Efficacy and Safety of Fixed-Dose-Rate Infusions of Gemcitabine Plus Erlotinib for Advanced Pancreatic Cancer

Alberto Muñoz*, Eider Azkona, Estíbaliz Iza, Eluska Iruarrizaga, Abigail Ruiz de Lobera, Itziar Rubio, Joan Manel Mañé, Sergio Carrera, Inés Marrodán Ciordia and Guillermo López-Vivanco

Medical Oncology Department, Hospital Universitario Cruces, Plaza de Cruces, S/N, 48903 Barakaldo, Spain

Abstract: *Purpose*: To evaluate the efficacy and safety of fixed-dose-rate infusions of gemcitabine in combination with erlotinib for advanced pancreatic cancer.

Methods/Patients: Patients with locally advanced (LAPC) or metastatic pancreatic cancer (MPC) without previous treatment for the advanced disease and Eastern Cooperative Oncology Group performance status ≤2 received 1500 mg/m^2 of gemcitabine in 150-minute infusions (10 mg/m^2/minute) on days 1, 8 and 15 in 4-week cycles combined with 100 mg/day of oral erlotinib. The primary endpoint was overall survival (OS).

Results: Sixty-two evaluable patients were enrolled (LAPC, n=16; MPC, n=46). Median OS was 10.0 (95% CI, 7.1-13.0) months. OS was longer in patients with LAPC (p=0.019), females (p=0.010) and patients not receiving opioids (p=0.027). A trend towards longer OS was shown in patients with grade ≥2 rash (p=0.078). In multivariate analysis, only gender remained statistically significant (p=0.01). Median PFS was 4.9 (95% CI, 3.1-6.8) months, which was longer in patients with LAPC (p=0.004) and females (p=0.013). Overall response rate was 12.9% (95% CI, 4.7-21.3), with eight patients achieving partial response, and tumour growth control rate was 67.7% (95% CI, 79.3-56.1). The main grade 3/4 adverse events were neutropenia (40.3%), asthenia (22.6%), anaemia (19.4%), thrombocytopenia (17.7%) and infections (14.5%). Three patients died due to septic shock, cholangitis or pulmonary embolism.

Conclusions: The combination of fixed-dose-rate infusions of gemcitabine and erlotinib represents a feasible and active regimen for advanced pancreatic cancer with a manageable safety profile.

Keywords: Adenocarcinoma, efficacy, erlotinib, fixed-dose-rate infusion, gemcitabine, pancreas, safety.

INTRODUCTION

Pancreatic cancer is a major health problem worldwide that represents the fourth leading cause of cancer-related mortality in the United States [1] and the fifth in Europe [2]. Gemcitabine has been considered as the standard first-line treatment for advanced pancreatic cancer over the last decade [3], based on the clinical benefit and the survival advantage conferred by its administration in 30-minute infusions in comparison with 5-fluorouracil [4]. However, further research has been done in order to improve its efficacy.

As gemcitabine is a pyrimidine analogue intracellularly converted into its active triphosphate nucleoside, the intracellular accumulation of active metabolites might be optimized using prolonged infusions [5]. Indeed, advantage in accumulation of gemcitabine triphosphate was shown using 1500 mg/m^2 of gemcitabine administered at a fixed-dose-rate of 10 mg/m^2/minute over 150 minutes in comparison with 30-minute infusions of 2200 mg/m^2 in patients with locally advanced or metastatic adenocarcinoma of the pancreas, as well as a modest overall improvement in survival [5]. Additionally, 150-minute infusions of 1500 mg/m^2 of gemcitabine administered at a fixed-dose-rate of 10 mg/m^2/minute showed a trend towards a better overall survival (OS) compared to 30-minute infusions of 1000 mg/m^2 of gemcitabine in a recently published phase III trial, though it was underpowered to detect differences in OS greater than 33% [6]. Our experience using fixed-dose-rate infusions of gemcitabine for advanced pancreatic and biliary tree adenocarcinoma is in line with these results, having shown that 150-minute fixed-dose-rate infusions of 1500 mg/m^2 of gemcitabine administered at 10 mg/m^2/minute has relevant antitumor activity and represents an interesting schedule to be combined with other chemotherapeutic agents [7].

