Compassionate use of Gemzar in advanced pancreatic cancer : a Belgian experience

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Abstract

Gemzar is a nucleoside analog that has been shown to be superior to 5-fluorouracil for the treatment of advanced pancreatic cancer in terms of both clinical benefit and survival. This open label program enrolled 214 patients. Patients eligible for this program had advanced or metastatic pancreatic cancer, received up to one previous chemotherapy, a baseline Karnofsky performance status (KPS) of at least 50, measurable or evaluable disease, adequate organ function defined as : absolute leucocyte count > 3 × 10^9/L, platelet count > 100 × 10^9/L, hemoglobin > 9 gr/dL, total bilirubin < 2 × upper limit of normal (ULN), creatinine < 2 × ULN, ALT and AST levels < 5 × ULN and were at least 18 years. A 1000 mg/m^2 of Gemzar was administered weekly up to 7 weeks followed by a week of rest, then once weekly for 3 weeks out of every 4 weeks. The median age at inclusion was 64 years, 52% of the patients were male, 27% were 70 year or older, 66% had stage IV disease, 66% had a KPS of 80 or higher and 34% had received no prior chemotherapy. The overall response rate is 7%. A time-to-first-serious-event analysis was performed since only a limited number of dates of death were available. The first serious event (FSE) was considered as the earliest of the following : increase by at least 2 of the pain score, deterioration of KPS of at least 20, documentation of progressive disease or death. The median time to FSE was 4 months, the free FSE rate at 1 year was 14%. We conclude that the results observed in this program confirm the established efficacy of Gemzar in pancreatic cancer. (Acta gastroenterol. belg., **2001**, 64, **305-308**).

Key words : adult, human, pancreatic neoplasms, deoxycytidine/* analogs.

Introduction

Advanced pancreatic cancer is a dreadful disease, one-year survival without treatment is below 10%. Pain, anorexia, decreased performance status (PS), jaundice, weight loss and other tumor related symptoms are common. Until recently 5-fluorouracil (5FU) has been the standard of treatment either as a single drug or in combination regimens, albeit with no impact on survival. Gemzar (gemcitabine hydrochloride, Eli Lilly and co. Indianapolis) is a nucleoside analog that has recently been shown by Burris *et al.* to be superior to 5FU for the treatment of advanced pancreatic cancer in terms of both clinical benefit and survival (1). Based on these data an increasing number of regulatory agencies worldwide have approved Gemzar for this indication.

This open-label program was opened in the US, Europe and Canada after completion of the phase III trial reported by Burris *et al.* (1) in order to give access to Gemzar to physicians and their patients diagnosed with unresectable or advanced adenocarcinoma of the pancreas.

Patients and methods

Patients eligible for this trial had histologically or cytologically proven advanced or metastatic pancreatic cancer. No more than one previous chemotherapy regimen was allowed. A baseline Karnofsky performance status (KPS) of at least 50 was required. The disease had to be measurable or evaluable. Adequate organ function was required and defined as : absolute leucocyte count > 3 × 10^9/L, platelet count > 100 × 10^9/L, hemoglobin > 9gr/dL, total bilirubin < 2 × upper limit of normal (ULN), creatinine < 2 × ULN, ALT and AST levels < 5 × ULN. Previous mitomycinC therapy, breast feeding and pregnancy were exclusion criteria. All patient had to be over 18 year old and signed informed consent had to be obtained before study entry. The protocol was approved by the relevant Institutional Ethics Committees.

Gemzar was administered at the dose of 1000 mg/m^2 as a 30-minute infusion weekly up to 7 weeks followed by one week of rest, then once weekly for 3 weeks out of every 4 weeks. Patients were treated until disease progression or the occurrence of unacceptable toxicity. Disease assessments were performed every other cycle. Karnofsky performance status, pain scores and analgesic consumption were recorded at each 4 week interval.

A time-to-first-serious-event analysis was performed since only a limited number of dates of death were available. The first serious event (FSE) was considered as the earliest of the following : a deterioration of the pain intensity evidenced by an increase of at least 2 of the pain score (7 points maximum), a deterioration of the KPS evidenced by a decrease of at least 20, the documentation of progressive disease or death.

