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Randomized phase III study comparing irinotecan combined with 5-fluorouracil and folinic acid to cisplatin combined with 5-fluorouracil in chemotherapy naive patients with advanced adenocarcinoma of the stomach or esophagogastric junction

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Background: We aimed to establish the superiority (or noninferiority if superiority was not achieved) in terms of time to progression (TTP) of irinotecan/5-fluorouracil (IF) over cisplatin/5-fluorouracil (CF) in chemonaive patients with adenocarcinoma of the stomach/esophagogastric junction.

Patients and methods: Patients received either IF: i.v. irinotecan 80 mg/m^2 30 min, folinic acid 500 mg/m^2 2 h, 5-fluorouracil (5-FU) 2000 mg/m^2 22 h, for 6/7 weeks or CF: cisplatin 100 mg/m^2 1–3 h, with 5-FU 1000 mg/m^2/day 24 h, days 1–5, every 4 weeks.

Results: In all, 333 patients were randomized and treated (IF 170, CF 163). Patient characteristics were balanced except more IF patients had Karnofsky performance status 100%. TTP for IF was 5.0 months [95% confidence interval (CI) 3.8–5.8] and 4.2 months (95% CI 3.7–5.5) for CF ($P = 0.088$). Overall survival (OS) was 9.0 versus 8.7 months, response rate 31.8% versus 25.8%, time to treatment failure (TTF) 4.0 versus 3.4 months for IF and CF, respectively. The difference in TTF was statistically significant ($P = 0.018$). IF was better in terms of toxic deaths (0.6% versus 3%), discontinuation for toxicity (10.0% versus 21.5%), severe neutropenia, thrombocytopenia and stomatitis, but not diarrhea.

Conclusion: IF did not yield a significant TTP or OS superiority over CF, and the results of noninferiority of IF were borderline. However, IF may provide a viable, platinum-free front-line treatment alternative for metastatic gastric cancer.

Key words: cisplatin, 5-fluorouracil, gastric, irinotecan, phase III

introduction

Cancer of the stomach is the second leading cause of cancer deaths worldwide, despite declining incidence and mortality in developed countries [1]. Patients with advanced disease, represent over two-thirds of newly diagnosed cases and 40% of those having undergone complete resection [2, 3], have a poor prognosis. Median survival, 3– months under best supportive care, is substantially prolonged by combination chemotherapy [4].

Combination chemotherapy has become standard in this indication due to higher response rates than single agents [4]. However, only one of seven phase III comparisons of single agent versus combination therapies found a survival advantage for the latter [5, 6]. In the absence of an established reference combination regimen or standard of care, the basis of the current standard combination therapy selection for untreated advanced gastric patients may seem controversial. However, antitumour activity has been demonstrated in phase II and III studies for both cisplatin/5-fluorouracil (CF) [7–11] and epirubicin cisplatin/5-fluorouracil (ECF) [12–14], and while a survival advantage was demonstrated for ECF [epirubicin, cisplatin and continuous infusion 5-flourouracil (5-FU)] over the previous standard FAMTX (doxorubicin, high-dose methotrexate and bolus 5-FU) [15], concerns remain over the role of epirubicin in this combination [16]. Cisplatin combined with infusional 5-FU has been used as standard first-line

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therapy, and although a survival advantage over single-agent 5-FU or FAMTX or docetaxel cisplatin/5-fluorouracil (DCF) was not shown in phase III trials [6, 8, 9], it was recommended as an acceptable combination for those patients for whom three-drug regimens are considered unacceptable [4]. The modest survival rates and relatively low response rates with a short median duration achieved by current treatment regimens have spurred on the continued investigation of new active agents, notably combinations involving both taxanes (paclitaxel, docetaxel), oral 5-FU prodrugs (capecitabine, S-1) and irinotecan.

Phase II trials of single-agent irinotecan administered every 2, 3 or 4 weeks in previously untreated gastric cancer reported response rates of 15%–23% [17–19]. Combinations of irinotecan with either 5-FU or cisplatin have been extensively explored in single-arm and randomized phase II trials. Irinotecan combinations based on the AIO weekly infusional 5-FU and folinic acid (FA) regimen have reported response rates of 42%–43%, progression-free survival (PFS) of 4.3–6.5 months and OS of 10.7–10.8 months [20, 21]. Recently, biweekly irinotecan has been combined with the LV5FU2 regimen (biweekly 2-day bolus and infusional 5-FU), yielding noteworthy results in terms of response rate (40%), PFS (6.9 months) and overall survival (OS; 11.3 months) [22]. Irinotecan has also been administered with cisplatin every 1, 2, 3 or 4 weeks, attaining response rates of 32%–59% and median OS ranging from 6.9 to 10.6 months [21, 23–26].

