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FOLFIRI regimen as second-line treatment of metastatic gastric cancer: a retrospective analysis of efficacy, safety and prognostic factors

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Summary. *Background:* There is no standard second-line treatment for mGC. FOLFIRI has shown efficacy and safety in this setting. *Methods:* Retrospective study of patients with mGC treated with FOLFIRI as a second line. We evaluated the response rate (RR), clinical benefit rate (CBR), progression-free survival (PFS), OS and toxicity. *Results:* Sixty-six patients were included. Among evaluable patients there was an overall response rate of 20% and stable disease in 34%. Median PFS was 3 months and median OS 6 months. The number of metastatic sites was found to be a prognostic factor for PFS (HR 2.23; p=0.005) and OS (HR 2.71; p<0.001). PFS in the first line was a prognostic factor for OS (HR 1.71; p=0.045), but not for PFS (HR 1.37; p=0.226). PFS in the first line <7 months and ≥2 metastatic sites were identified as poor prognostic factors. We defined two prognostic groups, with patients in the poor prognostic group having worse PFS (HR 2.08; p=0.030) and OS (HR 2.97; p=0.003). The most common grade 3-4 toxicity was neutropenia 27%. *Conclusions:* FOLFIRI is effective and well-tolerated as a second-line treatment in mGC. The number of metastatic sites and PFS in the first line are prognostic factors in this group of patients.

Key words: FOLFIRI, second-line, metastatic gastric cancer, prognostic factors

«Regime farmacologico FOLFIRI come trattamento di seconda linea per il cancro gastrico metastatico: analisi retrospettiva della efficacia, della sicurezza e dei fattori prognostici»

Riassunto. *Background:* Non esistono trattamenti standard di seconda linea per il cancro gastrico metastatico (mGC). FOLFIRI si è dimostrato efficace e sicuro in questo contesto. *Metodi*: Studio retrospettivo su pazienti con mGC ai quali è stato somministrato FOLFIRI come trattamento di seconda linea. Abbiamo valutato il tasso di risposta (RR), il tasso di beneficio clinico (CBR), la sopravvivenza in assenza di progressione di malattia (PFS), la sopravvivenza totale (OS) e la tossicità. *Risultati:* 66 pazienti sono stati inclusi nello studio. Tra i pazienti valutati, l'RR globale è stato del 20% e la stabilità della malattia è stata del 34%. Il PFS medio è stato di tre mesi e l'OS medio è stato di 6 mesi. Il numero delle sedi metastatiche è considerato un fattore prognostico per PFS (HR 2,23; p=0,005) e OS (HR 2,71; p<0,001). Il PFS nel trattamento di prima linea è stato un fattore prognostico per l'OS (HR 1,71; p=0,045), ma non per il PFS (HR 1,37; p=0,226). Il PFS nel trattamento di prima linea di durata < di 7 mesi e con sedi metastatiche ≥ 2, è stato identificato come fattore di scarsa prognosi. Abbiamo identificato 2 gruppi di fattori prognostici, con pazienti appartenenti al gruppo con fattore prognostico più scarso, aventi un peggior PFS (HR 2,08; p=0,030) e OS (HR 2,97; p=0,003). Il più comune grado di

tossicità di livello 3-4 è stata la neutropenia per il 27%. *Conclusioni*: FOLFIRI è un efficace e ben tollerato trattamento di seconda linea per il mGC. Il numero delle sedi metastatiche e il PFS nel trattamento di prima linea sono considerati fattori prognostici in questo gruppo di pazienti.

Parole chiave: FOLFIRI, trattamento di seconda linea, cancro gastrico metastatico, fattori prognostici

Introduction

Worldwide, gastric cancer is the fourth most common malignancy in men and the fifth most common in women, with more than 70% of cases occurring in developing countries. It is the second leading cause of cancer death in both sexes, accounting for 9.7% of global cancer deaths (1).

Although patients with early gastric cancer may be candidates for curative surgical treatment, the vast majority of patients are diagnosed at advanced stages or will relapse after surgical treatment, in which case they can only be offered systemic treatment with palliative intent (2).

