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Docetaxel
In Gastric Cancer

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Contents

Abstract

▲ Docetaxel is a taxane analogue that inhibits microtubule disassembly and, in cultured gastric cancer cells, induces apoptosis-associated binding activity of the transcription factor activating protein-1, and activates the proapoptotic genes *BCL2L1* and *BAX*.

▲ In patients with metastatic or locally advanced/recurrent gastric or gastro-oesophageal junction adenocarcinoma, the median time to tumour progression was significantly prolonged with 3-week cycles of intravenous (IV) docetaxel plus cisplatin and fluorouracil (5-fluorouracil) compared with 4-week cycles of IV cisplatin plus IV fluorouracil (5.6 vs 3.7 months) in a large (n = 445), randomised, multicentre, phase III trial.

▲ Furthermore, recipients of this triple regimen experienced a significantly longer median overall survival time, a higher overall response rate and delayed deterioration in health-related quality of life than those receiving cisplatin plus fluorouracil.

▲ These data are supported by two large (n > 100), randomised, phase II studies in patients with metastatic or locally advanced/recurrent gastric or gastro-oesophageal junction cancer.

▲ In general, combination therapy with docetaxel, cisplatin and fluorouracil was relatively well tolerated given the nature of chemotherapy in patients with metastatic or locally advanced/recurrent gastric or gastro-oesophageal adenocarcinoma.

Features and properties of docetaxel (Taxotere®)	
Featured indication	
Metastatic or advanced gastric adenocarcinoma, including gastro-oesophageal junction adenocarcinoma, in patients who have not received prior chemotherapy for metastatic or advanced disease	
Mechanism of action	
Inhibits microtubule disassembly, leading to the disruption of cell division, cell cycle arrest and cell death; activates the proapoptotic genes *BCL2L1* and *BAX* and induces the apoptosis-associated binding activity of transcription factor activating protein-1 in gastric cancer cell lines	
Dosage and administration (in combination with intravenous cisplatin and fluorouracil)	
Dose	75 mg/m^2
Route of administration	Intravenous 1h infusion
Frequency	Once every 3 weeks
Pharmacokinetic profile of intravenous docetaxel 20–115 mg/m^2 in patients with cancer	
Mean maximum plasma concentration (100 mg/m^2 dose)	3.7 μg/mL
Area under the plasma concentration-time curve (100 mg/m^2 dose)	4.6 μg • h/mL
Mean volume of distribution at steady state	113L
Mean total body clearance	21 L/h/m^2
Elimination α, β, and γ half-lives	4 min; 36 min; 11.1h
Grade 3 or 4 adverse events occurring in ≥10% of patients receiving docetaxel in combination with intravenous cisplatin and fluorouracil	
Neutropenia, stomatitis, anaemia, diarrhoea, lethargy, nausea, vomiting, infection	

Gastric cancer is the fourth most prevalent cancer and the second leading cause of cancer-related death worldwide.[1] It is an aggressive cancer that is often not diagnosed until an advanced stage;[2] patients with advanced disease have a median survival of 6–9 months.[3]

The primary curative treatment option for the early stages of gastric cancer is surgical resection,[4,5] although ≈60% of patients experience local or distant relapse following curative surgery and have a 5-year survival rate of <30%.[6,7] Despite advances in the treatment of gastric cancer, such as adjuvant chemoradiation after resection, the prognosis for patients with the disease remains poor, thus highlighting the importance of palliative therapy.[6]

At present, there is no standard single chemotherapeutic agent or combination regimen for gastric cancer therapy, although cisplatin and fluorouracil (5-fluorouracil)-based combinations are currently considered the treatment reference regimens.[2,6] Response rates to current treatment regimens are ≈30–40%, although the responses are generally short-lived and rarely complete in patients with advanced gastric cancer, spurring interest in the search for alternative cytotoxic agents and combination regimens for the treatment of this disease.[8]

Docetaxel (Taxotere®)[1], a member of the taxane class of chemotherapy agents, is an inhibitor of microtubule disassembly. In numerous preclinical and clinical gastric cancer studies it exhibited antitumour activity both alone and in combination with other chemotherapeutic agents. This article provides an overview of the pharmacological properties of docetaxel, and focuses on its clinical efficacy and tolerability in combination with cisplatin plus fluorouracil in patients with metastatic or locally advanced/recurrent gastric or gastro-oesophageal junction cancer.

