Biweekly Oxaliplatin and Irinotecan Chemotherapy in Advanced Gastric Cancer. A First-line Multicenter Phase II Trial of the Arbeitsgemeinschaft Medikamentöse Tumortherapie (AGMT)

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Abstract. *Background: The aim of the study was to evaluate the feasibility and efficacy of an outpatient oxaliplatin/irinotecan chemotherapy in chemonaive patients suffering from unresectable gastric cancer. Materials and Methods: Biweekly oxaliplatin (85 mg/m^2) and irinotecan (125 mg/m^2) was chosen since it has been shown previously in colorectal cancer that oxaliplatin (85 mg/m^2) is superior to a lower dose and toxicity of irinotecan is much lower if given fractionated. The irinotecan dose below the maximum tolerated dose takes into consideration concerns about increased toxicity in gastric cancer patients. Results: Fourty-three patients with histologically proven gastric adenocarcinoma and no previous palliative chemotherapy were selected. WHO grade 3 and 4 toxicities included neutropenia in 2/43 patients, anemia in 3/43 patients, nausea in 2/43 patients and diarrhea in 4/43 patients. Response rates were assessable in 38 patients as follows: complete response in three patients (8%), partial response in 19 (50%), stable disease in 11 (29%), and progressive disease in 5 patients (13%). The median time-to-progression was 5.3 months and median overall survival was 9.5 months. Conclusion: The outpatient combination of biweekly oxaliplatin/irinotecan was well tolerated and showed a response rate within the range of other first-line combination therapies. The favorable toxicity profile, however, renders oxaliplatin/irinotecan as an alternative first-line regimen.*

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The incidence of gastric cancer is decreasing throughout the Western world but remains one of the leading causes of death from intestinal neoplasias (1, 2). Survival of patients with gastric cancer is poor, with an overall five-year survival rate of less than 20% (3, 4).

Second-generation treatment regimens for advanced gastric cancer include the following combinations: sequential high-dose methotrexate and 5-fluorouracil (5-FU)/doxorubicin (FAMTX), etoposide/doxorubicin/cisplatin (EAP), etoposide/leucovorin/5-FU (ELF) and epirubicin/cisplatin/5FU (ECF) (5-8). A comparison of FAMTX, ELF and cisplatin/5-FU in patients with advanced gastric cancer showed a realistic response rate between 21% and 27%, with a median survival of 6-8 months (5, 7). Chemotherapy, however, has been shown to provide a significant benefit in the quantity and quality of life over best supportive care alone (9).

Several agents and their combinations have recently emerged as potential new options for treatment of advanced gastric cancer. The REAL-2 trial showed that in the ECF regimen, 5-FU can be substituted by capecitabine, and cisplatin can be substituted by oxaliplatin with equivalent efficacy and better tolerability (10). High response rates and prolongation of median survival compared to 5-FU/cisplatin have been reported recently (11) for the triple combination of 5-FU, cisplatin and docetaxel (DCF). These regimens, however, show considerable toxicities and are not suitable for every patient. Development of new treatment regimens is therefore warranted.

Irinotecan and oxaliplatin do not exhibit cross-resistance and proved clinically active in the treatment of gastric cancer patients, both as monotherapy and in combination with 5-FU. The synergism between topoisomerase I inhibitors and platinum salts was found to be due to the stabilization of

DNA-platinum adducts, when cells were exposed to the topoisomerase I inhibitors after the platinum compound. Furthermore, the clinical experience with both drugs as single agents has shown a nonoverlapping toxicity profile.

The activity of oxaliplatin in combination with 5-FU and folinic acid as first-line treatment in advanced metastatic gastric cancer was demonstrated with a response rate of 46% and a good safety/efficacy ratio (12). Irinotecan has been administered to patients with advanced gastric cancer, both as a single agent and in combination with 5-FU or cisplatin (5). In two independent single-center phase I trials which were conducted simultaneously with an identical design in patients with advanced gastrointestinal malignancies, including gastric cancer, the combination of oxaliplatin/ irinotecan was shown to be feasible. The recommended dose for subsequent phase II studies was 85 mg/m^2 for oxaliplatin and 200 mg/m^2 for irinotecan, administered every three weeks (13, 14).

The aim of the study was to evaluate the feasibility and efficacy of an outpatient oxaliplatin/irinotecan chemotherapy in chemonaive patients suffering from unresectable gastric cancer.

