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CLINICAL TRIAL REPORT

A phase I/II study of oxaliplatin and paclitaxel in patients with non-resectable cancer of the oesophagus and adenocarcinoma of the gastro-oesophageal junction: a study of the Arbeitsgemeinschaft Internistische Onkologie

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Abstract
Purpose To assess the efficacy and toxicity of paclitaxel and oxaliplatin in patients with non-resectable cancer of the oesophagus and adenocarcinoma of the gastro-oesophageal junction.
Methods Treatment consisted of oxaliplatin 85 mg/m^2 and paclitaxel 90 mg/m^2 on days 1, 15 and 29 every 6 weeks. Patients with a non-resectable cancer of the oesophagus and/or adenocarcinoma of the gastro-oesophageal junction were eligible.
Results Twenty-six chemotherapy-naive patients were enrolled who had the following characteristics: median age 59.5 years (range 46–81); ECOG scores of 0/1/2 for 7/16/3 patients, respectively, and 23 (88%) patients had metastatic disease. There were 5 patients (19%) with adenocarcinoma of the gastro-oesophageal junction and 21 patients (81%) with oesophageal cancer; 19 (73%) had a squamous cell cancer and 7 (27%) had an adenocarcinoma. NCI grade 4 toxicity (neutropenia) was observed in one patient. Non-haematological toxicity consisted mainly of grade 1/2 neurosensory toxicity. The overall response rate by the intention-to-treat analysis was 15% with 4 patients having confirmed partial response. Overall tumour control rate was 73%. Median overall survival was 12.3 months (range 1.5–66) and median time to progression was 4.5 months (range 0.8–19.3).
Conclusion This regimen is well tolerated and demonstrates a modest response rate with a favourable disease control rate.

Keywords Oxaliplatin · Paclitaxel · Cancer of the gastro-oesophageal junction · Oesophageal cancer · Chemotherapy

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Introduction

Carcinoma of the upper gastrointestinal tract represents a major health problem worldwide [1, 2]. About 90% of all patients diagnosed with oesophageal cancer will die as a consequence of this disease. Besides the predominantly late diagnosis, another reason for this poor prognosis of this tumour is the limited effectiveness of systemic therapy.

Even if there is no established standard chemotherapy regimen, cisplatin-containing combination therapies are accepted as a standard of care. Oxaliplatin is a third-generation platinum compound with a favourable toxicity profile as compared to cisplatin [3, 4].

Taxanes, microtubule-stabilising agents initially isolated from the Pacific yew, have been extensively studied in gastro-oesophageal cancer. Paclitaxel and Docetaxel demonstrated encouraging activity in single and combination therapy [5–8].

Oxaliplatin is a potent inhibitor of Survivin, which enhances paclitaxel-induced apoptosis and mitotic catastrophe in colon and gastric cancer cell lines. These findings made the combination of these two drugs an attractive option for clinical trials [9, 10].

This phase I/II study was conducted to assess the efficacy and tolerability of paclitaxel and oxaliplatin in patients with non-resectable cancer of the oesophagus and/or adenocarcinoma of the gastro-oesophageal junction. The treatment regimen was adapted from a phase II study by Petrasch in which paclitaxel 90 mg/m^2 was followed by cisplatin 50 mg/m^2 resulting in an overall remission rate of 40% (8/20) including 15% (3/20) clinically complete responses with a favourable toxicity profile [11]. By substituting oxaliplatin for cisplatin we aimed at obtaining an even better tolerability.

Methods

Patients

Patients with non-resectable cancer of the oesophagus and adenocarcinoma of the gastro-oesophageal junction were eligible for this study. A measurable lesion according to the RECIST criteria was required [12]. Prior surgery and/or radiochemotherapy was allowed as well as one prior chemotherapy in a neoadjuvant or adjuvant setting that did not contain oxaliplatin and/or taxanes. This chemotherapy had to be terminated at least 6 months prior to enrolment into the study. This paper focusses on the subgroup of 26 chemotherapy-naive patients (84% of the whole study population). The remaining five patients had previously received systemic chemotherapy. An ECOG performance status of $\leq$2 was mandatory as well as adequate bone marrow, kidney and liver function.

Chemotherapy schedules and treatment evaluation

Oxaliplatin 85 mg/m^2 was administered over 2 h followed by paclitaxel 90 mg/m^2 over 3 h both on day 1. Treatment was administered fortnightly.

All patients were assessed for toxicity during the study period according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC). Oxaliplatin-related peripheral neuropathy was described on a scale from 1 to 4 adapted from the classification of Wasserman et al. [13].

According to the study protocol an evaluation of tumour response was mandatory every 6 weeks. For locally advanced cancer a further evaluation regarding secondary resectability was obligatory after 12 weeks. Response and overall survival were assessed using an intent-to-treat analysis.

