

Docetaxel plus Oxaliplatin in Combination with Capecitabine as First-Line Treatment for Advanced Gastric Cancer

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Key Words

Capecitabine · Docetaxel · Gastric cancer · Oxaliplatin · Phase II

Abstract

Objective: In the present phase II study, we evaluated the efficacy and safety of a docetaxel-oxaliplatin-capecitabine combination as a first-line treatment in patients with advanced gastric cancer. **Patients and Methods:** A total of 27 patients (18 males) with histologically confirmed inoperable gastric adenocarcinoma were recruited. Docetaxel was given (50 mg/m² i.v.) on day 1 followed by oxaliplatin (75 mg/m² i.v.) also on day 1. Capecitabine (2,750 mg/m²) was given orally as two daily divided doses from days 1 to 7. Cycles were repeated every 2 weeks. All patients had measurable disease and 18 of them had a performance status (WHO) of 0. **Results:** A total of 240 treatment cycles were administered. All patients were evaluable for toxicity. Four patients who discontinued treatment early (having received only 3 chemotherapy cycles) were included as non-responders in an intention-to-treat response analysis. Complete response, partial response, stable disease and progressive disease were observed in 4 (15%), 12 (44%), 3 (11%) and 8 (30%) patients,

respectively. The observed response rate was 59%, and the disease control rate (complete response + partial response + stable disease) was 70%. At the time of analysis, 6 patients were still alive and the median survival was 18.0 months. The most common grade III/IV toxicities observed were neutropenia (5%), diarrhea (2%), palmar-plantar erythrodysesthesia (2%) and neurotoxicity (1%). All other toxicities were mostly of grade I/II and easily manageable. **Conclusion:** The combination of docetaxel, oxaliplatin and capecitabine in the described mode of administration represents a relatively active and well-tolerated regimen in patients with advanced gastric cancer and warrants further evaluation.

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Introduction

Gastric cancer is the fourth most commonly diagnosed cancer with an estimated number of 934,000 new cases diagnosed annually, causing 700,000 deaths worldwide [1]. Despite improvements in early diagnosis, many patients still present with unresectable locally advanced or metastatic disease. Advanced gastric adenocarcinoma remains an incurable disease. Median survivals of 7.5–12

months have been reported in patients receiving chemotherapy, compared with 3–5 months for those receiving best supportive care alone [2–4].

There is no globally accepted standard chemotherapy regimen for those patients; therefore, the need for more effective systemic therapy is urgent. Combination chemotherapy seems to be more advantageous than monotherapy [5]. Generally, 5-FU, cisplatin and docetaxel (and less commonly paclitaxel, epirubicin and irinotecan) represent the major components of various doublets and triplets tested in this poor-prognosis population in order to improve efficacy parameters along with quality of life amelioration [3, 5]. For many countries, the combination of cisplatin plus 5-FU has been adopted as the standard reference regimen showing a significant survival advantage [6, 7]. In Europe, triple-combination regimens, such as the combination of epirubicin, cisplatin and continuous 5-FU infusion (ECF regimen) represent acceptable alternatives [8].

The addition of docetaxel to the combination of cisplatin plus 5-FU (DCF regimen) has recently been shown to result in significantly higher response rates and superior time to progression [9]. However, the regimen was associated with significant hematologic toxicity [9]. Capecitabine, an orally administered prodrug of 5-FU, has been demonstrated to be non-inferior to 5-FU in the treatment of advanced esophagogastric cancer in two large phase III trials [10, 11]. In this context, a phase II study with a modified DCF regimen (including weekly docetaxel, carboplatin plus capecitabine) was tested [12]. The response rates and 1-year survival data were comparable to similar more complex regimens, and the combination was well tolerated [12]. Furthermore, oxaliplatin in combination with capecitabine seems to be as effective as 5-FU plus cisplatin in patients with previously untreated esophagogastric cancer [10].

Based on the reported encouraging efficacy of various doublets between docetaxel, capecitabine and oxaliplatin, we investigated the feasibility of combining all these three agents in a previous phase I trial in patients with different solid tumors [13]. In this phase I study, docetaxel plus oxaliplatin were concurrently given biweekly with capecitabine orally twice daily for 7 consecutive days. The regimen was associated with acceptable toxicity and considerable efficacy, particularly in patients with gastric cancer. Therefore, we decided to further investigate its efficacy and tolerability in a larger phase II study in this patient population.