On the basis of the promising activity observed in phase II trials, we undertook a phase II–III trial in previously untreated advanced gastric adenocarcinoma patients. In the phase II part, irinotecan combined with the infusional 5-FU AIO regimen [irinotecan/5-fluorouracil (IF)] was selected over irinotecan combined with cisplatin on the basis of the risk/benefit ratio [21]. At the time, the IF regimen was considered to be the most active irinotecan/5-FU/FA combination available. We report here the phase III part of the trial.

patients and methods

patient eligibility

Patients were to have histologically confirmed adenocarcinoma (including diffuse type, intestinal type and linitis) of the stomach or esophagogastric junction, with measurable or evaluable metastatic disease (cytology or histology was mandatory if a single metastatic lesion was the only manifestation of disease) or locally recurrent disease with one or more measurable lymph node; be 18–75 years old; have a Karnofsky performance status (KPS) >70%; hemoglobin ≥10 g/l, absolute neutrophil count (ANC) $\geq 2.0 \times 10^9$/l, platelet $\geq 100 \times 10^9$/l, serum creatinine ≤1.25 × upper normal limit (UNL) or ≤120 μmol/l (if creatinine >1 × UNL or >100 μmol/l, creatinine clearance was to be ≥60 ml/min), serum magnesium within normal values; total bilirubin ≤1.5 × UNL, aspartate and alanine aminotransferase ≤2.5 × UNL, alkaline phosphatase (AP) ≤5 × UNL (except with bone metastasis without liver disease) and have finished prior radiotherapy and surgery 6 and 3 weeks, respectively, before randomization. Previous adjuvant or neo-adjuvant chemotherapy was allowed if completed s12 months before first relapse. Patients with reproductive potential were to use adequate contraception.

Patients were excluded in the case of resectable locally advanced disease; pregnancy or lactation; prior palliative chemotherapy or treatment with camptothecin; cumulative dose of prior cisplatin >300 mg/m^2; bowel obstruction or subobstruction; uncontrolled hypercalcemia >12 mg/100 ml; history of inflammatory enteropathy, extensive intestinal resection or CNS metastasis; symptomatic peripheral neuropathy ≥grade 2; active disseminated intravascular coagulation; history of neoplasm other than gastric carcinoma, except for curatively-treated nonmelanoma skin cancer or *in situ* carcinoma of the cervix; any other severe condition during the 6 months before study entry; history of significant neurologic or psychiatric disorders; other serious underlying medical conditions and contraindications to atropine. The protocol was approved by national or local ethics committees as appropriate, and all patients provided written informed consent.

study treatments

Patients randomized to the IF arm received irinotecan 80 mg/m^2 as a 30-min i.v. infusion, followed by FA 500 mg/m^2 as a 2-h i.v. infusion, immediately followed by 5-FU 2000 mg/m^2 as a 22-h i.v. infusion, day 1 every week for 6 weeks followed by a 1-week rest. In the CF, patients received cisplatin 100 mg/m^2 as a 1- to 3-h i.v. infusion, day 1, followed by 5-FU 1000 mg/m^2/day as a 24-h i.v. infusion, days 1–5, every 4 weeks. Treatment was administered until disease progression, unacceptable toxicity or consent withdrawal.

All patients received antiemetic prophylaxis with i.v. ondansetron and dexamethasone. CF patients also received hyperhydration and metoclopramide and dexamethasone p.o. for 2–3 days after infusion. Granulocyte colony-stimulating factors (day 4 until recovery to ANC 1.0×10^9/l) were recommended for febrile neutropenia, neutropenic infection or neutropenia grades 3–4 >7 days. Atropine was administered for grades 2–4 acute cholinergic syndrome and loperamide for delayed diarrhea [21]. Treatment cycles could be delayed by up to 2 weeks for recovery from neutropenia ≥grade 2 or any thrombocytopenia or diarrhea. Dose reductions for one or both study medications were planned in the event of severe toxic effects [21]. Patients discontinued if they failed to recover after 2 weeks delay, needed more than two dose reductions, had grade 4 stomatitis or grades 3–4 peripheral neurotoxicity/ototoxicity.

evaluations

Baseline evaluations included medical history, physical exam, blood chemistry, complete blood count with differential, neurological, disease and quality-of-life (QoL) assessments. During treatment, adverse events (AEs) and hematological parameters were assessed at each visit, while blood chemistry and physical exam were assessed before each new cycle. Disease assessments, using the same methods as at baseline, and QoL assessments were to be undertaken every 8 weeks. During follow-up, patients were to undergo disease and QoL assessments every 8 weeks until disease progression was observed and then every 3 months until death.

