

Fixed-dose-rate gemcitabine infusion in patients with advanced pancreatic or biliary tree adenocarcinoma

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ABSTRACT

Aims and background. Gemcitabine is an effective agent in pancreatic adenocarcinoma. Fixed-dose-rate gemcitabine has an interesting biological and clinical rationale, with successful results in previous studies. We conducted a trial to confirm efficacy and toxicity of fixed-dose-rate gemcitabine in patients with pancreatic or biliary tree adenocarcinoma.

Methods. Eligible patients with locally advanced or metastatic pancreatic or biliary tree adenocarcinoma received fixed-dose-rate gemcitabine at a dose of 1500 mg/m² at a rate of 10 mg/m²/min weekly for 3 weeks every 28 days. Efficacy measures were overall survival, response rate and progression-free survival.

Results. Sixty-two patients were enrolled, and 59 were assessable for response. Seven patients (11.3%) had a partial response, 26 stable disease (41.9%) and 26 progressive disease (41.9%). Median time to progression was 21 weeks and median overall survival, 37.71 weeks. Main toxicities were grade 3-4 neutropenia (45.2%) and grade 2-3 asthenia (54.8%). No toxic deaths were documented.

Conclusions. Fixed-dose-rate gemcitabine has a relevant antitumor activity but with significant toxicity. It represents an interesting schedule and could be combined with other biological or chemotherapeutic agents. Free full text available at www.tumorionline.it

Introduction

Pancreatic adenocarcinoma is the fourth cause of cancer-related death in the United States and one of the most aggressive cancers in humans¹. Only 15 to 20% of patients present with resectable disease at diagnosis, and median overall survival for patients with locally advanced or metastatic disease ranges from 6 to 10 months and 3 to 6 months, respectively.

Biliary tree carcinoma represents a less frequent malignancy arising from epithelial cells of intra- and extrahepatic bile ducts, and it shares some aspects of biology and clinical behavior with pancreatic adenocarcinoma. Surgery provides the only possibility for cure², and, again, prognosis is extremely poor, with a 5-year overall survival of 5 to 10%. Traditional goals of palliative chemotherapy for these conditions are radiologic response rate, progression-free survival and overall survival, but symptomatic control and quality of life issues should also be addressed.

Gemcitabine, a nucleoside analogue antimetabolite, has shown modest response rates in advanced and metastatic pancreatic adenocarcinoma in several phase II trials. Burris *et al.*³, in their pivotal phase III trial, compared gemcitabine to single-agent 5-fluorouracil bolus. The authors reported an improved clinical benefit, response rate and survival for patients receiving gemcitabine, which since then has become standard. In the same way, gemcitabine has also shown antitumor activity in patients with advanced biliary tree carcinoma^{4,5}.

Key words: bile duct carcinoma, fixed-dose-rate infusion, gemcitabine, pancreatic cancer.

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In early phase I trials, some investigators^{6,7} found that the ability of mononuclear cells to phosphorylate gemcitabine is limited, and the optimal plasma concentration of the drug was obtained by using fixed-dose-rate (FDR) infusions of 10 mg/m²/min.

Following such rationale, two phase II trials and one phase III trial have been published. Tempero *et al.*⁸ published in 2003 a randomized phase II trial comparing gemcitabine as a 30 min infusion of 2200 mg/m² (considered the standard arm) and an FDR infusion of 1500 mg/m² of gemcitabine over 150 min (experimental arm). Median overall survivals were 8 vs 5 months in favor of the FDR infusional arm ($P = 0.013$). One and 2-year survivals were respectively 28% and 18.3% for the experimental arm and 9% and 2.2% for the standard arm.

Gelibter *et al.*⁹ published in 2005 another phase II study including 40 patients, 13 of them with biliary tree adenocarcinoma, who received 1000 mg/m² of FDR gemcitabine. Although the dose was reduced by 33%, the trial confirmed the promising activity of the regimen, with low toxicity.

Poplin *et al.*¹⁰ have recently published the results of the ECOG 6201 trial. They compared standard gemcitabine with FDR infusion of gemcitabine and with an FDR infusional gemcitabine combined with oxaliplatin. The negative results reported deserve an extensive discussion.

