Weekly high-dose 5-fluorouracil as a 24-h infusion and sodium folinic acid (AIO regimen) plus irinotecan in patients with locally advanced nonresectable and metastatic adenocarcinoma or squamous cell carcinoma of the oesophagus: a phase II trial

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In the majority of patients with oesophageal carcinoma, curative treatment proves to be impossible when diagnosis was established; therefore, most of the patients are candidates for palliative chemotherapy. The aim of this phase II study was to evaluate the efficacy and safety of 5-fluorouracil/folinic acid (AIO regimen) plus irinotecan in patients with locally advanced or metastatic carcinoma of the oesophagus. The methods used a prospective phase II trial, start: November 2002; patients: *n*=25; chemotherapy: irinotecan (80 mg/m^2) as a 1-h infusion and 5-fluorouracil (2000 mg/m^2) with sodium folinic acid (500 mg/m^2) as a 24-h infusion on days 1, 8, 15, 22, 29 and 36, repeated on day 57. Last date of evaluation: 28 February 2007; *n*=24; adenocarcinoma: *n*=13, squamous cell carcinoma (SCC): *n*=11; UICC III/IV: 3/21; grading G1/G2/G3/G4: 0/8/12/4; median age: 58 years (range 44–75); men/women: 19/5; Eastern Cooperative Oncology Group index 0/1/2: 3/17/4; applications: 460. Higher-grade toxicity: grade 3 diarrhoea: *n*=2, grade 4 diarrhoea: *n*=1, grade 4 vomiting: *n*=1, grade 4 nausea: *n*=1, grade 3 fatigue: *n*=1, grade 3 hyponatraemia: *n*=2, grade 4 elevation of creatinine: *n*=1, thrombosis of the vena subclavia: *n*=1, ischaemic lesion of the brain stem: *n*=1. Three patients died after two chemotherapeutic applications because of high tumour burden. Evaluable for response: *n*=19. Partial response: *n*=8 (33%), stable disease: *n*=9 (38%), progressive disease: *n*=2 (8%), not evaluable: *n*=5 (21%). Time-to-progression: 6.6 months (range 1.6–24.6). Total median survival: 13.6 months (median survival of adenocarcinoma: 20.3 months, median survival of SCC: 10.0 months). Secondary resection (R0): *n*=3. In oesophageal carcinomas, the AIO regimen plus irinotecan is excellently manageable as an outpatient treatment and shows efficacy in adenocarcinomas and SCCs of the oesophagus. *Anti-Cancer Drugs* 20:165–173 © 2009 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Oesophageal cancer represents the sixth leading cause of cancer death worldwide [1]. About 400 000 new cases are recorded each year, 80% of them in developing countries [2]. In 2007, the estimated numbers of new cases of oesophageal cancer in the United States will reach 15 560, and it is estimated that approximately 13 940 patients will die because of their disease [3].

Squamous cell carcinoma is the most common tumour type within the context of oesophageal malignancy. In Western industrial countries, however, a clearly elevated incidence rate of oesophageal adenocarcinomas has been observed in the last 20 years, mainly among the male population [4,5]. Adenocarcinoma of the oesophagus has had the most rapid rate of increase of any solid tumour malignancy [6], accounting for 40–50% of the oesophageal tumours in some regions of the Western world [7], thus even surpassing the incidence rate of squamous cell carcinoma [8].

In adenocarcinomas of the distal oesophagus an epidemiological correlation between gastro-oesophageal reflux and the rising incidence of these carcinomas is observable, accounting for an eight times higher risk among persons with a symptomatic reflux disease [9]. Barrett's

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oesophagus presents a facultative 'precancerous' stage for developing adenocarcinomas; its yearly rate of mutation into neoplasia amounts to approximately 0.5% [10]. In the industrialized countries, risk factors such as alcohol abuse and nicotine consumption are verifiable in 90% of the patients presenting with squamous cell carcinoma [11].

The average age for developing a squamous cell carcinoma is 55 years, thus being significantly lower than the average age of patients developing an adenocarcinoma (approximately 63 years) [12]. In most regions the incidence of oesophageal cancer is higher for the male population. In France, for example, the incidence in terms of male versus female is 6.5 : 1.0; in some high-risk regions of Asia, however, it is almost balanced (e.g. Linxian County, Henan, China: 1.5 : 1.0) [2,13].