Despite the improvement in survival observed in the last 20 years, the prognosis of patients with advanced gastric cancer remains poor. Today, the standard first-line chemotherapy regimens only achieve median overall survivals (OS) that are shorter than 12 months (3-5).

Many of the patients progressing after first-line treatment maintain a good performance status and are candidates to receive second-line therapy. While second-line chemotherapy in patients with metastatic gastric cancer (mGC) has shown benefit in OS compared with the best supportive care (6-8), there is no established standard regimen in this setting (9).

Irinotecan has shown activity in mGC in several phase II studies (10-12). In a phase III trial as a second-line treatment for mGC, irinotecan significantly prolonged OS compared to the best supportive care (6).

While a previous meta-analysis concluded that first-line combination chemotherapy improved survival compared with single-agent chemotherapy (13), this still needs to be evaluated in the second-line setting.

A combination of irinotecan and 5-fluorouracil (5-FU) has also proved active in first-line treatment of mGC in phase II studies (14, 15). In a phase III trial on first-line treatment, (16), there was no difference in terms of survival, between irinotecan/5-FU/folinic acid and cisplatin/5-FU.

The efficacy of irinotecan in combination with 5-FU and leucovorin (FOLFIRI regimen) in patients with previously treated mGC has been evaluated in phase II studies (17-21), proving to be an active and well-tolerated regimen.

On the other hand, there are retrospective studies that suggest that some clinico-pathological characteristics such as the grade of differentiation, carcino-embryonic antigen levels, performance status, time to progression in the first line and the number of metastatic sites, could be helpful to identify patients with a better prognosis (22-26), who might be ranked as candidates to receive second-line therapy.

We conducted a retrospective study to evaluate the efficacy and safety of a FOLFIRI regimen as a second-line treatment for mGC in daily clinical practice. In addition, we analyzed the clinico-pathological characteristics associated with the prognosis of patients in this setting.

Patients and methods

Patient eligibility

This is a retrospective study of patients with mGC who received a FOLFIRI regimen as a second-line treatment between October 2004 and September 2013, in the Department of Medical Oncology at the Hospital Clínico San Carlos, Madrid, Spain.

Eligible patients met the following criteria: age ≥ 18 years, histologically confirmed metastatic gastric adenocarcinoma, progressive disease (PD) after first-line treatment, having received FOLFIRI as a second-line treatment, Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 2, adequate bone marrow (platelets > 100,000/mm^3, white blood cells > 3,000/mm^3, neutrophils > 1,500/mm^3), and renal (serum creatinine ≤ 1.5 x UNL) and hepatic functions (aspartate aminotransferase/alanine aminotransferase ≤ 3 x UNL, serum bilirubin ≤ 2 x UNL). Exclusion criteria were the presence of some other severe medical illness or another active malignancy.

Study end-points

The primary endpoints were to assess objective response rate (ORR), clinical benefit rate (CBR) and toxicity. The secondary endpoints were to assess progression-free survival (PFS) and OS in the overall population and by subgroups (according to clinico-pathological characteristics).

Treatment

Patients received a FOLFIRI regimen (irinotecan 180 mg/m^2 in a 2-h infusion on day 1, then leucovorin 400 mg/m^2 in a 2-h infusion and 5-FU 400 mg/m^2 bolus on day 1, followed by 5-FU 2400 mg/m^2 in a 46-h continuous infusion) every 2 weeks. Atropine 0.25 mg was administered subcutaneously only if the patient had developed symptoms of cholinergic syndrome with prior administrations of irinotecan. Prophylactic antiemetic therapy was routinely given before chemotherapy. Patients were instructed to take loperamide in case of developing diarrhea. Treatment was continued until documented disease progression or unacceptable toxic effects.

Efficacy assessments

Tumor assessments were conducted at baseline and every 3 months from treatment start to PD or death. Tumor responses were evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST, criteria version 1.0). ORR was defined as the percentage of all patients with complete response (CR) or partial response (PR). CBR was defined as the percentage of all patients with CR or PR or stable disease (SD) for at least 6 months.