Patients and Methods

Eligibility Criteria

Patients with histologically or cytologically confirmed advanced gastric adenocarcinoma and measurable disease were eligible for the trial. Eligibility criteria included age <75 years, a life expectancy of at least 3 months, adequate performance status (WHO scale 0–1), adequate renal function (creatinine clearance >60 ml/min), adequate hepatic function (serum bilirubin <1.5 the upper limit of the reference range, transaminases <5 the upper limit of the reference range), adequate hematologic function (hemoglobin >10 g/dl, neutrophil count >1.5 × 10⁹/l; PLT >100 × 10⁹/l) and adequate cardiac function (left ventricular ejection fraction >50% and no history of myocardial infarction in the past 6 months). Patients with brain metastases were eligible if they had been irradiated, the brain lesions were radiographically stable, and clinical improvement was evident. The study excluded patients unable to receive oral medications, those with a history of allergic reaction to any of the study agents, peripheral neuropathy, or those receiving other investigational agents. Patients were also excluded if they demonstrated evidence of any other medical problems severe enough to affect their compliance with the protocol. The study was approved by the ethical and scientific committee of our institution, and written informed consent was obtained from all patients prior to screening and enrolment.

Treatment Schedule

Docetaxel was administered on day 1 as a 1-hour i.v. infusion at the dose of 50 mg/m². Oxaliplatin (75 mg/m²) was given on day 1 diluted in 500 ml of D/W 5% (dextrose and water) as a 2-hour i.v. infusion following docetaxel administration. Capecitabine (2,750 mg/m²) was administered orally on days 1–7, given as two daily divided doses taken with 150–200 ml water and within 30 min after a meal. This dosing schedule was adopted from our previous phase I study [13]. Compliance with the oral medication regimen was assessed by tablet counts at each clinical visit. To prevent palmar-plantar erythrodysesthesia (PPE) patients were advised not to use tight clothing and shoes, avoid direct sunlight and refrain from hot baths/showers [14]. Patients were medicated with dexamethasone (8 mg) orally every 12 h × 3 doses, starting the night before the scheduled docetaxel dose. All patients were premedicated with ondansetron (16 mg) or an equivalent 5-hydroxytryptamine-3 inhibitor. Cycles were repeated every 2 weeks if the absolute granulocyte count was >1.5 × 10⁹/l, the PLT >100 × 10⁹/l and non-hematologic toxicity was resolved.

Dose Modifications

Dose modifications were performed on the basis of toxicity. Administration of the agents was delayed until adequate hematologic recovery up to a maximum of 2 weeks. In case of grade 4 hematologic toxicity in individual patients, all chemotherapeutic drug doses were reduced by 25% for subsequent courses. More specifically, the oxaliplatin dose was reduced by 25% at subsequent courses in cases of persistent (>14 days) or temporary (7–14 days) painful paresthesia or functional impairment. In cases of persistent painful paresthesia or functional impairment despite a 25% dose attenuation, oxaliplatin was omitted in subsequent cycles. In general, the doses of both docetaxel and oxaliplatin were reduced by 25% for all subsequent chemotherapy cycles in patients who experienced a second occurrence of a given grade 2 toxicity or any grade 3 and 4 neurologic toxicity. Capecitabine

administration was interrupted if patients developed greater than grade 2 diarrhea, stomatitis and/or nausea/vomiting until resolution of the toxicity to grade 1. Doses of capecitabine omitted for toxicity were not replaced or restored on resolution of the toxicity to grade 1, and subsequent treatment cycles were given at the appropriate dose adjustment. As a general rule, the daily dose of capecitabine was reduced by 25% at the first occurrence of grade 3 toxicity or the second occurrence of grade 2 toxicity. The daily dose was reduced by 50% at the first occurrence of grade 4 toxicity, the second occurrence of grade 3 toxicity and the third occurrence of grade 2 toxicity. Capecitabine was discontinued at the second occurrence of grade 4 toxicity. No dose reductions or interruptions were performed for anemia or for any grade 1 toxicity.