Owing to a frequently delayed manifestation of symptoms combined with an early haematogenous and lymphogenous metastatic disease, a nonresectable stage, which is either locally advanced or metastatic, is present in more than 50% of patients at diagnosis [14]. Forty to 54% of the patients who underwent primary resection were defined as belonging to the UICC stage III category (T3/4, N1, M0) [14–17], so that despite secondary resection (R0 resection), 5-year overall survival could only be achieved in 10–15% of these patients [18]. The 5-year overall survival of all tumour stages is accordingly unfavourable; however, an increase from an initial 4% in the 1970s to nearly 14% could be attained now [14,19].

Thus, it is evident that the prognosis of oesophageal carcinoma is decisively dependent on the tumour stage. Although earlier, but rarer, tumour stages (UICC stage I and II) still imply the option of curative resection, the treatment most required in oesophageal carcinomas of UICC stage IV is a purely palliative approach. The treatment methods include radiotherapy alone, chemotherapy and combined radiochemotherapy or local endoscopy or radio-oncology procedures (e.g. afterloading). The median survival time of metastatic oesophageal carcinoma patients generally amounts to less than 6 months [20]; under palliative chemotherapy treatment based on diverse combination schedules it still amounts to less than 12 months [21].

In the range of chemotherapy treatment, cisplatin-based regimens, in particular, have been applied with palliative intent worldwide. Response rates of up to 35% have been achieved by means of combined cisplatin and 5-fluorouracil (5-FU) as a continuous infusion [22,23], albeit at the price of high-grade side effects, for example, in the form of grade 3–4 toxicity (14% of haematological toxicities and up to 27% of nonhaematological toxicities) [23]. Further trials combined cisplatin with paclitaxel, thus achieving response rates of up to 43%, whereas haematotoxic side effects [National Cancer Institute Common Toxicity Criteria (NCI-CTC) grade 4] occurred in 31% of the patients [24]. Furthermore, agents such as the anthracyclines doxyrubicine or epirubicine (ECF) and mitomycine (MCF) [25] as well as etoposid [26], each combined with cisplatin and 5-FU, have been applied. In more recent trials, cisplatin has been replaced by oxaliplatin, and 5-FU by capecitabine [27,28]. In further promising phase II trials, irinotecan has been administered combined with either cisplatin [29] or docetaxel [30,31] to treat oesophageal carcinomas.

Irinotecan is a topoisomerase inhibitor, which leads to ruptures of single DNA strings. In a phase III trial the combined regimen of 5-FU/folinic acid (AIO schedule) plus irinotecan has led to excellent results in terms of both efficacy and tolerance in the treatment of metastatic colorectal cancer [32]. Furthermore, irinotecan has also proved to be an active agent for oesophageal and gastric cancer in some early phase II trials [33,34].

In view of this background, this phase II trial for palliative first-line treatment of locally advanced or metastatic oesophageal carcinomas aims at assessing a treatment schedule consisting of 5-FU/sodium folinic acid as a 24-h infusion (AIO schedule) combined with irinotecan. The objective of this trial is to evaluate whether the chosen combination of cytostatic drugs offers an effective palliative combination treatment with only minor toxic side effects.

Patients and methods

Patients

From November 2002 to August 2006 a total number of 25 patients with either locally advanced or metastatic adenocarcinomas or squamous cell carcinomas of the oesophagus (UICC stage III or IV) were enrolled into the prospective present phase II trial. Previously, the cancerous disease had been defined as 'inoperable' by the daily interdisciplinary tumour board of Erlangen University. The assessment period terminated on 28 February 2007.

Before treatment a physical examination was carried out and a comprehensive medical history compiled. Laboratory tests comprising blood count, serum analysis, coagulation test and tumour marker determination (carcinoembryonic antigen, carbohydrate antigen 19-9, squamous cell carcinoma antigen), as well as a computed tomography of both the chest and the abdomen completed the initial examination.

Inclusion and exclusion criteria

Inclusion criteria were an advanced tumour stage (UICC stage III or IV), a sufficient performance status (Eastern Cooperative Oncology Group, ECOG, index 0–2) as well as sufficient renal and liver function (serum creatinine ≤ 2.0 mg/dl or bilirubin ≤ 2.0 mg/dl, respectively), and adequate bone marrow function (defined as leukocytes

3500/μl or thrombocytes 100 000/μl). The age ranged from 18 to 75 years. Furthermore, at least one two-dimensional lesion with a maximum diameter of ≥ 20 mm, measurable by radiological imaging procedures, had to be present.

