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ORIGINAL ARTICLE

Sequential chemotherapy with cisplatin, leucovorin, and 5-fluorouracil followed by docetaxel in previously untreated patients with metastatic gastric cancer: a phase II study

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Abstract
Background The combination of docetaxel, cisplatin, and 5-fluorouracil (5-FU) has demonstrated a survival advantage over cisplatin and 5-FU, but with substantial hematological toxicity. We aimed to evaluate the efficacy and toxicity of a sequential regimen with cisplatin, leucovorin, and 5-FU (PLF) followed by docetaxel in metastatic gastric cancer patients.
Methods Treatment consisted of 4 cycles of biweekly PLF (cisplatin 50 mg/m^2 as a 30-min infusion on day 1, leucovorin 200 mg/m^2 in a 2-h infusion, and 5-FU 2,800 mg/m^2 in a 48-h continuous infusion starting on day 1) followed, in cases of response or stable disease, by 3 cycles of docetaxel (75 mg/m^2, every 3 weeks).
Results Thirty-four patients were enrolled, with an average age of 64 years (range 34–69). The main cumulative grade 3–4 toxicities were: neutropenia (38.2%), febrile neutropenia (11.8%), and fatigue (14.7%). After the planned 7 cycles of treatment, the overall response rate was 38.2% (95% confidence interval [CI] 21.9–54.6), with 3 complete and 10 partial responses. Median progression-free survival and overall survival were 4.8 and 10.6 months, respectively.
Conclusions For patients with metastatic gastric cancer, the sequential administration of cisplatin, leucovorin, 5-FU, and docetaxel may be an effective palliative option and offers a far more favorable toxicity profile than the simultaneous use of docetaxel, cisplatin, and 5-FU.

Keywords Systemic chemotherapy · Cisplatin · 5-Fluorouracil · Docetaxel · Metastatic gastric cancer

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Introduction

Despite the general decreasing trend in incidence, gastric cancer remains one of the leading causes of cancer-related death worldwide [1]. Surgery is the mainstay for gastric cancer treatment. However, many patients are initially referred with locally advanced or metastatic disease, or have local and distant recurrences after the radical resection of a gastric tumor. For patients with relapsed or metastatic disease prognosis is still extremely poor, as survival at 2 years rarely exceeds 10% [2]. In this subset of patients, systemic chemotherapy has been found to improve quality of life and overall survival (OS) when compared to best supportive care alone [2].

In Western countries, regimens containing 5-fluorouracil (5-FU) and cisplatin (CDDP) remain an accepted standard regimen [3]. The biweekly 5-FU and leucovorin regimen according to the de Gramont et al. [4] schedule is popular in Europe for advanced colorectal cancer. This bimonthly combination of 5-FU/leucovorin and cisplatin 50 mg/m^2 is feasible and well tolerated, and has also been evaluated for gastric cancer [5, 6]. Furthermore, the simplified bimonthly regimen, which combines leucovorin and high-dose 5-FU infusion, is at least as effective as the initial de Gramont (Tournigand et al. [7]) schedule, but is more

convenient for the patient, less expensive, and easier to combine with other cytotoxic agents. Therefore, a combination of CDDP added to a simplified high-dose 5-FU infusion has become quite common in some European countries [8].

Recently, new chemotherapy regimens, including capecitabine, oxaliplatin, irinotecan, and docetaxel, have been investigated [9–12].

Docetaxel is one of the most active single agents in the treatment of gastric cancer. In the first-line setting, at a dose of 60–100 mg/m^2 repeated every 3 weeks, response rates ranged from 17 to 20% [13–16]. Docetaxel is the only taxane that has been evaluated in the context of a phase III study (TAX-V325 trial) [9]. The addition of docetaxel to 5-FU and CDDP (DCF regimen) significantly improved the efficacy of a standard 5-FU/CDDP combination (CF regimen) in terms of time-to-progression (TTP), better response rate, and OS. However, the addition of docetaxel to CF resulted in a significant increase in toxicity, mainly hematological, despite the quality of life and clinical benefit being better maintained in the patients treated with the DCF regimen [17, 18]. The efficacy and toxicity of a triple combination containing docetaxel, CDDP, and 5-FU was also confirmed in a randomized phase II trial from the Swiss Group for Clinical Cancer Research [19]. However, the toxicity profile of the DCF regimen has contributed to the limitation of using this combination in the first-line setting for patients with advanced gastric cancer. When adding a third drug to a double combination, toxicity may significantly increase despite the achievement of a slight increase of the response and survival rates. Subsequent attempts have tried to improve the tolerability of regimens containing CDDP, 5-FU, and docetaxel by reducing and fractioning the dose of docetaxel [20–22].