Safety assessments

Adverse events (AEs) were categorized by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE). The version of the NCI-CTCAE used depended on the year in which each patient was treated. Complete blood counts and serum chemistry were assessed on day 1 of every cycle.

Statistical analysis

Categorical data were summarized as frequency counts and percentages, and continuous variables were summarized using descriptive statistics. ORR was calculated on the basis of the best response until PD, based on the physician's judgment. PFS was defined as the interval from the initiation of FOLFIRI until the first occurrence of progression, death from any cause, or date of last follow-up if none of the preceding events had occurred. OS was defined as the interval from the first day of FOLFIRI treatment to death or the last follow-up visit. PFS and OS were summarized using Kaplan-Meier curves. The difference between the curves was analyzed using the log-rank test. Patients still responding at the time of this analysis were censored at the time of the last assessment of tumor response. Univariate analysis was performed using the Kaplan-Meier method and Cox proportional-hazards regression, to correlate the clinico-pathological characteristics with PFS and OS. Variables that were significantly associated with poor survival were used to define two prognostic groups. All statistical tests were two-sided and had a 95% confidence interval (CI), with the level of significance established at $p < 0.05$. The SPSS statistical package, version 19.0, for Windows (SPSS, Chicago, IL, USA), was used for all statistical calculations.

Results

Patient characteristics

Sixty-six patients were included in this study. The median age was 65 years (range, 40-81 years). Fifty-three patients (80%) were male and ECOG performance status at the start of second-line treatment was 0 or 1 in 53 patients (80%). Thirty-nine patients (59%) had metastatic disease in two or more organs. As first-line treatment, 40 patients (61%) received a platinum and fluoropyrimidine doublet (26% cisplatin-5FU, 30% cisplatin-capecitabine and 5% oxaliplatin-capecitabine), whereas 20 patients (30%) received a triple combination chemotherapy (docetaxel-cisplatin-5FU). The characteristics of the patients are summarized in Table 1.

Table 1. Patient characteristics (n=66).

	No. of patients	%
Age, years		
Median	65	
Range	40-81	
Sex		
Male	53	80
Female	13	20
ECOG PS at 2L		
0	8	12
1	45	68
≥ 2	13	20
Primary tumor site		
Esophagogastric junction	19	29
Gastric	47	71
Histological type		
Intestinal	18	27
Diffuse	9	14
Undifferentiated	2	3
Unknown	37	56
Grade of differentiation		
Well-differentiated	8	12
Moderately-differentiated	12	18
Poorly-differentiated	15	23
Unknown	31	47
First-line chemotherapy regimen		
CDDP-5FU	17	26
CDDP-Capecitabine	20	30
TPF	20	30
XELOX	3	5
Others	6	9
No of metastatic sites		
1	27	41
≥ 2	39	59

Efficacy

The median follow-up was 39 months (range, 0-73 months). Of all patients, 56 were assessable for response. The ORR was 20% and disease stabilization was observed in 34% of the patients (Table 2). The CBR was 40% (11 patients had disease stabilization for ≥ 6 months). The median PFS was 3 months (95% CI: 2.2-3.8) and the median OS was 6 months (95% CI: 3.1-8.9), with a one-year survival rate of 36%.

Patients with fewer metastatic sites (≥ 2 vs. 1) had a significantly prolonged PFS (3 months vs. 6 months; HR 2.23; p = 0.005) and OS (4 months vs. 15 months; HR 2.71; p <0.001). Furthermore, patients with a longer PFS in first-line treatment (< 7 months vs. ≥ 7 months) had a significantly increased OS (4 months vs. 9 months; HR 1.71; p = 0.045), although no significant difference was found in PFS (3 months vs. 4 months; HR 1.37; p = 0.226). Age, grade of histological differentiation, surgery of the primary tumor, response to the first-line treatment, ECOG performance status and dose reduction of chemotherapy, were not considered as prognostic factors for PFS and for OS. However, it is important to note that patients with well and moderately differentiated histology tumors and a good ECOG performance status showed a longer, although not significant OS (p=0.484 and p=0.279, respectively) (Table 3).

