Pegylated liposomal doxorubicin and mitomycin C in combination with infusional 5-fluorouracil and sodium folinic acid in the treatment of advanced gastric cancer: results of a phase II trial

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Mitomycin C (MMC) in combination with infusional 5-fluorouracil (5-FU) is a well-tolerated active combination therapy for advanced gastric cancer. Pegylated liposomal doxorubicin (Caelyx) has been combined with this regimen in a phase I study exhibiting promising activity in patients with upper gastrointestinal tumors. In the present study, we investigated activity and tolerability of this three-drug regimen in patients with gastric cancer. Patients with advanced or metastatic gastric cancer were recruited to receive weekly infusional 5-FU (2000 mg/m^2) mixed with sodium folinic acid (FA; 500 mg/m^2) in one pump (days 1, 8, 15, 22, 29, 36). On days 1 and 29, Caelyx (20 mg/m^2) was given as a 1-h, and MMC (7 mg/m^2) was applied as bolus injection on days 8 and 36. Treatment courses were repeated on day 57. Twenty-seven patients with a median age of 66 years were recruited in a single center; 56% had histologically proven peritoneal carcinomatosis and 26 patients are evaluable for toxicity. Common Toxicity Criteria of the National Cancer Institute grade 3 toxicity was recorded in 34% of the patients (anemia 12%, leukocytopenia 8%, febrile neutropenia 4%, thrombocytopenia 12%, nausea 15%, diarrhea 8% and mucositis 4%). One patient developed hemolytic–uremic syndrome. One complete (5%) and eight partial responses (42%) were observed in 19 patients evaluable for response according to WHO criteria. Seven patients had no change (37%) and three (16%) progressive disease. Six patients with peritoneal carcinomatosis not amenable to WHO response assessment had progression-free intervals between 8 and 21 months. Median survival for all patients was 14.7 months and median time to progression was 8.4 months. We conclude that this new three-drug combination regimen yields a promising overall response rate (47%) in patients with gastric cancer despite the inclusion of a majority of elderly patients at moderate or high risk of death in this trial. Its safety and good tolerability as established in the phase I trial was confirmed. *Anti-Cancer Drugs* 16:435–440 © 2005 Lippincott Williams & Wilkins.

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Introduction

Despite a declining incidence of about 25–30 annual cases per 100 000 people in western countries, gastric cancer still represents a major healthcare problem, accounting for 13 000 deaths in Germany in 2000 (http://www.rki.KREBS.de). It occurs more frequently in the elderly with a median age at diagnosis between 69 (men) and 73 years (women) in Germany. Once beyond the scope of curative surgery, median survival rarely exceeds 4–6 months. In this setting, palliative chemotherapy has demonstrated superiority over best supportive care in terms of quality of life and overall survival [1,2].

Nonetheless, no standard chemotherapy regimen exists. Older regimens like ELF [etoposide, 5-fluorouracil (5-FU) and folinic acid (FA)], FAMTX (5-FU, doxorubicin and methotrexate) and FUP (5-FU and cisplatin) exhibited low activity in a randomized EORTC trial with 399 patients and median survival of only 7 months [3].

In the UK, 5-FU as protracted infusion over several weeks combined with cisplatin and epirubicin (ECF) is recommended [4], since its superiority over FAMTX in terms of response rate, survival and toxicity has been shown [5]. In Germany, weekly infusional 24-h 5-FU plus FA [Arbeitsgemeinschaft für Internistische Onkologie (AIO) regimen] is frequently used as the backbone in combination regimens, e.g. with cisplatin ± anthracyclines [6,7] or mitomycin C (MMC) [8–10]. Response

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rates up to 40–50% and median overall survival of about 10 months have been reported.

Bolus 5-FU and MMC were used in the 1980s in combination with doxorubicin (FAM regimen) [11]. This combination regimen contained three of the most active drugs used in gastric cancer, but was inferior to the more toxic FAMTX regimen [12]. In an effort to deliver the former FAM regimen in a more effective manner, a phase I trial has been conducted to establish a new combination schedule by applying infusional 5-FU biomodulated by sodium FA, dose-dense MMC and pegylated liposomal doxorubicin (Caelyx) [13]. Promising activity in patients with upper gastrointestinal cancer was demonstrated and toxicity was low. The present phase II study aimed at determining the activity and tolerability of this new combination regimen in advanced gastric cancer.

Patients and methods

The study protocol was reviewed and approved by the local institutional review board, and the study was performed according to the Declaration of Helsinki as amended in Somerset West. All patients provided written informed consent.

