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ORIGINAL REPORT

Phase III Study of Docetaxel and Cisplatin Plus Fluorouracil Compared With Cisplatin and Fluorouracil As First-Line Therapy for Advanced Gastric Cancer: A Report of the V325 Study Group

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ABSTRACT

Purpose
In the randomized, multinational phase II/III trial (V325) of untreated advanced gastric cancer patients, the phase II part selected docetaxel, cisplatin, and fluorouracil (DCF) over docetaxel and cisplatin for comparison against cisplatin and fluorouracil (CF; reference regimen) in the phase III part.

Patients and Methods
Advanced gastric cancer patients were randomly assigned to docetaxel 75 mg/m^2 and cisplatin 75 mg/m^2 (day 1) plus fluorouracil 750 mg/m^2/d (days 1 to 5) every 3 weeks or cisplatin 100 mg/m^2 (day 1) plus fluorouracil 1,000 mg/m^2/d (days 1 to 5) every 4 weeks. The primary end point was time-to-progression (TTP).

Results
In 445 randomly assigned and treated patients (DCF = 221; CF = 224), TTP was longer with DCF versus CF (32% risk reduction; log-rank $P < .001$). Overall survival was longer with DCF versus CF (23% risk reduction; log-rank $P = .02$). Two-year survival rate was 18% with DCF and 9% with CF. Overall response rate was higher with DCF (χ^2 $P = .01$). Grade 3 to 4 treatment-related adverse events occurred in 69% (DCF) *v* 59% (CF) of patients. Frequent grade 3 to 4 toxicities for DCF *v* CF were: neutropenia (82% *v* 57%), stomatitis (21% *v* 27%), diarrhea (19% *v* 8%), lethargy (19% *v* 14%). Complicated neutropenia was more frequent with DCF than CF (29% *v* 12%).

Conclusion
Adding docetaxel to CF significantly improved TTP, survival, and response rate in gastric cancer patients, but resulted in some increase in toxicity. Incorporation of docetaxel, as in DCF or with other active drug(s), is a new therapy option for patients with untreated advanced gastric cancer.

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INTRODUCTION

Gastric cancer is the second most common cause of cancer death worldwide.[1] Advanced gastric cancer patients have a poor prognosis with a median survival time, if untreated, of 3 to 5 months.[2-4] There has been little progress in the therapy for patients with advanced disease; only a few large randomized phase III trials have been conducted in the past decade.[5-9] Patient selection (localized *v* metastatic; gastric *v* esophageal; potentially resectable *v* unresectable), trial methodology (with regard to stratification, principal end points, statistical methods, and expectations), and data monitoring have varied greatly among trials.[6-9] The results have been mostly unsatisfactory and, therefore, an acceptable standard regimen has not emerged. Clearly, new active regimens are needed to improve the outcome for gastric cancer patients.

Docetaxel has shown activity against gastric cancer as monotherapy[10-15] and in combination with other agents.[16-19] To investigate whether adding docetaxel to a reference regimen of cisplatin and fluorouracil (CF) could improve patient outcomes (time-to-progression [TTP], overall survival [OS], quality of life, and response rate for palliation), a multinational, multi-institutional, open-label, randomized phase II/III study, V325, was designed. The phase II randomized part of the V325 study examined which of two docetaxel-containing combinations should be investigated in the phase III

part: 155 patients received either docetaxel, cisplatin, and fluorouracil (DCF) or docetaxel and cisplatin (DC) and, based on overall response rate and safety data, the independent data monitoring committee selected DCF for comparison in the phase III part of the trial versus CF.[20] The primary end point of the phase III part was TTP; OS was one of the secondary end points. Herein we discuss the final efficacy and safety analyses of the phase III part of V325 involving the 445 patients randomly assigned to this phase III part.

PATIENTS AND METHODS

Patient Characteristics

Major inclusion criteria were: age 18 years or older; histologically proven gastric or esophagogastric junction adenocarcinoma; measurable and/or assessable metastatic disease according to WHO criteria,[21] or locally recurrent disease associated with one or more measurable lymph nodes; Karnofsky performance status higher than 70; no prior palliative chemotherapy; 6 weeks or longer from prior radiotherapy and 3 weeks or longer from surgery; adequate hepatic, renal, and hematologic function. Major exclusion criteria were concurrent cancer, neuropathy, brain, or leptomeningeal involvement, uncontrolled significant comorbid conditions, or if patient could not comprehend the purpose of the study and could not comply with its requirements. The protocol was approved by the institutional review board at each center. Patients provided written informed consent. An independent data monitoring committee evaluated safety throughout the V325 study period.

