Phase II study of docetaxel in combination with oxaliplatin in patients with metastatic or locally advanced esophagogastric cancer previously untreated with chemotherapy for advanced disease: results of the Central European Cooperative Oncology Group Study ESGAS.1.2.001

Michael Hejna[a], Markus Raderer[a], Johannes Zacherl[b], Ahmed Ba-Ssalamah[c], Andreas Püspök[d], Manuela Schmidinger[a], Ursula Pluschnig[a], Thomas Brodowicz[a,e] and Christoph C. Zielinski[a,e]

A phase II trial was performed to determine the efficacy and tolerance of docetaxel plus oxaliplatin with hematopoietic growth factor support in previously untreated patients with advanced gastroesophageal adenocarcinoma. Thirty-five patients were entered in this trial. Treatment consisted of 3-weekly docetaxel 80 mg/m^2 and oxaliplatin 100 mg/m^2 both infused on day 1. A prophylactic 5-day course of human granulocyte colony-stimulating factor 5 μg/kg/day was given subcutaneously, and erythropoietin (10 000 IU subcutaneously three times per week) was administered if hemoglobin was less than 12.0 mg/dl. The confirmed overall response rate was 34%, including two complete responses (6%) and 10 partial responses (28%). Fifteen patients (43%) had stable disease. The median time to response was 2.5 months (1–3.5), the median time to progression was 8.9 (4–42.5) months and the median overall survival time was 11.6 (2.5–51) months. Hematologic toxicity was common, though World Health Organization grade 3 or 4 neutropenia occurred only in six (17%) patients and anemia in six (17%) patients, respectively. Nonhematologic adverse reactions were usually mild-to-moderate. Our data suggest that the combination of docetaxel and oxaliplatin with granulocyte colony-stimulating factor and erythropoietin has a promising therapeutic index in patients with advanced gastroesophageal adenocarcinoma. ***Anti-Cancer Drugs*** **19:535–539 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Departments of [a]Internal Medicine I, Division of Oncology, [b]Surgery, [c]Radiology, [d]Internal Medicine III, Division of Gastroenterology, Medical University of Vienna, Vienna, Austria and [e]Central European Cooperative Oncology Group

Correspondence to Professor Michael Hejna, MD, Division of Clinical Oncology, Department of Internal Medicine I, Medical University of Vienna, Waehringer Guertel 18–20, A-1090 Vienna, Austria
Tel/fax: +43 1 40400 2296; e-mail: michael.hejna@meduniwien.ac.at

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Introduction

Surgical resection of all gross and microscopic disease remains the only proven, potentially curative treatment for localized gastric carcinoma, but recurrences are common even after potentially curative resection. Cytotoxic chemotherapy has been widely used in patients with recurrent, locally advanced or metastatic gastric cancer and has repeatedly been demonstrated to be effective in the palliative management of this disease. In randomized trials, a significant improvement in overall survival and in quality of life was noted when compared with best supportive care alone [1–3]. With a median time to progression of 4 months and a median overall survival of 8–9 months the results, however, are still unsatisfactory [4], and no single agent or combination therapy has emerged to become an accepted standard of care. Thus, the identification of new agents and/or drug combinations with an improved therapeutic index remains a principal goal of investigational efforts.

In the last few years the introduction of a new generation of cytotoxic agents, such as the taxanes, oxaliplatin, irinotecan, and oral fluoropyrimidines such as capecitabine and S-1, has renewed hope for more effective and better tolerated chemotherapeutic regimens.

