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CLINICAL TRIAL REPORT

Phase II study of a fixed dose-rate infusion of gemcitabine associated with erlotinib in advanced pancreatic cancer

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Abstract
Purpose To evaluate the feasibility, toxicity and efficacy of the combination regimen consisting of gemcitabine-FDR infusion plus erlotinib, in ACP patients.
Methods Forty-two patients with histologically confirmed, locally advanced or metastatic pancreatic cancer were included in this phase II trial. Main objectives were to assess the efficacy and safety of this regimen. Therapeutic regimen consisted of gemcitabine 1,200 mg/m^2 in 120-min infusion on days 1, 8 and 15, plus erlotinib 100 mg orally once daily. Cycles were repeated every 28 days.
Results A total of 160 courses of gemcitabine-FDR erlotinib were administered (median 3.8 courses per patient). The most common grade 3–4 AEs were neutropenia (21%), thrombocytopenia (10%), skin rash (10%) and asthenia (10%). Complete response was achieved in one patient (2%) and 11 (26%) achieved a partial response. Stable disease and progression disease were observed in 11 patients (26%) and 19 (45%), respectively. Median time to progression was 5 months (95%CI: 3.9–5.8 months) and median overall survival was 8 months (95% CI: 5.1–10.8). One-year survival rate was 35%.
Conclusions A regimen consisting of gemcitabine-FDR infusion plus erlotinib is active and well tolerated in APC patients. However, the results do not justify the conduct of a Phase III trial.

Keywords Gemcitabine · Pancreatic carcinoma · Erlotinib · FDR

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Introduction

Pancreatic adenocarcinoma ranks fourth among causes of cancer-associated death in the USA [1] and fifth in Europe [2]. It has been estimated that 58,000 new cases are diagnosed every year in Europe [2]. More than 80% of the patients have an unresectable tumour at diagnosis (locally advanced and/or metastatic). Curative therapeutic options for these patients are lacking. Pancreatic cancer is classically considered a chemoresistant tumour. However, a recently reported meta-analysis has shown that chemotherapy treatment improves median overall survival when compared with best supportive care (hazard ratio [HR] = 0.64; 95% CI [0.42–0.98] [3].

Gemcitabine as a single agent is the standard chemotherapy treatment for metastatic pancreatic cancer patients. This treatment showed clinical benefit in 24% of the patients as well as an improvement of the median overall survival when compared with bolus 5-fluororacil, in spite

of both an objective response rate inferior to 10% and a median overall survival inferior to 6 months [4]. Gemcitabine-based combination regimens have been evaluated in order to improve these modest results. However, although a number of phase III trials have been performed [5–12], only gemcitabine plus erlotinib showed a significant improvement in median overall survival when compared with gemcitabine alone ([HR] for death = 0.82; $P = 0.038$) [13].

Another strategy that has been tested in order to improve gemcitabine-alone results is to optimise its pharmacokinetic profile through its administration at a fixed dose rate (FDR). Gemcitabine is a prodrug which must be intracellularly phosphorilated by deoxycytidine kinase to be converted in its active metabolites difluorodeoxycytidine di- and triphosphate (dFdCDP and dFdCTP). The rate of formation of this metabolite is dose-rate dependent and can be increased through the use of prolonged infusion, thereby enhancing its cytotoxic effect [14, 15]. In a phase I trial of gemcitabine-FDR infusion alone, it was found that the maximum tolerated dose was 1,500 mg/m^2 administered in 150 min [16]. A randomised phase II trial that compared gemcitabine 2,200 mg/m^2 in 30 min and 1,500 mg/m^2 in 150 min showed that the FDR arm resulted in a higher response rate (16.5 vs. 2.7%) and also, in an improvement in one-year survival rate (23 vs. 0%). In addition, levels of dFdCTP in mononuclear cells were significantly higher in the FDR arm (336 vs. 114 μM; $P = 0.003$) [17].

Thus, in view of the activity of both gemcitabine-FDR infusion and erlotinib in pancreatic cancer, we designed a multicentre phase II trial in order to assess the efficacy and safety of a combination regimen consisting of gemcitabine-FDR infusion plus erlotinib, in advanced pancreatic cancer (APC) patients.

