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Original article

Gemcitabine Treatment in Pancreatic Cancer – Prognostic Factors and Outcome

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SUMMARY

Background: Pancreatic cancer is generally associated with a poor prognosis and often diagnosed in an advanced stage. The aim of the present study was to evaluate gemcitabine treatment concerning prognostic factors, clinical benefit, tolerance/toxicity and survival. Methods: Patients with surgically nonresectable, locally advanced or metastatic pancreatic cancer treated with gemcitabine were included. Different parameters, including clinical benefit, toxicity (WHO´s criteria) and survival were registered. Kaplan-Meier and Cox regression analysis were performed. Results: Forty-two consecutive patients were included. Median age was 62.5 years, 42% were men. Gemcitabine treatment lasted in median for 5 months (0.5-29 months). Median survival from diagnosis was 9.4 months and from start of treatment 8.1 months. Thirteen patients (32%) were alive 12 months after treatment start. The treatment was overall well tolerated concerning toxicity. Seven patients had transient grade 4 reactions. Of 8 parameters selected from the univariate analysis, 3 were identified as independent predictors for longer survival: age >60 years, ≤5 % weight loss at diagnosis and absence of metastases. Conclusions: Gemcitabine treatment in locally advanced and metastatic pancreatic cancer showed to be of potential benefit and well tolerated. Age, weight loss and metastases were independent prognostic factors for survival. The median survival time was longer than previously reported.

Keywords: pancreatic cancer; locally advanced; gemcitabine; treatment outcome; prognostic factors

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INTRODUCTION

Pancreatic cancer is one of the ten most common malignancies in the western world and known to be associated with a poor prognosis. The disease is responsible for the forth most common cause of cancer death by gender in the United States (US), with only four percent estimated survival.[1] The annual incidence in Sweden, as well as in other countries in the Western Europe and the US, is around 10/100 000.[2] There are several risk factors suggested to be associated with pancreatic cancer.[3] The two consistently reported and most important are age and cigarette smoking.

Surgical resection of the pancreatic tumour still remains the only potential way for cure. Adjuvant treatment with chemotherapy has been suggested to improve outcome after surgery with radical intent and has gained wide acceptance.[4,5]

Although attempts to find early symptoms for pancreatic cancer that can allow an earlier diagnosis have been made,[6] the majority of patients present with an advanced locally spread or metastatic disease, at the time of diagnosis. The management will therefore mainly aim at palliation and not cure.

During the last decades different cytostatic regimes have been introduced. Since the end of the twentieth century the nucleoside analogue gemcitabine (2'2'-difluoro-2'-deoxycytidine), has been part of standard palliative treatment in advanced non-resectable pancreatic cancer.[7,8] Gemcitabine has shown to be more effective than fluorouracil (5-FU) concerning disease-related symptoms and also has modest survival advantages[9,10] and is superior compared with other alternatives.[11] Since the treatment is purely palliative, special attention always must be paid to the side effects and toxicity profiles of the selected treatment regimes.

The aim of the present study was to evaluate gemcitabine treatment in advanced exocrine pancreatic cancer concerning prognostic factors as well as clinical benefit response, tolerance/toxicity, and survival.

PATIENTS AND METHODS

Patient population

All patients ≥18 years of age diagnosed with pancreatic cancer and treated with gemcitabine at the Department of Surgery, University Hospital of Lund, Sweden, between December 1998 and December 2004 were registered. One specific nurse was in charge of the treatment of these patients during the whole study period. Inclusion criteria were patients diagnosed with locally advanced or metastatic exocrine pancreatic cancer, treated with gemcitabine. Patients who had been operated with curative intent and who later developed an advanced cancer treated with gemcitabine were excluded (3 patients) as well as patients who had received another cytostatic drug (2 patients). Patient data were prospectively collected during treatment. All patients were followed up until May 2005.

