Weekly docetaxel and capecitabine is not effective in the treatment of advanced gastric cancer: a phase II study

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Background: Capecitabine and docetaxel have demonstrated preclinical antitumor synergy and activity in advanced gastric cancer. We assessed the clinical activity and the toxicity of weekly docetaxel in combination with capecitabine in untreated patients with advanced gastric cancer.

Patients and methods: A total of 38 patients were treated with docetaxel 36 mg/m² on days 1, 8, and 15 i.v., plus capecitabine, 625 mg/m² bid per os on days 5 to 18 repeated every 4 weeks.

Results: All patients were assessable for response to treatment and for toxicity. Major responses were observed in eight patients (21%), with three patients achieving a CR (7.8%) and five showing a PR (13%). The median time to progression was 5.4 months and the overall survival was 7.7 months. The safety profile of this schedule was acceptable with a low rate of myelosuppression, diarrhoea and hand-foot syndrome.

Conclusions: The combination of docetaxel and capecitabine at the doses and schedule investigated in this study is safe, but does not show significant activity in untreated patients with advanced gastric cancer.

Key words: docetaxel, capecitabine, gastric cancer

introduction

Although the incidence of gastric adenocarcinoma is declining worldwide, it is still the second most common gastrointestinal cancer in terms of mortality [1, 2]. The prognosis of advanced disease is poor, but combination chemotherapy results in a significant survival advantage when compared to best supportive care (BSC) in randomised clinical trials [3, 4]. However, despite a relatively high rate of responses achieved with many combination regimens, the time to treatment progression and the median survival remain usually short. These disappointing results prompted several investigators to evaluate the potential efficacy of recently developed new agents such as capecitabine and docetaxel [5].

Capecitabine, a novel, oral, selectively tumor-activated fluoropyrimidine, has shown a clinical activity as single agent in the range of 26–34% [6–8]. Small phase II trials of single-agent docetaxel in both the first- and second-line treatment settings have produced response rates in the range of 5–20% and the randomised phase III V-325 study showed an incremental benefit of adding docetaxel to cisplatin and 5-fluorouracil as first-line therapy for patients with advanced gastric cancer [9–13]. Furthermore, weekly administration of docetaxel has recently attracted interest, because of a more favourable toxicity profile with preservation of antitumor activity; severe neutropenia is rare with this schedule and recommended weekly doses range from 36 to 43 mg/m² [14]. Capecitabine and docetaxel combination has demonstrated preclinical antitumor synergy and no overlapping toxicities. This synergy is thought to occur for docetaxel-mediated up-regulation of thymidine phosphorylase (TP), the enzyme that converts 5-deoxy-5-fluorouridine (5-DFUR) to 5-Fluorouracil (5-FU) [15]. This up-regulation may translate into a clinical advantage, as shown in advanced breast cancer by better survival, time to progression and response rate obtained with the association of capecitabine and docetaxel compared with single-agent docetaxel [16]. However, preclinical studies suggest that TP up-regulation is transient with maximal activity shown between 6 and 10 days after treatment [15]. With the aim to maximize TP up-regulation, Nadella et al. developed a phase I study with weekly docetaxel (days 1, 8, 15) and capecitabine started on day 5 and continued for 14 days until day 18. Docetaxel 36 mg/m² on days 1, 8 and 15 and capecitabine 625 mg/m² twice daily on days 5–18 every 4 weeks were the doses recommended for phase II studies.
Furthermore an interesting antitumor activity was observed in 7 out 16 pre-treated patients [17]. Based on the safety profile and response rate, we planned a phase II study with this schedule in previously untreated patients with advanced gastric cancer.

patients and methods

eligibility

Patients with histologically proven metastatic gastric adenocarcinoma were considered eligible for the study if they met all of the following criteria: measurable disease; cytologically or histologically proven single metastatic lesion as the only manifestation of the disease; male or female, aged >18 years and <75 years; Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 2; life expectancy of more than 3 months; adequate bone marrow, hepatic and renal function; no prior palliative chemotherapy. Previous adjuvant (and/or neo-adjuvant) chemotherapy was allowed if more than 6 months had elapsed between the end of adjuvant (and/or neo-adjuvant) therapy and first relapse; at least 6 weeks from prior radiotherapy and 3 weeks from surgery. Consent was obtained, signed and dated before beginning specific protocol procedures. The following parameters were recorded in all patients: sex, age, T and N stage, surgery (yes or no) and type of resection (total gastrectomy versus partial resection), histology (intestinal versus diffuse), degree of histologic differentiation (moderately differentiated or poorly differentiated), PS, number of organs involved, CEA and CA19.9 serum levels, second line chemotherapy versus best supportive care.

treatment and toxicity assessment

Chemotherapy consisted of docetaxel 36 mg/m² on days 1, 8, and 15 i.v. plus capecitabine 625 mg/m² bid per os on days 5 to 18 repeated every 4 weeks. This regimen was administered until progression. Toxicity was assessed before starting using the National Cancer Institute Common Toxicity Criteria (NCI-CTG), version 2.0.