Stratification and Treatment

Random assignment was centralized and stratified for center, liver metastases, prior gastrectomy, measurable versus assessable cancer, and weight loss during the past 3 months ($\leq 5\%$ v $> 5\%$). Patients were randomly

Table 1. Patient and Cancer Baseline Characteristics (full analysis population)

Characteristic	Treatment (No. of patients)*					
	DCF		CF		Total	
	No.	%	No.	%	No.	%
Sex						
Male	159	72	158	71	317	71
Age, years						
Median	55		55		55	
Range	26-79		25-76		25-79	
< 65	167	76	169	75	336	76
≥ 65	54	24	55	25	109	24
Karnofsky performance status, %						
100	28	13	29	13	57	13
90	113	51	114	51	227	51
80	77	35	78	35	155	35
70	3	1	3	1	6	1
Weight loss in prior 3 months, %						
Median	7		7		7	
Range	0-37		0-35		0-37	
Primary tumor site						
Esophagogastric junction	42	19	56	25	98	22
Fundus	26	12	16	7	42	9
Antrum	56	25	65	29	121	27
Body	97	44	86	38	183	41
Disease status						
Locally advanced/recurrent	6	3	6	3	12	3
Metastatic	213	96	217	97	430	97
Histology						
Adenocarcinoma						
Diffuse	92	42	77	34	169	38
Intestinal	40	18	45	20	85	19
Other not specified	66	30	80	36	146	33
Linitis plastica	21	10	16	7	37	8
Other	2	1	6	3	8	2
No. of organs involved†						
1	33	15	47	21	80	18
2	86	39	76	34	162	36
> 2	100	45	100	45	200	45
Prior therapy						
Radiotherapy	5	2	5	2	10	2
Surgery‡	68	31	71	32	139	31
Curative	43	19	42	19	85	19
Palliative	25	11	28	13	53	12
Chemotherapy§	6	3	6	3	12	3

Abbreviations: DCF, docetaxel, cisplatin, and fluorouracil; CF, cisplatin and fluorouracil.
*As a percentage of all treated patients; because of rounding, not all percentages total 100.
†As determined by the external response review committee.
‡In the CF arm, one patient had both curative and palliative treatment and is excluded from the subgroups presented.
§Adjuvant/neoadjuvant.

Table 2. Treatment Exposure and Discontinuation

Parameter	Treatment (No. of patients) DCF	CF
Randomly assigned	227	230
Treated, full analysis population	221	224
Cycles	1,186	906
Median	6	4
Range	1-16	1-12
At least 1 dose reduction, %	41.2	36.2
At least 1 cycle delay, %	63.8	42.4
Reasons for treatment cessation, %	97.7	95.5
Progressive disease	29.9	43.8
AEs	27.1	25.0
Related (ie, toxicity)	23.5	21.0
Not related	3.6	4.0
Consent withdrawn	21.7	11.6
Deaths	10.4	9.4
Malignant disease	3.2	2.2
Toxicity from study medication	2.7	4.5
Other	4.5	2.7
Other	6.3	4.9
Other major protocol violation	0.9	0.9
Lost to follow-up	1.4	0

NOTE. Percentages calculated in treated patients.
Abbreviations: DCF, docetaxel, cisplatin, and fluorouracil; CF, cisplatin and fluorouracil;. AE, adverse event.