Disease response was evaluated according to World Health Organization criteria [27]. An External Radiological Review Committee (ERRC), blinded to treatment arm, reviewed all disease assessments and determined evaluability for response and date of progression. AEs and laboratory abnormalities were graded according to the National Cancer Institute of Canada—Clinical Trials Group Expanded Common Toxicity Criteria. QoL was evaluated using the EORTC QLQ-C30 version 3.0 and the EQ-5D instruments.

study design and statistical methods

The primary objective of this phase III study was to detect a statistically significant increase in TTP for the IF test arm relative to the CF control arm in the full-analysis population (i.e. all treated subjects analyzed in the arm to which they were randomized). The secondary end points were response rates, duration of response, time to treatment failure (TTF) and OS. The safety analysis included all patients according to the actual treatment received.

For the primary efficacy analysis, it was assumed that TTP in the IF and CF arms would be 6 and 4 months, respectively [hazard ratio (HR) of 1.5], and that a total of 263 events, corresponding to 318 patients (159 per arm) with a 5% lost to follow-up rate, would be necessary to provide a 90% power to detect the difference in TTP at a two-sided 5% significance level using an unadjusted log-rank test.

In addition, the protocol prospectively included a noninferiority comparison in case of a nonsignificant trend ($P < 0.10$) toward superiority of TTP for the IF arm, to be combined with the superiority comparison in a closed testing procedure that preserved type I error rate [28]. The noninferiority margin was set to preserve at least 50% of the treatment effect of CF over 5-FU alone [29]. Data on such effect of CF over 5-FU had been reported in Ohtsu et al. [6]. Thus, to be considered noninferior, the lower limit of the 95% confidence interval (CI) for the Cox model HR of TTP in the control arm to the test arm was to be ≥0.93. This corresponds to the null hypothesis for the noninferiority test that the IF arm has at most a 7.5% higher progression hazard rate relative to the CF arm. For the noninferiority analysis, the SAP specified that the results in both the full-analysis and per-protocol populations were to be considered [30, 31], and a concomitant benefit had to be demonstrated on the trial secondary end points of safety, QoL and clinical benefit. The per-protocol population consisted of patients who had no major protocol deviations and who were treated with at least two cycles of CF or five infusions of IF and were assessable for response.

Randomization was carried out using a biased coin method, applying stratification according to measurable versus evaluable disease, liver involvement (yes versus no), baseline weight loss ≤5% (yes versus no), prior surgery (yes versus no) and treatment center. TTP was measured from randomization until the date of progression or death, if death occurred within 12 weeks of the last evaluable tumor assessment. Patients without progression at last contact or receiving new antitumor therapy were censored at the date of their last assessment before last contact or new therapy, respectively. TTF was from randomization to progression, death or treatment discontinuation. The cut-off for the TTP analysis was set at the date that the 263rd event was obtained. The cut-off dates for TTP, TTF and response duration were 27 September 2002 and for OS was 04 July 2003. To be assessable for disease response, patients had to receive five or more infusions (IF) or two cycles (CF) and undergo disease assessment, unless early disease progression occurred.

Time to event data were analyzed using the Kaplan–Meier method. Distributions were compared between groups with the unadjusted log-rank test and Cox proportional hazards model. Comparison of categorical data employed the χ^2 test or Fisher's exact test, as appropriate.

QoL data will be reported in detail separately. Briefly, the primary QoL parameter was time to definitive deterioration by 5% of the global health status scale of the EORTC QLQ-C30 instrument, with time to 5% deterioration of the EQ-5D instrument also analyzed. Clinical benefit was evaluated by time from randomization to definitive worsening of KPS by 10%, appetite by one category [32], and weight loss by 5%, where definitive meant that no subsequent improvement was recorded. Pain-free survival was assessed in patients with no cancer pain at baseline, calculated as the time from randomization to first occurrence of cancer pain ≥grade 1 or death.