Exclusion criteria comprised hypersensitivity related to 5-FU, sodium folinic acid or irinotecan and earlier systemic chemotherapy alone, a second malignancy or evidence of cerebral metastases, chronic diarrhoea, chronic inflammatory bowel disease or subtotal bowel obstruction. Neoadjuvant chemoradiotherapy with 5-FU and cisplatin was not defined as an exclusion criterion. The monocentric trial was approved by the Local Ethics Committee of Erlangen University. Before admission to the trial, patients were informed about the contents, aims and risks of the trial. Subsequently, written informed consent was obtained from each patient.

Chemotherapeutic regimen

Before palliative first-line treatment, a Port-a-Cath was surgically implanted through the cephalic vein. For palliative first-line treatment, the patients received in outpatient care 80 mg/m^2 irinotecan as a 1-h intravenous infusion followed by 2000 mg/m^2 5-FU combined with 500 mg/m^2 sodium folinic acid as a 24-h infusion (AIO regimen) through a miniature pump system (FOLFusor, Baxter Germany GmbH, München-Unterschleißheim, Germany) applied on days 1, 8, 15, 22, 29 and 36. This procedure was repeated on day 57. One cycle comprised six applications followed by 2 weeks of rest.

Treatment was continued until tumour progression, unexpected toxicity or necessary measures, such as surgical intervention with secondary resection. As a prophylactic antiemetic, 1 mg granisetron (Kevatril, Roche Pharma AG, Grenzach-Wyhlen, Germany) was applied intravenously before every treatment. If, during the course of treatment, NCI-CTC toxicity $\geq$ grade 2 occurred, the antiemetic treatment was intensified by applying 8 mg of dexamethasone (Fortecortin, Merck Pharma GmbH, Darmstadt, Germany) intravenously. In addition, 0.25 mg atropine was given subcutaneously to avoid an acute cholinergic syndrome. In case of diarrhoea, the patient was instructed to take loperamide (Imodium; Janssen-Cilag, Neuss, Germany) as a standard treatment in accordance with the predefined guideline recommendations.

Evaluation and toxicity

Each week the patients were asked whether side effects had been observed and laboratory tests were carried out. Toxic side effects were categorized in accordance with the NCI-CTC. If, during the course of treatment, a CTC toxicity $\geq$ grade 2 occurred, treatment was interrupted for 1 week or up to recovery (i.e. NCI-CTC toxicity grade 1), respectively. In the event of repeated higher-grade toxic side effects (CTC toxicity ≥ 2), a dose reduction of 25% was administered. After terminating a therapeutic cycle, that is, after every 8 weeks, treatment response was checked by using imaging procedures (generally by computed tomography) and by a tumour marker control.

The response rate was defined in accordance with the valid WHO criteria, with a complete response (CR) being achieved when all target lesions had disappeared. A partial response (PR), in contrast, implied the reduction of the total diameter of all target lesions by at least 50% compared with the total diameter of all target lesions calculated before initiating treatment. The change of measured tumour markers had to be confirmed by repeated tests performed at least 4 weeks after the initial checks in order to be categorized as PR or CR. Progressive disease (PD) was defined as a 25% increase of the total diameter of all target lesions. Stable disease (SD) was evident if neither a decrease (classified in accordance with the PR criteria) nor an increase (classified in accordance with the PD criteria) of the target lesions was observed.

Statistical considerations and study endpoints

The trial presented here is a nonrandomized prospective phase II study. Due to an estimated number of approximately five to eight oesophageal carcinoma patients presenting each year for outpatient care in our gastroenterological–oncological outpatient department, the number of patients admitted for this trial was 25.

The primary endpoint was the median survival time from treatment initiation until the time of death or the last evaluation, secondary endpoints were the response rate (CR and PR in accordance with WHO criteria) and the proportion of patients with SD. Further endpoints related to the time-to-progression (TTP) and the NCI-CTC toxicity grade. The descriptive statistical values have been indicated both in percent and in median values. Both the survival time and the TTP have been analysed in accordance with the Kaplan–Meier method. Differences between the survival times have been checked for statistical significance using the log-rank test. The significance level α was defined as 0.05. All statistical tests were bilateral. All analyses were performed using the statistics software SPSS for Windows version 15.0 (SPSS Inc., Chicago, Illinois, USA).