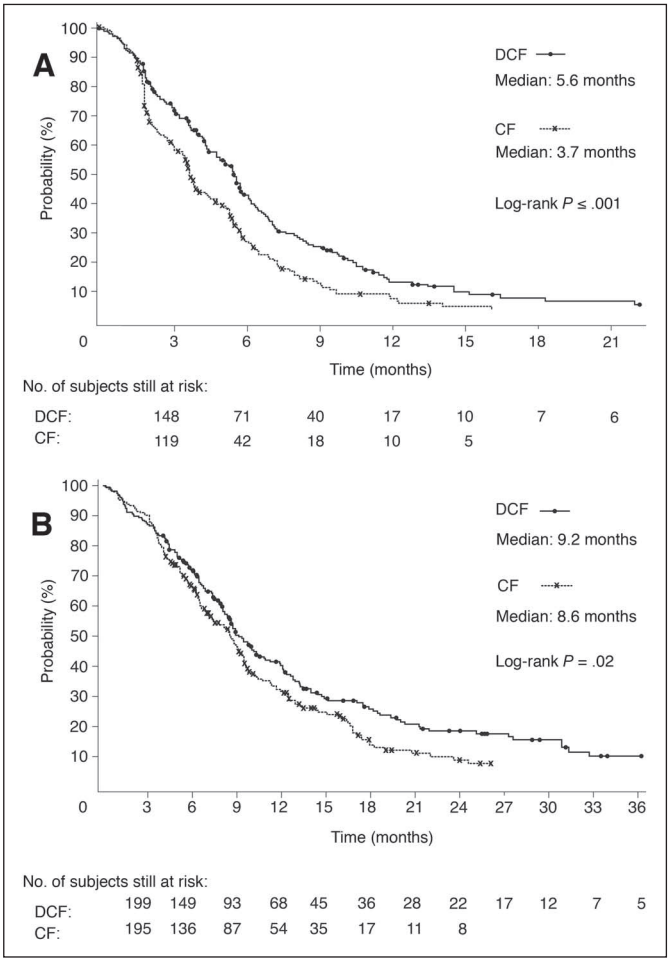

Fig 1. (A) Kaplan-Meier estimates of (A) time to progression and (B) overall survival among chemotherapy-naïve advanced gastric cancer patients treated with docetaxel, cisplatin, and fluorouracil (DCF) or cisplatin and fluorouracil (CF; full analysis population).

assigned (1:1) to either docetaxel (Taxotere; sanofi-aventis, Paris, France) 75 mg/m^2 (1-hour intravenous infusion) plus cisplatin 75 mg/m^2 (1- to 3-hour intravenous infusion) on day 1, followed by fluorouracil 750 mg/m^2/d (continuous intravenous infusion) for 5 days (DCF) every 3 weeks or cisplatin 100 mg/m^2 on day 1 followed by fluorouracil 1,000 mg/m^2/d for 5 days (CF) every 4 weeks. Dose modification criteria were predefined. All patients received appropriate hydration and premedications as previously reported.[20] Treatment continued until disease progression, unacceptable toxicity, death, or consent withdrawal.

Evaluation and Outcomes

Before random assignment, a complete medical history and physical examination were undertaken, including CBC, blood chemistries, and tumor assessments. Tumor measurements were undertaken every 8 weeks until progression in both arms to avoid bias in TTP calculations. All radiologic assessments were reviewed by an external response review committee and were assessed by WHO criteria.[21] TTP was measured from the day of random assignment to first evidence of progression or death occurring within 12 weeks of the last assessable tumor assessment. Survival was defined from the date of random assignment to death from any cause. Toxicities were graded according to the National Cancer Institute of Canada Common Toxicity Criteria, version 1.0.

Quality of life was assessed at the same intervals as tumor assessments and data were collected every 3 months after disease progression, using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (QLQ) -C30, version 3.[22] Time to 5% definitive deterioration in global health status assessed by QLQ-C30 was the primary quality of life parameter; time to definitive worsening of Karnofsky performance status by one or more categories was the primary clinical benefit end point.

Statistical Analysis

The primary objective was to demonstrate superiority in TTP for DCF over CF, using an unstratified log-rank test with a two-sided 5% significance level, from 4 months (CF) to 6 months (DCF), corresponding to a hazard ratio (HR) of 1.5 with a 95% power, requiring at least 325 events with 230 patients per arm. The major secondary objective was to demonstrate superiority in OS for DCF over CF, using the unstratified log-rank test with a two-sided 5% significance level, from 8 months to 12 months, corresponding to a HR of 1.5, and requiring at least 325 events. The Kaplan-Meier method was used to

Table 3. Best Overall Response Rate (full analysis population)

Parameter	Treatment DCF (n = 221) No.	%	CF (n = 224) No.	%
Overall response rate	81	37	57	25
95% CI	30.3 to 43.4		19.9 to 31.7	
P (χ^2 test)	.01			
Complete response	4	2	3	1
Partial response	77	35	54	24
No change/stable disease	67	30	69	31
Progressive disease	37	17	58	26
Not assessable	36	16	40	18

Abbreviations: DCF, docetaxel, cisplatin, and fluorouracil; CF, cisplatin and fluorouracil.

calculate TTP and OS. Overall response rates were compared using a χ^2 test. A HR more than 1 showed the efficacy benefit to be in favor of DCF.

TTP and OS were calculated on the predefined full analysis population (all randomly assigned and treated patients). Patients were considered assessable for response if they received two or more chemotherapy cycles (except for early progression). Safety analyses included all treated patients and involved the analysis of treatment-emergent adverse events (ie, those occurring or worsening during the treatment period), including events possibly or probably related to study medication and those regardless of causality.

