Docetaxel and capecitabine for advanced gastric cancer: investigating dose-dependent efficacy in two patient cohorts

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BACKGROUND: No comparisons of different doses of docetaxel-capecitabine in patients with advanced gastric cancer have been performed.

METHODS: Patients with previously untreated metastatic/locally advanced gastro-oesophageal or gastric adenocarcinoma were enrolled in a prospective multicentre phase II trial. Two sequential cohorts received docetaxel 75 mg m⁻² (day 1) plus capecitabine 1000 mg m⁻² twice daily (days 1–14) (cohort I) or docetaxel 60 mg m⁻² (day 1) plus capecitabine 800 mg m⁻² twice daily (days 1–14) (cohort II) every 3 weeks. The primary end point was confirmed overall response rate.

RESULTS: In all, 91 patients were enrolled (cohort I, n = 40; cohort II, n = 51) and 87 were evaluable for efficacy (n = 38, 49, respectively). Overall response rate was 50.0% in cohort I and 23.5% in cohort II (exploratory analysis, P = 0.014). Median times to tumour progression and overall survival were 5.6 and 10.1 months in cohort I and 3.7 and 7.2 months in cohort II, respectively. Dose reductions for docetaxel and capecitabine were required in 50.0% and 57.5% of patients in cohort I and 11.8% and 15.7% in cohort II, respectively.

CONCLUSION: Starting treatment with full doses and reducing promptly seems to be the more promisingly effective strategy than starting cautiously with lower doses. Docetaxel/capecitabine 75/2000 mg m⁻² is a manageable, convenient outpatient combination with promising efficacy against advanced gastric cancer.

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Recent epidemiological data indicate that 0.93 million new cases of gastric and gastro-oesophageal junction cancer are diagnosed annually worldwide (Kamangar et al., 2006). More than 60% of patients present with locally advanced or metastatic disease or develop metastases after initial resection (Parkin et al., 1999). In patients with advanced gastric cancer, chemotherapy improves overall survival compared with best supportive care (Wagner et al., 2010), but there is no single accepted standard chemotherapy regimen. Both cisplatin plus 5-fluorouracil (CF) (Kim et al., 1993; Vanhoefer et al., 2000; Ohtsu et al., 2003; van Cutsem et al., 2006) and epirubicin plus CF (ECF) (Webb et al., 1997; Ross et al., 2002) have established efficacy and are recognised reference regimens for comparative trials.

During the past decade, several new-generation cytotoxic agents, including capecitabine, irinotecan, oxaliplatin and docetaxel, have been investigated for the treatment of gastric cancer. The phase III V325 study (van Cutsem et al., 2006) established the efficacy of docetaxel as first-line therapy for advanced gastric cancer. The final results showed that adding docetaxel to the CF regimen (DCF) improved overall survival, response rate, time to disease progression and health-related quality of life, but was associated with a marked increase in haematological toxicity. As a result, various cooperative groups and institutions tested modified versions of the DCF regimen in phase II studies (Park et al., 2005; Thuss-Patience et al., 2005; Lorenzen et al., 2007; Al-Batran et al., 2008; Shah et al., 2010; Tebbutt et al., 2010). As part of this initiative, we demonstrated that a simplified regimen of docetaxel plus 5-fluorouracil had similar efficacy to ECF in patients with advanced gastric cancer in a randomised phase II study (Thuss-Patience et al., 2005), suggesting that cisplatin does not need to be a mandatory component of an effective combination.

As our study was conducted, two phase III trials have shown that the oral fluoropyrimidine, capecitabine, has at least equivalent
efficacy to infused 5-fluorouracil when given as part of a combination regimen in patients with advanced gastric cancer (Cunningham et al, 2008; Kang et al, 2009). Several phase II trials have reported promising efficacy with the combination of docetaxel and capecitabine in patients with advanced gastric cancer (Park et al, 2004; Chun et al, 2005; Kim et al, 2005; Lorenzen et al, 2005; Giordano et al, 2006; Rosati et al, 2007; Lo et al, 2010; Tebbutt et al, 2010).

