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The role of docetaxel in gastric cancer

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Abstract

To date, there has been no global standard chemotherapy for advanced gastric cancer and patient outcomes remain poor. This has led to a concerted effort to find more active treatments. Single-agent docetaxel has shown encouraging clinical activity, and Phase II studies have established docetaxel–cisplatin–5-fluorouracil (DCF) as the most promising docetaxel-containing regimen for further evaluation. TAX 325, the largest Phase III trial to date of patients with advanced gastric adenocarcinoma ($n = 445$), has demonstrated a significant survival advantage, higher overall response rate, improved clinical benefit and better preservation of quality of life for DCF vs. cisplatin–5-fluorouracil (CF) – a previous reference regimen. Although haematological toxicity was higher with DCF, prophylaxis with granulocyte colony-stimulating factor, awareness of the risk of neutropenic complications and early intervention can all help to manage the toxicity. Addition of docetaxel to CF or other active agent(s) represents an important new front-line option for patients with advanced gastric or gastro-oesophageal cancer and should be a new reference regimen for further clinical studies.

Keywords: Chemotherapy; Cisplatin; Docetaxel; Fluoropyrimidine; Gastric cancer

1. Introduction

Advanced gastric or gastro-oesophageal cancer is incurable and patients with this disease have a poor prognosis. Without systemic chemotherapy – the only available treatment option – patients can only expect to live for 4 months and, even with drug intervention, life expectancy rarely exceeds 1 year [1]. Despite an improvement in survival with chemotherapy, no single agent or combination regimen has become accepted as the standard of care and patient outcomes remain inadequate. In Western countries, the most frequently used chemotherapy regimens are cisplatin and continuously infused 5-fluorouracil (5-FU) (the cisplatin–5-FU [CF] regimen) and CF plus etoposide (the ECF regimen). As CF and ECF are the most common and widely studied combinations with the most reliable and consistent efficacy results, they are regarded as reference regimens by regulatory authorities across Europe and the Americas.

The introduction of newer cytotoxic agents, including docetaxel (Taxotere®), paclitaxel, oxaliplatin (Eloxatin®), irinotecan and the oral fluoropyrimidines, capecitabine and S-1, has renewed hope for improved patient outcomes in advanced gastric cancer. One of the most promising of these agents is docetaxel, which has demonstrated encouraging activity both as a single agent and in combination with conventional chemotherapeutic agents.

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2. Activity of single-agent docetaxel

Over the past 12 years, multiple Phase II studies have investigated the activity of single-agent docetaxel in patients with advanced gastric cancer. In these trials, single-agent docetaxel achieved an overall response rate (ORR) of 16% to 24% when used as front-line therapy and 5% to 21% when given to pretreated patients (Table 1) [2–11]. In both settings, a significant proportion of the remaining patients achieved disease stabilization (Table 1). The similarity of the results observed in previously untreated and pretreated patients suggests that treatment status does not markedly affect the efficacy of docetaxel. In all the studies, the major toxicities associated with docetaxel were haematological in nature.

3. The evolution of the DCF regimen: docetaxel in combination with cisplatin and 5-FU

3.1. The SAKK/EIO initiative

As a result of the encouraging activity of single-agent docetaxel, a collaborative Phase II study was undertaken by the Swiss Group for Clinical Cancer Research (SAKK) and European Institute for Oncology (EIO) to investigate the efficacy and tolerability of docetaxel in combination with cisplatin (DC), an agent with proven activity in gastric cancer [12]. In this non-randomized study, 48 patients with measurable, unresectable and/or metastatic gastric

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Table 1
Activity of single-agent docetaxel in Phase II studies[a]

Study	No. of evaluable patients	Prior palliative chemotherapy (%)	Docetaxel dose (mg/m^2) and schedule	ORR/SD (%)	Median TTP/PFS (months)
Sulkes [2]	33	0	100 q3w	24/33	7.5
Einzig [3]	41	0	100 q3w	17/7	2.8
Taguchi [4]	59	A/R	60 q3w	24/32	–
Mai [5]	59	A/R	60 q3–4w	24/34	–
Vanhoefer [6]	25	100	100 q3w	20/32	–
Graziano [7]	21	100	36 qw	5/38	–
Mavroudis [8]	30	0	100 q3w + G-CSF	20/23	6
Bang [9]	40	0	75 q3w	16/25	1.4
Giuliani [10]	30	100	100 q3w	17/30	–
Lee [11]	24	100	75 q3w	21/38	2.6