PFS in the first-line treatment < 7 months and ≥ 2 metastatic sites were identified as poor prognostic factors. We defined two prognostic groups: good prognosis (one metastatic site and PFS in the first-line treatment ≥ 7 months) and poor prognosis (PFS in the first-line treatment < 7 months and ≥2 metastatic sites). Patients in the poor prognosis

Table 2. Response rate (n= 56).

	No. of patients	%
Overall Response Rate (ORR)	11	20
Complete Response (CR)	2	4
Partial Response (PR)	9	16
Stable Disease (SD)	19	34
Progressive Disease (PD)	26	46
Clinical Benefit Rate (ORR + SD ≥ 6 months)	22	40

group had a significantly worse PFS (3 months vs. 5 months; HR 2.08; p = 0.030) and OS (4 months vs. 17 months; HR 2.97; p = 0.003), compared with patients in the good prognosis group, as shown in Figures 1 and 2. The one-year survival rate was 22% and 71% in each group, respectively.

Drug delivery and safety

The median number of chemotherapy cycles received was 7 (range, 1-64 cycles). Sixteen patients

Table 3. Efficacy analyses according to clinico-pathological characteristics.

	PFS			OS		
Characteristics	months	p	HR	months	p	HR
Age						
< 70	3 (2.4–3.6)	0.135	0.66	5 (2.5-7.5)	0.306	0.74
≥ 70	6 (2.5-9.5)			12 (6.5-17.5)		
Grade of differentiation						
Well/moderately- differentiated	3 (1.2-4.7)	0.776	0.90	12 (3.9-20.0)	0.484	1.30
Poorly-differentiated	4 (2.9-5.0)			6 (4.1-7.8)		
Prior Gastrectomy						
Yes	4 (2.7-5.2)	0.243	1.36	7 (0-13.7)	0.173	1.45
No	3 (2.1-3.8)			6 (3.6-8.3)		
Nº of Metastatic sites						
1	6 (3.5-8.5)	0.005	2.23	15 (11.2-18.7)	0.001	2.71
≥ 2	3 (2.5-3.6)			4 (3.1-4.8)		
ECOG PS at 2L						
≤ 1	4 (3.0-4.9)	0.555	1.22	8 (5.0-10.9)	0.279	1.43
≥ 2	3 (2.2-3.7)			4 (3.0-4.9)		
Dose reduction						
Yes	6 (0-11.8)	0.358	1.32	12 (3.9-20.0)	0.412	1.29
No	3 (2.2-3.7)			5 (3.4-6.5)		
PFS in 1L (months)						
≥ 7	4 (3.1-4.8)	0.226	1.36	9 (5.7-12.2)	0.045	1.71
< 7	3 (1.6-4.3)			4 (2.1-5.8)		
Sex						
Male	3 (2.2-3.7)	0.937	1.02	7 (3.5-10.4)	0.545	1.21
Female	4 (0-7.3)			4 (0-8.6)		
Response to 1L						
Yes	3 (2.1-3.8)	0.968	1.01	6 (1.9-10.0)	0.576	1.16
No	3 (1.5-4.4)			5 (1.5-8.4)		

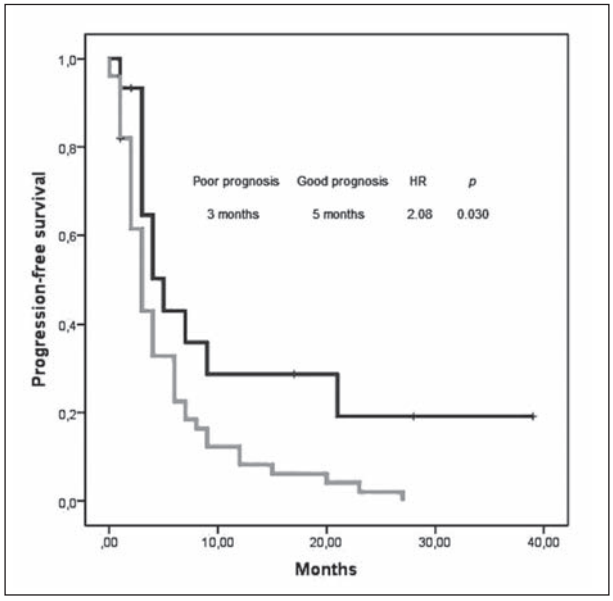

Figure 1. Progression-free survival according to prognostic groups.

