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Ireneusz Raczyński[1], Patryk Zając[2, 3], Joanna Streb[4, 5], Bogumiła Czartoryska-Arłukowicz[6], Aleksandra Chruściana-Bołtuć[7], Małgorzata Talerczyk[7], Katarzyna Wierzbicka[8], Agnieszka Siedlaczek[9], Weronika Radecka[10], Michał Jurczyk[5, 11], Barbara Radecka[3, 12]

[1]General Medical Practice, Warsaw, Poland
[2]Department of Clinical Biochemistry and Laboratory Diagnostics, Faculty of Medicine, University of Opole, Poland
[3]Department of Oncology, Tadeusz Koszarowski Cancer Center, Opole, Poland
[4]Department of Oncology, Jagiellonian University Medical College, Cracow, Poland
[5]Clinical Oncology Department, University Hospital in Cracow, Poland
[6]Clinical Oncology Department, Maria Sklodowska-Curie Bialystok Oncology Center, Poland
[7]Department of Clinical Oncology, West Pomeranian Oncology Center, Szczecin, Poland
[8]Oncology and Radiotherapy Clinic, Chemotherapy Unit, University Clinical Centre, Gdansk, Poland
[9]Faculty of Mathematics, Physics and Computer Science, University of Opole, Poland
[10]Department of Anatomy, University of Opole, Poland
[11]Department of Pathophysiology, Jagiellonian University Medical College, Cracow, Poland
[12]Department of Oncology, Institute of Medical Sciences, University of Opole, Poland

Systemic treatment of patients with advanced pancreatic cancer — is there still a place for gemcitabine in the first-line setting? Experience of Polish oncology centers

Address for correspondence:
Ireneusz Raczyński, MD
General Medical Practice
ul. Cylichowska 23 B, 04–769 Warsaw, Poland
tel.: +48 734 466 224
e-mail: ireneusz.raczynski@wp.pl

ABSTRACT

Introduction. Despite some progress in the treatment of patients with pancreatic cancer, it is still a malignancy with a poor prognosis, which results from its rapid local growth with a tendency to infiltrate surrounding tissues and metastasize, and late diagnosis at the advanced stage. The use of multi-drug regimens and modern targeted therapies did not completely eliminate the use of gemcitabine in monotherapy, which is a therapeutic option mainly in patients with poor performance status, ineligible for more advanced therapies.

This study aimed to evaluate the results of treatment with single-agent gemcitabine in everyday clinical practice in Poland and to attempt to identify the predictors of obtaining long-term responses resulting from this treatment.

Material and methods. A retrospective analysis of 167 patients with advanced pancreatic cancer treated with single-agent gemcitabine in five oncology centers in Poland in the years 2017–2022 was conducted. Gemcitabine was used as monotherapy at an initial dose of 1000 mg/m^2 of body surface area (BSA) weekly, 7 times in an 8-week cycle, then 3 times in a 4-week cycle.

Results. Median overall survival (OS) in the entire group of patients was 6.1 months (range — 0.2–32.3 months), and median progression-free survival (PFS) was 4.2 months (range — 0.2–31.3 months). A group of 60 patients was identified as "long responders" (LR), with a response of at least 6 months and a group of 107 as "short responders" (SR). Median PFS in the LR group was 9.15 months (range — 6.0–31.3 months) and in the SR group, it was 3.2 months (range — 0.2–5.8 months). Median OS was 11.6 months (range — 5.9–30.8) and 3.8 months (range — 0.2–32.3 months), respectively. In multivariate analysis, the likelihood of achieving at least a 6-month response (LR) was assessed using a logistic regression model. The model takes into account four variables: the neutrophil/lymphocyte (NLR) ratio, liver metastases, sex, and Hb level.

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Conclusions. The obtained results confirm that gemcitabine monotherapy is still useful in the first-line treatment of patients with advanced and metastatic pancreatic adenocarcinoma. An appropriate selection of patients for this treatment may improve the results while maintaining lower toxicity compared to combined treatment.
Keywords: advanced pancreatic cancer, gemcitabine, overall survival, progression-free survival

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Introduction

Pancreatic cancer is one of the cancers with the fastest increasing incidence. It is the 7th most common malignancy in Europe [1]. Over the last 3 decades, the incidence rate has more than doubled worldwide. It is believed that the burden of this disease will increase along with life expectancy because the incidence increases with age, and most patients are diagnosed at the age of over 65 [2].

Even more disturbing are the data on mortality, which is also increasing. Pancreatic cancer is 4th most common cancer-related cause of death in the world [3]. In Poland, pancreatic cancer is the 5th most common cause of cancer-related deaths among women and 6th among men, which accounts for 5% of all cancer-related deaths in 2020 [4].