Patient Evaluations

Baseline evaluations included the following: patient history, physical examination, chest X-rays, complete blood count with differential and platelet counts, blood chemistry, electrocardiograph, CT scans of the chest, abdomen and pelvis, while whole-brain CT scans were performed when clinically indicated. Complete blood counts with differential and platelet counts were performed twice weekly or daily in patients with severe myelosuppression; whole blood chemistry and a physical examination were performed every 2 weeks. All adverse events were documented. WHO performance status was assessed every 2 weeks. Response was assessed according to the Response Evaluation Criteria in Solid Tumors [15]. In case of complete response, patients received 4 additional chemotherapy cycles after the criteria of complete response were first met. Patients with partial response and stable disease were treated for a maximum of 12 cycles. Patients were withdrawn from the study upon encountering any evidence of progressive disease. Tumor responses had to be confirmed 4–6 weeks after their initial documentation.

Study Objectives and Statistics

The primary endpoint of the study was the efficacy of the regimen in terms of objective response rate in an intention-to-treat population. Patients were evaluable for response if they had received at least 4 chemotherapy cycles. Otherwise, they were included in the response analysis as non-responders. According to Simon's two-stage optimal design, and assuming that the expected overall response would be at least 40% and the minimum acceptable response rate 18%, a sample of 13 patients would be required in the first step [16]. If a minimum of 3 responses was observed, an additional 14 patients would be accrued onto the second stage of the study. Thereby, if at least 8 responses occurred among all 27 evaluable patients, the treatment would be declared sufficiently promising. The probability of accepting a treatment with a real response rate $\leq 17\%$ would be 5%. Conversely, the risk of rejecting a treatment (at the second stage) with a response rate $\geq 40\%$ would be 10%. Secondary endpoints were progression-free survival, overall survival and the safety of the chemotherapy regimen.

Results

From August 2005 to January 2010, 27 patients suffering from advanced or metastatic gastric cancer were enrolled into the study. Their median age was 65 years and

Table 1. Patient characteristics

| | n |
|--------------------------|-------------------|
| Patients enrolled | 27 |
| Median age, years | 65 (range: 40–80) |
| Gender | |
| Male | 18 (67%) |
| Female | 9 (33%) |
| Performance status (WHO) | |
| 0 | 18 (67%) |
| 1 | 9 (33%) |
| Stage | |
| IIIB | 4 |
| IV | 23 |
| Site of metastases | |
| Liver | 14 |
| Lymph nodes | 15 |
| Lung | 3 |
| Bone | 5 |
| Peritoneum | 6 |
| Previous treatment | |
| Surgery | 8 |
| Radiation therapy | – |
| Chemotherapy | 3 |

18 (67%) had a performance status (WHO) = 0. Eighteen were male and 23 had metastatic disease. All but 3 patients had not received previous chemotherapy. Those 3 patients had received a combination of cisplatin and 5-FU as adjuvant treatment and had relapsed after 3, 10 and 23 months, respectively. Patient characteristics at baseline are summarized in table 1.

Compliance to the Protocol

A total of 240 chemotherapy cycles were administered with a median of 9 cycles per patient. Toxicity data are available from all patients and all cycles. Four patients received only 3 treatment cycles because of an allergic reaction (2 patients), neutropenia grade 4 (1 patient) and performance status deterioration (1 patient). Nine patients received all the planned treatment cycles. Twenty-two patients stopped the treatment after at least 4 cycles for the following reasons: progressive disease (n = 8), allergic reaction (n = 2), neurotoxicity grade 3 (n = 2), PPE grade 3 (n = 2), neutropenia grade 4 (n = 1), fatigue grade 3 (n = 3), pleural effusion (n = 1) and loss to follow-up (n = 3). A total of 48 (20%) cycles were delayed due to unresolved PPE (7 cycles), neutropenia (31 cycles; in one case this was complicated with fever), diarrhea (3 cycles; one of them being febrile), thrombocytopenia (3 cycles), ane-

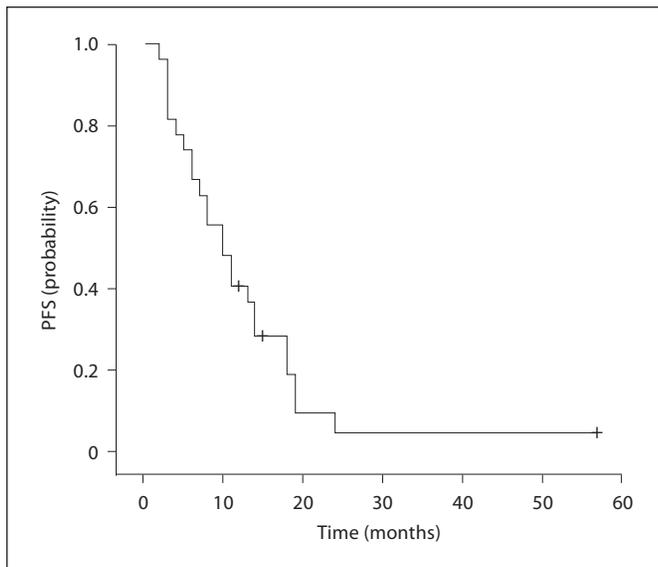


Fig. 1. Progression-free survival.