Patients and Methods

Patient characteristics. From 2001 until 2005, 43 patients with inoperable locally advanced or metastatic, histologically proven gastric adenocarcinoma were included. Major inclusion criteria were measurable or evaluable disease, age above 18 years, WHO performance status ≤2, signed informed consent, no previous palliative chemotherapy and/or immunotherapy, negative pregnancy test for women with childbearing potential, and sufficient hematological renal and hepatic function. Major exclusion criteria included pregnancy or breast-feeding, concomitant antitumoral treatment, prior adjuvant chemotherapy with oxaliplatin and/or irinotecan, prior history of chronic enteropathy, chronic diarrhea, unresolved bowel obstruction/ subobstruction, or extensive abdominopelvic radiation therapy, peripheral neuropathy (NCI CTC ≥ grade 1) and other uncontrolled serious nonmalignant diseases.

Treatment. Oxaliplatin (85 mg/m^2) was diluted in 5% dextrose and administered intravenoulsy (*i.v.*) over two hours. Irinotecan (125 mg/m^2) was diluted in 0.9% NaCl and intravenously administered over 30 minutes immediately after oxaliplatin. The chemotherapy was repeated every two weeks (1 cycle=4 weeks) until disease progression or unacceptable toxicity for a maximum of six cycles. Dose modification was made according to the worst toxicity observed. Oxaliplatin or irinotecan were decreased to 75 mg/m^2 or 100 mg/m^2 respectively in case of NCI Grade 3 or 4 neutropenia or thrombocytopenia, or NCI Grade 3 diarrhea or stomatitis, or other NCI Grade 3 major organ drug-related toxicity. Oxaliplatin dose was also reduced at next cycle according to the sensory peripheral neuropathy observed after a given cycle. Re-escalation to the starting level was not permitted. If treatment was delayed for more than 4 weeks, the patient dropped out of the study for toxicity.

Concomitant medications for the treatment of delayed diarrhea (onset >24 hours from the end of irinotecan infusion) were encouraged. The recommended antidiarrheal treatment consisted of high doses of loperamide (4 mg for the first intake and then 2 mg every 2 hours). Atropine (0.2 mg) was administered prior to irinotecan to prevent acute cholinergic syndrome.

All patients provided written informed consent before any study procedure, the trial was performed in accordance with the Declarations of Helsinki and approved by the local Ethical Committee.

Study objectives and evaluation. The primary objective of this multicenter open-labeled phase II trial was to evaluate its safety and feasibility. Secondary objectives were objective response rates, time to progression (TTP), and overall survival (OS). For this purpose, hematological and non-hematological toxicities were recorded according to the NCI-CTC criteria (http://ctep.cancer.gov/reporting/CTC-3.html). Response was evaluated according to the WHO criteria (15).

Results

Patients (n=43) with histologically proven unresectable and/or metastatic gastric adenocarcinoma and no previous palliative chemotherapy or immunotherapy were treated in four centers. The median age was 61 years (range 32-81 years) and the male/female ratio was 24/19. Eleven patients had a PS 0 and 32 patients had a PS of 1 or 2. Five patients presented with locally advanced cancer, 19 patients had a single metastatic site, and 19 patients had multiple metastases. Adjuvant radiochemotherapy was administered in four patients (Table I).

This chemotherapy was generally well tolerated. Frequently reported adverse events (more than 20% of patients) were WHO grade 1 or 2 and included neutropenia (44% of patients), thrombocytopenia (30% of patients), anemia (77% of patients), nausea (67% of patients), diarrhea (51% of patients), and alopecia (35% of patients). WHO grade 3 and 4 toxicities included neutropenia in 2/43 patients, anemia in 3/43 patients, nausea in 2/43 patients, and diarrhea in 4/43 patients. Five patients were withdrawn from the study due to treatment related toxicities (asthenia, nausea, reversible renal failure and diarrhea). Sensory neuropathy occurred only as grade 2 in 14% of patients. No grade 3/4 neurotoxicity was observed (Table II). Dose intensity was 93.1% for oxaliplatin and 93.7% for irinotecan.

A total of 38 patients were assessable for response, with three patients (8%) showing a complete response (CR), 19 patients (50%) showing a partial response (PR), 11 patients (29%) showing a stable disease (SD), and five patients (13%) showing a progressive disease (PD). Overall, 87% of patients gained a clinical benefit. The median TTP was 5.3 months and the median OS was 9.5 months (Figures 1 and 2). Best response was achieved after 8.4 weeks.

Nineteen patients (44%) received second-line chemotherapy after progression. Most of the regimens were 5-FU-based, while four patients received taxane-containing regimens.

Table I. *Patient characteristics*.