Results

A total of 214 patients were enrolled in 38 different hospitals in Belgium from March 1996 to April 1998. The median number of patients per hospital was four

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Table I

	Previous chemo allowed ?	N° of patients	Median survival	1 year survival	Response rate
Casper *et al.* (2)	No	44	5.6	23%	9%
Carmichael *et al.* (3)	No	34	nr	nr	6.3%
Rothenberg *et al.* (5)	No	63	3.8	4%	10.5%
Crino L *et al.* (4)	Yes	24	nr	nr	16%
Burris *et al.* (1)	No	63	5.6	18%	5.4%
Storniolo *et al.* (6)	Yes	3023	4.8	15%	12%
Rosemurgy *et al.* (7)	No	103	5.5	nr	nr
Moore *et al.* (8)	No	139	6.4	25%	nr

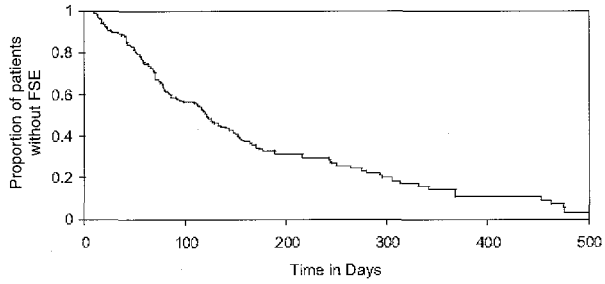

Fig. 1

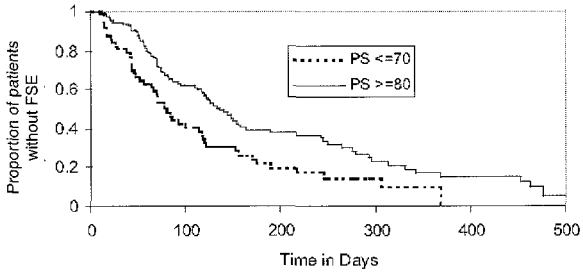

Fig. 2

Table II

	N° of patients (% of total) :
Male :	111 (52%)
Female :	103 (48%)
< 70 years	157 (73%)
≥ 70 years	57 (27%)
Stage III	43 (21%)
Stage IV	159 (66%)
PS ≤ 70	66 (34%)
PS ≥ 80	129 (66%)
No previous chemotherapy	142 (66%)
Previous chemotherapy	72 (34%)

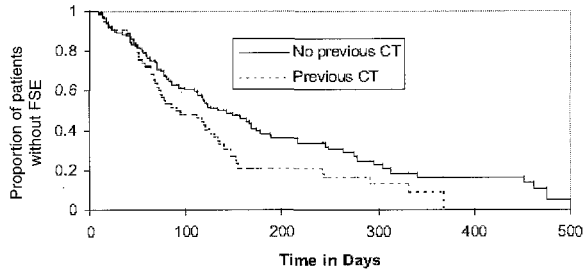

Fig. 3

(range 1-34). The median age at inclusion was 64 years, 52% of the patients were male, 27% were 70 year or older, 66% had stage IV disease, 66% had a KPS of 80 or higher and 34% (seventy-two patients) had received prior chemotherapy. Patient characteristics are summarized in table II.

A total of 784 cycles were administered with a median of 2 cycles per patient (range 1-27). One complete response has been observed, 14 patients experienced a partial response and stable disease was observed in 49 patients. The overall response rate is 7%.

The median time to FSE was 4 months, the free FSE rate at 1 year was 14%. This is graphically depicted in figure 1.

The association of time to first serious event and baseline characteristics has been assessed and detailed in table III.

A KPS of at least 80 at the first visit and the absence of previous chemotherapy exposure seem to be associated with a better prognosis. This is graphically depicted in fig. 2 and fig. 3 .

The evolution of the KPS has been analyzed during the first cycle of treatment. Patients have been categorized according to the evolution of their PS using the following classification : a) improvement : increase in PS, b) stabilization : no change, c) deterioration : decrease in PS. The evolutions have been dichotomized by grouping the "improvement" and "stabilization" categories into a "no deterioration" group. The rates of no deterioration were 61% (95% confidence interval : 53-69%).

Due to the nature of this program, toxicities were only collected if they fitted the definition of "Serious Adverse Events". The vast majority of these reported events related directly to disease progression. Events which were not clearly disease related are : fever, neutropenia and/or infection : 11 cases ; lung embolism : 5 cases ; vascular disorders : 3 cases ; interstitial pneumopathy : 1 case.

