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Docetaxel 75 mg/m^2 is Active and Well Tolerated in Patients with Metastatic or Recurrent Gastric Cancer: a Phase II Trial

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Objective: The aim of the present study was to confirm the efficacy and tolerability of docetaxel 75 mg/m^2 in a population of Korean patients with advanced gastric cancer.

Methods: Patients with metastatic or locally recurrent gastric cancer received docetaxel 75 mg/m^2 by intravenous infusion every 3 weeks. Objective response rate was the primary end-point.

Results: Forty-five patients were enrolled. Most showed adenocarcinomas of the gastric antrum and/or body of the stomach. All showed metastases and two-thirds retained the primary tumour. Forty-four patients received at least one docetaxel infusion ('treated' population), with 40 patients evaluable for response. A total of 159 cycles (median three cycles) were administered, with mean duration of treatment 10.9 weeks. The objective response rate in the treated population was 15.9% (17.5% in the per protocol population), with stable disease in 25.0% of patients and progressive disease in 50.0%. Grade 3–4 neutropenia occurred in 36 (81.8%) patients and 36.1% of cycles. However, febrile neutropenia occurred in only two (4.5%) patients and 1.3% of cycles. Grade 3 anorexia, experienced by two patients (4.5%) and during 1.9% of cycles, was the most frequent non-haematological adverse event possibly or probably related to docetaxel. No grade 4 non-haematological events occurred.

Conclusion: This study suggests that docetaxel 75 mg/m^2 is active in metastatic or locally recurrent adenocarcinoma with a low incidence of grade 3–4 adverse events. Docetaxel warrants further study in combination regimens for advanced gastric cancer.

Key words: chemotherapy – docetaxel – advanced gastric cancer

INTRODUCTION

Gastric cancer is a major international health problem, with a particularly high incidence in South America, in many former Eastern European countries and across Asia (1). Unfortunately, advanced gastric carcinoma is associated with a poor prognosis (2). For example, mitomycin C and 5-fluorouracil (5FU) monotherapy produce, at best, overall response rates (ORR) of 30 and 20%, respectively (3).

Combination therapies, usually based on 5FU and often incorporating cisplatin, provide higher response rates, although these remain suboptimal and a standard therapy has yet to be defined. There is a clear clinical need for new agents with complementary mechanisms of actions to existing therapy to improve outcomes in patients with advanced gastric cancer (4,5). A growing body of experimental and clinical evidence suggests that the taxane docetaxel might represent such an agent.

Docetaxel targets a fundamental step in the cell cycle: enhancing microtubule assembly and inhibiting tubulin depolymerization (6). Docetaxel is active against several human malignancies, with proven clinical efficacy in a number of solid tumours (7).

Several studies from Europe, the USA and Japan have assessed docetaxel monotherapy in the treatment of gastric cancer with generally consistent results. Key results for the intention to treat populations are detailed below. In a European study, 22% of patients with untreated advanced gastric cancer achieved partial responses for a median duration of 7.5 months

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after receiving docetaxel 100 mg/m^2 (8). Docetaxel was active in a variety of metastatic sites, including the liver and retroperitoneal lymph nodes. Furthermore, the benefit emerged after two cycles in six of the eight patients who responded. In an American study also considering chemonaive patients with advanced gastric cancer, a 17% response rate and median time of progression (TTP) of 2.8 months were achieved with docetaxel 100 mg/m^2 (9). Median overall survival was 7.8 months and the estimated survival at 18 months was 17%.

Two Japanese studies have considered docetaxel 60 mg/m^2 in the second-line management of advanced or recurrent gastric cancer (10,11). In one study, an ORR of 20% was achieved (10), while the second yielded an ORR of 22% (11).

These single-agent studies consistently achieve response rates comparable to those reported for the most active agents in advanced gastric cancer, such as 5FU, cisplatin, methotrexate, mitomycin C and doxorubicin (12). As a result, several phase II studies have assessed docetaxel in combination therapy, with phase III studies ongoing. The dose of docetaxel in these studies is typically 75 mg/m^2.

The aim of the present study was to confirm the efficacy and tolerability of docetaxel 75 mg/m^2 in a population of Korean patients with advanced gastric cancer. Our objective was to match the activity previously shown with the 100 mg/m^2 dose in this setting, while reducing associated toxicity.