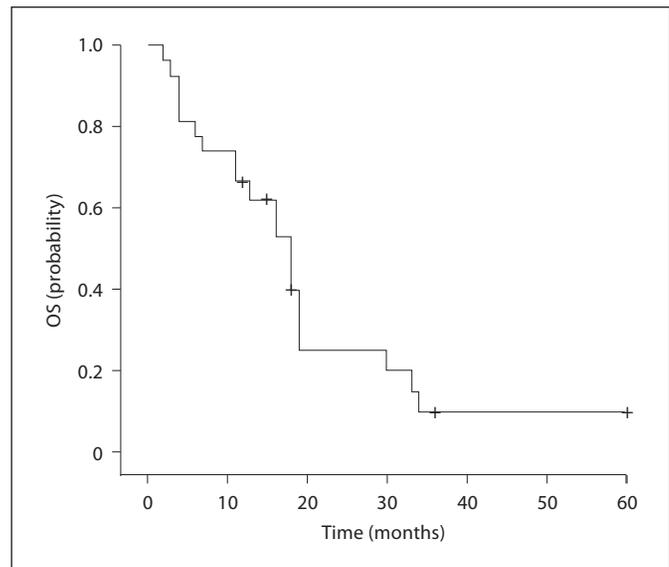


Fig. 2. Overall survival.

mia (1 cycle), respiratory infection (1 cycle), urinary infection (1 cycle) and allergic reaction (1 cycle). Dose reduction was required in 71 (29%) treatment cycles in total. More specifically, dose reduction of all three drugs was required in 45 (18%) cycles. The reasons for these reductions were neutropenia (29 cycles), febrile neutropenia (6 cycles), thrombocytopenia (1 cycle) and diarrhea (9 cycles). The dose of docetaxel alone was reduced in 4 (1%) additional cycles due to nail disorders, and that of capecitabine alone in 22 cycles (9%) due to PPE. The administered doses of docetaxel, oxaliplatin and capecitabine were 93.54, 93.24 and 94.43% of the protocol planned doses, respectively.

Response to Treatment

At the time of analysis, all 27 patients had measurable disease and 23 of them these completed at least 4 treatment cycles and were evaluable for response. Four patients that received only 3 treatment cycles were included in the response analysis as non-responders. Complete response was recorded in 4 (15%), partial response in 12 (44%), stable disease in 3 (11%) and progressive disease in 8 (30%) patients. Three out of four complete responders had been previously treated with a total gastrectomy and had relapsed distantly. The other patient had inoperable disease at presentation, and at the first documentation of complete response an endoscopy along with blind biopsies at the area of the initial disease presentation was performed.

Regarding complete responses, these were seen in: liver plus local disease (1 patient), liver and regional lymph nodes (1 patient), liver and peritoneal metastases (1 patient) and liver plus lung metastases (1 patient). These responses were achieved after 12, 12, 10 and 6 months, respectively. The median progression-free survival (PFS) was 10 months (95% CI: 6.2–13.8) (fig. 1). The median overall survival (OS) was 18.0 months (95% CI: 13.6–22.4) (fig. 2) and the estimated 1-year survival was 66.7%.

Hematologic Toxicity

Hematologic toxicity was generally mild. Grade 3/4 neutropenia occurred in 11 patients (41%) and 12 cycles (5%). In one case, neutropenia was complicated with fever requiring patient hospitalization for 7 days in order to administer i.v. antibiotics and rhG-CSF. The episode resolved uneventfully within 7 days. The granulocyte nadir usually occurred between days 9 and 12, and the median time to recovery was 5 days (range: 3–6). Grade 2/3 anemia was seen in 3 (11%) patients and 3 cycles (1%), and grade 2 thrombocytopenia was recorded in 3 (11%) patients and 3 (1%) cycles. Hematologic toxicity is summarized in table 2.