Table III

Covariate	n patients	n events	Median days (CI 95%)	Free-FSE Rate at 6 months (CI 95%)	p
Sex					0.31
female	103	63	133 (112-177)	40% (29-51)	
male	111	78	117 (79-133)	27% (17-37)	
Age					0.15
< 70 years	157	111	119 (86-140)	30% (22-38)	
> = 70 years	57	30	147 (80-245)	44% (28-60)	
PS visit 1					0.002
> = 80	66	48	135 (116-157)	39% (29-49)	
< = 70	129	83	79 (63-113)	22% (10-34)	
Stage					0.58
III	43	25	125 (75-249)	43% (34-52)	
IV	159	106	116 (86-143)	30% (21-39)	
Previous CT					0.02
no	142	89	133 (113-169)	39% (29-49)	
yes	72	52	91 (70-125)	21% (9-33)	

Discussion

In the European Community adenocarcinoma of the pancreas is the seventh most common cause of cancer-related mortality. The exact cause of pancreatic cancer remains elusive but cigarette smoking has been identified as a strong risk factor. The anatomy of the pancreas with its close proximity to vital structures and tissues account for the small number of patients who are candidate for a potentially curative resection. The use of radiation therapy is limited by the anatomic relations to surrounding structures prohibiting the delivery of tumoricidal doses of radiation. Therefore chemotherapy is a key element of treatment for a majority of patients.

The evaluation of response to therapy in patients with advanced pancreatic cancer based on changes in tumor measurements is unreliable. The malignant pancreatic masses are usually poorly circumscribed with indistinct irregular shapes making accurate tumor measurements difficult by any available imaging modality. In this context survival is a key endpoint. Additionally symptom control is of high importance.

Different phase II and phase III trials with Gemzar being used as a single drug in advanced or metastatic adenocarcinoma of the pancreas have been reported. The first reports of activity of Gemzar in pancreatic cancer have been made by Casper *et al.* and Carmichael *et al.* reporting response rates of 9% and 6.3% respectively (2,3). Crino *et al.* reported similar response rates and were the first to report on an improvement of PS and a reduction of analgesic consumption during Gemzar treatment (4). Rothenberg *et al.* have reported a 10.5% response rate with Gemzar in patients refractory to 5FU based chemotherapy (5).

The phase III trial reported by Burris *et al.* deserves particular attention. The primary endpoint was clinical benefit, a composite endpoint integrating the evolution of performance status, pain intensity, analgesic consumption and weight. Patients were to be included only if at least one of these parameters was significantly affected in relation to the disease status. The trial objective has been met showing an improvement of clinical benefit with Gemzar treatment opposed to 5FU. Additionally a survival benefit has been shown with 18% of the patients treated with Gemzar alive at 1 year.

Storniolo *et al.* have reported the largest series of patients treated by Gemzar single agent for pancreatic cancer with a 12% response rate and a 15% survival rate at one year (6). More data are also becoming available through randomized clinical trials where Gemzar is used as a gold standard arm against which new drugs are compared. Rosemurgy *et al.* reported during ASCO 99 a randomized four arm trial. In this trial 103 patients were treated with Gemzar monotherapy and had a median survival of 5.5 months (7). At ASCO 2000 Moore *et al.* reported on a series of patients with previously untreated pancreatic carcinoma of whom 139 were treated in a Gemzar reference arm (8). Median survival was 6.4 months with a 25% survival rate at one year. The slightly better 1-year survival in comparison to previously published series might be explained by the fact that patients did not need to have pain to be included. The results with Gemzar therapy in the above mentioned trials are summarized in table I.

This compassionate use program has been set up with the intent to provide access to a wide group of oncologists in Belgium to Gemzar use for patients with pancreas cancer. Although a number of data are missing or incomplete a meaningful statistical analysis could be performed by using more restrictive endpoints. Missing data were substituted with a corresponding worst outcome item as follows : time-to-first-serious-event instead of time to progressive disease or survival, "not done" tumor evaluation were considered as treatment failures.

The 7% objective response rate observed in this trial is similar to previously published results. The free FSE, endpoint which was used in substitution for survival, is also similar to previously published survival data.

