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ORIGINAL REPORT

Phase II Multi-Institutional Randomized Trial of Docetaxel Plus Cisplatin With or Without Fluorouracil in Patients With Untreated, Advanced Gastric, or Gastroesophageal Adenocarcinoma

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ABSTRACT

Purpose

The purpose of this study was to define the contribution of docetaxel to combination chemotherapy in the outcome of patients with advanced gastric or gastroesophageal adenocarcinoma. We compared the overall response rate (ORR) and safety of docetaxel plus cisplatin (DC) with DC plus fluorouracil (DCF) to select either DC or DCF as the experimental treatment in the ensuing phase III part of trial V-325.

Patients and Methods

In this phase II randomized study, untreated patients with confirmed advanced gastric or gastroesophageal adenocarcinoma received either DCF (docetaxel 75 mg/m^2, cisplatin 75 mg/m^2 on day 1, and fluorouracil 750 mg/m^2/d as continuous infusion on days 1 to 5) or DC (docetaxel 85 mg/m^2 and cisplatin 75 mg/m^2 on day 1) every 3 weeks. An independent data monitoring committee (IDMC) was to select one of the two regimens based primarily on ORR and safety profile.

Results

Of 158 randomly assigned patients, 155 (DCF, n = 79; DC, n = 76) received treatment. The confirmed ORR was 43% for DCF (n = 79) and 26% for DC (n = 76). Median time to progression was 5.9 months for DCF and 5.0 months for DC. Median overall survival time was 9.6 months for DCF and 10.5 months for DC. The most frequent grade 3 and 4 events per patient included neutropenia (DCF = 86%; DC = 87%) and GI (DCF = 56%; DC = 30%).

Conclusion

Both regimens were active, but DCF produced a higher confirmed ORR than DC. Toxicity profiles of DCF were considered manageable. The IDMC chose DCF for the phase III part of V-325, which compares DCF with cisplatin plus fluorouracil.

INTRODUCTION

Despite a declining incidence, gastric cancer remains a significant global health problem.[1] Once metastatic, gastric cancer is incurable, and few patients survive for more than 2 years. Randomized trials comparing combination chemotherapy with best supportive care have shown a survival benefit for patients receiving combination chemotherapy.[2,3] Although systemic therapy is an option for patients with good performance status, outcomes with single-agent therapy or combinations based on fluorouracil (FU) or cisplatin remain suboptimal. The search for more effective therapy must continue.

Docetaxel and irinotecan have both emerged as new active agents against gastric adenocarcinoma. In preclinical studies, docetaxel is two to 80 times more cytotoxic

than paclitaxel against human gastric cancer cell lines, and docetaxel also has superior activity against gastric cancers in vivo.[4] We investigated docetaxel in various combinations because, in clinical studies, docetaxel is active against advanced gastric cancer and a number of reports indicate a response rate ranging from 16% to 24% with single-agent docetaxel.[5-8]

In various phase II studies, docetaxel with cisplatin (DC) has been reported to have an overall response rate (ORR) ranging from 33% to 56%.[9-11] DC has also been combined with FU (DCF) in a phase I to II trial, resulting in a response rate of 51%.[12]

The purpose of the V-325 study was to define the value of docetaxel combination treatment in patients with gastric or gastroesophageal adenocarcinoma. This study was a multinational, multi-institutional trial performed in two parts. In the first part, the goal was to compare two experimental arms (DC and DCF) in a phase II randomized study so that an independent data monitoring committee (IDMC) could select which one of the two regimens based on the ORR should be the investigational arm for the second part of the trial, in which a phase III comparison would take place between the reference regimen, cisplatin plus FU, and the chosen experimental regimen. The primary end point of the phase III part of the trial was time to progression (TTP), and the secondary end point was overall survival (OS). This unique design allowed the investigators who participated in the phase II randomized portion of the study to continue to participate in the phase III portion without having to submit an entirely new protocol. This design also assured better similarity in patient populations between the phase II and phase III studies and an easier transition of the investigator from the phase II part to the phase III part. In this article, we present the final data of the phase II part of V-325 in which a total of 158 patients were accrued.

PATIENTS AND METHODS

The randomized, open-label, phase II study was conducted at 34 institutions in Asia, Europe, North America, and South America between June 1998 and September 1999. The protocol was approved by the ethics committee of each participating institution, and all patients gave written informed consent.