Non-Hematologic Toxicity

During the entire treatment period, a total of 12 patients experienced grade 3 non-hematologic toxicities. These included 3 patients with grade 3 diarrhea (4 cycles),

Table 2. Hematologic toxicity per cycle

| | Neutropenia | Anemia | Thrombocytopenia |
|---------|-------------|--------|------------------|
| Grade | | | |
| 1 | 3 (1) | 11 (5) | 8 (3) |
| 2 | 16 (5) | 2 (1) | 3 (1) |
| 3 | 8 (3) | 1 (1) | – |
| 4 | 4 (2) | – | – |
| Overall | 31 (13) | 14 (6) | 11 (5) |

Parentheses contain percentages.

Table 3. Non-hematologic toxicity per cycle

| | Diarrhea | Nausea | PPE | Nail disorders | Neurotoxicity | Conjunctivitis |
|---------|----------|--------|---------|----------------|---------------|----------------|
| Grade | | | | | | |
| 1 | 12 (5) | 3 (1) | 15 (6) | 5 (2) | 56 (23) | 2 (1) |
| 2 | 2 (1) | 5 (2) | 6 (3) | 4 (2) | 6 (3) | 1 (1) |
| 3 | 4 (2) | – | 5 (2) | – | 3 (1) | – |
| 4 | – | – | – | – | – | – |
| Overall | 18 (7) | 8 (3) | 26 (11) | 9 (4) | 65 (27) | 3 (1) |

Parentheses contain percentages.

4 patients with grade 3 PPE (5 cycles), 3 patients with grade 3 neurotoxicity (3 cycles), 1 patient with grade 3 mucositis (1 cycle) and 1 patient with grade 3 fatigue (1 cycle). In all cases with neurotoxicity, this presented as acral paresthesia and was attributed to oxaliplatin. Grade II nail disorders were recorded in 4 patients and this toxicity was attributed to docetaxel. Two patients experienced allergic reactions (1 patient immediately after docetaxel and 1 after oxaliplatin infusion). This was the reason for treatment interruption in both patients. Pleural effusion was recorded in 2 patients and pericardial effusion in 1 patient. Non-hematologic toxicity is summarized in table 3.

Discussion

Metastatic gastric cancer remains an incurable disease, with a relative 5-year survival rate of 7–27%. Chemotherapy, in order to improve OS and quality of life, is the main treatment option. At present, there is no widely

accepted best chemotherapy regimen for metastatic esophagogastric cancer [17, 18]. Older regimens such as FAM (fluorouracil, doxorubicin and mitomycin) [19], FAMTX (fluorouracil, doxorubicin and methotrexate) [20] and EAP (etoposide, doxorubicin and cisplatin) [21] have not clearly demonstrated any superiority over one another. Continuous infusion 5-FU may be more effective than bolus 5-FU. The ECF regimen demonstrated a survival advantage over FAMTX in patients with metastatic gastric cancer with a median survival of 8.7 months for ECF and 6.1 months for FAMTX [22]. The combination of capecitabine and docetaxel showed preclinical synergy and a clinical benefit was documented in subsequent trials [23–25]. Furthermore, the TAX325 trial established docetaxel as a new option for the treatment of metastatic gastric cancer [9]. The DCF regimen, as compared to cisplatin and 5-FU, demonstrated a statistically significant improvement in both median overall survival (9.2 vs. 8.6 months) and 1-year survival (40 vs. 32%) in patients with advanced gastric cancer. However, both regimens were complicated by a high incidence of toxicity. In the DCF arm, 81% of patients had grade 3/4 non-hematologic toxicity and 84% of patients developed grade 3/4 neutropenia. In addition, positioning of a central venous catheter for continuous 5-FU infusion was required. In the present study, we attempted to modify the DCF regimen in a regimen with reduced toxicity and similar activity. We selected a oral biweekly schedule of docetaxel plus oxaliplatin given concurrently with capecitabine for 7 consecutive days. Weekly and biweekly schedules of docetaxel may have less myelosuppression than an equivalent dose administered every 3 weeks [26–28]. Capecitabine has eliminated the need for a continuous 5-FU infusion. A 7-day course of capecitabine was utilized instead of the more widely used 14-day schedule, in order to better incorporate capecitabine into a biweekly regimen with oxaliplatin and docetaxel. It should be noted that, when combined with other chemotherapy agents, shorter courses of capecitabine may be as effective as a 14-day course. Indeed, comparison of 7- versus 14-day schedules of capecitabine in colorectal cancer, combined with oxaliplatin in a 14- versus 21-day cycle, demonstrated improved PFS in patients receiving the shorter course of capecitabine [28]. Although cisplatin has been widely used in combination with other agents in the treatment of advanced gastric cancer, oxaliplatin-based regimens have shown improved efficacy without substantially sacrificing tolerability in several combination chemotherapy regimens [10, 29]. Therefore, we substituted oxaliplatin for cisplatin to reduce nausea and maintain the comfort

