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Original article

Phase II multicenter trial of docetaxel, epirubicin, and 5-fluorouracil (DEF) in the treatment of advanced gastric cancer: a novel, safe, and active regimen

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Abstract

Background. **This study evaluated the efficacy and safety of docetaxel, epirubicin, and 5-fluorouracil (5-FU) [DEF] as treatment for locally advanced unresectable or metastatic gastric cancer.**

Methods. **Thirty-seven patients participated in the study (median age, 56 years; range, 22–73 years); Eastern Cooperative Oncology Group performance status [PS], 0–2). Docetaxel 75 mg/m² IV (day 1), 5-FU 500 mg/m² IV (days 1–3), and epirubicin 50 mg/m² IV (day 1) were administered every 3 weeks for six cycles.**

Results. **In total, 20/37 patients (54%) completed six treatment cycles. Thirteen patients (35%; 95% confidence intervals [CI], 20% to 51%) had an objective response; 1 patient (3%) achieved a complete response and 12 patients (32%) achieved partial responses. Stable disease was observed in 7 patients (19%) and progressive disease in 5 patients (14%). Twelve patients (32%) were unevaluable. Clinical benefit (based on PS, weight gain, and analgesic consumption) was observed in 11 patients (30%). Median follow-up was 41 months (range, 26–53 months), median time to progression was 6.6 months (range, 0.5–29.2 months), median overall survival was 10.7 months (range, 7.0–14.6 months), and 1-year survival was 40%. The regimen was well tolerated. Grade 3–4 febrile neutropenia occurred in 8 patients (22%; 6% of cycles) and grade 3–4 neutropenia in 1 patient (1% of cycles). The most frequent grade 3–4 toxicities were alopecia (11% of cycles), diarrhea (4% of cycles) and vomiting (2% of cycles); grade 1–2 asthenia and fatigue occurred in 43% of cycles.**

Conclusion. **DEF is effective in the treatment of advanced gastric cancer, and has a good safety profile.**

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Introduction

Gastric adenocarcinoma is the second leading cause of cancer worldwide. It occurs twice as often in men as in women, and is more frequent in the elderly, with a mean age at diagnosis of 70–73 years. As most cases are diagnosed at an advanced stage, the prognosis for this disease is extremely poor, with a 5-year survival of 5%–15% [1]. In Brazil, the incidence and mortality rates for gastric cancer are particularly alarming. According to the Brazilian Ministry of Health, 22150 new cases of gastric cancer were expected in 2003 [2]. As the second leading cause of cancer-related death in Brazil, there were, in fact, 11550 reported deaths in 2003 [2].

Surgery is the only potentially curative treatment for localized gastric cancer. Chemotherapy, which may or may not be administered with radiotherapy, is used to treat advanced or metastatic disease, and the efficacy of chemotherapy with palliative intent is now widely accepted [3].

5-Fluorouracil (5-FU) is effective and widely used in the treatment of advanced gastric cancer, producing a response rate of approximately 20%, with manageable toxicity [3]. Overall survival of 5–7 months has been reported for 5-FU monotherapy in phase III randomized studies [4,5], and all current reference combination regimens in advanced gastric cancer contain 5-FU. Many different combinations have been widely used in advanced gastric cancer, such as 5-FU, doxorubicin, and mitomycin (FAM); 5-FU, doxorubicin, and high-dose methotrexate (FAMTX); etoposide, doxorubicin, and

cisplatin (EAP); etoposide, leucovorin, and 5-FU (ELF); epirubicin, cisplatin, and 5-FU continuous infusion (ECF); cisplatin, epirubicin, leucovorin, and 5-FU (PELF); and several regimens of cisplatin and 5-FU [6]. In randomized studies, FAMTX, cisplatin/5-FU, and PELF have been demonstrated to be more effective than FAM [7–9]; median survival was also significantly greater with FAMTX versus FAM [8]. FAMTX showed similar responses rates to EAP [10] and cisplatin/5-FU and ELF [11], with no significant differences in median survival. ECF was reported to be more active than FAMTX [12].