1. Pharmacodynamic Profile

The pharmacodynamic activities of docetaxel are well established and have been reviewed in *Drugs*[9-11] and elsewhere.[12-14] Therefore, this section provides a brief overview of the pharmacodynamic properties of docetaxel, focusing on those which are relevant to its use in patients with gastric cancer. Data are from *in vitro* studies,[15-22] *in vivo* animal models[17,19,21-23] and the manufacturer's summary of product characteristics.[24]

- Docetaxel is a semisynthetic taxane that inhibits microtubule disassembly and promotes microtubule stabilisation, leading to disruption of microtubule-mediated cellular functions during cell division, cell cycle arrest at G_2/M transition and cell death.[13,24]

- Additional antineoplastic activities of docetaxel have been demonstrated *in vitro*.[15,16] In gastric cancer cell lines, docetaxel has been shown to activate proapoptotic genes, including *BCL2L1* and *BAX*, with cellular sensitivity to the agent correlating with apoptotic cell death.[15] Furthermore, the binding activity of activating protein-1, a transcription factor involved in cell proliferation and apoptosis, was induced by docetaxel within certain gastric cancer cell lines (MKN45 and MKN1).[16] The induction of such activity by docetaxel was significantly ($p < 0.05$) associated with the induction of messenger RNA from the growth arrest gene *DDIT3* and the formation of internucleosomal DNA ladders, suggesting a potential signalling pathway for docetaxel-triggered apoptosis in gastric cancer cells.[16]

- The cytotoxic and antineoplastic effects of docetaxel have been demonstrated *in vitro* in several human gastric[17,18] and mouse forestomach[19] cancer cell lines, as well as in clinical samples from patients with gastric cancers.[17]

- In addition, docetaxel has demonstrated antitumour activity in murine models of various cancers including gastric,[17] colon[25] and forestomach[19] cancers. For example, in a murine xenograft model of well, poorly and undifferentiated gastric cancer cell lines (MKN-28, MKN-45 and KKLS), inhibition of tumour growth was generally observed with docetaxel treatment regardless of histological tumour type.[17]

1 The use of trade names is for product identification purposes only and does not imply endorsement.

- In preclinical studies of human gastric cancer cell lines[18,20-22] and gastric cancer xenografts,[19,21-23] enhanced antitumour activity was demonstrated with docetaxel in combination with various anticancer agents including cisplatin,[20] fluoropyrimidines (fluorouracil,[21] capecitabine[23] and S-1[21,23]), gemcitabine,[18] batimastat[19] and the novel telomerase-selective oncolytic adenoviral agent OBP-401.[22]
- No cross-resistance was observed between docetaxel and several conventional chemotherapeutic agents (mitomycin, cisplatin and fluorouracil) in freshly resected tumour specimens from patients with advanced gastric cancer, highlighting the potential use of docetaxel combination regimens in this patient population.[26]

2. Pharmacokinetic Profile

This section provides a brief overview of the pharmacokinetic properties of intravenous docetaxel; these parameters are well established and have been extensively reviewed elsewhere.[9,10,12,27,28] Data were obtained from phase I trials in patients with cancer who received docetaxel 20–115 mg/m^2 reported in the manufacturer's US[29] and EU[24] prescribing information.