Considering that the aim of treatment in metastatic disease is palliation, great importance should be given to the tolerability of the treatment. The use of regimens having a good safety profile is highly warranted provided that the efficacy of such treatment can be maintained. Another possible option to better ameliorate tolerability could be the sequential administration of drugs. This approach has already been studied in the context of a phase II study in which sequential docetaxel treatment was given after an intensive weekly PELF (CDDP, epidoxorubicin, leucovorin, 5-FU) combination in patients with advanced gastric cancer [23].

Based on these premises, in the present study we aimed to evaluate the efficacy of a sequential regimen of CDDP, 5-FU, leucovorin, and docetaxel in patients with metastatic gastric cancer, for whom palliation is the standard goal of treatment.

Patients, materials, and methods

Patient selection

All patients in this study were aged between 18 and 69 years and had histologically confirmed, relapsed or metastatic adenocarcinoma of the stomach, or of the gastro-esophageal junction. Other eligibility criteria were: Eastern Cooperative Oncology Group (ECOG) performance status 0, 1, or 2; measurable disease; adequate liver, renal, and bone marrow functions; and estimated life expectancy $\geq$3 months. Patients with non-measurable disease as the only reference were not included, and if there had been radiotherapy to individual sites of disease, these patients were not considered evaluable for response. Patients who had received prior chemotherapy for metastatic disease were excluded. Previous adjuvant chemotherapy completed at least 12 months previously was allowed, but patients had to be untreated with docetaxel. Patients were also excluded if they had evidence of central nervous system metastasis, peripheral neuropathy $\geq$grade 2, serious uncontrolled concomitant disease, other primary malignancy (except for squamous or basal cell skin cancer or cervical carcinoma in situ) within the past 5 years, or if they were pregnant or breastfeeding.

Pre-treatment evaluation and treatment plan

In addition to a full medical history and physical examination, baseline assessments included complete blood counts, blood chemistries, urinalysis, electrocardiography, and ECOG performance status. All patients underwent chest, abdominal, and pelvic computed tomography scans within the 4-week period prior to starting the PLF regimen. Full medical history and physical examination including ECOG performance status and blood chemistries were assessed prior to each treatment cycle.

Sequential treatment consisted of 4 cycles of biweekly CDDP 50 mg/m^2 as a 30-min infusion, on day 1; and leucovorin 200 mg/m^2 diluted in a 250 ml normal saline solution in a 2-h infusion followed by 5-FU 2,800 mg/m^2 in a 48-h continuous infusion starting on day 1 (PLF). After 4 cycles of chemotherapy, patients were re-evaluated and those with a complete or partial response or stable disease received 3 cycles of docetaxel 75 mg/m^2 as a 1-h infusion in 250 ml of normal saline solution, on day 1, every 3 weeks. After 3 cycles with docetaxel, patients were re-evaluated for response to the sequential treatment, after which, subsequent treatment was left to the discretion of the investigator.

To avoid CDDP-induced renal damage, patients were hydrated on day 1 of each administration of CDDP.

Prophylactic administration of antiemetic medication (5-HT3 inhibitors plus corticosteroid) at a standard dose was routinely used to prevent nausea and vomiting during each course of PLF chemotherapy. Patients who received docetaxel were treated with dexamethasone 8 mg administered 24, 12, and 1 h before drug infusion and 8 mg twice daily for an additional 2 days.

Evaluation of toxicity and response

Toxicity was graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 3.0.