PATIENTS AND METHODS

This prospective, open-label, late phase II study performed in four Korean centres evaluated the response rate to docetaxel among patients suffering from metastatic or locally recurrent gastric adenocarcinoma. Two-thirds of the patients retained the primary tumour, a high-risk prognostic factor. Patients received docetaxel 75 mg/m^2 by intravenous infusion once every 3 weeks until disease progression, unacceptable toxicity, death or withdrawal of consent. Objective response rate represented the primary endpoint. Tolerance, duration of response, TTP, change in appetite, functional status and pain and survival (based on Kaplan–Meier analysis) were the secondary endpoints.

Patient Selection

The study enrolled patients with histologically proven gastric adenocarcinomas, including oesophagogastric junction neoplasms. Patients met the following criteria: advanced progressive disease with at least one two-dimensionally measurable lesion; a single metastatic lesion that underwent histology or cytology to confirm the diagnosis; locally recurrent disease that showed regional measurable lymph nodes (20×10 mm) by computed tomography (CT) scan.

Patients showed adequate haematology, renal and hepatic functions: haemoglobin ≥10 g/dL; absolute neutrophil count ≥2.0×10^9/L; platelets ≥100×10^9/L; creatinine ≤140 μmol/L [if borderline (130–140 μmol/L), a creatinine clearance was performed and was >60 mL/min]; total bilirubin ≤1×upper limit of normal (ULN); aspartate aminotransferase and alanine aminotransferase ≤2.5×ULN; alkaline phosphatase ≤5×ULN (unless bone metastasis was present in the absence of any liver disease).

Additional inclusion criteria included: 18–70 years old; Karnofsky performance status (PS) >70; life expectancy >3 months; prothrombin time ≤50% of lower normal value; no previous palliative chemotherapy; at least 12 months to have elapsed since the end of adjuvant (or neoadjuvant) therapy and the first relapse; at least 6 weeks from any previous radiotherapy and 3 weeks from surgery; recovered from side effects of any previous therapy; complete initial work-up within 2 weeks before the first infusion for imaging (chest radiograph, with or without chest CT scan, abdominal CT scan, other as indicated) and within 8 days before the first infusion for clinical evaluation and biological work-up; able to comply with scheduled follow-up and toxicity management.

The local ethics committees approved the study and each patient gave written informed consent.

Patient Evaluation

Pre-treatment evaluation comprised complete blood cell counts, differential and routine chemistry measurements, chest radiograph, with or without chest CT scan, abdominal CT scan and other tests when clinically indicated. Full and differential blood counts were performed weekly during the first two cycles, reducing to the end of each cycle if no toxicity requiring dose reduction occurred. Biochemistry was performed at the end of each cycle.

Treatment Schedule

Docetaxel 75 mg/m² was given by 1 h intravenous infusion once every 3 weeks. This represents one cycle. Treatment continued until disease progression, unacceptable toxicity, death or withdrawal of consent. All patients received routine prophylactic corticosteroid medication with dexamethasone 8 mg os (or equivalent) starting 24 h before the infusion and then at 12 h intervals for a total of six doses per treatment cycle to prevent the onset of hypersensitivity reactions and to reduce and/or delay skin toxicity and fluid retention. Patients could also receive appropriate treatment for adverse events, including granulocyte-colony stimulating factor (G-CSF) for febrile neutropenia, antiemetics and management of hypersensitivity reactions.

Response and Toxicity Evaluation

Efficacy was assessed as the percentage of patients who achieved objective response rates according to World Health Organization (WHO) guidelines. The objective response was based on clinical or radiological criteria or both. Tumour assessment for all lesions was performed at the end of every two cycles and every 3 months on follow-up visits. The primary efficacy variable was the overall response rate (complete plus partial responses) confirmed by two evaluations at least 4

weeks apart. The secondary efficacy variables were the duration of response, TTP, change in appetite, functional status and pain and survival. Clinical and laboratory toxicities and symptoms were graded according to the National Cancer Institute of Canada (NCIC) criteria. An External Response Review Committee (ERRC) reviewed the data.