However, the standard 30-min infusion of gemcitabine has yielded worse outcomes than those obtained with the combination with platinum salts^{11,12} or with erlotinib¹³ at the expense of higher toxicity or higher costs.

With this body of evidence, we investigated the efficacy and toxicity of FDR gemcitabine at a dose of 1500 mg/m² over 150 min in patients with advanced pancreatic or biliary tree adenocarcinoma.

Patients and methods

Patients with histologically confirmed unresectable (locally advanced or metastatic) pancreatic or biliary tree adenocarcinoma were eligible for the study. Eligibility criteria included age >18 years, ECOG performance status ≤ 2 , a life expectancy of more than 3 months, measurable disease, and an adequate bone marrow function (absolute neutrophil count $>1500 \times 10^9/L$ and a platelet count $>100,000 \times 10^9/L$). Exclusion criteria were inadequate hepatic (bilirubin >1.5 mg/dL) or renal function (creatinine >1.3 mg/dL) and the presence of serious comorbidities for chemotherapy or follow-up. Written informed consent was required before patient inclusion in the study.

Treatment and study design

Patients received gemcitabine, 1500 mg/m² at a rate of 10 mg/m²/min weekly on days 1, 8 and 15 every 4

weeks. Treatment was given until progression or unacceptable toxicity. Patients were evaluated by a physical examination, complete anamnesis and performance status. Analytical studies included complete blood count, blood chemistry measurements with creatinine, bilirubin and CA 19.9 (normal level below 37 U/ml). Radiological baseline evaluation was performed with computed tomography, and the presence of at least one measurable lesion was required.

Response was assessed every 2 cycles according to RECIST criteria. During treatment, blood count and physical examination were performed on days 1, 15 and 28. Toxicity was evaluated according to NCI-CTCAE v. 3.0. Doses were administered at 75% in the next cycle if a grade 3-4 hematological toxicity was experienced. Intracycle doses were reduced by 50% if granulocyte count dropped to $0.5-0.99 \times 10^9/L$ or platelet count to $50-74 \times 10^9/L$. No gemcitabine was given when granulocyte count was less than $0.5 \times 10^9/L$ or platelet count less than $50 \times 10^9/L$. In case of grade 2 nonhematological toxicity (except nausea and vomiting), gemcitabine was reduced to 75% of the doses, and for grade 3 or more we stopped treatment until toxicity recovered to grade 2 or better.

We also evaluated some indicators of clinical benefit such as the best ECOG performance status recorded during treatment and the evolution of CA19.9 levels, determined at baseline and in each cycle.

Statistical methods

On the basis of previous studies that established efficacy and toxicity of FDR gemcitabine, the study began by the end of 2003. A retrospective review was performed to determine outcomes in the patients.

Overall survival was the main objective and was defined as the time from the date of the first cycle of chemotherapy until death or last follow-up. Patients lost to follow-up were censored on the last visit. Probability estimates for overall survival were calculated by the Kaplan-Meier method¹⁴.

Univariate and multivariate Cox proportional hazard regression model analyses were performed. Included in the multivariate analysis were factors that were significant in the univariate analysis ($P < 0.05$) and factors that did not reach significance but in the medical literature were considered relevant.

Results

Between September 2003 and March 2007, 62 patients with advanced or metastatic pancreatic or biliary tree adenocarcinoma were treated in our institution. All patients were assessable for toxicity and 59 for response. Patient characteristics are shown in Table 1. Of note, 11 patients received 6 cycles of adjuvant chemotherapy

Table 1 - Patient characteristics

Characteristic	No.	%
Median age, yr (range)	61.5 (42-77)	
Gender		
Male	43	69.4
Female	19	30.6
Location		
Pancreas	46	74.2
Biliary tree	16	25.8
Locally advanced	18	29.0
Metastatic	44	71.0
ECOG PS		
0	22	35.5
1	41	54.8
2	8	9.7
Other chemotherapy:		
Adjuvant	11	17.1
Palliative	21	33.8
Radiotherapy	5	8

with 5-fluorouracil and folinic acid. After FDR gemcitabine failure, 21 patients received second-line therapy with capecitabine or mainly with oxaliplatin plus capecitabine.

