Split-dose docetaxel, cisplatin and leucovorin/fluorouracil as first-line therapy in advanced gastric cancer and adenocarcinoma of the gastroesophageal junction: results of a phase II trial

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Background: Phase II and III trials of docetaxel, cisplatin and fluorouracil (DCF) have shown superior efficacy versus cisplatin and fluorouracil alone but high rates of hematologic toxicity in advanced gastric cancer. To reduce toxicity while maintaining the efficacy of DCF, we investigated split doses of docetaxel (T), cisplatin (P), leucovorin (L) and fluorouracil (F).

Patients and methods: Chemotherapy-naive patients with advanced gastric-/esophageal adenocarcinomas received T 50 mg/m^2 and P 50 mg/m^2 on days 1, 15 and 29 and L 500 mg/m^2 plus F 2000 mg/m^2 weekly, every 8 weeks. Because significant dose reductions to <80% became necessary in 80% of patients, the regimen was amended after the first 15 patients to T 40 mg/m^2, P 40 mg/m^2, L 200 mg/m^2 and F 2000 mg/m^2. The primary endpoint was response rate.

Results: Sixty patients were enrolled: 24 had locally advanced (LA) tumors and 36 had metastatic disease. Grade 3/4 toxicities included neutropenia (22%), febrile neutropenia (5%), diarrhea (20%) and lethargy (18%). The overall response rate was 47%. Twenty-three LA patients underwent secondary surgical resection (96%); complete resection was achieved in 87%. Overall, median time to progression and overall survival were 9.4 and 17.9 months, respectively (8.1 and 15.1 months, respectively, for patients with metastatic disease).

Conclusion: T-PLF regimen is highly active and has a favorable toxicity profile.

Key words: cisplatin, gastric cancer, leucovorin/fluorouracil, split-dose docetaxel

Introduction

Advanced gastric and gastroesophageal cancer remains one of the leading causes of death by neoplasia worldwide [1]. While current fluorouracil- and cisplatin-based combination chemotherapy regimens confer a survival benefit when compared to best supportive care [2], outcomes remain suboptimal.

In phase II studies, docetaxel has shown activity against gastric and gastroesophageal cancer as both monotherapy [3–5] and as part of combination chemotherapy [6–9]. In patients with untreated gastric cancer, the triple combination docetaxel–cisplatin–fluorouracil (DCF) is superior in terms of response rate to docetaxel–cisplatin (DC), epirubicin–cisplatin–fluorouracil and cisplatin–fluorouracil (CF) [7,9,10]. Results of the V325 trial demonstrate that the addition of docetaxel to CF results not only in a higher response rate, but also a prolonged time to progression (TTP) and overall survival (OS), improved quality of life and greater clinical benefit [10]. However, the high incidence of grade 3–4 neutropenia (82%) and febrile neutropenia (29%) observed in this study remains a concern.

To improve tolerability while maintaining the efficacy of the DCF regimen, the optimal dosing and scheduling of docetaxel-based chemotherapy needs to be refined. Phase I and II studies have demonstrated that the tolerability profile of docetaxel can be improved markedly when it is administered on a weekly schedule [11]. With weekly administration, complicated
neutropenia as a result of myelosuppression is rarely reported [12–14]. A split-dose regimen, with biweekly scheduling of docetaxel and cisplatin, may be a more tolerable regimen.

We performed a phase II trial to investigate the efficacy and safety of the split-dose docetaxel, cisplatin, leucovorin and fluorouracil regimen (T–PLF) in untreated patients with locally advanced (LA) or metastatic gastric cancer or adenocarcinoma of the esophagogastric junction.

patients and methods

This multicenter study was conducted at 10 institutions in Germany. It was coordinated within the study network of the Munich Centre for Clinical Studies. The protocol was approved by the ethics committee for human research at the Technische Universitaet Muenchen, Munich, and conformed to the principles of the Declaration of Helsinki and its subsequent amendments.