All approaches to optimise docetaxel–fluoropyrimidine-based regimens focus on modifying chemotherapy dose and application. As there are no phase III trials investigating this question, it is unclear whether or not changes in chemotherapy dose affect efficacy. To our knowledge, there has been no comparison of different doses of docetaxel–capecitabine. Therefore, in this study of the Arbeitsgemeinschaft Internistische Onkologie (AIO), we examined two sequential patient cohorts treated with different doses of docetaxel in combination with capecitabine to determine if maximal doses are really necessary in the palliative setting or if lower doses might have similar efficacy with better tolerability.

MATERIALS AND METHODS

Study design

This was a prospective, non-randomised, multicentre phase II trial. Patients were recruited sequentially to two separate cohorts and treated with different doses of docetaxel plus capecitabine; the first 40 patients received higher doses of docetaxel–capecitabine (cohort I) and the next 51 patients received lower doses (cohort II).

After completion of cohort I, it was decided to enrich the information gained by this trial by an amendment, lowering the dose of chemotherapy in a similar study population. Although the regimen tested in cohort I proved to be effective, safe and tolerable, frequent dose reductions were necessary and Common Toxicity Criteria (CTC) grade 1 and 2 toxicities were frequent, which were bothersome for the patient. As the treatment setting was palliative and benefit should be maximised by minimal side effects, an alternate strategy was investigated. Cohort II was initiated with a dose reduction of both drugs by 20% to investigate whether grade 1–4 side effects can be reduced, further dose adjustments can be avoided, but efficacy can be maintained. A reduction by 20% resulted in dose levels for each individual drug, which were investigated previously (Lee et al, 2008; Tebbutt et al, 2010).

The study was conducted according to the Declaration of Helsinki, registered in www.clinicaltrials.gov (no. NCT00142038) and the protocol was approved by the local ethics body. All patients provided written informed consent before study entry.

Patient population

Ambulatory patients aged 18–75 years with histologically confirmed, locally advanced or metastatic adenocarcinoma of the stomach or gastro-oesophageal junction were eligible. Measurable disease was required for study inclusion. No previous chemotherapy for advanced/metastatic disease or concurrent radiotherapy was allowed. Patients were required to have an Eastern Cooperative Oncology Group performance status of 2 or less (Karnofsky performance index of ≥ 60%). Adequate bone marrow (leukocyte count > 3.0 × 10^9/l, platelet count > 100 × 10^9/l), renal (serum creatinine < 1.25 × upper limit of normal and/or creatinine clearance > 60 ml min^-1 according to Cockcroft–Gault formula) and liver (serum bilirubin < 1.5 mg dl^-1, alanine aminotransferase and aspartate aminotransferase ≤ 3 × upper limit of normal) function was required. Patients with a co-existing secondary tumour (except basal cell carcinoma of the skin or carcinoma in situ of the cervix), uncontrolled infection, central nervous system metastases, recent major surgery (< 2 weeks), anatomical or inflammatory intestinal problems, or an inability to take oral medication were excluded. The eligibility criteria for both study cohorts were identical.

Study evaluation

At baseline, clinical investigations were performed within 8 days, and tumour imaging within 21 days, before study inclusion. The baseline evaluation included a physical examination, assessment of medical history and symptoms, evaluation of performance status and routine blood analysis (haematology and biochemistry). During treatment, full blood count was repeated every week and all other parameters were re-evaluated before each chemotherapy cycle.