Efficacy. Partial response was seen in 7 patients (11.3%), stable disease in 26 (41.9%), and progressive disease in 26 (41.9%). Three patients were not evaluated (4.8%): 1 case was lost to follow-up, and 2 died before response evaluation (one after complications of endoscopic retrograde cholangiopancreatography and the other after complications of a surgical procedure due to bowel perforation). No response was observed among patients with biliary tree carcinoma.

Two patients were further resected and one of them was still free of disease at the last control. A clinical benefit, measured by an improvement in performance status, was observed in 20 patients (32.25%) during chemotherapy.

Forty-five (72.58%) patients had elevated basal levels of CA19.9 (in 25 [40.32%] of them, CA19.9 levels were above 1000 U/ml). After therapy, 24 (53%) of these 45 patients had a decrease of at least 50% in CA19.9 levels, which represented a biological response to therapy.

Toxicity. Most treatment-related adverse events were grade 2-3, but grade 4 neutropenia was observed in 12 patients (19%). Hematological and nonhematological toxicities are shown in Tables 2 and 3, respectively. One patient developed hemodynamic angor during chemotherapy and another a myocardial stroke causing gemcitabine withdrawal. Seven patients (11.29%) developed venous thrombosis and anticoagulant therapy was indicated.

Dose intensity. The mean number of cycles administered was 4.61 (range, 1-17). Of the planned 868 infusions of chemotherapy, there were 102 omissions (11.75%) and 138 dose reductions (15.89%).

Survival. Median overall survival was 37.71 weeks (95% CI, 27.44-47.99) (Figure 1), and 32% of the patients

Table 2 - Hematological toxicity (no. of patients and in parenthesis, percentage)

	Grade 3	Grade 4
Anemia	8 (12.9)	1 (1.6)
Neutropenia	16 (25.8)	12 (19.4)
Thrombocytopenia	5 (8.1)	3 (4.8)

Table 3 - Non-hematological toxicity (no. of patients and in parenthesis, percentage)

	Grade 2	Grade 3	Grade 4
Vomiting	9 (14.5)	3 (4.8)	-
Diarrhea	10 (16.1)	-	-
Asthenia	24 (38.7)	10 (16.1)	-
Anorexia	4 (6.4)	-	-
Liver toxicity	1 (1.6)	-	1 (1.6)
Skin rash	3 (4.8)	1 (1.6)	-
Mucositis	8 (12.9)	-	-

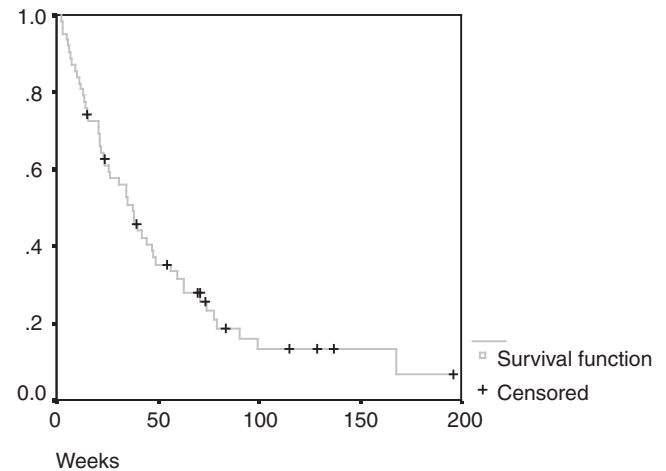


Figure 1 - Overall survival.

were alive at 1 year. In spite of the difference in response rates between pancreatic and biliary tree adenocarcinomas, no statistical differences were noted in survival. Time to progression for the entire group was 21 weeks (95% CI, 13.09-28.91) (Figure 2).

In the univariate analysis related to survival, we investigated the following factors: age (<70 vs ≥70 years), gender, location (pancreas vs biliary tree), extent of disease (locally advanced vs metastatic), performance status, CA 19.9 levels (normal vs high). Of all the variables, only performance status reached statistical significance ($P = 0.0017$). However, when we used different cutoffs for CA19.9 level, high levels (normal vs ≥1000 U/ml) were associated to a poor prognosis ($P = 0.013$).