Results

Patient characteristics

From November 2002 to August 2006 a total of 25 patients were enrolled in our trial. One patient was defined 'not entered', as he did not present for treatment despite having initially given his written informed consent. Therefore, the data of 24 patients, in total, have been evaluated. The last date of evaluation was 28 February 2007. At that time one patient still received first-line treatment.

The majority of the patients were male ($n = 19$; 79%) and the median age was 58 years (range: 44–75). Concerning the performance status, the majority of the patients ($n = 17$; 71%) had an ECOG index = 1, three patients had an ECOG index = 0 (12%), and four an index = 2 (17%). When treatment began four patients were treated with opiate analgesia because of severe pain. Multimorbidity was often observed in the patients' collective; for example, five patients had diabetes mellitus (21%). Two of these five patients required insulin. Further comorbidities were arterial hypertonia in nine patients (37.5%), coronary artery disease in three patients (12.5%) and chronic obstructive pulmonary disease in a further three patients (12.5%).

The ratio of adenocarcinomas was higher than of squamous cell carcinomas (54 vs. 46%). In 11 out of the 13 patients presenting with adenocarcinomas, the gastro-oesophageal junction was affected [adenocarcinoma of the oesophagogastric junction (AEG) I: 33%; AEG II: 12%]. Eighty-eight percent of the patients belonged to the UICC stage IV category, most of them with either distant metastases affecting the lymph nodes (M1LYM; 58%) or liver metastases (M1HEP; 50%).

At initial examination the carcinoembryonic antigen value was elevated (> 5 ng/dl) in 33% ($n = 8$) of the 24 patients, and the carbohydrate antigen 19-9 value in 29% ($n = 6$) of 21 examined patients (> 37 U/ml). The squamous cell carcinoma antigen tumour marker was determined in 19 patients, being positive (> 1.5 ng/ml) in 32% ($n = 6$).

Before treatment three patients had undergone primary surgical intervention (i.e. an abdomino-thoracic oesophageal resection). In two of them an initial R0 resection could be performed. In one patient, however, only an R2 resection proved to be feasible. At enrollment to this trial, the R0-resected patients already revealed either relapsed or metastasized cancer. Five patients had received a combined chemo-radiotherapy, in two cases with neoadjuvant intent, and in three cases with curative intent. Here combination regimens with cisplatin or paclitaxel, combined with 5-FU were applied. For an overview of the basic patient characteristics, see Table 1.

Table 1 Patient characteristics

Characteristic	Number	Percentage
Total	24	100
Age (years)		
Median	58	
Range	44–75	
Sex		
Female	5	21
Male	19	79
Performance status (ECOG)		
0	3	12
1	17	71
2	4	17
Histology		
Adenocarcinoma	13	54
Squamous cell carcinoma	11	46
Grading		
G2	8	33
G3	12	50
G4	4	17
UICC Stage		
III	3	12
IVa	4	17
IVb	17	71
Localisation of the metastases		
Lymph nodes (M1LYM)	14	58
Liver (HEP)	12	50
Lungs (PUL)	6	25
Peritoneum (PER)	2	8
Skeleton (OS)	2	8
Prior treatment		
None	16	67
Surgery	3	12
Radiochemotherapy	5	21

ECOG, Eastern Cooperative Oncology Group.

Table 2 Maximum toxicity per patient and item ($n = 24$)

	NCI-CTC grade [n (%)]				
Toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Haematological					
Anaemia	3 (12)	18 (75)	3 (12)	–	–
Leukopenia	15 (62)	5 (21)	4 (17)	–	–
Thrombopenia	24 (100)	–	–	–	–
Nonhaematological					
Diarrhoea	5 (21)	11 (46)	5 (21)	2 (8)	1 (4)
Nausea	2 (8)	21 (88)	–	–	1 (4)
Vomiting	16 (67)	6 (25)	1 (4)	1 (4)	–
Loss of appetite	10 (42)	10 (42)	4 (16)	–	–
Fatigue	12 (50)	11 (46)	–	1 (4)	–
Hand–foot syndrome	21 (88)	3 (12)	–	–	–
Stomatitis	20 (83)	3 (12)	1 (4)	–	–
Alopecia	20 (83)	3 (12)	1 (4)	–	–
Thromboembolism	22 (92)	–	–	1 (4)	1 (4)
Hyperbilirubinaemia	22 (92)	2 (8)	–	–	–
Hyponatraemia	19 (80)	3 (12)	–	2 (8)	–
Increase of creatinine	22 (92)	1 (4)	–	–	1 (4)
Infections	16 (67)	3 (12)	4 (16)	1 (4)	–
Fever	23 (96)	–	1 (4)	–	–

NCI-CTC, National Cancer Institute Common Toxicity Criteria.