Treatment

Gemcitabine hydrochloride (Gemzar®; Eli Lilly and Company, Indianapolis, IN, USA) was administered intravenously as an infusion, 1000 mg per m^2 body area, over 30 minutes. The first treatment cycle consisted of gemcitabine treatment once a week for up to seven weeks followed by a week of rest. Thereafter, gemcitabine was administered once a week for three consecutive weeks followed by a week of rest. This cycle was then repeated for as long as the treatment was considered to be effective or until the patient decided not to continue. Vital blood parameters and signs of toxicity were monitored during the treatment period and were used as guidance for individualising the regime. Due to individually noticed toxicity, it was thus sometimes needed to decrease the dose or alternatively postpone or cancel therapy sessions. Patients could also omit the treatment due to social or other reasons. Intravenous injections of tropisetron hydrochloride (Navoban®, Novartis, Basel, Switzerland) and betamethasone sodium phosphate (Betapred™, Swedish Orphan, Stockholm, Sweden) as prophylaxis against the side effects were administered before each therapy session.

Cyclooxygenase-2 (COX-2) inhibitors, i.e. celecoxib (Celebra®, Pfizer, New York, NY, USA), valdecoxib (Bextra®, Pfizer) or rofecoxib (Vioxx®, Merck Sharp and Dohme Sweden AB, Sollentuna, Sweden), were given as part of the pharmacological pain treatment to some patients. When administered at a minimum of four weeks this was registered as part of the treatment.

Data collection

Basic patient and tumour characteristics were noted, including all diagnostic procedures and operations throughout the whole study period. C-reactive protein (CRP) at time of diagnosis as well as basic blood parameters at treatment start and after 1, 2, 3, 4 and 6 month and thereafter every third months as long as the treatment lasted, were registered. The last treatment month was noted separately, no matter when it occurred. No patient was lost for follow up.

Efficacy and safety evaluation

Results from abdominal computed tomography (CT) after treatment start were used to classify regression, stable disease or progression of the disease in order to evaluate tumour development and treatment effect. CT was usually conducted every third month.

Clinical benefit derived from measurement of three of the most common symptoms in patients with advanced disease, i.e. pain, functional impairment and weight loss, were registered as changes in the use of analgesics, Karnofsky performance status (KPS) and weight. Response in pain intensity was judged by the change in type and dose of analgesic used as positive, negative or stable. The same categories were used for KPS and weight response. KPS was categorised in three groups; KPS 80-100, KPS 50-70 and KPS <50. These groups were assessed with the help of patient chart notifications, and a difference of ≥20 points was required to be considered a positive or negative response. For weight response at least two kilograms weight change from baseline was required. Parameter changes lasting for at least two weeks were considered as a change.

Treatment safety was monitored by assessing and noting toxicity of the treatment using World Health Organization (WHO) criteria.[12] Survival data was registered.

Statistical analysis

Values are given as mean ± Standard Deviation or median and range, for continuous variables. For categorical data, absolute numbers in addition to percentages are given. Univariate analysis was made using the log-rank test. Multivariate analysis was performed using a stepwise forward and backward Cox regression analysis. Inclusion criteria for the full model was $P<0.2$ and the limit for stepwise forward and backward elimination was $P<0.1$. The Kaplan-Meier estimate of the survivor function was used to plot long-term survival. A probability level of a random

difference of *P* less than 0.05 was considered significant. Statistical analyses and graphs were performed with Intercooled Stata version 9.0, 2005 statistical package for Mac OS X (Stata Corporation, College Station, Texas, USA).

RESULTS

Patient characteristics

Totally 42 patients were included in the study, out of which 18 (42%) were men. Median age was 62.5 years (45-75 years). All patients had locally advanced or metastatic exocrine pancreatic cancer. Seven patients (17%) had diabetes at the time of diagnosis and another 6 patients developed diabetes after cancer diagnosis. BMI was in average 25±4.2 (19-41) and the mean weight loss was 6.4±5 kg (0-23kg) at diagnosis. Twenty-two patients (52%) had surgical exploration and frequent by pass procedures prior to initiation of cytostatic treatment (in 7 cases only exploration and biopsy was performed, while 15 had some kind of palliative gastrointestinal and/or biliary by pass, like gastroenteroanastomosis and/or hepaticojejunostomy). Thirty-four patients used analgesics regularly. Before treatment start 20 patients had Karnofsky performance status of ≥80, while the others were in the range of 50-70. Tumour characteristics and laboratory values before treatment are listed in Table 1. The median follow up time from diagnosis was 9.2 months (1.9-32 months).