Several combinations of treatments with gemcitabine have been assessed to improve gemcitabine efficacy [3], among which the addition of the epidermal growth factor receptor tyrosine kinase inhibitor erlotinib to 30-minute infusions of gemcitabine has been shown to prolong progression-free survival (PFS) and OS of patients with advanced pancreatic cancer in comparison with administration of gemcitabine alone [8]. Thus, erlotinib was firstly

*Address correspondence to this author at the Medical Oncology Department, Hospital Universitario Cruces, Plaza de Cruces, S/N, 48903 Barakaldo, Spain; Tel: +34 946006320; Fax: +34 946006256;
E-mail: alberto.munozllarena@osakidetza.net

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approved for pancreatic cancer in combination with gemcitabine in 2005. Further research to achieve improvements in the treatment of advanced pancreatic cancer recently led to the assessment of erlotinib in combination with 1200 mg/m^2 of gemcitabine administered as 120-minute fixed-dose-rate infusions, showing that this combination is active and well tolerated for advanced pancreatic cancer treatment [9]. However, there is not further data available on the combination of erlotinib with fixed-dose-rate infusions of gemcitabine for advanced pancreatic cancer.

In light of the above and based on our previous experience on the fixed-dose-rate infusions of gemcitabine for the treatment of advanced pancreatic and biliary tree adenocarcinoma [7], we decided to evaluate the efficacy and safety of the administration of 1500 mg/m^2 of gemcitabine in 150-minute fixed-dose-rate infusions in combination with erlotinib for advanced pancreatic cancer.

MATERIALS AND METHODS

Patient Population

Patients with pathologically confirmed unresectable locally advanced or metastatic pancreatic adenocarcinoma were eligible for the study. Other eligibility criteria included age ≥18 years; measurable/evaluable disease; absence of previous treatment for the advanced disease; Eastern Cooperative Oncology Group (ECOG) performance status ≤2; adequate bone marrow, hepatic and renal function; and written informed consent.

Study Treatment

Patients received 100 mg/day of oral erlotinib (Tarceva®; F. Hoffmann-La Roche Ltd, Basel, Switzerland) combined with 1500 mg/m^2 of gemcitabine (Gemzar®; Eli Lilly and Company, Indianapolis, USA) administered as 150-minute intravenous infusions at a fixed-dose-rate of 10 mg/m^2/minute on days 1, 8 and 15 in 4-week cycles. In patients with locally advanced pancreatic cancer, a maximum of six cycles was allowed prior to radical radiotherapy with concurrent capecitabine administered twice a day at 825 mg/m^2. In patients with metastatic pancreatic cancer, the study treatment was administered until disease progression, unacceptable toxicity or patient's withdrawal.

The dose of erlotinib was reduced and delayed as described in the Summary of Product Characteristics, while gemcitabine dose delays and reductions were performed as described by Tempero *et al*. [10]. Thus, doses of gemcitabine were reduced to 50% when the absolute granulocyte count dropped to between 0.99x10^9/l and 0.5x10^9/l, or when the platelet count was between 74x10^9/l and 50x10^9/l. No gemcitabine was administered when either the absolute granulocyte count was lower than 0.5x10^9/l or the platelet count was less than 50x10^9/l. Gemcitabine dose was reduced to 50% for non-haematological toxicities, and held for grade 3/4 toxicities. Patients experiencing grade 4 granulocytopenia, thrombocytopenia or non-haematological toxicities during a course of therapy were administered 75% of the starting dose in the following cycle.

Assessments

Clinical and laboratory assessments were performed on days 1, 8 (at physician's criterion) and 15 of every cycle. Response to treatment was assessed every three cycles using the Response Evaluation Criteria in Solid Tumours guidelines [11]. OS was calculated from the date of the first administration of the study treatment to the date of death or last visit. PFS was calculated from the date of the first administration of the study treatment to the date of progression, death or last visit without progression. The safety profile of the study treatment was assessed at every visit up to 30 days after the last dose of study treatment using the National Cancer Institute Common Toxicity Criteria for Adverse Events version 3.0 [12].