An electrocardiogram and abdominal computed tomography scan were performed in all patients at baseline, with further imaging if clinically indicated (i.e. bone scan, head computed tomography). During treatment, imaging of target lesions and non-target lesions was repeated every two cycles (every 6 weeks) using the same imaging procedures as at baseline. Tumour response was classified according to Response Evaluation Criteria In Solid Tumours 1.0 guidelines and verified 4–6 weeks later (Therasse et al, 2000), and evaluated by independent radiologists. After the end of study treatment, patients were followed up every second month until death. Toxicity was evaluated on a weekly basis using the National Cancer Institute-CTC (Version 2.0).

Tumour-related symptoms were assessed by the treating physician every 3 weeks on direct questioning. Symptomatic improvement was defined as subjective improvement as stated by the patient of at least one tumour-related symptom without worsening of any other or appearance of any new tumour-related symptom.

Treatment

Patients in cohort I received intravenous docetaxel 75 mg m^-2 on day 1 given as a 1-h infusion plus oral capecitabine 1000 mg m^-2 twice daily on days 1–14, every 3 weeks. Patients in cohort II received docetaxel 60 mg m^-2 on day 1 and capecitabine 800 mg m^-2 twice daily on days 1–14, every 3 weeks. Patients received chemotherapy for up to a maximum of 10 cycles, or until tumour progression or unacceptable toxicity.

Premedication with oral dexamethasone 8 mg was given the evening before day 1 of each cycle, as well as on the morning and evening of days 1 and 2. A 5-HT3 antagonist was also recommended on day 1. Prophylactic granulocyte-colony-stimulating factor was recommended in patients older than 70 years.

Treatment in both cohorts was delivered up to the beginning of toxicity and then interrupted or dose reduced: for grade 2 toxicities (except for isolated neutropenia/leukopenia/anaemia or alopecia), treatment was interrupted until symptoms had resolved to grade 0 or 1. For a second occurrence of grade 2 toxicity or a grade 3 event, treatment was interrupted until symptoms had resolved to grade 0 or 1 and docetaxel and capecitabine doses were reduced by 25%. For a second occurrence of grade 3 toxicity or a grade 4 event, treatment was interrupted until symptoms had resolved to grade 0 or 1 and docetaxel and capecitabine doses were reduced to 50%. Uncomplicated neutropenia/leukopenia grade 3 or 4 did not lead to dose reductions of docetaxel/capecitabine or interruption of capcitabine as long as it resolved to grade 1 before starting the next cycle. For grade 3/4 neutropenia/leukopenia lasting longer than 1 week or complicated by febrile neutropenia (body temperature ≥ 38.5°C), the docetaxel dose was reduced by 25%. Granulocyte-colony-stimulating factor was not recommended as secondary prophylaxis in patients younger than 70 years.
Statistical analysis

The primary study end point was overall response rate, and secondary end points were overall survival, time to tumour progression and toxicity. Time to tumour progression was defined as the time from study inclusion to documented progressive disease. Overall survival was defined as the time from study inclusion to death from any cause. Symptomatic improvement was defined as subjective improvement of at least one tumour-related symptom (e.g., dysphagia, weight loss, loss of appetite, pain, abdominal fullness after meals) without worsening of any other symptom or appearance of any new tumour-related symptom. Kaplan–Meier methods were used to estimate time-to-event end points. Statistical comparisons of efficacy end points between the two patient cohorts were exploratory only. The statistical model was not prospectively designed for this comparison.

The study was designed according to the two-stage optimum design for phase II studies (Simon, 1989). For the null hypothesis, it was assumed that the true response rate was less than 25%, with an expected response rate of 45%. If at least 4 of the first 14 patients showed a response, the study was to be expanded to 44 patients. If at least 15 responses were documented in these 44 patients, the null hypothesis was rejected. This design provides a probability of 10% of accepting a regimen with a response rate of less than 25%, and a probability of 10% of rejecting a regimen with a response rate of more than 45%.

When the null hypothesis was rejected after 44 included patients (cohort I), the protocol was amended to continue with lower doses of docetaxel and capecitabine to optimise tolerability (cohort II). The same statistical design as for cohort I was applied for cohort II. The study was continued to a maximum of 95 patients (including drop outs) (see Figure 1).

