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ORIGINAL ARTICLE

Phase I study of docetaxel, oxaliplatin and capecitabine (TEX) as first line therapy to patients with advanced gastro-oesophageal cancer

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Abstract

Background. ECF (epirubicin, cisplatin, 5-FU) has been a standard first-line regimen in patients with advanced gastro-esophageal cancer (GEC). If cisplatin is substituted by oxaliplatin (Eloxatin®) – E) and 5-FU by capecitabine (X - Xeloda®) this regimen is easily administered with at least comparable efficacy and lower toxicity. Recent studies indicate that efficacy can be improved by adding docetaxel (Taxotere® - T) to CF. We initiated a phase I trial of T, short-time infusion of E and continuously X (TEX) as first-line therapy in GEC to establish the recommended dose (RD) for further therapy. *Materials and methods.* Patients were enrolled in cohorts of three at five dose levels. Patients had histologically confirmed GEC adenocarcinoma. Therapy was administered day 1 with escalating doses of docetaxel (60 mg/m^2 to 75 mg/m^2 iv as a 60 minutes infusion), oxaliplatin (85 to 130 mg/m^2 iv as a 30 minutes infusion) and oral capecitabine (1 000 to 1 250 mg/m^2/day). TEX was repeated every third week for a maximum of eight cycles. Toxicity was evaluated according to CTCAE v3.0 and dose limiting toxicity (DLT) was evaluated after the first course of TEX. *Results.* From June 2007 to April 2009, 23 consecutive patients received TEX. At dose level V, two of four patients experienced DLT and therefore we included additional seven patients at dose level IV. Only one of seven experienced DLT but dose-intensity was reduced to 75% in four of seven patients after three courses of TEX. Therefore we defined dose level III as RD. Efficacy was promising with response rate 38%, PFS 9.4 months and OS 12.5 months. *Conclusion.* The recommended dose of TEX (docetaxel 60 mg/m^2 iv day 1, oxaliplatin 115 mg/m^2 iv day 1 and oral capecitabine 1250 mg/m^2/day continuously) every three weeks is easily administered in an out-patient setting. Efficacy is promising and will be evaluated in a phase II study.

Gastric cancer is the fourth most common cancer worldwide [1]. In Europe the 5-year relative survival rate of gastro-esophageal cancer (GEC) is 10–21% [2]. The poor prognosis is mainly due to most cases being diagnosed at a non-resectable stage.

Palliative treatment prolongs survival and improves quality of life [3–6]. Presently, there is no combination chemotherapy regimen considered to be standard treatment for advanced GEC. In Europe however the combination of epirubicin, cisplatin and 5-fluorouracil (5-FU) infusion (ECF) is often considered as reference therapy [7]. The ECF regimen requires continuously i.v. infusion of 5-FU through a central venous catheter. This is a time demanding procedure and there is a risk of infections and thrombosis. Cisplatin is severely emetogenic and requires i.v. hydration to avoid renal damage, furthermore it is both oto- and neurotoxic. There has been a request to find regimens with similar or even higher efficacy but easier to administer and hopefully with lower toxicity. In 2008, a large randomized phase III trial, REAL-2 used ECF as standard-arm and substituted cisplatin with oxaliplatin (Eloxatin® - E) and/or infusion 5-FU with capecitabine (Xeloda® - X) in a 2 × 2 factorial design [8]. There was no significant difference in response rate (RR) among the four regimens, but a trend toward a longer progression-free survival (PFS) and overall survival (OS) in patients receiving capecitabine and eloxatin. A Danish multicenter phase I and II trial evaluated a similar regimen EXE (epirubicin, Eloxatin® , Xeloda®,) and demonstrated comparable results and toxicity. Furthermore the

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regimen could easily be administered in an out-patient setting [9,10]. Most recently one of the "new-generation" agents docetaxel (Taxotere® - T) has been tested in several phase II trials and demonstrated promising activity in advanced gastric cancer. In V-325, patients were randomized to CF (cisplatin 100 mg/m^2 and 5-FU 1 000 mg/m^2/d day 1–5 every four weeks) or DCF (docetaxel 75 mg/m^2, cisplatin 75 mg/m^2 and 5-FU 750 mg/m^2/d day 1–5 every three weeks). DCF was significant superior to the doublet in terms of RR (37% vs 25%), PFS (5.6 months vs 3.7 months) and OS (9.2 months vs 8.6 months). However the DCF regimen was as expected also more toxic [11]. The combination of T and X appears to be excellent because of the modest overlaps in terms of key side effects [12]. In addition, T up regulates thymidine phosphorylase in tumor tissue acting synergistically with X in breast cancer xenograft models [13]. Based on these excellent results and the promising results with various double combinations of docetaxel, capecitabine or oxaliplatin we wanted to develop an easily administered and save regimen hopefully with high activity. In this phase I study we administered increasing doses of docetaxel in combination with short-time oxaliplatin [14] and capecitabine (TEX) as first line therapy in patients with gastric adenocarcinoma to establish a new out-patient regimen.