Cytostatic treatment

The duration of gemcitabine treatment was in median 5 months (0.5-29) and the median number of treatments administered were 15 (2-60). Due to toxic side effects of the treatment, the relative dose administered was at some point temporarily reduced to 75% of the original in 40% of the cases (*n*=17). Twenty-three patients (55%) had the standard dose throughout the treatment period and the dose was elevated for two patients to 1250 mg per m^2 body area. Three patients died during the cytostatic treatment, one due to hyperglycaemic coma and possible sepsis with circulatory collapse and the other two due to rapid progression of the cancer. Thirty-five patients discontinued the treatment due to progression of the disease. One patient chose to end treatment due to adverse effects. At the end of the study period, six patients (14%) were still alive, three continuing with the gemcitabine treatment.

Table 1. Pancreatic tumour characteristics at diagnosis and laboratory values before start of chemotherapy.

Patient characteristics	
Tumour size pancreas (cm)	5(2-7)
Metastases*	23
Tumour stage*	19
III/IV A	23
IV B	
Haemoglobin (g/L)	126(98-149)
CRP (mg/L)	17(5-221)
Leukocytes (10^9/L)	7.8(4-15)
Platelets (10^9/L)	289(131-535)
Bilirubin (μmol/L)	9.5(5-218)
Creatinine (μmol/L)	56(30-85)

Values are median(range) except when absolute numbers. C-reactive protein (CRP) measured at the time of diagnosis, other values measured before treatment start.*

Toxicity

Gemcitabine was well tolerated. When taking the highest grade of toxicity for every patient in any of the 8 grades for laboratory toxicity and 18 for symptomatic toxicity, two patients had at some point maximum grade 1; 18 patients grade 2; 15 patients grade 3 and 7 patients grade 4 toxicity reactions. Survival did not significantly differ for patients with grade 1-2 toxicity compared to grade 3-4 (*P*=0.061). Toxic adverse effect on haemoglobin was the most common (83% had Hb <110 g/L). The ten most frequent reactions of toxicity are presented in Table 2. One patient ended the cytostatic treatment due to toxicity (elevated temperature and anaemia).

Clinical benefit and efficacy of treatment

Stable disease during the time of gemcitabine treatment as well as developed response (positive) or impairment (negative) concerning pain, Karnofsky performance

Table 2. The ten most common toxicity parameters observed during chemotherapy for patients in the study, according to the World Health Organization (WHO) definition[12].

	Grade				
Parameter	0	1	2	3	4
Haemoglobin	7(17)	17(40)	16(38)	2(5)	0
AST and ALT	9(21)	17(40)	10(24)	4(10)	2(5)
ALP	9(21)	24(57)	8(19)	1(2)	0
Leukocytes	14(33)	9(21)	13(31)	5(12)	1(2)
Granulocytes	19(45)	4(10)	10(24)	6(14)	3(7)
Nausea	11(26)	14(33)	9(21)	8(19)	0
Consciousness	15(36)	19(45)	7(17)	1(2)	0
Infection	23(55)	9(21)	7(17)	2(5)	1(2)
Fever	26(62)	13(31)	3(7)	0	0
Constipation	27(64)	10(24)	4(10)	1(2)	0

Absolute numbers, values in parentheses are percentages. ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

status and weight are presented in Figure 1A-C. Abdominal CT was performed usually every three months after treatment start. Evaluation of regression, progression or stable disease, measured as radiologically observed tumour development, was estimated (Table 3).

Additional medication and interventions

Seven patients had surgery with gastroenteroanastomosis after that treatment with gemcitabine had been initiated, and one patient had a thoracoscopic splanknichectomy performed. Seventeen patients received a Porth-a-Cath.

