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ORIGINAL REPORT

Weekly Infusional High-Dose Fluorouracil (HD-FU), HD-FU Plus Folinic Acid (HD-FU/FA), or HD-FU/FA Plus Biweekly Cisplatin in Advanced Gastric Cancer: Randomized Phase II Trial 40953 of the European Organisation for Research and Treatment of Cancer Gastrointestinal Group and the Arbeitsgemeinschaft Internistische Onkologie

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ABSTRACT

Purpose
This multicentric, randomized, two-stage phase II trial evaluated three simplified weekly infusional regimens of fluorouracil (FU) or FU plus folinic acid (FA) and cisplatin (Cis) with the aim to select a regimen for future phase III trials.

Patients and Methods
A total of 145 patients with advanced gastric cancer where randomly assigned to weekly FU 3,000 mg/m^2/24 hours (HD-FU), FU 2,600 mg/m^2/24 hours plus *dl*-FA 500 mg/m^2 or *l*-FA 250 mg/m^2 (HD-FU/FA), or FU 2000 mg/m^2/24 hours plus FA plus biweekly Cis 50 mg/m^2, each administered for 6 weeks with a 1-week rest. The primary end point was the response rate.

Results
Confirmed responses were observed in 6.1% (two of 33) of the eligible patients treated with HD-FU, in 25% (12 of 48, including one complete remission [CR]) with HD-FU/FA, and in 45.7% (21 of 46, including four CRs) with HD-FU/FA/Cis. The HD-FU arm was closed after stage 1 because the required minimum number of responses was not met. The median progression-free survival of all patients in the HD-FU, HD-FU/FA, and HD-FU/FA/Cis arm was 1.9, 4.0, and 6.1 months, respectively. The median overall survival was 7.1, 8.9, and 9.7 months, and the survival rate at 1 year was 24.3%, 30.3%, and 45.3%, respectively. Grade 4 toxicities were rare. The most relevant grade 3/4 toxicities were neutropenia in 1.9%, 5.4%, and 19.6%, and diarrhea in 2.7%, 1.9%, and 3.9% of the cycles in the HD-FU, HD-FU/FA, and HD-/FU/Cis arms, respectively.

Conclusion
Weekly infusional FU/FA plus biweekly Cis is effective and safe in patients with gastric cancer.

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INTRODUCTION

Adenocarcinoma of the stomach is a leading cause of cancer-related deaths worldwide. Advances in surgical technology led to an increase in R0 resections and to decreased perioperative mortality. Nevertheless, more than 80% of the patients still die as a result of their disease, either because they have an advanced tumor at the time of diagnosis or because of incurable recurrences after resection.[1] Perioperative chemotherapy improves the results of surgery alone,[2] and palliative chemotherapy has the potential to ameliorate symptoms or prolong survival in metastatic disease. However, the benefit from current treatment options is limited and clearly there is a need for other active and well-tolerated regimens.

Several randomized trials demonstrated that fluorouracil (FU) -based chemotherapy significantly improves overall survival (OS) and quality of life in patients with metastatic disease.[3-5] The activity of FU may be enhanced further by prolonged infusion or by modulation with folinic acid (FA), as shown by the European Organisation for Research and Treatment of Cancer (EORTC) and others in

colorectal cancer.[6,7] In addition, because infusional FU is less myelotoxic than the bolus application,[6] this type of administration enables the combination with cisplatin (Cis) or other myelosuppressive drugs. In fact, the regimen of continuous infusion of FU in combination with intermittent epirubicin/Cis (ECF) is currently considered as a standard regimen because it increases median survival compared with FU, doxorubicin, methotrexate (FAMTX).[8,9] This trial was designed to screen the activity of three different weekly infusional FU regimens, either with modulation by FA or in combination with Cis. None of the three regimens require protracted infusion and thus may be less cumbersome than ECF.