Patients

Patients aged ≥ 18 years with histologically confirmed metastatic or locally advanced gastric cancer were eligible. Previous palliative chemotherapy was not allowed. Major inclusion criteria were: ECOG performance status 0–2, life expectancy of ≥ 3 months. Exclusion criteria were inadequate bone marrow function (leukocyte count $< 3000/\mu l$, platelet count $< 100\,000/\mu l$) and renal or hepatic insufficiency (serum creatinine > 1.4 mg/dl, serum bilirubin > 2 mg/dl). Left ventricular ejection fraction assessed by echocardiography had to be $> 50\%$. Patients with clinically suspected brain metastases were excluded. Concomitant treatment with allopurinol, dipyridamol, trimethoprim or pyrimethamin was not permitted. Patients of child-bearing potential were required to be using appropriate contraception.

Treatment schedule, toxicity and dose modification

Treatment was administered weekly for a total of 6 weeks followed by a 3-week rest period. It consisted of a weekly 24-h continuous infusion of 5-FU 2000 mg/m^2 mixed with sodium FA (500 mg/m^2) in a portable pump administered via a central venous port system. Bolus MMC was applied at a dose of 7 mg/m^2 on days 8 and 36, and Caelyx was given as a 1-h infusion on days 1 and 29 at a dose of 20 mg/m^2. Treatment courses were repeated on day 57. All patients received antiemetics (ondansetron 8 mg or tropisetron 5 mg). Dexamethasone 8 mg was added to MMC to reduce the likelihood of pulmonar toxicity, and patients received 8 mg dexamethasone and 0.5 mg clemastine i.v. prior to Caelyx infusion to prevent allergic reactions. Toxicities were recorded weekly and graded according to the Common Toxicity Criteria of the National Cancer Institute (NCI-CTC) version 2.0.

Treatment was delayed until full recovery in case of diarrhea, stomatitis, leukocytopenia, thrombocytopenia and palmoplantar dysesthesia on days 1, 8, 29 and 36. On days 15 and 22 (application of 5-FU/FA) treatment was administered if toxicity did not exceed NCI-CTC grade 1. With the exception of alopecia and nausea, NCI-CTC grade $\geq$ II led to a treatment delay until complete recovery followed by a dose reduction of 25% of all drugs. In case of higher grades of toxicity doses were reduced by 50% (NCI-CTC grade 3) or 75% (NCI-CTC grade 4). Discontinuation of MMC treatment was required in case of suspected red cell fragmentation (e.g. hemolytic–uremic syndrome) or pulmonar toxicity.

Adverse events were recorded weekly. The treatment was continued until tumor progression or unacceptable toxicities occurred.

Evaluation procedures

Before admission to the study all patients underwent a complete history, physical examination, electrocardiogram, cardiac ultrasonography and chest X-ray. A complete blood count and blood chemistry values including tumor markers (CEA, CA 72-4 and CA 19-9) were obtained within 14 days prior to the start of treatment. A computed tomography (CT) or magnetic resonance imaging (MRI) scan of the tumor-bearing region was performed within 4 weeks prior to the start of therapy. During the study period weekly blood count monitoring was performed and serum chemistry was repeated fortnightly. Left ventricular ejection fraction and tumor markers were assessed before the start of a new treatment cycle. Indicator lesions were assessed every 8 weeks by CT or MRI scan. Responses were classified according to standard WHO criteria.

Statistical analysis was performed within the full analysis set (intent-to-treat). Overall and progression-free survival was calculated according to Kaplan and Meier. The 95% confidence intervals (CIs) for survival and time to progression were calculated using the method of Brookmeier. For parameter estimation of binomial distributions the two-sided method of Clopper and Pearson was in place at a 95% level (statistical calculations were performed with the DKFZ-Statistics-Package ADAM, version 2.30).

Results

Patient characteristics

Between July 2002 and November 2003 a total of 27 patients (male $n = 17$, female $n = 10$) were enrolled in

the study on a monocentric basis. One patient died before the initiation of therapy. Patient characteristics are summarized in Table 1. The median age was 66 years (range 40–76); 56% of the patients had histologically confirmed peritoneal carcinomatosis and 48% had at least two metastatic sites, and 23% of patients had histologically confirmed peritoneal carcinomatosis without measurable lesions and were therefore not amenable to response assessment by WHO criteria.

Using the risk stratification according to clinical determinants of survival recently published by Chau *et al.* [14], 7.5% of patients in this trial were considered to be at low risk, 85% at moderate risk and 7.5% at high risk of death.