Dose modifications were performed on the basis of toxicity. Full doses of anticancer drugs were given if the neutrophil count was $\geq$1,500/mm^3 and the platelet count $\geq$100,000/mm^3. Granulocyte colony-stimulating factor (G-CSF) was administered when grade 4 neutropenia, or grade 3 or 4 neutropenia with fever, was observed. Prophylactic G-CSF administration was allowed as needed in all subsequent cycles. Chemotherapy was delayed until recovery if neutrophils decreased to $\leq$1,500/mm^3, or the platelet count decreased to <100,000/mm^3. A 20% dose reduction of chemotherapeutic drugs was mandatory if grade 4 neutropenia; febrile neutropenia; grade 3–4 thrombocytopenia; or grade 2–3 mucositis, diarrhea, or hand–foot syndrome occurred. Treatment was stopped if grade 4 mucositis, diarrhea, or hand–foot syndrome occurred. In the presence of other grade 4 NCI-CTCAE toxicities, patients were to be withdrawn from the study. Patients were also to be removed from the study for any treatment delays exceeding 3 weeks. Treatment was continued as planned until disease progression, unacceptable toxicity, patient refusal, or the physician's decision.

Responses were evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, after 4 cycles of PLF and after 3 cycles of docetaxel.

Statistical plan

This was a multicenter phase II study. The primary endpoint was the cumulative objective response rate of the planned sequential treatment (4 cycles of PLF and 3 cycles of docetaxel). Secondary endpoints were toxicity, progression-free survival (PFS), and OS. The mini-max two-stage design was adopted for this phase II trial. The treatment program was designed to reject an overall response rate for the sequential PLF regimen followed by docetaxel <20% (p0) and to provide a statistical power of 80% in assessing the activity of the regimen (in terms of response rate) as 40% (p1). Early discontinuation of the study was provided for in the case of <4 responses in the first 18 assessable patients treated with PLF and docetaxel (α and β error probabilities 0.05 and 0.020). This sequential regimen was to be considered promising if at least 10 responses were observed in a total of 33 enrolled patients. PFS was measured from the onset of chemotherapy to the date of progression (per investigator assessment), or death from any cause. OS was calculated from the onset of chemotherapy until death or until the last visit for patients still alive. Patient survival was examined using the Kaplan–Meier product limit method. The protocol was approved by each local institutional review board and written informed consent was given by all patients.

Results

From May 2006 to December 2008, 34 patients were enrolled from two institutions (Pesaro and Rome). The characteristics of the patients are summarized in Table 1. The median patient age was 64 years (range 34–69). Metastases were primarily in the lymph nodes (58.8%), liver (44.1%), and peritoneum (32.4%). At least two organs were involved in nearly two-thirds of the patients. Nearly 80% of the patients had a moderate to poor Royal Marsden Hospital (RMH) prognostic index [24].

Response evaluation

One patient could not be evaluated for response as he was removed from the study after one cycle of chemotherapy due to spondylodiscitis, which prevented the restarting of chemotherapy within 3 weeks. However, he was included in the intention-to-treat analysis. After the PLF regimen, 1 patient achieved a complete response, 10 patients showed a partial response, 14 patients had stable disease, and 8 patients progressed, for an overall response rate of 32.3% (95% CI 16.6–48.1) (Table 2).

Out of the 25 patients achieving a response or stabilization of disease, 24 received the following pre-planned docetaxel. One patient had persistent thrombocytopenia lasting more than 3 weeks after the third cycle of PLF; for this reason, he was excluded from the study and did not receive docetaxel. Responses to docetaxel were improved in 4 (16.7%; 95% CI 1.8–31.6) out of the 24 patients, 2 patients with a partial response achieved a complete response, and 2 patients with stable disease achieved a partial response. Ten patients experienced stabilization of disease with docetaxel, 9 patients had progressive disease, and one patient died due to febrile neutropenia and severe diarrhea after the second cycle of docetaxel, without signs of disease progression. The overall response rate for the overall group of patients at the end of the sequential treatment was 38.2% (95% CI 21.9–54.6).

