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Efficacy of gemcitabine in patients with non-resectable pancreatic cancer: prospective clinical studies

Tadeusz Popiela, Bogusław Kędra, Marek Sierżęga

A i m. Cancer of the pancreas continues to be a leading cause of cancer deaths. The aim of our study was to assess the effect of gemcitabine-based chemotherapy regimen on treatment outcomes in patients with non-resectable pancreatic cancer.
M a t e r i a l a n d m e t h o d s. Sixty-one patients were qualified on the basis of intraoperative tumour staging. On day 10 following surgery patients were randomised to form a treatment group receiving 1000 mg/m² gemcitabine (group I) and a control group (group II).
R e s u l t s. No statistically significant differences were seen between the groups regarding clinical and pathological characteristics. A positive response to chemotherapy was noted in 11 (35.5%) of the patients so treated. An objective positive response (reduction in tumour size or no change) was confirmed in follow-up diagnostic imaging examinations in 7 patients in group I and 1 patient in group II ($p<0.05$). The percentage of patients whose tumours increased in size by less than 10% from baseline was considerably higher in the treatment group (62.9%) than in the control group (33.3%), at $p<0.01$. Group I patients also required less use of analgesics, more often experienced no weight loss and were clinically better off than the controls in group II ($p<0.01$). Mean survival time of gemcitabine-treated patients was 6.7 months, which was significantly longer than in the control group (4.5 months, $p<0.01$). Side effects, mostly transient leukopenia, were observed in 22% of patients during the study.
C o n c l u s i o n. On the basis of these results, the authors recommend gemcitabine-based chemotherapy regimens as the treatment of choice in non-resectable pancreatic carcinoma.

Ocena skuteczności gemcytabiny w leczeniu chorych z nieresekcyjnym rakiem trzustki: prospektywne badania kliniczne

Rak trzustki pozostaje nadal jedną z wiodących przyczyn zgonów na nowotwory złośliwe. Celem niniejszej pracy była ocena wpływu chemioterapii, opartej na gemcytabinie, na wyniki leczenia chorych z nieresekcyjnym rakiem trzustki. W oparciu o śródoperacyjną ocenę stopnia zaawansowania nowotworu do badania włączono 61 chorych. W 10 dobie po zabiegu operacyjnym chorych randomizowano do grupy terapeutycznej, otrzymującej gemcytabinę w ilości 1000 mg/m² (grupa I) lub grupy kontrolnej (grupa II). Nie stwierdzono istotnych statystycznie różnic, dotyczących cech kliniczno-patologicznych między badanymi grupami. U 11 (35.5%) chorych, otrzymujących chemioterapię, stwierdzono cechy odpowiedzi pozytywnej. Obiektywną odpowiedź pozytywną w postaci częściowej regresji lub stabilizacji wymiarów guza stwierdzono w kontrolnych badaniach obrazowych u 7 chorych w grupie I i 1 chorego w grupie II ($p<0.05$). Odsetek chorych, u których stwierdzono progresję masy guza poniżej 10% stanu wyjściowego, w grupie otrzymującej chemioterapię był znacznie wyższy (62.9%), w porównaniu do grupy kontrolnej (33.3%); $p<0.01$. Chorzy w grupie I wymagali stosowania mniejszej ilości środków przeciwbólowych, częściej utrzymywali stałą wagę ciała oraz byli w lepszym stanie klinicznym w porównaniu do grupy II ($p<0.01$). Średni czas przeżycia chorych otrzymujących gemcytabinę wynosił 6.7 miesiąca i w porównaniu z grupą kontrolną (4.5 miesiąca) był znacząco dłuższy ($p<0.01$). W czasie badania objawy uboczne chemioterapii obserwowano u 22% chorych i dotyczyły one głównie przejściowej leukopenii. Na podstawie uzyskanych wyników autorzy rekomendują stosowanie chemioterapii, opartej na gemcytabinie, jako leczenie z wyboru w przypadku nieresekcyjnych raków trzustki.