Materials and methods

Patient selection

Patients were required to have histologically confirmed adenocarcinoma of the lower oesophagus, gastro-oesophageal junction or stomach not amenable to surgical resection. Eligibility criteria included measurable or non-measurable disease; estimated life expectancy$>$12 weeks; World Health Organisation performance status 0–1; age$>$18 years; no prior chemotherapy other than adjuvant chemotherapy completed at least six months before inclusion; adequate bone marrow function (neutrophil count$>1.5 \times 10^9$ /l; platelets$>100 \times 10^9$ /l); adequate hepatic function (serum bilirubin $\leq 1,5 \times$ upper normal limit (UNL); transaminase $\leq 3 \times$ UNL, however in cases of liver metastases, there were no upper limit for transaminases); adequate renal function (calculated creatinine clearance$\geq$60 ml min^{-1} by the Cockroft and Gault formula). Other inclusion criteria were treatment start within eight days after inclusion, ability to tolerate oral medication, no peripheral neuropathy, no co-existent severe medical illness, no sign of brain metastases and no concomitant treatment with other anticancer drugs. Females were not included if they were pregnant or lactating.

The study was approved by the local ethics committee and the Danish Health Authority. Signed informed consents were obtained from all participants before study entry.

Study design and treatment

In order to find the best combination of the three drugs, maintaining the efficacy of DCF hopefully with less toxicity we decided to use escalating doses of all the tree drugs [15]. Patients were included in cohorts of three at progressively higher dose levels. In case of dose limiting toxicity (DLT) among one of the three patients during the first course of treatment additional three patients were added at the respective dose level. Dose escalation was continued if none of three or one of six patients experienced DLT.

Patients were planned to receive escalating doses of docetaxel (60 mg/m^2 to 75 mg/m^2) as a 60 minutes infusion day 1, oxaliplatin (85 mg/m^2 to 135 mg/m^2) as a 30 minutes infusion day 1 and capecitabine (1 000 mg/m^2 to 1 250 mg/m^2) taken orally with water within 30 minutes after ingestion of food and divided in two daily doses every 12 hours continuously (Table I). Therapy was repeated every three weeks to a maximum of eight cycles of treatment unless stopped because of disease progression, unacceptable toxicity or patient refusal.

In case of radical resection of the cancer during treatment patients were offered treatment after resection to a maximum of eight cycles in total.

Evaluation of toxicity, dose limiting toxicity and dose adjustment

Toxicity was measured and graded using the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 (CTCAE). Subjective symptoms, physical examination, performance status, haematology (also day 10 of first course) and adverse reactions were recorded before starting each treatment cycle. DLT was evaluated after the first cycle and defined as the occurrence of any of the following toxicities: Grade ¾ non-haematological toxicity; febrile neutropenia$>$five d"ys; grade 4 neutropenia more than seven days (absolute neutrophil

Table I. Dose escalation scheme of TEX.

Dose level	Docetaxel (T) mg/m²	Oxaliplatin (E) mg/m²	Capecitabine (X) mg/m²/day
I	60	85	500 × 2
II	60	100	625 × 2
III	60	115	625 × 2
IV	75	115	625 × 2
V	75	130	625 × 2

count < 0, 5×10^9/l); thrombocytopenia (platelet count $< 25 \times 10^9$/l); grade$\geq$2 infection or delay of treatment for more than two weeks due to side effects. If a patient experienced DLT at a certain dose level the dosage of all medicaments was reduced to 75% and additional three patients were included at that dose level.

The maximum tolerated dose (MTD) was defined as the dose level that produced DLT in at least two of the first three patients or in at least two of six patients. The recommended dose (RD) was defined as one dose level below MTD.

