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Docetaxel in gastric cancer

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Abstract

Patients with advanced gastric cancer have a poor prognosis. 5-Fluorouracil (F) and cisplatin (C) based regimens are often considered to be reference regimens in the treatment of patients with advanced gastric cancer. Best supportive care in advanced gastric carcinoma results in median survival times of 3–4 months. Docetaxel (D) plus cisplatin and 5-fluorouracil was selected by an Independent Data Monitoring Committee as the test regimen for the second (phase III) stage of the V325 study on the basis of the response rate in the randomised phase II first stage. Chemotherapy–naïve patients were randomised to receive either DCF or CF. Tumour assessments were independently reviewed. At a planned interim analysis on 223 patients (111 DCF/112 CF) both the median time to progression and overall response rate were statistically superior in the DCF arm (5.2 months versus 3.7 months, and 39% versus 23%, respectively). The increase in median survival, 10.2 months compared with 8.5 months in this interim analysis did not yet reach statistical significance. The results of the full study population are awaited eagerly.

Keywords: Docetaxel; Gastric carcinoma; Interim analysis; Phase III

1. Introduction

Gastric cancer is a debilitating, aggressive disease that is frequently not diagnosed until it has reached an advanced stage and is a major health problem in many parts of the world. Patients with metastatic disease have a poor prognosis [1]. The median survival of patients with advanced gastric cancer is low. In several randomised trials of Best Supportive Care (BSC) versus chemotherapy, BSC care results in median survival times of only 3–4 months versus 7–9 months for chemotherapy. In two trials it was shown that the quality of life of patients treated with chemotherapy was better than the quality of life of patients treated with BSC [2,3].

Currently, no single agent or combination regimen is accepted as standard treatment. Early chemotherapeutic regimens such as the combination of mitomycin C, doxorubicin and 5-fluorouracil (5-FU) (FAM regimen), effected only a short-lived response in a small proportion of patients [4]. In the 1980s and 1990s, a number of combination regimens, such as 5-FU combined with cisplatin (FUP), doxorubicin and methotrexate (FAMTX regimen), etoposide and folinic acid (ELF), and epirubicin plus cisplatin (ECF), or the combination etoposide, doxorubicin and cisplatin (EAP regimen) produced encouraging results [5–8]. However, the high response rates achieved in initial studies were not always supported by subsequent more extensive studies. Although gastric cancer is a relatively chemosensitive cancer, the responses are often short-lived and the complete response rate is very low. Moreover toxicity is often important for these patients who often have a poor performance status. In light of the data from different trials, 5-FU and cisplatin-based regimens are considered as reference regimens. Although the ECF regimen is probably the most widely used and the best validated of these regimens, several options are possible. These are the ECF regimen

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(epirubicin 50 mg/m^2 and cisplatin 60 mg/m^2 on day 1 every 3 weeks in combination with 5-FU 200 mg/m^2/day), the FUP regimen (5-FU 1000 mg/day on days 1–5 in combination with cisplatin 100 mg/m^2 day 1), the weekly AIO regimen plus cisplatin (50 mg/m^2 every 2 weeks) and LV5FU2 plus cisplatin (50 mg/m^2 every 2 weeks). The preferred regimen is different for different countries.

Among the newer cytotoxic agents with potential activity in advanced gastric cancer, irinotecan and docetaxel have been of considerable interest. Both have been shown to be active alone [9–11] and in combination with cisplatin [11–14] and 5-FU [15–18]. In the irinotecan studies, 5-FU was combined with folinic acid (FA). In a recent randomised phase II study, the efficacy and toxicity profile of a combination of irinotecan and 5-FU/FA were found to be favourable compared with 5-FU/FA alone [19]. A randomised phase III trial comparing irinotecan plus 5-FU/FA with cisplatin plus 5-FU is currently in progress [20].

A review of the main clinical trials using docetaxel in advanced gastric cancer has recently been published [11]. Eight phase II trials reported the use of docetaxel as a single agent. In these studies, which included a total of 262 evaluable patients, the mean response rate was 19% (95% CI 14–24%) and docetaxel was well tolerated, with myelosuppression being the dose-limiting effect. Administration of docetaxel in combination with cisplatin resulted in response rates of 56%, 37% and 36% in three phase II trials, and with a response rate of 35% in one phase III trial.