As chemotherapy used in patients with disseminated disease, who fare in a particularly poor way, is aimed at producing palliative effects, both anticancer activity and side effects must carefully be taken into account. The results of published trials in patients with metastatic gastric carcinoma have suggested that both docetaxel and oxaliplatin are active and well tolerated. Docetaxel is a novel semisynthetic taxane developed in the 1980s and has both demonstrated activity against human gastric carcinoma cell lines *in vivo* as well as *in vitro* [5]. Many phase II trials using docetaxel as a single agent for first-line treatment have shown response rates ranging between 17 and 24% [6–8]. In addition, an overall

response rate of 18–24% was observed when given as second-line treatment [9,10]. The combination of docetaxel and cisplatin using a 2-weekly or 3-weekly administration schedule has already been investigated in phase II trials in advanced gastric cancer [11–13]. An encouraging response rate of 37–56% has been reported, though in one of these trials a very high rate of hematotoxicity was noted [11]. Similarly, oxaliplatin has shown antitumor activity in human gastric cell lines [14] and has been used in the first-line treatment of advanced gastric cancer and various combination regimens have been reported with response rates between 38 and 55% [15–17]. Data from the REAL-2 trial have confirmed the notion that oxaliplatin may be substituted for cisplatin and appears to be associated with significantly improved efficacy [18].

This study was performed to evaluate the therapeutic potential of a combination of docetaxel and oxaliplatin in patients with metastatic or locally advanced esophagogastric adenocarcinoma previously untreated with chemotherapy for advanced disease. To counteract myelosuppression that was likely to constitute the dose-limiting toxicity of this combination, and to maintain the planned dose intensity, granulocyte colony-stimulating factor (G-CSF) was given after the days of scheduled chemotherapeutic drug administration according to published data [13]. As various reports have suggested that erythropoietin enhances the effect of G-CSF and improves quality of life in cancer patients receiving platinum and nonplatinum chemotherapy with a possible beneficial effect on overall survival, we decided to co-administer this hematopoietic growth factor in patients with hemoglobin levels below 12 mg/dl [19,20].

Patients and methods

Patient selection

Patients eligible for this study had to have histologically confirmed advanced gastric cancer (including carcinomas of the esophagogastric junction) with bidimensionally measurable disease not previously treated with palliative chemotherapy and not amenable to curative resection. All patients were required to be younger than 76 years, to have a World Health Organization (WHO) performance status ≤ 2, to have an expected survival time of more than 12 weeks, and to have adequate bone marrow [hemoglobin ≥ 10 g/dl, absolute neutrophil count (ANC) $\geq 3000/\mu l$, platelet count $\geq 100\,000/\mu l$], adequate renal [serum creatinine concentration $\leq 1.25 \times$ upper normal limit (UNL)] and adequate hepatic function (total serum bilirubin $\leq 1.5 \times$ UNL, serum glutamic oxaloacetic transaminase and serum glutamic pyruvic transaminase $\leq 2.5 \times$ UNL, alkaline phosphatase $\leq 5 \times$ UNL). Patients were ineligible if they had a history of earlier or concomitant malignancy, except for curatively treated nonmelanoma skin cancer or in-situ cervical cancer. Pregnant or lactating female patients were not eligible for inclusion. Preexisting motor or sensory neurologic symptoms ≥ 2 grade according to National Cancer Institute of Canada–Clinical Trials Group criteria served as inclusion criteria, as did active infections or other serious underlying medical conditions impairing the ability of the patient to receive treatment according to the protocol. All patients had to give written informed consent according to institutional regulations.

Treatment protocol

Chemotherapy consisted of docetaxel 80 mg/m^2 dissolved in 250 ml of physiological saline infused over 1 h on day 1, and oxaliplatin 100 mg/m^2 diluted in 500 ml of 5% glucose solution administered as a 2-h infusion on day 1. To avoid fluid retention and/or anaphylactic reactions, patients were premedicated with 8 mg dexamethasone taken orally the night before, the morning of, and the evening after chemotherapy. In addition, 5-HT$_3$ antagonists were routinely given before cytotoxic drug administration. Treatment courses were repeated every 3 weeks, and – if restaging after three cycles showed at least stable disease – were to be continued for a total/maximum of six courses. A 5-day course of human G-CSF 5 μg/kg/day was given subcutaneously to prevent neutropenia; in addition, if hemoglobin was less than 12.0 mg/dl, erythropoietin 10 000 IU was administered subcutaneously three times per week.

