Poor outcome for patients with gastric cancer and lung metastases treated with ramucirumab and paclitaxel

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The aim of this report is to investigate the activity of ramucirumab in combination with paclitaxel in patients with metastatic gastric cancer (GC) and lung metastases. We retrospectively reviewed clinical data from patients with GC treated in second line with ramucirumab and paclitaxel according to the presence or not of lung metastases. Thirty-one patients were eligible. Five (16.1%) patients had lung metastases. The median progression-free survival was 156 days in patients without lung metastases compared with 54 days in patients with lung metastases. The median survival also showed a trend in favour of patients without lung metastases. Despite the small number of patients and the retrospective nature of the data, our analysis showed relatively poor efficacy of ramucirumab plus paclitaxel as a second-line treatment in patients with lung metastases from GC. Further studies are required to evaluate novel treatments in this subset of patients. *Anti-Cancer Drugs* **30:745–748**

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Introduction

Gastric cancer (GC) is the fifth most common malignancy and the third leading cause of cancer death worldwide [1]. Surgical resection represents the only chance of cure in limited-stage GCs [2]. Unfortunately, most patients are diagnosed at an advanced stage or develop recurrent metastatic disease after primary treatments, with a 5-year survival rate of less than 10% and a median overall survival (OS) of ~12 months [3,4]. Currently, the first-line treatments for advanced or recurrent GC are combination chemotherapy regimens consisting of fluoropyrimidines and platinum compounds, with or without a third agent (taxanes or anthracycline if HER2 negative GC, or trastuzumab in case of HER2 overexpression).

For patients who progressed after a first line of treatment, the use of ramucirumab, a human IgG1 monoclonal antibody against VEGFR2, which acts by preventing ligand-binding and receptor-mediated vascular endothelial growth factor (VEGF) pathway activation in endothelial cells, has an increased survival rate, also offering a favourable safety profile [5–8]. After the results of the large RAINBOW phase III study [8] were reported, the combination of ramucirumab and paclitaxel has become the new gold standard in second-line treatment for patients with an Eastern Cooperative Oncology Group Performance Status of less than 30% of patients respond to ramucirumab, underlying the need to individuate predictors biomarkers of efficacy.

Lung metastases occur in ~15% of GCs [9,10] and are more common when the primary tumour is localized at the cardia. Frequently, lung and liver metastases present synchronously. To date, few data are available on the efficacy of ramucirumab in metastatic GC to the lung. Therefore, the aim of this report is to evaluate the activity of paclitaxel + ramucirumab in patients with advanced GC with lung metastases.

Patients and methods

The methodology of this study has been reported previously and here it is summarized for convenience [11].

From October 2015 to November 2017, we retrospectively evaluated patients with histologically proven advanced or metastatic GC treated with paclitaxel + ramucirumab in the second line of therapy. Patients were evaluated if they progressed after a first line of chemotherapy with platinum and fluoropyrimidine (doublet or triplet). Patients had measurable disease, an Eastern Cooperative Oncology Group Performance Status of 0–1 and an adequate hepatic, renal and bone marrow function. Severe comorbidities (mainly cardiac or gastrointestinal) were a criterion of exclusion for the treatment

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with paclitaxel + ramucirumab. This study was approved by the local ethical and scientific committee and each patient provided written informed consent for chemotherapy before the initiation of treatment. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Treatment consisted of paclitaxel 80 mg/m^2 intravenously on days 1, 8 and 15 and ramucirumab 8 mg/kg intravenously on days 1 and 15 of a 28-day cycle. Patients received study treatment until disease progression, unacceptable toxicity or consent withdrawal. Tumour response was assessed according to the guidelines of the Response Evaluation Criteria in Solid Tumors, version 1.1 [12]. This is a retrospective cohort study that aims to investigate the efficacy of ramucirumab in patients with lung metastases from GC. For this, we divided the patients into two groups according to the presence/absence of lung metastases. The primary end point was progression-free survival (PFS) calculated as the time from the first chemotherapy infusion to disease progression or death. The secondary end points included OS, measured from the date of treatment start to the date of death, and response rate. The Kaplan–Meier method was used to determine PFS and OS. The log-rank test was performed to analyse the difference in PFS and OS in relation to the status of the lung metastasis. The threshold for statistical significance was established at *P* values of less than 0.05. Statistical analysis was carried out using STATA software; StataCorp LLC, Texas, USA.