Despite response rates of up to 51% in these trials, the median survival in patients with advanced disease was consistently less than 10 months. Moreover, toxicities such as leukopenia or alopecia are often present in cisplatin- or etoposide-based regimens.

There is a clear necessity for new drugs and new therapeutic interventions to be studied in order that response rates and survival can be improved. The taxanes, docetaxel and paclitaxel, are one of the most promising groups of cytotoxic agents in clinical use — expressing good antitumor activity, particularly in adenocarcinomas such as breast, lung, and ovarian cancers [13]. Positive results have been achieved with both paclitaxel [14–16] and docetaxel [17–22] as single agents in the treatment of gastric cancer: in phase II trials, overall response rates of 17%–32% have been reported with a 3-weekly regimen of paclitaxel (doses ranging from 200 to 250 mg/m^2) [14–16] and 17%–24% with 3-weekly docetaxel (doses ranging from 60 to 100 mg/m^2) [17–22]. Higher overall response rates have been achieved using taxane-based combination regimens, usually with platinum and/or 5-FU [23–28]; overall response rates of 32%–66% have been observed with paclitaxel combination therapies [23,29,30] and rates of 33%–60% with docetaxel combination regimens [24–28].

In the present trial, we studied the efficacy and safety of docetaxel 75 mg/m^2 intravenous (IV), epirubicin 50 mg/m^2 IV and 5-FU 500 mg/m^2 IV (DEF) in the treatment of advanced gastric cancer. Epirubicin was chosen over doxorubicin as, in addition to being a relatively less toxic anthracycline, in vitro data from human tumor cells suggest that epirubicin is more active than doxorubicin against gastric cancer cells [31]. The underlying rationale for the proposed triplet regimen is that it combines three drugs with different mechanisms of action, providing efficacy with almost no overlapping toxicity.

Patients and methods

Patient selection

To be eligible for this study, patients had to have: pathologically confirmed, nonresectable locally advanced or metastatic malignant gastric cancer; at least one measurable lesion in a nonirradiated area; not received prior chemotherapy; an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 2 or less; age 18–75 years; life expectancy of 12 weeks or more; and adequate hepatic, renal, and bone marrow function.

Patients were excluded from the study if they experienced symptomatic peripheral neuropathy of National Cancer Institute Common Toxicity Criteria (NCI-CTC, version 2.0) [32] grade 2 or more; were pregnant or breastfeeding or were of child-bearing potential without using adequate contraception; had any other current or prior malignancy (with the exception of excised cervical carcinoma in situ or squamous cell skin carcinoma treated by surgery only); showed clinical evidence of major organ failure; had central nervous system (CNS) metastases; had bone metastases as the sole disease site; had active uncontrolled infection or disease; had a neurologic or mental disease not consistent with adequate comprehension of the patient information sheet; or were receiving concurrent treatment with any other drugs that could potentially interfere with the study evaluation (such as longterm administration of corticosteroids). The local ethics committee approved the protocol, and written informed consent was obtained from all patients.

Study design

In this multicenter, open-label, phase II trial, patients received DEF, i.e., docetaxel 75 mg/m^2 (60-min IV infusion) on day 1, epirubicin 50 mg/m^2 (15-min IV infusion) on day 1, and 5-FU 500 mg/m^2 (15-min IV infusion) on days 1, 2, and 3. Patients were treated on an outpatient basis and premedicated with dexamethasone 8 mg orally to be given the night before and on the morning of the docetaxel infusion and 1 h before each docetaxel infusion. Additionally, dexamethasone was given on the night of chemotherapy administration and in the morning and evening of the day after the end of the docetaxel infusion. Ondansetron 8 mg was given before epirubicin administration and metoclopramide 20 mg was given before 5-FU administration.