In a dose-finding study with FU as single agent, a weekly infusion of 3,000 mg/m^2/24 hours was recommended. Preliminary results in six patients with advanced gastric cancer yielded two objective responses, indicating activity of this simple regimen (Wilke et al, unpublished data). If FU is modulated by FA, the recommended dose levels are 500 mg/m^2 of FA and 2,600 mg/m^2 FU weekly.[10,11] This regimen was investigated in 17 patients after failure of first-line chemotherapy, which included FU in 14 of the patients (etoposide, doxorubicin, Cis; FAMTX; etoposide, FA, and FU; and so on). Three patients with partial remission (response rate [RR] of 18%; 95% CI, 0% to 38%) and seven patients with stable diseases (41%; 95% CI, 17% to 64%) were observed in this group with an unfavorable prognosis, and the median survival time was 5 months.[12] FU/FA and biweekly Cis was evaluated in a small German multicenter trial.[13] Here, the recommended dose of FU was 2,000 mg/m^2 and the recommended dose of Cis was 50 mg/m^2. The overall RR in 50 patients was 66%. Outpatient treatment was well tolerated using implantable venous access systems and portable pumps. Median time to progression was 8 months and the median survival time was 11 months. Thus, all three regimens are active in gastric cancer, with no clear advantage of one of them.

The EORTC GI Group therefore initiated this randomized phase II trial to define a regimen for comparison against a standard arm in a future phase III study. The main goal was to evaluate whether simplified, moderately toxic, and economically favorable FU regimens would be of interest. Initially, the trial was designed as a four-arm study using the three HD-FU–containing regimens (HD-FU, HD-FU/FA, HD-FU/FA/Cis) and FAMTX as a well-established and widely used internal control. The trial was amended and the FAMTX arm was closed after seven patients had been included because it became obvious after the publication of one large phase III trial that FAMTX is inferior to ECF.[9] These results were supported by our own experience from a randomized phase III trial (EORTC 40902), in which FAMTX had only modest activity (response rates of 12%) with relevant toxicity (five treatment-related deaths in 133 patients).[14] In this article, we present the final report of the EORTC trial 40953 in the 145 patients assigned to the three infusional FU-based regimens.

PATIENTS AND METHODS

This was an open, prospective, randomized, multicenter, two-stage, phase II trial. Patients were centrally randomly assigned at the EORTC Data Center (Brussels, Belgium) and stratified according to institution, WHO performance status (0 or 1 *v* 2) and stage of disease (locally advanced *v* metastatic) using the minimization technique.

Patient Population

The eligibility criteria were as follows: age ≤ 75 years with histologically confirmed, locally advanced, unresectable, and/or metastatic gastric cancer; at least one bidimensionally measurable target lesion; no prior chemotherapy or radiotherapy; WHO performance status ≤ 2; WBC ≥ 3,500/μL; platelets ≥ 100,000/μL; serum bilirubin ≤ 30 μmol/L; serum creatinine within normal limits; no unstable cardiac disease; no active infection; no signs of CNS metastases or mental disorders; no second malignancies except carcinoma in situ of the cervix uteri or nonmelanomatous skin cancer; and written informed consent according to national and local regulations.

Treatment

The HD-FU regimen consisted of a weekly intravenous (IV) infusion of FU 3,000 mg/m^2/24 hours. HD-FU/FA consisted of *dl*-FA 500 mg/m^2/2 hours or *l*-FA 250 mg/m^2/2 hours, immediately followed by FU 2,600 mg/m^2/24 hours, each by IV infusion. The HD-FU/FA/Cis regimen consisted of Cis 50 mg/m^2/1 hour IV infusion with hyperhydration on days 1, 15, and 29, and *dl*-FA 500 mg/m^2/2 hours or *l*-FA 250 mg/m^2/2 hours, followed by FU 2,000 mg/m^2/24 hours IV infusion on days 1, 8, 15, 22, 29, and 36. One cycle of chemotherapy always included six weekly administrations followed by 1 week of rest.