Table 1 Patient characteristics

Characteristics	*n*	%
No of patients	34	
Sex, male/female	22/12	64.7/35.3
Age (years)		
Median (range)	64 (34–69)	
Performance status		
0	17	50.0
1	13	38.2
2	4	11.8
Lauren classification		
Intestinal type	15	44.1
Diffuse type	18	52.9
Mixed	1	3.0
Primary tumor		
Esophago-gastric junction	3	9.1
Stomach	31	90.9
Prior therapy		
Surgery	15	44.1
Adjuvant chemotherapy	2	5.9
Number of organs involved		
1	12	35.3
2	6	17.6
3–5	16	47.1
Metastatic sites		
Lymph nodes	20	58.8
Liver	15	44.1
Peritoneum	11	32.4
Bone	4	11.8
Lung	2	5.9
Other	5	14.7
Royal Marsden Hospital prognostic index		
Good	7	20.6
Moderate	22	64.7
Poor	5	14.7

Survival analysis

Thirty-four patients were included in the survival analysis on an intention-to-treat basis. The median follow-up time was 25 months (range 7–43 months). The median PFS was 4.8 months (Fig. 1) and the median OS was 10.6 months, with 44.1% of patients alive at 1 year (Fig. 2).

Treatment administration

Thirty-four patients were administered a total of 127 cycles (median number 4, range 1–4) of PLF and a total of 67 cycles (median number 3, range 1–3) of docetaxel. The median relative dose intensities were 95.5% (range

Table 2 Best response rates according to RECIST

Response	PLF ($n = 34$)	Docetaxel ($n = 24$)	Overall ($n = 34$)
Complete response	1	2	3
Partial response	10	2	10
ORR (95% CI)	32.3% (16.6–48.1)	16.7% (1.8–31.6)	38.2% (21.9–54.6)
Stable disease	14	10	12
Progressive disease	8	9	8
Not assessable	1	1	1

PLF cisplatin, leucovorin, 5-fluorouracil, *RECIST* Response Evaluation Criteria in Solid Tumors, *ORR* overall response rate, *CI* confidence interval

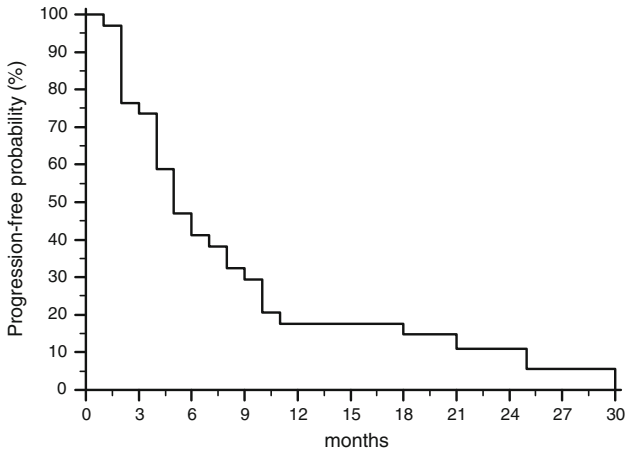

Fig. 1 Kaplan–Meier curve of progression-free survival ($n = 34$)

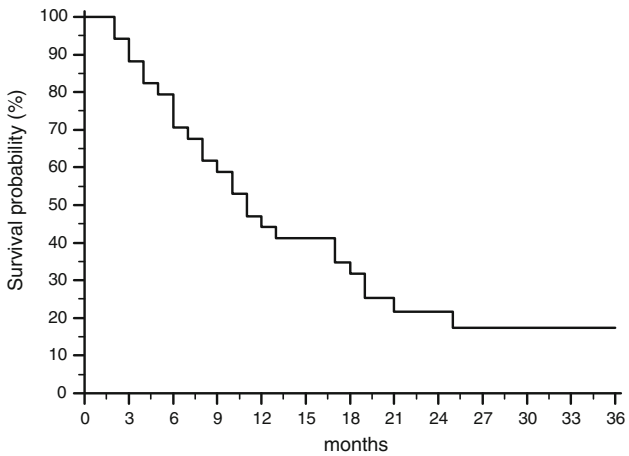

Fig. 2 Kaplan–Meier curve of overall survival ($n = 34$)

70.0–100%) for CDDP, 95.5% (range 70.0–100%) for 5-FU, and 97.4% (range 78.0–100%) for docetaxel. Treatment administration of PLF and docetaxel was delayed for 1 week in 8 (23.5%) and 2 (8.3%) patients, respectively. The major causes of delays in administration were neutropenia, febrile neutropenia, and thrombocytopenia. Dose reductions of CDDP, 5-FU, and docetaxel were made in 3 (8.9%), 3 (8.9%), and 4 (11.8%)/34 patients, respectively.