Cycles were repeated every 3 weeks for six cycles, unless progressive disease or unacceptable toxicity occurred, or patient consent was withdrawn. In the event of toxicity (NCI-CTC definitions), the following dose reductions and treatment delays were planned. In the

case of insufficient hematologic function (neutrophil count <1500/mm^3; platelet count <100000/mm^3) on day 21 of any cycle, treatment was delayed for up to 14 days. If recovery did not occur at this point, treatment was discontinued. Patients with febrile neutropenia or a delay in therapy as a result of myelosuppression were to be treated with granulocyte colony-stimulating factor (G-CSF) on subsequent cycles.

Dose modifications

In the case of grade 4 thrombocytopenia or subsequent febrile neutropenia not controlled with G-CSF, docetaxel was reduced by 20%. An additional docetaxel dose reduction (20%) was conducted upon a third episode of febrile neutropenia. If further febrile neutropenia occurred, treatment was discontinued. Patients who developed hepatic function abnormalities during therapy had the dose of docetaxel reduced by 20% if there was either an increase in aspartate aminotransferase (AST) or alanine aminotransferase (ALT) (2.5–5 times upper limit of normal [ULN]) with alkaline phosphatase (≤2.5 times ULN) or if alkaline phosphatase was 2.5–5 times ULN and AST or ALT were 1.5–5 times ULN. Elevations of any of these enzymes (>5 times ULN) resulted in docetaxel being withheld for a maximum of 2 weeks; the patient was withdrawn from the study if recovery did not occur in that timeframe. Grade 3 skin toxicity, diarrhea, or mucositis also indicated docetaxel, epirubicin, and 5-FU dose reductions of 20%. Grade 4 hematologic toxicity resulted in the patient being withdrawn from the study.

Study evaluations

In the week preceding treatment, patients underwent a complete medical history, physical examination, and electrocardiogram (ECG). A chest radiograph, computed tomography (CT) scan, magnetic resonance imaging (MRI; if indicated), evaluation of nonmeasurable lesions, and endoscopy (for locally advanced disease) were carried out in the 4 weeks preceding the initiation of treatment. Biologic parameters (blood cell count, serum creatinine, bilirubin, AST, ALT, and alkaline phosphatase) were measured at baseline and before each treatment cycle. Blood cell count was also measured on day 8 of each cycle.

All adverse events were graded using the NCI-CTC criteria (version 2) at each cycle. Tumor evaluation was carried out at the end of the second and the sixth cycles, according to standard World Health Organization (WHO) criteria [33], with appropriate clinical and radiologic examinations, and responses were to be confirmed within 4 weeks. The clinical benefit of the regimen was assessed using a modified version of the system developed to assess clinical benefit responses in patients receiving treatment for advanced pancreatic adenocarcinoma [34]. Evaluation of responses involved three components: pain (based on analgesic consumption and pain intensity measured by analog nonvisual scale), ECOG PS, and weight gain.

Clinical response

Each parameter was measured at baseline and then regularly (every two cycles) during the study. Clinical benefit response was defined as a sustained improvement (>4 weeks) in at least one parameter without a worsening of any other. The intent-to-treat (ITT) population consisted of all patients enrolled in the study. All efficacy and safety analyses were conducted using the ITT population. The overall response rate was calculated with 95% confidence intervals (CI). Progression was defined as clinical progression or death due to any cause, and the progression and survival times were measured from the time of study entry until the occurrence of either event. Overall survival (OS) was measured from the initial treatment until death. These values were estimated using the Kaplan–Meier method.

Results

Patient characteristics

Between November 1999 and January 2002, 37 patients were enrolled in the study at five Brazilian centers.

Patient characteristics are listed in Table 1. Twenty-five (68%) patients were male and 12 (32%) were female. Most patients had a good PS (83% had an ECOG PS of 0 or 1). All patients had histologically confirmed adenocarcinomas, the majority of which were poorly or moderately differentiated (32% and 35%, respectively), and distant metastases were identified in 68% of patients. One patient had a resectable tumor and was considered a protocol deviation, as was another patient with a PS of 3.