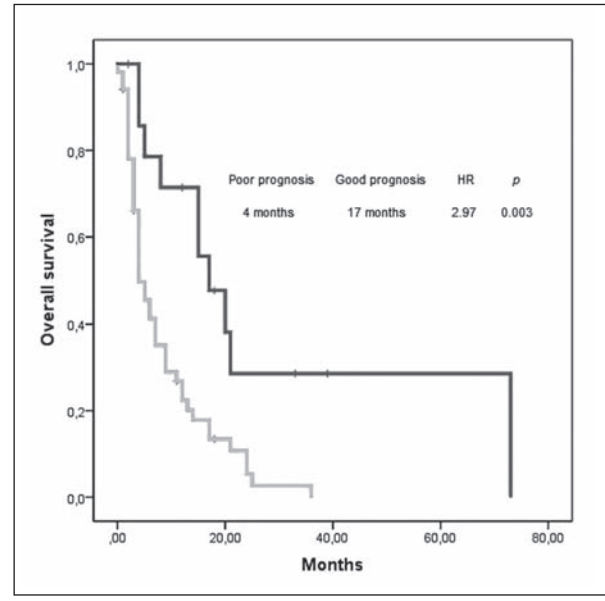

Figure 2. Overall survival according to prognostic groups.

(24%) required dose reductions from the initial dose, and treatment was discontinued in 2 patients (3%), due to toxicity. Adverse events observed during treatment are listed in table 4. The most common adverse events (any grade) were anemia (86%), neutropenia (60%), asthenia (60%) and diarrhea (60%). Grade 3 or 4 hematologic toxicities included neutropenia in 18 patients (27%), leukopenia in 8 patients (12%) and anemia in 7 patients (11%). There were two cases of febrile neutropenia, leading to death in one of them. The most common grade 3 or 4 non-hematologic toxicities were asthenia (n=11, 16%) and diarrhea (n=6, 9%).

Discussion

First-line treatment in advanced gastric cancer is based on the combination of fluoropyrimidines and cisplatin with or without taxanes (3,4), showing benefit in terms of response rates and survival. Despite this, the vast majority of patients will progress after the first-line treatment; however there is no standard regimen in the second-line setting.

Irinotecan monotherapy has been evaluated as a second-line treatment for mGC in phase 2 and 3 trials (12,6). Although the response rate is low, it has been observed that treatment with irinotecan

Table 4. Adverse events (n=66).

Adverse events	No. of patients (%)				
	Grade 1	Grade 2	Grade 3	Grade 4	Total
Anemia	34 (51)	16 (24)	5 (8)	2 (3)	57 (86)
Trombopenia	7 (11)	1 (1)	1 (1)	1 (1)	10 (14)
Leukopenia	17 (26)	13 (20)	4 (6)	4 (6)	38 (58)
Neutropenia	6 (9)	16 (24)	14 (21)	4 (6)	40 (60)
Neutropenic fever	0 (0)	0 (0)	1 (1)	1 (1)	2 (2)
Diarrhea	20 (30)	14 (21)	5 (8)	1(1)	40 (60)
Asthenia	9 (14)	20 (30)	10 (15)	1 (1)	40 (60)
Stomatitis	18 (27)	8 (12)	1 (1)	0 (0)	27 (40)
Hand-foot Syndrome	3 (4)	3 (4)	0 (0)	0 (0)	6 (8)
Transaminase elevation	6 (9)	0 (0)	1 (1)	0 (0)	7 (10)

alone achieves a high rate of disease stabilization (50%), with a significant impact on survival.