Treatment and toxicity

A total of four hundred and sixty chemotherapy applications were administered (each patient received from a minimum of two applications to a maximum of 60 applications, the median being 12 applications). This was equivalent to 77 chemotherapeutic cycles (range: 0–10, median value: 2). An overview of the toxicity experienced per patient is given in Table 2. Higher-grade haematological side effects (toxicity grade 3 or 4) did not occur, CTC toxicities grades 3 and 4, such as diarrhoea ($n = 3$; 12%), nausea ($n = 1$; 4%) and vomiting ($n = 1$; 4%), affected the gastrointestinal tract in particular. Two patients ($n = 2$; 8%) developed hyponatraemia (toxicity grade 3), one patient ($n = 1$; 4%) revealed a significant increase of creatinine (grade 4) because of exsiccosis accompanied by nausea. One patient who had been implanted a Port-a-Cath developed a subclavia thrombosis, another patient with known arteriosclerosis

suffered an infarct of the brain stem; we are of the opinion that a relationship between these events and the chemotherapy regimens administered seems questionable.

In seven patients (29%) a dose reduction of 25% proved to be necessary; in five of these cases the reduction of irinotecan alone was sufficient. These reductions became necessary because of repeated diarrhoea (grade ≥ 2) as well as a grade 2 stomatitis in one case or vomiting (NCI-CTC toxicity grade 3).

Three patients died after having received two applications of chemotherapy because of both a high tumour burden and a clinically suspected tumour progression. After having received two chemotherapy applications, one patient refused both further treatment and follow-up because of higher-grade nonhaematological toxicity [nausea and increase of creatinine (toxicity grade 4)], which required hospitalization and inpatient treatment; therefore, this patient is statistically recorded as 'lost to follow-up'. Another patient discontinued treatment without further explanation after having received only four applications of chemotherapy; this patient died nearly 5 months after having received the last chemotherapy application. The two above-mentioned patients could not be evaluated for response and TTP as they had to be registered as 'lost to follow-up'; they were, however, evaluated for the calculation of the median survival period.

Response rate, time-to-progression and median survival time (Table 3)

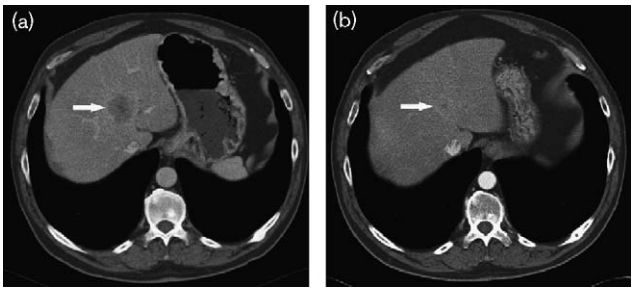
The median period of observation (follow-up) amounted to 10 months (range: 0.8–39.5 months). Due to the previously described treatment discontinuations, five patients (21%) were not evaluable for treatment response; therefore, altogether, only 19 out of 24 patients (79%) could be evaluated for treatment response. Eight patients (33%) showed PR (Fig. 1), nine patients (38%) could be registered as SD cases and the remaining two patients (8%) had PD. Twelve out of the 19 (63%) evaluable patients had an adenocarcinoma; in seven patients a squamous cell carcinoma had been diagnosed (37%).

Table 3 Response rate, survival time and time-to-progression

Response	Number	Percentage
Total	24	100
Partial response	8	33
Stable disease	9	38
Progressive disease	2	8
Not evaluable	5	21
	Median	95% CI
Time period (months)		
Overall survival	13.6	7.1–20.1
Adenocarcinoma	20.3	8.5–32.2
Squamous cell carcinoma	10.0	3.9–16.1
Time-to-progression	6.6 (range 1.6–24.6)	

CI, confidence interval.

Fig. 1



Multislice computed tomography with intravenous application of contrast media, 5 mm axial slices (Somatom Sensation 64, Siemens, Germany): a 51-year-old man with hepatic metastasis from squamous cell oesophageal cancer (see arrow) before (a) and after (b) three cycles of chemotherapy with 5-fluorouracil/sodium folinic acid (AIO regimen) and irinotecan presenting a partial response.