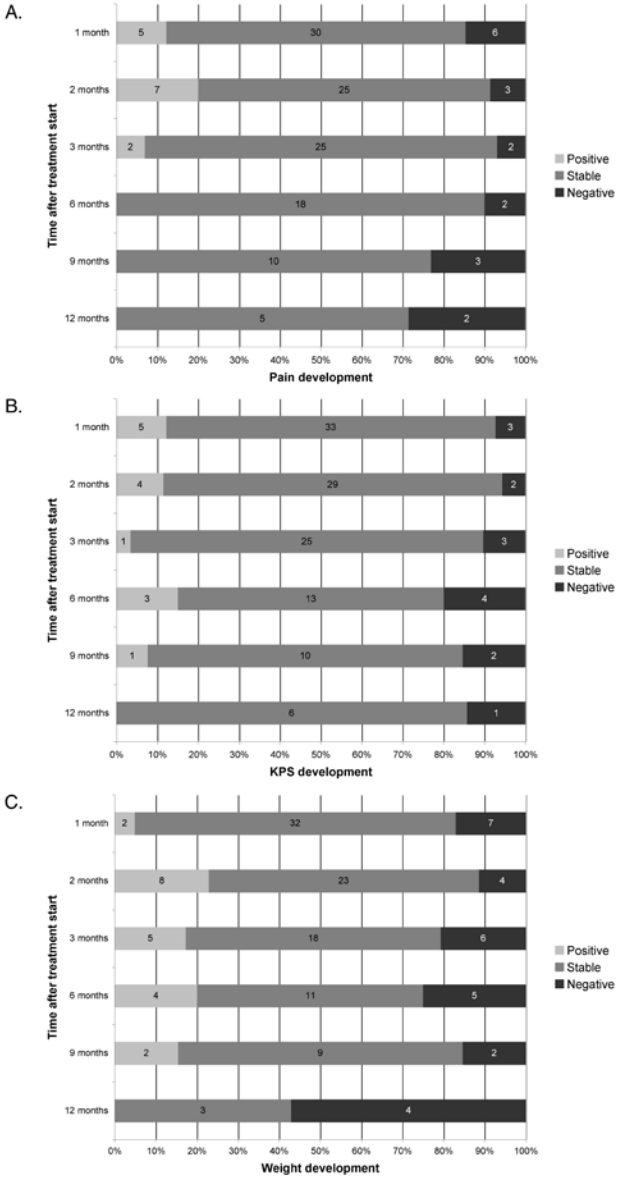

Fig. 1.A. Pain response during gemcitabine treatment.**B.** Karnofsky performance status (KPS) response during gemcitabine treatment. **C.** Weight response during gemcitabine treatment.

Table 3. Results of abdominal computed tomography after start of gemcitabine treatment.

CT evaluation number	Tumour regression	Stable disease	Tumour progression
1	6(16)	13(35)	18(49)
2	6(23)	11(42)	9(35)
3	3(20)	6(40)	6(40)
4	0	4(40)	6(60)
5	0	1(50)	1(50)
6-7	0	0	1(100)

Absolute numbers, values in parentheses are percentages calculated on the group of patients in which computed tomography (CT) was performed.

Twelve patients received COX-2 inhibitors for a minimum of one month. Nineteen patients were supplemented with pancreatic enzymes.

Survival

At the end of the follow-up period 36 patients had died. The median survival time after diagnosis in the whole group was 9.4 months. After treatment start the median survival was 8.1 months, with 83% 3-month survival, 60% 6-month survival, 32 % 12-month survival and 10 % 2-years survival (Figure 2).

Uni- and multivariate analysis of prognostic factors

Clinically relevant parameters obtained before start of gemcitabine treatment and in addition the use of COX-2 inhibitor were included in the analysis. Four variables were significantly relevant for improved prognosis (P<0.05) in