Toxicity and dosage modification guidelines

Adverse reactions were evaluated according to WHO standard criteria. Treatment could be delayed for up to 2 weeks if the ANC was lower than 1.0×10^9/l and/or platelet count was lower than 50.0×10^9/l. A prolonged administration of G-CSF was recommended in the former group of patients. Drug doses were reduced by 25% if the ANC was lower than 3.0×10^9/l and/or platelet count was lower than 75.0×10^9/l after a maximum time of 2 weeks following nadir counts. Patients who experienced either febrile neutropenia, WHO Grade 4 thrombocytopenia, or bleeding associated with thrombocytopenia received a reduced dose of 50% for the following cycle. A subsequent, stepwise increase to the original dose was allowed provided that the patient tolerated treatment at the 50% level. Docetaxel was stopped in case of any grade 4 skin toxicity and grade 3 anaphylactoid reactions. Both chemotherapeutic drugs were discontinued if severe toxicity recurred despite dose attenuation. Similarly, any patient who required more than 3 weeks for full recovery from adverse reactions (except alopecia and mild neuropathy) was taken off study.

Pretreatment and follow-up evaluation

Pretreatment evaluation included a complete medical history and physical examination, routine hematology and biochemistry analyses, ECG and CT scans of thorax and

abdomen to define the extent of disease. Complete blood counts and differential counts were obtained weekly, and biochemical profiles were assessed before each treatment cycle. Measurable lesions were reassessed every three chemotherapeutic cycles by CT scan or any other technique allowing for retrospective and independent evaluation, depending on initial imaging findings and techniques applied.

Assessment of response

The primary objective was to evaluate the time to progression as calculated from the start of therapy to the time of progression or relapse, and the secondary objective was assessment of tolerance and safety of the docetaxel/oxaliplatin combination. In addition, the overall response rates (evaluated according to the WHO standard criteria), duration of response (measured from the onset of the best response to the date of disease progression or death) and overall survival were determined.

Results

Patient characteristics

Between March 2003 and July 2006, a total of 40 patients took part in this trial. Five of these 40 patients were not evaluable. One patient with locally advanced disease not amenable to curative resection developed a radiological complete response (CR) after three courses of treatment and thus underwent potentially curative resection, which also showed a pathological CR. After resection, the patient now remains in ongoing CR for 13 months. Two patients having stable disease after three courses refused further treatment for personal reasons, whereas another two patients discontinued therapy after one cycle.

In total, 35 patients were considered evaluable. The demographic data, extent of disease and extent of previous surgery are listed in Table 1. Five patients suffered from adenocarcinoma of the distal esophagus, 25 patients had the tumor located in the stomach and five patients had a local recurrence. The median age was 58.6 years (range, 28–75 years), and the median WHO performance status was 1 (range, 0–2). Except for 22 patients, all had multiple metastases involving two or more organ systems. Thirty patients (86%) had been newly diagnosed with disseminated disease, with one patient requiring palliative surgical intervention. The remaining five patients had metastatic disease recurrence after having undergone previous potentially curative resection. In these patients, the median interval from initial diagnosis to relapse was 20.6 (range, 2–44) months. A total of 173 treatment courses with docetaxel/oxaliplatin were administered to these 35 patients, with the median number of courses being 4.9 (range, 2–6).