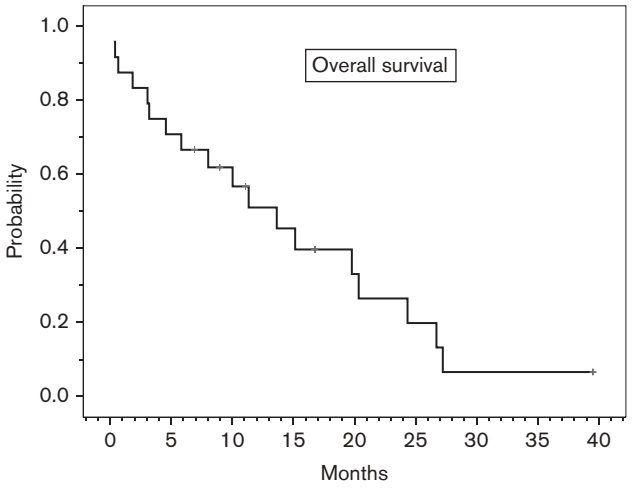
Among the eight patients with PR, five suffered from adenocarcinoma, and three from squamous cell carcinoma. Six patients with adenocarcinoma and three patients with squamous cell carcinoma were assessed as SD cases; one patient in the adenocarcinoma group and another one in the squamous cell carcinoma group had PD. The median TTP amounted to 6.6 months (range: 1.6–24.6).

Nine patients (37.5%) received second-line treatment after tumour progression. In five cases, a combined regimen consisting of cisplatin and 5-FU/ sodium folinic acid was administered, in two cases oxaliplatin combined with 5-FU/sodium folinic acid (AIO regimen) was applied. In other oncological centres, one patient received second-line treatment with docetaxel in combination with 5-FU, a further patient was given vinorelbin and carboplatin as second-line treatment. None of the patients received third-line treatment.

Up to the last data assessment 18 patients (75%) had died. In two patients with PR (initial UICC stage IVa or IVb because of lymph node metastases) and in one patient with SD (UICC stage III) a secondary R0 resection could be performed. At the time of the last (i.e. most recent) data assessment the median survival in these patients was 11.1, 16.8 and 39.5 months, respectively.

The median survival time of the total collective amounted to 13.6 months [95% confidence interval (CI): 7.1–20.1 months] (Fig. 2), with the median survival time of the adenocarcinoma being clearly more favourable with 20.3 months (95% CI: 8.5–32.2) compared with 10.0 months in patients suffering from squamous cell carcinoma (95% CI: 3.9–16.1). Due to the low case number, however, the difference was not significant [log-rank (Mantel–Cox): $\chi^2 = 1.0$; d.f. = 1, $P = 0.328$].

Fig. 2



Kaplan–Meier estimates of overall survival among patients with advanced oesophageal carcinoma treated with 5-fluorouracil/sodium folinic acid (AIO regimen) and irinotecan.

In contrast, a significant correlation between the response rate and the median survival time could be established: the patients with PR had a median survival time of 24.3 months (95% CI: 14.6–34.4), those with SD 13.6 months (95% CI: 7.1–20.2) compared with the patients who had PD and presented a median survival of only 1.8 months [log-rank (Mantel–Cox): $\chi^2 = 25.8$; d.f. = 2, $P < 0.001$].

Discussion

At initial diagnosis, more than 50% of oesophageal carcinomas are locally advanced or metastasized [14]; furthermore, in the course of time, even those patients who were curatively treated in the beginning frequently tend to develop either local recurrence or distant metastases corresponding to their UICC stage because of an early lymphogenous and haematogenous metastatic spread. Therefore, during the course of disease the majority of oesophageal cancer patients will become candidates for palliative chemotherapy treatment. As these patients are frequently multimorbid patients, mostly in a reduced general state of health and an unfavourable nutritional condition, it should be the objective of trials to evaluate the efficacy and tolerance of chemotherapy regimens applied in outpatient care.

Throughout the world, cisplatin combined with 5-FU as a continuous infusion is a frequently applied and analysed regimen in squamous cell carcinoma of the oesophagus achieving response rates between 25 and 35% [22].