RESULTS

Patients

A total of 457 patients (DCF = 227; CF = 230) were randomly assigned from 72 centers in 16 countries between November 1999 and January 2003; 445 patients (DCF = 221; CF = 224) received the allocated combination and, thus, comprised the full analysis population and were analyzed for efficacy and safety. Both treatment groups were well balanced for baseline characteristics (Table 1). At baseline, 84% of patients had clinical signs and symptoms with 27% being severe (grade 3 or 4 by National Cancer Institute of Canada Common Toxicity Criteria, version 1.0). Fifty-seven percent of patients had 5% or greater weight loss 3 months before registration.

Chemotherapy

In total, 1,186 cycles of DCF and 906 cycles of CF were administered, with a median of six cycles with DCF (range, 1 to 16) and four with CF (range, 1 to 12; Table 2). The median time between random assignment and first intravenous infusion was similar between both arms: 1 day (0 to11) in the DCF arm and 1 day (0 to 11) in the CF arm. The median duration of therapy was 19 weeks with DCF (range, 3 to 56 weeks) and 16 with CF (range, 4 to 50 weeks). The median actual dose intensities of fluorouracil and cisplatin were similar in both arms. Cycle delays occurred in 141 patients (64%) for DCF and 95 patients (42%) for CF. Dose reductions occurred in 91 patients with DCF (41%) and 81 patients with CF (36%). In both arms, the fluorouracil dose was most commonly reduced. Gastrointestinal toxicities were the most common adverse events leading to dose reduction in DCF and CF. The most common adverse event leading to cycle delay was lethargy for DCF and neutropenia for CF. The main reason for therapy discontinuation was progressive disease in both groups, although this was less frequent with DCF than CF (30% *v* 44%), followed by adverse events (27% *v* 25%), consent withdrawal (22% *v* 12%), and death (10% *v* 9%; Table 2). The median number of chemotherapy cycles for patients withdrawing consent was six for DCF and five for CF. Based on the number of patients treated at an individual cycle, the percentage of patients within each cycle who discontinued due to consent withdrawal was similar between the treatment arms. The percentage of patients with grade 3 to 4 adverse events at the last cycle before consent withdrawal was similar between both arms (46% in the DCF arm and 42% in the CF arm).

Efficacy: Primary End Point (TTP)

At a median follow-up of 13.6 months, 341 (77%) of 445 patients had progressive cancer. The median TTP was significantly longer for DCF versus CF (5.6 months; 95% CI, 4.9 to 5.9; *v* 3.7 months; 95% CI, 3.4 to 4.5; HR, 1.47; 95% CI, 1.19 to 1.82; log-rank $P < .001$; risk

Table 4. Hematologic and Nonhematologic Toxicities (NCIC-CTC version 1.0)

	Treatment (No. of patients)							
	DCF (n = 221)				CF (n = 224)			
	Grade 3-4		All Grades		Grade 3-4		All Grades	
Toxicity	No.	%	No.	%	No.	%	No.	%
Hematology*								
Neutropenia†	181‡	82	210	95	126‡	57	185	83
Leukopenia†	144‡	65	211	96	70‡	31	180	81
Anemia†	40	18	213	97	57	26	208	93
Thrombocytopenia†	17	8	56	25	30	13	87	39
Febrile neutropenia and/or neutropenic infection§			63‡	29			27‡	12
Nonhematologic TEAEs‖								
Gastrointestinal	108	49	205	93	106	47	204	91
Stomatitis	46	21	131	59	61	27	135	60
Diarrhea	43‡	19	165	75	18‡	8	103	46
Nausea	32	14	159	72	38	17	168	75
Vomiting	32	14	135	61	39	17	158	71
Anorexia	23	10	99	45	20	9	101	45
Lethargy	41	19	124	56	31	14	105	47
Infection	28	13	37	17	16	7	27	12
Neurosensory	17‡	8	84	38	6‡	3	53	24

Abbreviations: NCIC-CTC, National Cancer Institute of Canada Common Toxicity Criteria; DCF, docetaxel, cisplatin, and fluorouracil; CF, cisplatin and fluorouracil; TEAE, treatment-emergent adverse event.

*Patients were assessable for hematologic toxicity if they had one or more cycles with a blood count for the given test between day 2 and the first infusion of the next cycle, and had received no prophylactic treatment during the cycle.

†Number of assessable patients: DCF = 220; CF = 223 (222 for neutropenia). Data presented are regardless of granulocyte-colony stimulating factor (neutropenia/leukopenia) or erythropoietin/red blood cell transfusions (anemia).