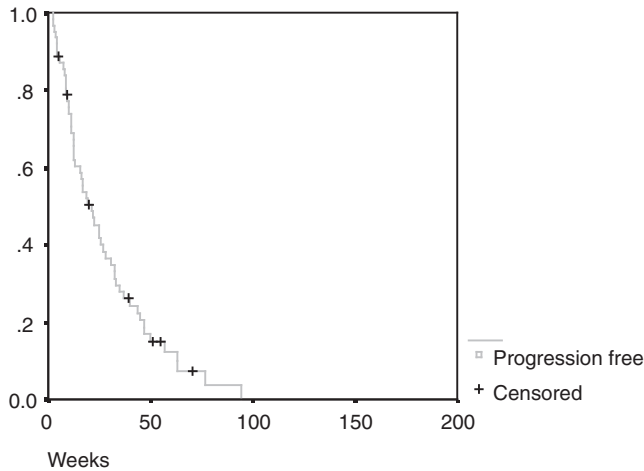


Figure 2 - Progression-free survival.

Multivariate analysis was performed for performance status, high CA19.9 value, and disease extent. Only performance status and high CA19.9 value showed statistical significance ($P = 0.044$, HR = 1.63, 95% CI 1.01-2.64 and $P = 0.041$, HR = 1.94, 95% CI 1.02-3.68, respectively).

Discussion

The randomized trial by Burris *et al.*³ obtained a significant improvement in overall survival of 5 weeks that translated into a 28% improvement in median survival. The weekly 30-min short infusion of gemcitabine at a dose of 1000 mg/m² represents one of the best alternatives for patients with primary diagnosis of nonsurgical pancreatic or biliary tree adenocarcinoma. It has been adopted as a standard by most oncologists, although the reported median time to progression of 2.3 months and median overall survival of 5.6 months need to be improved, with a disappointing 18% of survivors at 12 months.

In this sense, efforts to surpass this regimen have been conducted in the direction of combining gemcitabine with other cytotoxic agents^{10-12,15} or with targeted agents or modifying the gemcitabine infusion schedule. In many studies, the short infusion of gemcitabine has been the control arm.

Louvet *et al.*¹¹, in a phase III trial comparing gemcitabine with the combination of gemcitabine and oxaliplatin, reported promising results. The pooled analysis of two randomized trials of gemcitabine with a platinum analogue, reported by Heineman *et al.*¹², suggested the superiority of combined therapy. Gemcitabine combination chemotherapy seems to produce a certain benefit in overall survival, with a 9% reduction in risk of death in the meta-analysis of Sultana *et al.*¹⁶ (14 trials, 4,060 patients; HR = 0.91; 95% CI, 0.85-0.97).

However, increased knowledge of molecular pathways in pancreatic adenocarcinoma has prompted the combination of gemcitabine with some molecular-targeted agents. Some publications have recently explored the potential role of blocking the epidermal growth factor receptor or vascular endothelial growth factor in the clinical setting^{13,17}. In this way, combination with erlotinib, a small molecule EGFR tyrosine kinase inhibitor, was associated with a statistically significant survival benefit over gemcitabine alone in locally advanced or metastatic disease¹³. The phase III trial, conducted by the National Cancer Institute of Canada, showed a median survival of 6.24 vs 5.91 months in the combination arm versus the standard arm (HR 0.81, $P = 0.028$). Progression-free survival was 3.75 vs 3.55 in favor of the combination (HR 0.77, $P = 0.004$), and the toxicity profile was similar to gemcitabine monotherapy except for diarrhea and skin rash. The addition of bevacizumab to the combination did not result in increased overall survival but prolonged progression-free survival¹⁸.

A recent phase I study with FDR gemcitabine and gefitinib concluded that the combination is feasible and tolerable, with 1200 mg/m² as the recommended dose of gemcitabine¹⁹.

With these results, the role of the 30-min weekly infusion of gemcitabine as a standard might be questioned, bearing in mind the fact that the benefit of combination chemotherapy is at the expense of a higher toxicity and the combination with erlotinib is far more expensive for a short clinical improvement.

The FDR infusion of gemcitabine can thus be considered an attractive alternative to improve outcome in these patients as early studies suggested and our trial confirms. Our results compare favorably with previous publications of a standard short bolus of gemcitabine and are similar to other trials with FDR gemcitabine. The present trial had an estimated time to progression of 21 weeks, an overall survival of 37.7 weeks, with 32% 1-year survivors. Tempero *et al.*⁸ reported 3.4 months, 8.0 months and 28.8%, respectively, and Gelibter *et al.*⁹ 19 weeks, 40 weeks and 25.8%, respectively.