Statistical Considerations

On the basis of previous studies, the study assessed the efficacy and toxicity of fixed-dose-rate infusions of gemcitabine plus erlotinib. A retrospective review was performed to determine outcomes in patients.

The primary endpoint was OS, which was estimated using the Kaplan-Meier method. Additionally, bivariate analyses to assess the effect of variables such as gender, ECOG performance status, disease stage, grade of rash and opioid treatment on OS were performed using the Kaplan-Meier method and log-rank test, as well as a multivariate Cox proportional hazard regression model analysis.

Secondary efficacy endpoints included PFS, response rates and safety. PFS was estimated using the Kaplan-Meier method. The effect of variables such

as gender, disease stage, grade of rash and opioid treatment on PFS was assessed using the Kaplan-Meier method and log-rank test. Descriptive analyses were used for the assessment of response to treatment. Overall response rate (ORR; complete response plus partial response) and tumour growth control rate (complete response plus partial response plus stable disease) were calculated, together with their 95% confidence intervals (CI). The safety of the study treatment was assessed according to reported adverse events using descriptive analyses.

Missing data were not considered in the analyses and a significance level of 0.05 was used for statistical testing. The statistical analyses were performed with the Predictive Analytics Software (PASW) Statistic 18 (SPSS Inc, Chicago, Illinois, USA).

Table 1: Baseline Patient Characteristics (N=62)

Patient characteristics	Value
Median age, years (IQR)	63.5 (58.0-70.0)
Male, n (%)	36 (58.1)
ECOG performance status:	
ECOG 0, n (%)	19 (30.6)
ECOG 1, n (%)	40 (64.5)
ECOG 2, n (%)	3 (4.8)
Staging of disease:	
Locally advanced, n (%)	16 (25.8)
Metastatic disease, n (%)	46 (74.2)
Location of disease:	
Median number of locations (IQR)	2.0 (1.0-2.0)
Loco-regional, n (%)	55 (88.7)
Liver, n (%)	34 (54.8)
Lymph nodes, n (%)	15 (24.2)
Peritoneum, n (%)	6 (9.7)
Lung, n (%)	6 (9.7)
Others, n (%)	2 (3.2)
Measurability of tumour:	
Only measurable, n (%)	55 (88.7)
Only evaluable, n (%)	1 (1.6)
Both, n (%)	6 (9.7)
Previous treatments:	
None, n (%)	45 (72.6)
Surgery, n (%)	15 (24.2)
Surgery and adjuvant chemotherapy, n (%)	2 (3.2)
Median CA 19-9 level, U/ml (IQR)	629.0 (99.5-7799.3)

ECOG: Eastern Cooperative Oncology Group; IQR: interquartile range.

RESULTS

Patient Characteristics

Between September 2007 and December 2009, a total of 64 patients with locally advanced or metastatic pancreatic adenocarcinoma received the study treatment in the Medical Oncology Department at Hospital Universitario Cruces. Two of them were considered non-eligible as a result of having received previous treatment with gemcitabine (n=1) or having an ECOG performance status of 3 (n=1). Thus, the evaluable population comprised 62 patients, whose characteristics are described in Table **1**.

Study Treatment

The median (interquartile range [IQR]) number of cycles received by patients was 4.0 (2.0-6.0) (Table **2**). Median (IQR) dose intensity of gemcitabine was 891.6 (746.2-1017.3) mg/m^2/week and that of erlotinib was 100.0 (85.2-100.0) mg/day, corresponding to relative dose intensities of 0.76 and 0.90, respectively (Table **2**). Additionally, 10 (16.1%) patients with locally advanced pancreatic cancer received radical radiotherapy (mean±SD dose, 45.5±1.7Gy) with concurrent 825 mg/m^2 of capecitabine administered twice a day after having received a maximum of six cycles of study treatment.