- The area under the plasma concentration-time curve (AUC) is dose proportional after 1- to 2-hour intravenous (IV) infusions of docetaxel 70–115 mg/m^2, with the profile of the drug fitting a three-compartment model.[29] Following a 1-hour infusion of docetaxel 100 mg/m^2, the mean maximum plasma concentration and AUC values for docetaxel were 3.7 μg/mL and 4.6 μg • h/mL.[24]
- Docetaxel is >95% plasma protein bound and had a mean steady-state volume of distribution of 113L in patients with cancer.[24]
- Metabolism of docetaxel occurs via the cytochrome P450 (CYP) 3A4 isoenzyme, according to *in vitro* studies.[29] Within 7 days, docetaxel was primarily (75%) eliminated via faeces, with 6% excreted in urine, after administration of a radiolabelled dose in three patients with cancer.[24]
- The mean total body clearance of docetaxel was 21 L/h/m^2 in patients with cancer and had an interpatient variation of ≈50%.[24]
- The α, β and γ elimination half-lives of docetaxel were 4 minutes, 36 minutes and 11.1 hours, respectively, following docetaxel administration in patients with cancer.[24] The relatively long late phase is partly due to the slow movement of docetaxel from the peripheral compartment.
- The pharmacokinetics of docetaxel do not appear to be affected by patient age or sex according to a pharmacokinetic analysis in patients (n = 535) receiving docetaxel 100 mg/m^2.[29] In the same analysis, docetaxel total body clearance was reduced by an average of 27% and exposure was increased by 38% in patients with mild to moderate hepatic impairment. However, docetaxel is not recommended in patients with gastric adenocarcinoma who have elevated bilirubin levels above the upper limit of normal (ULN) and serum ALT and/or AST levels >1.5 × ULN concomitant with alkaline phosphatase >2.5 × ULN,[24,29] with the US prescribing information carrying a black box warning in this regard.[29]
- As predicted from the extensive metabolism of docetaxel by the CYP enzyme CYP3A4, coadministration of CYP3A4 inhibitors, inducers and/or substrates (such as ketoconazole and cyclosporin) may affect docetaxel metabolism and thus exposure.[24]
- The pharmacokinetic profiles of docetaxel, cisplatin and fluorouracil were not affected upon coadministration in 12 patients with solid tumours.[24] Furthermore, docetaxel infusion shortly before cisplatin administration had no effect on the pharmacokinetics of cisplatin.[24]
- Total body clearance of docetaxel is not affected by dexamethasone pretreatment according to a population pharmacokinetic analysis.[29] However, coadministration of docetaxel and carboplatin may increase carboplatin clearance according to limited data from one uncontrolled study, although the clinical relevance of this finding is unknown.[24]

3. Therapeutic Efficacy

The clinical efficacy of docetaxel in combination with cisplatin and fluorouracil therapy has been

evaluated in three large (n > 100), randomised, open-label, multinational phase II[30,31] or III[32] trials in patients with unresectable,[31] metastatic[30-32] or locally advanced[30-32] or recurrent[30,32] gastric[30-32] or gastro-oesophageal junction[30,32] cancer conducted by the Swiss Group for Clinical Cancer Research (SAKK)[31] or the V325 study group.[30,32] These data are supported by results from several, small (n ≤ 52), noncomparative, phase I/II trials in patients with metastatic or locally advanced/recurrent gastric cancer[33] and phase II trials in patients with metastatic[34,35] and/or unresectable[35] gastric cancer. Discussion in this section focuses on data from large trials (n > 100).

In the SAKK trial, eligible patients had bidimensionally measurable lesions, a WHO performance status of ≤1 and had not received prior chemotherapy.[31] Median patient age was ≈59 years, 82–95% had distant metastatic disease, ≈61% had a WHO performance status of 0 and 18–32% had previously had a gastrectomy.

In the V325 phase II[30] and III[32] trials, eligible patients had a Karnofsky performance status of >70% and had received no palliative chemotherapy. In the phase II trial, patients who had received adjuvant and/or preoperative chemotherapy >12 months prior to the trial were also eligible.[30] Patients in this trial had a median age of 57 years, 95% of patients had metastatic disease, 79% had two or more organs involved and 37% had received prior surgical intervention. Those in the phase III trial also were required to have received no radiation therapy in the previous 6 weeks prior to enrolment.[32] These patients had a median age of 55 years, 99% had a Karnofsky performance status of ≥80, 97% had metastatic disease and 45% had more than two organs involved. Exclusion criteria in both studies included concurrent cancer, leptomeningeal or brain involvement, or neuropathy.

