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PHASE II STUDIES

The influence of prior ramucirumab treatment on the clinical activity of FOLFIRI as third-line therapy in patients with metastatic gastric Cancer

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Summary

Purpose Few data described the activity of chemotherapy after ramucirumab plus paclitaxel progression in metastatic gastric cancer patients. The aim of this phase II study is to assess the efficacy and safety of the FOLFIRI regimen as a third-line of treatment. *Methods* The study enrolled patients with histologically proven metastatic gastric cancer or gastroesophageal junction carcinoma whose disease had progressed after ramucirumab-based second line of treatment. Treatment consisted of biweekly irinotecan 150 mg/m2 as a 1-h infusion on day 1, folinic acid 100 mg/m2 intravenously on days 1–2, and 5-fluorouracil as a 400 mg/m2 bolus and then 600 mg/m2 continuous infusion over 22 h on days 1–2. Primary end-point was tumor response rate (confirmed complete and partial response). *Results* Twenty-six patients were enrolled. Overall response rate and disease control rate were 11.5% and 38.5%. The median progression free survival (PFS) was 52 days (95% CI:42–74), and the median overall survival was 117 days (95% CI: 94–154). no unexpected adverse events have been observed. A longer PFS and OS were observed in patients who had achieved PFS ≥ 3 months during prior ramucirumab treatment. *Conclusions* Our findings suggest a poor efficacy of the FOLFIRI regimen in metastatic gastric or gastroesophageal junction cancer patients whose disease progressed during a ramucirumab-based second line of treatment. However, FOLFIRI could be an option for patients who responded to prior ramucirumab.

Keywords Gastric cancer · Irinotecan · Ramucirumab · Third line

Introduction

Gastric cancer or gastroesophageal junction carcinoma is still one of the most lethal tumors in Western countries [1]. Surgical resection is the standard for long-term curative results [2]; however, only a small percentage of patients are candidates for an optimal surgery as most patients are diagnosed in a metastatic/advanced stage. For these patients, a 5-year survival rate of 4.5% has been estimated [3] and underlies the urgent need to improve the survival of patients with metastatic stage of disease. Recently, based on the positive results of the REGARD and RAINBOW trials [4, 5], the monoclonal antibody ramucirumab that targets vascular endothelial growth receptor 2 (VEGFR2), in combination with chemotherapy or alone has been approved for the treatment of metastatic gastric cancer or gastroesophageal junction carcinoma for patients whose disease progressed after the standard first line of chemotherapy. In particular, the RAINBOW trial that investigated paclitaxel plus ramucirumab versus paclitaxel plus placebo showed a significantly longer overall survival (OS), progression-free survival (PFS), and higher tumor response for the combination of ramucirumab plus paclitaxel. Based on these results, this combination is considered the standard second-line of treatment for patients with a good performance

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status, while ramucirumab monotherapy is administered to patients with a non-optimal performance status. Unfortunately, there are few data to describe the activity of therapies after ramucirumab plus paclitaxel progression.

Irinotecan alone or in combination with a 5-fluorouracil, leucovorin, and irinotecan (FOLFIRI) regimen showed some activity as second-line chemotherapy over best supporting care [6, 7]. Based on these data, the FOLFIRI regimen could be used as a salvage chemotherapy for metastatic gastric cancer or gastroesophageal junction carcinoma for patients whose disease progressed during a ramucirumab-based second line of treatment. Therefore, the aim of this observational phase II study is to evaluate the efficacy and safety of the FOLFIRI regimen as a third-line chemotherapy in metastatic gastric cancer or gastroesophageal junction carcinoma.

Patients and methods

Eligibility criteria

The study enrolled patients with histologically proven metastatic gastric cancer or gastroesophageal junction carcinoma whose disease had progressed after ramucirumab-based second line of treatment. The other eligibility criteria included Eastern Cooperative Oncology Group performance status ≤2 (ECOG PS), aged more than 18 years, neutrophil count ≥1500/μL, platelet count ≥100,000/μL, normal renal function (serum creatinine ≤1.5 mg/dl), normal liver function (serum bilirubin ≤2 mg/dL), normal cardiac function, absence of a second primary tumor (other than non-melanoma skin cancer), no concurrent uncontrolled medical illness, and a life expectancy of at least 3 months,

Patients with operable metastatic disease were excluded from the study, as were those with severe cardiac dysfunction, chronic diarrhea or uncontrolled sites of infection, or no prior treatment with ramucirumab. This study was approved by the local ethical and scientific committee and all the patients gave their written informed consent.