Major Eligibility Criteria

Eligibility criteria included age ≥ 18 years; metastatic or locally recurrent adenocarcinoma of the stomach or gastroesophageal junction; Karnofsky performance status more than 70%; and adequate hematologic, renal, and hepatic functions. If a patient presented with a single metastatic lesion as the only manifestation of the cancer, confirmation by cytology or histology was mandatory. Patients had measurable or assessable metastatic cancer. Patients with locally recurrent disease were enrolled provided that they presented with one or more measurable lesion. No prior palliative chemotherapy was permitted in patients with advanced disease. Adjuvant and/or preoperative chemotherapy was allowed if more than 12 months had elapsed between end of therapy and registration.

Patients were excluded if they had concurrent cancer, hypercalcemia, neuropathy, brain or leptomeningeal involvement, or uncontrolled significant comorbid conditions. Patients were also excluded if they could not comprehend the purpose of the study and could not comply with its requirements.

Treatment Assignment and Schedule

Randomization was centralized (Aventis, Antony, France) and was stratified for center, liver and/or peritoneal metastases, prior gastrectomy, and measurable versus assessable disease. Patients were randomly assigned (1:1 ratio) to receive either DCF (docetaxel 75 mg/m^2 plus cisplatin 75 mg/m^2 administered on day 1 with FU 750 mg/m^2/d as a continuous intravenous infusion on days 1 through 5) every 3 weeks or DC (docetaxel 85 mg/m^2 plus cisplatin 75 mg/m^2 on day 1) every 3 weeks. Docetaxel was administered over 1 hour, and cisplatin was administered over 1 to 3 hours. Premedications (corticosteroids and antiemetics) and hydration were administered in a standard manner, which consisted of six doses of dexamethasone (8 mg orally; administered the night before chemotherapy, upon waking the morning of chemotherapy, 1 hour before infusion, the night of day 1, and the morning and evening of day 2). Antiemetics were mandatory, but although a schedule was proposed to centers, implementation was left to current hospital practice. The recommended antiemetic schedule comprised ondansetron 8 mg (administered intravenously at the beginning of cisplatin infusion and 4 and 8 hours afterward) and dexamethasone 20 mg (administered intravenously at the beginning of cisplatin infusion and 8 hours after). Treatment was continued until disease progression, unacceptable toxicity, death, or consent withdrawal.

Granulocyte colony-stimulating factor (G-CSF) was used only as secondary prophylaxis once patients had febrile neutropenia or documented neutropenic infection. Toxicities were graded according to National Cancer Institute of Canada Clinical Trials Group Expanded Common Toxicity Criteria, version 1.0. A 20% dose reduction for individual drug was required based on predefined criteria. Briefly, docetaxel was reduced by 20% in case of the following toxicities: grade 3 or 4 neutropenia lasting more than 7 days (or in presence of fever); second or third incidence of febrile neutropenia despite G-CSF support administered after the first occurrence; grade 4 recurrent grade 3 diarrhea; and grade 3 (third episode) or grade 4 (recurrent) stomatitis. FU dose was reduced by 20% on occurrence of grade 3 or 4 diarrhea or grade 3 stomatitis. Administration of FU was stopped in case of grade 4 or recurrent grade 3 stomatitis or recurrent grade 4 diarrhea. If toxicity with plantar-palmar syndrome was observed, then the FU dose was reduced by 50 and 75 mg/m^2/d for grade 2 and 3 toxicity, respectively. Cisplatin dose was reduced by 20% in case of grade 2 peripheral neuropathy and ≥ grade 2 nephrotoxicity where clearance of creatinine was 40 to 59 mL/min.

Evaluations Before and During Therapy

Before registration, a complete medical history and physical examination were obtained including CBC, blood chemistries (including liver and renal functions), and tumor assessments. The primary end point of the phase III part of the V-325 study was TTP; therefore, to avoid bias, evaluations were performed every 8 weeks. All pertinent imaging studies (except for those of four patients) were reviewed by an External Response Review Committee (ERRC) who assessed the response rate according to WHO

criteria. In brief, a complete response (CR) was defined as disappearance of all known cancer, whereas a partial response was a ≥ 50% decrease in the sum of the largest diameters of all lesions. CR and partial response had to be confirmed for ≥ 4 weeks. Progressive disease was defined as a ≥ 25% increase in the size of at least one measurable lesion or the appearance of a new lesion.