The relatively low haematological toxicity of 5-FU when administered by continuous infusion, and its role in the efficacy of other 5-FU-based regimens, make it a logical choice for addition to the combination of docetaxel and cisplatin. Studies have shown that 5-FU can be added to docetaxel/cisplatin without the need for dose reduction of either of these two drugs [17,18]. Against this background, a multinational trial (V325) was set up to evaluate the value of docetaxel in combination with cisplatin, with or without continuous infusion 5-FU, in metastatic gastric carcinoma. The trial comprised two stages. The first stage was a randomised phase II clinical trial comparing docetaxel/cisplatin with docetaxel/cisplatin/continuous 5-FU (DCF), and was intended to identify the test arm to be taken forward into a phase III comparison with cisplatin/5-FU (CF). An Independent Data and Safety Monitoring Committee (IDMC) was set up to make this decision according to the response rate and safety reported with each regimen. The DCF arm was associated with a higher response rate than the docetaxel/cisplatin arm (43% versus 26%, respectively) [21,22] and was thus selected as the regimen to be compared with CF in the randomised phase III trial. The preliminary data from a planned interim analysis of this trial are reported here [23,24].

2. Patients and methods

This was a phase III, multicentre, randomised trial comparing DCF with CF in patients with locally advanced or metastatic gastric adenocarcinoma.

2.1. Patient eligibility

Eligibility criteria were: histologically proven metastatic or locally recurrent gastric adenocarcinoma (including gastro-oesophageal adenocarcinoma); age >18 years with a Karnofsky performance status (KPS) of >70%; no prior adjuvant chemotherapy (except where 12 months have elapsed between prior adjuvant chemotherapy and recurrence); adequate haematology, hepatic and renal function; no brain or leptomeningeal metastases; no significant peripheral neuropathy ($\geqslant$ grade 2 according to National Cancer Institute-Common Toxicity Criteria [NCI-CTC]); no previous or concurrent malignancies; written informed consent.

Biased-coin randomisation was used to stratify for institution, liver metastases, prior gastrectomy, weight loss (>5 or $\leqslant$ 5% over prior 3 months) and the measurability of disease. Biased-coin randomisation is a dynamic allocation procedure used to minimise the overall imbalance in prognostic factors by allocating new treatment on the basis of the characteristics of previously randomised patients. The allocation is not deterministic (the ''preferred'' treatment just has a higher chance of being allocated, but it is not systematically allocated).

2.2. Summary of treatment

Patients were randomised to receive either docetaxel (75 mg/m^2 over 1 h) followed by cisplatin (75 mg/m^2 over 1–3 h), both given intravenously on day 1 only, plus 5-FU (750 mg/m^2/day as a continuous infusion over days 1–5) with cycles repeated every 3 weeks, or cisplatin (100 mg/m^2, on day 1) plus 5-FU (1000 mg/m^2/day as a continuous infusion over days 1–5), with cycles being repeated every 4 weeks.

A standard supportive regimen of adequate hydration and as-required anti-emetics was provided.

2.3. Assessments

The primary end-point was time to disease progression. The major secondary end-point was overall survival, other secondary end-points being response rate, time to treatment failure, safety and quality of life.

Tumour response was assessed every 8 weeks, irrespective of the treatment schedule. Responses were assessed by the investigator and then reviewed by an independent external response review committee. All responses were overseen by the IDMC.

2.4. Statistical considerations

The final analysis of this trial will be conducted on an intention-to-treat basis. With the recruitment of 230 patients per arm, the study will have 95% power to show an increase in the median time to progression from 4 to 6 months and an increase in median overall survival from 8 to 12 months. A total of 325 events and 325 deaths are required, respectively, to show improvements in time to progression and overall survival, using the unadjusted log-rank test with two-sided, 5% significance level for statistical analysis.

An interim analysis was built into the study design when 50% ($n = 162$) of the time to progression events required for the interim analysis had occurred. The pre-specified boundaries for superiority at this point were $P = 0.0036$ for the time to progression and $P = 0.0053$ for overall survival.

3. Results

To date, 463 patients have been randomised to receive treatment. At the time of the planned interim analysis, data were available for 223 patients: 111 in the DCF arm and 112 in the CF arm.

3.1. Demographics

Patient and tumour characteristics were generally comparable between the two treatment groups (Table 1). Over two-thirds of the patients in each arm were male, and nearly a quarter of the patients in each arm were 65 years or older. The majority of patients (63%) had a good performance status (KPS 90–100%). More than half of the patients (55%) had suffered a greater than 5% weight loss in the previous 3 months.