The prognosis in pancreatic cancer patients remains unfavorable. It is a high-grade tumor characterized by rapid local growth, with a tendency to infiltrate surrounding tissues and metastasize — primarily in the peritoneum, lymph nodes, and liver. In most patients, pancreatic cancer is diagnosed at a locally advanced or metastatic stage, and only 10-15% of patients are diagnosed at an early stage [5–7]. In the latter group, radical surgical treatment is possible, but 80% of patients undergoing surgery experience a recurrence within 2 years [8].

Diagnosis at a late stage (in more than half of cases in the dissemination stage) and limited treatment options for advanced disease result in an unfavorable prognosis [9, 10]. Median overall survival (OS) in patients with metastatic pancreatic cancer ranges from 3 to 6 months, and the 5-year survival rates have been in single digits for years [3, 5].

Due to clinical characteristics of pancreatic cancer, most patients require systemic treatment at various stages of the disease. The treatment of patients with advanced pancreatic cancer involves chemotherapy using single drugs or multidrug regimens with gemcitabine, fluoropyrimidine, nab-paclitaxel (nab-P), or irinotecan. A choice of the first-line treatment regimen should be adapted to the patient's performance status (PS) [7, 11–13]. According to the recommendations of the European Society of Medical Oncology (ESMO), multidrug regimens (FOLFIRINOX and nab-P with gemcitabine) should be used in patients in good or very good condition, e.g. with PS 1 or 0 according to the Eastern Cooperative Oncology Group (ECOG) scale. Patients with poorer performance status (ECOG PS 2) should receive gemcitabine monotherapy. A performance status of 3–4 on the ECOG scale, and the presence of comorbidities is an indication for the best supportive care (BSC) [14]. The National Comprehensive Cancer Network (NCCN) guidelines also recommend combination therapy (FOLFIRINOX, nab-P with gemcitabine, and other regimens, e.g. gemcitabine with erlotinib) in patients with good PS, while monotherapy (gemcitabine, capecitabine, or fluorouracil) is recommended in patients with poor performance status [15].

For several years, attempts have been made to use molecularly targeted therapies (olaparib, larotrectinib, entrectinib) [16, 17] and immunotherapy (pembrolizumab) [18]. The study results indicate some advantages of these drugs over classical chemotherapy, which was the basis for the registration and introduction of new drugs into clinical practice (e.g. olaparib is currently available under the B.85 drug program). However, these drugs can only be used in selected patients with specific molecular targets (*BRCA1/2* gene mutation, *NTRK* gene fusion, mismatch repair deficiency, and microsatellite instability, respectively). Such patients constitute a small percentage of the whole population of patients with advanced pancreatic cancer.

Despite progress in the treatment of pancreatic cancer, including the use of multidrug regimens and modern compounds, there is still a place for gemcitabine, which was introduced into clinical practice in 1997 after Burris et al. demonstrated its advantages over fluorouracil [19]. The PRODIGE-4 and Metastatic Pancreatic Adenocarcinoma Clinical Trial (MPACT) studies showed the superiority of the FOLFIRINOX regimen and nab-paclitaxel with gemcitabine, respectively, over gemcitabine alone; however, at the cost of increased toxicity [12, 13].

Therefore, a question arose about the criteria for qualifying patients for particular methods of systemic treatment. It seems that patients with ECOG PS 2 and patients with relative contraindications to the use of

oxaliplatin, irinotecan, or long-term fluorouracil infusions could be natural candidates for chemotherapy with nab-paclitaxel and gemcitabine. Such patients constituted less than 10% of the MPACT study population; therefore, it is difficult to clearly comment on the effectiveness of the treatment compared to gemcitabine alone.

Our study aimed to evaluate the results of gemcitabine monotherapy in daily clinical practice in Poland. An attempt was also made to determine predictors of long-term responses to such a therapy.

Material and methods

We performed a retrospective analysis of 167 patients with advanced pancreatic cancer treated with gemcitabine monotherapy in five oncology centers in Poland (Oncology Center in Opole, Oncology Clinic of the Jagiellonian University in Kraków, Oncology Center in Białystok, West Pomeranian Oncology Center in Szczecin, Oncology and Radiotherapy Clinic in Gdańsk).

Patients treated between 2017 and 2022 were included in the analysis. Demographic and clinical data extracted from medical records were anonymized before analysis. We obtained approval from the Bioethics Committee of the District Medical Chamber in Opole (resolution no. 347/2023).

All patients received gemcitabine monotherapy in first-line treatment. In each participating site, treatment with nab-P patients in combination with gemcitabine was available as part of the B.85 drug program. The majority of patients (68%) eligible for gemcitabine treatment did not meet the inclusion criteria for the drug program (primarily due to the absence of metastases or ECOG PS > 1).

The analysis included variables related to the patient's profile, disease biology and stage, and complete blood count (CBC). Follow-up was completed on December 1, 2022. Due to the retrospective nature of the analysis, the causes of death were not determined. Overall survival was defined as the time from the treatment initiation to death due to any cause, and PFS was defined as the time from treatment initiation to disease progression or death due to any cause, whichever occurred first. Response to treatment was defined as no clinical and/or radiological evidence of disease progression.