RESULTS

In all, 95 patients were registered to the trial; four patients were excluded from the analysis owing to major violations of the inclusion criteria (see Figure 1). Therefore, a total of 91 evaluable patients were recruited from four centres in Germany from March 2004 to December 2006 (cohort I, n = 40; cohort II, n = 51). At the time of analysis (May 2008), 84 patients had died, six patients were alive and one patient was lost to follow-up.

Patient baseline characteristics are presented in Table 1. Baseline characteristics were generally well balanced between the two cohorts, except that patients in cohort I had more tumours of the gastro-oesophageal junction (50.0% vs 39.2% in cohort II) and more patients with >2 metastatic sites (37.5% vs 47.1%).

Treatment exposure

The total number of chemotherapy cycles administered in cohort I was 257 (median 6, range 1–10) and in cohort II was 247 (median 4, range 1–10). Treatment modifications were required more frequently in cohort I than in cohort II (Table 2). Dose reductions became necessary after a median of three cycles of full-dose docetaxel and capecitabine in cohort I and three cycles of capecitabine and four cycles of full-dose docetaxel in cohort II, respectively. The total dose of chemotherapy that could be delivered was higher in cohort I. The main reasons for dose modifications were non-haematological toxicities. The majority of uncomplicated neutropenia was short lasting and did not result in a dose reduction. Calculating the planned dose of chemotherapy for the delivered number of cycles, in cohort I 88.2% of the planned dose of docetaxel and 83.7% of the planned dose of capecitabine could be administered compared with 94.2% of the planned dose of docetaxel and 92.4% of the planned dose of capecitabine administered in cohort II. The main reason for treatment termination was tumour progression (cohort I: 62.5%; cohort II: 78.4%). Toxicity (cohort I: 5%; cohort II: 5.9%) or withdrawal of consent (cohort I: 0%; cohort II: 2.0%) rarely lead to treatment termination.

Efficacy

A summary of confirmed response rates is presented in Table 3. Complete and partial responses were documented in 2 and 18
patients in cohort I, respectively, and in 0 and 12 patients in cohort II, respectively. The null hypothesis from the statistical design could be rejected in cohort I, but not in cohort II (see Figure 1). Overall response rates, the primary study end point, were 50.0% (n = 20) in cohort I and 23.5% (n = 12) in cohort II. The study was not powered or designed to compare the two cohorts. In an exploratory analysis, the observed difference was statistically significant (P = 0.014) (Fisher’s exact test, two sided).

Symptomatic improvement was evident in 27 of 37 (73.0%) patients with baseline symptoms in cohort I and 27 of 40 (67.5%) patients in cohort II.

Kaplan–Meier curves for time to tumour progression and overall survival are shown in Figure 2. Median time to tumour progression was 5.6 months (95% confidence intervals 3.9–7.3) in cohort I and 3.7 months (95% confidence intervals CI) 2.5–5.0) in cohort II. Median overall survival was 10.1 months (95% CI: 7.3–13.0) in cohort I and 7.2 months (95% CI: 4.1–10.2) in cohort II. Exploratory statistical analysis of the observed differences in time to tumour progression (P = 0.10, log-rank test; hazard ratio = 0.71; 95% CI: 0.47–1.08) and overall survival (P = 0.20, log-rank test; hazard ratio = 0.75; 95% CI: 0.48–1.16) were not significant.

Safety

All patients were evaluated for safety. A summary of all adverse events by grade is provided in Table 4. All toxicities occurred more frequently in cohort I than in cohort II.