Table 2: Treatment Delivery (N=62)

Treatment characteristics	Value
Median number of cycles (IQR)	4.0 (2.0-6.0)
Median dose intensity (IQR):	
Gemcitabine, mg/m^2/week	891.6 (746.2-1017.3)
Erlotinib, mg/day	100.0 (85.2-100.0)
Relative dose intensity:	
Gemcitabine	0.76
Erlotinib	0.90

IQR: interquartile range.

After a median (IQR) length of study treatment of 3.7 (1.8-5.8) months, three (4.8%) patients still remained on treatment. The main causes of treatment discontinuation were disease progression (26 [41.9%] patients), achievement of maximum benefit (24 [38.7%] patients), toxicity (8 [12.9] patients) and patient's wish (1 [1.6%] patient). Thereafter, 28 (45.2%) patients received a second-line therapy: combination of capecitabine and oxaliplatin (XELOX regimen) (n=15), re-treatment with fixed-dose-rate infusions of

gemcitabine plus erlotinib (n=8), standard 30-minute infusions of gemcitabine plus erlotinib (n=4) or administration of gemcitabine without erlotinib (n=1). Only two (3.2%) patients received a third-line therapy: re-treatment with fixed-dose-rate infusions of gemcitabine plus erlotinib (n=1) or combination of 5-fluorouracil, adriamycin and mitomycin (n=1).

Efficacy

Patients showed a median OS of 10.0 (95% CI, 7.1-13.0) months (Figure **1**). The results obtained from the bivariate analyses showed statistically significant longer OS in patients with locally advanced pancreatic cancer than in those with metastatic pancreatic cancer (median, 17.5 [95% CI, 10.3-24.7] *versus* 7.0 [95% CI, 2.9-11.1] months; p=0.019), as well as shorter OS in male than in female patients (median, 7.0 [95% CI, 1.7-12.3] *versus* 11.7 [95% CI, 7.3-16.1] months; p=0.010) and patients receiving opioid treatment compared to those who did not receive it (median, 6.8 [95% CI, 2.9-10.7] *versus* 11.4 [95% CI, 9.0-13.9] months; p=0.027). Despite not reaching statistical significance, patients with grade ≥2 rash showed a trend towards longer OS (median, 12.6 [95% CI, 8.6-16.6] *versus* 7.0 [95% CI, 3.9-10.1] months; p=0.078). Multivariate analysis results showed that only gender remained as an independent prognostic factor (HR, 0.646 [95% CI, 0.447-0.932]; p=0.02).

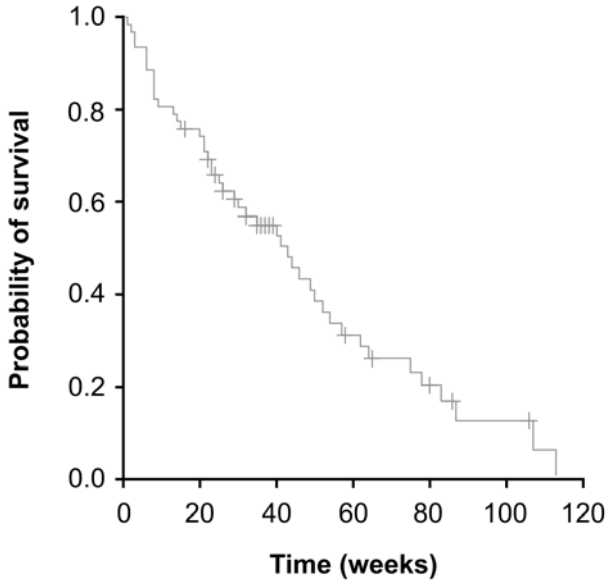

Figure 1: Kaplan-Meier estimates for overall survival.

The assessment of PFS showed that patients attained a median PFS of 4.9 (95% CI, 3.1-6.8) months (Figure **2**). This PFS was significantly longer in patients with locally advanced pancreatic cancer than in those with metastatic pancreatic cancer (median, 8.9 [95% CI, 5.4-12.4] *versus* 2.8 [95% CI, 0.9-4.7] months; p=0.004), and in female compared to male patients (median, 7.9 [95% CI, 5.3-10.5] *versus* 3.5 [95% CI, 1.0-6.0] months; p=0.013). No significant differences were detected according to the presence of acneiform rash (p=0.124) or opioid treatment (p=0.081).