Statistical considerations

The response rate was the primary end point of this phase I/II trial. Chemotherapy-naive and pre-treated patients were analysed separately. A Chi-square test was utilised.

For chemotherapy-naive patients a sample size of 38 patients, who were assessable for response evaluation, was calculated to reject an initial hypothesis (H0) of a response rate $\leq$30% with an alpha error of 0.1.

For the calculation of the sample size the programme, nQuery Advisor Release 3.0 (Statistical Solutions Ltd., Cork, Ireland, 1999), was used.

An interim analysis after inclusion of 25 chemo-naive patients revealed that the response rates were too low to reject the H0 hypothesis. Subsequently, recruitment was stopped prematurely.

Results

Between November 2002 and May 2005 31 patients were enrolled into the study at the two participating centres (University hospitals of Ulm and Mainz in Germany). A total of 64 cycles was administered to 26 chemotherapy-naive patients. The patient demographic data and characteristics are summarised in Table 1. Patients with CNS metastasis, uncontrolled heart disease and/or clinical evidence of pre-existing peripheral neuropathy were excluded.

Toxicity

Of the 26 chemo-naive patients, 23 (88%) were evaluable for toxicity; 3 patients could not be evaluated owing to early withdrawal of consent or early dropout for reasons other than toxicity prior to, or during, the first cycle of treatment. The majority of toxic effects were grade 1/2, whereas grade 3/4 toxicity was rare. Events leading to hospitalisation occurred in five patients; one patient had two hospitalisations. Three patients required endoscopic intervention because of an increase in dysphagia (n = 3). Other causes were ileus owing to peritoneal carcinosis (n = 1), hypercalcemia (n = 1) and pneumonia (n = 1).

Haematological toxicity

Haematological toxicity was rare. Overall 13% of patients (n = 3) experienced grade 3/4 neutropenia. Febrile neutropenia was not observed. One patient had grade 3 thrombopenia.

Table 1 Characteristics of chemo-naive patients ($n = 26$)

Characteristic	Number of patients	%
Sex		
Male	23	88
Female	3	12
Age (years)		
Median	59.5	
Range	46–81	
ECOG performance status		
0	7	27
1	16	61
2	3	12
Tumour stage (UICC)		
III	3	12
IV	23	88
Tumour localisation		
Oesophagus	21	81
Mid-part	12	46
Lower part	9	35
Gastro-oesophageal junction	5	19
Tumour histology		
Squamous cell carcinoma	19	73
Adenocarcinoma	7	27

Non-haematological toxicity

No grade 4 non-haematological toxicity was encountered; 87% ($n = 20$) encountered neurosensory toxicity ≥grade 1, but only 13% ($n = 3$) had grade 3 neurosensory toxicity leading to a dose reduction of oxaliplatin. One patient had a hypersensitivity grade 2 shortly after infusion of paclitaxel during the third treatment cycle. There was only grade 1/2 gastrointestinal toxicity that included diarrhoea grade 1 in 17%, nausea in 22%, emesis in 9% and mucositis in 9% of the patients. These findings are summarised in Table 2.

Treatment efficacy

Response

The overall confirmed response rate for all treatment-naive patients ($n = 26$) by the intention-to-treat analysis was 15% with four patients having a confirmed partial response. Together with 15 patients who achieved stable disease during the initial restaging the disease control rate was 73%. This included two patients enrolled who did not undergo radiological response evaluation, because they exited the study early for reasons other than tumour progression: one patient exited the study during the first treatment cycle owing to early withdrawal of consent; one patient was excluded owing to surgery of symptomatic bone metastasis that was already prevalent at the time of entering the trial.

Time to progression

Twenty-four patients were included for the calculation of TTP. Two patients who changed to another treatment regimen (definitive radio-chemotherapy) without progress during the investigational treatment were excluded from

Table 2 Toxicity and efficacy of the treatment

Toxicity NCI grade 2/3/4 ($n = 23$)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)
Neutropenia	4 ($n = 1$)	9 ($n = 2$)	4 ($n = 1$)
Thrombopenia	–	4 ($n = 1$)	–
Neurosensory toxicity	9 ($n = 2$)	13 ($n = 3$)	–
Nausea	22 ($n = 5$)	–	–
Emesis	9 ($n = 2$)	–	–
Infection (broncho-pulmonary or PEG-infection)	22 ($n = 5$)	4 ($n = 1$)	–
Allergic reaction (due to paclitaxel)	4 ($n = 1$)	–	–
Cutaneous toxicity (aggravation of neurodermitis)	–	4 ($n = 1$)	–
Mucositis	9 ($n = 2$)	–	–
Hand-foot syndrome	4 ($n = 1$)	–	–
Efficacy intent-to-treat analysis ($n = 26$)			
Confirmed PR	4 (15%) (per protocol analysis 17%, $n = 24$)		
Stable disease (SD)	15 (58%)		
PR + SD	19 (73%) (confirmed PR + SD 58%, $n = 15$)		
PD	7 (27%)		
Median TTP ($n = 24$)	4.5 months		
Median OS	12.3 months		

the TTP analysis. The median TTP was 4.5 months (range 0.8–19.3) with a 1-year progression-free survival rate of 13%.