Efficacy

Of the 37 patients, 12 (32%) were not assessed for response due to: informed consent withdrawal (4 patients), discontinuation due to adverse events (4 patients), early death (2 patients; 1 due to pneumonia and 1 due to septicemia), and protocol deviation (2 patients). These 12 patients were included in the ITT analysis of response rate, progression-free survival, and overall survival. Response rates are shown in Table 2. There were 13 (35%; 95% CI, 20% to 51%) objective responses, including 1 (3%) complete response and 12 (32%) partial responses.

Table 1. Patient characteristics, ITT population ($n = 37$)

Characteristic	*n* (%)
Sex	
Male	25 (68)
Female	12 (32)
Median age, years (range)	56 (22–73)
ECOG performance status	
0	9 (24)
1	22 (59)
2	5 (14)
3[a]	1 (3)
Histopathologic differentiation[b]	
Adenocarcinoma	
Grade I	0
Grade II	13 (35)
Grade III	12 (32)
Undifferentiated	3 (8)
Not specified	9 (24)
Staging	
Locally advanced	12 (32)
Metastatic	25 (68)

ECOG, Eastern Cooperative Oncology Group; ITT, intent to treat; TNM, tumor node metastases
[a] Protocol deviation
[b] Laurén (1965)[35]

Table 2. Response rates, ITT population ($n = 37$)

Response	*n* (%)	95% CI
Complete response	1 (3)	—
Partial response	12 (32)	—
Stable disease	7 (19)	—
Progressive disease	5 (14)	—
Not assessable	12 (32)	—
Overall response rate	13 (35)	20 to 51

CI, confidence intervals; ITT, intent to treat

Clinical benefit was observed in 11 (30%) patients. In 2 patients, all three parameters (pain, ECOG PS reduction, and weight gain) improved. In 5 patients, two parameters were improved; in the remaining 4 patients, one parameter was improved. Time-related efficacy parameters for all 37 patients were updated as of March 2004. Median follow-up was 41 months (range, 26–53 months); median time to progression was 6.6 months (range, 0.5–29.2 months; Fig. 1); and median OS was 10.7 months (range, 0.5–36.2 months; Fig. 2). One-year survival was 40% (Fig. 2).

Toxicities

A total of 149 cycles were administered (mean, 4 cycles per patient; range, 0–6), with 6.0% of cycle delays being caused by adverse events (only 1.3% for hematologic toxicity and 1 cycle because of vomiting). Overall, the regimen was well tolerated. All patients (ITT population) were evaluated for toxicity (Table 3). WHO grade 3–4 febrile neutropenia occurred in 8 patients (22%) and in 6% of cycles. Grade 3–4 neutropenia occurred in 1 patient (3%) and in 1% of cycles. The most frequent grade 3–4 toxicities were alopecia, diarrhea, and vomiting, which occurred in 11%, 4%, and 2% of cycles, respectively. Grade 1–2 asthenia and fatigue were observed in 43% of cycles. Grade 3 stomatitis occurred in 1 patient (3%), grade 3 vomiting in 3 patients (8%), and grade 3–4 diarrhea in 5 patients (14%). One patient had reversible grade 4 gastrointestinal bleeding. Two patients (5%) died as a result of febrile neutropenia and sepsis. Four (10.8%) patients withdrew from the study due to adverse events. The early (60-day) mortality rate was 10.8% (4 patients).