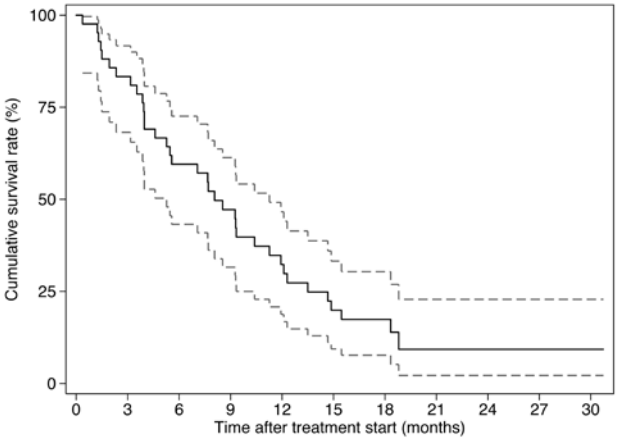

Fig. 2. The Kaplan-Meier estimate of the survival for all patients (n=42) with advanced pancreatic cancer treated with gemcitabine (solid line), with 95% confidence limits (dashed lines).

the univariate analysis, and 8 of 13 variables, all with a *P* value of less than 0.200 were selected for the multivariate analysis (Table 4). In the multivariate analysis age ≤60 years, weight loss >5% and metastases were found to be independent predictors associated with shorter survival (Table 5). Kaplan-Meier curves (Figure 3A-C) illustrate difference in survival for these significant parameters. A comparison of serum CRP levels ≤10 mg/L versus >10 mg/L at diagnosis did not reach statistical difference, the survival curve for the two groups shows in Figure 3D.

Table 4. Univariate analyses of the potential prognostic factors before treatment start (except COX-2 inhibitor) and their impact on survival.

Characteristics	Patients n (%)	Median survival (months)	Univariate analysis P value
Age, years			0.005
≤60	19(45)	4.6	
>60	23(55)	9.3	
Gender			0.261
Male	18(43)	6.6	
Female	24(57)	8.7	
Tumour size, cm			0.529
≤4	20(48)	8.5	
>4	22(52)	7.9	
Metastases			0.026
No	19(45)	11.9	
Yes	23(55)	5.3	
Weight loss, %			0.004
≤5	15(36)	11.3	
>5	27(64)	7.7	
CRP, mg/L			0.064
≤10	15(36)	11.9	
>10	27(64)	5.6	
Hemoglobin, g/L			0.123
≤110	6(14)	11.1	
>110	36(86)	7.9	
Leukocytes, 109/L			0.441
≤10	34(81)	8.7	
>10	8(19)	5.4	
Total bilirubin, mmol/L			0.919
≤20	35(83)	7.7	
>20	7(17)	8.5	
Diabetes			0.748
No	35(83)	7.6	
Yes	7(17)	11.9	
Surgery			0.033
No	20(48)	5.5	
Yes	22(52)	11.7	
KPS			0.092
≤70	22(52)	5.4	
≥80	20(48)	9.3	
COX-2 inhibitor*			0.106
No	30(71)	7.6	
Yes	12(29)	9.3	

** During treatment.*

COX-2, cyclooxygenase-2; CRP, C-reactive protein; KPS, Karnofsky performance status. Univariate statistical analysis by log-rank test.

Table 5. Predictors for shorter survival identified by multivariate analysis.

Variable	Hazard ratio	P
Age ≤60 years	2.40(1.17-4.93)	0.003
Weight loss >5%	3.55(1.51-8.32)	0.002
Presence of metastases	2.31(1.11-4.83)	0.009

Multivariate analysis by stepwise forward and backward Cox regression analysis.

DISCUSSION

In general the prognosis of patients with locally advanced or metastatic pancreatic cancer is poor, with a median survival of 3-4 months.[1] Since the only potentially curative treatment, i.e. radical operation, is not applicable for these patients it is extremely important to define good palliative treatment, both in order to improve the quality of life and the survival time. In the present study, the aim was to evaluate gemcitabine treatment administered in these patients with non-resectable pancreatic cancer, both concerning clinical benefit, efficacy, safety and survival. In addition, prognostic factors for the patient group were identified, information that may be useful when deciding palliative treatment regimes.

One of the first studies with gemcitabine alone demonstrated marginal effect without profound toxicity.[7] Later studies have shown notable improvements in disease related symptoms and survival.[8] Median survival with this regime in the present study was 8.1 months, i.e. in general better than presented in several other reports on gemcitabine treated patients, with 4.8-5.7 months survival.[7-10,13] The relatively high proportion of patients with locally advanced disease in the present study may have contributed to the outcome.