Key words: pancreatic cancer, chemotherapy, gemcitabine
Słowa kluczowe: rak trzustki, chemioterapia, gemcytabina

1st Chair of General Surgery
and the Department of Gastroenterological Surgery,
Collegium Medicum, Jagiellonian University, Cracow, Poland

Introduction

Cancer of the pancreas accounts for 5-8% of all cancers and is the fifth most frequent cause of cancer-related deaths in Western European countries and the USA [1-3]. Since 1960, the pancreatic cancer mortality rate in Poland has been growing to reach 13.1 per 100.000 in 1996 [4]. This form of cancer is usually diagnosed at an advanced stage so that only 20-30% of patients are qualified for resection surgery while others can only benefit from palliative treatment that ameliorates the clinical symptoms [3, 5-7]. Palliative treatment will usually make possible a temporary remission of a few months' duration in about 30% of patients. Mean survival time of patients with an advanced pancreatic carcinoma is 3-6 months, with 90% not surviving beyond one year since diagnosis. Chemotherapy regimens used to date for patients with advanced pancreatic cancer, based on 5-fluorouracil, adriamycin, streptozocin or mitomycin C, have produced a positive clinical response only in 4-5% of patients [8-10]. At the same time, literature on gemcitabine published in recent years suggests better treatment outcomes in advanced pancreatic cancer with gemzar-based chemotherapy [11-14].

The aim of this study was to evaluate the effect of gemcitabine on clinical outcomes in patients with non-resectable cancer of the pancreas.

Patients and methods

The participants of the study were patients with a confirmed diagnosis of pancreatic cancer who underwent surgery at the 1st Chair of General Surgery CM UJ between September 1996 and December 1998. In all patients the diagnosis and local staging data were verified intraoperatively during a laparotomy procedure. The following criteria were used in qualifying patients for treatment:

1. Histopathologically confirmed adenocarcinoma of the pancreas
2. Intraoperatively confirmed non-resectable tumour (stage IV according to TNM/UICC)
3. Patient age: 18-70 years
4. Clinical status >50 pts (Karnofsky scale)
5. Plasma bilirubin <32 mmol/l
6. AspAT, AlAT <80 U/l
7. Plasma albumin >28 g/l
8. Leukocyte count >4000, platelet count >100,000/mm^3
9. Absence of signs of cardiovascular or respiratory insufficiency
10. Informed consent to participate obtained from the patient

Patients who met all the above criteria were randomised into two clinical groups: Group I, which received gemcitabine-based palliative chemotherapy, and Group II, receiving only symptomatic treatment.

Palliative chemotherapy was based on the following regimen: starting from the tenth day following surgery, 1000 mg/m^2 gemcitabine was given in a continuous intravenous infusion over 30 minutes, once a week over 7 weeks. After a week's break, treatment was continued for another 3 weeks. Treatment outcomes were evaluated in both groups at 12 weeks after surgery. If a positive response was observed, treatment was continued until the disease was in progress, toxic side effects occurred or the patient withdrew consent to further treatment.

Examinations carried out in both groups every week included body weight measurements and toxicity assessment based on the ECOG scale. Additionally, the tumour mass was monitored using imaging diagnostics (CT, USG): tumour size was measured before the surgery and at 12 weeks after the surgery. Quality of life was also assessed using general status data (based on the Karnofsky scale) and the amount and type of analgesic medications required. A positive clinical response was defined as an improvement of one of the parameters continuing over 4 weeks without deterioration in any other parameter, and in the setting of increasing tumour size. An objective positive response was defined as stabilisation or reduction of tumour size seen in the follow-up imaging exam.

The results were analysed using the Statistica 5.5 software package (StatSoft). Variables were tested using the chi-squared test, long-term survival in the study groups was evaluated by the Kaplan-Meier method and compared using the log-rank test. The value of $p=0.05$ was regarded as statistically significant.

Results

Sixty-one patients treated for pancreatic cancer between September 1996 and December 1998 were qualified for the study (32 men, 29 women). Demographic characteristics are presented in Table I. Following intraoperative clinical staging of the tumour, the patients were randomised into two clinical groups.

Tab. I. Demographic data breakdown per study group

	Gemcitabine n=31	Controls n=30	P
Gender			
F	14	15	NS
M	17	15	
Tumour location			
Head	19	18	NS
Body	9	10	
Tail	3	2	
TNM classification stage			
IVA	12	14	NS
IVB	19	16	
Type of surgical procedure			
Choledochoduodenostomy + gastroenterostomy	19	18	
Gastroenterostomy	3	1	NS
Laparotomy	9	11	

Group I (gemcitabine group) consisted of 31 patients (14 women and 17 men) aged 59.9±12.3 years. 19 patients had carcinoma of the pancreatic head, 9 had a lesion in the body and the remaining three, in the tail of the pancreas. 12 patients had a stage IVA tumour and the remaining 19 had a stage IVB tumour, according to the TNM/UICC classification (1997) [15]. Bypass anastomoses (choledochoduodenostomies and gastroenterostomies) were formed in the 19 patients with carcinoma of the head, 3 patients had only gastrostomy performed and in the remaining 9 the surgical intervention was limited to an exploratory laparotomy.