The Mann-Whitney and Wilcoxon tests were used for continuous data and Fisher's and χ^2 tests for categorical data. The Shapiro-Wilk test was used to evaluate the normality hypotheses. A logistic regression model was used in multivariate analysis. For appropriate selection of variables, a model with all variables, models with each variable analyzed individually, and a model using the stepwise method selected in the R program, in accordance with the Akaike information criterion (AIC), were taken into account. Tests based on Wald statistics were used to assess the significance of parameters in the logistic regression equation. Moreover, the model selected using the AIC criterion was tested with a likelihood ratio test, comparing the model with one variable and adding further variables until four selected variables were obtained.

Results

Clinical characteristics

The median age was 71 years, and almost 60% of patients were female. More than half of patients had a normal body mass index (BMI), and one-third were overweight or obese. Almost all patients had good (61%) or moderate (30%) PS (Tab. 1). Only one patient underwent genetic consultation and *BRCA1/2* gene status determination.

More than half of patients were in clinical stage IV, and the liver was the most common location of metastases (42.5%). Histological differentiation grade was not analyzed due to missing data in two-thirds of patients. In most patients (71%), the CA19-9 serum level at the time of treatment initiation was above the upper limit of normal (ULN) (median — 675, range 0–5657311 U/mL).

At the time of treatment initiation, more than 60% of patients had anemia, mainly grade 1, according to the Common Terminology Criteria for Adverse Events (CTCAE), v. 5.0 (Tab. 1). Parameters of CBC allowed for assessment of white blood cell fraction disorders and calculation of the absolute neutrophils to absolute lymphocytes ratio [neutrophils/lymphocytes ratio (NLR)] and the absolute platelets to absolute lymphocytes ratio [platelets/lymphocytes ratio (PLR)] in peripheral blood. The median NLR was 2.69 (range — 0.3–36.65) and PLR — 146.54 (range — 18.53–1118.57).

Gemcitabine treatment course

Gemcitabine was used as monotherapy at an initial dose of 1000 mg/m^2 of BSA every week, 7 times in an 8-week cycle, then 3 times in a 4-week cycle. The treatment was well tolerated; grade 3 and 4 adverse events (AEs) were reported in 20% of patients (the most common — thrombocytopenia and neutropenia; Tab. 2).

Table 1. Patient characteristics

Characteristic	Number of patients = 167 (%)
Age at diagnosis [years]	
Median	71.24
Range	(47.44–85.87)
Sex	
Women	97 (58.08%)
Men	70 (41.92%)
BMI at treatment initiation	
Median	22.84
Range	(14.88–34.11)
Underweight	22 (13.17%)
Standard	92 (55.09%)
Overweight and obesity	53 (31.74%)
ECOG PS at treatment initiation	
0	7 (4.19%)
1	102 (61.08%)
2	50 (29.94%)
3	7 (4.19%)
No data	1 (0.60%)
Baseline clinical stage according to the TNM classification	
III	59 (35.33%)
IV	95 (56.89%)
No data	13 (7.78%)
Location of the primary tumor	
Head of the pancreas	81 (48.50%)
Pancreatic body	42 (25.15%)
Tail of the pancreas	19 (11.38%)
Multiple locations	12 (7.19%)
No data	13 (7.78%)
Location of metastases at treatment initiation	
Liver and possibly other locations	71 (42.51%)
Other locations excluding the liver	36 (21.56%)
No metastases	60 (35.93%)
CA19-9 serum level at treatment initiation [U/mL]	
Median	675
Range	(0–5657311)
Within normal range	22 (13.17%)
Above ULN	119 (71.26%)
No data	26 (15.57%)
Hemoglobin level at treatment initiation [g/dL]	
Median	12.05
Range	(6.4–14.8)
Below LLN	108 (64.67%)
Within normal range	58 (34.73%)
No data	1 (0.60%)
Leukocyte count at treatment initiation [G/L]	
Within normal range and below LLN	119 (71.26%)
Above ULN	48 (28.74%)
NLR at treatment initiation	
Median	2.69
Range	(0.5–36.65)
Platelet count at treatment initiation [G/L]	
Within normal range and below LLN	134 (80.24%)
Above ULN	33 (19.76%)
PLR at treatment initiation	
Median	146.54
Range	(18.53–1118.57)

BMI — body mass index; ECOG — Eastern Cooperative Oncology Group; LLN — lower limit of normal; NLR — neutrophil/lymphocyte ratio; PLR — platelet/lymphocyte ratio; PS — performance status; ULN — upper limit of normal