Gemcitabine provides a potential impact on clinical benefit, a measure of disease related symptoms usually based on pain, KPS and weight change.[9] Since pain and weight loss represent dominant problems for these pa-

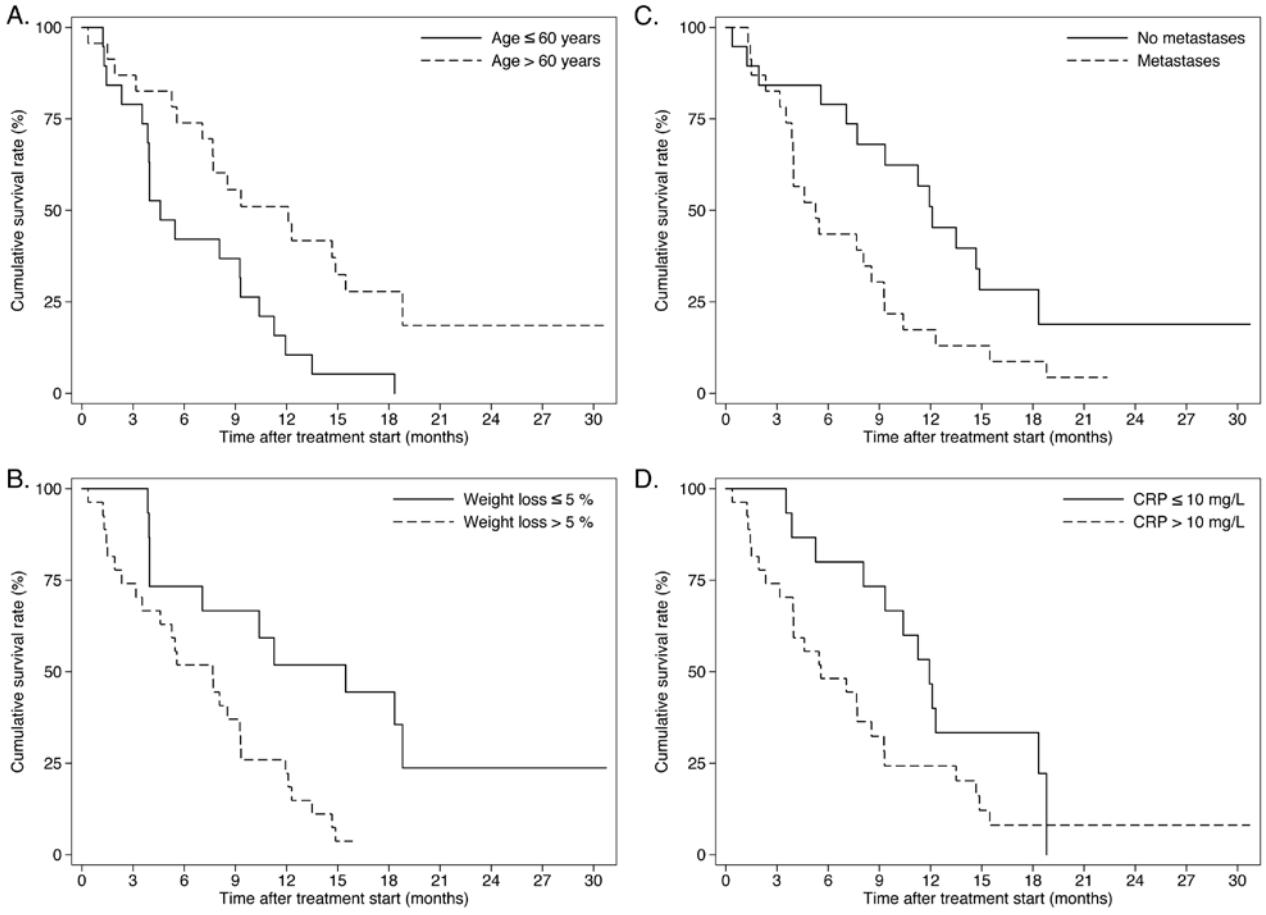

Fig. 3A-D. The Kaplan-Meier estimate comparing survival of patients treated with gemcitabine according to age ≤60 years versus >60 years (P=0.005), weight loss ≤5 % versus >5% (P=0.004), presence or absence of metastases (P=0.026) and C-reactive protein (CRP) ≤10 mg/L versus >10 mg/L (P=0.064) at the time of diagnosis. Univariate analysis, log-rank test.