Patient evaluation

The pre-treatment evaluation, performed within 2 weeks before study entry, included a detailed history and physical examination, a complete blood cell count with differential and platelet counts, whole-blood chemistry, and computed tomography (CT) scans and/or magnetic resonance imaging (MRI) of the chest and abdomen. During treatment, a physical examination and blood test were mandatory before each course of treatment; however, the left ventricular ejection fraction was assessed at baseline and only if clinically indicated. Treatment response according to CT scan and/or MRI was evaluated every 4 cycles of 2 weeks or sooner if clinically indicated. Tumor response was assessed using the RECIST 1.1 criteria [8].

Treatment delivery

Every 2 weeks patients received irinotecan 150 mg/m^2 as a 1-h infusion on day 1, folinic acid 100 mg/m^2 intravenously on days 1–2, and 5-fluorouracil as a 400 mg/m^2 bolus and then as a 600 mg/m^2 continuous infusion over 22 h on days 1–2. Chemotherapy was generally administered for a maximum of 12 cycles, and after that, patients without evidence of disease progression received maintenance treatment with folinic acid and 5-fluorouracil every 2 weeks. Treatment was continued until disease progression or unacceptable toxicity.

Toxicity

Toxicity was assessed using the common toxicity criteria of the National Cancer Institute (NCI), version 3.0. Treatment was delayed if, on the planned day of treatment, the neutrophil count was <1500/mm^3, the platelet count was <100,000/mm^3, or the patient had persistent diarrhea > grade 1. Any patient who required more than 2 weeks for recovery from adverse reactions was excluded from the study. In the event of grade 4 hematological or any other severe (≥ grade 3) adverse events in individual patients, the doses of chemotherapy drugs were reduced by 25% for subsequent courses. In case of persistent (>14 days) diarrhea, irinotecan was omitted from the subsequent cycles until recovery. To prevent nausea and vomiting, IV hydroxytryptamine-3 antagonists plus dexamethasone (8 mg) were administered before the chemotherapy infusion. Oral loperamide 2 mg every 2 h and oral rehydration were prescribed in the case of delayed diarrhea. No cytokine prophylactic treatment was recommended. The other concomitant medications were primarily used to palliate pain.

Statistical considerations

The primary objective of this phase II study was to evaluate the tumor response rate (confirmed complete and partial response). At the time of the conception of this study, no robust data were available about the use of FOLFIRI in patients with metastatic gastric cancer or gastroesophageal junction carcinoma which had progressed after ramucirumab-based chemotherapy. Assuming a response rate of approximately 10% and a target level of interest of 30% with an α of 0.05 and a β of 0.80, a sample size of 26 patients was planned in accordance with Simon's minimax design [9]. Secondary endpoints were OS, PFS, and tumor response. PFS was calculated as the time from the first chemotherapy infusion to disease progression or death. Secondary end points included safety and OS (measured from the date of start of treatment to the date of death). The Kaplan-Meier method was used to determine PFS and OS. Statistical analyses were conducted by STATA IC 2012 software.

Results

Patients characteristics

From March 2016 to November 2017, a total of 26 patients with a median age of 67 years (range, 43–76) were included in this study. Patients' characteristics are illustrated in Table 1. The primary tumor site was stomach in 21 patients (80.8%) and the gastroesophageal junction in 5 patients (19.2%). Primary tumor resection was carried out in 11 patients (42.3%), 19 (73.1%) were male and 15 (57.7%) had an ECOG PS = 2, 9 (34.5%) had >2 sites of metastasis, and 10 (38.4%) presented peritoneal metastases. All patients had disease progression after 2 lines of therapies including ramucirumab.

A doublet chemotherapy was the most frequently used first line of treatment (20 [76.9%] patients) while the PFS during first-line chemotherapy was ≥6 months in 7 patients (26.9%). Subsequent ramucirumab+paclitaxel had been administered for a median of 8 courses; no CR (complete response) was observed, and the DCR (disease control rate) was 76.9% (20/26 patients) with a median PFS of 4.7 months (95% CI 3.4–6.3).