‡Fisher's exact test < .05, all in favor of CF.

§Possibly or probably related to study treatment and regardless of granulocyte-colony stimulating factor use.

‖Possibly or probably related to study treatment: treatment-emergent nonhematologic toxicities occurring at grade 3 to 4 in 5% or more of either group.

reduction 32%; Fig 1A). Of note, 32% and 41% of patients received further chemotherapy in the DCF and CF arms, respectively.

Efficacy: Secondary End Point (OS)

At a median follow-up time of 23.4 months, 162 patients (73%) on DCF and 172 patients (77%) on CF had died. The median OS was significantly longer for DCF versus CF (9.2 months; 95% CI, 8.4 to 10.6; *v* 8.6 months; 95% CI, 7.2 to 9.5; HR, 1.29; 95% CI, 1.0 to 1.6; log-rank $P = .02$; risk reduction 23%; Fig 1B). The fraction of patients alive at 1 year was 40% for DCF and 32% for CF and at 2 years was 18% for DCF and 9% for CF.

Efficacy: Secondary End Point (Overall Response Rate)

The overall confirmed response rate was significantly higher with DCF (37%) than CF (25%; $P = .01$; Table 3). Prolonged duration of response ($\geq$ 9 months from the onset of the response) was noted in 21 patients with DCF and 8 patients with CF.

Safety: Secondary End Point

All patients on DCF experienced at least one treatment-emergent adverse event (irrespective of relationship to treatment), as did all but three patients on CF. However, related grade 3 or 4 treatment-emergent adverse events occurred in 69% of patients on DCF and 59% of patients on CF. Main related treatment-emergent adverse events are summarized in Table 4.

Grade 3 to 4 neutropenia was more frequent with DCF, as was complicated neutropenia (febrile neutropenia or neutropenic infection: 29% with DCF and 12% with CF). In the DCF arm, complicated neutropenia was 27% without and 12% with the use of secondary granulocyte colony-stimulating factor prophylaxis. In patients age 65 years or older, grade 3 to 4 infection (related to treatment) was more frequent with DCF (20%) than CF (9%). The number of deaths occurring within 30 days of the last infusion was 23 (10%) with DCF and 19 (8%) with CF. The main cause of toxic deaths was infection in both arms (7 of 8 in DCF; 8 of 12 in CF); this occurred mainly in cycle one of DCF treatment.

Quality of Life and Clinical Benefit

The time to 5% deterioration of global health status (QLQ-C30) was significantly longer for DCF than CF (HR 1.44; 95% CI, 1.08 to 1.93; log-rank $P = .01$). Furthermore, the time to definitive worsening of Karnofsky performance status was significantly longer for DCF than CF (log-rank $P = .009$; HR 1.38; 95% CI, 1.08 to 1.76).

DISCUSSION

The V325 phase III study in patients with advanced gastric cancer showed that adding docetaxel to CF significantly improved TTP, survival, and overall response rate compared with CF, although with an expected increase in toxicities. These efficacy results with DCF are particularly important given that a new drug has not been approved for the treatment of advanced gastric cancer in the last 20 years and, of the few randomized trials performed, nearly all have been disappointing[5-9] (mostly due to poor efficacy). The strategy of combining a new active agent with the reference regimen and comparing it to that regimen has been successfully used in numerous phase III trials in pancreatic cancer and colon cancer,[23-29] but has been rarely employed for advanced gastric cancer, in part because of a lack of a globally accepted reference treatment. However, cisplatin-based combinations (particularly CF) have been accepted as one of the references against which new regimens may be compared. The V325 study compared docetaxel in combination with CF versus CF alone. Consequently, this trial provides a clear understanding of the impact on efficacy and safety of adding docetaxel to CF.

Compared with recent randomized phase III trials in advanced gastric cancer,[5-7] the V325 study population had a very poor prognosis: 97% of patients had metastatic cancer, 81% had two or more organs involved, 84% were symptomatic at baseline, and 57% had more than 5% weight loss. Furthermore, patients were excluded if they could potentially undergo tumor resection after a response. This contrasts with previous studies where 13% to 40% of included patients had locally advanced disease that was potentially resectable after tumor response.[6,7,30] In the V325 study, patients were stratified for five factors and the study had 95% power to detect differences in TTP or OS. Overall response rates, as well as the dates of progression, were reviewed and confirmed by the external response review committee, while the independent data monitoring committee continuously