Additionally to the conventional efficacy parameters of response rate and survival the results we obtained confirm the beneficial effects of Gemzar on tumor related symptoms.

Good performance status at the beginning of the treatment and no prior exposure to previous chemotherapy were both identified as predictive factors of a longer time to FSE. Two reasons to treat pancreatic cancer before the occurrence of the devastating tumor related symptoms whenever possible. Quite similarly, the trial by Moore *et al.* (8) on a series of patients who were not required to have tumor related pain at study entry has the highest survival rate at 1 year reported so far.

Conclusions

The results observed in this trial compares favorably with previously published results of single agent Gemzar in pancreatic cancer. Albeit a more stringent data analysis had to be performed, the results obtained are in the same range as other previously published series.

Even though advanced pancreatic cancer can rarely be cured Gemzar has consistently shown a significant activity with objective response rates varying from 5.4% to 12%. A significant survival benefit has consistently been demonstrated in different trials. The use of Gemzar mono-chemotherapy as a reference arm in new drug trials further reinforces its widespread acceptance as a gold standard for advanced pancreatic cancer.

References

1. BURRIS III H.A., MOORE M.J., ANDERSEN J., GREEN M.R., ROTHENBERG, M.L., MODIANO M.R., CRIPPS M.C., PORTENOY R.K., STORNIOLO A.M., TARASSOFF P., NELSON P., DORR F.A., STEPHENS C.D., VON HOFF D.D. Improvements in Survival and Clinical Benefit With Gemcitabine as First-Line Therapy for Patients With Advanced Pancreas Cancer : A Randomized Trial. *J. Clin. Oncol.*, 1997, **15** : 2403-2413.
2. CASPER E.S., GREEN M.R., KELSEN D.P., HEELAN R.T., BROWN T.D., FLOMBAUM C.D., TROCHANOWSKI B., TARASSOFF P.G. Phase II trial of gemcitabine (2,2'-difluorodeoxycytidine) in patients with adenocarcinoma of the pancreas. *Investig. New Drugs*, 1994, **12** : 29-34.
3. CARMICHAEL J., FINK U., RUSSEL R.C.G., SPITTLE M.F., HARRIS A.L., SPIESSI G., BLATTER J. Phase II study of gemcitabine in patients with advanced pancreatic cancer. *British Journal of Cancer*, 1996, **73** : 101-105.
4. CRINO L., MOSCONI A.M., CALANDRI C., CORGNA E., DARWISH S., TONATO M. Gemcitabine in advanced pancreatic cancer : a phase II trial. *Eur. J. Cancer*, 1997, **33** : A1266.
5. ROTHENBERG M.L., MOORE M.J., CRIPPS M.C., ANDERSEN J.S., PORTENOY R.K., BURRIS H.A. 3rd, GREEN M.R., TARASSOFF P.G., BROWN T.D., CASPER E.S., STORNIOLO A.M., VON HOFF D.D. A phase II trial of gemcitabine in patients with 5-FU-refractory pancreas cancer. *Ann. Oncol.*, 1996, **7** : 347-353.
6. STORNIOLO A.M., ENAS N.H., BROWN C.A., VOI M., ROTHENBERG M.L., SCHILSKY R. An Investigational New Drug Treatment Program for Patients with Gemcitabine. Results for Over 3000 Patients with Pancreatic Carcinoma. *Cancer*, 1999, **85** :1261-1268.
7. ROSEMURGY A., BUCKELS J., CHARNLEY R., WINSTON R., STEWARD W., STADDON A., CURTIS L., RUGG T., RASMUSSEN H. A Randomized Study Comparing Marimastat to Gemcitabine as First Line Therapy in Patients with Non-Resectable Pancreatic Cancer. *Proc. Am. Soc. Clin. Oncol.*, 1999, **18** : 261a (abstract 1005).
8. MOORE M.J., HAMM J., EISENBERG, DAGENAIS M., HAGAN K., FIELDS A., GREENBERG B., SCHWARTZ B., OTTAWAY J., ZEE B., SEYMOUR L. A Comparison between Gemcitabine and the Matrix Metalloproteinase Inhibitor BAY12-9566 in Patients with Advanced Pancreatic Cancer. *Proc. Am. Soc. Clin. Oncol.*, 2000, **19** : 240a (abstract 930).