A Phase II Trial of Weekly Irinotecan in Cisplatin-refractory Esophageal Cancer

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Abstract. *Background: This study investigated the efficacy and toxicity of weekly single-agent irinotecan in patients with metastatic disease relapsing after cisplatin-based chemotherapy. Patients and Methods: Fourteen patients were enrolled. A total number of 29 cycles (one cycle consisted of CPT-11 100 mg/m^2 on days 1, 8, 15, qd 28) were applied. Irinotecan was continued until disease progression or unacceptable toxicity occurred. Where toxicity was less than WHO grade 3, the dose of irinotecan was escalated in 20 mg steps in subsequent cycles up to a maximum dose of 140 mg/m^2. Patients were assessed for response according to WHO criteria every second cycle. Results: Of the 13 evaluable patients, 2 achieved a partial response (PR) and 3 disease stabilisation (NC); progressive disease (PD) was noted in 8 patients. Median time to progression was 2 months (range: 1-8 months) and median survival from start of study treatment was 5 months (range: 2-16 months). Grade 3 toxicity consisted of diarrhea (n=3), fever (n=1) and pain (n=1). Conclusion: Single-agent irinotecan has moderate activity in cisplatin-refractory esophageal cancer.*

The incidence of esophageal carcinoma has been rising in the Western world in the past few decades (1). Affected patients are mostly diagnosed at advanced stages with lymph node involvement or distant metastases. At the time of diagnosis, about 75% of the patients suffer from UICC stage III or IV disease (2). Despite multidisciplinary approaches with extensive surgical treatment, including neoadjuvant approaches containing chemo therapy and chemoradiotherapy, local and distant recurrences are common. Metastatic esophageal carcinoma is still an incurable disease with a median survival time ranging from 4 to 8 months (3).

5-Fluorouracil (5-FU)- and cisplatin (DDP)-based combination regimens are established as first-line chemotherapy for advanced or metastatic esophageal and gastroesophageal junction cancer, with response rates reported between 23% and 65% (4-6). Patients with progression or relapse after initial treatment have a dismal prognosis.

Irinotecan (CPT-11) has shown promising activity in a number of gastrointestinal malignancies, including esophageal cancer (7, 8). Irinotecan is a prodrug that is converted *in vivo* to the active metabolite SN38, which acts as a DNA topoisomerase I inhibitor (9, 10). In chemotherapy-naive patients with metastatic esophageal carcinoma, a 57% objective response rate has been achieved with weekly irinotecan plus cisplatin (11). Median survival was 15.2 months. Similar response rates were observed for patients with adenocarcinoma and squamous cell carcinoma (11). Single-agent irinotecan in pretreated patients with adenocarcinoma of the esophagus and gastric cardia was applied in 7 patients, resulting in one complete remission and 5 disease stabilisations (12).

Due to the intensity of their pretreatment and their life style most patients with metastatic or locally advanced esophageal cancer who may be suitable for second-line chemotherapy have a reduced performance status. Thus, single-agent chemotherapy preferably given in the outpatient setting appears to be a reasonable approach. This phase II study assessed the antitumor activity and toxicity of irinotecan in pretreated patients with metastatic or locally relapsed esophageal cancer. Irinotecan was applied weekly for three weeks, followed by one week's rest. The irinotecan dose was planned to be escalated intraindividually from 100 mg/m^2 to 140 mg/m^2 in 20 mg steps as long as no severe toxicity occurred.

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The main objective of the study was to determine the overall response rate to irinotecan as second-line therapy in patients with esophageal cancer. Secondary objectives were progression-free survival, 1-year survival rate and the assessment of the toxicity.

Patients and Methods

This phase II trial was conducted between May 2001 and January 2004 at Tübingen University Hospital, after approval by the local ethical committee. All patients were informed of the investigational nature of this study and had provided written informed consent.

Eligibility. Main inclusion criteria were as follows: patients with histologically proven, measurable metastatic or locally advanced esophageal adeno- or squamous cell carcinoma, tumor progression during or after previous chemotherapy with cisplatin and 5-FU; age >18 years; WHO performance status ≤2 and a life expectancy of at least 3 months.

Other inclusion criteria consisted of pretreatment neutrophil count ≥2000/μl, platelet counts ≥100000/μl, haemoglobin level ≥10 g/dl, total serum bilirubin level <2 x upper normal value.