Results

From October 2015 to November 2017, 31 patients with metastatic GC fulfilled the inclusion criteria and were evaluated retrospectively in this study. Of these, five (16.1%) had lung metastases, a proportion that is in line with literature data. Baseline characteristics of the patients are presented in Table 1. Most patients with lung metastases had poor prognostic factors, including at least three metastatic sites, peritoneal metastases, poorly differentiated tumours and disease progression within 6 months after the start of the previous therapy (Table 1). Three of five patients presented lung metastasis since the diagnosis of advanced disease, whereas two patients developed lung metastasis after progression from first-line treatment.

All patients received at least one cycle of paclitaxel and ramucirumab, and were evaluable for response. The median PFS was 132 days [95% confidence interval (CI): 93–186 days], 156 days in patients without lung metastases versus 54 days in patients with lung metastases ($P < 0.01$; Fig. 1). Median OS was 264 days (95% CI: 180–330 days), and, in agreement with PFS results, showed a statistically significant trend in favour of patients without lung metastases ($P < 0.01$; Supplementary Fig. 1S, Supplemental digital content 1, *http://links.lww.com/ACD/A307*). No complete tumour response was observed, whereas documented partial responses were observed in nine (29%) patients, a percentage similar to that reported previously in the RAINBOW trial.

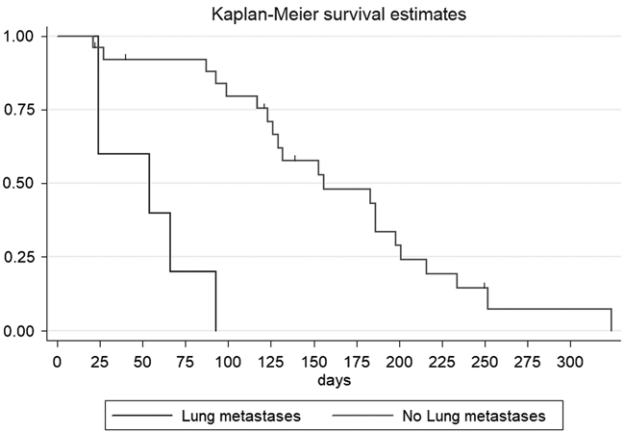
All nine patients who experienced a partial response belonged to the group without lung metastases (no tumour response in the lung metastases group).

Table 1 Patient characteristics

Characteristics	All patients	Patients without lung metastases	Patients with lung metastases
Number of patients	31	26	5
Age (years)			
Median	64	64.5	59
Range	44–75	48–74	44–71
Sex			
Male	22	18	4
Female	9	8	1
ECOG PS			
0	12	10	2
1	19	16	3
Tumour location			
Stomach	24	20	4
Gastro-oesophageal junction	7	6	1
Differentiation			
Well differentiated	3	3	0
Moderate	10	9	1
Poorly differentiated	18	14	4
Primary tumour resected			
Yes	13	11	2
No	18	15	3
Previous treatment			
Triplet	6	5	1
Doublet	23	19	4
HER2	2	2	0
Time to progressive disease on first-line therapy (months)			
<6	18	14	4
≥6	13	12	1
Number of metastatic sites			
0–2	21	20	1
≥3	10	6	4
Peritoneal metastases	12	9	4

ECOG PS, Eastern Cooperative Oncology Group Performance Status.

Fig. 1



Estimated progression-free survival for ramucirumab + paclitaxel in patients with lung metastasis or without lung metastasis.