The second group (control group) consisted of 30 patients (15 women and 15 men) aged 60.2±11.3 years. Location of the tumour was similar to that observed in group I, with involvement of the pancreatic head in 18 patients, body in 10 and tail in the remaining 2. Fourteen patients had a stage IVA tumour, and the remaining 16, an IVB tumour. The number and type of surgical procedures performed were similar to those carried out in group I patients. There were no statistically significant differences between the groups regarding demographics, tumour stage and type of surgical intervention (Tab. I).

Following a course of 10 cycles of gemcitabine treatment, a positive response was observed in 11 (35.5%) patients. An objective positive response was noted in 7 patients and the remaining 4 showed only clinically positive response, that is improvement in overall clinical status, disappearance of pain and stabilisation of body weight. The remaining 20 patients (64.5%) showed no signs of a positive response (Tab. II).

Tab. II. Response to chemotherapy (n=31)

	Positive response n = 11		No response n = 21	P
	objective n=6	clinical n=4		
Gender				
F	3	2	10	NS
M	4	2	11	
Mean age (years)	59.2	62.1	58.2	NS
Tumour location				
Head	2	2	15	NS
Body or tail	5	2	6	
TNM/UICC stage				
IVA	4	2	7	
IVB	3	2	14	NS

There were no differences in age or gender between those patients on chemotherapy who responded and those who did not. A relatively higher percentage of responders was seen with carcinomas of the body and tail (7/13) compared to carcinomas of the pancreatic head (4/19). However, this finding was not statistically significant. No relationship was also established between the TNM/UICC tumour stage and a positive response, which was observed symmetrically in patients with IVA and IVB stage tumours.

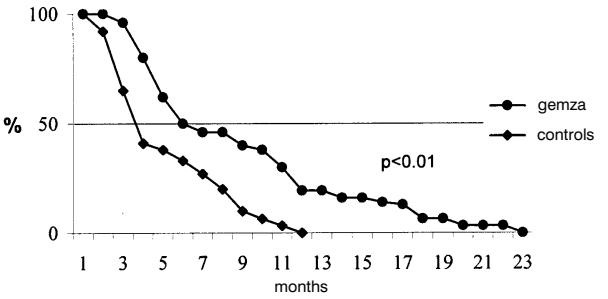

Fig. 1. Long-term survival in the study groups

In 92% (57/61) of the patients, tumour size was objectively determined at the follow-up examination. In the remaining patients, adequate tumour images could not be obtained due to technical difficulties so that a reliable assessment was impossible. Table III shows the results of the measurement. In group I, reduction or stabilisation of the size of the tumour mass was observed in 25.9% (7) of the patients, compared to 3.3% (1) in the control group and these between-group differences were statistically significant ($p<0.05$). Reduction of tumour size was seen in 2 patients in group I, which made it possible to perform palliative resection of the body and tail of the pancreas following 6-month chemotherapy in one of them. Increase in tumour size was seen in the majority of the patients in both groups: 74% (20) of patients in the gemcitabine group and 96.7% (29) of patients in the control group, but the „profile" of disease progression was different. In group I, an increase in tumour size of more than 10% from baseline was seen in 11.1% (3) of patients, compared to as many as 63.4% (19) of patients in group II. More patients in group I (62.9%) had an increase in tumour size of less than 10% above baseline than in group II (33.3%). These differences were also statistically significant ($p<0.01$).

Tab. III. Change in tumour size (ultrasound, CT)

Size of tumour mass	Gemcitabine n=27	Controls n=30	P
Reduction	2 (7.4%)	0 (0%)	<0.05
Stabilisation	5 (18.6%)	1 (3.3%)	
Increase	20 (74.0%)	29 (96.7%)	
< 10%	17 (62.9%)	10 (33.3%)	<0.01
> 10%	3 (11.1%)	19 (63.4%)	

The changes in the size of tumour mass correlated with the clinical picture in both groups, as shown in Table IV. Overall clinical status, assessed using the Karnofsky scale, was considerably better in the patients receiving Gemzar. More than 51% (16) of the patients in this group scored above 70 points, compared to 17% (5) in the control group. Also, in the control group more than 83% (25) scored below 70 points ($p<0.01$). Weight loss was also markedly faster among patients in the control group (93% vs 64%) compared to the gemcitabine-treated pa-

tients ($p<0.01$). Patients in the control group also required more analgesics than those in group I ($p<0.01$) and the proportion of narcotic drugs among analgesics was higher in the control group, too. Mean survival time in group I was 6.7 months and was longer by more than 2 months than in group II (4.5 months, $p<0.01$). Mean survival time was 11.1 months in patients with a positive response. The longest survival time was seen in the patient in whom, following 6-month chemotherapy, palliative resection surgery was performed.