The reasons for the discontinuation of sequential PLF and docetaxel were adverse events in 2/34 patients (5.9%) and progressive disease in 8/34 patients (23.5%). After the sequential PLF and docetaxel regimen, 3 patients restarted the PLF schedule and 6 patients received additional cycles of docetaxel. Eleven of the 24 patients who started docetaxel (45.8%) received second-line chemotherapy.

Toxicity

The toxicity profile of the PLF regimen was acceptable (Table 3). Only two patients suffered from grade 4 toxicity (neutropenia and thrombocytopenia, respectively) and 12 patients (35.3%) experienced acute grade 3 adverse events: neutropenia in 8 (23.5%) patients, fatigue in 2 (5.9%) patients, and febrile neutropenia and anorexia in 1 (2.9%) patient.

According to the treatment protocol, 24 patients started docetaxel. Acute adverse events are listed in Table 3. Grade 4 toxicity occurred in 6 patients: 4 (16.7%) patients had neutropenia and 2 (8.3%) patients had febrile neutropenia. Eight patients had grade 3 toxicity: fatigue in 3 (12.5%) patients, neutropenia in 2 (8.3%) patients, stomatitis in 2 (8.3%) patients, and febrile neutropenia in 1 (4.2%) patient. Docetaxel was delayed for a week in 2 (8.3%) patients, while 3 (12.5%) patients received a dose reduction of docetaxel, mainly because of neutropenia, febrile neutropenia, or fatigue. Asthenia was the most frequent chronic adverse event and it proved to be grade 1 or 2 in 12 patients (50.0%), followed by anemia (11 patients, 45.8%). None of the patients experienced hypersensitivity reactions or fluid retention syndrome.

All cases of severe neutropenia were managed with G-CSF administration (19 patients receiving PLF, 14 patients receiving docetaxel) and dose reductions of CDDP, 5-FU, and docetaxel for subsequent cycles.

Table 3 also shows the cumulative toxicities per patient. The main grade 3–4 toxicities were reported as follows: 13 (38.2%) patients with neutropenia, 4 (11.8%) patients with febrile neutropenia, 5 (14.7%) patients with fatigue, 2 (5.9%) patients with stomatitis, and 1 (2.9%) patient each with anorexia, thrombocytopenia, and neurological toxicity.

Discussion

The prognosis of metastatic gastric cancer still remains dismal. In this setting, systemic chemotherapy represents the cornerstone of treatment and, in particular, it improved median OS compared with best supportive care by nearly 7 months [2]. During the past few decades new drug combinations were explored for this disease, with limited improvement of response rates, PFS, and OS [2, 3]. Docetaxel was recently approved for the first-line of treatment on the basis of the TAX-V325 trial [9]. DCF in comparison with CF significantly improved TTP (5.6 vs. 3.7 months, respectively; $p < 0.001$), response rate (37 vs. 25%, respectively; $p = 0.01$), and OS (9.2 vs. 8.6 months;

Table 3 Toxicity (NCI-CTCAE, version 3.0) according to treatment

Grade	PLF *n* (%)			Docetaxel *n* (%)			Cumulative toxicity PLF/docetaxel *n* (%)		
	1–2	3	4	1–2	3	4	1–2	3	4
Neutropenia	6 (17.6)	8 (23.5)	1 (2.9)	9 (37.5)	2 (8.3)	4 (16.7)	11 (32.4)	8 (23.5)	5 (14.7)
Anemia	14 (41.2)	0 (0)	0 (0)	11 (45.8)	0 (0)	0 (0)	16 (40.3)	0 (0)	0 (0)
Thrombocytopenia	3 (8.8)	0 (0)	1 (2.9)	0 (0)	0 (0)	0 (0)	3 (8.8)	0 (0)	1 (2.9)
Febrile neutropenia	–	1 (2.9)	0 (0)	–	1 (4.2)	2 (8.3)	–	2 (5.9)	2 (5.9)
Nausea	15 (44.1)	0 (0)	0 (0)	1 (4.2)	0 (0)	0 (0)	15 (44.1)	0 (0)	0 (0)
Vomiting	7 (20.6)	0 (0)	0 (0)	3 (12.5)	0 (0)	0 (0)	9 (26.5)	0 (0)	0 (0)
Diarrhea	5 (14.7)	0 (0)	0 (0)	7 (29.1)	0 (0)	0 (0)	11 (32.3)	0 (0)	0 (0)
Stomatitis	8 (23.5)	0 (0)	0 (0)	3 (12.5)	2 (8.3)	0 (0)	8 (23.5)	2 (5.9)	0 (0)
Fatigue	17 (49.9)	2 (5.9)	0 (0)	12 (50.0)	3 (12.5)	0 (0)	19 (55.8)	5 (14.7)	0 (0)
Anorexia	1 (2.9)	1 (2.9)	0 (0)	1 (4.2)	0 (0)	0 (0)	2 (5.9)	1 (2.9)	0 (0)
Neurological	3 (8.8)	0 (0)	0 (0)	4 (16.7)	0 (0)	0 (0)	5 (14.7)	1 (2.9)	0 (0)
Others	3 (8.8)	0 (0)	0 (0)	1 (4.2)	0 (0)	0 (0)	4 (11.8)	0 (0)	0 (0)