results

From June 2000 to March 2002, 337 patients were randomized (172 IF, 165 CF, Table 1). Two patients in each arm were never treated (one due to fatal disease progression, three due to grades 3–4 AEs). Thus, the full-analysis population, defined as treated patients, analyzed in the arm to which they were randomized, consists of 333 patients (170 IF, 163 CF). The per-protocol population excluded 62 patients (18.6%) who were ineligible (12 IF, 12 CF), inevaluable for response (16 IF, 29 CF), and/or with a major protocol deviation during treatment (six IF, three CF) (Table 1). The rate of inevaluability for response was imbalanced between arms (IF 9.4% versus CF 16.8%, $P = 0.025$), largely due to the higher rate of early discontinuations for toxicity in the CF arm (see below). Three patients randomized to IF actually received CF; safety was analyzed according to actual treatment received (167 IF, 166 CF). Patient characteristics were well balanced between arms (Table 2), with the exception of a higher rate of patients with KPS 100% in the IF arm (26.5% versus 16.6%, $P = 0.028$). The median age was 59 years (range 29–77), median KPS was 90%, 19.5% of patients had the primary tumor located in the esophagogastric junction, surgery with a curative intent had been attempted in 24.9% of the population and almost all patients had metastatic disease at randomization (95.5%).

Table 1. Patient disposition

	Randomized to			
	IF		CF	
	n	%	*n*	%
Randomized	172		165	
Treated (full analysis)	170	100.0	163	100.0
Per-protocol	144	84.7	127	77.9
Excluded from per-protocol	26	15.3	36	22.1
Ineligible	12	7.1	12	7.4
Inevaluable for response	16[a]	9.4	29[a]	17.8
Early discontinuation for AE				
Related AE	2	1.2	9	5.5
Unrelated AE	6	3.5	5	3.1
Consent withdrawn	2	1.2	5	3.1
No evaluable lesion/not properly assessed	7	4.1	10	6.1
Other anticancer therapy	–		2	1.2
Major deviation during study	6[b]	3.5	3	1.8

[a]Three patients had more than one reason.
[b]Includes three patients who were treated with CF.
IF, irinotecan/5-fluorouracil; CF, cisplatin/5-fluorouracil, AE, adverse event.

treatment

At the cut-off time for analysis, 97.6% of patients had discontinued treatment. The principal reasons for discontinuations were disease progression (51.4% of patients), treatment-related AEs or deaths (15.6%) and withdrawal of consent (13.2%). These were balanced between arms, except for treatment-related AEs (10.0% IF, 21.5% CF; $P = 0.004$). Given that the majority of these discontinuations occurred within the first 2 months of treatment, this imbalance contributed significantly to the higher rate of exclusions from the CF per-protocol population. The most frequent causes of discontinuation were asthenia, diarrhea and infection in the IF arm and stomatitis, neurotoxicity and nephrotoxicity in the CF arm. Median treatment duration was 21 weeks (range 1–75

Table 2. Patient characteristics in the full-analysis population

	IF ($N = 170$)		CF ($N = 163$)	
	n	%	*n*	%
Sex				
Male	125	73.5	108	66.3
Female	45	26.5	55	33.7
Age (years)				
Median (range)	58 (29–76)		59 (28–77)	
≥65	56	32.9	44	27.0
Karnofsky performance status (%)				
100	45	26.5*	27	16.6*
90	66	38.8	68	41.7
80	58	34.1	66	40.5
70	1	0.6	2	1.2
Weight loss (%)				
≤5%	99	58.2	97	59.5
5%–10%	50	29.4	50	30.7
>10%	21	12.4	16	9.8
Hemoglobin abnormal	89	52.4	84	51.5
Alkaline phosphatase abnormal	83	48.9	71	43.6
Primary anatomic site				
Antrum	61	35.9	51	31.3
Body	53	31.2	66	40.5
Fundus	22	12.9	15	9.2
Esophagogastric junction	34	20.0	31	19.0
Histological type				
Adenocarcinoma	170	100.0	163	100.0
Diffuse	60	35.3	46	28.2
Linitis plastica	3	1.8	4	2.5
Intestinal	49	28.8	42	25.8
Not specified	58	34.1	71	43.6
Metastatic disease	163	95.9	155	95.1
Number of metastatic organs involved				
0	10[a]	5.9	8[a]	4.9
1	71	41.8	63	38.7
2	64	37.6	66	40.5
>2	25	14.7	26	16.0
Organs involved				
Stomach	101	59.4	97	59.5
Lymph nodes	103	60.6	104	63.8
Liver	85	50.0	78	47.9
Peritoneum	40	23.5	41	25.2
Lung	16	9.4	13	8.0
Pleura	18	10.6	9	5.5
Adrenal gland	12	7.1	9	5.5
Prior surgery	70	41.2	66	40.5
Curative	43	25.3	40	24.5
Palliative	27	15.9	26	16.0
Prior radiotherapy	4	2.4	2	1.2
Prior chemotherapy	9	5.3	6	3.7

[a]Metastatic disease sites detected only by invasive methods such as surgery not included, accounting for discrepancy with number of patients with metastatic disease.