[a] A/R, Advanced or recurrent disease; G-CSF, Granulocyte colony-stimulating factor; ORR, Overall response rate; PFS, Progression-free survival; qw, Weekly; q3w, Every 3 weeks; q3–4w, Every 3–4 weeks; SD, Stable disease; TTP, Time to progression.

carcinoma were treated with first-line docetaxel 85 mg/m^2 and cisplatin 75 mg/m^2, administered every 3 weeks for up to 8 cycles. In terms of efficacy, DC was associated with a favourable ORR of 56% (including 2 complete responses), a median time to progression (TTP) of 6.6 months and a median overall survival (OS) of 9 months. In addition, DC was well tolerated with a predictable and manageable toxicity profile. As expected, the vast majority of grade 3–4 toxicities were haematological (neutropenia 81%, anaemia 32%, thrombocytopenia 4%), and while there were 9 episodes of febrile neutropenia, none was fatal.

A Phase I–II dose-finding study was subsequently conducted by the same study group to establish the feasibility of adding a protracted continuous infusion of 5-FU 300 mg/m^2/day for 2 weeks – a drug and schedule associated with minimal haematological toxicity – to first-line DC (DCF) in patients with measurable, unresectable and/or metastatic gastric carcinoma [13]. As well as producing a similar ORR (51%; $n = 41$) and median OS (9.3 months), the safety profile of DCF was similar to that observed previously for DC administered at the same dosage in the SAKK/EIO study [12]. Consequently, a randomized, three-arm study (SAKK 42/99) was undertaken to directly compare the efficacy and safety of DCF vs. DC or the standard reference regimen, ECF, in previously untreated patients with advanced gastric carcinoma [14] (Fig. 1). The overall objective of this study was to determine which docetaxel-containing regimen would be the more promising combination for comparison against ECF in a randomized Phase III study. The primary endpoint of the study was ORR. Although the docetaxel-containing regimens were slightly more toxic, both combinations appeared to be more efficacious than ECF. In an interim analysis of the data, DCF achieved a higher ORR (55% vs. 42%, respectively) and median TTP (7.3 vs. 4.3 months, respectively) compared with the DC regimen. DCF and DC had a similar toxicity profile, with the exception that the rate of febrile neutropenia and diarrhoea was higher in

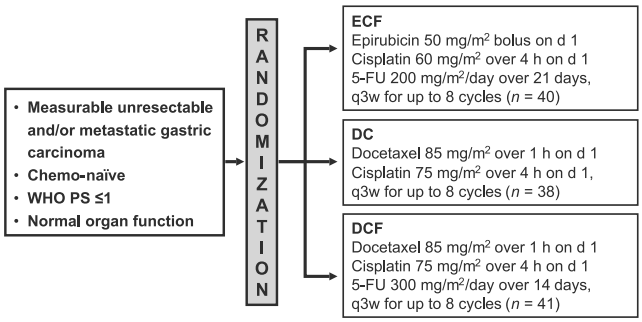

Fig. 1. Design of the Phase II SAKK 42/99 study. 5-FU, 5-fluorouracil; q3w, every 3 weeks. Stratified by centre, liver involvement and World Health Organization performance status (WHO PS). Docetaxel dose reduced to 75 mg/m^2 after first 21 patients.

DCF-treated patients. The majority of episodes of febrile neutropenia associated with DCF treatment occurred in the first 21 patients (10 episodes), which led to a docetaxel dose reduction to 75 mg/m^2 and, in turn, a marked reduction in the incidence of this complication. Based on these data, DCF was chosen for formal comparison against ECF in a Phase III study.

3.2. The TAX 325 initiative

Alongside the SAKK/EIO studies, another group, the TAX 325 Study Group, had also undertaken a multinational, randomized Phase II study to compare the efficacy and safety of DC with DCF in 158 previously untreated patients with metastatic (accounting for 95% of patients) or locally advanced/recurrent gastric or gastro-oesophageal adenocarcinoma [15]. The purpose of this trial was to identify the experimental regimen to be taken forward into a Phase III comparison with CF. In the Phase II study, patients received either DCF (docetaxel 75 mg/m^2 on day 1, cisplatin 75 mg/m^2 on day 1, and 5-FU 750 mg/m^2/day as a continuous infusion on days 1–5) or DC (docetaxel 85 mg/m^2 and cisplatin 75 mg/m^2 on day 1), administered every 3 weeks until disease progression, unacceptable

toxicity or consent withdrawal. Interestingly, the length of 5-FU infusion was much shorter than that used in the corresponding SAKK/EOI Phase II study [14]. In terms of efficacy, DCF was superior to DC for ORR (primary endpoint; 43% vs. 26%, respectively) and median TTP (5.9 vs. 5.0 months, respectively, equating to a 20% reduction in the risk of progression). While median OS was slightly longer in the DC group (10.5 months vs. 9.6 months in the DCF group, respectively), 1-year survival was similar (41.7% vs. 35.4%, respectively). The most frequent grade 3–4 toxicities – which were considered manageable – were neutropenia (DCF 86%, DC 87%) and gastrointestinal events (DCF 56%, DC 30%). Based on these results, the independent data monitoring committee selected DCF for further investigation in the Phase III stage of the TAX 325 study.