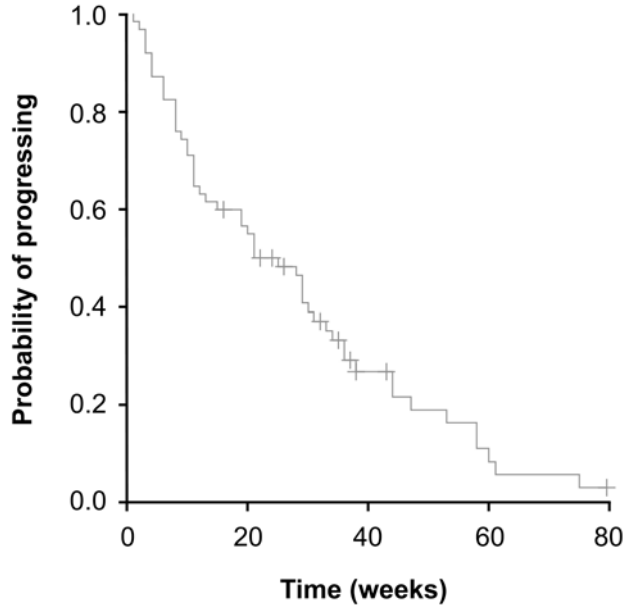

Figure 2: Kaplan-Meier estimates for progression-free survival.

Tumour response to treatment was not assessed in seven (11.3%) patients. Partial response was observed in eight (12.9%) patients, stable disease in 34 (54.8%) and disease progression in 13 (21.0%). The ORR was 12.9% (95% CI, 4.7-21.3) and tumour growth control rate was 67.7% (95% CI, 79.3-56.1).

Salvage surgery was performed in four (6.5%) patients, who had locally advanced pancreatic cancer, with R0 resection in two (3.2%) patients, R1 resection in another (1.6%) and palliative R2 resection in another (1.6%).

Safety

The most common adverse events reported during the study are described in Table **3**. Acneiform rash occurred in 35 (56.5%) patients, which was grade 1 rash in 16 (25.8%) patients, grade 2 rash in 16 (25.8%) and grade 3 rash in three (4.8%). The main grade 3/4 haematological adverse events were neutropenia, anaemia and thrombocytopenia (Table **3**). The main grade 3/4 non-haematological adverse events were asthenia, infections and anorexia (Table **3**).

Table 3: Main Adverse Events Reported During the Study (N=62)

Main adverse events	All grades	Grade 3/4
Haematological adverse events:		
Anaemia, n (%)	62 (100)	12 (19.4)
Neutropenia, n (%)	48 (77.4)	25 (40.3)
Thrombocytopenia, n (%)	41 (66.1)	11 (17.7)
Increased GPT levels, n (%)	26 (41.9)	5 (8.1)
Increased GOT levels, n (%)	23 (37.1)	3 (4.8)
Increased bilirubin levels, n (%)	16 (25.8)	4 (6.5)
Glycaemia, n (%)	8 (12.9)	2 (3.2)
Non-haematological adverse events:		
Asthenia, n (%)	53 (85.5)	14 (22.6)
Diarrhoea, n (%)	37 (59.7)	3 (4.8)
Acneiform rash, n (%)	35 (56.5)	3 (4.8)
Nausea, n (%)	29 (46.8)	2 (3.2)
Anorexia, n (%)	28 (45.2)	6 (9.7)
Vomiting, n (%)	25 (40.3)	4 (6.5)
Infection, n (%)	21 (33.9)	9 (14.5)
Mucositis, n (%)	18 (29.0)	1 (1.6)
Fever, n (%)	18 (29.0)	0 (0.0)
Constipation, n (%)	11 (17.7)	0 (0.0)
Haemorrhage, n (%)	11 (17.7)	0 (0.0)
Alopecia, n (%)	10 (16.1)	0 (0.0)
Thrombosis, n (%)	7 (11.3)	8 (8.1)
Oedema, n (%)	7 (11.3)	0 (0.0)

All-grade adverse events occurring at a frequency ≥10% are presented.
GPT: glutamate-pyruvate transaminase; GOT: glutamate oxaloacetate transaminase.