*$P = 0.028$.

IF, irinotecan/5-fluorouracil; CF, cisplatin/5-fluorouracil.

weeks) in the IF arm and 17 weeks (range 4–73 weeks) in the CF arm.

efficacy

At the cut-off date for the TTP analysis, 79.0% of patients had progressed or died. In the full-analysis population, median TTP was 5.0 months (95% CI 3.8–5.8 months) in the IF arm and 4.2 months (95% CI 3.7–5.5 months) in the CF arm [log-rank $P = 0.088$, Cox HR 1.23 (95% CI 0.97–1.57), Table 3, Figures 1 and 2]. While superiority of IF treatment was not established in the primary efficacy analysis, a trend toward significance was observed ($P < 0.10$), allowing for the predefined investigation of the noninferiority hypothesis.

The noninferiority criterion of the lower limit of the 95% CI of the Cox HR being ≥0.93 was satisfied for TTP in the full-analysis population. For the per-protocol population, the median TTP was identical in the two treatment arms: IF 5.1 months (95% CI 3.9–5.8) and CF 5.1 months (95% CI 4.0–5.6), with a HR of 1.14 (95% CI 0.88–1.49). Thus, the noninferiority criterion was not satisfied for TTP in the per-protocol population. The estimated probabilities of PFS at 6 and 9 months, in the full-analysis population, were 38% and 20% for the IF arm and 31% and 12% for the CF arm, respectively.

According to the ERRC review, 31.8% of IF patients in the full-analysis population experienced a confirmed objective response compared with 25.8% ($P = 0.23$) of CF patients. The median duration of response was 7.6 months (95% CI 7.0–9.3) in the IF arm and 7.4 months (95% CI 6.4–8.3) in the CF arm, [HR = 1.45 (95% CI 0.90–2.35)].

A significantly longer median TTF ($P = 0.018$) was observed in the IF full-analysis population (4.0 months, 95% CI 3.6–4.8) than in the CF arm (3.4 months, 95% CI 2.5–3.8), with a HR of 1.43 (95% CI 1.14–1.78). This significant difference reflects the higher rate of discontinuations for toxicity in the CF arm and not surprisingly it was not observed in the per-protocol population (HR 1.22, 95% CI 0.96–1.56). At the cut-off date for survival, a total of 292 patients had died (IF: 148, 87.1%; CF: 144, 88.3%). The median OS was 9.0 months (95% CI 8.3–10.2) in the IF arm and 8.7 months (95% CI 7.8–9.8) in the CF arm [Figure 3; HR = 1.08 (95% CI 0.86–1.35)]. The estimated probabilities of survival at 12 months were 37% and 31% in the IF and CF arms, respectively.

safety

A total of six treatment-related deaths occurred, one (0.6%) in the IF arm due to neutropenic infection and five (3.0%) in the CF arm due to hematotoxicity (two patients) and febrile neutropenia, cardiac toxicity and intestinal obstruction (one patient each).

While hematotoxicity was the most frequent toxicity in both arms, the incidence of neutropenia grades 3–4 was higher with CF (51.6%) than with IF (24.8%) ($P < 0.001$). Neutropenia was accompanied by fever or infection in 16 CF patients (10.2%) and eight IF patients (4.8%; Table 4). Thrombocytopenia was more frequent in CF patients, reaching grades 3–4 in 11.7% of patients versus 1.8% of IF patients ($P = 0.0003$). Digestive toxicity was frequently observed in both arms, with a higher rate of diarrhea in the IF arm (21.6% versus 7.2% grades 3–4; $P < 0.001$), similar rates of nausea and

Table 3. Time to event efficacy results, full-analysis population

	IF			CF			Log-rank *P*	Cox hazard ratio (95% CI)
	No. of patients	% events	Median, months (95% CI)	No. of patients	% events	Median, months (95% CI)		
TTP	170	78.8	5.0 (3.8–5.8)	163	79.1	4.2 (3.7–5.5)	0.088	1.23 (0.97–1.57)
TTF	170	97.6	4.0 (3.6–4.8)	163	100.0	3.4 (2.5–3.8)	0.018	1.43 (1.14–1.78)
Response duration	54	68.5	7.6 (7.0–9.3)	42	76.2	7.4 (6.4–8.3)	0.13	1.45 (0.90–2.35)
OS	170	87.1	9.0 (8.3–10.2)	163	88.3	8.7 (7.8–9.8)	0.53	1.08 (0.86–1.35)

IF, irinotecan/5-fluorouracil; CF, cisplatin/5-fluorouracil; TTP, time to progression; TTF, time to treatment failure; OS, overall survival; CI, confidence interval.