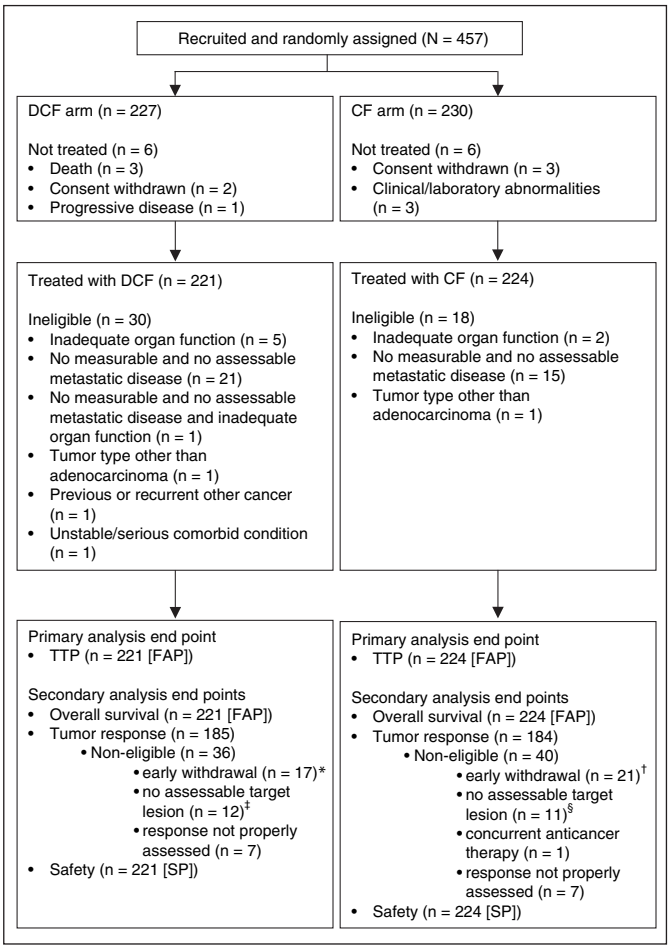

Fig 2. The CONSORT diagram depicting the trajectory of the trial. *Due to adverse event (n = 8), death (n = 6), consent withdrawn (n = 2), lost to follow-up (n = 1). †Due to adverse event (n = 9), death (n = 7), consent withdrawn (n = 4), progression at D4 cycle 1 (n = 1). ‡One patient in this group was also ineligible because of early withdrawal due to consent being withdrawn. §Two patients in this group were also ineligible because of early withdrawals due to adverse event (n = 1) and consent being withdrawn (n = 1). DCF, docetaxel, cisplatin, and fluorouracil; CF, cisplatin and fluorouracil; TTP, time-to-progression; FAP, full analysis population; SP, safety population.

monitored the study. V325 is the first global phase III randomized study conducted by investigators from 72 institutions in 16 countries. Thus, V325 was a highly monitored trial that aspired to avoid methodologic deficiencies.

The median administered dose intensity of cisplatin and fluorouracil was the same for the DCF and CF arms. Furthermore, the V325 results with CF appear consistent with those previously published, in particular, the study by Dank and colleagues.[8] Therefore, we could evaluate the impact of adding docetaxel to CF on efficacy and safety. Treatment with DCF reduced the risk of disease progression by 32% (log-rank $P < .001$) and reduced the risk of death by 23% (log-rank $P = .02$) compared with CF. Although the curves came near each other at the median survival point, considerable benefit was observed in the late observation period with the 2-year survival rate of 18% for DCF and 9% for CF. A 2-year survival rate exceeding 11% has only been observed in one other trial, a multicenter randomized trial in which 40% of the patients had locally advanced disease and half of the locally advanced patients with response underwent secondary surgery.[5]

Treatment with DCF resulted in a higher frequency of complicated neutropenia than CF, emphasizing the need for vigilant patient selection, education, monitoring, and active management. As most treatment-related fatal infections (the main cause of treatment-related deaths) occurred at cycle one and were concomitant with grade 3 to 4 neutropenia, primary prophylactic granulocyte colony-stimulating factor should be strongly considered in the management of these patients. Interestingly, the higher incidence of toxicity seen with DCF did not appear to impact quality of life and clinical benefit, which were significantly favorable in the DCF arm and may have been due to higher antitumor activity of DCF.