Three (4.8%) patients died as a result of adverse events: septic shock probably related to study treatment (n=1), cholangitis probably not related to study treatment (n=1) and bilateral pulmonary embolism probably not related to study treatment (n=1).

DISCUSSION

Administration of 1500 mg/m^2 of gemcitabine in 150-minute fixed-dose-rate infusions in combination with erlotinib was a feasible and active regimen for patients with advanced pancreatic cancer. The activity of this treatment combination resulted in a median OS of 10.0 months, with patients with locally advanced pancreatic cancer, females and those not receiving opioid therapy obtaining a greater benefit. A trend towards longer OS was also observed in patients with grade ≥2 rash that did not reach statistical significance probably because of the relatively small sample size of our study. However, only gender remained significant as an independent prognostic factor for OS in the multivariate analysis carried out in the study. Furthermore, patients showed a median PFS of 4.9 months, which was longer in patients with locally-advanced pancreatic cancer and females, an ORR of 12.9%, and a tumour growth control rate of 67.7%. The identification of patients who are more likely to benefit from therapy and predictive-biomarkers of therapeutic activity plays a main role in the achievement of improvements in pancreatic cancer treatment [13]. Indeed, there is a growing interest in the identification of EGFR pathway biomarkers that may serve as prognostic and/or predictive targets. Even though limited data is still available in patients with pancreatic cancer treated with erlotinib, study findings have pointed out the KRAS status as a potential prognostic biomarker [14] and the EGFR intron 1 polymorphism as a predictive marker of pancreatic cancer aggressiveness and erlotinib sensitivity [15]. Unfortunately, our study cannot provide additional data on molecular biomarkers and further studies are still needed to confirm their role.

The OS shown in our study was slightly longer than the 8 months reported by the only study that addressed the administration of fixed-dose-rate infusions of gemcitabine plus erlotinib, with a median time to progression of 5 months [9]. The regimen used in this study was slightly different to ours, consisting of a lower dose of gemcitabine of 1200 mg/m^2 being administered during shorter infusions of 120 minutes. Like in our study, both OS and PFS were shorter in patients with metastatic disease and, although patients with grade ≥2 rash attained longer OS, this difference did not reach statistical significance. Even though the ORR reported by this study was 28%, the tumour growth control rate remained at 54%. However, these slight differences do not ensure the existence of real differences between the treatment regimens, as direct comparisons would be needed to confirm them.

The use of fixed-dose-rate infusions of gemcitabine instead of the standard 30-minute bolus appears to improve the efficacy of gemcitabine and erlotinib combination. Although no direct comparison has been carried out, 1000 mg/m^2 of gemcitabine administered in 30-minute infusions plus erlotinib appears to achieve lower benefit, with a median OS of 6.2 months, a median PFS of 3.8 months, an ORR of 8.6% and a tumour growth control rate of 57.5% [8]. However,

female gender [8] and grade ≥2 rash have been identified as factors that may be associated with a higher likelihood of achieving greater benefit [8, 16]. The potential greater benefit of fixed-dose-rate infusions of gemcitabine in comparison with its administration in 30-minute bolus infusions has been previously reported in a randomized trial, which also demonstrated an advantage in accumulation of gemcitabine triphosphate in the fixed-dose-rate infusion arm [10]. However, the fixed-dose-rate infusion schedule also appeared to have a more toxic effect, with 48.8% of patients experiencing grade 3/4 neutropenia and 37.2% grade 3/4 thrombocytopenia. Conversely, another randomized trial did not reach statistical significance in the improvement achieved with fixed-dose-rate infusions in comparison with 30-minute bolus infusions, may be because of differences in patients' baseline characteristics and dose modifications [6]. In this study, the addition of oxaliplatin to 100-minute infusions of 1000 mg/m^2 of gemcitabine also did not achieve significant improvements, reaching a median OS of 5.7 months, a median PFS of 2.7 months, an ORR of approximately 9.4%, and with myelosuppression as the most significant toxicity. Although further information comparing the addition of agents to fixed-dose-rate infusions of gemcitabine is not available, our results have also shown better OS, with comparable or also improved PFS and ORR, than other recently reported treatment combinations such as the addition of capecitabine (OS, 7.1-8.4 months; PFS, 5.3-4.3 months; ORR, 10.0%-19.1%) [17, 18], bevacizumab (OS, 5.8 months; PFS, 3.8 months; ORR, 13%) [19] or cetuximab (OS, 6.3 months, PFS, 3.4 months; ORR, 12%) [20] to conventional 1000 mg/m^2 gemcitabine infusions, or the addition of bevacizumab to gemcitabine plus erlotinib (OS, 7.1 months; PFS, 4.6 months; ORR, 13.5%), with neutropenia being reported as the main grade 3/4 toxicity [17-21].