4. The TAX 325 Phase III study

The TAX 325 Phase III study is one of the most important clinical trials to have been undertaken in advanced gastric cancer during the past decade and has led to the first approval of a chemotherapy regimen (DCF) for the treatment of advanced gastro-oesophageal cancer in 30 years. The study is reported in full elsewhere [16]; the following is a summary of available data that have been reported previously in abstract form [17–19].

This international, randomized study compared the efficacy and tolerability of DCF (the superior regimen from the Phase II stage of the study) [15] with CF in 457 patients with advanced gastric (including gastro-oesophageal junction) adenocarcinoma who had received no prior palliative treatment (Fig. 2) [17,19]. In the study, treatment was

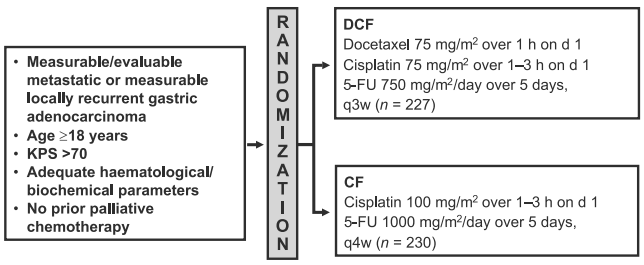

Fig. 2. Design of the Phase III TAX 325 study. 5-FU, 5-fluorouracil; KPS, Karnofsky performance status; q3w, every 3 weeks; q4w, every 4 weeks.

given until disease progression, withdrawal of consent or unacceptable toxicity, and tumour assessments were carried out every 8 weeks. Patients with potentially resectable cancers were not eligible and all patients were stratified according to centre and prognostic factors (presence of liver metastases, prior gastrectomy, 5% weight loss and tumour measurability) [17,19].

4.1. Study rationale

As described above, the DCF regimen was chosen as the experimental arm by an independent data monitoring committee on the basis of the TAX 325 Phase II comparison of DCF with DC [15], the results of which were consistent with those of the independently conducted SAKK 42/99 study [14]. CF was selected as the reference regimen because: (1) it is an accepted standard reference therapy for regulatory purposes; (2) it was already being used as a reference regimen in two large Phase III trials (European and Japanese) that were ongoing at the time when the TAX 325 study was designed [23,24]; and (3) an international poll of medical oncologists taken prior to the study revealed that CF was the most commonly used regimen. In addition, CF is the most widely studied regimen in advanced gastric cancer with the most reproducible efficacy results (Table 2) [20–24].

Table 2
Activity of cisplatin–5-FU in Phase II/III studies[a]

Study	No. of evaluable patients	ORR (%)	Median TTP/PFS (months)	Median OS (months)
Lacave [20]	53	42	–	10.6
Kim [21]	103	51	5.0	8.5
Rougier [22]	83	43	–	9.0
Vanhoefer [23]	125	20	4.1	7.2
Ohtsu [24]	99	34	3.9	7.3

[a] ORR, Overall response rate; OS, Overall survival; PFS, Progression-free survival; TTP, Time to progression.

4.2. Study endpoints

The primary endpoint of the TAX 325 Phase III study was median TTP [17,19]. However, the study had equal statistical power to assess median OS [17]. In contrast to most trials in this setting that assess the non-inferiority of new treatments compared with reference therapy, the TAX 325 study had a sample size that was large enough to determine whether or not DCF was superior to CF in terms of TTP and OS. Additional secondary endpoints included quality of life (QoL), clinical benefit, ORR and safety [17–19].

The inclusion of QoL and clinical benefit as endpoints in the study was important as it is recognized from clinical experience that the ability to maintain a normal life during chemotherapy, with minimal cancer- and treatment-related symptoms, is as important to patients as improving OS. Moreover, very few Phase III studies have evaluated QoL as an endpoint (examples include Ross et al. [25] and Webb et al. [26]) and none has investigated clinical benefit. The primary QoL endpoint was the time to 5% definitive deterioration of global health status (measured using the EORTC QLQ-C30) compared with baseline [18]. The primary clinical benefit endpoint was time to definitive worsening of Karnofsky performance status (KPS) by one category versus baseline [18]. Both QoL and clinical benefit

were assessed over an extended 14-month period (during treatment and follow-up).