Chemotherapy was administered for four cycles unless there was documented disease progression, unacceptable toxicity, or patient refusal. Cisplatin was only administered during the first three cycles. Chemotherapy was delayed for at least one week in case of any diarrhea or mucositis at the day of planned treatment, or if granulocytes were less than 1,200/μL, platelets were less than 75,000/μL or hand-foot syndrome more than grade 2 occurred. FU was reduced by 20% if maximum diarrhea/mucositis exceeded grade 2. FU and Cis were reduced by 20% if granulopenia or thrombocytopenia was grade 4. Cisplatin was discontinued if neurotoxicity more than grade 1 or nephrotoxicity more than grade 2 occurred.

Pretreatment Evaluation and Follow-Up

Baseline evaluation included a complete medical history and physical examination, blood cell count, electrolyte analysis, liver and renal function tests, ECG, chest x-ray, abdominal ultrasound, and computed tomography scan of the target lesion(s). Before each weekly treatment, blood cell count and toxicity were assessed. Before each new cycle and at the end of treatment, physical examination, ECG, and measurement of disease were performed. In patients who had not experienced disease progression at the end of treatment, disease continued to be measured every 8 weeks until progression. Thereafter, patients were observed once every 3 months.

Toxicity and Response Evaluation

Toxicity was evaluated and graded according to the Common Toxicity Criteria defined by the US National Cancer Institute and extended by the National Cancer Institute of Canada. Tumor response was evaluated according to the WHO criteria. Only bidimensionally measurable lesions (skin, lymph node, liver, or soft tissue metastases > 2.5 cm in their largest diameter, or lung metastases > 2 cm in their largest diameter and not adjacent to any structure) were considered eligible as target lesions. Primary tumors were considered assessable but nonmeasurable. Responses had to be confirmed after 4 weeks. The data files and computed tomography scans were reviewed centrally by the study coordinators.

Statistical Design

The primary end point was the response rate. Toxicity was a secondary end point. The trial was designed using a Simon two-stage minimax design for each arm.[15] With a type I error of 0.10 to conclude the activity of an unattractive regimen (RR < 20%) and a type II error of 0.05 of rejecting an active regimen (RR > 40%), 21 patients were required in each arm for the first stage. If the number of responses during the first stage were less than four, then this arm would be closed. Otherwise, 24 additional patients would be accrued for that arm, up to 45 patients. If the number of responses was at least 13 (RR > 29%), the regimen would be considered sufficiently active for additional investigation.

RRs were evaluated for all patients with at least one measurable lesion. Although not originally foreseen in the protocol, progression-free survival (PFS) and median survival curves were also calculated using the method of Kaplan and Meier. Overall survival (OS) was defined as the time interval between the date of random assignment and the date of death. PFS was defined

as the time interval between the date of random assignment and the date of disease progression or death, whichever occurred first. Response duration was calculated as the time interval between random assignment and date of progression (for responders only). If the event was not observed at the time of last information, the patient was censored at that time point. All eligible patients who started treatment were considered assessable for response. All patients who started treatment were considered assessable for toxicity. OS and PFS analyses included all entered patients.

RESULTS

From January 1996 to August 1999, 145 patients were enrolled by 17 institutions (37 patients to HD-FU, 54 patients to HD-FU/FA, and 54 patients to HD-FU/FA/Cis). The median number of patients treated per institution was nine (range, one to 25 patients); seven centers entered fewer than five patients.