The dose of gemcitabine used in our study was 1,200 mg/m^2 in 120 min and erlotinib 100 mg/d. This dose of gemcitabine corresponds to the immediately dose level below to the maximum tolerated dose reached in the Phase I study of gemcitabine-FDR by Touroutoglou [16]. The reasons to proceed thus were based on the results of a randomised phase II trial, which showed that using the maximum tolerated dose of gemcitabine (1,500 mg/m^2 in 150 min), resulted in high rates of haematologic adverse events, specifically grade 3–4 thrombocytopenia and neutropenia in 37 and 49% of the patients, respectively [17]. On the other hand, this dose coincides with the recommended dose in another phase I trial, which assessed the combination of gemcitabine-FDR infusion plus gefitinib [18].

Materials and methods

Patient population

From September 2007 to June 2009, 42 patients with histologically or cytologically confirmed APC entered in this study. Patients were treated in the Medical Oncology Departments of five Spanish hospitals. Eligible patients had (1) locally advanced or metastatic disease not potentially curable by other therapeutic modalities; (2) Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 2; (3) an estimated life expectancy of at least 12 weeks; (4) at least 2 weeks recovery from any surgical procedure; (5) adequate bone marrow function, that is, a granulocyte count of 2×10^9/l or greater, and a platelet count of 100×10^9/l or greater; (6) normal renal function, as defined by a serum creatinine level of less than 115 μmol/l and a creatinine clearance over 60 ml/min; (7) adequate hepatic function, that is, serum bilirubin of less than 35 μmol/l, serum glutamic oxaloacetic transaminase (SGOT) and serum pyruvic transaminase (SGPT) levels less than three times the upper normal limit, unless these alterations were due to metastatic disease, in which case an increase up to five times the upper normal limit was allowed. Patients with any prior chemotherapy for advanced disease, brain or meningeal metastases, or a history of any other malignancy were excluded, except in cases of basal-cell carcinoma or in situ cervical carcinoma adequately treated. The study was performed after approval by the appropriate independent ethical committee of each site and in accordance with the Declaration of Helsinki, Good Clinical Practices, and local ethical and legal requirements. Patients provided written informed consent according to directives of local ethical committees.

All patients had measurable disease, as defined by the presence of at least one lesion clearly measurable by computed tomography scan according to the Response Evaluation Criteria in Solid Tumours (RECIST) [19]. Pleural effusion, ascites, osteoblastic lesions or previously irradiated lesions were not accepted as measurable disease. Patients who had received radiotherapy were eligible if there was at least one measurable lesion outside the radiation field.

Treatment plan

The study regimen consisted of gemcitabine 1,200 mg/m^2 in 120 min once weekly for three consecutive weeks, given through an infusion pump in a 4-week cycle. Erlotinib (100 mg/day orally ≥1 h before or after food) was given continuously from day 1 of cycle 1. Courses were repeated every 28 days for a minimum of three per patient, unless progressive disease, unacceptable toxicity or consent withdrawn.

Gemcitabine dose was delayed for 1 week if neutrophil count was $<1.5 \times 10^9$/l or platelet count was $<100 \times 10^9$/l on the first day of the course. Therapy was definitely discontinued if toxicity persisted after a 2-week delay. A 50% reduction in the dose of gemcitabine was performed on days 8 and 15 of every course in the case of a neutrophil

count between 1 and 1.5×10^9/l or a platelet count between 75 and 100×10^9/l; gemcitabine dose was omitted in the case of lower counts of neutrophil or platelets. In the case of grade 3–4 non-haematological toxicity, the dose was omitted. Erlotinib dose was interrupted in patients with intolerable rash and was reduced or discontinued if symptoms persisted for ≥10–14 days. Erlotinib dose was reduced for grade 2 diarrhoea persisting for ≥48–72 h and for grade 3 diarrhoea following resolution to grade 1; erlotinib was permanently discontinued for grade 4 diarrhoea.

Assessments

Patients had a full clinical history, physical examination, PS assessment, haematological and biochemical profiles (including CA19-9 level), a chest X-ray and a computed tomography scan of the chest and abdomen at baseline. Additional imaging investigations were performed if clinically indicated. A blood analysis including haematological counts, serum chemistry and creatinine level was performed weekly. A computed tomography scan was repeated every 8 weeks. Response and progression were evaluated using the Response Evaluation Criteria in Solid Tumors [19]. At the end of chemotherapy, all clinical, laboratory and imaging studies were repeated and patients underwent follow-up examination every 2 or 3 months until death. Toxicity was assessed at every visit using the National Cancer Institute Common Toxicity Criteria version 3.0 (NCI-CTCAEv3.0).