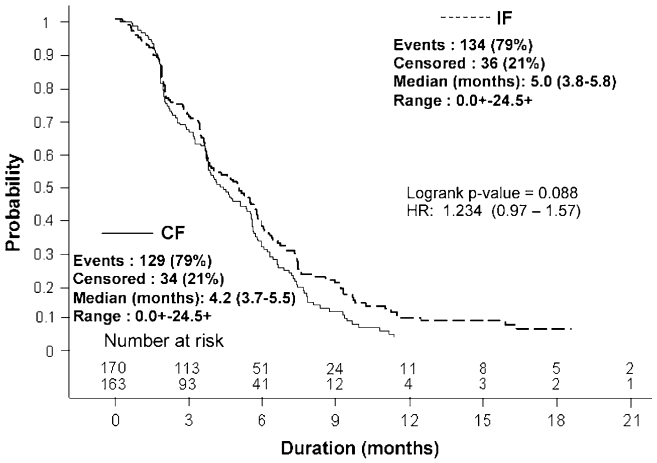

Figure 1. Time to tumor progression (full-analysis population).

vomiting and more stomatitis in the CF arm (16.9% versus 2.4%; $P < 0.001$). Neurological toxicity was more frequent in the CF arm (CR: 22.9% grades 1–4 events, IF: 5.4%). Grades 1–2 irinotecan-specific cholinergic syndrome occurred in 13.2% of patients. Cardiovascular toxicity had a similar incidence in both arms (2.4% IF versus 6.0% CF).

QoL and clinical benefit

The median time to 5% deterioration of the global health status scale of the EORTC QLQ-C30 questionnaire in the 288 assessable patients was 4.9 months (95% CI 3.7–7.0) for IF patients and 5.9 months (95% CI 4.8–7.7) for CF patients, ($P = 0.62$). It is possible that the evaluation of this parameter was affected by the 10%–20% lower rate of completed questionnaires in the CF arm after the first 8 weeks of treatment. In contrast to the QLQ-C30 results, the median time to 5% deterioration of the EQ-5D instrument in 192 assessable patients was 5.6 months (95% CI 4.1–9.3) in the IF arm and 4.1 months (95% CI 2.5–5.8) in the CF arm, ($P = 0.069$). Median times to definitive worsening of KPS, appetite and weight loss and pain-free survival, all favored IF (Figure 2), without reaching statistical significance.

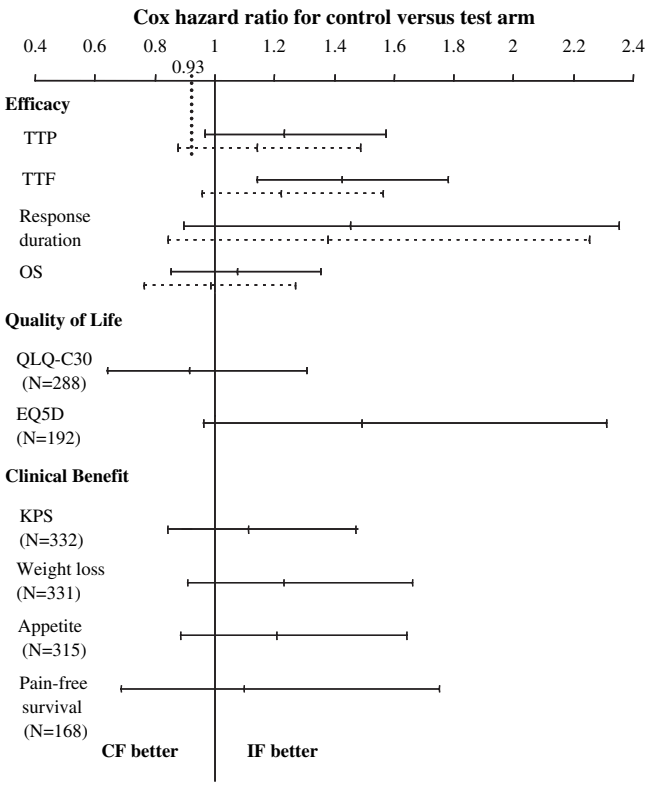

Figure 2. Cox model hazard ratios (HRs), with 95% confidence intervals (CIs), for efficacy, quality of life (QoL) and clinical benefit. Solid horizontal lines represent the full-analysis population and broken lines the per-protocol population. The vertical line at a HR of 0.93 represents the noninferiority margin on the lower limit of the 95% CI. QoL measures report time to definitive worsening of global scale by 5%. Clinical benefit measures report time to definitive worsening by 10% for Karnofsky performance status, one category for appetite and 5% for weight loss.