CBCs were performed weekly. Patients were regularly assessed for potential adverse events and disease-related signs and symptoms. The study was continuously monitored, and case report forms were filled out and audited as necessary. Patients who had ended treatment but had not experienced disease progression were observed every 8 weeks until progressive disease and every 3 months thereafter.

Data Analysis

The primary end point of ORR was evaluated in both the modified intent-to-treat (ITT; all patients who were randomly assigned and treated) and per-protocol (treated patients eligible and assessable for response without major predefined protocol deviations) populations. The primary efficacy end point was initially the CR rate in the per-protocol population. However, because CRs were infrequent in this study, the IDMC based its decision regarding treatment selection on the best ORR. Patients were considered assessable for response if they had received at least two cycles of treatment and at least one follow-up tumor assessment (unless early progression occurred).

Secondary end points included safety, TTP, and OS and were analyzed on the modified ITT population. The TTP was determined from the day of random assignment to the date of any progression, death, or last contact. Patients who had not progressed at the time of the final analysis were censored at the date of their last tumor assessment. OS was calculated from the day of random assignment to death. Patients alive at the final survival analysis were censored using the last contact date. All treated patients were included in the safety analyses.

The IDMC reviewed the data periodically and was responsible to select either DCF or DC as the investigational arm for the planned phase III portion of the V-325 protocol based on the first 70 randomly assigned patients. Assuming a true difference in the ORRs for the two test groups of 10% (5% *v* 15%) and given 30 assessable patients per group, there was a 90% probability of correctly ranking the two test groups according to their observed ORR.[13]

RESULTS

Patients

V-325 required that the IDMC review mature data on an initial 70 patients to choose an experimental arm for the phase III part; however, by the time all necessary data on 70 patients were verified, the study had accrued a total of 158 patients. Of the 158 patients recruited, 155 (DCF, n = 79; DC, n = 76) received chemotherapy and were included in the safety and efficacy analyses. Of the 158 patients, 16 (DCF, n = 9; DC, n = 7) were ineligible for the study because of renal criteria (n = 6), locally recurrent disease alone without lymph node involvement (n = 2), no measurable nor assessable metastatic disease (n = 9), and other previous or current cancer (n = 1; two patients had > one reason for ineligibility). The per-protocol population comprised 124 patients (DCF, n = 60; DC, n = 64). All data reported are for the ITT population (155 patients) unless otherwise stated.

Patient and cancer characteristics are listed in Table 1. As determined by the ERRC, 123 patients (79%) had at least one bidimensionally measurable lesion (DCF, n = 68; DC, n = 55), 21 patients (14%) had assessable cancer (DCF, n = 6; DC, n = 15), one patient (1%) had unidimensional cancer, and 10 patients (6%) had nonassessable cancer. Only two patients (1%; one patient in each group) had received prior chemotherapy (adjuvant/neoadjuvant). The two groups were well balanced for baseline characteristics.

Exposure to Study Medication

In total, 438 cycles of DCF and 428 cycles of DC were administered, with a median of six cycles in each arm (range, one to 13 cycles of DCF and one to 14 cycles of DC). The median duration of treatment was 19 weeks for DCF (range, 3 to 43 weeks) and 18 weeks for DC (range, 3 to 56 weeks). The median relative dose intensity was 0.93 for docetaxel (range, 0.57 to 1.04), 0.92 for cisplatin (range, 0.39 to 1.05), and 0.92 for FU (range, 0.22 to 1.04) in the DCF arm, and 0.98 for docetaxel (range, 0.71 to 1.03) and 0.96 for cisplatin (range, 0.54 to 1.04) in the DC arm.

At lease one dose reduction was required in 13% of DCF cycles and in 6% of DC cycles. Stomatitis, impaired renal function, lethargy, and neuropathy were the most frequent reasons for dose reductions or delays. Hematologic toxicity alone required dose reduction in only one cycle (< 1%) of DC and six cycles (1%) of DCF.

A similar proportion of patients received second-line chemotherapy (DCF = 39%; DC = 45%). Progressive disease was the most frequent reason for treatment discontinuation (DCF = 39%; DC = 51%).

Objective Response

All image tumor assessments, except for four patients, were reviewed by the ERRC. The ORRs for both the ITT and per-protocol populations are listed in Table 2. The confirmed ORR for the ITT population was 43% for DCF (95% CI, 32% to 55%) and 26% for DC (95% CI, 17% to 38%). All responses were partial except one CR in the DC arm. Table 3 lists the ORRs according to prognostic factors in the per-protocol population.