In most patients, the primary tumour site was the antrum, and this proportion was slightly higher in the DCF arm than in the CF arm (72% versus 63%). The vast majority of patients (98% and 97%) had metastatic disease and over 40% of patients had liver involvement. Disease was measurable in over 80% of patients.

Table 1
Patient and disease characteristics (interim analysis)

Characteristics	DCF ($n = 111$)	CF ($n = 112$)
Male	69%	71%
Median age, years (range)	52 (26–79)	54 (25–74)
$\geqslant 65$ years	24%	23%
>5% Weight loss in prior 3 months	55%	55%
Karnofsky performance score		
90–100	63%	63%
80	37%	35%
Site of primary tumour		
Antrum, body	72%	63%
Gastro-oesophageal junction, fundus	28%	37%
Metastatic cancer	98%	97%
Liver involvement	43%	41%
Measurable disease	83%	88%

3.2. Chemotherapy

3.2.1. Chemotherapy delivery

The median duration of treatment was 19 weeks for the DCF arm and 16 weeks for the CF arm, while the median dose intensity of cisplatin delivered was similar in the two arms (23 and 24 mg/m^2/week, respectively). The median dose intensity of 5-FU was slightly higher in the CF arm (1194 mg/m^2/week) than in the DCF arm (1110 mg/m^2/week). The median delivered dose intensity of docetaxel was 23 mg/m^2/week. Dose reduction was required in 12% of cycles in each arm.

3.2.2. Treatment discontinuation

Compared with the docetaxel arm, nearly twice as many patients receiving CF discontinued treatment due to progressive disease (27% versus 47%). Other reasons for discontinuation in the DCF and CF arms were adverse events (23% and 21%, respectively) and withdrawal of patient consent (27% and 16%, respectively).

3.3. Efficacy

3.3.1. Response rate

Altogether, 86% of patients in each treatment arm were evaluable for response. DCF was associated with a significantly higher overall response rate than CF (39% versus 23%, $P = 0.012$) (Table 2). Complete responses were seen in 3% of patients in each arm. Stable disease/no change was reported in 31% and 35% of patients in the DCF and CF arms, respectively, with progressive disease in 18% and 28%.

Table 2
Response rate (interim analysis)

Response[a]	DCF ($n = 111$)	CF ($n = 112$)
Complete response (CR)	3%	3%
Partial response (PR)	36%	21%
Overall response rate (CR + PR) [95% CI]	39% [30–49]	23% [16–32]
P value for overall response rate	0.012	
No change/stable disease	31%	35%
Disease progression	17%	28%
Not evaluable	14%	14%

CI, confidence intervals.
[a] All responses were confirmed independently by external response review.

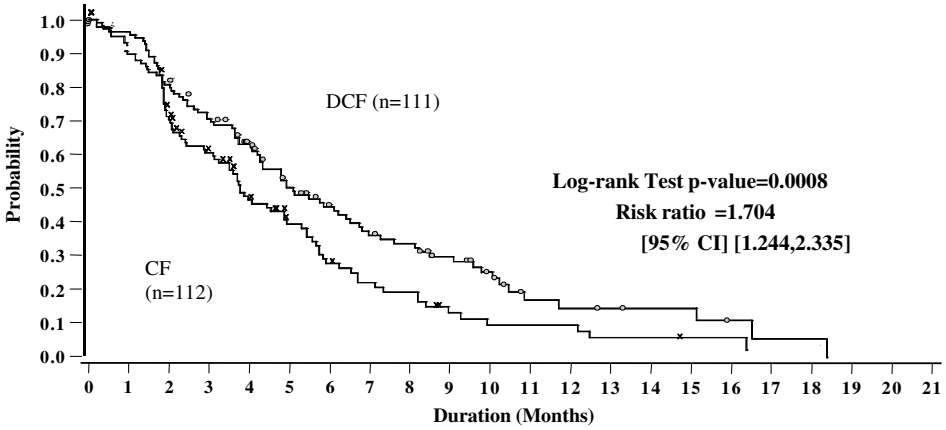

Fig. 1. Time to progression (interim analysis).

3.3.2. Time to progression

Of the 162 time to progression events occurring, 77 were in the DCF arm and 85 in the CF arm. The median time to progression was significantly longer in the DCF arm than in the CF arm (5.2 [95% CI 4.3–6.8] versus 3.7 [95% CI 3.1–4.8] months, $P = 0.0008$) (Fig. 1). The level of significance for difference between the two treatments was greater than the pre-specified boundary for superiority ($P = 0.0036$). The hazard ratio (HR) for disease progression with DCF versus CF was 1.704. The probability of progression-free survival at 9 months was almost three times greater in the DCF arm than in the CF arm (31% versus 11%) (Fig. 2).