Table 1 Patient characteristics

No. of patients	26
Age, years	
Median	67
Range	43–76
Sex	
Male	19
Female	7
ECOG PS	
0–1	11
2	15
Tumor location	
Stomach	21
Gastroesophageal junction	5
Differentiation	
Well differentiated	2
Moderate	7
Poorly differentiated	17
Primary tumor resected	
Yes	11
No	15
Number of metastatic sites	
0–2	17
≥3	9
Peritoneal metastases	10
Previous first line of treatment	
Triplet	6
Doublet	20
HER2	0
Previous platinum-based therapy	
Oxaliplatin	20
Cisplatin	6
Time to progressive disease on first-line therapy	
<6 months	19
≥6 months	7
Previous Ramucirumab+paclitaxel	
PFS <3 months	19
PFS ≥3 months	7

Efficacy

The efficacy of third-line FOLFIRI measured by outcome is reported in Table 2. We observed no complete response, 3 (11.5%) partial response (PR), 7 (27%) stable disease (SD), and 16 (61.5%) progressive disease (PD), resulting in a DCR of 38.5%. After a median follow-up of 101 days, the median PFS was 52 days (95% CI:42–74), and median OS was 117 days (95% CI: 94–154) (Fig. 1). Univariate analysis, using the Cox proportional hazard model, showed that a PFS <3 months during ramucirumab-based second line of treatment (HR 3.05, 95% CI 1.0–8.5, $P = 0.03$), an ECOG PS = 2 (HR 1.25, 95% CI 1.0–2.0, P = 0.03), and the presence of peritoneal metastases (HR 1.37, 95% CI 1.2–1.9, $P = 0.05$) were independent poor prognostic factors. In particular, patients who achieved PFS ≥3 months during ramucirumab treatment had a median PFS of 74 days (95% CI 34–112) in comparison to 46 days (95% CI 32-not-reached; P = 0.05) for patients with PFS < 3 months (Fig. 2) and a median OS of 154 days (95% CI 101–225) in comparison to 94 days (95% CI 78-not-reached; $P = 0.02$) was achieved in patients with PFS ≥3 months and PFS <3 months, respectively, during prior ramucirumab treatment (Fig. 3). Data on the efficacy of FOLFIRI according to prior ramucirumab therapy are reported in Table 3.

Toxicity

Toxicities are listed in Table 4. A total of 116 cycles of FOLFIRI were analyzed in 70 patients, with a median of 4 cycles administered per patient (range, 1–12). Overall, 22 (84.6%) patients experienced at least one adverse event, and 9 (34.6%) patients had at least 1 at Grade > 2. The most common G3–4 toxicities were neutropenia (19.2%) and diarrhea (11.5%); however, we observed only 2 (7.7%) cases of G4 neutropenia. Treatment discontinuation was necessary in 1 patient (3.8%). A 25% dose reduction was required in 4 patients (15.4%) for recurrent G3 diarrhea and G4 neutropenia. In addition, 4 patients (15.4%) delayed the administration of chemotherapy, mostly correlated with G3 adverse events. Two

Table 2 Outcomes summary

Enrolled patients	26
Median number of cycles	4 (1–12)
Tumor Response	
CR	0
PR	3 (11.5%)
SD	7 (27%)
PD	16 (61.5%)
Survival	
PFS, median (days; 95% CI)	52 (42–74)
OS, median (days; 95% CI)	117 (94–154)

patients required granulocyte colony-stimulating factor (G-CSF) for G4 neutropenia.

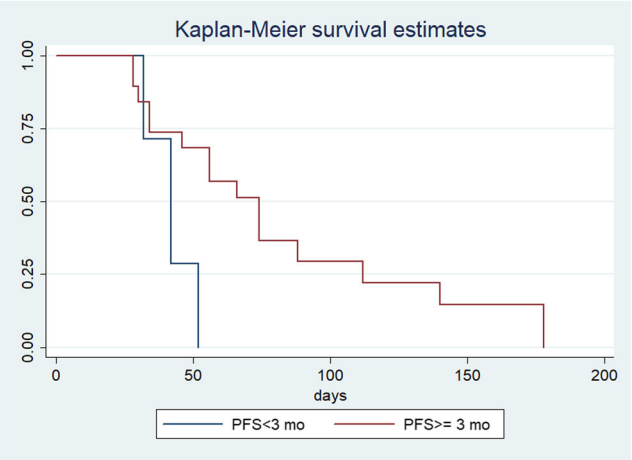

Fig. 2 Estimated PFS for following FOLFIRI in patients with PFS ≥ 3 months (red) or < 3 months during prior ramucirumab

Discussion

In the present study, we reported that the use of FOLFIRI in the third line of therapy for ramucirumab-pretreated patients with metastatic gastric cancers was associated with an objective response rate of 11.5% and a DCR of 38.5%. Median PFS and OS were 52 days and 117 days, respectively.