patient characteristics

Eligibility criteria included: histologically confirmed metastatic or LA adenocarcinoma of the stomach or gastroesophageal junction; age 18 years or older; Eastern Cooperative Oncology Group performance status 0–1; unidimensionally measurable lesion ≥1 cm in diameter detected by CT scan or MRI; absolute neutrophil count ≥5000/μl; platelet count ≥100 000/μl; total bilirubin ≤1.5 × upper limit of normal (ULN) and creatinine clearance ≥60 ml/min; and no prior chemotherapy except in the adjuvant or neoadjuvant setting ≥6 months prior to study entry. Exclusion criteria included: second malignancy; uncontrolled infection; neuropathy grade ≥3; hand–foot syndrome grade ≥2; and pregnant or lactating women. All patients gave written informed consent.

treatment

Initially, docetaxel was administered as 50 mg/m² followed by cisplatin 50 mg/m² on days 1, 15 and 29, and leucovorin 500 mg/m² and fluorouracil 2000 mg/m² on days 1, 8, 15, 22, 29 and 36, every 8 weeks (1 cycle). The dose was amended to docetaxel 40 mg/m², cisplatin 40 mg/m², leucovorin 200 mg/m², and fluorouracil 2000 mg/m² after treatment of the first 15 patients. Docetaxel and cisplatin were administered over 1 hour, leucovorin over 2 hours, and fluorouracil as continuous intravenous infusion over 24 hours. Patients received standard hydration and premedication with corticosteroids and antiemetics. Prophylactic granulocyte-colony stimulating factor (G-CSF) support was not permitted.

Toxicity was graded according to National Cancer Institute Common Toxicity Criteria (NCI-CTC, version 3.0). Depending on the severity of side effects, chemotherapy was paused or the dose was reduced. Fluorouracil infusion was paused or omitted in cases of diarrhea, mucositis, or hand–foot syndrome grade ≥1, and the dose reduced to 80% if diarrhea, mucositis, or hand–foot syndrome of grade ≥2 occurred. Cisplatin and docetaxel were delayed in the event of diarrhea, mucositis, and hand–foot syndrome of grade ≥2 and neutropenia (<1500/μl) or thrombocytopenia (<100 000/μl). If these events improved to grade <2, the dose was reduced to 80% for the subsequent treatment. Cisplatin and docetaxel doses were reduced to 80% in cases of peripheral neuropathy grade ≥2. Study treatment was discontinued if a toxicity grade ≥2 recurred despite dose reductions.

evaluation

Before registration, a complete medical history was taken, tumor-related symptoms were recorded and a full body examination was performed. Complete blood cell count (CBC), blood chemistry analyses, electrocardiograph, measurement of creatinine clearance and tumor assessment were carried out in all patients at study entry. CBC was evaluated weekly and electrolyte measurements every second week. Patients were assessed weekly for potential adverse events and disease-related signs and symptoms. Patients who had ended treatment but had not experienced disease progression were observed every 8 weeks until progressive disease and every 3 months thereafter.

Tumor measurements were undertaken every 8 weeks according to RECIST criteria [15]. Patients were considered assessable for response and toxicity if they had received ≥1 cycle of treatment. Patients were considered to be non-responders if no response assessment had been performed within the first 8 weeks of treatment. Treatment continued until best response, or until there was evidence of disease progression, unacceptable toxicity, death or consent withdrawal.

statistical analysis

The primary study endpoint was the proportion of patients who responded to T–PLF. The study was designed as a two-stage trial assuming a response rate of >40%. With a power of 80%, this resulted in a sample size of 15 patients for the first stage. The size of the second stage was determined by the observed number of responses and by the prespecified precision of 10%. In the event of ≥5 responders (complete or partial remission) in the first stage, the study population could be continued to a total of 45 patients (second stage). Due to dose adjustments after the first 15 enrolled patients, the total number of recruited patients was increased to 60 in order to have an adequately powered second stage. The statistical analysis was performed using SPSS software (version 12.0; SPSS, Inc., Chicago, IL, USA). Ninety-five percent confidence intervals (CI) were calculated for all relevant estimates using StatXact (version 5; Cytel, Inc., Cambridge, MA, USA). All statistical analyses were performed at a 5% level of significance.