Non-haematological adverse events reported most frequently with the docetaxel–capecitabine regimen were asthenia, alopecia, nausea, hand–foot syndrome and diarrhoea. Regardless of the doses of capecitabine and docetaxel administered, these events were mostly mild to moderate in severity (grades 1 and 2), and grade 3 events were manageable (Table 4). Grade 4 non-haematological events were documented in a total of four patients: cohort I, vomiting (n = 1) and pulmonary embolism (n = 1);
Table 3  Confirmed response rates (RECIST)

|                  | Cohort I (N = 40) | Cohort II (N = 51) |
|------------------|-------------------|--------------------|
| Overall response | 20 (50.0)         | 12 (23.5)          |
| P-value          | 0.014             |                    |
| Complete response| 2 (5.0)           | 0 (0)              |
| Partial response | 18 (45.0)         | 12 (23.5)          |
| Stable disease   | 15 (37.5)         | 24 (47.1)          |
| Disease progression | 3 (7.5) | 13 (25.5)          |
| Not evaluable 8 | 2 (5.0)           | 2 (3.9)            |

Abbreviations: b.i.d. = twice daily; RECIST = Response Evaluation Criteria In Solid Tumours. *Reasons for not being evaluable: early treatment termination after one (3 pts.), or two cycles (1 pt.) due to toxicity, doctor's decision or withdrawal of consent with incomplete staging investigations, but without clinical signs of tumour progression.

Figure 2  Time to tumour progression (A) and overall survival (B) in cohort I (higher dose, n = 40) and cohort II (lower dose, n = 51) treated with docetaxel and capecitabine. (A) Median time to tumour progression: cohort I, 5.6 months (95% CI: 3.9–7.3), cohort II, 3.7 months (95% CI: 2.5–5.0), P = 0.10 (log-rank test). (B) Median overall survival: cohort I, 10.1 months (95% CI: 7.3–13.0), cohort II, 7.2 months (95% CI: 4.1–10.2), P = 0.20 (log-rank test).

cohort II, cardiac arhythmia (n = 1) and pulmonary oedema (fluid retention) (n = 1). One patient in cohort I died at home after the first cycle of chemotherapy due to a pulmonary embolism (grade 5 event).

Table 4  Toxicity by grade

|                  | Cohort I (N = 40) | Cohort II (N = 51) |
|------------------|-------------------|--------------------|
| Non-haematological toxicity |                    |                    |
| Asthenia | 32 (80.0)         | 4 (10.0)           |
| Alopecia | 33 (82.5)         | 0 (0)              |
| Nausea | 27 (67.5)         | 1 (2.5)            |
| Hand–foot syndrome | 17 (42.5) | 8 (20.0)           |
| Diarrhoea | 18 (45.0)         | 6 (15.0)           |
| Nail changes | 24 (60.0) | 0 (0)              |
| Stomatitis | 15 (37.5)         | 4 (10.0)           |
| Neutropenic fever | 0 (0)            | 5 (12.5)           |
| Non-neutropenic fever | 14 (35.0) | 1 (2.5)            |
| Neutropenic fever | 0 (0)            | 5 (12.5)           |
| Dizziness | 10 (25.0)         | 2 (5.0)            |
| Fluid retention | 8 (20.0)         | 1 (2.5)            |
| Cardiac arhythmia | 1 (2.5)          | 2 (5.0)            |
| Neutropenia | 3 (7.5)           | 3 (7.5)            |

Abbreviations: b.i.d. = twice daily; CTC, Common Toxicity Criteria. *One of these patients died due to a pulmonary embolism (CTC grade 5).

Neutropenia and leukopenia were the most frequently reported haematological toxicity (Table 4). While both thrombocytopenia and anaemia were generally grade 1 or 2 events, grade 3/4 neutropenia and leukopenia were common in both patient cohorts. Grade 3 and 4 neutropenia was documented in 8 (20.0%) and 13 (32.5%) patients in cohort I, respectively, and in 4 (7.8%) and 8 (15.7%) patients in cohort II, respectively.