Treatment regimens are summarised in figure 1. The median number of cycles were as follows: 4 (docetaxel, cisplatin and fluorouracil regimen 1 [DCF1]), 5 (docetaxel plus cisplatin [DC]) and 5.5 (epirubicin, cisplatin plus fluorouracil [ECF]) cycles in the SAKK trial;[31] 6 cycles each in the DCF regimen 2 (DCF2) and DC groups in the V325 phase II trial;[30] and 6 (DCF2) and 4 (cisplatin plus fluorouracil [CF]) cycles in the V325 phase III trial.[32] In the V325 trials, treatment continued until unacceptable toxicity, disease progression, consent withdrawal or death. Within each individual trial, patient baseline characteristics were well balanced between treatment groups.[30-32]

The primary endpoint in phase II trials was the overall response rate (partial plus complete response rates)[30,31] and that in the V325 phase III trial[32] was the time to tumour progression (TTP). Secondary or other endpoints were TTP,[30,31] overall survival[30-32] and overall response rate.[32] Analyses were based on the modified intent-to-treat population (i.e. those randomised and treated).[30-32] Results were assessed by investigators and an independent review panel.[30-32]

In addition to these primary and secondary endpoints, the V325 phase III trial also assessed health-related quality of life (HR-QOL), using the

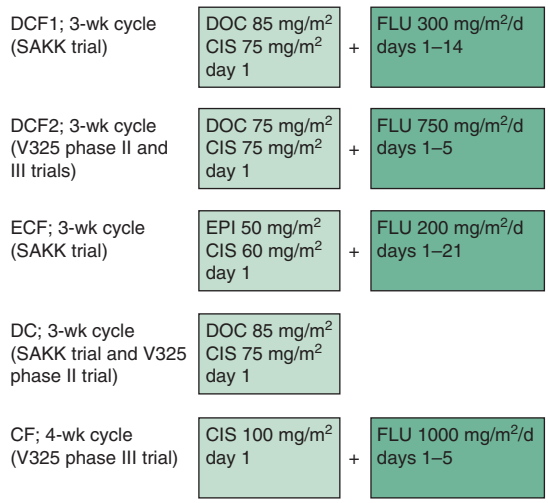

Fig. 1. Treatment regimens for large, randomised trials conducted by SAKK[31] and the V325 Study Group.[30,32] All agents given intravenously; docetaxel (DOC) as a 1-hour infusion; cisplatin (CIS) as a 4-hour[31] or 1- to 3-hour infusion;[30,32] epirubicin (EPI) as a bolus injection; fluorouracil (FLU) as a continuous infusion. In the SAKK trial, the DOC dose was reduced in the DOC, CIS plus FLU (DCF1) and DOC plus CIS (DC) arms to 75 mg/m2 because of the high incidence of febrile neutropenia. **CF** = cisplatin plus fluorouracil; **DCF2** = docetaxel, cisplatin plus fluorouracil regimen 2; **ECF** = epirubicin, cisplatin plus fluorouracil.

European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30[32,36] and the EuroQol EQ-5D questionnaire.[36] The primary HR-QOL endpoint was EORTC QLQ-C30-assessed time to 5% definitive deterioration from baseline on the global health status QOL scale[32,36] and the primary clinical benefit endpoint was definitive worsening of Karnofsky performance status by one or more categories.[32,37] Secondary HR-QOL endpoints included the time from baseline to definitive deterioration of global health status, physical and social functioning, nausea/vomiting, pain (EORTC QLQ-C30) and definitive deterioration on the EQ-5D visual analogue scale.[36]

Phase II Trials

The principal aim of both phase II trials was to establish the relative efficacy of triple versus dual docetaxel-based regimens in the treatment of gastric cancer.[30,31]

- Addition of fluorouracil to DC was more effective than a regimen of DC alone as determined by between-group differences in objective response rates in the two phase II trials (figure 2) [primary endpoint].[30,31] The predefined between-group difference to rank these two regimens with a ≥90% probability was 10% in the V325 trial[30] and ≥15% in the SAKK trial.[31]
- In the SAKK trial, the median TTP was 4.6 months (95% CI 3.5, 5.6) in recipients of DCF1 compared with 3.6 (95% CI 2.8, 4.5) and 4.9 months (95% CI 3.2, 6.1) in DC and ECF recipients.[31] Furthermore, the median overall survival in the respective treatment groups was 10.4 (95% CI 8.3, 12.0), 11.0 (95% CI 7.8, 12.5) and 8.3 (95% CI 7.2, 13.0) months at a median of 27.6 months of follow-up.
- In the phase II V325 trial, patients receiving DCF2 exhibited a median TTP of 5.9 months (95% CI 4.8, 7.2) compared with 5.0 months (95% CI 3.7, 6.3) in DC recipients, with a hazard ratio (HR) of 0.80 (95% CI 0.52, 1.22).[30] Furthermore, the median overall survival of DCF2 and DC recipients was 9.6 (95% CI 7.7, 11.4) and 10.5 (95% CI 9.5, 12.9) months at a median 17.5 months' follow-up. The corresponding HR was 1.19 (95% CI 0.83, 1.69).