As in our study, Gelibter *et al.*⁹ included 13 patients with biliary tree carcinoma (32%), who fared worse than patients with pancreatic adenocarcinoma. The convenience of this could be argued, because the heterogeneity of the tumors might minimize some conclusions. In any case, other studies have demonstrated the moderate efficacy of single-agent gemcitabine on biliary tract cancer²⁰, with one study of 15 patients with biliary tree carcinoma treated with FDR gemcitabine that concluded in minimal activity of the schedule²¹.

In palliative chemotherapy, one very important analysis must be balancing the trade offs between quality of life and survival²². In this way, toxicity and some clinical indicators are of capital importance. In our trial, 32.25% of patients improved their performance status and 24 patients showed a decrease in tumor markers. Our toxi-

city was moderate, with more than 45% of grade 3-4 neutropenia; nevertheless, no toxic death was occurred.

Tempero *et al.*⁸ reported a similar rate of neutropenia but thrombopenia was higher, which could be explained by our different policy of reductions and omissions and the lack of hematological control on the 8th day of the cycle. A high incidence of asthenia has been described in trials on other tumors where FDR gemcitabine was compared to the standard short infusion²³.

The study of Gelibter *et al.*⁹ showed similar response rates and survival compared with our trial, but toxicity was mild with only 12.5% and 10% grade 3-4 neutropenia and thrombocytopenia, respectively. The study design was similar to ours but doses were 33% lower. In fact, in their study, the dose of gemcitabine evaluated was 1000 mg/m² based on the lack of evidence of dose intensity impact on response rates and the hematological toxicity from the trial of Tempero *et al.*⁸ Consequently, hematological toxicity and rate of omissions and reductions of doses were also lower.

The results of the ECOG 6201 trial, designed to establish the exact role of FDR gemcitabine, have just been published by Poplin *et al.*¹⁰ The multi-institutional trial compared the standard 30-min infusion of gemcitabine at a dose of 1000 mg/m² vs 1500 mg/m²/150 min of FDR gemcitabine vs 1000 mg/m²/100 min of FDR gemcitabine combined with oxaliplatin (GEMOX). The authors sought an ambitious 33% difference in median survival and included 832 patients. The median survivals were 4.9, 6.2 and 5.7 months for standard gemcitabine, FDR gemcitabine and GEMOX. One-year survivals were 16%, 21% and 21%, respectively. Comparison of standard gemcitabine to FDR gemcitabine showed a HR = 0.83, 95% CI 0.69-1.00, and stratified logrank *P* = 0.04. The differences did not meet the specified criteria for significance. As in our trial, predominant toxicity was myelosuppression (as grade 3-4 neutropenia and thrombocytopenia were more important with FDR gemcitabine) and fatigue.

The authors concluded that neither GEMOX nor FDR gemcitabine substantially improve survival or clinical benefit over standard gemcitabine. However at least three aspects should be considered: 1) there was a clear tendency in favor of the FDR arm (*P* = 0.04), 2) the design of the study might have missed smaller but real differences, not reaching 33%, and 3) the results of the study argue against the possible benefit of combination chemotherapy, suggested by previous trials and a meta-analysis. The outcomes of the ECOG 6201 trial in all arms are below expectations, perhaps because of different patient characteristics. So these results are indeed very important, but in our opinion still not definitive.

In conclusion, FDR gemcitabine is an active schedule with consistent results across different studies. Median overall survivals are over 6 months and 1-year survivals over 25%. Clinical benefit is also reproducible, and our results also coincide with previous results regarding tox-

icity. Hematological toxicity and asthenia are considerable, but with adequate dose adjustment these toxicities may be considered manageable.

On the basis of these outcomes, FDR gemcitabine can be considered a suitable approach. Probably, in a next step, pharmacogenomic selection of patients may further improve response to gemcitabine. In view of the divergent results across studies, it is questionable whether combination with other chemotherapeutic agents will result in a clear benefit, but associations of FDR gemcitabine with new targeted agents may represent an important field for clinical and biological investigation.

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