median dose of carboplatin based on AUC using the Calvert formula (14), was 1.63 mg/ml*min (range 1.41 to 1.94) in the 100 mg/m2 group, and respectively 2.60 mg/ml*min (range 2.29-3.0) in the 150 mg/m2 group. We did not find a relation with relative platelet count reductions in the first 3 cycles and carboplatin target AUC (R=0,24).

Table 2: Toxicity of chemotherapy

	Carboplatin dose level 100 mg/m^2 (n=8, cycles 81)				Carboplatin dose level 150 mg/m^2 (n=4, cycles 40)			
	WHO grade				WHO grade			
	I	II	III	IV	I	II	III	IV
Mucositis	5	1	1					
Nausea	4	2			3	1		
Diarrhea			1			2		
Leucopenia	9	4	3		9	4	1	1
Trombopenia	25	6	2		10	5	1	1

Tumor response: All patients had measurable lesions. Eight patients completed 8 weeks of treatment until the first planned response evaluation, so four patients were lost for response evaluation and considered non-responders. Of these four patients one patient had probably progressive disease, based on clinical findings. Two patients refused further treatment after respectively 4 and 6 cycles; one of them was evaluated and had stable disease. In one patient the treatment was stopped after 5 cycles due to gastric perforation, however clinical findings indicated response. Of the 8 evaluated patients after 8 weeks of treatment, 6 patients had a partial response (PR). In none of these patients additional surgical intervention was feasible. Two patients had a stable disease(SD), resulting in an objective response rate of 50% (95% CI 22%-78%) after 8 cycles.

One patient with PR refused further treatment after the first response evaluation, she had a complete response on a repeated tumor evaluation after 2 years. The remaining 7 patients had a second evaluation after the planned total of 14 cycles. One patient had a PR after a SD in the first evaluation. Two patients with a PR in the first evaluation had evidence of ongoing PR at the time of the second evaluation. For the other 4 patients the situation between the first and second evaluation was unchanged. Thus the overall objective response rate was 58% (95% CI 31%-85%) after 14 weeks. The median survival was 11.25 months (range 1.5 –100+months).

Of the 3 patients with locally advanced surgically irresectable disease one died of tumor progression after 24 months. However the other two patients are currently still alive with no clinical evidence of disease at respectively 9 and 6 years post treatment. The first patient had a stage IIIb, intestinal type adenocarcinoma and was treated at the 150 mg/m2 dose-level (7 cycles) with an actual dose intensity of 77%, the second patient had a stage IIIb, undifferentiated adenocarcinoma and was treated at the 100 mg/m2 dose-level with an actual dose intensity of 71 % (13 cycles). Both long-term survivors received no additional treatment.

DISCUSSION

Although the incidence of gastric cancer declines it is still the world's second leading cause of cancer related death. The mainstay of treatment remains a radical surgical resection, which seems feasible in about 40 % of the patients (American Joint Committee on Cancer stagin (AJCC) stage I-III). This results in a 5 year survival of approximately 58-95% in stage I, 34-54% stage II, 20-37% stage IIIa and 8-11% stage IIIb disease (Hundahl *et al*., 2000; Karpeh *et al*., 2000). Even after apparent curative resections, local recurrences or distant metastasis occur in up to 60% of the patients. Unfortunately, most patients present with an advanced stage of disease with a dismal outcome. This group consists of patients with locally advanced surgically incurable disease (±30 %) and patients with metastatic disease (±30 %). In that situation the prognosis is worse with a median survival in case of locally advanced disease of 12-15 months and 7-10 months in case of relapsed or metastatic disease (Wilke *et al*., 1991; Rivera *et al*., 2007).