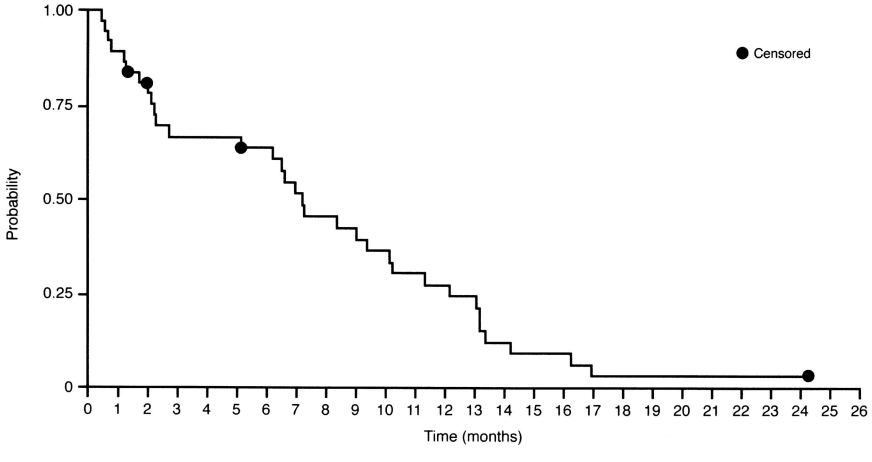

Fig. 1. Time to disease progression

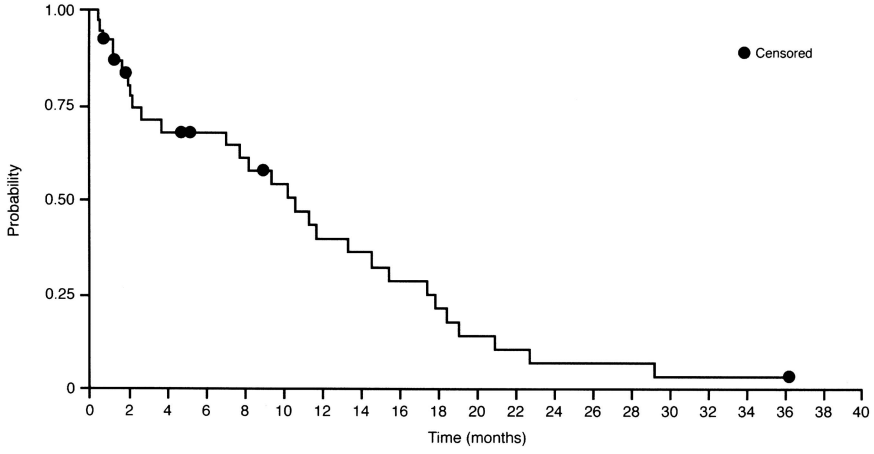

Fig. 2. Overall survival

Table 3. Toxicity, expressed as percentage of cycles ($n = 149$)

	NCI-CTC grade[a]	
Toxicity	3	4
Vomiting	2	0
Alopecia	11	0
Stomatitis	1	0
Diarrhea	3	1
Peripheral edema	0	0
Neuropathy	0	0
Myalgia	0	0
Infection	1	0
Neutropenia	1	0
Febrile neutropenia	3	3
Thrombocytopenia	1	0
Bleeding	0	1
Anemia	1	0
Asthenia/fatigue	0	0

NCI-CTC, National Cancer Institute Common Toxicity Criteria
[a] NCI-CTC version 2.0

Discussion

Although gastric adenocarcinoma is the most chemosensitive gastrointestinal tumor, very few studies have shown improvement in patient survival or quality of life with chemotherapy [6]. The introduction of FAM at the end of the 1970s raised the possibility that combination chemotherapy could be more effective than a single agent. However, Cullinan et al. [36] demonstrated, in a comparative study, that FAM was not superior to 5-FU alone in terms of OS. Second-generation regimens, such as FAMTX, ELF, EAP, and ECF, have achieved an objective response in up to 51% of patients and a complete response in 10%–17% of patients. A median OS of 7–10 months and 2-year survivals of 5%–10% have also been demonstrated [3,6].

The taxanes, docetaxel and paclitaxel, may provide a treatment option that potentially improves efficacy and survival among patients with gastric cancer. Paclitaxel shows moderate activity as single-agent therapy [14–16] and shows good activity when combined with 5-FU: a response rate of 65.5%, complete response rate of 24%, and median OS of 12 months (range, 2–30+ months) have been reported in one study with this combination [23]. Furthermore, clinical benefit based upon weight gain, PS improvement, and analgesic consumption reduction was noted in 51.7% of patients [23]. However, these results need to be interpreted with care, because they were not obtained from an ITT analysis. Other studies have reported overall response rates of 32% with paclitaxel–5-FU–folinic acid [30] and 48%–51% with paclitaxel–5-FU–cisplatin with or without folinic acid [29,37].