Treatment delays and dose modification were based on the worst adverse effects observed during the previous cycle. In case of grade 2 neutropenia or grade 2 thrombocytopenia the treatment with docetaxel was held until resolution of the toxicity to grade 1/0 without dose reduction. For patients who experienced grade 4 thrombocytopenia the dose of docetaxel was reduced by 25%.

For febrile neutropenia or documented infection a treatment with G-CSF was started with no dose reduction after the first episode; if the patients experienced for the second time a febrile neutropenia, despite the use of G-CSF, the dose of docetaxel was reduced by 25% and another reduction by 25% was considered after the third episode of febrile neutropenia. At the fourth episode of febrile neutropenia the patients were removed from the study.

For grade 3 cutaneous reactions docetaxel was stopped for one week or until resolution to grade 1 with a dose reduction of 25%, if the toxicities failed to resolve after holding treatment for 2 weeks or in case of grade 4 cutaneous reactions the patients were withdrawn from the study.

For grade 3 diarrhea and/or a first episode of grade 4 diarrhea which were not controlled by using the standard schedules of loperamide the treatment was stopped and docetaxel was reinitiated at a lower dose reduced by 25%. In case of recurrent grade 4 diarrhea, who were those patients removed from the study.

In patients developing grade 2–3 liver dysfunction docetaxel was held and started again at a lower dose of 75%.

For other unexpected grade 3–4 toxicities caused by either docetaxel or capecitabine the administration of the drugs was discontinued for 2 weeks or until the toxicity had decreased to less than grade 2. The treatment was started again at full or reduced dose at the discretion of the physician.

Together with reductions in the dose of docetaxel, the assumption of capecitabine was stopped in the event of grade 3 or 4 hematologic and non-hematologic toxicity until resolved to grade 0/1, then continued at 75% of initial doses.

study end points

Before study entry (within 4 weeks prior to first infusion) all patients underwent the following studies: physical examination, PS, haematology, biochemistry, CEA, CA19-9, evaluation of disease (chest and abdominal CT scan, ultrasound endoscopy, and any other diagnostic procedure which might be considered necessary to define the disease extension). During treatment, on days 1, 5, 8, 15 hematology tests and physical examination, PS were performed. Every 4 weeks during treatment physical examination, PS, hematology, biochemistry, CEA, CA19-9 were performed. Tumor evaluation was assessed every 8 weeks according to the RECIST criteria [18]. Treatment was continued until disease progression or unacceptable toxicity occurred or until a patient chose of to discontinue treatment. All patients who completed at least three cycles of chemotherapy were deemed assessable for response. All eligible patients were included on an ‘intent-to-treat’ basis.

The primary end point of the study was the rate of responses achievable with this regimen and the feasibility of this regimen in the same population. Secondary end points were the time to tumor progression, the overall survival and the quality of life of the treated patients.

statistical analysis

The number of patients required for the study was calculated according to a Simon optimal design. An interim analysis was carried out after the first 18 assessable patients had completed treatment. Since more than two responses were observed, 18 additional patients were recruited. The regimen was considered active if the response rate exceeded 30% [19].

Statistical analysis was carried out using the BMDP statistical package (BMDP Statistical Software Inc., Los Angeles, California). Time to progression and overall survival were analyzed using the product-limit method (Kaplan-Meier).

results

patient characteristics

Between August 2003 and December 2005, 38 patients were enrolled onto the study, and all patients were assessable for safety and response. The characteristics of the patients are summarized in Table 1.

The median age was 61 years and the majority of patients had a PS 0 according to the ECOG scale. A G3 undifferentiated tumor was present in 26 patients (68%) and the intestinal histotype was observed in 21 patients (55%). The study population was metastatic at the diagnosis and 21 out of 38 patients were treated before chemotherapy with a palliative surgery (13 received a total gastrectomy and eight a partial resection of the stomach). Liver (12 out 38 patients, 31.5%), nodes (13 out 38 patients, 34%) and peritoneum (seven out 38 patients, 18%) were the most common sites of disease. No patients had received prior radiotherapy.

tumor response

Major responses were observed in eight patients (21%; 95% CI, 8–34%), with three patients achieving a CR (7.8%) and five showing a PR (13%). Stabilization of disease was obtained in
22 additional patients (58%) and progressive disease was observed in eight patients (21%). The overall tumor growth control (CR+PR+SD) was 78% (30 out of 38 patients).

**survival**

All patients were included in the survival analysis on an intention-to-treat basis. The median follow-up was 7.7 months (range, 3–29.7 months). The median TTP was 5.4 months (95% CI 4–13) (Figure 1). At the time of analysis (31 December 2005), 27 patients had died and 11 were alive. The median OS was 7.7 months (95% CI 6–11). At the time of analysis, two out of three patients who achieved a CR were disease-free at 29.7 and 9 months of follow-up, respectively. Following documentation of disease progression, 10 patients received a second-line oxaliplatin or irinotecan-based chemotherapy showing a median OS of 13 months (95% CI 11–21), and patients receiving only best supportive had a median OS of 6 months (95% CI 4–7).