The last decade a lot of effort has been put into the development of more effective systemic therapies for those patients with advanced gastric cancer to improve quality of life and prolongate survival. At first multiple single agent regimens were tested, later much effort has been put in combination chemotherapy in order to improve response rate and survival. In these regimens 5-FU was combined with, either etoposide and leucovorin (ELF), doxorubicin and methotrexate (FAMTX) or epirubicin and methotrexate (FEMTX). These treatments resulted in response rates of approximately 50 % objective responses and 10 % complete responses with median survival rates of 8 to 11 months, but essentially no long term survivors were reported (Glimelius *et al*., 1997; Murad *et al*., 1993b; Pyrhonen *et al*., 1995; Wils *et al*., 1991; Webb *et al*., 1997a; Cascinu *et al*., 1997). Two randomized controlled trials were conducted using these 5-FU based regimens versus cisplatin and 5-FU based schedules. One study compared ELF or FAMTX versus cisplatin and 5-FU, with no significant differences in either response or survival (Vanhoefer *et al*., 2000). The other study showed higher response rates for epirubicin, cisplatin and 5-FU versus FAMTX, with comparable survival rates (Webb *et al*., 1997b). The favorable response rate of the combination of epirubicin, cisplatin and 5-FU (PELF) was confirmed in a phase II trial in a weekly schedule (Cascinu *et al*., 1997). Although high response rates do not necessarily translate into prolonged survival, they might be valuable in the neo-adjuvant setting and in the situation where a rapid palliation, for instance of obstruction problems, is required. A few years later the value of perioperative chemotherapy on survival in resectable gastric cancer was confirmed in the MAGIC trial (Cunningham *et al*., 2006).

At the moment that the weekly regimen caught our attention, the 3 weekly regimen was not yet considered standard treatment. The current study showed that the weekly CELF regimen was feasible in an outpatient setting with an acceptable toxicity at a carboplatin dose of 100 mg/m^2. Toxicity in the first three cycles of chemotherapy, limiting the dose dense intention of the schedule, was observed at a dose level of 150 mg/m^2. The MTD of 100 mg / m^{2,} induced in three cycles WHO grade III leukopenia and in two cycles grade III thrombopenia, during later cycles. Grade 3-4 toxicity data reported for the PELF regimen (13) are comparable to the data reported here. The CELF regimen showed a promising response rate of 58% (95% CI 31%-85%) comparable to the objective response rate of 62% in the phase 2 study of weekly PELF (13).

The mature data on this weekly regimen show interesting and not expected long-term event free survival of two patients in this study of respectively 9 and 6 years. Both patients had locally advanced surgically irresectable disease, one patient received 7 courses (150 mg/m^2 carboplatin) and one patient received 13 courses (100 mg/m^{2}carboplatin) of CELF. Both had a partial response after chemotherapy, and at that time it was judged that curative resection was still not feasible.

The fate of patients deemed surgically incurable is usually considered to be grim. In the era of best supportive care all patients die within 1 year after diagnosis (Glimelius *et al*., 1997; Murad *et al*., 1993b; Pyrhonen *et al*., 1995). Subsequently in the western world this group has been entered in chemotherapy studies, sometime recognizable in stratified subgroups; one or more metastasis or locally advanced disease (Cascinu *et al*., 1997; Nakajima *et al*., 1997; Waters *et al*., 1999; Kakeji *et al*., 1998; Nomura *et al*., 2001; Kunieda *et al*., 2002). In such patients an interesting 55.6 -68% 4-5 years survival have been reported in patients who were considered to be resectable after chemotherapy (Cascinu *et al*., 2004; Cascinu *et al*., 1997; Nakajima *et al*., 1997). Especially in Japanese studies local treatments (extended surgery, local chemotherapy) have been added tot these regimens (Yoshida *et al*., 2004). In this study only 3 long term survivors, after only chemotherapy, out of 643 patients were described. One of them survived more than 5 years, two others ultimately succumbed to their disease (Yoshida *et al*., 2004).

In view of our results it seems not unlikely that a subgroup of patients with especially surgically incurable, but still limited disease, not only will have palliative benefit, but may even find cure from chemotherapeutic intervention.

CONCLUSION

Long-term follow-up of this feasible phase I trial, with promising response rates, uncovered two long-term survivors. Late evaluations of studies in gastric cancer patients are uncommon however for some subgroups of patients such analyses might be worthwhile. Based on our results we therefore would like to encourage other researchers to perform late analysis of data in order to help to discover patient and tumor characteristics resulting in long-term survivorship.

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