The secondary study endpoints were median OS, TTP and toxicity. Analysis of TTP and OS was performed using the Kaplan–Meier life-table method. Comparisons between groups of patients were made by log-rank test. Median survival and hazard ratios (HR), calculated by Cox proportional hazards model, were reported, with 95% CIs. TTP and OS were analyzed in the intent-to-treat (ITT) population. TTP was determined from the day of study assignment to the date of any progression, death or last contact. Patients who had not progressed at the time of the final analysis were censored at the date of their last tumor assessment. OS was calculated from the day of assignment to death. Patients alive at the final survival analysis were censored using the last contact date.

The safety analysis included all treatment-emergent adverse events, including events possibly or probably related to study medication and those regardless of causality.

results

patient characteristics

Sixty patients were enrolled between March 2004 and August 2005. The primary tumor was located at the esophagogastric junction in 24 patients and in other parts of the stomach in the remaining 36 patients. Twenty-four patients had LA tumors without distant metastases (clinical T3 [cT3]–cT4, N0–N+, M0) and 36 patients presented with metastatic disease, with lymph nodes, liver, peritoneum and lung as the predominant metastatic sites (Table 1).

chemotherapy

In total, 112 cycles of T–PLF were administered, with a median of two cycles (range 1 to 4) per patient. There was
The median time until early treatment discontinuation was 5 weeks (range 1 to 13). The main reason for therapy discontinuation was toxicity (17%), followed by progressive disease (7%), consent withdrawal (3%) and death (2%). There were no treatment-related deaths. One patient with peritoneal carcinomatosis died within 60 days following study assignment due to bowel perforation, presumably as a delayed sequela of prior exploratory surgery.

Second- or third-line chemotherapy was given in 27/40 patients (68%), consisting mainly of irinotecan (12 patients) and oxaliplatin (11 patients)–based regimens. Additionally, two patients received both irinotecan- and oxaliplatin-based chemotherapy, three patients received a cisplatin-based regimen, and two patients were treated with either capecitabine or vinorelbine monotherapy.

toxicity

All 60 patients were assessable for toxicity. Hematologic and non-hematologic adverse events are summarized in Table 2. Treatment was generally well tolerated, with severe adverse events occurring in 10/112 cycles (9%). Overall, 38 patients (63%; 95% CI, 49.8% to 75.5%) experienced grade 3/4 adverse events. The most frequent grade 3/4 hematologic toxicity was neutropenia, occurring in 22% of patients and 19% of cycles. Febrile neutropenia occurred in only 5% of patients and 6% of cycles. The most frequent grade 3/4 non-hematologic toxicities possibly or probably related to study treatment were gastrointestinal toxicities, including diarrhea (20% of patients, 11% of cycles) and nausea and emesis (8% of patients each, 5% of cycles). No signs of fluid retention or nephrotoxicity were observed.

response

Fifty-six patients (93%) were assessable for response according to RECIST criteria. Four patients were not assessable (one patient died due to postoperative bowel perforation, one patient was lost to follow-up, and two patients stopped T-PLF therapy within the first cycle because of toxicity and were switched to second-line treatment without prior tumor assessment) but are included in the ITT analysis (Table 3).

The overall response rate (ORR; complete response + partial response) was 47% (95% CI, 33.3% to 61.4%). Response rates appeared to be similar before and after study amendment.

secondary resection

Of the 24 patients presenting with LA disease, 23 patients (96%) underwent secondary resection. One patient (4%) had newly developed distant lymph node metastases as detected by the follow-up CT, which did not allow for surgical resection. In patients with proximal gastric cancer, surgical therapy was a transhiatal extended gastrectomy and an extended D2-lymphadenectomy. A total gastrectomy was performed in seven patients and a subtotal esophagectomy with proximal partial gastrectomy in five patients. Tumor-free resection margins (R0) were achieved in 20 patients (87%). Two patients (9%) had microscopically incomplete tumor resection (R1) and the resection status could not be determined in one patient (4%). Among the 23 patients who underwent secondary resection

Table 1. Patient and tumor characteristics at baseline

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of patients</th>
<th>%</th>
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<td>1</td>
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<tr>
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Abbreviation: ECOG, Eastern Cooperative Oncology Group.

no difference in the median number of cycles between patients with LA or metastatic disease. The median duration of treatment was 12 weeks (range 1 to 18). The median relative dose intensity was 1.0 for docetaxel (range 0.33 to 1.0), 1.0 for cisplatin (range 0.33 to 1.0) and 0.92 for fluorouracil (range 0.17 to 1.0).