**toxicity**

A total of 169 cycles were administered, with a media of four cycles for patients (range 4–9), and a total of 15 out of 38 patients received at least four cycles. The occurrence and the incidence of main toxicities are reported in Table 2.

**discussion**

This study addresses the activity and safety of the combination of capecitabine and weekly docetaxel in patients with untreated metastatic gastric cancer. The rationale for the development of this schedule includes the preclinical observation that TP up-regulation by docetaxel is transient with maximal induction recorded between 6 and 10 days after docetaxel exposure, the clinical synergism observed for these two agents and the antitumor activity shown in advanced gastric cancer for each agent [5, 15–16]. Our experience confirms that the combination of weekly docetaxel and capecitabine is feasible but fails to show the activity previously reported in other trials with similar schedules of combination. In fact, despite the interim analysis which showed more than two objective responses over the first 18 assessable patients, the overall response rate was 21% and therefore, according to the statistical design of the study, the regimen was considered as low activity because the response rate did not exceed 30%. In other trials with similar regimens, the activity observed was significantly higher. Park et al. in a phase II study treated 42 patients with capecitabine (1250 mg/m² orally twice daily) plus docetaxel (75 mg/m²) on day 1 of a 21-day cycle. The overall response rate was 60%, median PFS was 5.2 months, and OS was 10.5 months [20]. Furthermore, Kim et al., with this regimen, reported an overall response rate of 43.8%. The median TTP and median OS for all patients was 5.07 months and 8.4 months, respectively [21]. Only the study published by Chun et al. employed a weekly regimen of docetaxel (36 mg/m² days 1 and 8) with capecitabine (1000 mg/m² orally twice daily on days 1–14) every 3 weeks and recorded a response rate of 40.4% with a TTP and a OS of 4.5 months and 12.0 months, respectively [22].

Even if a retrospective analysis of the O’Shaughnessy study showed no reduction in activity when doses of capecitabine and docetaxel were reduced because of toxicities, our objective response rate of 21% could be related to the use of a less dose-intense regimen of capecitabine (625 mg/m² twice daily
on days 5–18 of a 4-week cycle). This is supported by the results of a recent study by the North Central Cancer Treatment Group in which the dose of capecitabine (825 mg/m² twice daily on days 1–14) was less than that used in the former studies. In fact the response rate of 39% was lower than that observed in the previous studies, while the TTP was 4.2 months and the OS was 9.4 months [23]. However, despite the worst response rate, the TTP recorded in our study (5.4 months), compared favorably with those reported above, suggesting the need to expand the effectiveness of current combination chemotherapy regimens.

The safety profile of our schedule was acceptable. In particular, the low incidence of severe hand-foot syndrome could be explained by the lower dose of capecitabine used, while the low rate of myelosuppression could be related to a favorable toxicity profile when docetaxel is administered on a weekly schedule.

Furthermore, taken together with the results of other trials, these data show that patients who receive second-line chemotherapy may survive longer than patients receiving only best supportive care [24, 25]. In conclusion, the association of docetaxel and capecitabine at the doses and schedule investigated in this study is safe, but does not show significant activity in chemo-naïve patients with advanced gastric cancer. These results are remarkable considering that the patients enrolled in our trial were probably more ‘fit’ for chemotherapy (27 out 38 patients had a PS 0–1) [26].

### Table 2. Main toxicities according to NCI-CTC scale

<table>
<thead>
<tr>
<th>Toxicities</th>
<th>Grade 1–2 (%)</th>
<th>Grade 3–4 (%)</th>
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</thead>
<tbody>
<tr>
<td><strong>Hematologic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>6 (15)</td>
<td>9 (23)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>5 (13)</td>
<td>6 (15)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>8 (21)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Anemia</td>
<td>9 (23)</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>—</td>
<td>1 (2)</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>7 (18)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5 (12)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6 (15)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>stomatitis</td>
<td>4 (10)</td>
<td>1 (2)</td>
</tr>
<tr>
<td><strong>Dermatologic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dermatitis</td>
<td>8 (21)</td>
<td>4 (10)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>5 (13)</td>
<td>1 (2)</td>
</tr>
<tr>
<td><strong>Allergic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dermatitis</td>
<td>2 (5)</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

Additional references:

13. Moseyenko V, Ajani J, Tjulandin S. Final results of a randomized controlled phase III trial (TAX 325) comparing docetaxel (T) combined with cisplatin (C) and 5-fluorouracil (F) to CF in patients (pts) with metastatic gastric adenocarcinoma (MGC). J Clin Oncol 2005; 23: 308s.