After stage 1 of the trial, the HD-FU arm was closed because only two responses had been observed, which did not meet the required minimum of at least four responses in the first 21 eligible patients. Total number of patients in this arm was 37 (33 eligible) because inclusion was not interrupted before interim analysis. Of the 145 patients entered, four did not start protocol treatment (one in the HD-FU/FA arm and three in the HD-FU/FA/Cis arm). Treatment and toxicity information was thus available for 141 patients (37 patients for HD-FU, 53 patients for HD-FU/FA arm, and 51 patients for HD-FU/FA/Cis). Thirty-eight patients in each arm received *dl*-FA; the remainder received the *l*-form. The patient characteristics for those who started treatment are listed in Table 1. All patients were white. Age, sex, performance status, histologic subtype, and location of the primary were well balanced, although there was a trend toward more patients having metastatic disease in the HD-FU/FA arm. Half of the patients had had prior surgery.

Eleven patients were considered ineligible (two with HD-FU, four with HD-FU/FA, and five with HD-FU/FA/Cis), mainly because of nonmeasurable disease (two in each arm) and because of incomplete files rendered the eligibility verification impossible (two with HD-FU, one with HD-FU/FA, three with HD-FU/FA/Cis; Fig 1). In total, 127 eligible patients started treatment and were thus assessable for response (33 patients with HD-FU, 48 patients with HD-FU/FA, 46 patients with HD-FU/FA/Cis). The median follow-up was 3.75 years.

Safety and Dose-Intensity

In the 141 patients who started chemotherapy, the total number of cycles administered was 67 (median, one; range, one to four) for HD-FU, 144 (median, three; range, one to seven) for HD-FU/FA, and 143 (median, three; range, one ot seven) for HD-FU/FA/Cis. Forty-five patients (31.0%) received one cycle of chemotherapy (20 [54.1%] in HD-FU, 15 [28.3%] in HD-FU/FA, 10 [19.6%] in HD-FU/FA/Cis), 31 patients (21.4%) received two cycles (nine [24.3%] in HD-FU, 11 [20.8%] in HD-FU/FA, 11 [21.6%] in HD-FU/FA/Cis), 26 patients (17.9%) received three cycles (three [8.1%] in HD-FU, 11 [20.8%] in HD-FU/FA, 12 [23.5%] in HD-FU/FA/Cis), and 32 patients (22.1%) completed the four cycles of treatment (20 [54.1%] in HD-FU, 15 [28.3%] in HD-FU/FA, 10 [19.6%] in HD-FU/FA/Cis). Seven patients (4.8%) received more than the four predefined cycles of treatment, with a maximum of seven cycles.

The toxicities are listed in Table 2. Severe (grade 3/4) toxicity was rare in all three arms. Grade 3 neutropenia was more frequent with HD-FU/FA/Cis and there was somewhat more frequent nausea and vomiting in this arm. The incidence of alopecia was moderate. Grade 3 neurotoxicity was observed in four patients (7.8%) treated with Cis. There was one treatment-related death in the HD-FU/FA/Cis arm as a result of a bilateral pneumonia probably caused by aspiration.

Toxicity-related dose-reductions and dose delays were reported in seven patients (18.9%) and seven patients (18.9%) in the HD-FU arm, in 19 patients (35.8%) and eight patients (15.1%) in the HD-FU/FA arm, and in 22 patients (43.1%) and 17 patients (33.3%) in the

Table 1. Baseline Characteristics (patients who started treatment)

Characteristic	HD-FU (n = 37)		HD-FU/FA (n = 53)		HD-FU/FA/Cis (n = 51)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
Age, years						
Median	58		65		62	
Range	33-73		31-74		39-75	
Sex						
Male	30	81.1	42	79.2	40	78.4
WHO PS						
0-1	34	91.9	49	92.5	49	96.1
2	3	8.1	4	7.5	2	3.9
Tumor characteristic						
Locally advanced	8	21.6	6	11.3	6	11.8
Metastatic	29	78.4	47	88.7	45	88.2
Upper third tumors	15	40.5	24	45.2	20	39.2
Intestinal type	20	54.1	27	50.9	22	43.1
Diffuse type	6	16	10	18.9	13	25.5
Subtype not classified	11	29.7	16	30.2	15	29.4
Prior surgery	22	59.5	26	49.1	23	45.1
Measurable disease	36	97.3	53	100	50	98.0

Abbreviations: HD-FU, high-dose fluorouracil; FA, folinic acid; Cis, cisplatin; PS, performance status.