TTP and Survival

The median TTP was 5.9 months for DCF (range, 0 to 12 months; 95% CI, 4.80 to 7.16 months) and 5.0 months for DC (range, 0 to 10 months; 95% CI, 3.68 to 6.31 months; Fig 1), with a hazard ratio (DCF/DC) of 0.80 (95% CI, 0.52 to 1.22). The probability of remaining progression-free by 6 months was 49.6% and 37.5% for the DCF and DC groups, respectively. At a median follow-up of 17.5 months, the median OS was 9.6 months for DCF (range,

Table 1. Patient and Cancer Characteristics for Modified ITT Population

Characteristic	DC (n = 76)		DCF (n = 79)		Total (n = 155)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
Male	53	70	61	77	114	74
Age, years						
Median	57		57		57	
Range	21-83		30-76		21-83	
Primary tumor site						
Esophagogastric junction/fundus	20	26	29	37	49	32
Stomach, antrum/body	56	74	50	63	106	68
Disease status						
Locally advanced	4	5	1	1	5	3
Metastatic	72	95	75	95	147	95
Locally recurrent	0	0	3	4	3	2
Histology						
Adenocarcinoma	76	100	79	100	155	100
Diffuse	17	22	30	38	47	30
Intestinal	20	26	16	20	36	23
Not stated/specified	35	46	28	35	63	41
Linitis plastica	4	5	5	6	9	6
Karnofsky performance status, before first infusion						
100%	10	13	7	9	17	11
90%	32	42	40	51	72	46
80%	33	43	32	41	65	42
70%	1	1	0	0	1	1
No. of organs involved*						
1	17	22	15	19	32	21
2	30	39	32	41	62	40
> 2	29	38	32	41	61	39
Prior therapy						
Radiotherapy	1	1	1	1	2	1
Surgery	30	39	28	35	58	37
Chemotherapy	1	1	1	1	2	1

NOTE. In certain cases, some percentages do not add up to the complete sum because of rounding.
Abbreviations: DC, docetaxel-cisplatin; DCF, docetaxel-cisplatin-fluorouracil; ITT, intent to treat.
*As determined by the External Response Review Commitee.

0.2 to 22 months; 95% CI, 7.69 to 11.43 months) compared with 10.5 months for DC (range, 0.5 to 23 months; 95% CI, 9.46 to 12.85 months; Fig 2); the hazard ratio (DCF/DC) was 1.19 (95% CI, 0.83 to 1.69). Estimated 1-year survival rate was 35% and 42% for the DCF and DC groups, respectively.

Table 2. Responses for the Modified ITT and Per-Protocol Populations

Response	Modified ITT Population				Per-Protocol Population*			
	DC (n = 76)		DCF (n = 79)		DC (n = 64)		DCF (n = 60)	
	No.	%	No.	%	No.	%	No.	%
Overall response rate	20	26	34	43	20	31	33	55
Complete response	1	1	0	0	1	2	0	0
Partial response	19	25	34	43	19	30	33	55
No change/stable disease	33	43	20	25	32	50	20	33
Progressive disease	13	17	11	14	12	19	7	12
Not assessable	10	13	14	18	NA	NA	NA	NA

NOTE. In certain cases, percentages do not add up to 100% because of rounding.
Abbreviations: DC, docetaxel-cisplatin; DCF, docetaxel-cisplatin-fluorouracil; ITT, intent to treat; NA, not applicable.
*Includes eligible and assessable patients who received ≥ two treatment cycles and had ≥ one complete follow-up tumor assessment (unless early progression occurred) without major protocol deviations.

Table 3. Best Overall Response Rate According to Prognostic Factors at Random Assignment for the Per-Protocol Population*

Factor	DC (n = 64)		DCF (n = 60)	
	No. of Responding Patients/No. of Patients	%	No. of Responding Patients/No. of Patients	%
Karnofsky performance status				
< 100%	18/56	32	28/54	52
100%	2/8	25	5/6	83
Weight loss†				
≤ 5%	10/27	37	14/27	52
> 5%	10/34	29	17/28	61
Site of primary tumor				
Esophagogastric junction/fundus	6/14	43	13/22	59
Stomach	14/50	28	20/38	53
Histology‡				
Diffuse	5/13	38	14/22	64
Intestinal	4/16	25	7/12	58
Linitis plastica	1/3	33	3/4	75
NOS	10/32	31	9/22	41
No. of organs involved				
1	6/13	46	6/11	55
2	8/25	32	15/22	68
> 2	6/26	23	12/27	44
Liver/peritoneum involvement‡				
Yes	19/50	38	28/48	58
No	1/14	7	5/12	42
Prior surgery‡				
Yes	9/27	33	10/20	50
No	11/37	30	23/40	58