Statistical analysis

The primary endpoint was response rate and secondary endpoints were overall survival, time to progression and safety profile. Dose intensity was calculated by dividing the total mg/m^2 of drug given by the number of weeks elapsed from the beginning of therapy to the end of the last cycle. We anticipated that any first-line regimen for APC associated with at least 20% response rate would be of further interest. The sample size was designed to reject a response rate of less than 20%. According to the Fleming method [20], 19 patients were first included. As the response rate was over 21%, up to 35 patients were included plus a 10% to allow for losses, which gives 38 patients. The Kaplan–Meier method was used to estimate median overall survival, median time to progression and 1-year survival rate.

Results

Patient characteristics

A total of 42 patients were included in the study. Demographic characteristics are listed in Table 1. Six patients (14%) had unresectable locally advanced tumours, as it was assessed by means of a laparotomy procedure. Thirty-six patients (86%) had metastatic disease, including five with relapse after prior primary tumour radical resection. All patients meet eligibility criteria, received at least one dose drug and were evaluable for response and toxicity.

Table 1 Patient characteristics

Characteristics	Patients (%)
Gender	
Male	22 (52%)
Female	20 (48%)
Median age, years (range)	62 (47–79)
ECOG performance status	
0	8 (19%)
1	21 (50%)
2	13 (31%)
Pain score (range)	
0–29	21 (50%)
30–49	13 (31%)
50–100	8 (19%)
Weight loss	
None	10 (24%)
1–10%	20 (48%)
>10%	12 (28%)
Disease at presentation	
Locally advanced	6 (14%)
Metastatic disease	36 (86%)
Sites of metastatic disease	
Liver	27 (64%)
Lymph nodes	13 (31%)
Lung	6 (14%)
Peritoneum	4 (10%)
Others	6 (14%)

ECOG Eastern Cooperative Oncology Group

Treatment summary

A total 160 chemotherapy cycles were administered (mean by patient 3.8; range 1–12). Five patients received seven or more cycles. Nine patients received less than three cycles: seven as a consequence of disease progression, including two patients who died by intestinal obstruction, one patient who was lost to follow-up and another one who withdrew consent after having received the first cycle. All the patients were included in toxicity and efficacy analysis, following an intention-to-treat analysis.

Median dose intensity of erlotinib was 679 mg/m^2/week and that of gemcitabine was 828 mg/m^2/week, which corresponded to 97 and 92% of the pre-planned dose, respectively. Erlotinib dose was reduced by 25% in 4

Table 2 Toxicity (NCI-CTCv 3.0) per patient during the whole trial

Toxicity	Grade 0	Grade 1–2	Grade 3–4
Neutropenia	25 (60%)	8 (19%)	9 (21%)
Thrombocytopenia	32 (76%)	6 (14%)	4 (10%)
Asthenia	27 (64%)	11 (26%)	4 (10%)
Skin rash	23 (54%)	15 (36%)	4 (10%)
Anaemia	21 (50%)	18 (43%)	3 (7%)
Diarrhoea	28 (66%)	12 (29%)	2 (5%)
GOT	37 (88%)	4 (10%)	1 (2%)
GPT	36 (86%)	5 (12%)	1 (2%)
Nausea/vomiting	33 (79%)	9 (21%)	0

Table 3 Therapeutic results in 42 patients

Results	Patients (%)
Complete response	1 (2%)
Partial response	11 (26%)
Stable disease	11 (26%)
Progressive disease	19 (45%)
Overall response rate	12 (28%)

patients (10%) and weekly gemcitabine dose was also reduced by 25% in 12 patients (30%).

Toxicity

All 42 patients were evaluable for toxicity (Table 2). Treatment was well tolerated, and the main toxicity was haematologic. Observed grade 3–4 toxicities were as follows: neutropenia in 9 patients (21%), thrombocytopenia in 4 patients (10%), anaemia in 3 (7%), asthenia in 4 (10%) and diarrhoea in 2 (5%). Four patients (10%) experienced grade 3 skin rash and another 9 (21%) experienced grade 2 skin rash. In addition, transient transaminases increase was observed in one patient and nephrotic syndrome in another one. Adverse events led to permanent discontinuation of the treatment in 3 patients (7%).