Patients were excluded if they had secondary malignancies, except for skin basalioma or carcinoma *in situ* of cervix uteri, symptomatic tumor infiltration of the trachea or presence of tracheoesophageal fistula, serious or uncontrolled concurrent medical illness, pretreatment with irinotecan, chronic diarrhoea, unresolved bowel obstruction or inflammatory bowel disease. Pregnant or breast-feeding women were also excluded from this trial.

Treatment protocol. Patients were treated with irinotecan 100 mg/m^2 as an intravenous infusion over 30 minutes given on days 1, 8, and 15 every 4 weeks. The irinotecan dose was intraindividually escalated from 100 mg/m^2 to 140 mg/m^2 in 20 mg/m^2 dose steps in following cycles in the absence of grade 3/4 toxicity during the previous cycle. Occurrence of grade 3 or 4 toxicity led to a dose reduction by 20 mg/m^2 to a minimum dose of 80 mg/m^2 in the subsequent cycle. Treatment was continued when neutrophil counts had recovered to >2000/μl, platelet counts to ≥75000/μl and non-haematological toxicity was <grade 2.

All patients received prophylactic antiemetic therapy with 5-HT_3 receptor inhibitors. In the first cycle, no prophylactic treatment was recommended for early diarrhoea and/or cholinergic syndrome. If severe cholinergic symptoms occurred during or after the irinotecan infusion, 0.25 mg atropine was applied *s.c.* in all subsequent cycles. Specific guidelines for the treatment of delayed diarrhoea were provided. Loperamid 2 mg *p.o.* every 2 h was started at the first occurrence of liquid stool for at least 12 h and up to 12 h after the last episode of diarrhoea for a maximum of 48 h. Admission to the hospital for parenteral rehydration was recommended if diarrhoea persisted for more than 48 h and in case of febrile neutropenia.

Evaluation of response and toxicity. The principal objective of the trial was to assess the therapeutic activity of irinotecan in patients with advanced osephagus carcinoma prior exposure to platinum-based chemotherapy. The principal end-point was an objective response to treatment, as defined by the WHO criteria (13). For patients presenting with an objective response, the duration of response was assessed.

The secondary objective was to characterize the safety of irinotecan. Adverse drug reactions were graded according to the International "World Health Organisation Criteria" (14).

All patients were assessed prior to treatment by physical examination, blood cell counts, CEA levels, biochemical profile, baseline toxicity evaluation and endoscopic gastroscopy. Tumor measurement was performed using chest X-ray, ultrasound and CT-scans. Physical examination, performance status, subjective symptoms and all adverse reactions, blood cell counts and biochemical profile were obtained prior to each treatment cycle. Tumor size was measured after every second treatment cycle and 4 weeks after cessation of treatment using the above methods.

Treatment was continued until the occurrence of progressive disease, unacceptable toxicity, delay for more than 10 days or withdrawal of consent. Duration of response was defined as the interval from the onset of response until disease progression.

Statistical analysis. The trial was conducted as an open label, non-comparative phase II study. A Simon two-step design was used with an Alpha of 0.1 and a Beta of 0.1. The hypothesis for response rate was a P0 of 10% and a P1 of 30%, respectively. The calculated total number of patients was 25 patients with 14 patients in step 1 and 11 patients in step 2, respectively. The trial may be discontinued with 16 patients according to the following stopping rule: if <1 response, stop, no further evaluation; if ≥1 response, stop, conclusion further evaluation required; otherwise, continuation until 25 patients are evaluable (15).

Exact 95% confidence intervals (CI) around the observed response rate were calculated from the binominal distribution. The Kaplan-Meier method was used to determine overall and progression-free survival distributions (16). The overall survival calculation used death – defined as the interval from the date of study until death (or last contact if the patient was still alive) – due to any cause as endpoint. Progression-free survival (PFS) was measured from the start of the treatment until disease progression or death from any cause. The duration of response was defined as the interval from the onset of response until evidence of disease progression.

Results

Fourteen patients, 13 male and one female, were enrolled. The median age was 57 years (range: 32-72 years). Five patients had a WHO performance status of 0 and 9 patients of 1. Seven patients had a histology of adenocarcinoma and 7 squamous cell carcinoma. All patients had been pretreated with cisplatin-based chemotherapy with a median of 4 cycles (range: 2-10). Median time-to-progression after cisplatin-based first-line therapy was 13 months (range: 1-31 months).