Patient evaluation

Assessment of medical history, physical examination, evaluation of performance status, complete blood count and biochemical tests were performed before treatment start and prior to each cycle. A CT-scan of thorax and abdomen was carried out at baseline and after every three cycles to exclude progression and evaluate response. Response was assessed by investigators according to RECIST version 1.0.

Blood counts regarding tumor biology was analyzed before second, fourth and seventh cycle and four weeks after ended treatment. After completion of treatment patients were followed every third month until progression or death.

Table II. Baseline characteristics.

Number of patients	23
Age, years	
Median	59
Range	43–74
Sex	
Male	21 (91%)
Female	2 (9%)
WHO performance status	
0	12 (52%)
1	11 (48%)
Primary tumor site	
Upper 1/3	13 (57%)
Middle 1/3	4 (17%)
Lower 1/3	6 (26%)
Status of primary tumor	
R0 resection	3 (13%)
R2 resection	3 (13%)
No surgery	17 (74%)
Stage	
Local advanced	7 (31%)
Metastatic	16 (69%)
No. of organs involved	
1	4 (17%)
2	10 (44%)
$\geq$3	9 (39%)
Increased	
Alkaline phosphatase ($>$ 300 U/l)	2 (9%)
ALAT ($>$ 40 U/l)	4 (17%)
Platelets ($> 400 \times 10^9$ /l)	9 (39%)
ANC ($> 7{,}5 \times 10^9$ /l)	7 (31%)

Statistical methods

The primary end point of this phase I study was to determine MTD of TEX. Secondary end points were to assess toxicity and establish the recommended dose for a phase II study. In addition response rate, progression-free survival (PFS) and overall survival (OS) were evaluated.

Non-parametric statistics were applied. All median values are followed by range in brackets. After completed therapy patients without documented disease progression were followed every three months with clinical and radiological evaluation. PFS and OS were generated according to the Kaplan-Meier method and updated at December 2009. Data were recorded and analyzed in a Medlog® database. All analyses were done an intention-to-treat population.

Results

Patient characteristics

From September 2007 to April 2009 23 consecutive patients from two Danish oncology centres were enrolled in this phase I trial. Data was updated December 2009. All patients were evaluated for safety and efficacy calculations. Patient characteristics at baseline are listed in (Table II). The median age was 59 years (range 43–74) and the majority of patients were males (91%). Performance status was none in 12 (52%) patients and one in 11 (48%). No patients had previously received adjuvant chemotherapy or radiotherapy. All patients had histological confirmed gastric adenocarcinoma located in the upper 1/3 in 13, middle 1/3 in four and lower 1/3 in six patients. Six patients were previously resected; three patients (13%) had had a R0 resection and other three a R2 resection. At baseline, seven patients (31%) had locally advanced disease and 16 (69%) presented with metastatic disease.

Toxicity

A total of 23 patients were treated at five different dose levels in a 21-day cycle. No DLT was seen after the first course through the first four dose levels. At dose level V two of four patients developed DLT after the first cycle of chemotherapy and another two patients developed grade IV ANC toxicity lasting less than seven days (Table III). Dose level V was definitely too toxic, and therefore the investigators decided to include further patients at dose level IV. Among the additional seven patients included only

Table III. Compliance to TEX and DLT.

Dose Level	No. patients	No. of courses	Mean no. courses	DLT
I	3	8,8,8	8	0/3
II	3	8,8,6	7	0/3
III	3	8,8,8	8	0/3
IV	3+7	7,8, 8,8,6,6,2,6,6,1	6	1/10
V	3+1	5,5,8,5	5	2/4

DLT: 1. grade III vomiting; 2. ANC grade IV, grade III nausea and vomiting; 3. ANC grade IV, grade III nausea and vomiting.

one patient developed a DLT (nausea, vomiting, ANC) (Table III). However overall dose-intensity was reduced to 75% in four of seven patients when they commenced the fourth course of TEX and thus we re-defined level IV as MTD and recommended dose level III for phase II.

Only three of the 10 patients at dose level IV completed all eight cycles of therapy. Toxicity grade 2–4 after the first cycle of TEX is summarized in (Table IV). Worst toxicity for all patients and all cycles are listed in (Table V) multiple toxicities in the same patient are scored as separate events. Most frequent grade 3 non-hematologic toxicity included; nausea (22%), diarrhoea (13%), vomiting (22%), fatigue (17%) and nail toxicity (17%). Six patients (26%) experienced peripheral neuropathy grade 3.