3.3.3. Overall survival

The median overall survival was also longer in the DCF arm compared with the CF arm (10.2 [95% CI 8.5–12.3] versus 8.5 [95% CI 6.6–9.5] months, $P = 0.0064$) (Fig. 3). However, level of significance for a difference between the treatment arms was lower than the pre-specified boundary for superiority ($P = 0.0053$). The hazard ratio (HR) for risk of death in test versus control arm was 1.505.

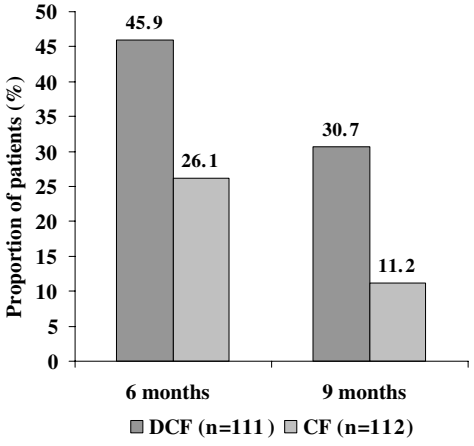

Fig. 2. Probability of progression-free survival at 6 and 9 months of treatment (interim analysis).

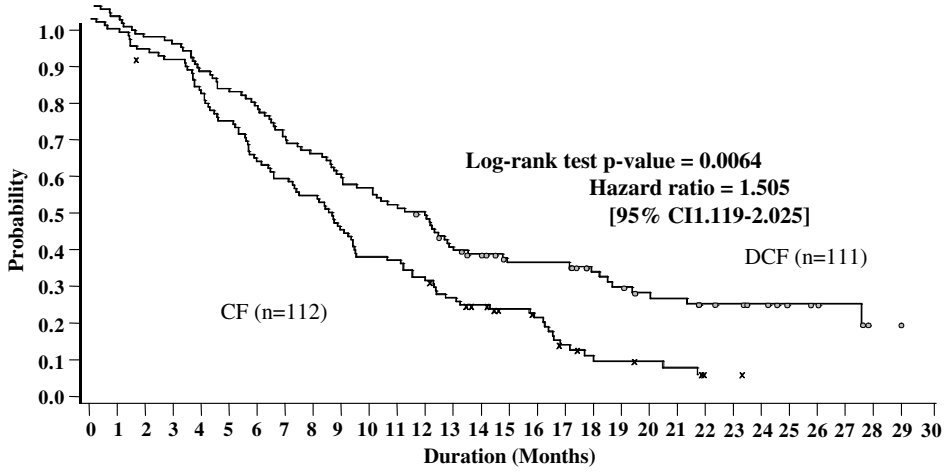

Fig. 3. Overall survival (interim analysis).

Table 3
Grade 3/4 haematological and non-haematological toxicity (interim analysis)

Toxicity	DCF ($n = 111$) (%)	CF ($n = 112$) (%)
Haematological toxicity		
Grade 3/4 neutropenia	84	60
Febrile neutropenia[a]	16	6
Neutropenic infection[b]	14	7
Grade 3/4 treatment-related non-haematological toxicity		
Neurosensory	8	5
Infection	12	6
Anorexia	13	13
Nausea	14	20
Vomiting	15	21
Lethargy	20	19
Diarrhoea	20	8
Stomatitis	23	30
At least 1 treatment-related non-haematological grade 3/4 adverse event	68	65

[a] Grade $\geqslant 2$ fever concomitant with grade 4 neutropenia (without infection).
[b] Grade $\geqslant 2$ related infection concomitant with grade 3/4 neutropenia.

3.4. Safety

Mortality from any cause within 30 days of the first infusion of treatment was 2% and 3% in DCF and CF arms, respectively.

3.4.1. Haematological toxicity

Grade 3/4 neutropenia occurred in the majority of the patients receiving DCF (84%) and more than half of the CF treated patients (60%) (Table 3). The occurrence of febrile neutropenia and neutropenic infection was also higher in the DCF arm.

3.5. Non-haematological toxicity

The incidence of treatment-related grade 3/4 adverse events was similar in both arms, with at least one treatment-related event being recorded in 68% and 65% of DCF and CF arms respectively (Table 3). Grade 3/4 adverse events were mainly related to the gastro-intestinal system and included stomatitis, nausea, vomiting and diarrhoea. Lethargy and anorexia were also noted.