After the enrollment of 15 patients between March and May 2004, the chemotherapy regimen was amended to reduce hematologic and gastrointestinal toxicity, which had necessitated dose reductions in 12/15 patients (80%). Dose reductions (including docetaxel and cisplatin in 10/15 patients [67%] and fluorouracil reduction in 2/15 [13%]) were due to grade 3/4 neutropenia in five patients (33%), febrile neutropenia in one patient (7%), grade 3/4 diarrhea in four patients (27%), and hand–foot syndrome in one patient (7%).

After study amendment, a further 45 patients were enrolled between June 2004 and August 2005. At least one dose reduction was performed in 27/45 patients (60%) due to grade 3/4 toxicity, including reductions for both docetaxel and cisplatin in 11/45 patients (24%) and fluorouracil in 16/45 patients (36%). Overall, at least one dose reduction for either one or two agents was required in 39/60 patients (65%).
resection, a complete histopathologic response was seen in four patients (17%) and a subtotal response (<10% residual tumor) in five (22%). A total of eight patients (35%) had partial regression (10% to 50% residual tumor) and six patients (26%) had minimal or no tumor regression (>50% residual tumor).

At a median follow-up of 25.5 months, 40 patients (67%) presented with progressive disease. At the time of this analysis, 25 of the 60 patients enrolled (42%) are alive: 14/23 patients (61%) with LA disease and secondary resection and 11/37 patients (30%) with metastatic disease.

The median TTP was 9.4 months (95% CI, 8.3 to 10.5 months; Figure 1A). In patients with metastatic disease, median TTP was 8.1 months (95% CI, 6.3 to 9.9 months; HR 5.33; 95% CI, 2.43 to 11.72; log-rank P < 0.001; Figure 2A). Median survival in patients with LA disease and secondary resection has not yet been reached. The 1-year survival rate for patients with metastatic disease was 57%, with an estimated 2-year survival rate of 31%.

**discussion**

Our study showed a high response rate (47%) and a promising OS of 17.9 months in patients with advanced gastric cancer receiving T–PLF. These results are important because, until now, an optimal chemotherapy for this disease has remained elusive.

The V325 trial demonstrated an incremental benefit of adding docetaxel to the reference CF regimen as first-line therapy in patients with advanced or locally recurrent gastric cancer [10]. However, the high incidence of hematologic toxicities may be a limitation for the broad use of this highly active regimen. Modification of DCF may result in a less intense and more tolerable treatment. Myelosuppression, the most significant side effect, can be minimized when docetaxel is administered on a weekly schedule [11–13,16,17]. Due to these observations, we evaluated biweekly scheduling of DC combined with weekly fluorouracil–leucovorin. Based on experiences in a single arm phase II study and the results of a randomized trial conducted by the European Organization for Research and Treatment of Cancer (EORTC 40953), the cisplatin–fluorouracil–leucovorin combination was considered as the backbone chemotherapy regimen [18,19].

One possible limitation of our trial is that the study population was heterogeneous, including patients with LA and metastatic disease. LA disease is commonly associated with a better prognosis and chemotherapy was given as part of a neoadjuvant strategy to achieve surgical resection. In order to obtain comparable results with other studies, subgroup analyses were performed for each group.