discussion

The predefined aim of this phase III trial was to establish the superiority in terms of TTP, or, failing that, the noninferiority of combined irinotecan/infusional 5-FU over combined cisplatin/infusional 5-FU in previously untreated metastatic or locally recurrent gastric adenocarcinoma patients. A trend toward longer TTP was observed in the IF arm. The criterion for protocol-defined noninferiority for TTP was met in the full-analysis population but not in the per-protocol population. Further analysis revealed that this discrepancy was due primarily to the fact that the proportion and characteristics of patients excluded from the per-protocol population favored the

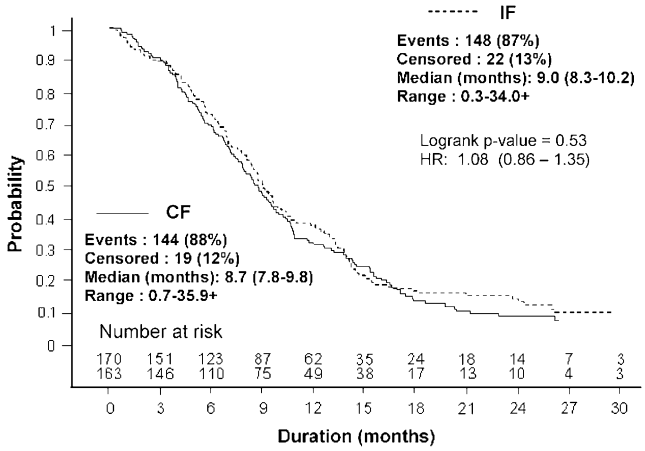

Figure 3. Overall survival (full-analysis population).

Table 4. Principal treatment-related adverse events or laboratory abnormalities, worst grade per patient, in treated patients, according to treatment received

	% of patients			
	IF ($N = 167$)		CF ($N = 166$)	
	Grades 1–4	Grades 3–4	Grades 1–4	Grades 3–4
Gastrointestinal				
Anorexia	16.2	3.0	21.1	4.2
Diarrhea	63.5	21.6	32.5	7.2
Nausea	50.9	4.8	59.0	9.0
Stomatitis	15.6	2.4	41.6	16.9
Vomiting	39.5	6.6	44.6	8.4
Hematological				
Leukopenia	64.5	16.3	76.1	24.5
Neutropenia	66.1	24.8	79.0	51.6
Febrile neutropenia/ neutropenic infection	4.8	4.8	10.2	10.2
Anemia	88.0	11.4	93.3	17.2
Thrombocytopenia	9.0	1.8	34.4	11.7
Hepatic				
AST elevated	27.2	2.5	29.0	1.3
ALT elevated	29.7	3.2	16.0	–
AP elevated	52.9	5.2	54.9	6.5
Hyperbilirubinemia	12.3	8.4	12.8	4.5
Neurological				
Altered hearing	1.2	–	10.8	1.2
Sensory	5.4	–	13.9	3.0
Skin				
Alopecia	15.6	–	21.7	–
Local toxicity	12.6	1.2	6.6	–
Other				
Asthenia	38.3	7.2	38.6	6.6
Cholinergic syndrome	13.2	–	–	–
Creatinine elevation	9.3	0.6	26.1	1.9
Fever in absence of infection	14.4	1.8	9.6	1.8
Infection	7.2	3.0	8.4	4.8

IF, irinotecan/5-fluorouracil; CF, cisplatin/5-fluorouracil.

CF arm. The number of patients excluded due to premature dropout was significantly higher in the CF arm. There was a significant correlation between exclusion from the per-protocol population and discontinuation due to AEs in the CF arm only (χ^2 P value = 0.015). As a result, the median TTP for patients excluded from the per-protocol population was lower in the CF arm (2.2 months) than for those excluded from the IF arm (3.6 months) with a HR (CF/IF) of 1.78 (95% CI 0.94–3.38, log-rank $P = 0.075$). This explains the larger increase in median TTP from the full-analysis to the per-protocol populations in the CF arm (0.9 months) than in the IF arm (0.1 months). In assessing noninferiority, the ICH guidance E9 recommends that both the full-analysis and per-protocol populations be analyzed. This is because the full analysis will usually result in a HR closer to 1 than a per-protocol analysis. However, this was not the case in this study where as shown above the removal of patients from the per-protocol analysis actually creates a bias in the per-protocol analysis in favor of CF. Thus, the full analysis gives the proper conclusion of noninferiority.