In 1997, Bleiberg *et al.* [23] compared single agent cisplatin versus cisplatin combined with 5-FU in the context of a randomized phase II trial ($n = 92$), treating patients with advanced squamous cell carcinoma. In the combined schedule treatment arm both a mean survival period of 8.25 months and a response rate of 35% could be achieved compared with a mean survival period of 7 months and a response rate of 19% in the single agent arm. Bleiberg *et al.* [23], however, reported on increased toxicities in the combination treatment arm, that is, leukopenia (NCI-CTC grade 3/4) and thrombopenia (NCI-CTC grade 3/4) in 14%, as well as nausea and vomiting in 27% of the patients. Altogether, seven cases of treatment-related death (16%) had to be registered, all of them pertaining to the combination treatment arm. Therefore, at that time the authors concluded that, because of severe side effects, the treatment of advanced squamous cell carcinomas of the oesophagus with a combined regimen consisting of cisplatin and 5-FU cannot be recommended.

In 1999, Warner *et al.* [35] observed both a response rate of 27% including two complete remissions (CR: 6.7%) and a mean survival period of 6 months under cisplatin combined with 5-FU in the form of a bolus application. In six cases (20%) toxicity grade 4 neutropenia occurred, five of them presented concomitant fever. Nausea and vomiting (NCI-CTC grade 3/4) were observed in 36.7% and diarrhoea (NCI-CTC grade 3) in 16.7%.

In a further phase II trial the Caroli-Bosc team evaluated the efficacy of cisplatin combined with 5-FU as a 24-h infusion and leucovorin (AIO regimen) in patients suffering from tumours of the upper gastrointestinal tract [36]. In the context of this trial, a response rate of 40% and a survival period of 10.6 months could be achieved in patients with oesophageal carcinomas ($n = 10$). Toxic side effects included, in particular, cases of higher-grade neutropenia (i.e. neutropenia of NCI-CTC toxicity grade 3/4 in 16%, and febrile neutropenia of NCI-CTC toxicity grade 3/4 in 13%), which consequently required a dose reduction, especially in the oesophageal cancer group.

The study group around Hayashi reported on 42 patients with squamous cell carcinoma of the oesophagus achieving a response rate of 33% and a mean survival period amounting to 7.5 months while receiving cisplatin combined with continuous infusional 5-FU [37]; Sekiguchi *et al.* [38] observed a response rate of 55% in 20 patients with locally advanced squamous cell carcinoma of the oesophagus UICC stage III, albeit as a result of a chemotherapy regimen administered in the context of neoadjuvant intent.

Combined schedules of both cisplatin and paclitaxel [24] also achieved good response rates of up to 43% and mean survival periods amounting to 9 months. However, toxicities such as neutropenia (NCI-CTC grade 3/4) in a total of 70% patients and neurotoxicities (NCI-CTC grade 1/2) in up to 63% of this patients' collective were observed.

Furthermore, combined chemotherapy schedules consisting of three agents were evaluated. Polee *et al.* [26] reported on a phase II trial conducted on the basis of a combined cisplatin, 5-FU and etoposide regimen. Here, response rates of 34% and a mean survival period of 9.5 months were achieved in 69 patients with squamous cell carcinoma of the oesophagus. Toxicities ranged from leukocytopenia (NCI-CTC grade 3–4 in 33%), febrile leukopenia (19%), thrombocytopenia (NCI-CTC grade 4; 7%), to nonhaematotoxic side effects such as nausea and vomiting (NCI-CTC grade 3; 32%), mucositis (NCI-CTC grade 3/4) in 23% and diarrhoea (NCI-CTC grade 3) in 6% of the patients.

Another randomized phase II trial ($n = 574$ patients) evaluated cisplatin/5-FU as a continuous infusion administered in combination with mitomycine (MCF) versus cisplatin/5-FU as a continuous infusion combined with epirubicine (ECF) [25]. In this trial, patients with either adenocarcinoma or squamous cell carcinoma of the oesophagus were enrolled along with patients suffering from gastric cancer (43%) and a small group of patients with 'unknown primary' (carcinoma of unknown primary syndrome; 2.3%). Comparable results were achieved for the MCF regimen (response rate 44.1%, median survival 8.7 months) and the ECF regimen (response rate 42.4%; median survival 9.4 months). In terms of quality of life [data ascertainment was done by the EORTC (European Organization for Research and Treatment of Cancer) questionnaire]; however, the ECF regimen turned out to be superior. The CTC grade 3/4 toxicities varied according to the applied regimens, in particular, neutropenia (32%), nausea (11%), fatigue (18%) and alopecia (NCI-CTC grade 2; 59%) were noted. The efficacy of irinotecan in the treatment of patients with oesophageal carcinomas could yet be proved in several phase II trials.