DISCUSSION

Several modified forms of DCF have been tested in an attempt to improve the toxicity profile of this regimen (Park et al, 2005; Lorenzen et al, 2007; Al-Batran et al, 2008; Shah et al, 2010; Tebbutt et al, 2010). Only the US trial (Shah et al, 2010) included a reference regimen as comparator and could demonstrate a promising improvement of tolerability and efficacy by a modified DCF. In a previous phase II study, we demonstrated that docetaxel plus infused 5-fluorouracil had similar efficacy to the standard ECF regimen in the first-line treatment of patients with advanced gastric cancer (Thuss-Patience et al, 2005). As substitution of oral capcitabine for 5-fluorouracil is now accepted in patients with gastric cancer (Thuss-Patience et al, 2005), docetaxel and capcitabine is a logical combination in this setting. Several phase II studies have tested capcitabine in combination with docetaxel as first-line therapy in patients with advanced gastric cancer (Park et al, 2004; Chun et al, 2005; Kim et al, 2005; Giordano et al, 2006; Orditura et al, 2006; Tebbutt et al, 2010), but none has studied the effects of different doses.
In this study, we tested two different doses of docetaxel–
capcitabine in sequential cohorts of patients with inoperable,
locally advanced or metastatic gastric cancer. As it is not a
randomised trial, by principle some bias cannot be ruled out. To
minimise bias, consecutive patients were included. The two
cohorts had similar baseline characteristics; the mild imbalance
between gastro-oesophageal and gastric body cancer is not
expected to influence primary end points, as published previously
(Chau et al, 2009). A very promising response rate of 50.0% was
observed in patients treated with higher doses of docetaxel–
capcitabine (docetaxel 75 mg m\textsuperscript{-2} on day 1 plus capcitabine
2000 mg m\textsuperscript{-2} on days 1–14 every 3 weeks) compared with patients
treated with lower doses (23.5%). Although the study was not
designed to support a statistical comparison of the two patient
cohorts, an exploratory analysis showed that there was a
significant difference in favour of the higher dose regimen in
terms of overall response rate. Time to tumour progression and
overall survival were also both extended by approximately 2
months with the higher dose regimen compared with the lower
dose regimen. These findings are mature as nearly all events had
occurred at the time of analysis.

The toxicity profile of the docetaxel–capcitabine regimen in
our study was characterised by mild-to-moderate non-haematolo-
gical adverse events. Leukopenia/neutropenia was the most
frequent haematological adverse event; grade 3/4 events were
reported in 30–50% of patients depending on the docetaxel dose
used. This profile of events is in keeping with other phase II
studies of the docetaxel–capcitabine regimen (Park et al, 2004;
Chun et al, 2005; Kim et al, 2005). Our data suggest that
docetaxel–capcitabine at both dose levels investigated can be
given safely in an ambulatory setting without unexpected toxicity.
The lower dose regimen had an improved toxicity profile and
required fewer dose reductions. Despite more dose reductions
during the course of treatment, the higher dose regimen (cohort I)
was also tolerable. A median of three cycles could be administered
at full dose before dose reductions became necessary (Table 2).

To our knowledge, this is the first study that allows a
comparison of two dose levels of the same regimen. Starting
 treatment with a higher dose of docetaxel and capcitabine is
significantly more effective than starting with a moderate dose,
even though many more dose reductions were necessary with the
higher starting dose. It is the first study showing dose-dependent
efficacy of docetaxel and capcitabine in gastric cancer.

This trial evaluates two different palliative strategies: strategy 1 –
treat aggressively with a high-dose regimen and reduce doses as
necessary; or strategy 2 – start cautiously with a less aggressive
form of chemotherapy. On the basis of our findings, we suggest
that a high-dose strategy, with dose reductions as needed, is more
effective than a conservative approach. As the median age was only
62 years and only a minority of patients were 70 years and older
(cohort I, 11 patients; cohort II, 13 patients), our trial unfortunately
cannot answer the question whether this strategy also applies to elderly patients. Al-Batran et al (2010) could demon-
strate that elderly patients also tolerate intense chemotherapy and
benefit which would support this strategy. Further support for high
starting doses with dose reductions as needed comes from the
study of O’Shaughnessy et al (2002) in patients with metastatic
breast cancer. In this study, it was demonstrated that the efficacy
of docetaxel–capcitabine was not compromised by dose reduc-
tions required for the management of toxicity.