Safety and dose intensity

Twenty-six patients were evaluable for toxicity according to protocol. A total of 70 treatment courses and a median of three courses per patient (range 1–5) were administered; 77% of the patients received at least two courses. The relative dose intensities for each drug applied in Course 1 ($n = 26$ patients) and 2 ($n = 20$ patients) are shown in Figure 1. The values were [median/mean (%)]: Course 1, Caelyx 100/94, MMC 100/95, 5-FU 100/97; Course 2, Caelyx 100/87, MMC 100/87, 5-FU 100/90. The mean cumulative doses applied over all treatment cycles were Caelyx 95 mg/m^2, MMC 35 mg/m^2 and 5-FU 28 860 mg/m^2. The most frequent reasons for dose reductions were diarrhea and leukocytopenia. Two patients received only one injection of Caelyx and MMC (rapid tumor progress $n = 1$ and consent withdrawn due to nausea and vomiting $n = 1$). In eight patients (31%) therapy had to be postponed due to toxicity for a median of 10 days (range 7–42). Three patients received oxaliplatin-based second-line chemotherapy. Toxicity data are summarized in Table 2. Treatment was generally well tolerated. Eight percent of the patients developed NCI-CTC grade 3 leukocytopenia, including one patient with neutropenic fever; 12% of patients had thrombocytopenia NCI-CTC grade 3, but no bleeding episode was observed. Hematological toxicities grade 4 did not occur. The most common non-hematological toxicities grade 3 were nausea (15%), diarrhea (7%) and mucositis (4%). Seven percent experienced alopecia grade 2 and 19% of the patients reported palmoplantar dysesthesia grade 2. One female patient developed hemolytic–uremic syndrome after a cumulative dose of MMC of 63 mg/m^2. She came in need of dialysis, but died of tumor progression.

Table 1 **Patient characteristics**

	N	%
Patients enrolled	27	
male	17	63
female	10	37
Age (years) [median (range)]	66 (40–76)	
ECOG performance status		
0	3	11
1	20	74
2	4	15
Metastatic sites		
peritoneum	15	56
lymph nodes	15	56
liver	12	44
primary	9	33
pleura	4	15
lungs	3	11
other	4	15
Risk factor analysis[a]		
good risk	2	7
moderate risk	23	85
high risk	2	7

[a]The risk factor analysis was performed according to Chau *et al.* [14].

Table 2 **Worst toxicity per patient ($n = 26$) during the study period, classified according to NCI-CTC criteria (version 2.0)**

Toxicity	NCI-CTC grade (%)			
	1	2	3	4
Hematologic				
anemia	31	19	15	0
leukocytopenia	8	38	12	0
febrile neutropenia	–	–	1	0
thrombocytopenia	0	15	12	0
Gastrointestinal				
nausea/vomiting	31	27	15	0
diarrhea	35	12	8	0
mucositis/stomatitis	23	15	4	
Other				
palmoplantar dysesthesia	23	19	0	0
alopecia	19	8	0	0
pulmonal	4	0	0	0
renal[a]	0	0	0	4
allergy[b]	15	0	0	0

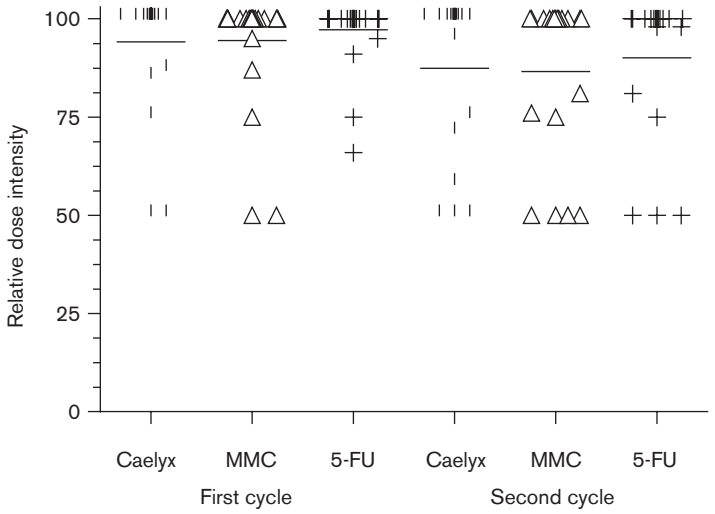
[a]Hemolytic–uremic syndrome.
[b]Following Caelyx application.

Efficacy

One patient was lost to follow-up after one treatment cycle before restaging. Therefore, 25 patients were subject to response assessments. Six patients had histologically confirmed peritoneal carcinomatosis without measurable lesions. One of these patients had a progression-free survival of 21 months and an overall survival of 25 + months. The remaining five patients had progression-free survival intervals between 8 and 14 months. Nineteen patients had bidimensionally measurable tumor masses. One complete remission was observed (5%; 95% CI 0–26%) and partial remissions were noted in eight patients (42%; 95% CI 20–67%) resulting in an overall response rate of 47%. A no-change situation was seen in seven patients (37%). Three patients (16%) had progressive disease.