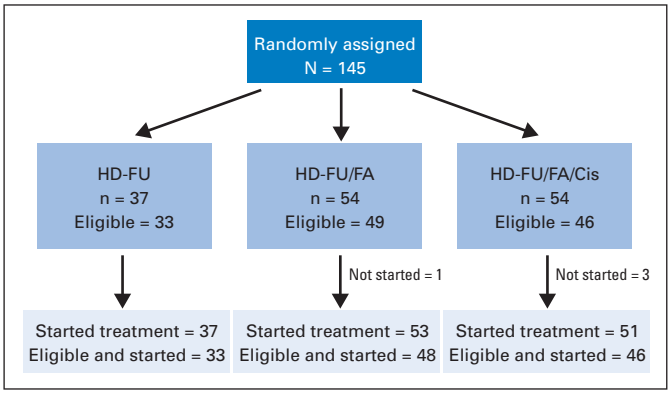

Fig 1. Consolidated Standards of Reporting Trials chart. HD-FU, high-dose fluorouracil; FA, folinic acid; Cis, cisplatin.

HD-FU/FA/Cis arm, respectively. This resulted in a median relative FU dose-intensity of 89.7% with HD-FU, 84.3% with HD-FU/FA, and 86.8% with HD-FU/FA/Cis. The median relative dose-intensity for Cis in the HD-FU/FA/Cis arm was 77.8%.

Response and Response Duration

One-hundred twenty-seven patients had measurable lesions, started treatment, and are included in the analysis of response (Table 3). Confirmed responses were observed in two patients (no complete remissions [CRs], two partial remissions [PRs]) in the HD-FU arm, in 12 patients (one CR, 11 PRs) in the HD-FU/FA arm, and in 21 patients (four CRs, 17 PRs) in the HD-FU/FA/Cis arm. Inclusion in the HD-FU arm was stopped after stage 1 of the trial. Of the two regimens that continued to stage 2, only HD-FU/FA/Cis passes the statistical requirement of at least 14 responses in 45 patients. The response rates were 6.1% (95% CI, 0.0% to 14.4%) for HD-FU, 25.0% (95% CI, 12.5% to 27.5%) for HD-FU/FA, and 45.7% (95% CI, 31.0% to 60.4%) for HD-FU/FA/Cis. HD-FU/FA/Cis was also associated with the lowest rate of progressive disease (13.0%), compared with 57.6% with HD-FU and 33.3% with HD-FU/FA. The duration of response was similar for HD-FU/FA (6.8 months, 95% CI, 5.7 to 9.7 months) and for HD-FU/FA/Cis (6.7 months, 95% CI, 6.0 to 8.9 months).

PFS and OS

The median PFS and the PFS at 1 year, respectively, were 1.9 months (95% CI, 1.6 to 3.3 months) and 8.1% (95% CI, 0% to 16.9%) for HD-FU, 4.0 months (95% CI, 3.1 to 5.5) and 5.6% (95% CI, 0.0% to 11.7%) for HD-FU/FA, and 6.1 months (95% CI, 5.0 to 7.3 months) and 15.1% (95% CI, 5.5% to 24.7%) for HD-FU/FA/Cis.

The median OS and survival rates at 1 year were 7.1 months (95% CI, 6.0 to 8.6 months) and 24.3% (95% CI, 10.5% to 38.2%) for HD-FU, 8.9 months (95% CI, 7.1 to 11.9 months) and 30.3% (95% CI, 17.9% to 42.7%) for HD-FU/FA, and 9.7 months (95% CI, 7.6 to 17.4 months) and 45.3% (95% CI, 31.9% to 58.7%) for HD-FU/FA/Cis, respectively. Twenty-five percent of the patients treated with HD-FU/FA/Cis were alive after 2 years (95% CI, 13.3% to 37.3%; Fig 2).