of an outpatient basis of administration. The dose and scheduling of the present regimen was adopted from a previous phase I study conducted recently in our department [13]. In this study, which was performed on patients with different solid tumors, an important level of efficacy was noticed – in addition to excellent tolerability – particularly in patients with gastric cancer. Thus, we felt it would be of interest to further investigate the regimen in patients with this type of cancer.

Regarding efficacy, the observed response rate (59%) is among the best recorded in the literature, comparing favorably to the response rates of other combination chemotherapy regimens for esophagogastric cancer. A recently reported study using the same drug combination but in a different mode of administration showed a disease control rate of 82% along with an excellent toxicity profile. However, although the median OS was not recorded, the median PFS was 6.7 months, which is substantially inferior to that of our study [30]. Furthermore, the median PFS of 10 months along with a median OS of 18 months achieved in the present study is substantially better than the median survivals of 9.9, 9.9, 9.3 and 11.2 months recorded for ECF, ECX, EOF and EOX regimens, respectively, which were examined in the REAL-2 trial and represent the current reference regimens in the treatment of gastric cancer [10]. A similar response rate of 52% along with an excellent OS of 15.1 months was recently reported by Shah et al. [31] using a modified DCF regimen administered every 2 weeks versus the standard DCF administered every 3 weeks. This study was prematurely closed due to unacceptable toxicity of the standard DCF regimen, which additionally supports the advantages of the biweekly mode of administration [31]. The excellent performance status of the majority of our patients may have substantially contributed to those remarkable efficacy parameters. This is additionally supported by the fact that 12 patients in our study were eligible to receive second-line treatment at disease progression.

The hematologic toxicity of the regimen was mild-to-moderate, as grade 3 neutropenia was noticed in 7 patients and grade 4 in 4 patients, with only one neutropenic episode requiring patient hospitalization. This episode was easily resolved within 7 days, after administration of rhG-CSF and wide spectrum antibiotics. Anemia grade 3 was seen in only 1 patient, whilst thrombocytopenia was only grade 2, with no patient requiring blood or platelet transfusion. Similarly, non-hematologic toxicity was modest, with only 3 patients developing grade 3 diarrhea. In 2 of these, the episodes were of short duration and resolved easily after capecitabine interrup-

tion and standard loperamide treatment. Only 1 patient required hospitalization for 3 days for hydration because the episode was complicated with grade 2 nausea/vomiting. Grade 3 PPE was recorded in 4 patients, but this was not a treatment problem. Three patients developed grade 3 neurotoxicity after at least 5 cycles, which presented as acral paresthesia, and this toxicity was attributed to oxaliplatin. Omission of oxaliplatin in subsequent cycles substantially improved this symptom. With the exception of 1 case with grade 3 fatigue and another patient who developed grade 3 mucositis, all other toxicities were of grade 1/2 and easily manageable. This low incidence of toxicity with the present regimen should be attributed to the 7-day (instead of the commonly utilized 14-day) administration schedule of capecitabine. The 7-day schedule permits an early evaluation and a faster recovery from a developing toxicity before proceeding to the next treatment cycle. Similarly, the lower dosing of both docetaxel and oxaliplatin with the modified biweekly administration may additionally contribute to this low incidence of toxicity which is usually present with these agents.

In conclusion, the present regimen is easily administered, well tolerated and shows important efficacy. It thus represents a reasonable alternative for patients and physicians who desire a regimen without a continuous 5-FU infusion and low toxicity, given on an outpatient basis. The main hope for significant advances in the near future is the combination of new targeted biological agents (such as trastuzumab) with the existing first-line regimens [32]. Therefore, we intend to further explore the present regimen in combination with trastuzumab in HER-2-positive patients with advanced gastric cancer.

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