Primary tumor resection had been performed in five patients. Nine patients had been treated with chemoradiotherapy prior to study inclusion with a median dose of 43 Gy (range: 8-65 Gy).

At the start of the protocol, all patients had metastatic disease. Sites of metastases included lymph nodes in 8 patients, the lungs in 8 patients, liver in 5 patients, bone in 2 patients, and other sites n=8. A single patient had only one metastatic site, 7 patients had two and 6 patients had three or

more.*Toxicity.* A total number of 29 cycles with a median of 2 (range: 1-4 cycles) per patient were applied. Dose escalations of irinotecan up to a maximum dose of 120 mg/m^2 were performed for 6 patients. Toxicity related dose modifications were made for 3 patients.

The most common hematological side-effect was anemia; however, only a single patient developed grade III anemia. Grade III non-hematological side-effects were observed with diarrhoea (n=3), fever (n=1) and grade IV hypercalcaemia (n=1). Detailed information on side-effects is given in Table I.

Response evaluation. Of 13 evaluable patients, two (15%) attained a partial remission. The response durations were 2 and 4.5 months. Disease stabilization was observed in three patients lasting for 4, 4 and 8 months respectively. Eight patients had progressive disease at the first response evaluation.

Median progression-free survival was 2 months (range: 1-8 months; 95% CI: 1.8-2.2 months). Median overall survival was 5 months (range: 2-16 months; 95% CI: 1.5-8.5 months) and the 1-year survival rate was 16%.

Table I. *Treatment-related toxicity (n=14 pts).*

Definition of toxicity	No. of patients		
	Grade I/II	Grade III	Grade IV
Anemia	3	1	0
Leukocytopenia	3	0	0
Infection	1	0	0
Diarrhoea	5	3	0
Constipation	2	0	0
Nausea	4	0	0
Vomiting	2	0	0
Fatigue	4	0	0
Fever	1	1	0
Pain	6	0	0
Anorexia	4	0	0
Dizziness	2	0	0
Paresthesia	1	0	0
Cough	3	0	0
Dyspnea	1	0	0
Hypercalcaemia	0	0	1

Discussion

Palliative chemotherapy in patients with metastatic esophageal cancer is frequently limited by a reduced performance status, malnutrition and accompanying medical problems. New drugs, such as taxanes, gemcitabine or oxaliplatin, have shown promising activity in previously untreated patients (17-19). In a phase II study, the combination of weekly cisplatin plus irinotecan as a first-line therapy yielded in objective responses in 20 of 35 patients (57%), including two complete remissions, with similar efficacy in adeno- and squamous cell carcinoma. The median overall survival was 14.6 months (20).

No data are available regarding the benefit of second-line chemotherapy in metastatic esophageal carcinoma pretreated with a cisplatin-based regimen. In the current study, using weekly single-agent irinotecan a partial remission rate of 15% and disease stabilisations in 23% of patients were determined.

In a pilot study from Mühr-Wikenshoff *et al.* (21), thirteen patients with unresectable esophageal carcinoma were treated with single-agent irinotecan (125 mg/m^2 x 6). Eight out of the 13 patients were pretreated by surgery, radio-, or chemotherapy. Nine patients were evaluable for response. Response rates and survival data were comparable with this series. Two patients achieved a partial response (22%) and two others a disease stabilization (22%). The median time-to-progression was 3.8 months and the median overall survival 6.1 months. At present, the available results indicate no major difference in response rates or survival data of patients with esophageal adenocarcinoma or squamous cell carcinoma treated with irinotecan (21). WHO grade III (n=10) and grade IV (n=3) toxicity included diarrhoea, neutropenia and vomiting.

Despite the intensive pretreatment, WHO grade III/IV side-effects were rarely seen in the present phase II trial. The starting dose of irinotecan at 100 mg/m^2 was lower compared to the trial of Mühr-Wikenshoff *et al.* Planned dose escalations of irinotecan were only performed in 6 patients to a maximum of 120 mg/m^2.

Conclusion

The topoisomerase I-inhibitor irinotecan showed at least moderate activity in pretreated cisplatin-refractory patients with esophageal carcinoma.

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