DISCUSSION

Gastric cancer is considered to be chemotherapy sensitive. FU-based chemotherapy doubles the median survival time in randomized trials when compared with best supportive care.[3-5] Older phase II trials with combinations such as etoposide, doxorubicin, and Cis; etoposide, FA, and FU; FAMTX; and 5-day Cis/FU regimens achieved objective response rates of 40% to 50%. Unfortunately, these results could not be confirmed in randomized studies. When compared with FU, doxorubicin, and mitomycin or modifications of FU, doxorubicin, and mitomycin, the response rates rarely exceeded 25% and the median survival times were approximately 7 months.[14,16] Moreover, some of these combinations were toxic or could only be administered in specialized centers. Additional developments focused on alternative application schedules of FU in combination with other drugs, such as Cis. Preclinical and clinical evidence in colorectal cancer demonstrated that weekly or biweekly 24- to 48-hour infusion of increased doses of FU or continuous infusion over months could increase its efficacy or overcome FU resistance with a favorable toxicity profile,

Table 2. Grade 3/4 Hematologic and Nonhematologic Toxicities in Patients Who Started Treatment (all cycles)

	HD-FU (n = 37)				HD-FU/FA (n = 53)				HD-FU/FA/Cis (n = 51)			
	Grade 3		Grade 4		Grade 3		Grade 4		Grade 3		Grade 4	
Toxicity	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
WBC	1	2.7							4	7.8		
Granulocytes	1	2.7	1	2.7	1	1.9			10	19.6		
Platelets									1	2.0		
Hemoglobin	2	5.4			1	1.9	1	1.9	3	5.9	2	3.9
Fever without infection							1	1.9				
Infection	1	2.7									3	5.9
Nausea	4	10.8			2	3.8			7	13.7		
Vomiting	2	5.4			1	1.9	1	1.9	4	7.8		
Stomatitis									2	3.9		
Diarrhea	1	2.7			4	7.5	1	1.9			2	3.9
Neurotoxicity									4	7.8		
Lethargy	1	2.7			1	1.9			1	2.0		
Alopecia (grade 2-3)	2	5.4	1	2.7	1	1.9	1	1.9	9	17.6		

Abbreviations: HD-FU, high-dose fluorouracil; FA, folinic acid; Cis, cisplatin.

Table 3. Response to Treatment (eligible patients who started treatment)

Response	HD-FU (n = 33)			HD-FU/FA (n = 48)			HD-FU/FA/Cis (n = 46)		
	No. of Patients	%	95% CI	No. of Patients	%	95% CI	No. of Patients	%	95% CI
Partial response	2	6.1		11	22.9		17	37.0	
Complete response	—			1	2.1		4	8.7	
Overall response	2	6.1	0 to 14.4	12	25	12.5 to 37.5	21	45.7	31 to 60.4
No change	10	30.3		18	37.5		17	37.0	
Progressive disease	19	57.6	40.6 to 74.6	16	33.3	21.1 to 47.3	6	13.0	3.1 to 22.9

Abbreviations: HD-FU, high-dose fluorouracil; FA, folinic acid; Cis, cisplatin.

probably because long-term exposure preferably results in inhibition of thymidylate synthase and thus inhibition of DNA synthesis, whereas the FU bolus application instead promotes incorporation into nascent RNA.[6] This effect may be enhanced further by the addition of reduced folates, which are necessary for ternary complex formation of 5-fluorodesoxymonophosphate with thymidylate synthase. Because the protracted infusion is less myelotoxic, combinations of FU with other active but myelosuppressive drugs became feasible.