4. Discussion

This planned interim analysis showed that addition of docetaxel to a regimen of cisplatin/5-FU for the treatment of mainly metastatic gastric carcinoma significantly increased the tumour response rate and prolonged the time to progression, in accordance with pre-determined significance boundaries. At 6 and 9 months, progression free survival in the DCF arm was almost double that in the active control arm. Overall survival was also significantly improved, although the level of significance was lower than that of the pre-determined boundary.

As these results represent an interim analysis, it is premature to compare them with final results from other phase III trials. However, it is interesting to note that the median overall survival times in both arms of the study were higher than those seen in two phase III trials with 5-FU alone, uracil/tegafur/mitomycin C, ELF, FAMTX and FUP [5,25]. In addition, the median overall survival with DCF was longer than that seen in phase III trials using ECF [26,27].

All cause mortality within 30 days of the first treatment infusion was comparable in both arms (2% and 3%). Interestingly, the observed death rate in the CF arm was only half that reported for the CF regimen in a phase III trial conducted by the European Organization for Research and Treatment of Cancer (6%) [5]. All cause mortality within 30 days of the last infusion was slightly higher with DCF (12%) than with CF (8%). The observed mortality rate for CF at this stage of the study is comparable to that reported in a phase III trial of the Japan Clinical Oncology Group (7%) [25], even though lower doses of CF were administered in the Japanese study.

The haematological toxicity observed with DCF was predictable and manageable. The type and incidence of non-haematological toxicities were similar in both arms. The nausea and vomiting characteristic of the cisplatin component were not exacerbated by the addition of docetaxel, the predominant gastrointestinal adverse events in the DCF arm being stomatitis (23%) and diarrhoea (20%).

The results from this interim analysis are extremely encouraging for a disease that generally has a very poor prognosis, and the final analysis should confirm the role of DCF in metastatic gastric carcinoma. The results from this trial are particularly promising because of the robust nature and power of the trial. The V325 protocol is designed to have 95% power to show 50% increases in median time to progression and overall survival. As such, this is the highest-powered trial conducted in metastatic gastric carcinoma to date. More importantly, it has 90% power to reveal a significant difference between treatments in time to progression and overall survival, assuming these parameters are independent of each other. An additional factor in the design of this trial is that the weight loss boundary has been set at the relatively stringent level of $\geqslant 5\%$ compared with the 10% level used in the majority of trials. The activity of docetaxel in gastric cancer ensures this drug a role in the treatment of metastatic disease. It will be necessary to determine the combinations of docetaxel and other chemotherapeutic agents which demonstrate optimum

efficacy. A phase I/II trial has shown the feasibility of administering a combination of docetaxel, capecitabine and cisplatin as first-line therapy, and showed it to be highly active and tolerable (68% response rate among 40 patients) [28]. Docetaxel in combination with irinotecan has also been shown to be a potential treatment option [29].

In conclusion, this planned interim analysis showed that DCF significantly improved response rate, time to progression and overall survival compared with CF and had acceptable toxicity. The median overall survival obtained with DCF, at 10 months, is particularly encouraging. In view of these findings, we suggest that DCF should be considered as first-line therapy for patients with advanced gastric carcinoma. Results from the final analysis are awaited.

Appendix

The investigations who comprise the TAX325 Study Group are: Ajani, Anelli, Arbeloa, Azevedo, Baez, Bakri, Barone, Barroso, Benson, Boni, Cabral Filho, Chao Y., Chen, Clemens, Consteala, Crilley, De Greve, Di Costanzo, Feldman, Fodor, Fontes, Goker, Gonzales Baron, Gravalcs, Geco, Haller, Heim, Holland, Kelsen, Kirschung, Kohne, Kroening, Lilenbaum, Majus, Malzyner, Marsh, Martinez, Matos, Mauricio, Mc Cann, Mitchell, Moiseyenko, Morgan, Narvaez, Nunez, Olivares, Olivatto, Olivella, Ortrz, Pandit, Pasini, Picus, Pimentel, Pizao, Presant, Rodrigues, Rowland, Salas, Salek, Sastre, Scholnik, Scullin, Silingardi, Tekuzman, Thomas, Tjulandn, Tonato, Vallejos, Van Cutsem, Van Laethem, Vochyakova, Voznyi, Yilmaz.

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