Table 2. Gemcitabine treatment course

Characteristic	Number of patients = 167 (%)
Reduction in initial body weight during treatment by > 10%	
Yes	19 (11.38%)
No	147 (88.02%)
No data	1 (0.60%)
Toxicity ≥ 3 grade	
No	132 (79.04%)
Yes	35 (20.96%)
Reason for treatment discontinuation:	
Radiological disease progression	73 (43.71%)
PS deterioration without progression	59 (35.33%)
Toxicity	8 (4.79%)
Other	25 (14.97%)
Treatment continuation	2 (1.20%)
Further systemic treatment	
None	118 (71.52%)
FU/LV	4 (2.42%)
FOLFOX	20 (12.12%)
NALIRI	2 (1.21%)
FOLFIRI	2 (1.21%)
Other (e.g. clinical trial)	18 (11.52%)

FOLFIRI — fluorouracil, leucovorin, irinotecan; FOLFOX — fluorouracil, leucovorin, oxaliplatin; FU/LV — fluorouracil/leucovorin; NALIRI — lysosomal irinotecan

A reduction in initial body weight by > 10% during treatment was observed in 11% of patients. The most common reason for treatment discontinuation (44%) was disease progression (radiological or clinical) detected by the treating physician and deterioration of performance status without objective signs of progression (35%); in only 5% of patients, treatment was discontinued due to toxicity (most often persistently recurring thrombocytopenia). Next-line systemic treatment was used in only 30% of patients — the most frequent was the FOLFOX regimen (12% of all patients), and other regimens were occasionally used (exceptionally, treatment as part of clinical trials).

Treatment results

Median OS in the entire group of patients was 6.1 months (range — 0.2–32.3 months), and median PFS reached 4.2 months (range — 0.2-31.3 months) (Fig. 1 and 2). The 1-year survival rate was 24.5%.

For this analysis, we identified a group of 60 patients who achieved a response lasting at least 6 months [long responders (LR)], and the remaining 107 patients achieved a shorter response [short responders (SR)].

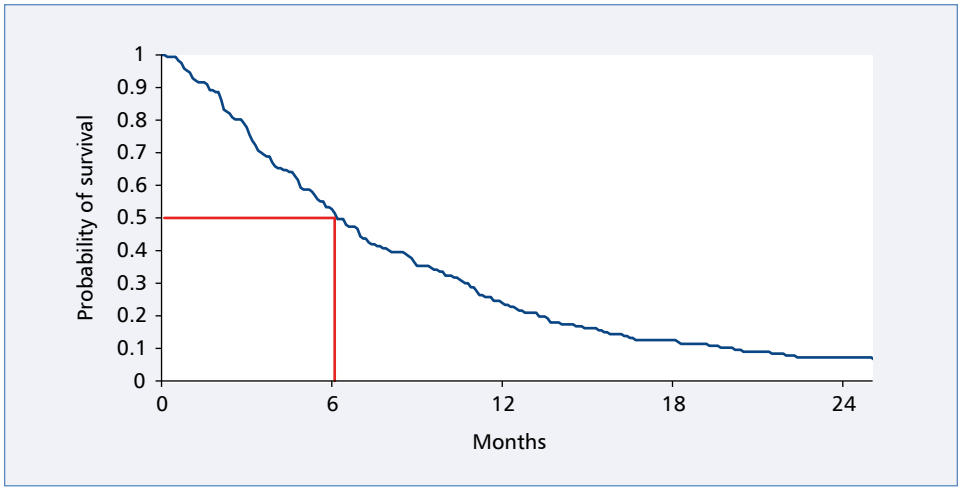

Figure 1. Overall survival in the entire study group

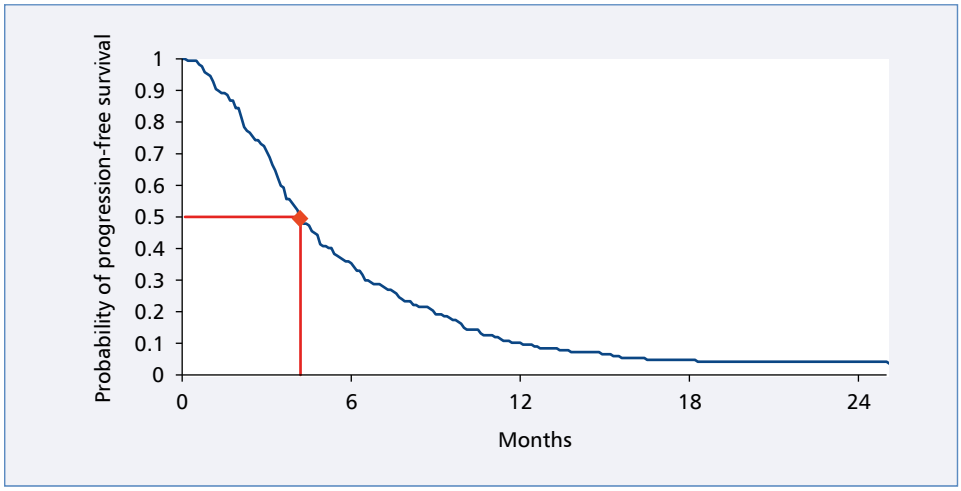

Figure 2. Progression-free survival in the entire study group

The time criterion was established based on median PFS obtained in patients receiving first-line treatment with gemcitabine in combination with nab-paclitaxel in MPACT (Metastatic Pancreatic Adenocarcinoma Clinical Trial), which was 5.5 months. Median PFS in the LR group was 9.15 months (range — 6.0–31.3 months) while in the SR group — 3.2 months (range — 0.2––5.8 months). Differences were also noted in terms of OS, whose median was three times longer in the LR group compared to SR [11.6 months (range — 5.9–30.8) and 3.8 months (range 0.2–32.3), respectively] (Fig. 3).