Statistical Analysis

For a target of ≥20% response rate [95% confidence interval (CI) ±12.5%], 40 patients evaluable for response were required. To allow for a possible 10% of patients non-evaluable for response, 45 were to be enrolled.

Categorical data were tabulated. The distributions of continuous data were summarized as the minimum, maximum, mean, standard deviation and, if appropriate, median. The distribution of TTP and survival were described by the Kaplan–Meier method (13) and life tables. A 95% CI was calculated for the median event time of the distributions (14).

Treated patients who could be evaluated for response and who did not incur a major deviation during the study constituted the 'per protocol population'. Patients had to receive at least two infusions of docetaxel unless early progression occurred to be evaluable for response. Moreover, all baseline lesions must have been assessed at least once after the second administration. Those who received at least one docetaxel infusion constituted the 'treated' population. TTP was determined by the interval between initiation of therapy to the time of first disease progression or death. Patients who had not progressed at the time of final analysis were to be censored at the date of their last tumour assessment. Survival was calculated from the onset of chemotherapy. Patients alive at the final analysis were to be censored at their last contact date. Response rate and TTP were analysed in both populations. Survival and the additional secondary outcomes (appetite, functional status and pain) were analysed only in the treated population.

RESULTS

Patients' Characteristics

Forty-five patients, median age 57 years (range 23–70 years), were enrolled (Table 1). Of these, 28 (62.2%) were male, with males predominating in both the per protocol and treated cohorts. One patient withdrew his consent after inclusion and was neither treated nor included in the analysis. Of the 44 patients who received treatment, one patient was ineligible because of non-measurable disease. Three other patients were non-evaluable for response owing to early withdrawal after the first cycle (two patients withdrew their consent and one patient experienced an unrelated adverse event). Therefore, 40 patients were evaluable for response.

At baseline, the median Karnofsky PS score was 90%, with 84.1% of patients having a score of 90%. The mean percentage weight loss was 6.0%. Twenty-five (56.8%) of the 44 patients who received treatment had a fair appetite; only four patients (9.1%) had a poor appetite. Twenty-nine (65.9%) patients presented with at least one abnormal haematology value at baseline, most commonly haemoglobin, which occurred in 27 (61.4%) patients. Twenty-two (50.0%) patients presented with at least one abnormal biochemistry value at baseline, most frequently alkaline phosphatase (16 patients; 36.4%) and serum glutamic oxaloacetic transaminase (nine patients; 20.5%).

All patients had adenocarcinomas: 34.1% were diffuse, 29.5% intestinal and 34.1% were not specified. In 93.2% of

Table 1. Patients' characteristics at baseline (treated population; $n = 44$)

Patient characteristics	No.	%
Gender		
Male/female	28/16	63.6/36.4
Age (years)		
Median (range)	57 (23–70)	
Karnofsky performance status		
Median (range)	90 (80–100)	
Weight loss		
Median (range)	6.0 (0–22)	
Appetite		
Poor	4	9.1
Fair	25	56.8
Good/excellent	15	34.1
Histology of primary tumour		
Adenocarcinoma (diffuse type)	15	34.1
Adenocarcinoma (intestinal type)	13	29.5
Adenocarcinoma (NOS)	15	34.1
Linitis plastica	1	2.3
Anatomical site		
Oesogastric junction and fundus	3	6.8
Stomach (antrum, body)	41	93.2
No. of organs involved		
1	6	13.6
2	17	38.6
≥3	21	47.7
Organ involvement		
Lymph nodes	33	75.0
Stomach	27	61.4
Liver	22	50.0
Peritoneum	12	27.3
Adrenal gland	4	9.1
Ovary	4	9.1
Pleura	4	9.1
Lung	3	6.8
Bone	2	4.5
Connective soft tissue	2	4.5
Spleen	1	2.3

Table 2. Best overall response (per protocol and treated population*)

Best overall response	No. of patients (%)	
	Treated (n = 44)	Per protocol (n = 40)
Response		
Partial response	7 (15.9)	7 (17.5)
No change/stable disease	11 (25)	11 (27.5)
Progressive disease	22 (50.0)	22 (55.0)
Not evaluable	3 (6.8)	–
Overall response rate (CR and PR)	7 (15.9)	7 (17.5)
95% CI	6.6–30.1	7.3–32.8

*The 44 patients who received at least one docetaxel infusion constituted the 'treated' population and the 40 patients who received at least two infusions constituted the 'per protocol population'.
CR = complete response; PR = partial response.

patients, the adenocarcinoma was located in the gastric antrum and/or body of the stomach. Forty-three patients had two-dimensionally measurable lesions; the other patient had 'evaluable disease' only (the disease could not be measured, but responses could be determined).