NCI-CTCAE National Cancer Institute Common Terminology Criteria for Adverse Events, *PLF* cisplatin, leucovorin, 5-fluorouracil

$p = 0.02$). However, the positive effect of the addition of docetaxel to the CDDP/5-FU combination on outcome was achieved at the price of significant toxicity, especially hematological, with grade 3–4 neutropenia (82%), febrile neutropenia (29%), and grade 3–4 diarrhea (19%). Despite the quality of life being better maintained in the patients treated with the DCF regimen and a clinical benefit also being demonstrated with DCF compared to CF [17, 18], the toxicity profile has contributed to the limitation of the use of this regimen in the first-line treatment of advanced disease.

Our phase II study was initiated to assess the antitumor efficacy and also the tolerability for the treatment of metastatic gastric cancer when CDDP, 5-FU, and docetaxel were to be used in a sequential fashion instead of simultaneously. In metastatic disease, palliation is the endpoint of treatment. Therefore, it could be interesting to evaluate whether the sequential administration of drugs, as opposed to their concomitant administration, could maintain endpoint efficacy while ameliorating the toxicity profile. Although cross-study comparisons should be made with caution, the response rate achieved in the present trial (38.2%; 95% CI 21.9–54.6) was in the range of that reported previously for gastric cancer in phase III randomized trials [9, 11, 12, 25], or phase II trials evaluating combinations of CDDP, 5-FU, and docetaxel [20–22]. The PFS reported in the present trial was 4.8 months, which seems lower than that reported in some phase III randomized trials [3], but it was within the reported PFS times ranging between 3.7 and 7.0 months [3]. Different factors may explain this relatively low PFS in our trial, such as the higher percentage of patients with more than 2 metastatic sites involved, the relatively high percentage of patients with peritoneal disease, and the eligibility for the study, which allowed the inclusion of patients with ECOG performance status 1 or 2, who are not well represented in some trials [9, 12], and the inclusion of patients with recurrent or metastatic disease, thus excluding those patients with locally advanced disease. Furthermore, the OS in our cohort of patients seemed to be quite similar to that reported in other previous phase II and III studies [3]. Thus, the sequential regimen of PLF and docetaxel may suggest a comparable efficacy to what has been previously observed.

Considering the safety profile, our sequential PLF and docetaxel regimen showed grade 3–4 neutropenia and febrile neutropenia in 38 and 11.8% of patients, respectively. The most common non-hematological grade 3–4 toxicities were fatigue (14.7%) and stomatitis (5.9%). Furthermore, the acceptable and manageable toxicity of this sequential regimen made it possible to administer high relative dose intensities of each drug. Unfortunately, one patient died after the second cycle of docetaxel due to severe diarrhea and neutropenia. In the present study, we adopted a low dose of docetaxel, 75 mg/m^2 every 3 weeks, based on previous reports [14, 16] showing a high median dose intensity, but efficacy and toxicity at this dose of the drug comparable to results with higher doses of docetaxel. The death reported in the present study is unlikely to be attributable to the dose of docetaxel (75 mg/m^2), which is the same as that used in combination regimens, such as DCF [9], while it is lower than that previously reported as a single-agent dose [13, 14]. Rather, this event confirms the need for careful monitoring in patients who may be frail, such as patients with metastatic gastric cancer.