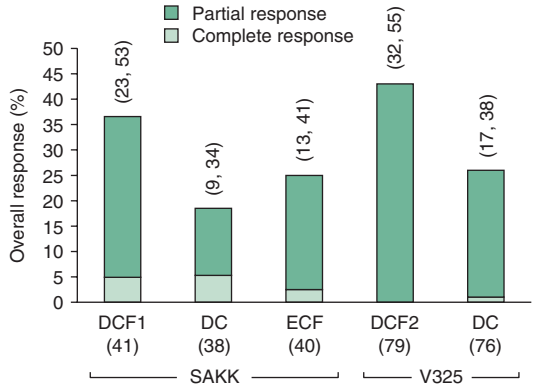

Fig. 2. Efficacy of docetaxel-based chemotherapy in palliative chemotherapy-naive patients with metastatic or locally advanced/recurrent gastric or gastro-oesophageal junction cancer. Overall response rates in two randomised, phase II trials conducted by SAKK[31] and the V325 Study Group[30] (see figure 1 for treatment regimen details). Participants in the SAKK trial[31] received a median of 4.0–5.5 cycles, and those in the V325 trial[30] a median of 6 cycles. Assessments were reviewed by independent panels, with analyses based on the modified intent-to-treat population (i.e. all patients randomised and treated). The numbers below the bar are the number of patients evaluated and those above the bar are the 95% confidence intervals. **DC** = docetaxel plus cisplatin; **DCF** = docetaxel, cisplatin plus fluorouracil; **ECF** = epirubicin, cisplatin plus fluorouracil.

Phase III Trial

The main aim of the phase III trial was to establish the efficacy of a 3-weekly DCF regimen relative to that of a 4-weekly CF regimen.[32]

- DCF2 treatment (n = 221) was significantly more effective than CF therapy (n = 224) with regard to median TTP (primary endpoint) in patients with metastatic or locally advanced/recurrent gastric or gastro-oesophageal junction adenocarcinoma (figure 3).[32] The median TTP was >1.5-fold longer ($p < 0.001$) in DCF2 than in CF recipients, with an HR of 1.47 (95% CI 1.19, 1.82). This corresponds to a reduction in the risk of tumour progression of 32% in DCF2 versus CF recipients.
- DCF2 treatment was also more effective than CF in terms of secondary endpoints.[32] The median overall survival was significantly longer in patients receiving DCF2 than in those receiving CF (figure

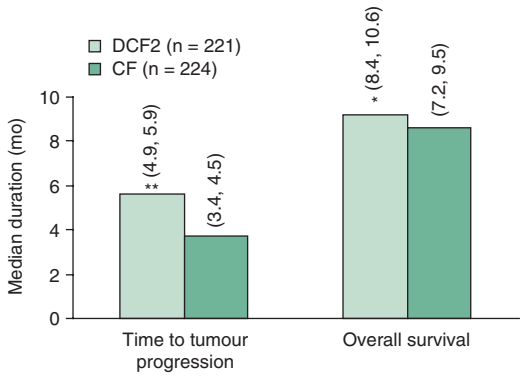

Fig. 3. Efficacy of docetaxel in combination with cisplatin plus fluorouracil (DCF2) in gastric cancer. Median time to tumour progression (primary endpoint) and overall survival in a large, randomised, open-label, multicentre, phase III trial in chemotherapy-naive patients with metastatic or locally advanced/recurrent gastric or gastro-oesophageal junction adenocarcinoma[32] (see figure 1 for details of treatment regimens). The median number of cycles was six for the DCF2 regimen and four for the cisplatin plus fluorouracil (CF) regimen. Analyses were based on the modified intent-to-treat population (i.e. all patients randomised and treated). The median follow-up was 23.4 months. The numbers in brackets are the 95% confidence intervals. * p = 0.02, ** p < 0.001 vs CF.