The safety profile of the combination of 1500 mg/m^2 gemcitabine in 150-minute fixed-dose-rate infusions and erlotinib observed in our study was manageable, with neutropenia, anaemia, thrombocytopenia, asthenia and infections being reported as the main grade 3/4 adverse events. Similarly, the only study that previously addressed the administration of 1200 mg/m^2 in 120-minute infusions plus erlotinib in patients with advanced pancreatic cancer also reported neutropenia, thrombocytopenia, asthenia and anaemia as the most commonly observed grade 3/4 toxicities [9]. Haematological toxicity has also been reported during the administration of 30-minute infusions of gemcitabine plus erlotinib, though in a lower percentage of patients [8, 16]. The pattern of non-haematological toxicities was on overall similar, mainly including grade 1/2 asthenia/fatigue, rash, gastrointestinal disorders (diarrhoea and nausea/vomiting) and infections [8, 16]. As toxicities may restrict the administration of cancer therapies, especial attention should be paid to improve treatment tolerance; thus, the adequate prevention and management of both treatment toxicities and toxicity-related complications represent key points to be taken into account. Although fixed-dose-rate infusions of gemcitabine might be associated with increased haematological toxicities compared to the standard 30-minute infusions [6, 8, 10, 16] and some recently reported 30-minute infusion combinations [17-21], the overall tolerance of fixed-dose-rate infusions of gemcitabine plus erlotinib has been reported to enable rates of early treatment discontinuation to remain low and treatments to be administered at over 90% of pre-planned doses [9]. Furthermore, the administration of fixed-dose-rate infusions of gemcitabine plus erlotinib in our study did not cause adverse events different from those already reported during the administration of 30-minute infusions, the percentage of grade 3/4 toxicities remained acceptable and the dose intensity finally administered supports its tolerability. Thus, the manageable toxicity profile and the benefit obtained in our patient population highlights the importance of balancing risk-benefits when tailoring the treatment to patients needs.

Several limitations should be considered when interpreting our results. These limitations include the relatively small sample size of our study and the absence of a control group. Additionally, biases derived from the potential influence of the administration of second- and third-line therapies in our findings cannot be ruled out. Since results obtained in a single-site study are difficult to generalize to the whole population of patients with locally advanced or metastatic pancreatic cancer, further multicenter studies are still needed to confirm the generalisability of our results. Even though our findings should be considered with caution, the authors still believe that they provide valuable information for the treatment of locally advanced and metastatic adenocarcinoma of the pancreas.

In conclusion, the combination of fixed-dose-rate infusions of gemcitabine and erlotinib represents a feasible and active regimen for advanced pancreatic cancer, which has a manageable safety profile.

Although greater benefit might be obtained in patients with locally advanced pancreatic cancer, females and patients not receiving opioid therapy, only gender showed to be an independent prognostic factor. Therefore, further assessment of predictive and prognostic factors is still needed to tailor the therapeutic approach for advanced pancreatic cancer to patient needs. Additionally, even though fixed-dose-rate infusions of gemcitabine might be associated with the increase in haematological toxicities, the combination of prolonged infusions of gemcitabine and targeted therapies merits further evaluation for patients with advanced pancreatic cancer in randomized clinical trials.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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