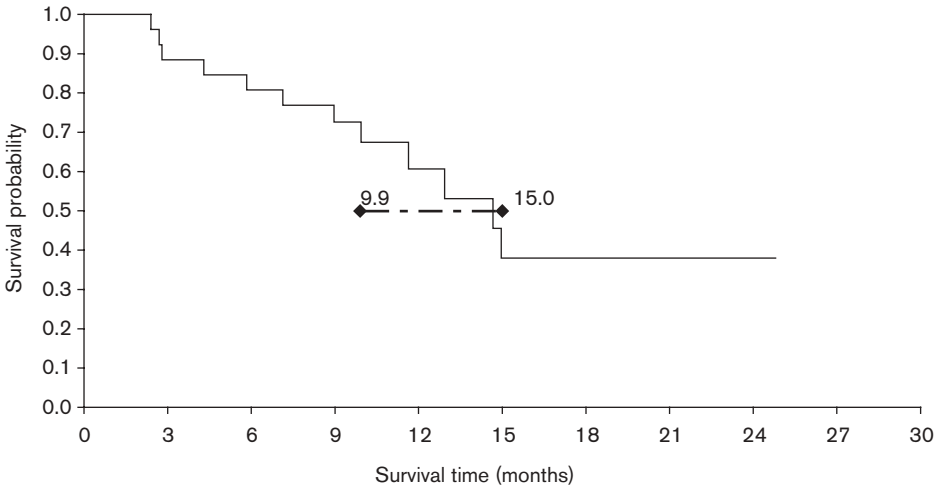
At the time of analysis (August 2004), 12 of 26 patients had died (46%). The median follow-up of surviving patients was 8 months. Median survival for the whole group amounted to 14.7 months (95% CI 9.9–15.0; range 2.4–24.8 +). Since more than half of the patients are still alive median survival is likely to become greater than the

Fig. 1



Scattergram of the relative dose intensities of Caelyx, MMC and 5-FU administered during the first and second cycle of chemotherapy. Note that in Cycle 1 two patients received a single dose of Caelyx/MMC explaining the total dose intensity of 50%.

Fig. 2



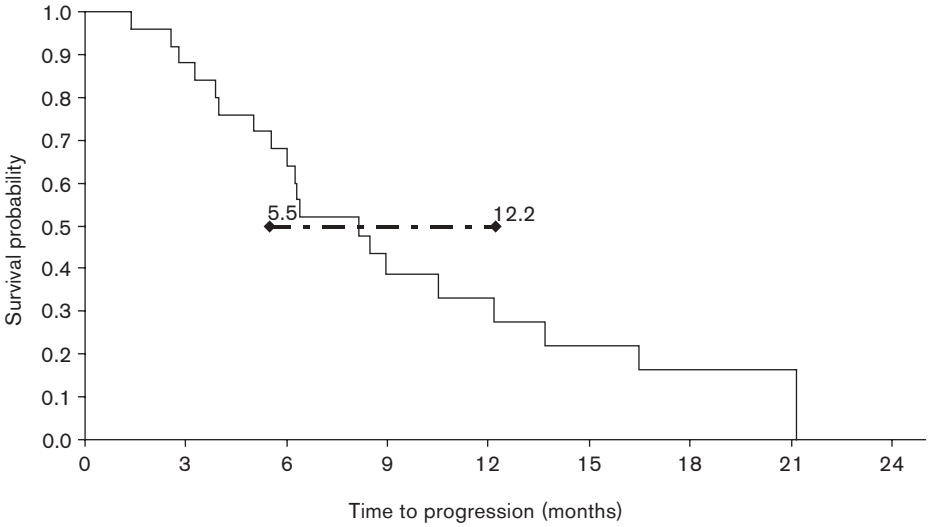
Overall survival calculated according to Kaplan–Meier for patients with advanced gastric cancer ($n=26$, 14 patients censored). Median survival was 14.7 months.

given amount (upper bound of the CI is not yet reliable). The median time to progression was 8.1 months (95% CI 5.5–12.2; range 1.4–21); 25 patients were evaluable, five were censored. The Kaplan–Meier estimates for overall survival and time to progression are shown in Figures 2 and 3.