To date, the first choice for the treatment of metastatic gastric cancer or gastroesophageal junction carcinoma is chemotherapy; usually a combination between platinum-based and fluoropyrimidine chemotherapy, or the use of trastuzumab-based chemotherapy for the subgroup of HER2 positive metastatic gastric cancers [12]. Until 2014, irinotecan and taxane regimens have been accepted as salvage treatment options as they are more efficacious than best supportive care alone [13]. Recently, ramucirumab has been the first drug able to prolong survival for patients with metastatic gastric cancer whose disease progressed after a standard first line of chemotherapy [4, 5]. Unfortunately, few data are available for the optimal regimen after ramucirumab-based second-line progression. In this scenario, several different targeted agents against different molecular pathways showed no advantage for survival [14]. Therefore, there is a need for further active treatments beyond second-line chemotherapy. To the best of our knowledge, this is the first observational study on the use of chemotherapy as third-line treatment in patients with disease progression after ramucirumab in non-Asian patients.

In the past, it was estimated that about 20% of patients were candidates for a third line of therapy; this was because of a worsening in performance status that did not allow the administration of further chemotherapy. However, in the new era of molecular targeted agents such as ramucirumab, patients can still maintain a good performance status after progression on a second-line of therapy. As a result, the number of patients suitable for a third line of chemotherapy is growing, and

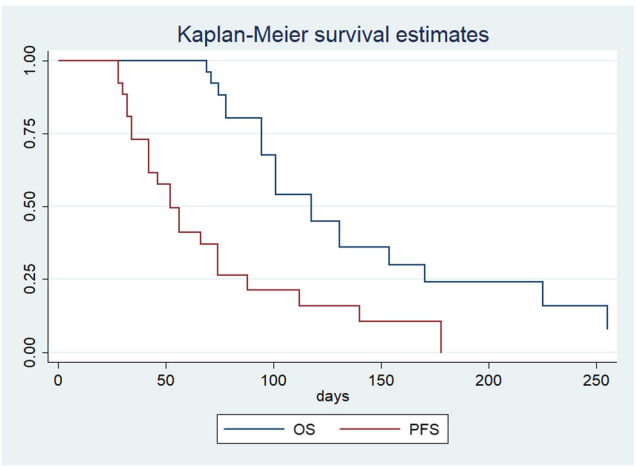

Fig. 1 Data on PFS (red) and OS (blu) with FOLFIRI for third line of treatment

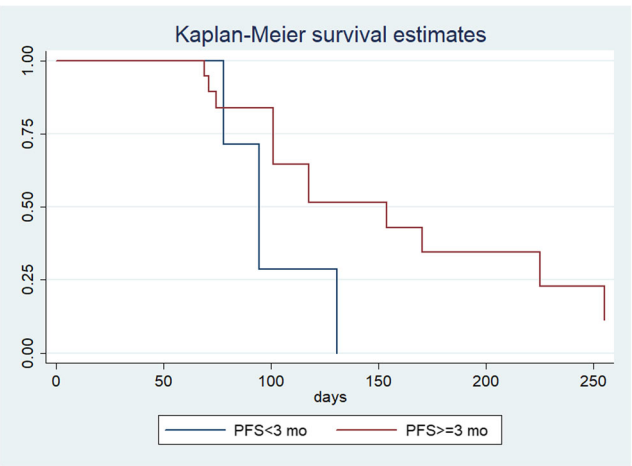

Fig. 3 Estimated OS for following FOLFIRI in patients with PFS ≥ 3 months (red) or < 3 months during prior ramucirumab

Table 3 Efficacy of FOLFIRI according response to prior ramucirumab

Efficacy of prior Ramucirumab	FOLFIRI	
	PFS Median, days	OS Median, days
Tumor Response (Patients)		
PR [6]	66	154
SD [10]	46	101
PD [6]	42	94
PFS (Patients)	$P = 0.04$	P = 0.02
≥3 months [7]	74	154
< 3 months [11]	42	94

around 20%–90% of patients have continued on active third-line treatment or more [10, 15]. Generally, taxanes and irinotecan are possible options in a third-line setting. In fact, previous studies on taxane-based chemotherapy or irinotecan-based chemotherapy (either monotherapy or in combination with 5-FU) showed an overall response rate of 10%–25% with PFS 2.1–3.3 months and OS 5.6–10.9 months [10, 16]. In addition, a recent study aimed to evaluate the efficacy and safety of the modified 5-fluorouracil, leucovorin, and irinotecan (mFOLFIRI) regimen as a third-line chemotherapy, after failure of fluoropyrimidine, platinum, anthracycline, and taxane; mFOLFIRI showed an objective response rate of 19% and a DCR of 50% with a median PFS and OS of 3.8 months and 6.8 months, respectively [17]. Although these data derived from a retrospective analysis, they compared well with those reported in our study with FOLFIRI treatment after ramucirumab and suggest that irinotecan-based combination chemotherapy is still feasible in a selected subgroup of patients with metastatic gastric cancer or gastroesophageal junction carcinoma. In our opinion, these subgroups will be found in patients with tumor response (PR) and with a PFS > 3