3), with an HR of 1.29 (95% CI 1.0, 1.6). Furthermore, the overall response rate was significantly higher in the DCF2 group than in the CF group (37% vs 25%; p = 0.01).[32]

- Deterioration of HR-QOL in patients with metastatic or locally advanced/recurrent gastric or gastro-oesophageal junction cancer was significantly delayed with DCF2 compared with CF therapy.[32,36] The median time taken from baseline for patients to experience a 5% worsening in global health status was significantly (p = 0.012) longer in the DCF2 than in the CF group (6.5 vs 4.2 months), with an HR of 1.45 (95% CI 1.08, 1.93).[36]

- The median time to a definitive deterioration in Karnofsky performance status was also significantly (p = 0.009) longer in DCF2 than CF recipients (6.1 vs 4.8 months), with an HR of 1.38 (95% CI 1.08 1.76).[37]

- Furthermore, compared with CF therapy, treatment with DCF2 significantly reduced the speed at which HR-QOL deterioration occurred in patients with metastatic or locally advanced/recurrent gastric or gastro-oesophageal junction adenocarcinoma with regard to most secondary HR-QOL parameters.[36]

4. Tolerability

Discussion in this section focuses on the recommended[24,29] docetaxel combination regimen of IV docetaxel 75 mg/m^2 plus cisplatin 75 mg/m^2 on day 1 followed by continuous fluorouracil 750 mg/m^2 on days 1–5 (DCF2). Data are reported from the phase II[30] and phase III[32] V325 trials comparing DCF2 therapy with DC[30] and CF[32] in patients with metastatic or locally advanced/recurrent gastric or gastro-oesophageal junction adenocarcinoma (see section 3 for study details) and the manufacturer's summary of product characteristics.[24] Tolerability data were generally reported descriptively.

- Given the nature of the chemotherapeutic treatments available for advanced gastric cancer, docetaxel in combination with cisplatin plus fluorouracil was generally well tolerated in patients with metastatic or locally advanced/recurrent gastric or gastro-oesophageal junction adenocarcinoma in the phase II[30] and III[32] V325 trials. The nature of adverse events was typical of that seen with chemotherapy.

- Clinically relevant grade 3 or 4 adverse events that occurred in ≥10% of patients receiving DCF2 were: neutropenia (83.2% of patients), stomatitis (23.7%), anaemia (20.9%), diarrhoea (19.7%), lethargy (19.0%), nausea (16.0%), vomiting (14.3%) and infection (11.7%).[24]

- Neutropenia-related toxicity is commonly associated with docetaxel therapy and, as a result, prophylactic granulocyte-colony stimulating factor (G-CSF) treatment is recommended.[24] In a pooled analysis[24] (n = 300) of data from the DCF2 treatment arms of the phase II and III V325 trials,[30,32] febrile neutropenia and neutropenic infection were observed in 12.1% and 3.4% of patients who received G-CSF treatment compared with 15.6% and 12.9% in those who did not (statistical analyses were not reported). Secondary prophylactic G-CSF therapy was initiated in a total of 19.3% of patients.[24]

- Severe fluid retention may occur during treatment with docetaxel;[29] however, severe oedema

(grade 3 or 4) occurred in <2% and 1% of DCF2 and DC treatment cycles during the phase II V325 clinical trial.[30]

Versus Docetaxel plus Cisplatin

- Treatment-emergent adverse events (all grades) that occurred in >70% of patients in either the DCF2 or DC treatment group and with a ≥5% between-group difference in the phase II trial included anaemia (95% vs 100%), stomatitis (72% vs 29%), nausea (77% vs 68%) and diarrhoea (77% vs 63%).[30] Other than stomatitis, the only treatment-emergent adverse event that occurred in more than twice as many DCF2 than DC recipients was thrombocytopenia (35% vs 16%).
- The most commonly reported severe (grade 3 and 4) treatment-emergent adverse events were generally haematological toxicities in both DCF2 and DC treatment groups, with neutropenia (86% vs 87% of patients) and leukopenia (69% vs 65%) the most common.[30]
- Severe non-haematological treatment-emergent adverse events were mostly gastrointestinal in nature, with those considered drug related occurring in 56% and 30% of DCF2 and DC recipients.[30] Severe gastrointestinal adverse events that occurred in ≥10% of either DCF2 or DC recipients and in ≥5% more patients treated with DCF2 than DC included stomatitis (32% vs 0%), nausea (20% vs 11%), diarrhoea (20% vs 5%) and anorexia (15% vs 10%).[30] However, these severe adverse events were considered manageable.