In this setting, FOLFIRI has proved to be an active regimen in retrospective analysis (20) and phase 2 studies (17,18,21), showing response rates of 18-29%, with survival benefit (PFS and OS of 2-3.7 months and 5-7 months, respectively).

In our retrospective study, patients previously treated with a fluoropyrimidine- platinum combination with or without taxanes, achieved a 20% response rate, with a median PFS of 3 months and a median OS of 6 months with FOLFIRI. These results are comparable to those previously reported. It is important to note that despite a low response rate, 34% of patients showed SD and 20% of patients had long stabilizations.

The therapeutic doses used in our center (Irinotecan 180 mg/m^2, day 1, along with 5-FU 400 mg/m^2 bolus and LV 400 mg/m^2 followed by 5-FU 2400 mg/m^2 over 48 hour) differ from those used in the Asian population. Although retrospective studies have shown no significant differences in efficacy, there is a different toxicity profile according to the scheme used (20).

Irinotecan was compared to FOLFIRI in a second-line setting in a small randomized phase 2 study of 52 patients (27), finding no significant differences in response rate (17% vs. 20%; p = 0.52) or survival (PFS 2.2 months vs. 3 months; p = 0.48 and OS 6 months vs. 7 months; p = 0.51, respectively). However, given the small sample size, definitive conclusions could not be drawn from this study.

Previous studies have evaluated the presence of prognostic factors in the second-line setting, finding that fewer metastatic sites, a longer time to progression with the first-line treatment and good ECOG performance status were significantly associated with longer PFS and OS in the second-line treatment (20, 21). Other prognostic factors associated with survival are serum albumin and a history of previous gastrectomy (28).

Our analysis showed that PFS in the first-line treatment and the number of metastatic sites were prognostic factors for OS (both) and PFS (only the number of metastatic sites). Although there were differences in OS according to the grade of histological differentiation (12 months vs. 6 months) and ECOG PS (8 months vs. 4 months), these were not significant (p=0.484 and p=0.279, respectively), probably due to the lack of histological information (in approximately 50% of cases the histological grade of differentiation was not reported) and to the small sample size.

Catalano *et al.* (23) defined three different prognostic groups (low, intermediate and high risk) according to the prognostic factors that they found (performance status, hemoglobin, CEA level, number of metastatic sites and PFS in the first line) with significant differences in survival: low-risk 12.7 months vs. intermediate-risk 7.1 months vs. high-risk 3.3 months, with 1-year survival rate of 60% vs. 21% vs. 4%, respectively (p< 0.001). Patients in our study were divided into poor or good prognostic groups (according to PFS in first line and number of metastatic sites) finding significant differences between them in PFS (3 months vs. 5 months; p = 0.030) and OS (4 months vs. 17 months; p = 0.003).

The toxicity profile shown in our patients is very similar to other populations treated with FOLFIRI as a second line, with neutropenia and anemia as the most common G3-4 toxicities, and a low rate of diarrhea. Some first-line studies of FOLFIRI reflected a worse tolerance in Western populations, suggesting ethnical differences (higher incidence of UGT1A1 gene mutations in white populations), explained by a reduction of the enzymatic conversion of irinotecan into its inactive metabolite (SN-38G) (29). Nevertheless, our analysis does not show a worse tolerance than previous studies, although they are not fully comparable.

Despite evidence of the benefit of chemotherapy in the second-line treatment of mGC, there are significant regional differences, due to the lower use of second-line treatments in western populations, and the absence of any defined standard regimen. Our results provide evidence of the efficacy and good tolerance of the FOLFIRI regimen as a second-line treatment for mGC in a western cohort. Moreover, the significant survival benefit shown in the good prognosis group raises the need for optimal selection of the best candidates for treatment in this setting.

It might be interesting to conduct phase 3 comparative studies on a larger number of patients to demonstrate the superiority of FOLFIRI versus Irinotecan monotherapy and to establish the most effective and safe version of the FOLFIRI regimen.

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