Efficacy

Median numbers of cycles per patient were seven (range 1–8), total 152 courses. Twelve patients (52%) completed all eight series of chemotherapy. The reasons for discontinuation of therapy were progressive disease or deterioration of health (n=3), toxicity (n=7) and doctors decision (n=1).

Among all the 23 included patients, 17 (74%) had measurable disease. Patients without measurable disease and without any sign of progression after three cycles of therapy were considered as having stable disease. Two patients discontinued therapy due to deterioration of health after respectively one and two cycles of therapy. Eight patients (35%) obtained PR and two of these patients had subsequently a R0 resection. Additional 11 patients (52%) had stable disease during therapy. Only two patients had PD during treatment. Overall disease control rate was thus 91%, PFS was 9.4 months and OS was 12.5 months (Figure 1). Eight patients are still alive.

Table IV. Toxicity, level 1–5 after first course of TEX.

Hematologic toxicity	Grade II n (%)	Grade III n (%)	Grade IV n (%)
Neutropenia	5 (22%)	3 (13%)	8 (35%)
Thrombocytopenia	0	2 (9%)	0
Febrile neutropenia	–	1 (4%)	1 (4%)
Non-hematologic toxicity	**Grade II n (%)**	**Grade III n (%)**	**Grade IV n (%)**
Nausea	4 (17%)	2 (9%)	0
Diarrhoea	6 (26%)	0	0
Vomit	4 (17%)	3 (13%)	0
Neuropathy	1 (4%)	0	0
Fatigue	7 (31%)	0	0

Table V. Worst Toxicity, level 1–5 after all courses of TEX.

Hematologic toxicity	Grade II n (%)	Grade III n (%)	Grade IV n (%)
Neutropenia	3 (13%)	6 (26%)	10 (43%)
Thrombocytopenia	0	2 (10%)	1 (4%)
Febrile neutropenia	–	7 (31%)	1 (4%)
Non-hematologic toxicity	**Grade II n (%)**	**Grade III n (%)**	**Grade IV n (%)**
Nausea	4 (17%)	5 (22%)	0
Diarrhoea	9 (35%)	3 (13%)	0
Vomit	4 (17%)	5 (22%)	0
Neuropathy	6 (26%)	6 (26%)	0
Fatigue	10 (43%)	4 (17%)	0
Nail toxicity	10 (43%)	4 (17%)	–

Discussion

The combination of docetaxel, oxaliplatin and capecitabine (TEX) has the potential to become a new standard regimen in patients with GEC. The primary aim of the present study was to determine the RD for the planned phase II study. DLT was evaluated after the first course of TEX and five different dose levels were examined. The most frequent DLT was neutropenia. At dose level V, DLT was seen in two of four patients and another two patients developed grade IV hematologic toxicity. Therefore we decided not to include further patients at dose level V and to add further patients at dose level IV. Seven additional patients were enrolled at dose level IV. Only one DLT was observed after the first course of TEX. However, a large number of grade 3 or 4 toxicities were observed during the subsequent courses (Table V). Hematologic toxicity, primarily neutropenia, was the principal grade 3–4 toxicity in 16 (69%) of the patients and in particular at dose levels IV and V. Febrile neutropenia grade 4 was observed in one patient (4%) at dose level V and grade 3 febrile neutropenia was observed in seven patients (31%). There was no treatment related deaths in the study. Due to reduced number of cycles at dose level IV and due to reduced dose-intensity after the first course, we defined dose level IV as the MTD. Thus the RD level for phase II was set at dose