Docetaxel is also active in advanced gastric cancer as single-agent therapy [17–22]. For example, in a phase II European Organisation for Research and Treatment of Cancer (EORTC) trial [17], 37 eligible patients with advanced, untreated gastric carcinoma were given docetaxel 100 mg/m^2 as a 60-min IV infusion once every 3 weeks. Of the 33 evaluable patients, 8 (24%) achieved partial remission for a median of 7.5 months, and 11 patients had stabilization of disease. Docetaxel has also been tested in combination with other agents. Preliminary results of a phase II study suggest response rates of 37% with docetaxel–cisplatin–5-FU (DCF) compared with 25% with epirubicin–cisplatin–5-FU (ECF) and 18.5% with docetaxel–cisplatin (DC) [38]. Moiseyenko and colleagues [39] conducted a phase III multinational study comparing DCF with the doublet cisplatin–5-FU (CF; V325), early results of which suggested the superiority of DCF over CF in patients with advanced gastric cancer. Updated interim results of this study also suggest that DCF may provide significantly higher response

rates than CF [40,41]. In total, 463 patients were randomized to two treatment arms: DCF given every 21 days (docetaxel 75 mg/m^2 and cisplatin 75 mg/m^2 on day 1 and 5-FU 750 mg/m^2 per day [continuous IV infusion] for 5 days) and CF given every 28 days (cisplatin 100 mg/m^2 on day 1 and 5-FU 1000 mg/m^2 per day [continuous IV infusion] for 5 days). DCF was superior to CF in terms of objective response rate (38.7% vs 23.2%, respectively; $P = 0.012$), median time to disease progression (5.2 months vs 3.7 months, respectively; $P = 0.0008$), and median OS (10.2 months vs 8.5 months, respectively; $P = 0.0064$) [40,41]. Notably, the probability of survival at 1 year with DCF was 44.1% [40].

The study of moiseyenko and colleagues [39] is the largest prospective, randomized phase III study to date in patients with advanced gastric cancer. It lends strong support for the use of docetaxel in the systemic therapy of patients with gastric cancer. However, there was a greater incidence of grade 3–4 neutropenia, febrile neutropenia, and neutropenia with infection in the DCF-treated patients compared with CF. While the incidence of diarrhea was higher among DCF-treated patients, the risk of nausea, vomiting, and stomatitis was greater in patients treated with CF [41]. These findings raise the question of whether cisplatin is the best agent to use in combination with docetaxel and 5-FU.

In our investigation, which, as far as we are aware, is the first published study of DEF in gastric cancer the toxicity profile of epirubicin was better than might be expected with cisplatin. Epirubicin has activity in advanced gastric cancer equivalent to that of 5-FU [42] and, in gastric cancer cell lines, epirubicin seems to be more effective than doxorubicin [31]. Response rates, median time to progression, median OS, and 1-year survival with DEF were equivalent to those for DCF (35% vs 38%, 6.6 months vs 5.2 months, 10.7 months vs 10.2 months, and 40% vs 44.1%, respectively). However, the toxicity profile of DEF appears to be better: grade 3–4 neutropenia, vomiting, stomatitis, and diarrhea occurred more frequently in DCF- than in DEF-treated patients (84% vs 5%, 15% vs 8%, 23% vs 3%, and 20% vs 14%, respectively), although a direct comparison between studies cannot be made. It must be stated, however, that blood count was checked only at 21-day intervals. This may explain the low incidence of neutropenia observed with our regimen. Another advantage of the DEF regimen is the use of bolus 5-FU instead of continuous infusion, removing the requirement for infusion pumps. It is also important to point out that — based on analgesic consumption, weight gain, and ECOG PS improvement — DEF produced a clinical benefit in 11 patients (30%).

The results obtained in this study indicate that DEF could be an alternative to DCF for the treatment of advanced gastric cancer, based on possible equivalent efficacy and a better toxicity profile, in addition to the easier mode of 5-FU administration. A phase III trial has been planned to further confirm the advantages of the DEF regimen.

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