DCF should be considered as one of the reference regimens. But the quest to find more active combinations must continue. To make considerable improvements in the coveted end points (particularly, OS), the addition of targeted agents to active chemotherapy will be required. Such efforts could lead to a prolongation of TTP beyond 6 months and OS beyond 12 months, more consistently. The addition of another cytotoxic to established combinations is not likely to be well tolerated or efficacious. In order to make rapid progress in this field, it would be important to focus on meticulously designed phase III trials with a large sample size (at least 600) that are asking superiority questions (with enough statistical power to clearly discern OS differences), using rigorous trial methodology, and comparing a chemotherapy combination (for example, DCF) with a novel biochemotherapy combination that has a favorable safely profile and promising efficacy profile. In addition, correlative research with studies of patient genetics and tumor biology should become an integral part of such trials and could speed up the urgently needed progress and understanding of this disease.

In conclusion, the final results of the V325 study demonstrate that the addition of docetaxel to CF, a reference regimen, resulted in significantly improved TTP (primary end point), OS, and overall response rate (secondary end points), with global health status (quality of life) and Karnofsky performance status (clinical benefit) preserved for a longer time. Addition of docetaxel, as in DCF or with other active drug(s), is a new option for therapy for untreated gastric carcinoma.

REFERENCES

1. Parkin DM: Global cancer statistics, 2002. CA Cancer J Clin 55:74-108, 2005

2. Glimelius B, Ekstrom K, Hoffman K, et al: Randomized comparison between chemotherapy plus best supportive care with best supportive care in advanced gastric cancer. Ann Oncol 8:163-168, 1997

3. Murad AM, Santiago FF, Petroianu A, et al: Modified therapy with 5-fluorouracil, doxorubicin, and methotrexate in advanced gastric cancer. Cancer 72:37-41, 1993

4. Pyrhönen S, Kuitunen T, Nyandoto P, et al: Randomised comparison of fluorouracil, epidoxorubicin and methotrexate (FEMTX) plus supportive care with supportive care alone in patients with non-resectable gastric cancer. Br J Cancer 71:58-91, 1995

5. Waters JS, Norman A, Cunningham D, et al: Long-term survival after epirubicin, cisplatin and fluorouracil for gastric cancer: Results of a randomized trial. Br J Cancer 80:269-272, 1999

6. Ohtsu A, Shimada Y, Shirao K, et al: Randomized phase III trial of fluorouracil alone *v* fluorouracil plus cisplatin *v* uracil and tegafur plus mitomycin in patients with unresectable, advanced gastric cancer: The Japan Clinical Oncology Group Study (JCOG9205). J Clin Oncol 21:54-59, 2003

7. Vanhoefer U, Rougier P, Wilke H, et al: Final results of a randomized phase III trial of sequential high-dose methotrexate, fluorouracil, and doxorubicin *v* etoposide, leucovorin, and fluorouracil *v* infusional fluorouracil and cisplatin in advanced gastric cancer: A trial of the European Organization for Research and Treatment of Cancer Gastrointestinal Tract Cancer Cooperative Group. J Clin Oncol 18: 2648-2657, 2000

8. Dank M, Zaluski J, Barone C, et al: Randomized phase 3 trial of irinotecan (CPT-11) + 5FU/folinic acid (FA) vs CDDP + 5FU in 1st-line advanced gastric cancer patients. Proc Am Soc Clin Oncol Gastrointestinal Cancers Symposium, 2005 (abstr 61)

9. Ross P, Nicolson M, Cunningham D, et al: Prospective randomized trial comparing mitomycin, cisplatin, and protracted venous-infusion fluorouracil (PVI 5-FU) with epirubicin, cisplatin, and PVI 5-FU in advanced esophagogastric cancer. J Clin Oncol 20: 1996-2004, 2002

10. Bang YJ, Kang WK, Kang YK, et al: Docetaxel 75 mg/m^2 is active and well tolerated in patients with metastatic or recurrent gastric cancer: A phase II trial. Jpn J Clin Oncol 32:248-254, 2002

11. Einzig AI, Neuberg D, Remick SC, et al: Phase II trial of docetaxel (Taxotere®) in patients with adenocarcinoma of the upper gastrointestinal tract previously untreated with cytotoxic chemotherapy: The Eastern Cooperative Oncology Group (ECOG). Med Oncol 13:87-93, 1996

12. Graziano F, Catalano V, Baldelli AM, et al: A phase II study of weekly docetaxel as salvage chemotherapy for advanced gastric cancer. Ann Oncol 11:1263-1266, 2000

13. Mai M, Sakata Y, Kanamaru R, et al: A late phase II clinical study of RP56976 (docetaxel) in patients with advanced or recurrent gastric cancer: A Cooperative Study Group trial (group B). Jpn J Cancer Chemother 26:487-496, 1999 [Japanese]