Versus Cisplatin plus Fluorouracil

- In the phase III trial, the most common treatment-emergent adverse events (all grades) that occurred in >70% of either DCF2 or CF recipients and with a ≥5% between-group difference included leukopenia (96% vs 81%), neutropenia (95% vs 83%), diarrhoea (75% vs 46%) and vomiting (61% vs 71%).[32] Notably, complicated neutropenia (including neutropenic infection and febrile neutropenia) occurred in a significantly ($p < 0.05$) greater proportion of DCF2 than CF recipients (29% vs 12%).
- Severe treatment-related adverse events occurred in 69% and 59% of DCF2 and CF recipients.[32] Of these events, neutropenia (82% vs 57%), leukopenia (65% vs 31%), diarrhoea (19% vs 8%) and neurosensory adverse events (8% vs 3%) occurred in significantly (all $p < 0.05$) more patients treated with DCF2 than CF.
- Twenty-seven percent of DCF2 recipients discontinued treatment because of adverse events versus 25% of those in the CF group.[32]

5. Dosage and Administration

Docetaxel in combination with cisplatin plus fluorouracil is approved in the EU[24] for use in patients with metastatic gastric adenocarcinoma, including gastro-oesophageal junction adenocarcinoma, who have received no prior chemotherapy for metastatic disease, and for use in the US[29] in patients with advanced gastric or gastro-oesophageal junction adenocarcinoma who have not received prior chemotherapy for advanced disease.

The recommended dosage is docetaxel 75 mg/m^2 (1-hour IV infusion; day 1), followed by cisplatin 75 mg/m^2 (1- to 3-hour IV infusion; day 1) followed by fluorouracil 750 mg/m^2 per day (continuous 24-hour IV infusion; days 1–5), repeated every 3 weeks.[24,29]

Docetaxel may be administered only if the neutrophil count is ≥1500 cells/mm^3 and should not be given to patients who are hypersensitive to it or who have elevated bilirubin levels above the ULN and serum ALT and/or AST levels >1.5 × ULN concomitant with alkaline phosphatase >2.5 × ULN.[24,29] Severe fluid retention may occur with docetaxel therapy.[29] This information features in a black box warning in the US prescribing information.[29]

Prophylactic G-CSF therapy is recommended to reduce the potential risk of haematological adverse events,[24] as is pretreatment with an oral corticosteroid, such as dexamethasone, prior to docetaxel therapy to minimise fluid retention.[24,29] During therapy, the docetaxel dosage may be reduced from 75 to 60 mg/m^2 in patients who experience febrile or prolonged neutropenia or neutropenic infection despite G-CSF treatment, or grade 4 thrombocytope-

nia.[24,29] Local prescribing information should be consulted for further information regarding dosage modifications, contraindications, drug interactions and other precautions.

6. Docetaxel: Current Status in Advanced Gastric Cancer

In Europe[24] and the US,[29] a triple regimen of docetaxel plus cisplatin and fluorouracil (3-weekly cycle) is approved for use in patients with metastatic or advanced gastric cancer and/or gastro-oesophageal junction adenocarcinoma who have not received chemotherapy for metastatic or advanced disease. In the phase III trial in this patient population, this triple regimen (DCF2) was effective and generally well tolerated (given the nature of chemotherapy). Furthermore, DCF2 recipients had a longer TTP, and better overall survival and response rates than those receiving CF. The efficacy of docetaxel in combination with other cytotoxic agents, such as oxaliplatin and the oral fluoropyrimidine S-1, is currently being evaluated in large phase II and phase III clinical trials, having shown promise in initial studies.[38]

Disclosure

During the peer review process, the manufacturer of the agent under review was offered an opportunity to comment on this article; changes based on any comments received were made on the basis of scientific and editorial merit.

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