All patients presented with metastases. In 47.7% of patients, the metastases involved three or more organs. The most frequent sites were the lymph nodes (75.0%), stomach (61.4%), liver (50.0%) and peritoneum (27.3%).

No patients had received previous radiotherapy. Seventeen (38.6%) of the 44 patients who received treatment had undergone previous surgery: seven (15.9%) had undergone complete gastrectomy, the remainder partial gastrectomies. Two patients (4.5%) had received previous chemotherapy with adjuvant 5FU.

DOSING

Of the 45 patients enrolled, 44 (97.8%) received at least one infusion of docetaxel and one patient withdrew consent. The median number of cycles received was three. Overall, 159 cycles were administered, with 157 cycles administered to patients without dose reduction. There were two treatment cycles in which one reduction in dosage was required as a result of non-haematological toxicity, with convulsions during the infusion necessitating permanent discontinuation.

Thirty-six (81.8%) of the 44 patients who received at least one cycle discontinued treatment when their disease pro-

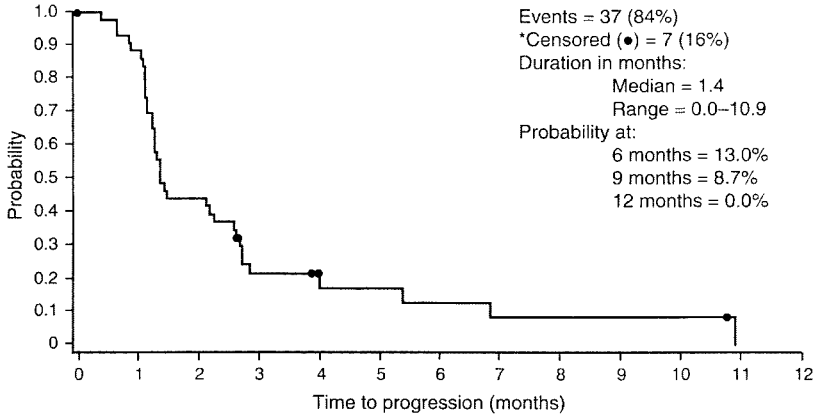

Figure 1. Time to progression in the treated population (n = 44). *Data from seven (16%) patients in the treated population with no progression at the cut-off date were censored.

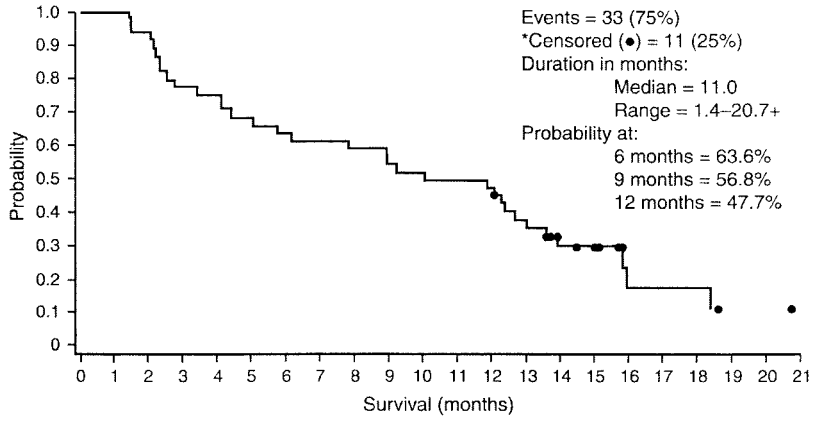

Figure 2. Survival in the treated population (n = 44). *Data from 11 (25%) patients in the treated population with no progression at the cut-off date were censored.