The CF arm in the present trial yielded results at the upper limit of other phase III trials of cisplatin combined with 5-FU. These studies have reported median TTPs ranging from 3.7 to 4.1 months, median OSs from 7.2 to 8.6 months and response rates from 20% to 34% [6, 8, 9], lending support to the conclusion that the consistently higher, but except for TTF not statistically significantly different, efficacy results obtained with IF in this trial (Table 3) suggest that IF is comparable to CF in this treatment setting. Indeed the evidence of a significant difference for TTF in favor of IF (4.0 versus 3.4 months; $P = 0.018$) would support this view. In addition, QoL analyses taking the continuous nature of the data into account showed a statistically significant benefit for IF over CF in terms of several QoL parameters including nausea and vomiting and physical functioning [33].

The overall results of this trial compare well with those reported for ECF in two randomized studies against FAMTX or MCF in patients with advanced esophagogastric cancer [12, 13]. In these two studies, the median OSs for ECF were 8.7 and 9.4 months as compared with 9.0 months for IF in the present study. The significance of the high failure-free survival for ECF observed in the two studies (7.0 and 7.4 months) and high response rates (42% and 45%) are difficult to compare with the results of the present study due to the higher rates of esophageal or esophagogastric disease (43%) and locally advanced disease (37%) in those studies. More recently, a trial, also in patients with advanced esophagogastric cancer, comparing four different regimens has reported an OS of 9.9 months for ECF [34]. However, it should be noted that the triplet cytotoxic combination of epirubicin, oxaliplatin, and capecitabine carried out best in this study with an OS of 11.2 months [34].

The design assumption for the current study that the median TTP for IF would be 6 months was on the basis of the 6.5-month TTP for the same regimen in the phase II part of this trial, in which a median OS of 10.7 months was also reported [21]. The difference in results obtained in the phase II and III parts, which were conducted under identical criteria, may be explained by a moderate overall worse population

prognosis in the phase III study, notably with respect to presence of liver or peritoneal metastases and baseline AP levels, both of which are prognostic factors for survival and disease response in advanced esophagogastric cancer [35].

Overall, the IF arm displayed a better safety profile than the CF arm, the latter being notably characterized by an unacceptable rate of treatment-related deaths and an elevated rate of discontinuations due to toxicity. This difference may be due, at least partially, to the closer follow-up of patients with a weekly regimen. The significantly longer TTF observed in the IF arm reflects the favorable risk/benefit ratio of the test regimen, as a result of comparable efficacy and improved tolerance. The safety and efficacy profile of CF treatment in this study is consistent with that reported for other phase III trials of this regimen, being characterized by relatively elevated rates of toxic death (1.6%–5.4%), discontinuations for toxicity (16%–21%) and grades 3–4 neutropenia (35%–57%) [6, 8, 9]. Particularly, it should be noted that the OS for CF, at 8.7 months, was similar to that for the study of Van Cutsem et al. (8.6 months) [9], whilst the OS for IF (9.0 months) was closer to that of DCF (9.2 months) in the same study [9], confirming that the results for the control arm of the present trial were representative of what could be achieved with CF. No statistically significant differences were apparent between the two treatment arms in any of the clinical benefit parameters analyzed in the present trial.

The potential benefit of irinotecan-based regimens for the treatment of advanced gastric cancer has been further explored in the last few years, especially with the availability of new targeted agents. In recent phase II studies, cetuximab in combination with IF has been reported to achieve a response rate of 55% and a disease control rate of 100% [36] and in combination with FOLFIRI a response rate of 44.1% and a disease control rate of 91.2% [37]. Irinotecan in combination with cisplatin and bevacizumab, first achieved a response rate of 61%, but this was tempered by concerns about bevacizumab-associated thromboembolic events in gastric cancer patients [38, 39].

In summary, IF did not yield a significant TTP or OS superiority over CF. In view of the fact that the noninferiority in TTP was only established for the full-analysis population and not the per-protocol population, it is important to acknowledge that some uncertainty remains as to whether noninferiority in TTP (the primary end point) is truly established. Nevertheless, the results of the current study remain relevant since IF is a platinum-free regimen that has similar efficacy to CF but with improved tolerance. As such, IF could represent a potential platinum-free alternative backbone to be combined with new targeted agents to be explored for the treatment of metastatic gastric cancer.

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