4.3. Patients

Patients had a median age of 55 years and a median KPS of 90 (64% of patients had a KPS ⩾90) [19]. Weight loss in the previous 3 months was 5% to 10% in 29% of patients and >10% in 27% of patients [17]. Unlike most previous trials in this setting, almost all patients (97%) had metastatic disease (81% with ⩾2 organs involved) [19], indicating that patients had a very high tumour burden.

4.4. Efficacy

DCF was significantly superior to CF for median TTP (the primary endpoint), median OS, ORR and median time to treatment failure (Table 3; Fig. 3). Compared with CF, DCF treatment resulted in a 32% reduction in the risk of progression and a 23% reduction in the risk of death. While the absolute median OS times appeared to be quite similar in the two groups, these values do not reflect the temporal differences between treatments. The benefit of DCF is most evident after 9 months, as reflected in the higher long-term (2-year) survival rate – double that achieved with CF (Table 3).

Table 3
TAX 325 Phase III efficacy results [17,19] [a]

Parameter	DCF	CF	Risk reduction (%)	*P*-value
No. of patients	221	224	–	–
Median TTP, months	5.6	3.7	32	0.0004
Median OS, months [b]	9.2	8.6	23	0.0201
2-year survival, %	18	9	–	–
ORR, % [c]	37	25	–	0.0106
PD, %	17	31	–	–
Median TTF, months	4.0	3.4	–	0.0335

[a] ORR, Overall response rate; OS, Overall survival; PD, Progressive disease (best response); PFS, Progression-free survival; TTF, Time to treatment failure; TTP, Time to progression.
[b] Median follow-up 23 months.
[c] Confirmed and independently reviewed.

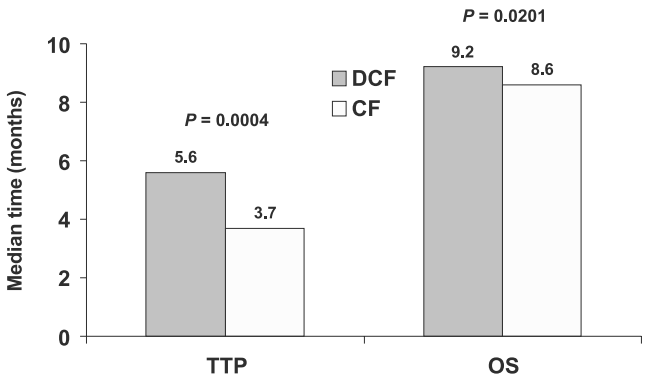

Fig. 3. TAX 325 results: effect of first-line DCF and CF on time to progression (TTP) and overall survival (OS) in patients with advanced gastric adenocarcinoma.

4.5. Quality of life and clinical benefit

Even though DCF was the more intense regimen, DCF-treated patients had a better QoL and achieved greater clinical benefit from treatment than CF-treated patients [18]. The difference between treatments for the primary QoL and clinical benefit endpoints was highly significantly in favour of the DCF regimen [18] (Fig. 4). DCF was also superior to CF for nearly all secondary QoL analyses (time to definitive deterioration in: social functioning; nausea/vomiting; appetite loss; pain and EuroQoL ED-5D thermometer) ($P < 0.05$). A non-significant trend in favour of DCF was also observed for time to definitive deterioration in physical functioning ($P = 0.1349$). With regard to secondary clinical benefit analyses, there was a non-significant trend in favour of DCF for preservation of weight and appetite ($P = 0.0776$ and $P = 0.1143$, respectively). No difference between treatments was observed for pain-free survival and time to first cancer pain requiring opioids.

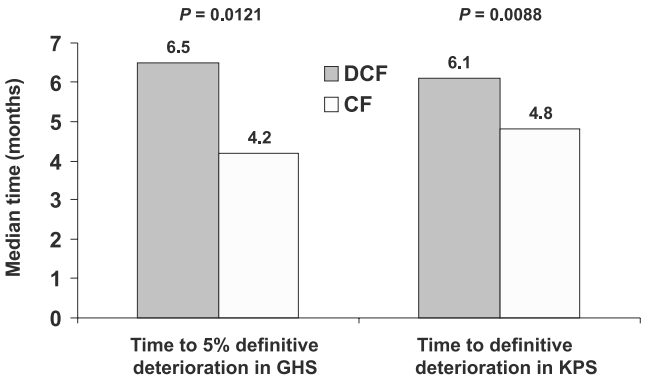

Fig. 4. TAX 325 results: effect of first-line DCF and CF on quality of life and clinical benefit endpoints in patients with advanced gastric adenocarcinoma. GHS, global health status; KPS, Karnofsky performance status.