Table 3. Number of patients with grade 3 or 4 adverse events possibly or probably related to study treatment* – worst grade during the study (treated population)

NCIC term by NCIC classification	Treated patients (n = 44)			
	Grade 3	Grade 4	All	
	n	n	n	%
Haematological				
Neutropenia	11	25	36	81.8
Febrile neutropenia	2		2	4.5
Leucopenia	10	3	13	29.5
Anaemia	1	–	1	2.3
Gastrointestinal				
Anorexia	2	–	2	4.5
Diarrhoea	1	–	1	2.3
Stomatitis	1	–	1	2.3
Flu-like symptoms				
Fever in absence of infection	1	–	1	2.3
Skin				
Alopoecia	1	–	1	2.3

*Each patient could report more than one adverse event.

Table 4. Number of cycles with grade 3 or 4 adverse events possibly or probably related to study treatment* – worst grade during study (treated population)

NCIC term by NCIC classification	Treatment cycles (n = 159)			
	Grade 3	Grade 4	All	
	n	n	n	%
Haematological				
Neutropenia	21	35	56	35.2
Febrile neutropenia	2		2	1.3
Leucopenia	15	4	19	11.9
Anaemia	2	–	2	1.3
Gastrointestinal				
Anorexia	3	–	3	1.9
Diarrhoea	1	–	1	0.6
Stomatitis	1	–	1	0.6
Flu-like symptoms				
Fever in absence of infection	1	–	1	0.6
Skin				
Alopoecia	1	–	1	0.6

*Each cycle could have more than one adverse event.

gressed. One patient (2.3%) died from malignant disease, three (6.8%) additional patients discontinued treatment following adverse events, three (6.8%) withdrew consent and the investigator decided to change the treatment for one patient (2.3%) after six treatment cycles.

The mean duration of treatment was 10.9 weeks (range: 3.0–54.0 weeks). The median cumulative dose of docetaxel was 222.7 mg/m^2 and the median actual dose intensity was 25.01 mg/m^2 per week. The median relative dose intensity was 1.0, with 97.7% of patients receiving a relative dose intensity of 0.9–1.1. One patient (2.3%) had a relative dose intensity of <0.6.

Twenty-nine (65.9%) of the 44 patients received further chemotherapy with pyrimidine analogues. Of these, 28 (63.6%) patients received 5FU and platinum compounds. No patient received a regimen that included another taxane.

Efficacy

The 44 patients who received at least one docetaxel infusion constituted the 'treated' population. The 40 patients who received at least two infusions constituted the 'per protocol population'.

The objective response rates for the treated population are shown in Table 2 and described below. No patient showed a complete response. However, seven (15.9%) experienced partial responses before the disease progressed. Thus, the objective response rate was 15.9% (17.5% in the per protocol population). Eleven patients (25.0%) showed no change in disease or stable disease. Twenty-two patients (50.0%) experienced progressive disease.

There was no difference in partial responses between diffuse and intestinal cancer. However, in the per protocol population, progressive disease was more common among patients who showed involvement in at least three organs: 73.7% showed progressive disease compared with 40.0 and 33.3% of those with two organs or a single organ involved, respectively. Similarly, those patients with liver or peritoneal involvement or both were also more likely to show progressive disease: 64.0% compared with 40.0% in those without involvement of either organ. Progressive disease appeared to be more likely in patients who had not undergone surgery: 66.7% compared with 37.5% in those who had previous surgery.

TTP in the treated population is shown in Fig. 1. The median follow up was 77 weeks. Data from seven patients in the treated population with no progression at the cut-off date were censored. The median TTP was 1.4 months (95% CI: 1.3–2.6). The probability of being free from progression at 6 months was 13% (low patient numbers render the probability of being free from progression at 9 and 12 months unreliable; therefore, this result is not provided). TTP was similar for both the treated and per protocol populations (data not shown; available from the authors).

Survival in the treated population is shown in Fig. 2. Eleven patients with no events at the cut-off date were censored. Median survival was 11.0 months (95% CI: 5.7–13.6). The probabilities of being alive after 6, 9 and 12 months was 63.6, 56.8 and 47.7%, respectively.