Tab. IV. Quality of life comparison

	Gemcitabine n=31	Controls n=30	P
Use of analgesic medications	12	23	<0.01
non-narcotic	9	13	
narcotic	3	10	
General status (Karnofsky scale)			<0.01
<70 pts	15	25	
>70 pts	16	5	
Body weight			<0.01
stable	11	2	
lower	17	18	
cachexia	3	10	
Mean survival time (months)	6.7 (11.1)*	4.5	<0.01

* Responding patients

The assessment of toxicity of the gemcitabine treatment revealed only minor side effects (Table V), with transient leukopenia in 22.5% of the patients, thrombocytopenia in 19.3%, anaemia in 12.9%, nausea and vomiting and transient peripheral oedema in 19.3% of the gemcitabine-treated patients.

Tab. V. Chemotherapy toxicity assessment (WHO criteria)

Parameter	I°	II°	III°	VI°	%
Leukopenia	4	2	1	-	22.5
Thrombocytopenia	2	3	1	-	19.3
Anaemia	2	1	1	-	12.9
Nausea/vomiting	3	2	1	-	19.3
Diarrhoea	1	1	-	-	6.4
Oedema	2	3	1	-	19.3

Discussion

Gemcitabine (gemcitabine hydrochloride) is a new cytostatic of the antimetabolite group. It is a deoxycytidine analogue which exhibits cytostatic activity following transformation to active metabolites. Deoxycytidine kinase mediates the phosphorylation of gemcitabine to bi- and triphosphates. These block DNA synthesis and error correction through inhibitory action on DNA polymerase and ribonucleotide reductase. Clinical studies carried out to date have demonstrated that gemcitabine is effective in patients with non-small cell carcinoma of the lung and other solid tumours, mainly carcinomas of the breast and ovary [8, 16]. Since the mid-1990's it has also been approved in the USA for palliative treatment of pancreatic carcinoma.

Prospective randomised clinical studies of gemcitabine in a homogeneous group of patients with inoperable pancreatic cancer minimise the possibility of an error in evaluating the efficacy of gemcitabine. Preoperative staging of pancreatic cancer is not fully reliable despite the use of modern diagnostic procedures [18, 19]. It was for this reason that only patients in whom intraoperative staging was carried out were qualified for the study.

Our results confirm earlier reports by other authors that gemcitabine is highly effective in the treatment of pancreatic cancer [11-14]. A positive response noted in more than 30% of all patients receiving Gemzar represented a much higher percentage than has been observed with other chemotherapy regimens [8-10].

Partial regression of the tumour in 2 of the patients (7.4%), confirmed by follow-up imaging examinations, made it possible to carry out a palliative resection procedure in one of them later on. Even though the percentage of patients with tumour size reduction was small, it indicates potential benefits of using Gemzar as a neoadjuvant in the treatment of locally advanced pancreatic carcinoma. Despite signs of progression of disease in 74% of the patients receiving chemotherapy, the increase in tumour size was usually much less marked than in the control group. A slowing down of the rate of disease progression, seen in most of the patients receiving Gemzar, led to a considerable improvement in their overall clinical status. Stabilisation of body weight and reduction of the amount of analgesics required, together with the improvement in general status, are indicative of high palliative efficacy of the chemotherapy regimen under study. Thus, even in the setting of progressing cancer, patients can be offered effective palliative management.

Prolongation of patient survival time is the most objective criterion of treatment efficacy. Our analysis showed a significant lengthening of mean survival time in the gemcitabine group compared to the control group (6.7 vs 4.5 months), which concurs with the findings of other authors [8, 10-14]. Mean survival time was even longer (11.1 months) among the 11 (32%) responding patients.

Untoward side effects associated with gemcitabine are not different from those produced by other cytostatics medications. Minor bone marrow suppression seen in 22.5% of the patients indicates that the chemotherapy treatment under study is considerably safe.

Conclusions

On the basis of their results, the authors recommend gemcitabine-based chemotherapy as the treatment of choice for patients with non-resectable pancreatic cancer. The high efficacy of the Gemzar treatment in the group of patients in this study prompted the authors to

undertake another clinical study where gemcitabine is used as supplementary treatment following resection of pancreatic carcinoma in monotherapy or combination therapy with leucovorin and cisplatin.

Professor Tadeusz Popiela M.D. Ph.D.
1st Department of General and Gastrointestinal Surgery
Collegium Medicum, Jagiellonian University
ul. Kopernika 40
31-501 Kraków, Poland

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