Table 4 Number (%) of patients experiencing the most frequent treatment-related adverse events

Hematologic	All grades	Grade ≥3
Neutropenia	9 (34.6)	5 (19.2)
Anaemia	4 (15.4)	1 (3.8)
Thrombocytopenia	2 (7.7)	0
Non-hematologic	All grades	Grade ≥3
Nausea	3 (11.5)	1 (3.8)
Vomiting	3 (11.5)	1 (3.8)
Diarrhoea	6 (23.1)	3 (11.5)
Mucositis	3 (11.5)	1 (3.8)
Asthenia	2 (7.7)	1 (3.8)

following prior ramucirumab as second-line therapy, because these patients in our study achieved results similar to those reported in the literature. However, we must report that the dosage of irinotecan was lower than the standard usually administered in a FOLFIRI regimen. However, our analysis was performed in a small number of patients and caution should be exercised before drawing firm conclusions; therefore, we deem that further larger studies are needed to define the exact role of FOLFIRI in a third-line treatment setting.

Over the years, several agents with different mechanisms of action have been investigated as a third-line treatment for patients with metastatic gastric cancer or gastroesophageal junction carcinoma. Among these, Apatinib, also known as YN968D1, is a novel receptor tyrosine kinase inhibitor selectively targeting the intracellular ATP-binding site of VEGFR2 [18]. In 2013, a phase II trial compared 2 schedules of apatinib (425 mg twice daily or 850 mg daily) with placebo, demonstrating a longer OS, PFS, and tumor response rate for apatinib [19]. Of note, all the enrolled patients had disease progression after 2 lines of therapy and about 30% were treated with ≥3 lines of prior therapy. Subsequently, a phase III trial using apatinib compared with placebo confirmed the efficacy of apatinib (at the dose of 850 mg once daily) with regard to OS, PFS, and tumor response [11]. However, all these data derive from studies that enrolled Chinese patients and data on the efficacy of apatinib for Non-Asian patients are not yet available. In addition, everolimus (an oral inhibitor of the mammalian target of the rapamycin serine-threonine kinase pathway) did not improve the OS for patients with metastatic gastric cancer or gastroesophageal junction carcinoma that had progressed after 2 lines of previous systemic chemotherapy compared with best supportive care [20]. In addition, regorafenib (an oral multikinase inhibitor which targets multiple proangiogenic and not signaling pathways) showed a significantly longer PFS compared with placebo [21] in a phase II study; however, a phase III trial is awaited to confirm the role of regorafenib in the treatment of metastatic gastric cancer or gastroesophageal junction carcinoma. Finally, immunotherapy is now the novel oncological treatment focused on targeting specific factors, particularly the inhibitory ligand-receptor interactions, serving as physiological brakes on the immune system "immune checkpoints" (PD-1 and CTLA-4) in the stimulation of regulatory T cells. Although preliminary results showed a certain efficacy of novel PD-1 or PD-L1 therapies in heavily pretreated patients with metastatic gastric cancer or gastroesophageal junction carcinoma, these drugs are not available in routine clinical practice [22]. Regarding toxicity, no unexpected adverse events have been observed; there were only 2 cases of grade 4 neutropenia, while among non-hematological adverse events diarrhea was the most reported. In addition, the incidences of treatment interruption or delays were lower than those reported in previous studies [6, 10, 16, 17]. This may be due

to the lower dose of irinotecan that we administered to our patients. However, we have to report that patients were not genotyped for UDP-glucuronosyltransferase UGT1A1 enzyme that is mainly involved toxicity from irinotecan-based chemotherapy.

In conclusion, although there is the limitation of small simple size, additional studies are awaited to clarify the optimal role of FOLFIRI regimen in advanced metastatic gastric cancer or gastroesophageal junction carcinoma, especially in the light of the possible introduction of immunotherapy. We suggest that the FOLFIRI regimen could be a valid option for third-line treatment of patients who responded to prior ramucirumab-based therapy.

Compliance with ethical standards

Conflict of interest Roviello G declares that he has no conflict of interest. Petrioli R declares that he has no conflict of interest. Multari AG declares that he has no conflict of interest. Conca R declares that he has no conflict of interest. Paganini G declares that he has no conflict of interest. Chiariacò G declares that he has no conflict of interest. Aieta M declares that he has no conflict of interest.

Ethical approval Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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