Considering the additional outcomes assessed in the 44 treated patients, 38.6% experienced at least one deterioration in Karnofsky PS during the study, while 4.5% experienced at

least one improvement. In total, 50.0% of patients experienced at least one deterioration in appetite class during the study, while 18.2% patients experienced at least one improvement in appetite class. Of the 45.5% of patients with cancer pain at baseline, 40.9% experienced no deterioration. Of the 54.5% of patients without cancer pain at baseline, 40.9% experienced no deterioration. Most patients did not receive analgesics during the study. However, 36.4, 20.5, 6.8 and 4.5% of patients received analgesics at cycles 1, 2, 3 and 4, respectively. There was no analgesia use during the other cycles.

SAFETY

All patients experienced at least one adverse event. Thirty-nine patients (88.6%) experienced at least one adverse event that was possibly or probably related to docetaxel. At least one adverse event was reported in nearly all treatment cycles (99.4%), with at least one adverse event possibly or probably related to study medication occurring in 143 (89.9%) cycles. Table 3 shows the number of patients with grade 3–4 adverse events (excluding laboratory variables) possibly or probably related to treatment. Table 4 summarizes the number of cycles in which grade 3–4 adverse events possibly or probably related to treatment occurred.

Grade 3–4 neutropenia was reported in 36 (81.8%) patients and 56 (36.1%) cycles during the study. Most (97%) of the patients who could be evaluated recovered by day 22 ± 3. Febrile neutropenia occurred in two (4.5%) patients and during two (1.3%) treatment cycles. Leucopenia followed a similar pattern to neutropenia. Grade 3 or 4 anaemia, thrombocytopenia, changes in liver enzymes, bilirubin and creatinine were infrequent. Three (6.8%) patients showed fluid retention despite corticosteroid premedication.

Anorexia, experienced by two patients (4.5%), was the most frequently reported non-haematological grade 3 adverse event possibly or probably related to docetaxel and occurred in three (1.9%) treatment cycles. All other grade 3 adverse events were each experienced by one patient only. NCIC grade 3–4 non-haematological adverse events considered to be related to docetaxel were reported in seven (4.4%) cycles. All other grade 3 adverse events were each reported in one (0.6%) treatment cycle only. One patient died within 30 days of the last infusion as a result of malignant disease.

Three (6.8%) patients discontinued treatment due to adverse events: grade 2 infection (not related to docetaxel) after one cycle; grade 4 bilirubin levels (unlikely to have been related to the study medication) after one cycle; and grade 2 seizure (possibly related to docetaxel) not requiring anti-convulsant therapy after two cycles. There was no recurrence of seizure after treatment discontinuation.

DISCUSSION

This study confirms that single-agent docetaxel is active in metastatic or locally recurrent adenocarcinoma. Seven patients experienced partial responses, giving an objective response rate of 15.9% (17.5% in the per protocol population). Moreover, 11 patients (25.0%) showed stable disease and there was no difference in partial response rates between patients with diffuse and intestinal cancer.

Other outcome measures confirm docetaxel's activity. The median TTP was 1.4 months (95% CI: 1.3–2.6), with a 13% probability of being free from progression after 6 months. Median survival was 11.0 months (95% CI: 5.7–13.6) and the probability of being alive after 6, 9 and 12 months was 63.6, 56.8 and 47.7%, respectively. However, the confidence interval is fairly broad and the median occurs in a plateau, artificially lengthening the median survival. Despite this and the relatively small study size, this trial suggests that docetaxel is active in metastatic or locally recurrent adenocarcinoma and warrants further investigation in combination regimens.

In this study, docetaxel was shown to be active despite the cohort's high tumour burden: 47.7% of patients showed involvement of at least three organs. Moreover, two-thirds retained the primary tumour, another high-risk prognostic factor (15).

The findings of this study add to the emerging evidence that docetaxel monotherapy is active in gastric cancer. For example, the results are similar to those of Einzig et al. (9), who showed an ORR of 17% among treated patients. The study population enrolled was similar to that in our study, but a higher docetaxel dose of 100 mg/m^2 was given.

The study results are also broadly consistent with those from Sulkes et al. (8) (ORR 22%) given that, first, docetaxel was administered at a dose of 100 mg/m^2 and, second, the patient population characteristics suggest that they were likely to show a better response than in the present study. For example, only 32 and 8% of patients showed liver and peritoneal involvement, respectively, compared with 50.0 and 27.3%, respectively, in the current study.