14. Mavroudis D, Kourousis C, Androulakis N, et al: Frontline treatment of advanced gastric cancer with docetaxel and granulocyte colony-stimulating factor (G-CSF): A phase II trial. Am J Clin Oncol 23:341-344, 2000

15. Sulkes A, Smyth J, Sessa C, et al: Docetaxel (Taxotere™) in advanced gastric cancer: Results of a phase II clinical trial. Br J Cancer 70:380-383, 1994

16. Ridwelski K, Gebauer T, Fahlke J, et al: Combination chemotherapy with docetaxel and cisplatin for locally advanced and metastatic gastric cancer. Ann Oncol 12:47-51, 2001

17. Roth AD, Maibach R, Martinelli G, et al: Docetaxel (Taxotere)–cisplatin (TC): An effective drug combination in gastric carcinoma. Swiss Group for Clinical Cancer Res (SAKK), and the European Institute of Oncology (EIO). Ann Oncol 11:301-306, 2000

18. Constenla M, Garcia-Arroyo R, Lorenzo I, et al: Docetaxel, 5-fluorouracil, and leucovorin as treatment for advanced gastric cancer: Results of a phase II study. Gastric Cancer 5:142-147, 2002

19. Hawkins R, Cunningham D, Soerbye H, et al: Randomized phase II trial of docetaxel plus irinotecan *v* docetaxel plus 5-fluorouracil in patients with untreated advanced gastric adenocarcinoma. Proc Am Soc Clin Oncol 22:257, 2003 (abstr 1032)

20. Ajani JA, Fodor MB, Tjulandin SA, et al: A multi-institutional phase II randomized trial of docetaxel plus cisplatin (DC) or DC plus 5-fluorouracil (DCF) in patients with untreated, advanced gastric, or gastroesophageal adenocarcinoma. J Clin Oncol 23:5660-5667, 2005

21. Miller AB, Hoogstraten B, Staquet M, et al: Reporting results of cancer treatment. Cancer 47: 207-214, 1981

22. Aaronson NK, Ahmedzai S, Bergman B, et al: The European Organization for Research and Treatment of Cancer QLQ-C-30: a quality of life instrument

for use in international clinical trials in oncology. J Natl Cancer Inst 85:365-376, 1993

23. Berlin JD, Catalano P, Thomas JP, et al: Phase III study of gemcitabine in combination with fluorouracil *v* gemcitabine alone in patients with advanced pancreatic carcinoma: Eastern Cooperative Oncology Group trial E2297. J Clin Oncol 20:3270-3275, 2002

24. Colucci G, Giuliani F, Gebbia V, et al: Gemcitabine alone or with cisplatin for the treatment of patients with locally advanced and/or metastatic pancreatic cancer. Cancer 94:902-910, 2002

25. Rocha Lima CM, Green MR, Rotche R, et al: Irinotecan plus gemcitabine results in no survival advantage compared with gemcitabine monotherapy in patients with locally advanced or metastatic pancreatic cancer despite increased tumor response rate. J Clin Oncol 22:3776-3783, 2004

26. Louvet C, Labianca R, Hammel P, et al: Gemcitabine in combination with oxaliplatin compared with gemcitabine alone in locally advanced or metastatic pancreatic cancer: Results of a GERCOR and GISCAD phase III trial. J Clin Oncol 23:3509-3516, 2005

27. Douillard JY, Cunningham D, Roth AD, et al: Irinotecan combined with fluorouracil compared to fluorouracil alone as first line treatment for metastatic colorectal cancer: A multicenter randomised trial. Lancet 355:1041-1047, 2000

28. de Gramont A, Figer A, Seymour M, et al: Leucovorin and fluorouracil with or without oxaliplatin as first line treatment in advanced colorectal cancer. J Clin Oncol 18:2938-2947, 2000

29. André T, Boni C, Mounedji-Boudiaf L, et al: Oxaliplatin, fluorouracil and leucovorin as adjuvant treatment for colon cancer. N Engl J Med 350:2343-2351, 2004

30. Webb A, Cunningham D, Scarffe JH, et al: Randomized trial comparing epirubicin, cisplatin, and fluorouracil *v* fluorouracil, doxorubicin and methotrexate in advanced esophagogastric cancer. J Clin Oncol 15:261-267, 1997

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Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

Authors' Disclosures of Potential Conflicts of Interest

Although all authors completed the disclosure declaration, the following authors or their immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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