Discussion

The results of second-generation regimen like ELF, FAMTX and FUP in gastric cancer were disappointing [3]. Third-generation regimens based on infusional 5-FU provide incremental steps forward. In the UK, protracted infusional 5-FU, cisplatin and epirubicin (ECF) serves as reference treatment given its superiority over FAMTX [5]. In Germany, weekly infusional 5-FU (2600 mg/m^2) biomodulated with FA (500 mg/m^2) has demonstrated superiority over 5-FU (3000 mg/m^2) in a randomized phase II trial [15] and serves as the backbone for third-generation combination regimen, e.g. with cisplatin or MMC [6–10]. Survival times in the range of 9–11 months have been reported with these third-generation regimens.

Fig. 3



Progression-free survival calculated according to Kaplan–Meier for patients with advanced gastric cancer ($n=25$, five patients censored). Median time to progression was 8.1 months.

Lately, there has been a move towards more aggressive treatment combining newer agents like taxanes with cisplatin in order to further improve the treatment results in advanced gastric cancer. Preliminary data of a randomized trial comparing DCF (docetaxel, cisplatin and infusional 5-FU) with FUP were presented at the ASCO meeting in 2003 [16]. The three-drug regimen significantly improved the response rate (38.7 versus 23.2%), the time to progression (5.2 versus 3.7 months) and the overall survival (10.2 versus 8.5 months). Nevertheless, the DCF was toxic with grade 3 and 4 neutropenia compromising 84% of the patients (including febrile neutropenia in 16%). Twenty-seven percent of the patients treated with DCF withdrew their consent to the study (16% in the FUP arm). Similar data were obtained in a randomized phase II trial conducted by the SAKK [17]. In 41 patients treated with docetaxel, cisplatin and infusional 5-FU in this trial, a rate of 80% patients with neutropenia grades 3 and 4 including 39% with febrile neutropenia was noted. Ten percent of the patients received granulocyte colon stimulating factor (G-CSF). The efficacy compared well with the DCF regimen: response rate was 36.6% and overall survival was 10.4 months.

Reviewing the data of both trials, it is questionable if these regimens are safe enough for routine use in patients with advanced gastric cancer, particularly since comparably younger patients were included in these two trials (median age 54 and 61 years, respectively). In view of the known reduced bone marrow function of elderly patients and given the usual median age of 69–73 years in patients with gastric cancer, highly hematotoxic regimen like DCF should be used with caution in the elderly, maybe using prophylactic G-CSF support. Feasibility trials in this patient group might be justified.

The regimen investigated in the present study (pegylated liposomal doxorubicin, MMC and infusional 5-FU/FA) was established in a previous phase I trial as a low-toxicity schedule that also meets the requirement of treatment of elderly patients. The results of the phase II study confirmed the safety data obtained with this combination in the phase I trial [13]. Thus, it may serve as an example for a comparatively low-toxic three-drug regimen for the treatment of gastric cancer. The toxicity of this regimen compares adequately with the two-drug MMC/infusional 5-FU/FA regimen which uses somewhat higher doses of 5-FU (2600 mg/m^2) and MMC (10 mg/m^2) instead of a third drug [9,10]. Of note, the palmoplantar dysesthesia—regarded as overlapping toxicity of 5-FU and pegylated liposomal doxorubicin—was noted in only 12% of the patients.

Although the response rate obtained with this regimen was in the same range as those obtained with other infusional 5-FU/FA-based regimen, the time to progression of 8.1 months and the overall survival of 14.7 months appeared to be promising. Usually, the most striking explanation for outstanding survival data observed in phase II trials is patient selection, i.e. enrolment of patients at low risk of death. Nevertheless, up until now no tools for assessing the risk of death (and the probability of good survival data) by clinical determinants have been available for gastric cancer. Recently, Chau *et al.* developed a simple prognostic index to define three risk

groups using four prognostic factors [14]: performance status ≥ 2, liver metastases, peritoneal carcinomatosis and alkaline phosphatase ≥ 100 U/l. Using this index, 92.5% of the patients in our study had poor or moderate risk of death and the median survival for the present study population would have been calculated at 7 months. Thus, the survival results of the present trial are unlikely to be attributable to mere patient selection. It may be speculated that the good tolerability allowing for the application of three different drugs at high dose intensity may lead to superior data for time to progression and overall survival.

In conclusion, the pegylated liposomal doxorubicin/MMC/infusional 5-FU/FA regimen was safe also in elderly patients in the present trial. It may serve as a well-tolerable alternative three-drug regimen. Promising survival data have been observed in this study population, exhibiting moderate to high risk of deaths in the vast majority of patients.

To define the benefit of adding pegylated liposomal doxorubicin to infusional 5-FU/FA and MMC, and to assess the real magnitude of this new three-drug regimen, a randomized trial comparing 5-FU/FA/MMC ± Caelyx is warranted.

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