Characteristic	No. of patients
No. of patients	43
Male/female	24/19
Age (years)	
Median	61
Range	32-81
ECOG performance status	
0	11
1-2	31
Not determined	1
No. of metastatic sites	
Single	19
Multiple	19
Site of disease	
Liver	13
Lung	13
Lymph nodes	6
Bone	4
Other	15
Previous chemotherapy	
Adjuvant <6 months	4
Adjuvant >6 months	1
Previous radiotherapy	5
LDH (mg/dl)	
Median	174
Range	85-1490

LDH, Lactate dehydrogenase.

Table II. *Most frequent adverse events (43 assessable patients)*.

	NCI-CTC Grade (%)	
Adverse event	3	4
Neutropenia	2	2
Thrombopenia	-	-
Anemia	7	-
Nausea/Vomiting	2	2
Diarrhea	7	2
Hand-foot syndrome	-	-
Neurotoxicity	-	-
Alopecia	-	-
Stomatitis	-	-
Other	7	4

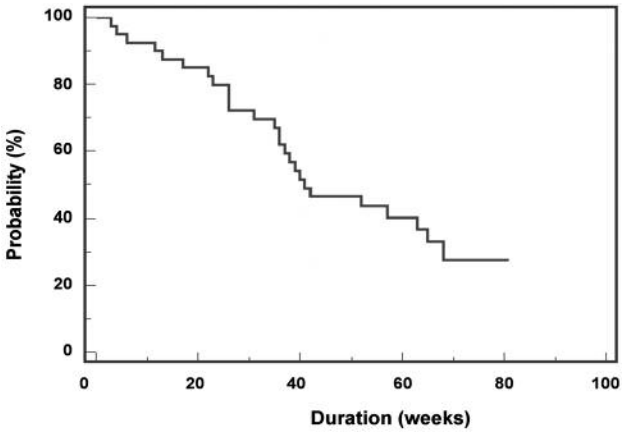

Figure 1. *Kaplan-Meier plot of overall survival*.

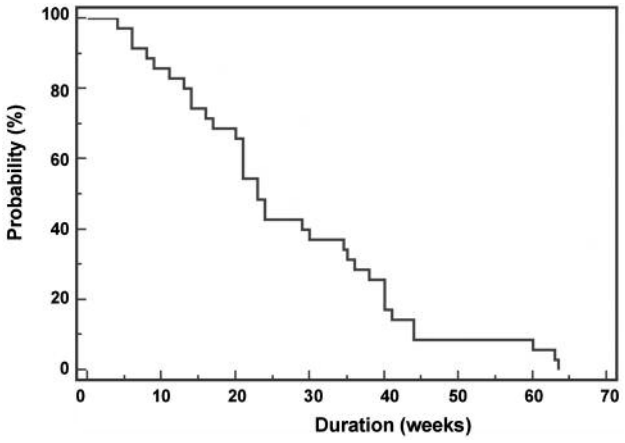

Figure 2. *Kaplan-Meier plot of progression-free survival*.

Discussion

Based on the results of a previously performed phase I study in patients with advanced digestive malignancies (16), we chose the biweekly regimen of oxaliplatin (85 mg/m^2) and irinotecan (125 mg/m^2) for the present phase II trial. The biweekly regimen of oxaliplatin (85 mg/m^2) proved to be superior in colorectal cancer as compared to that with a lower dose (17). As far as irinotecan is concerned, less toxicity was observed if given fractionated into two doses (18). Furthermore, administration of irinotecan one dose level below the maximum tolerated dose (MTD) takes into consideration concerns of increased toxicity of irinotecan in gastric cancer as compared to colorectal cancer (19). To date, only one study investigated the combination of irinotecan and oxaliplatin in this patient setting. Using a three-weekly interval, however, similar response rates were obtained with a somewhat higher toxicity rate (20).

In the present study, the biweekly regimen of oxaliplatin/irinotecan was very well tolerated. The rate of WHO grade 3/4 toxicities was very low. In particular, severe diarrhea and

neurotoxicity were rare, which renders this regimen as an ideal outpatient chemotherapy. A high overall dose intensity was achieved for both drugs.

The study population had very poor prognostic features, with 74% of the patients presenting in PS 1 or 2 and 88% of the patients presenting with metastatic disease. With respect to these features, the response rates are encouraging. Both the median OS of 9.5 months and the median TTP of 5.3 months are well within the range of other first-line regimens. In contrast to other first-line chemotherapy protocols, however, our protocol proved to be superior in terms of toxicity and tolerability. The fact that almost half of the patients received second-line treatment supports this view.

In conclusion, the low toxicity profile, the patient convenience and the favorable response rates favor the biweekly combination of oxaliplatin and irinotecan as a promising first-line regimen. In view of its toxicity profile, this regimen warrants further assessment in combination with a molecular targeting agent. We are currently investigating this protocol together with cetuximab, an EGFR-targeting monoclonal antibody.

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