In order to determine the factors that influence the likelihood of achieving a long-term response, individual clinical features were compared in the SR and LR groups (Tab. 3).

Among the analyzed factors, the following had a significant impact on achieving a long-term response (LR): initial clinical stage, presence of liver metastases, leukocyte count, NLR, and the occurrence of grade 3 and/or 4 toxicity during gemcitabine treatment.

In multivariate analysis, the probability of achieving at least a 6-month treatment response (LR) was assessed using a logistic regression model. Variables for creating the model were selected based on data from the literature and histoclinical characteristics of the study group and included: age, BMI, NLR, sex, initial clinical stage according to the TNM classification, location of the primary tumor, location of metastases, ECOG PS, leukocyte count, hemoglobin level (in terms of a categorical variable). Models with one of the above-mentioned

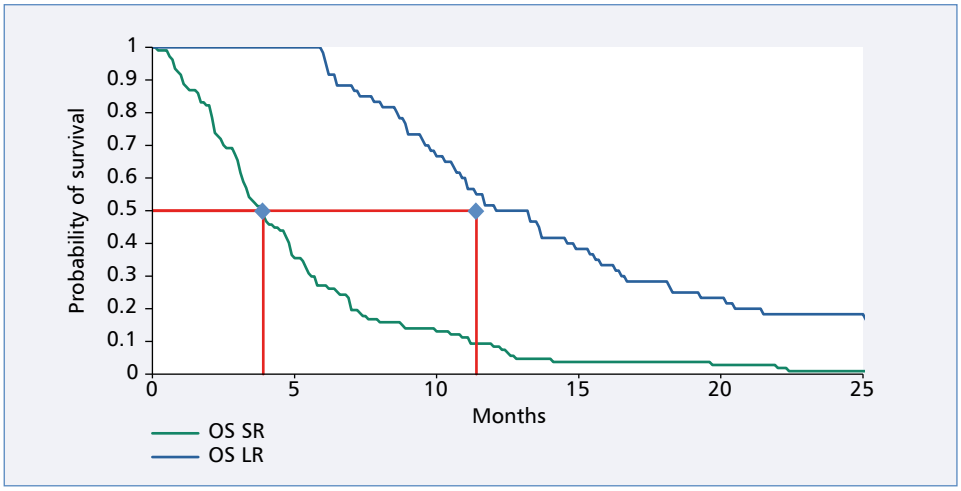

Figure 3. Overall survival (OS) in short (SR) and long-response (LR) subgroups

variables were analyzed successively. Significance tests were performed for all models, and additionally, for models with one variable, log odds plots against this variable were analyzed. On this basis, a model was selected that takes into account 4 variables: the NLR (continuous variable), liver metastases (yes or no), sex, and hemoglobin level (within normal range or below LLN).

The relationships between the logarithm of the odds and the values for individual variables are presented in Figure 4. The graphs present the differences in the chance of achieving a long-term response depending on patient characteristics, for the variables that were selected for the model. A woman with anemia and liver metastases was less likely to achieve a long-term response compared to a man with normal hemoglobin levels and no liver metastases.

As the NLR increased, the chance of achieving a long-lasting response decreased. The coefficient for the NLR variable is exp (–0.1905) = 0.83, so with an increase in the NLR by one unit, the chance that the patient would be in the LR group decreased by 17%, with other parameters unchanged. The absence of liver metastases increased the chance of achieving a long-term response [exp(1.5427) = 4.68], which means that the chance in a patient without liver metastases increased by 368%, compared to a patient with liver metastases, with other parameters unchanged. The chance of obtaining a long-term response for a patient with a normal hemoglobin level was 112% higher than for a patient with a hemoglobin level below the norm, with other parameters unchanged [exp(0.7531) = 2.12]. Men were 89% more likely to achieve a long-lasting response than women with all other parameters equal [exp(0.6348) = 1.89]. The following formula can be used to predict the probability that a patient will be in the LR group:

$$\ln \frac{P(\times)}{1\text{-}P(\times)} = -1.5117 - 0.1905 \times \text{NLR} - 1.5427 \times \text{metastases} + 0.6348 \times \text{sex} + 0.7531 \times \text{Hg},$$

where:

$$\text{metastases} = \begin{cases} 0, \text{ when patient has liver metastases,} \\ 1, \text{ when patient has no liver metastases;} \end{cases}$$

$$\text{sex} = \begin{cases} 0, \text{ when patient is female,} \\ 1, \text{ when patient is male;} \end{cases}$$

$$\text{Hg} = \begin{cases} 0, \text{ when patient has hemoglobin level below LLN,} \\ 1, \text{ when patient has hemoglobin level within normal range} \end{cases}$$

and the NLR takes the value calculated for a given patient. The relationship between the variables included in the model and the odds ratio of achieving a response to treatment lasting at least 6 months is shown in Figure 5.