Abbreviations: DC, docetaxel-cisplatin; DCF, docetaxel-cisplatin-fluorouracil, NOS, not otherwise specified.
*Includes eligible and assessable patients who received ≥ two treatment cycles and had ≥ one complete follow-up tumor assessment (unless early progression occurred) without major protocol deviations.
†Weight loss data unavailable for three patients in the DC arm and five patients in the DCF arm.
‡As declared by investigator.

Toxic Effects

Hematologic (regardless of relationship to study medication) and nonhematologic adverse events (considered possibly or probably related to study medication) are listed by patient in Table 4 and by cycle in Table 5. With the exception of thrombocytopenia, the incidence of hematologic toxicities was similar in the two arms. As anticipated,

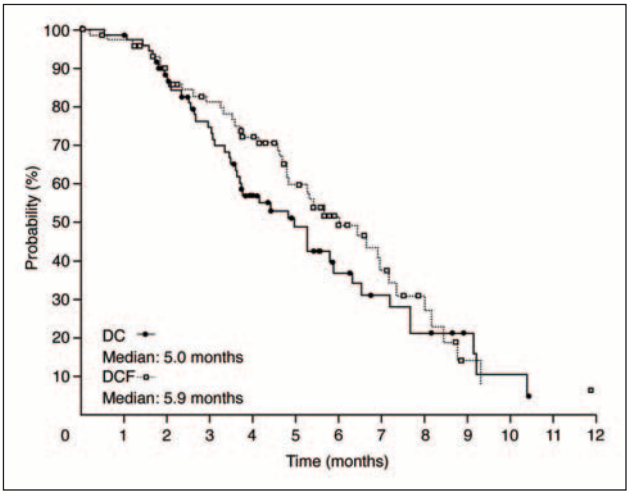

Fig 1. Time to progression by treatment arm (Kaplan-Meier curve). DC, docetaxel-cisplatin; DCF, docetaxel-cisplatin-fluorouracil.

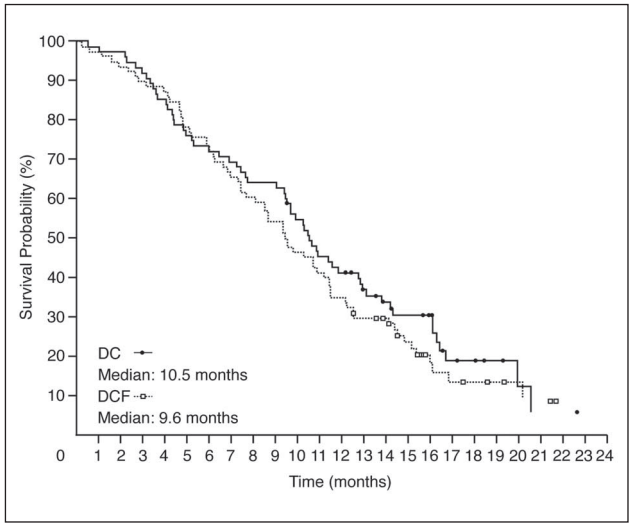

Fig 2. Overall survival by treatment arm (Kaplan-Meier curve). DC, docetaxel-cisplatin; DCF, docetaxel-cisplatin-fluorouracil.

Table 4. Patients With Hematologic and Nonhematologic Toxicities

Toxicity	DC (n = 76)						DCF (n = 79)					
	All Grades		Grade 3		Grade 4		All Grades		Grade 3		Grade 4	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Hematologic toxicity*												
Neutropenia	70	93	15	20	50	67	73	95	12	16	54	70
Anemia	75	100	18	24	6	8	73	95	20	26	2	3
Thrombocytopenia	12	16	1	1	0	0	27	35	6	8	3	4
Leukopenia	71	95	34	45	15	20	74	96	36	47	17	22
Nonhematologic toxicity†												
GI												
Stomatitis	22	29	0	0	0	0	57	72	22	28	3	4
Nausea	52	68	8	11	0	0	61	77	16	20	0	0
Diarrhea	48	63	3	4	1	1	61	77	12	15	4	5
Anorexia	41	54	4	5	4	5	42	53	8	10	4	5
Vomiting	44	58	7	9	2	3	52	66	5	6	6	8
Lethargy	44	58	14	18	0	0	49	62	16	20	0	0
Neurosensory	33	43	8	11	0	0	29	37	9	11	0	0
Infection‡	12	16	1	1	1	1	14	18	6	8	1	1
Myalgia	22	29	5	7	0	0	11	14	1	1	0	0