Table 1 Patient characteristics

Patients	35
Sex	
Male	30
Female	5
Age, years	
Median	58.6
Range	28–75
WHO performance status	
0	10
1	22
2	3
Histological grading	
G1	2
G2	18
G3	15
Site of primary tumor	
Esophagus (distal)	5
Stomach	25
Cardia	13
Fundus	2
Corpus	9
Antrum	1
Anastomosis	5
Previous surgery	
Curative	6
Palliative	1
Diagnostic laparoscopy	12
None	17
Location of metastases	
Abdominal lymph nodes	14
Liver	15
Peritoneal carcinomatosis	12
Lung	2
Bone	1
Involved organs	
Single	22
Multiple	12

Response to therapy

The median time to progression was 8.9 months (range, 4–42.5) and the median survival was 11.6 months (range, 2.5–51+) with two patients (2%) still being alive at the time of this report. The overall objective response rate was 34%, including two complete (6%) and 10 partial (28%) responses; the median duration of response was 7.2 months (range, 3.5–40). Fifteen additional patients (43%) showed disease stabilization and nine (23%) progressed while on treatment (for details, see Table 2).

Ten patients, who failed to respond to docetaxel/oxaliplatin or experienced tumor progression within 6 months after completion of chemotherapy, received second-line therapy consisting of various regimens at the discretion of the treating physician.

Toxicity

All 35 patients, who received a total of 173 courses, were assessable for toxicity. Myelosuppression was the most commonly encountered adverse reaction, although according to the ANC-adapted use of G-CSF, the time to white blood cell/ANC recovery was generally short, and 95% of the episodes of leucopenia/neutropenia resolved within 7 days. Leukocytopenia occurred in 14 patients (40%), and was grade 3 or 4 in four (12%) and one (3%) patients, respectively. Neutropenia was observed in 10 cases, and was grade 3 or 4 in one (3%) and five patients (14%), despite administration of G-CSF after the day of scheduled chemotherapeutic drug administration,

Table 2 Summary of treatment efficacy

Complete response	2 (6)
Partial response	10 (28)
Stable disease	15 (43)
Progression	8 (23)
Overall response rate	12 (34)
Median time to response, months	2.5
Median time to progression, months	6.4; range, 1.5–40
Median survival time, months	11.6; range, 2.5–51

Figures in parentheses are percentages.

as indicated in the protocol. Four patients (12%) developed documented infections, but only one required hospitalization for intravenous antibiotics. Anemia was commonly observed (91%) and was grade 3 or 4 in five (14%) and one (3%) patients, respectively. Nineteen patients (54%) received erythropoietin because their pretreatment value was, or dropped below 12.0 mg/dl during chemotherapy, and 10 (53%) responded to this hematopoietic growth factor support. Grade 1 thrombocytopenia was noted in only five patients (14%). Among nonhematologic adverse reactions, gastrointestinal symptoms were the most frequently encountered toxicities. Nausea and vomiting occurred in 17 patients (49%); symptoms, however, were generally mild or moderate (grade 1 or 2 in nine and seven, respectively) and responsive to standard antiemetic therapy. Grade 1 or 2 diarrhea was noted in 11 patients (31%) and grade 3 in three patients (9%), respectively. Grade 1 or 2 oral mucositis occurred in seven patients (20%) and grade 3 mucositis in one patient (3%). Thirty-one patients (89%) developed grade 1 or 2 peripheral neuropathy. One patient developed an anaphylactoid reaction despite premedication with steroids. Loss of appetite and fatigue were reported in six patients (17%) each, and minor fluid retention in two patients (6%). Alopecia was noted in a total of 13 patients (37%) and mild constipation in three patients (9%) (Table 3).

Table 3 Side effects (hematologic and nonhematologic)

	WHO grade			
Side effect	I	II	III	IV
Leukopenia	7 (20)	2 (6)	4 (11)	1 (3)
Neutropenia	2 (6)	2 (6)	1 (3)	5 (14)
Anemia	17 (49)	9 (26)	5 (14)	1 (3)
Thrombocytopenia	5 (14)	–	–	–
Emesis	9 (26)	7 (20)	1 (3)	–
Diarrhea	6 (17)	5 (14)	3 (9)	–
Constipation	1 (3)	2 (6)	–	–
Infection	–	4 (11)	–	–
Polyneuropathy	20 (57)	11 (31)	–	–
Loss of appetite	5 (14)	1 (3)	–	–
Oral mucositis	5 (14)	2 (6)	1 (3)	–
Alopecia	5 (14)	8 (23)	–	–
Fatigue	5 (14)	1 (3)	–	–

Figures in parentheses are percentages.