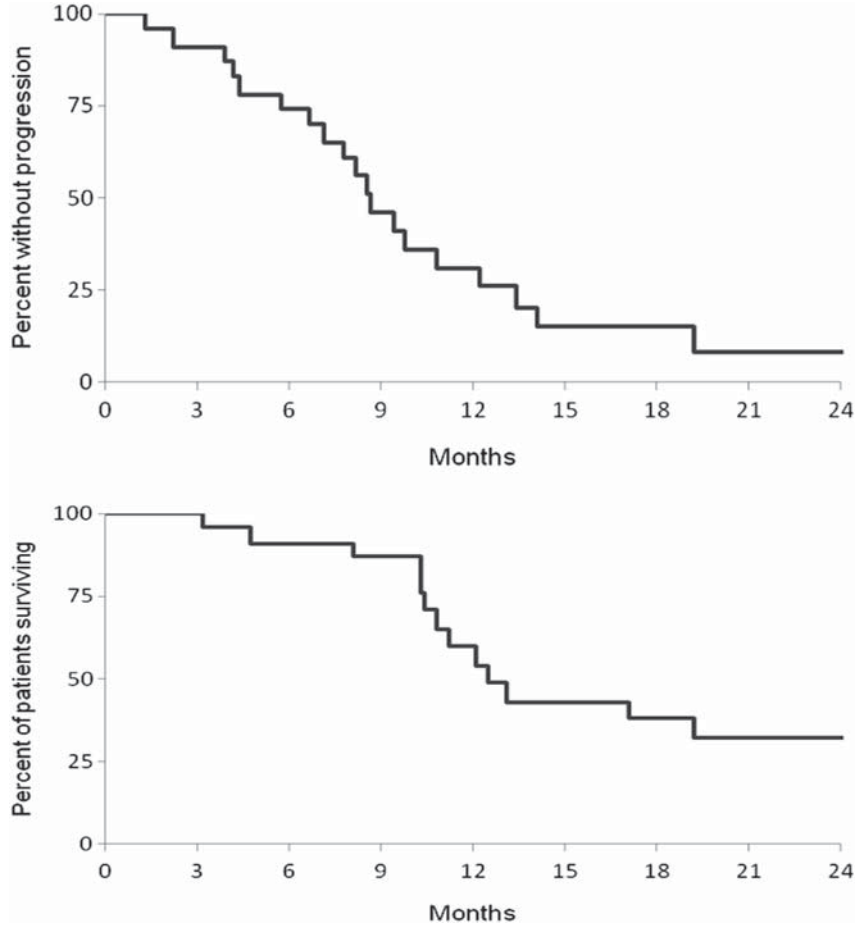

Figure 1. Time to progression and overall survival. Kaplan-Meier curves of time to progression (median 8.7 months; 95% CI 7.1-10.8 months) and overall survival (median 12.5 months; 95% CI 10.8-19.2 months).

level III where no DLT was seen and all patients received all planned courses of therapy (Table I). Chemotherapy-induced severe neutropenia can result in treatment-related hospitalization and even mortality. The incidence of complicated neutropenia may be reduced with the use of secondary granulocyte–colony-stimulating factor (GCSF) prophylaxis but presently GCSF is not routinely offered in Denmark to patients receiving palliative therapy. Several trials have evaluated docetaxel in GEC and shown higher RR and prolonged OS if docetaxel is used in a triplet regimen. This was demonstrated in the V-325 study where the triplet DCF regimen significantly increased RR and prolonged TTP and OS [11]. Unfortunately, DCF generated severe hematologic toxicity with neutropenia seen in 82% and febrile neutropenia in 29% despite the use of GCSF. Furthermore a schedule including continuous i.v. infusion of 5-FU and administration of cisplatin requires hospitalization in most departments. The substitution with oxaliplatin and capecitabine makes the administration much more simple and hopefully as effective with lower toxicity [8–10].

In several Danish oncology centres the EXE regimen is presently used as standard treatment in GEC. The primary aim of our phase I trial was to design a new easily administered out-patient regimen that would preserve efficacy without increasing toxicity of DCF.

In a randomized phase II trial by Roth et al., 119 patients were randomized either to ECF (epirubicin, cisplatin, 5-FU), DC (docetaxel, cisplatin) or DCF (docetaxel, cisplatin, 5-FU). The recommended dose of docetaxel was 85 mg/m^2 but because of an unexpected high incidence of febrile neutropenia in spite of the use of GCSF, docetaxel was reduced to 75 mg/m^2 after enrolment of the first 29 patients. Despite the reduction of docetaxel the incidence of neutropenia and febrile neutropenia in the DCF arm was 80% and 41% respectively. Dose reductions were performed in 44% of the cycles and 14% of these reductions was related to docetaxel. Due to a high RR rate (37%) but with substantial toxicity the authors concluded that the DCF regimen was to be considered in patients requiring a rapid tumor regression especially in the neoadjuvant setting [16].