4.6. Safety

DCF was associated with increased toxicity compared with CF (Table 4). Clinically significant grade 3–4 toxicities

Table 4
TAX 325 Phase III safety results: key grade 3–4 toxicities (regardless of relationship to study treatment) [17,19]

Grade 3–4 toxicity	Patients (%)	
	DCF	CF
Stomatitis	21	27
Diarrhoea	19	8
Neutropenia	82	57
Febrile neutropenia/neutropenic infection	30	14
Anaemia	18	26

occurring more commonly with DCF included diarrhoea, neutropenia and febrile neutropenia/neutropenic infection. In contrast, grade 3–4 stomatitis and anaemia occurred more frequently with CF. Despite the increased toxicity, the QoL and clinical benefit data suggest that DCF-treated patients found the regimen to be acceptable.

While the high incidence of complicated neutropenia with DCF is concerning, it should be noted that the incidence of this complication was reduced to that observed with CF in patients who received secondary prophylaxis with granulocyte colony-stimulating factor (G-CSF). In the 19% of DCF-treated patients who received secondary G-CSF, the incidence of febrile neutropenia/neutropenic infection was only 12%, compared with 14% in CF-treated patients (and 15% of the 9% of CF-treated patients who also received secondary G-CSF) [19]. This finding suggests that primary prophylaxis with G-CSF would dramatically reduce the rate of complicated neutropenia associated with DCF. This treatment strategy is consistent with new European and North American guidelines that recommend the routine use of primary G-CSF prophylaxis when using a chemotherapy regimen that is associated with a high (>20%) risk of febrile neutropenia, such as DCF [27–29].

5. Paclitaxel–platinum combinations in gastric cancer

There are limited Phase II data available for paclitaxel–platinum combinations in advanced gastric cancer. Paclitaxel 175 mg/m^2 over 3 hours on day 1 combined with 5-FU 750 mg/m^2 over 24 hours on days 1–5 and cisplatin 20 mg/m^2 over 2 hours on days 1–5, every 28 days, achieved an overall response rate of 51% and median survival duration of 6 months in a study of 41 patients with metastatic, unresectable advanced, or relapsed gastric cancer [30]. The main toxicity was myelosuppression, with grade 3–4 neutropenia reported in 34% of patients.

Another study of 45 patients with previously untreated unresectable, locally advanced or metastatic gastric cancer assessed 6 weeks of therapy (followed by 2 weeks without therapy) with paclitaxel 175 mg/m^2 as a 3-h infusion on days 1 and 22, cisplatin 50 mg/m^2 as a 1-h infusion on days 8 and 29, and 5-FU 2 g/m^2 given over 24 hours, weekly, preceded by folinic acid 500 mg/m^2 over 2 hours [31]. The overall response rate was 51% (95% CI, 35.8–66.3%) and median progression-free and overall survival times were 9 months and 14 months, respectively. Grade 3–4 neutropenia was reported in 7 patients (15%); other grade 3–4 toxicities included nausea/vomiting in 5 patients (11%), alopecia in 22 patients (49%), and diarrhoea in 1 patient (2%).

6. Conclusions

Phase II studies have established DCF as the most promising docetaxel-containing chemotherapy regimen in advanced gastric cancer. The pivotal TAX 325 Phase III study has subsequently shown that treatment with DCF results in a significantly longer TTP and OS, a doubling of the 2-year survival rate, a higher ORR, improved clinical benefit and better preservation of QoL than treatment with CF – a previous standard reference regimen. Importantly, these benefits in outcomes were achieved even though the vast majority of patients had metastatic gastric cancer and therefore represented a very sick patient population.

Although DCF is associated with a high risk of febrile neutropenia, this complication may be prevented by primary G-CSF prophylaxis, a treatment strategy advocated in current practice guidelines. Other haematological and non-haematological toxicities are predictable, acceptable and manageable. However, overall toxicity management can be improved further through proper patient selection, early intervention, improved awareness of the treatment entity and better patient education.

In the TAX 325 study, the addition of docetaxel to CF resulted in improved endpoints suggesting that it should now be incorporated in all front-line regimens used for the treatment of patients with advanced gastric or gastro-oesophageal cancer.

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