Abbreviations: DC, docetaxel-cisplatin; DCF, docetaxel-cisplatin-fluorouracil.
*Hematologic toxicity for all assessable patients (DC, n = 75; DCF, n = 77) regardless of whether prophylactic treatment was administered; patients were assessable if they had ≥ one cycle with a blood count for the given test between day 2 and the first infusion of the next cycle.
†Possibly or probably related to study treatment; treatment-emergent nonhematologic toxicities occurring at grade 3 to 4 in ≥ 5% of patients in either group.
‡Infection includes neutropenic infections.

neutropenia was the most common grade 3 to 4 hematologic toxicity; regardless of prophylactic G-CSF, neutropenia occurred in 86% of patients and 49% of cycles for DCF and in 87% of patients and 60% of cycles for DC. The treatment-related febrile neutropenia or neutropenic infection rate was similar for both arms, involving 27% of patients and 7% of cycles for DCF and 27% of patients and 5% of cycles for DC. Prophylactic G-CSF (used in only 14 patients in the DC arm and 17 patients in the DCF arm) was associated with a decrease in the incidence of grade 3 to 4 neutropenia in both arms.

The most frequent grade 3 to 4 nonhematologic toxicities possibly or probably related to study treatment were GI and were more frequent for DCF (56% of patients, 19% of cycles) than for DC (30% of patients, 8% of cycles). The most frequent of these toxicities (at any grade) were stomatitis, nausea, diarrhea, anorexia, and vomiting.

There was little difference between the two arms with respect to consent withdrawals (DC = 12%; DCF = 19%). Eight deaths (10.1%) occurred in the DCF arm and six deaths (8.0%) occurred in the DC arm within 30 days of the last administration of study medication (or after 30 days if the death was considered treatment related). However, among these deaths, 4% were DCF related, and 1% were DC related. The remaining deaths were not related to study drugs. In addition, there was only one neutropenia-related death as a result of DCF.

DISCUSSION

This is the largest phase II randomized trial of docetaxel in patients with advanced gastric cancer. The purpose of the pivotal V-325 study was to define the contribution of docetaxel to TTP and OS of patients with advanced gastric cancer. To choose one of the two experimental regimens (DCF or DC) of interest, this phase II randomized trial was completed. The protocol required that the IDMC review data on at least 70 patients (minimum of 60 assessable patients) to make their decision; however, by the time mature data on 70 patients were verified, the study had accrued 158 patients.

All images to assess ORR (except for four patients) were externally reviewed by the ERRC. All responses were confirmed. In the ITT population, response rates of 43% with DCF and 26% with DC were observed. These data are similar to data reported recently by Roth et al[14] who compared DC and DCF against epirubicin, cisplatin, and FU in a phase II randomized study. In this study as well, the responses were confirmed and independently reviewed. The ORRs for DC and DCF were 18% and 37%, respectively. Our larger study and the study of Roth et al[14] suggest that the addition of FU results in a substantially increased ORR in patients with untreated, advanced gastric or gastroesophageal junction adenocarcinoma.

In our study, the TTP and OS were similar for both regimens, but this study was not powered to detect modest