With the assumed significance level of 0.05, not all variables turned out to be statistically significant in the adopted model. However, this is not the only criterion for selecting variables for the model [20]. The model with these variables is statistically significant, which means that it best explains the studied phenomenon — achieving a treatment response lasting at least 6 months — compared to the other models considered. This model was the best, taking into account the AIC criterion and using the likelihood ratio test for the selected model, the p-value was 0.00001154285.

Examples of predictions for patients with a favorable and unfavorable profile are presented in Table 4.

Table 3. Clinical features with significantly different presentations in the short response (SR) and long response (LR) subgroups

Characteristic	Patient percentage		
	SR group (n = 107)	LR group (n = 60)	p value
Age at diagnosis [years]			
Median	71.0	72.5	0.583
Range	47.4–85.5	48.8–85.9	
Sex			
Women	65	32	0.442
Men	42	28	
BMI at treatment initiation			
Median	22.5	23.5	0.108
Range	14.9–33.6	15.4–34.1	
ECOG PS at treatment initiation			
0	3	4	0.371
1	64	38	
2	36	14	
3	4	3	
No data	0	1	
Baseline clinical stage according to the TNM classification			
III	30	25	**0.007**
IV	70	29	
No data	7	6	
Location of the primary tumor			
Head of the pancreas	48	33	0.116
Pancreatic body	27	15	
Tail of the pancreas	16	3	
Multiple locations	10	2	
No data	6	7	
Presence of liver metastases			
Yes	60	11	**< 0.001**
No	47	49	
Hemoglobin level at treatment initiation [g/dL]			
Median	12.0	12.1	0.4155
Range	8.4–14.5	6.4–14.8	
Below LLN	71	36	
Within normal range	35	23	
No data	1	1	
Leukocyte count at treatment initiation [G/L]			
Within normal range and below LLN	69	50	**0.016**
Above ULN	38	10	
NLR at treatment initiation			
Median	3.02	2.25	**< 0.001**
Range	0.5–36.7	0.525–7.56	
Grade 3 and 4 toxicity			
Yes	17	18	**0.046**
No	90	42	

BMI — body mass index; ECOG — Eastern Cooperative Oncology Group; LLN — lower limit of normal; NLR — neutrophil/lymphocyte ratio; PS — performance status; ULN — upper limit of normal

Discussion

Pancreatic adenocarcinoma is characterized by constantly increasing incidence and mortality [1–4] and has a consistently poor prognosis due to the aggressive disease biology and diagnosis occurring at the advanced stage [5–8]. The basis of treatment in patients with advanced pancreatic cancer is chemotherapy. For the last decade, some progress has been observed in this field, which was mainly related to the introduction of the