A total of seven patients were subsequently treated in third line, mainly with irinotecan-based chemotherapy; one of these patients had lung metastases [13]. Cox proportional hazards regression analysis confirmed the absence of lung metastases as a prognostic factor for PSF and OS (hazard ratio = 0.44, 95% CI: 0.21–0.49, $P = 0.03$ and hazard ratio = 0.58, 95% CI: 0.35–0.88, $P = 0.05$).

Discussion

Recently, several drugs have been shown to increase survival against placebo in advanced GC; apatinib, a small selective VEGFR2 tyrosine kinase inhibitor, is now approved in China [14], nivolumab, a monoclonal antibody inhibitor of programmed death-1, is approved in Japan [15,16] and, more recently, trifluridine/tipiracil, a novel oral combination cytotoxic drug, also known as TAS-102 [17]. Nonetheless, the combination of ramucirumab with paclitaxel is widely considered the optimal second line of treatment in metastatic GC. The results of the current study indicate a lower efficacy of second-line paclitaxel + ramucirumab in the treatment of advanced GC in patients with lung metastases in comparison with patients without secondary disease to the lung (PFS = 54 days and no tumour response in patients with lung metastases).

It is well known that the main site of metastasis in GC is intra-abdominal and that the incidence of lung metastasis is relatively small, presenting in 15% of the cases in the largest reported series [9]. Some series even reported a lower incidence [10]. Poor outcome has been found in patients with GC and lung metastases as secondary localization to the lung is associated frequently with the presence of metastases in other organs [9], whereas only 20% of GC patients with lung metastases have isolated pulmonary side of disease [9]. The most frequently observed pattern of lung metastasis was haematogenous metastasis (52.3%), followed by pleural (35.2%) and lymphangitic (26.4%). The presence of haematogenous pulmonary metastasis was associated significantly with the co-presence of hepatic metastasis and male sex [10]. Other biological or clinical parameters such as histology, grading or initial stage of disease do not seem to impact on the risk of development of lung metastases. Patients with GC localizing at the cardia have twice the risk of developing lung secondaries in comparison with other anatomical localizations of the primary lesion. Unfortunately, the median survival after the diagnosis of pulmonary metastasis was very poor [10].

In 2017, a pooled analysis from patients randomized in the two phase III trials of ramucirumab (REGARD and RAINBOW) found 12 independent prognostic factors of poor survival of ramucirumab-based therapy [18]. Other data suggest that hypertension may be predictive of better outcomes in GC patients who receive paclitaxel + ramucirumab [11,19]. However, lung metastases were not investigated in these large series. Then, in our analysis, we focused on lung metastases that were found to be a poor predictor of efficacy for paclitaxel + ramucirumab. The presence of lung metastases in advanced GC seems to identify a more aggressive biology, leading to different sensitivity to ramucirumab plus chemotherapy. Although we did not carry out any bio-molecular analysis to evaluate this issue, we know that the presence of lung metastases is generally accompanied by liver metastases; conversely, the presence of liver metastases is rarely accompanied by peritoneal metastases, indicating that GC typically metastasizes either within the peritoneum or haematogenically, and seldom by both routes [9]. In view of this, it may be speculated that GCs with lung metastases develop more aggressive cellular clones that are less sensitive to biological ramucirumab-based therapy.

Although comparable efficacy as in the RAINBOW trial in terms of clinical outcomes of PFS and OS were reported in our unselected population, in the subgroup with lung metastases, a worse outcome and lower clinical response were observed, suggesting a poor efficacy of ramucirumab as second line in patients with lung metastases from GC.

Unfortunately, our analysis has the limitations of a small number population evaluated, which makes it difficult to carry out a meaningful statistical analysis, and the retrospective nature of the data. Nevertheless, these results underline the pressing need for prospective large-scale trials, with the aim of evaluating novel treatments in the subset of patients with advanced GC and lung metastases.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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