In the present study, the median TTP was 1.4 months (95% CI: 1.3–2.6) and the probability of being free from progression at 6 months was 13%. Although the median TTP is half that reported by Einzig et al. (9), the latter used a higher dose of 100 mg/m^2 docetaxel. The median survival of 11.0 months (95% CI: 5.7–13.6) in the present study, with a 47.7% probability of being alive at 1 year, appears to compare favourably with the median survival of 7.8 months reported by Einzig et al. (9).

Several factors may explain the survival results of this study, including the survival-curve plateau alluded to above, the broad confidence interval due to the small sample size and the relatively high use of further chemotherapy (29 patients; 65.9%). On the other hand, the fact that benefits emerged despite the high use of further chemotherapy indicates that docetaxel does not show cross-resistance with other commonly used regimens. This suggests that docetaxel is appropriate for inclusion in further studies of combination regimens for the treatment of gastric cancer.

Indeed, the initial results of docetaxel-containing combinations in the management of gastric cancer are encouraging. For example, Ridwelski et al. (16) showed that docetaxel 75 mg/m^2 (the dose used in this study) plus cisplatin 75 mg/m^2 every 3

weeks was associated with an ORR of 37.2% in patients with advanced gastric cancer, with acceptable toxicity.

Van Cutsem et al. have also assessed a 75 mg/m^2 dose of docetaxel in combination with cisplatin 75 mg/m^2 and 5FU 750 mg/m^2 (17). This regimen was compared with docetaxel 85 mg/m^2 plus cisplatin 75 mg/m^2 in a randomized phase II study of 158 patients. An initial analysis of data from 155 treated patients showed that docetaxel–cisplatin provided an ORR of 30%, with no change in 41% of patients. The addition of 5FU was associated with an increased response rate (ORR 44%; no change 24%). The safety profile was found to be acceptable, with haematological toxicity similar in both arms. The high response achieved with docetaxel–cisplatin–5FU has led to the inclusion of this regimen in a currently ongoing phase III clinical trial.

Other studies using different doses offer further proof of principal of docetaxel's potential in gastric cancer. For example, Roth et al. (18) showed that docetaxel 85 mg/m^2 plus cisplatin 75 mg/m^2 produced an ORR of 56%.

Docetaxel demonstrated acceptable tolerability in the present study. Although 81.8% of patients developed grade 3–4 neutropenia, adverse events of this severity arose in only 36.1% of cycles. Importantly, the incidence by patients and by cycles of febrile neutropenia or neutropenic infection was low (4.5 and 1.3%, respectively). Anorexia was the most common non-haematological grade 3 toxicity, both by patients (4.5%) and by cycles (1.9%). No grade 4 non-haematological toxicities occurred. Overall, the safety profile suggests that docetaxel is associated with acceptable tolerability given the indication.

Other studies confirm these tolerability findings, albeit at higher doses. However, the higher doses offer an additional reassurance about docetaxel's tolerability. Einzig et al. (9) reported that 88% of patients receiving 100 mg/m^2 docetaxel showed grade 4 neutropenia, compared with 56.8% in our study. Furthermore, a dose reduction was required in 46% of patients due to associated fevers (9). Similarly, Sulkes et al. (8) found that grade 3–4 neutropenia occurred in 95% of patients receiving 100 mg/m^2 docetaxel. However, the grade 4 neutropenia did not appear to be cumulative, patients recovered promptly and the adverse event appears to be manageable. For example, concomitant granulocyte colony-stimulating factor (G-CSF) with docetaxel 100 mg/m^2 has been shown to reduce the prevalence of grade 3–4 neutropenia to 36% (19). The evidence available suggests that docetaxel 75 mg/m^2 might offer a similar effectiveness with a lower risk of side-effects, in particular grade 3–4 neutropenia, than 100 mg/m^2.

In conclusion, this study indicates that docetaxel 75 mg/m^2 is active in patients suffering from either metastatic or locally recurrent adenocarcinoma, including that of the oesophagogastric junction. Safety was acceptable, with predictable and manageable haematological toxicities the major adverse events. The balance of risks and benefits in this study, the first phase II trial of docetaxel monotherapy for this indication using a dose of 75 mg/m^2, suggests that docetaxel warrants further study in combination regimens for gastric cancer.

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