tients, these are important gains of therapy. In our study even patients with poor KPS and great weight loss started gemcitabine treatment. Only the oldest patients (>80 years) were just candidates for best supportive care and not chemotherapy. Stable disease during gemcitabine treatment was frequently obtained, and in some cases there was even regression of objective disease. The present study thus supports a positive effect on survival and symptom improvement following gemcitabine treatment, at least as compared to previous studies and historical controls.

Since the impact of gemcitabine-based chemotherapy still is considered to be modest, novel approaches such as combine gemcitabine with other agents are being pursued, one of these being COX-2 inhibitors. COX-2 receptors are frequently overexpressed in pancreatic cancer.[14] Selective COX-2 inhibitors have, in the preclinical setting, shown to demonstrat activity against pancreatic cancer cell lines and to potentiate gemcitabine-induced growth inhibition and apoptosis[15]. Additional treatment with COX-2 inhibitors was administered to a sub-group of patients in the present study, primarily as part of the pharmacological pain treatment. No change in survival time was seen in this group.

Gemcitabine alone is usually well tolerated.[8,9] This was confirmed by the present study. Only one patient chose to end treatment due to toxic effects and no toxic reaction was permanent or contributed to death in any patient. It is known that combination regimes with other cytotoxic drugs can increase toxic side effects.[16] Combination with 5-FU and gemcitabine has, although well tolerated, not improved overall median survival.[9,17] However, there are studies implying that combination regimes with cisplatin have tolerable toxicity and greater activity as compared with gemcitabine alone.[13,18] Combination of gemcitabine with radiotherapy is debatable but has been shown to be well tolerated with prolonged clinical benefit response in unresectable cancer,[19] while severe toxicity has also been described.[20] As adjuvant treatment the chemoradiotherapy has, however, shown deleterious effect on survival.[4,5]

In previous studies, a number of factors have been identified as predictors for survival in patients presenting with all stages of pancreatic cancer, while a limited number of studies have focused on patients with unresectable cancer[21] and patients receiving different systemic chemotherapy regimes, including gemcitabine.[22-25] Information from these studies are important in order to provide useful tools to estimate therapy-dependent prognosis, and also when deciding palliative treatment regimes for the individual patient.

One previous study has looked at prognostic factors in gemcitabine treated patients.[25] They, however, chose to describe factors changing over treatment time, showing a prognostic value of CA 19-9. In our study, we have focused on the initial measured variables and additive treatment with COX-2 inhibitors, to estimate the influence of these parameters on survival in gemcitabine treated patients. As independent prognostic factors age, weight loss and metastases were identified. In the univariate analysis palliative surgery before start of cytostatic treatment was also a significant prognostic factor, while serum CRP level did not reach statistical significance as a predictor for survival. Previous studies have, however, shown the CRP level to be of importance in pancreatic cancer patients, but with other treatment regimes.[21,24,26] The Kaplan Meier curve in the present study showed that patients with CRP > 10 mg/L presented a less favourable survival for the first 18 months, thereafter this difference subsided. One could speculate whether the treatment could have influenced the result. Another factor is our comparably long-follow up time. It would be of interest to evaluate the impact of CRP for survival in a larger study population with gemcitabine treated patients.

In conclusion, gemcitabine treatment in advanced pancreatic cancer was well tolerated with low toxicity. Significant prognostic factors for longer survival, not previously published for this patient group, were absence of metastases, less weight loss and older age. The development of KPS score, weight as well as pain during the treatment was favourable and the overall survival after treatment start was longer than previously described. The present study shows that this treatment has several advantages and is useful for patients with locally advanced or metastatic pancreatic cancer. Further evaluation of the value of combining various other agents with gemcitabine treatment is warranted, but in the meantime gemcitabine seems to be an attractive treatment for patients with advanced pancreatic cancer, also in the elderly.

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