Discussion

The continuing lack of substantial progress in the treatment of advanced gastric cancer, particularly in patients with poor performance status or compromised organ function unlikely to tolerate potentially active but toxic regimens, has prompted investigators to explore new agents and/or drug combinations [11,12,21,22]. This phase II study was initiated to evaluate the potential of docetaxel combined with oxaliplatin in patients with metastatic or locally advanced esophagogastric adenocarcinoma previously untreated with chemotherapy for advanced disease. Prophylactic use of G-CSF was performed to minimize acute toxicities and counteract myelosuppression that was likely to constitute the dose-limiting toxicity of this combination [11]. Furthermore, we decided to coadminister erythropoietin in patients with hemoglobin levels below 12 mg/dl.

With a response rate of 34%, including 6% complete remissions, a median time to progression of 6.4 months, and median overall survival time of 11.6 months, the results of this phase II trial suggest a marked antitumor activity of the combination in patients with metastatic or locally advanced esophagogastric adenocarcinoma. The nonrandomized phase II study design, as has repeatedly been demonstrated, certainly does not allow firm conclusions to be drawn or for comparison with other regimens. In fact, other drug combinations with even higher objective response rates than observed in this study have been described, and have failed to show superiority in subsequent phase III trials [23,24]. Therefore, results must be interpreted with caution, and warrant confirmation in a randomized setting. A potential advantage of our study as compared with the epirubicin, cisplatin, 5-fluorouracil -regimen or docetaxel, cisplatin, and 5-fluorouracil-regimen [18,25,26] is the potential administration on an outpatient basis and the nonrequirement of a central venous access and external infusion devices with their associated risks and costs [27,28].

In terms of tolerance of this regimen, neutropenia was a commonly encountered adverse reaction, but WHO grade 3 or 4 toxicity occurred in only 17% of our patients. Although, again, our data does not allow for direct comparison, this seems to be relatively low as opposed to 47–81% reported in other trials using docetaxel and a platinum compound [11,15]. In addition, none of the 173 courses had to be delayed for hematologic toxicity, and there was no febrile neutropenic episode, which was probably owing to the prophylactic use of G-CSF. The rather high rate/incidence of anemia in our patient population was probably not only caused by therapy, but also influenced by the underlying malignant disease. Seventeen patients received recombinant human erythropoietin according to the protocol and nine of them (53%) responded to the hematopoietic growth factor support.

Apart from a grade 3 oral mucositis in one patient and grade 3 diarrhea in three patients, nonhematologic adverse reactions were generally mild-to-moderate and fully reversible. Interestingly, there were no cases of severe

peripheral neuropathy, which has also been observed in other studies using docetaxel and oxaliplatin [15,29].

In conclusion, the combination of docetaxel plus oxaliplatin with G-CSF and/or erythropoietin is effective and well tolerated in the first-line treatment for patients with advanced esophagogastric adenocarcinoma, and deserves further testing in a phase III trial. Compared with previous phase II/III investigations of docetaxel and platinum-compound combinations, the incidence of severe neutropenia as well as of certain other nonhematologic adverse reactions seems to be low. In view of the promising therapeutic index of the described regimen, further evaluation of this combination in comparison with other active regimens (e.g. the docetaxel, cisplatin, 5-fluorouracil regimen, and the epirubicin, cisplatin, 5-fluorouracil regimen, or the epirubicin, oxaliplatin, capecitabine regimen) in a randomized fashion, in patients with advanced esophagogastric adenocarcinoma, including its use in the neoadjuvant setting, seems warranted.To further improve treatment results in this dismal disease, the addition of targeted therapy to cytotoxic agents should, however, be considered. In addition, precise definition of the impact of correcting anemia with erythropoietin in terms of quality of life and therapeutic outcome could be an interesting feature of future studies.

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