An alternate strategy might be to start at lower doses and
escalate if possible. So far no data support this strategy in gastric
cancer. In our view, it seems questionable whether similarly high
treatment exposure can be achieved in the first cycles to result in
best possible efficacy, but this needs to be investigated.

Several different regimens combining capcitabine and docetax-
el have been tested in phase II trials as first-line therapy in patients
with advanced gastric cancer (Table 5). Response rates in these
studies ranged from 26 to 60%, median time to disease
progression/progression-free survival from 4.4 to 5.2 months and
median overall survival from 8.4 to 12.0 months. Lower doses of
docetaxel administered weekly seem to be less promising in terms
of efficacy compared with a 3-weekly administration. The efficacy
of our higher dose regimen is consistent with these data, whereas
our lower dose regimen is among the least active of those
described (Table 5). The rates of neutropenia reported in these
trials were highly variable, influenced by the dose and scheduling
of docetaxel (Tebbutt et al, 2010).

The patients in our study were assigned to sequential cohorts
rather than randomised to treatment. Although the baseline
characteristics of the two cohorts were generally similar, the study
should be viewed with this limitation in mind. The sample size was
determined for each cohort separately rather than for a
comparison of treatments; therefore, the statistical comparisons
in the present report are exploratory only.

In conclusion, docetaxel–capcitabine is an active first-line
regimen in patients with advanced gastric cancer, which can be
given on an outpatient basis. We propose that it may be better to
start docetaxel–capcitabine at a higher dose, with dose reduc-
tions as needed, rather than initiating therapy with lower doses to
avoid dose reductions. It is a possible hypothesis that this strategy
may be relevant for all first-line chemotherapy regimens in
patients with advanced gastric cancer, although this requires
confirmation in prospective trials.

| Study            | N  | Docetaxel (mg m\textsuperscript{-2}) | Capcitabine (mg m\textsuperscript{-2}) | ORR (%) | Median PFS or TTP (months) | Median OS (months) | Grade 3/4 events (%) |
|------------------|----|-------------------------------------|--------------------------------------|---------|---------------------------|-------------------|----------------------|
| Park et al (2004)| 42 | 75 dl                                | 1250 b.i.d.                           | 60      | 5.2                       | 10.5              | 15                   |
| Kim et al (2005)| 32 | 75 dl                                | 1000 b.i.d.                           | 44      | 5.1                       | 8.4               | 10                   |
| Giordano et al (2006)| 44 | 75 dl                                | 825 b.i.d.                            | 39      | 4.4                       | 9.4               | 78                   |
| Present trial    | 40 | 75 dl                                | 1000 b.i.d.                           | 50      | 5.6                       | 10.1              | 53                   |
| Chun et al (2005)| 55 | 36 dl and B                          | 1000 b.i.d.                           | 40      | 4.5                       | 12.0              | 36                   |
| Oridoura et al (2006)| 38 | 36 dl, 8 and 15                      | 625 b.i.d. d5–18                      | 21      | 5.4                       | 7.7               | 23                   |
| Tebbutt et al (2010)| 56 | 30 dl and B                          | 800 b.i.d.                            | 26      | 4.6                       | 10.1              | 2                    |
| Modified DCF     | 47 | 5.9                                  | 11.2                                 | 10      | 6                         |

Abbreviations: b.i.d. = twice daily; DCF = docetaxel plus cisplatin plus 5-fluouracil; NR = not reported; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; TTP = time to tumour progression. Repeated every 4 weeks.
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