Table 5. Cycles With Hematologic and Nonhematologic Toxicities

Toxicity	DC (n = 428)						DCF (n = 438)					
	All Grades		Grade 3		Grade 4		All Grades		Grade 3		Grade 4	
	No. of Cycles	%	No. of Cycles	%	No. of Cycles	%	No. of Cycles	%	No. of Cycles	%	No. of Cycles	%
Hematologic toxicity*												
Neutropenia†	336	80	115	27	135	32	310	72	87	20	124	29
Anemia‡	394	93	40	9	10	2	384	89	31	7	2	<1
Thrombocytopenia‡	28	7	1	<1	0	0	50	12	7	2	3	1
Leukopenia§	334	79	133	31	21	5	307	71	109	25	21	5
Nonhematologic toxicity‖												
GI												
Stomatitis	45	11	0	0	0	0	203	46	39	9	3	1
Nausea	165	39	13	3	0	0	206	47	21	5	0	0
Diarrhea	108	25	4	1	1	<1	165	38	15	3	4	1
Anorexia	109	25	6	1	4	1	109	25	11	3	5	1
Vomiting	119	28	8	2	2	<1	145	33	9	2	7	2
Lethargy	135	32	24	6	0	0	152	35	34	8	0	0
Neurosensory	121	28	10	2	0	0	94	21	9	2	0	0
Infection¶	17	4	3	1	1	<1	17	4	6	1	1	<1
Myalgia	67	16	7	2	0	0	31	7	1	<1	0	0
Alopecia	333	78	16	4	0	0	318	73	2	<1	0	0
Edema	60	14	3	1	0	0	60	14	1	<1	1	<1
Nail changes	43	10	7	2	0	0	41	9	8	2	0	0

Abbreviations: DC, docetaxel-cisplatin; DCF, docetaxel-cisplatin-fluorouracil.
*Hematologic toxicity for all assessable cycles regardless of whether prophylactic treatment was administered; cycles were assessable if they had ≥ one blood count for the given test between day 2 and the first infusion of the next cycle.
†No. of assessable cycles: DC = 420; DCF = 429.
‡No. of assessable cycles: DC = 423; DCF = 430.
§No. of assessable cycles: DC = 423; DCF = 431.
‖Possibly or probably related to study treatment; treatment-emergent nonhematologic toxicities occurring at any severity in ≥ 10% of cycles in either group (infection also included).
¶Includes neutropenic infections.

differences between DCF and DC on these end points. Addition of FU to the combination of DC resulted in a higher rate of severe nonhematologic (GI) toxic effects, but these were considered manageable. Hematologic toxicities had a high incidence but were comparable between treatment arms. The rate of grade 3 or 4 neutropenia, which occurred in 85% of patients, is high, but uncomplicated neutropenia may not be of consequence. However, the complicated neutropenia that occurred in seven patients receiving DCF is of concern. Fortunately, there was only one death caused by complicated neutropenia. Occurrence and management of significant chemotherapy-related morbidity or mortality is also a function of the infrastructure of the institution and familiarity of the investigator(s) with the combination(s). At one US site that accrued 55 patients on the V-325 protocol, there was not one death within 30 days of the last chemotherapy infusion or any treatment-related death. This could suggest that there is a learning curve associated with complex therapies.

In conclusion, both DCF and DC are active regimens against advanced untreated gastric or gastroesophageal adenocarcinoma. DCF resulted in a higher confirmed externally reviewed ORR than DC and was chosen as the investigational arm for the phase III portion of the V-325 protocol.

Appendix

The following investigators participated in this study: Dr A. Anelli, Hospital A.C. Camargo, São Paulo, Brazil; Dr H. Bleiberg, Institut Jules Bordet, Bruxelles, Belgium; Dr C. Boni, Arcispedale Santa Maria Nuova, Reggio Emilia, Italy; Dr T.-Y. Chao, Tri Service General Hospital, Taipei, Taiwan; Dr J.S. Chen, Chang Gung Memorial Hospital, Taoyuan, Taiwan; Dr M. Constenla, Centro Hospitalario de Pontevedra, Pontevedra, Spain; Dr J. De Greve, Academisch Zienkenhuis der Vrije Universiteit Bruxeilles, Bruxelles, Belgium; Dr G. Delgado, Conjunto Hospitalar de Sorocaba, Sorocaba, São Paulo, Brazil; Dr F. Fontes, Instituto Portugues de Oncologia de Coimbra, Coimbra, Portugal; Dr M. Gonzalez Baron, Hospital Universitario La Paz, Madrid, Spain; Dr D. Kelsen, Memorial Sloan-Kettering Cancer Center, New York, NY; Dr J. Laplante, Hôpital du Sacré-Coeur de Montréal, Montréal, Quebec, Canada; Dr R.C. Lilenbaum, Mount Sinai Medical Center, Miami, FL; Dr A. Malzyner, Clinica de Oncologia

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Authors' Disclosures of Potential Conflicts of Interest

Although all authors have completed the disclosure declaration, the following authors or their immediate family members have 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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