In a comparable and recently published phase I trial by Sym et al. [17], the authors recommended docetaxel 60 mg/m^2, oxaliplatin 100 mg/m^2 and capecitabine 1 000 mg/m^2 twice daily day 1–14 repeated every three weeks. The principal toxicity was hematologic seen in 75% having neutropenia grade 3–4 and 25% experiencing febrile neutropenia. Despite severe hematologic toxicity the median dose intensity of docetaxel, oxaliplatin and capecitabine for the first six cycles of treatment was 89%, 94% and 94%, respectively. They found a remarkable high antitumor activity with a RR at 78.6% and an overall PFS and OS of 10.6 and 15.7 months respectively. It is not stated in the paper whether GCSF was recommended. Their TEX regimen was easily administered in the outpatient setting and patients obtained a high RR. Unfortunately haematological toxicity was comparable to the DCF regimen in the V-325 trial and therefore the authors recommend the regimen to patients being in a good performance status where down-staging is required.

The TEX regimen has also been evaluated in other malignancies. In a phase I trial by Amarantidis et al., docetaxel was given as a fixed dose at 50 mg/m^2 with escalating doses of capecitabine from 2 000–2 750 mg/m^2 day 1–7 and oxaliplatin 70–85 mg/m^2 every two weeks [18]. The RD in that trial was docetaxel 50 mg/m^2, oxaliplatin 75 mg/m^2 and capecitabine 2 750 mg/m^2 every second week. The study had a remarkable low grade of hematologic toxicity with neutropenia seen in only 5% of the cycles and dose intensity at the RD for all drugs was 84%. Unfortunately they only obtained a response rate at 29% which might be related to the mixture of different tumors included in the trial.

Previously Evans et al. reported a phase I study with the combination of docetaxel 35 mg/m^2, oxaliplatin 50 mg/m^2 day 1 + 8 and capecitabine 750 $\times$ 2 mg/m^2 for 10 days in a three week regimen [19]. As in the study by Amarantidis they observed a low degree of hematologic toxicity; neutropenia grade 3–4 and febrile neutropenia seen in only 6%. Dose-intensity is not discussed in the study, but no treatment cycle was delayed even though the use of GCSF was prohibited, the overall RR obtained was 18%. Evans concluded that the regimen was well tolerated and easily administered in the outpatient setting [19].

Triplet regimens with docetaxel appear superior to doublets in GEC. Furthermore there is a trend that docetaxel every three weeks produce more hematologic toxicity than therapy every or every second week. A randomized phase III study investigated docetaxel weekly (35 mg/m^2) versus docetaxel every three weeks (75 mg/m^2) in patients with metastatic breast cancer. There was no significant difference in PFS and OS among the two regimens, but they found a higher RR (35% vs 20%) in favor of therapy every three weeks but also significant increased grade 3–4 toxicity (88% vs 56%). Therefore, the authors concluded that the decision of which docetaxel schedule to use must depend on the purpose of the treatment and because of the lack of survival benefit between the two arms the weekly schedule with less toxicity may be considered in the palliative setting [20]. In our phase I study non-hematologic toxicities were generally moderate and predictable. The most frequent severe non-hematologic toxicities were diarrhoea, nausea, fatigue and peripheral neuropathy. The latter was observed in 26% of the patients, probably due to administration of two neurotoxic substances docetaxel and oxaliplatin. Oxaliplatin was administered as a 30 minutes infusion, but in prior studies we did not observe additional neurotoxicity [14,21]. The frequency of neuropathy in our study was equal to the comparable three week regimen by Sym et al. even though oxaliplatin here was given over the traditional two hours [17]. Our phase I study was not designed to evaluate efficacy, but we found an inspiring RR of 35%, PFS of 9.4 months and an OS at 12.5 months indicating the benefit of adding docetaxel to oxaliplatin and capecitabine. Unfortunately we saw substantial hematologic toxicity at dose level IV and patients here had on average two treatment courses lesser than patients at dose level III. In addition, dose-reductions were performed earlier in the course of treatment at dose level IV. The use of GCSF could probably have solved some of these problems but since it is not recommended routinely in the palliative setting in Denmark, we decided dose level III to be the RD.

Conclusion

The combination of docetaxel 60 mg/m^2, oxaliplatin 115 mg/m^2 and capecitabine 625 mg/m^2 twice daily continuously every three weeks is a well tolerated easily administered regimen in the out-patient setting showing promising antitumor activity. This combination will be evaluated in a Danish ongoing phase II study. The primary endpoint is RR and secondary endpoints are PFS and OS. As a consequence of the results seen in the Toga trial [22] patients being HER2 positive will be offered inclusion in a phase I study to find the best combination of TEX + Herceptin every three weeks.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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