Overall survival

The median OS for chemotherapy-naive patients was 12.3 months (range 1.5–66) with 1-year survival rate of 50%. Table 2 provides an overview.

Information on the second-line treatment was available for 24 patients (92%); 10 patients (42%) did not receive further systemic treatment after discontinuation of the study, whilst 4 patients had radio-chemotherapy and 10 patients had chemotherapy alone.

Discussion

This study was conducted to assess the efficacy and tolerability of paclitaxel and oxaliplatin in patients with non-resectable cancer of the oesophagus and/or adenocarcinoma of the gastro-oesophageal junction. The primary goal of the study to reject the initial hypothesis (H0) of a response rate $\leq$30% was not met.

Oxaliplatin was given at a dose of 85 mg/m^2 fortnightly which is commonly used within the FOLFOX4-regimen in colorectal cancer or the FLO-regimen in gastric cancer [4, 14]. The oxaliplatin dose administered compared well to other oxaliplatin/taxane-containing doublets for the treatment of oesophago-gastric cancer. A phase II trial by Richards used 130 mg/m^2 oxaliplatin together with Docetaxel 60 mg/m^2 on day 1 of a 3-week treatment cycle in patients with advanced gastric cancer and/or adenocarcinoma of the gastro-oesophageal junction [15]; 36% had a partial response and 40% of the patients in this trial had at least stable disease 6 months after entry into the study. Median PFS and OS were 4.3 and 8.5 months, respectively; 70% had grade 3/4 neutropenia.

In oesophageal cancer the use of paclitaxel was investigated in different platinum-containing doublets: in a phase I study in metastatic oesophageal cancer paclitaxel was administered weekly as a 1-h infusion at a dose of 100 mg/m^2 followed by a 1-h infusion of carboplatin targeting an AUC of 2–5 mg $\times$ min/ml. Of 37 patients evaluable for response, 1 complete response and 19 partial responses accounted for an overall response rate of 54% [16]. In a phase II study for patients with resectable squamous cell carcinoma of the oesophagus, paclitaxel 180 mg/m^2 and cisplatin 60 mg/m^2 were given fortnightly with a similar response rate of 59%; a grade 3/4 neutropenia occurred in 71% of patients. With a median OS of 9 months for all patients this excellent response rate did not lead to an improved OS [17]. One reason for the inferior response rate in our trial was that we examined a lower dose of paclitaxel (90 mg/m^2 every 2 weeks as compared to 175 mg/m^2 every 3 weeks or 135 mg/m^2 every 2 weeks), although we used an equivalent dose of oxaliplatin.

The drug combination of paclitaxel and oxaliplatin was used in first-line treatment of patients with advanced NSCLC and ovarian cancer (paclitaxel 175 mg/m^2 and oxaliplatin 130 mg/m^2 given every 21 days), in both tumours with impressive response rates [18, 19]. In advanced gastric cancer, a phase II trial added leucovorin 400 mg/m^2 and 5-FU 2,400 mg/ m^2 to paclitaxel 135 mg/m^2 and oxaliplatin 85 mg/m^2 given fortnightly; 12 out of 21 patients with measurable lesions had a treatment response. In 30% of the patients, neutropenia grade 3/4 occurred [20].

Our study protocol differs from other recently published trials that yielded response rates higher than 40% [3, 4, 7, 8] owing to the lack of a fluoropyrimidine compound, which might be a reason for the lower response rate observed here. We used a sequence of oxaliplatin followed by paclitaxel as compared to the reverse sequence applied in the other trials [18, 19]. Pre-clinical data published shortly after the end of our recruitment period revealed that in human cancer cell lines the sequence of paclitaxel followed by oxaliplatin showed synergistic effects on apoptosis, whereas the opposite sequence potentially yielded antagonistic effects [21]. In contrast, a recently published phase I study provided a favourable pharmacokinetic profile for the sequence used in our study regimen [22].

Conclusions

Taken together, in a palliative setting when response rate is not paramount, our treatment protocol achieved a satisfactory disease control rate. The mTTP of 4.5 months observed in this trial and the mOS of 12.3 months are also comparable to other but often more toxic regimens. However, a second-line treatment which was administered in 58% of patients might have influenced this parameter. However, the response rate observed does not qualify our treatment regimen for a neoadjuvant setting. Thus, our results suggest that this regimen with oxaliplatin and paclitaxel is a very well tolerable palliative treatment option for patients with non-resectable advanced cancer of the oesophagus and the gastro-oesophageal junction.

Conflict of interest statement The authors declare that they have no competing interests.

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