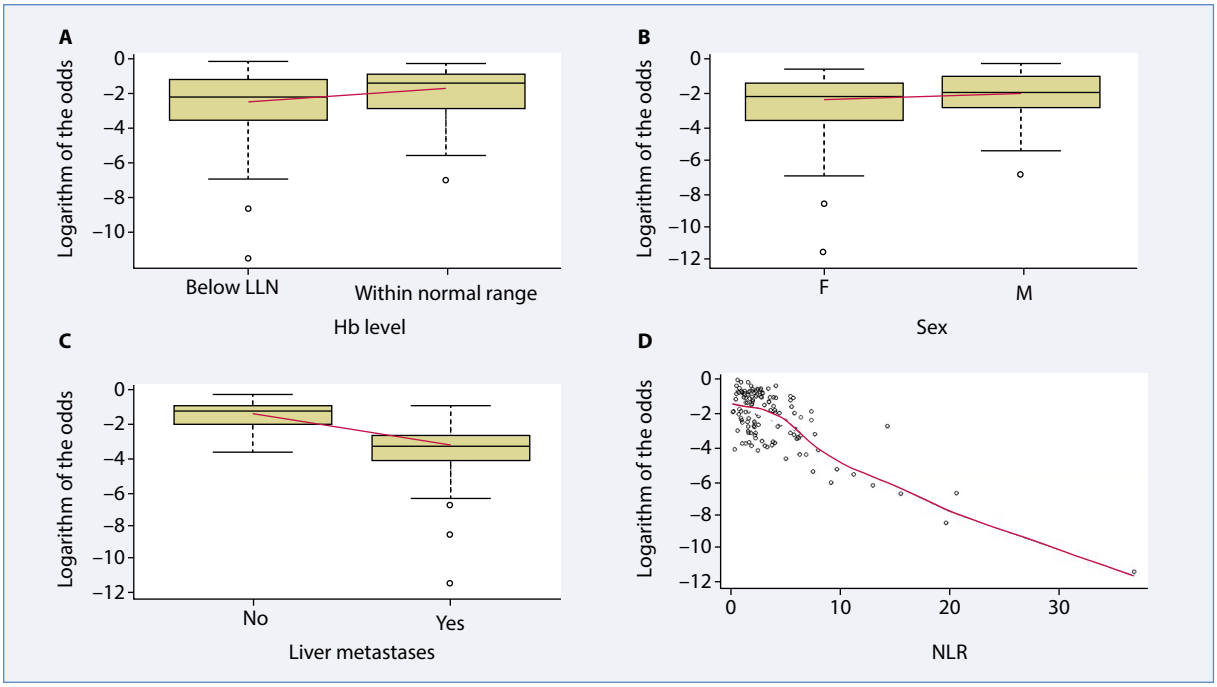

Figure 4. Box plots of logarithms of the odds depending on individual variables: hemoglobin (Hb) level (**A**), sex (**B**), presence of liver metastases (**C**) (median logarithms of the odds for individual values are connected by segments), and a plot of the dependence of the logarithm of the odds on the neutrophil/lymphocyte ratio (NLR) (**D**) (with locally weighted regression curve highlighted); F — female; LLN — lower limit of normal; M — male

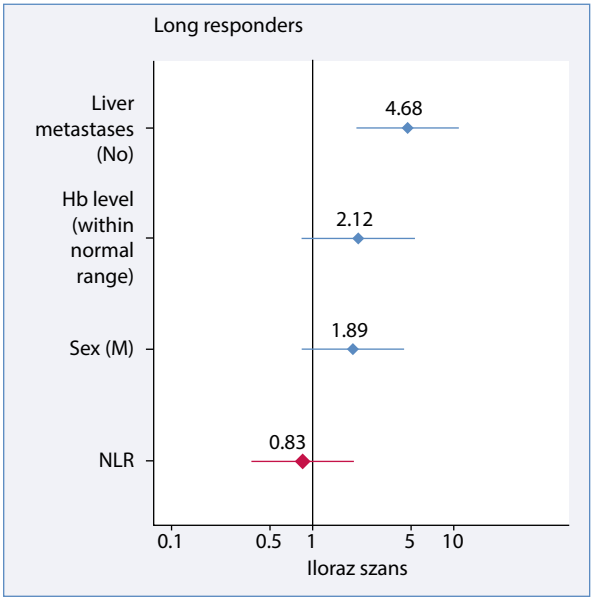

Figure 5. Forest plot for the selected model; Hb — hemoglobin; M — male; NLR — neutrophil/lymphocyte ratio

multi-drug regimen FOLFIRINOX and nab-P [7, 11–13] and immunotherapy and PARP inhibitors in selected patient populations [16, 18]. Despite the introduction of new therapeutic options, gemcitabine monotherapy still has an important place in treatment algorithms. The benefits of this treatment were demonstrated a quarter of a century ago, showing the advantage of gemcitabine monotherapy over fluorouracil [19], and this agent is still included in the guidelines of ESMO, NCCN [14, 15], and the Polish Society of Clinical Oncology [21]. The ESMO recommends the use of gemcitabine monotherapy in patients with poor performance status (ECOG PS 2) or with bilirubin level exceeding 1.5 times the upper limit of normal, and the NCCN recommends gemcitabine monotherapy in patients with poor performance status. This is related to the results of the PRODIGE-4 and MPACT trials, in which the FOLFIRINOX and nab-P with gemcitabine were superior to gemcitabine monotherapy, but at the cost of increased toxicity [12, 13].

However, following the above-mentioned guidelines has a certain limitation in Poland, which is due to drug reimbursement. Firstly, in Poland, treatment of patients with advanced pancreatic cancer with a combination of nab-P and gemcitabine is possible within the so-called Drug Program, whose inclusion criteria are metastatic disease, ECOG PS 0 or 1, and ineligibility to use of FOLFIRINOX chemotherapy. It has to be mentioned that in the MPACT study, such a patient population represented less than 10% of the overall patient population. In this study, there were 57% patients with metastatic

Table 4. Examples of predictions for achieving at least 6 months of progression-free survival [long responders (LR) patient]

Patient profile	Clinical features	LR probability	Interpretation
Favorable	NLR = 2.5 Male sex Liver metastases: NO Hb level within normal range	0.7196345	LR chance equal to 2.57, i.e. approximately 257:100; We predict that of 357 patients with these characteristics, 257 will achieve LR
Unfavorable	NLR = 8 Female sex Liver metastases: YES Hb level below LLN	0.04585096	LR chance equal to 0.048, i.e. approximately 48:1000; We predict that of 1048 patients with these characteristics, 48 will achieve LR

Hb — hemoglobin; LLN — lower limit of normal; NLR — neutrophil/lymphocyte ratio

disease, and 57% and 66% patients with a performance status of 0 or 1, respectively. This means that arbitrarily adopted reimbursement criteria may limit access to the treatment for which patients would be eligible when only clinical criteria were applied. Secondly, in patients treated with gemcitabine monotherapy, a very wide range of individual values is observed. In the presented analysis, median OS in the entire group was 6.1 months (range — 0.2–32.3 months) and median PFS was 4.2 months (range — 0.2–31.3 months).