In patients with metastatic gastric or gastroesophageal cancer, the T–PLF regimen compares favorably with the results in patients with advanced gastric cancer receiving T–PLF.
With an ORR of 47%, an encouraging median TTP of 8.1 months, and a median OS of 15.1 months in patients with metastatic disease, the activity of the T–PLF regimen exceeded the study hypothesis. As patient characteristics (such as performance status and age) are in the same range as in previously reported trials, our results cannot be attributed to patient selection alone. For interpretation of the results that were obtained in the whole study population, however, it has to be taken into account that nearly half of the patients had locally advanced, non-metastatic disease which is associated with a better prognosis. Furthermore, the split-dose regimen resulted in much less severe hematologic toxicity and—consequently—fewer episodes of serious infection, compared to the high incidence of grade 3/4 neutropenia seen with 3-weekly administration of DCF. Prophylactic G-CSF support was not given in our study and has therefore not contributed to the lower incidence of hematologic toxicity. With the exception of severe diarrhea, which occurred in 20% of all patients, other hematologic and non-hematologic toxicities were infrequent or mild-to-moderate in severity. Furthermore, there were no treatment-related deaths. Besides our efforts to reduce the toxicity of the DCF regimen by splitting doses of the cytotoxic agents, phase II and III trials with newer agents were conducted. In these recently presented trials the third generation platinum compound oxaliplatin and the oral fluoropyrimidine capecitabine proved to be equal in terms of efficacy but were associated with slightly reduced toxicity and better tolerability compared to cisplatin and infusional fluorouracil, respectively. Therefore, in
future studies, oxaliplatin and capecitabine may be considered treatment alternatives for cisplatin and infusional fluorouracil.

However, despite the promising safety data, dose reductions of one to two agents were required in 65% of patients. After enrollment of the first 15 patients, the safety assessment showed an unexpectedly high rate of dose reductions and the regimen was amended. Following dose reduction for all four agents, there was a decrease in the incidence of myelosuppression, and the rate of dose reductions for cisplatin and docetaxel decreased to 24%. This corresponds well with the SAKK/EIO [9] and V325 trials [10], which reported dose modifications in 44% and 41% of patients treated with DCF, respectively. However, after protocol amendment in our study, the rate of dose reductions for fluorouracil increased from 13% to 36%, with gastrointestinal toxicity as the most common adverse event. This finding correlates with the toxicity analysis from V325 [10], which showed that fluorouracil was the most commonly dose-reduced agent due to gastrointestinal toxicity. Interestingly, there were no differences in response rates between patients treated before and after the study amendment, indicating that moderate dose reductions can improve tolerability without major impairment of efficacy.

Our study also shows that the T–PLF schedule had at least similar antitumor activity as previously reported docetaxel-containing triple therapies in metastatic gastric and gastroesophageal cancer. With a 1-year survival rate of 57% and an estimated 2-year survival rate of 31% in metastatic disease, the T–PLF regimen appears to be a reasonable treatment approach in this setting. These promising efficacy data are consistent with the 1- and 2-year survival rates (40% and 18%, respectively) reported in the DCF arm of the V325 study [10]. In that study, 97% of patients had metastatic disease. Despite our promising results, the small number of patients with primarily metastatic disease limits their generalization to clinical practice. In 24 patients, tumors were initially classified as LA with the option of potentially curative surgery if the size of the cancer could be reduced, and 23 underwent secondary tumor resection. Complete resection (R0) was achieved in 20 initially unresectable patients (87%), with a high rate of histopathologic responders, which may correlate with the encouraging follow-up time in this patient group. For this patient population, the median survival has not yet been reached. These results suggest that neoadjuvant therapy with a docetaxel-containing regimen deserves further investigation.

In conclusion, the split-dose T–PLF regimen is an active treatment with high efficacy in terms of tumor response rate, TTP and OS. In patients with metastatic disease the considerably high survival rate of 15.1 months supports further investigation of the schedule. T–PLF was well tolerated, with moderate and manageable myelotoxicity. Compared to previously published studies, the reduction in hematologic toxicity may translate into quality of life advantages (e.g. in terms of fewer hospitalizations due to infection). Nevertheless, the high incidence of grade 3/4 diarrhea remains a concern and careful patient selection is warranted. The T–PLF regimen would be an appropriate comparator with other newly established reference regimens in advanced gastric cancer, and should be further investigated in large-scale randomized trials.

**References**