Response and survival

A complete response was achieved in one patient (2%), a partial response in 11 patients (26%) and stable disease in 11 patients (26%). Progression disease was observed in 19 patients (45%). Overall response rate was 28% (95% CI: 16–45%) (Table 3). Response rate was correlated with neither stage nor percentage of weight loss nor ECOG PS. Median time to progression was 5 months (95% CI: 3.9–5.8) (Fig. 1), median overall survival was 8 months (95% CI: 5.1–10.8) (Fig. 2) and one-year survival rate was 35%. The median time to progression in patients with stage IV was 4 months (95% CI: 3.1–5 months) and the medial overall survival was 7 months (4.7–9.2 months). Median overall survival in the group of patients who experienced a grade ≥2 skin rash was 10 months, whereas it was 7 months in the group of patients who did not; this difference was statistically non-significant.

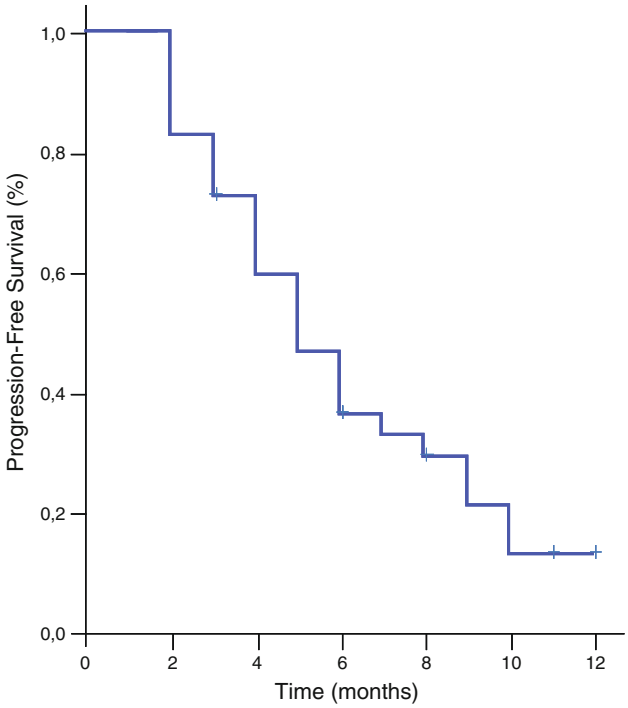

Fig. 1 Kaplan–Meier estimates for time to tumour progression

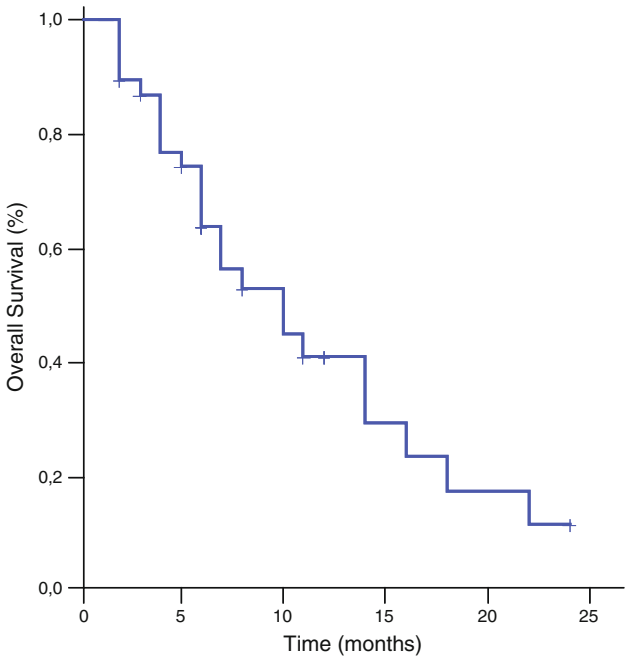

Fig. 2 Kaplan–Meier estimates for overall survival

Discussion

Pancreatic cancer represents an important health problem. Among gastrointestinal tumours, it ranks last in five-year survival rate. During the last decade, gemcitabine, administered in a 30-min bolus, has been the standard chemotherapy treatment for APC [4]. As it has recently been reported, the addition of erlotinib to gemcitabine has improved the results of gemcitabine alone, resulting in an 18% reduction of the risk of death (HR = 0.82) [13]. However, in spite of these advances, median overall survival is still about 6 months. Thus, it is essential to continue the research on new agents or therapeutic strategies in order to improve these results.