Among 1174 patients with locally advanced unresectable or metastatic pancreatic ductal adenocarcinoma included in the German TPK registry (*Tumorregister Pankreaskarznom*), 23% were treated with gemcitabine monotherapy in the first line [22]. This group included mainly elderly patients (median age — 78 years) with poorer performance status (73% of patients with ECOG PS ≥ 1). Median PFS in this group was 4.6 months, median OS was 6.8 months, the 6-month survival rate was 58%, and the disease control rate (DCR) was 30%. In patients receiving gemcitabine monotherapy in the PRODIGE-4 trial, median OS was 6.8 months, median PFS was 3.3 months, and the overall response rate (ORR) was 9.4% [12]. In turn, in the MPACT trial, median OS, median PFS, and 1- and 2-year survival rates were 3.7 months, 6.7 months, 22%, and 4%, respectively. The authors of these studies drew attention to the similarity of the results obtained in the group treated with gemcitabine to the results obtained in the study by Cunnigham et al. and in other phase III studies with this drug [23]. The results of our study also show many similarities although of course a direct comparison and conclusions would be unjustified. Nevertheless, the wide range of survival parameters encourages the search for patients who could particularly benefit from gemcitabine monotherapy.

In this analysis, an attempt was made to determine predictors of long-term responses in patients receiving gemcitabine monotherapy. The criterion for such a benefit was obtaining a response of at least 6 months. Various models were initially evaluated, and a model taking into account NLR, presence of liver metastases, sex, and hemoglobin level was selected for the final analysis. These factors differ from the parameters of better response to combined treatment established in the ESMO recommendations, NCCN recommendations, and the PRODIGE-4 and MPACT studies, which mainly included the clinical disease stage, ECOG performance status 3–4, age, and the presence of comorbidities. This is especially true for the NLR. In recent years, many researchers have paid attention to the prognostic value of this indicator in cancer and other diseases (e.g., cardiovascular and infectious diseases) [24]. In our analysis, the median NLR was 2.69 (range — 0.5–36.65). The wide range of values and the inclusion of this indicator in the model assessing the chances of obtaining a long-term response indicate that the NLR may have prognostic significance.

Many studies have attempted to define a prognostic model enabling determination of the prognosis in patients with advanced pancreatic cancer. One of the most frequently assessed is the NLR. A high NLR is associated with worsened OS in many solid tumors and is an easily available and inexpensive biomarker [25]. Many studies have confirmed these observations in patients with pancreatic cancer [26, 27] as well as meta-analyses assessing the prognostic significance of the NLR in patients with pancreatic cancer [28, 29].

Other studies have shown a significant impact of preoperative CA19-9 and CA125 levels on long-term survival of patients with pancreatic cancer [30], as well as the PLR, whose high values also indicate an unfavorable prognosis in terms of OS and PFS in patients with advanced pancreatic cancer [31, 32].

However, the authors of the mentioned publications draw attention to the need to take into account additional data in prognostic models (e.g. chemotherapy regimen or comorbidities).

Conclusions

The obtained results confirm that gemcitabine monotherapy is still used in the first-line treatment of patients with advanced and metastatic pancreatic adenocarcinoma. It seems that an appropriate selection of patients for this treatment may improve results while maintaining lower toxicity compared to combined treatment. The model assessing the chances of obtaining a long-term response indicated in our analysis may be the basis for proper patient qualification although it requires confirmation in further prospective studies with a larger number of patients involved.

Article Information and Declarations

Data availability statement

All analyzed data are included in this article. Further inquiries may be directed to the corresponding author.

Ethics statement

Approval of the Bioethics Committee of the District Medical Chamber in Opole was obtained (resolution no. 347/2023).

Author contributions

I.R.: should be considered the main author, author of the concepts, methods, research, data analysis, literature review, original manuscript; data collection, and the author giving final approval of the article; P.Z.: data collection; statistical analysis, and final approval of the article; A.S.: statistical analysis, final approval of the article; J.S., B.Cz.-A., A.Ch.-B., M.T., K.W., A.S., W.R., M.J.: data collection, final approval of the article; B.R.: should be considered the senior author, author of the concepts, methods, research, data analysis, literature review, original manuscript; data collection, and the author giving final approval of the article.

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Conflict of interest

All authors declare no conflict of interest in connection with this article.

Supplementary material

None.

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