A response rate of 22.2% was achieved by applying single agent irinotecan [39], whereas irinotecan combined with cisplatin as a weekly regimen, administered for a period of 4 weeks followed by 2 weeks of rest led to a high response rate of 57%; however, this was accompanied by toxic side effects such as neutropenia (NCI-CTC grade 3/4) in 46% and diarrhoea (NCI-CTC grade 3) in 11% of the patients [29]. An identical combination schedule, applied on days 1 and 8, followed by 1 week of rest, resulted in a response rate of 36% with neutropenia (NCI-CTC grade 3/4) occurring in only 22% of the patients [40].

Furthermore, irinotecan was evaluated as a combined regimen applied together with docetaxel. In the context of a phase II trial [30], a response rate of 30% was achieved, the mean survival, however, amounted to only 4.6 months; furthermore, 71% of the patients suffered from haematotoxicities (NCI-CTC grade 4) together with febrile neutropenias (43%). In a further phase II trial [31], which applied irinotecan combined with docetaxel in second-line treatment for oesophageal cancer patients pretreated with cisplatin, febrile neutropenia occurred in all patients ($n = 4$) under a 3-weekly course of treatment. Consequently, the authors decided to change to an application once a week together with a dose reduction in the remaining 24 patients. Due to this dose reduction, haematotoxicities (NCI-CTC grade 3/4) could be avoided; 20.8% of the patients, however, developed asthenia and 12.5% diarrhoea (CTC toxicity grade 3/4). The response rate in second-line treatment was 12.5%. A randomized phase III study showed that the combination of irinotecan/5-FU did not achieve a significant overall survival superiority over cisplatin/5-FU, but may offer a possible alternative to a first-line treatment with platinum agents in advanced adenocarcinoma of the stomach or AEG [41].

In treating locally advanced or metastatic oesophageal cancer with a weekly regimen of 5-FU and sodium folinic acid (AIO regimen) combined with irinotecan, we observed a response rate of 33.3% in terms of PR. The partial remissions occurred more frequently (in 62.5%) in patients with adenocarcinoma, whereas in only 37.5% of the patients with squamous cell carcinoma a partial remission could be observed. Tumour control in terms of PR and SD was achieved in 71% altogether. The median survival period amounted to 13.6 months; here again the adenocarcinoma patient group achieved a more favourable result (i.e. 20.3 months) than the squamous cell carcinoma group with 10 months, a result without significance, however, because of the small case number. In contrast, a significant correlation could be established between response rate and median survival: patients with PR ($n = 8$) showed a median survival of 24.3 months, whereas those with SD ($n = 9$) achieved a median survival of 13.6 months. Patients with PD ($n = 2$), however, only achieved a median survival period of 1.8 months.

In the phase II trial presented, higher-grade toxicities (NCI-CTC grade 3/4) occurred rarely and consisted mostly of gastrointestinal side effects such as diarrhoea (12.5%), nausea (4.2%) and vomiting (4.2%). Thus, according to our present evaluation, this regimen is being well tolerated even by a multimorbid patient group and is, in addition, excellently applicable in outpatient care.

A comparison of the various types of therapeutic regimens in phase II trials can hardly lead to reliable results because of the variety of patients within the groups and the low number of cases. The patient group of many phase II trials, for example, may differ not only as to primary tumour localization (e.g. oesphageal cancer, adenocarcinoma of the oesophageal–gastric junction, a so-called AEG tumour, or gastric cancer), but also as to histology (adenocarcinoma, squamous cell carcinoma), stage of disease and pretreatment modalities.

Summing up the results, the excellent response rates, in particular in adenocarcinoma patients, who achieve a comparatively long median survival period, emphasize the efficacy of 5-FU/sodium folinic acid (AIO regimen) plus irinotecan in the treatment of locally advanced or metastatic oesophageal carcinoma. Therefore, further trials with that combination and a significantly higher number of cases seems to be highly desirable, maybe also as a three-drug regimen with new targeted agents, for example, using the human monoclonal antibody cetuximab, which has shown some promising results in the treatment of local advanced or metastatic gastric cancer or gastro-oesophageal junction adenocarcinoma [42].

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