For patients with advanced gastric cancer, the use of docetaxel, both as a single agent or in addition to other drugs, represents an important achievement. However, the associated toxicity may be noteworthy and requires proper patient selection. Also when considering the use of docetaxel as a single agent, its use necessitates careful observations and monitoring of the toxicity profile to prevent treatment-associated toxicities. Sequential therapy allows the optimal delivery of single-drug therapy and potentially reduces the risk of toxicity, which may improve quality of life. This strategy could be especially appropriate in patients who may be unable to tolerate the toxicity of combination therapy [26]. Given the natural history of advanced gastric cancer, and the availability of new active drugs in this lethal disease, second-line chemotherapy has become an option for some patients [27, 28], and irinotecan or docetaxel are commonly used in this setting. However, a three-drug docetaxel-containing regimen as first-line chemotherapy is to be considered a valuable approach. Furthermore, in gastric cancer we have no data suggesting the use of a particular drug after the disease has progressed on a first-line chemotherapy doublet regimen instead of using all the three commonly used drugs (i.e., docetaxel, cisplatin, and 5-FU) simultaneously (or sequentially, as reported in the present trial). Our attempt should be considered in the perspective of the search for a more tolerable approach, especially if we consider the elderly patients in everyday practice.

Other than the toxicity and manageability of the classical DCF regimen, a reason for concern limiting the worldwide diffusion of this regimen is the selection of patients enrolled in the TAX-V325 trial [9], which did not reflect the general population with metastatic gastric cancer. Participants included in the TAX-V325 trial had a relatively low median age (55 years) and a good performance status, with only 1% of patients having a Karnofsky performance status of 70. In the present study, the baseline characteristics were relatively unfavorable according to the RMH prognostic index [24]. Only 20% of the patients had a good RMH prognostic index and 64% of the patients had a moderate RMH prognostic index, which was associated

with an OS time of 8.6 months [24]. Despite these negative characteristics, the sequential PLF and docetaxel regimen showed promising evidence of efficacy.

To overcome the substantial toxicity of DCF, different modifications of the original DCF regimen were tested by fractioning the dose of docetaxel [20–22]. All these modifications showed similar response rates, ranging from 37 to 47% [20, 21], as well as decreased toxicity, mainly hematological. Recently, the Australasian Gastro-Intestinal Trials Group [22] presented the results of a phase II study in which patients with esophago-gastric cancer were randomly assigned to weekly docetaxel (30 mg/m^2 on days 1 and 8, every 3 weeks) plus CDDP and 5-FU (wTCF) or capecitabine (wTX). The wTCF regimen achieved a response rate of 47%. Grade 3–4 neutropenia was observed in 10% of the patients and febrile neutropenia in 6% of the patients. The other most significant common grade 3–4 adverse events were diarrhea in 22% of the patients; and stomatitis, anorexia, and fatigue in 18% of the patients, each. The triple combination of docetaxel, cisplatin, and 5-FU offers an alternative option to other combinations and could be promising for patients with locally advanced disease, a situation in which regimens with high response rates are required.

In other situations, such as metastatic disease, when at best the main aim is palliation, treatment with a good safety profile is highly recommended in order to preserve quality of life. Considering that more than half of the patients with metastatic disease do not respond to chemotherapy and about 20–30% progress during treatment, it could be important to prevent the occurrence of unnecessary severe toxicity in these patients. Sequential chemotherapy may help to select the population of patients who may further respond to non-cross-resistant agents, thereby restricting the toxicity of a third drug, in this case docetaxel, reserving its use only for those showing a clinically fair course of disease.

In conclusion, the sequential PLF-docetaxel chemotherapy used in the present study offers encouraging efficacy and a favorable toxicity profile compared with the concomitant administration of CDDP, 5-FU, and docetaxel. However, given the non-randomized nature of the study, we cannot conclude that our regimen is safer and more active than the previous three-drug combinations. Sequential PLF-docetaxel could be worth pursuing in patients with metastatic gastric cancer necessitating palliative treatment, and we would consider the development of this sequential regimen in the population of elderly patients.

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Conflict of interest The authors declare no conflict of interest.

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