Our study should be placed in this setting. It is the first phase II trial assessing efficacy and safety of a combination of gemcitabine-FDR infusion in combination with erlotinib. This regimen is active, showing a 28% overall response rate, a median time to progression of 5 months and a median overall survival of 8 months. These results seem to be superior to both the results achieved with standard gemcitabine 30-min bolus plus erlotinib (overall response rate 8%, median time to progression 3.75 months and median overall survival 6.37 months) [13] and the results achieved with gemcitabine-FDR alone (overall response rate 10–14%, median time to progression 3.3–3.5 months and median overall survival 6.2–6.4 months) [21, 22]. However, direct comparisons between the results of our study and the ones of other studies should be considered with caution as our sample size is relatively small and there are five (12%) censored cases. Furthermore, it is necessary to take into account possible differences in the characteristics of the patients. In this sense, it should be highlighted that patient characteristics in our study were a bit more unfavourable than the patients included in the study of Moore et al. [13] regarding both ECOG PS 2 (31 vs. 19%) and the percentage of locally advanced tumours (14% vs. 23%).

As the erlotinib dose we used is similar to the one used in the study of Moore et al. [13], the differences should be attributed to the administration of gemcitabine as a FDR infusion. This form of administration allows to reach both gemcitabine plasmatic concentrations and intracellular levels of dFdCTP, which are significantly higher than the levels achieved with the gemcitabine 30-min infusion [17, 21]. In orthotopic tumour xenografts, it was demonstrated that erlotinib significantly inhibited the phosphorylation of ErbB-1 and other downstream kinases and significantly promoted gemcitabine-induced apoptosis in vivo [23]. Thus, it is possible to speculate that gemcitabine-FDR infusion, after achieving higher intracellular concentrations of its active metabolites, would optimise these gemcitabine-erlotinib synergistic effects.

Palliation is the main objective of the treatment of APC. Thus, it is essential to take treatment-associated adverse events into account. Haematologic was the most important toxicity observed. Grade 3–4 neutropenia and thrombocytopenia were observed in 21% and 10% of the patients, respectively. These rates are clearly inferior to the rates reported (neutropenia 59% and thrombocytopenia 33%) in a phase III trial which used gemcitabine-FDR alone at 1,500 mg/m^2 in 150 min [21], in one out of three arms. In fact, gemcitabine-associated adverse events led to the permanent discontinuation of the treatment in 19% of the patients in the gemcitabine-FDR arm of this study. On the contrary, toxicity of our regimen has been moderate and allowed the administration of 92% of the pre-planned gemcitabine dose as well as 97% of the pre-planned erlotinib dose. Moreover, only 7% of the patients required permanent discontinuation of the treatment. Good tolerance results were due to that gemcitabine dose in our study was inferior to the dose administered in previous studies [17, 21] which used the maximum tolerated dose achieved in a phase I trial of gemcitabine-FDR infusion alone [16].

In the last few years, several phase III clinical trials on APC have been conducted, on the basis of promising results of phase II studies. These randomised studies have finally shown negative results [8, 11, 24]. As a result of this, caution is advisable when interpreting the results of phase II clinical trials. Recently, it has been recommended that the primary end point in Phase II studies carried out in advanced pancreatic cancer should be the overall survival [25]. According to this criteria, although the median survival obtained in our study is relevant (8 months), the limits of the CI (5.1–10.8) do not guarantee that the results have been superior to those obtained with other schemes. Therefore, despite the high rate of objective responses achieved, we cannot recommend the implementation of Phase III studies.

However, the results of our study (28% responses and 35% survival per year) suggest that there is a group of patients who may benefit of this treatment. Unfortunately, no clinical or molecular markers for benefit derived from erlotinib-based treatments are currently available [13, 26]. Although grade of skin rash has been considered as a predictive factor for erlotinib benefit [13, 27], our study failed to show this relationship, probably due to a small sample size. Regarding gemcitabine, the value of the polymorphisms in the deoxycytidine kinase [28] and cytidinedeaminase [29] genes as well as of the genes related with gemcitabine transport [30, 31] is currently under investigation. Identification of these markers will probably allow for better selection of the patients who would benefit from this treatment.

In conclusion, a combination regimen consisting of gemcitabine-FDR infusion plus erlotinib is active and well

tolerated in APC patients. However, because of its modest impact on survival and the previously reported results of the E6201 trial [21], evaluation of this regimen in a Phase III trial is not justified.

Conflict of interest The authors report no conflict of interest.

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