ECF, the current standard in the treatment of advanced gastric cancer, is based on the continuous infusion of FU for months in combination with IV epirubicin and Cis. ECF increased response rates and significantly improved median survival times as compared with FAMTX,[8] and was equivalent to MCF, with an overall response rate of 42.4% and median survival time of 9.4 months.[17]

The results of the present multicentric, randomized, phase II study suggest that another infusion scheme of FU, the weekly infusion of FU during 24 hours, is active when combined with either FA or with FA and Cis, with response rates of 25% and 46%, including complete responses in one of 48 and in four of 49 patients, respectively. Although this is a phase II study and a formal comparison between the three treatment arms was not carried out, the activity results seem to favor the HD-FU/FA/Cis combination as compared with HD-FU/FA, and also with regard to HD-FU, where only two partial responses were observed in 33 patients (6.1%). A trend to longer median survival with HD-FU/FA/Cis is also suggested as compared with HD-FU/FA or HD-FU (9.7 *v* 8.9 *v* 7.1 months, respectively). Overall, the activity of HD-FU/FA/Cis in this study is in the same range than that observed with ECF, with an apparently similar median survival.

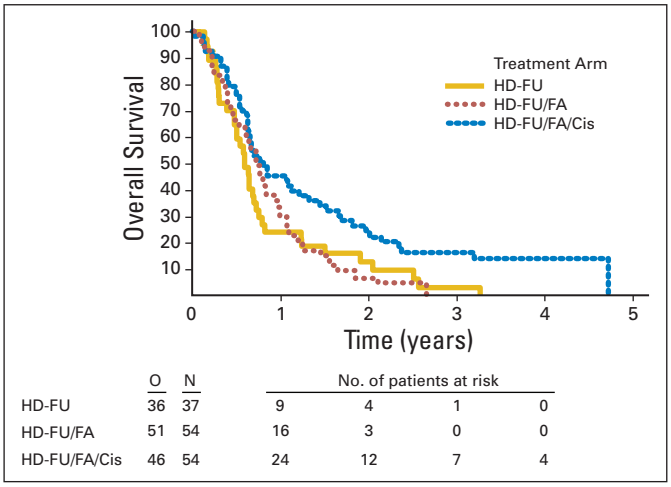

Fig 2. Overall survival. O, number of events; N, number of patients; HD-FU, high-dose fluorouracil; FA, folinic acid; Cis, cisplatin.

Infusional FU is less toxic than FU administered as a bolus application.[6] In our hands, toxicity of either HD-FU/FA or HD-FU/FA/Cis was moderate, with less than 2% with grade 4 myelotoxicity in the HD-FU/FA arm and less than 4% in the HD-FU/FA/Cis arm. We observed three episodes of serious infections in 143 cycles in the 51 patients in the HD-FU/FA/Cis arm, with one death as a result of toxicity after aspiration of gastric contents and resulting pneumonia. With HD-FU/FA/Cis, dose reductions were necessary in 43% of the patients and dose delays were reported in 33%. Again, these results are in the same range than those reported with ECF (41% dose reductions and 32% dose delays, respectively),[9] and compare favorably with FAMTX, for which 56% dose reductions and dose delays were reported.[14]

In summary, our results suggest that the addition of FA and Cis to FU increases its activity in gastric cancer. This has not been shown in this tumor type before. In addition, the increase of activity was not associated with a substantial increase in adverse effects. Moreover, activity and survival results of HD-FU/FA/Cis seem to be in the same range as those achieved with ECF,[9] with other infusional FU/Cis regimens,[18] or with novel combinations such as FU plus irinotecan,[19] oxaliplatin,[20] docetaxel,[21] or docetaxel/Cis.[22,23]

We conclude that HD-FU/FA/Cis is safe and active in gastric carcinoma. This simple regimen might be a convenient alternative for patients who cannot or do not want to be treated with more aggressive combination chemotherapy or with protracted infusion of FU over months. Because of its simplicity and moderate toxicity, it might be well suited as a perioperative regimen. Confirmation is necessary from phase III trials.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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