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Paliatywne leczenie systemowe chorych na raka trzustki, w kontekście polskiej praktyki klinicznej

Rozprawa doktorska

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SPIS TREŚCI

WYKAZ STOSOWANYCH SKRÓTÓW

Skrót	ENG.	PL
5-FU	5-fluorouracil	5-fluorouracyl
ASCO	American Society of Clinical Oncology	Amerykańskie Towarzystwo Onkologii Klinicznej
BMI	Body Mass Index	wskaźnik masy ciała
ECOG	Eastern Cooperative Oncology Group	Wschodnia Grupa Onkologiczna
ESMO	European Society for Medical Oncology	Europejskie Towarzystwo Onkologii Klinicznej
g*BRCA*m	germline BRCA mutations	mutacje germinalne w genie BRCA1 i/lub BRCA2
LR	Long Responders	osoby z długotrwałą odpowiedzią
nab-P	nab-paclitaxel	nab-paklitaksel
NCCN	National Comprehensive Cancer Network	Narodowa Sieć Pełnoprofilowych Ośrodków Onkologicznych
NLR	Neutrophil-to-Lymphocyte Ratio	stosunek bezwzględnej liczby neutrofili do bezwzględnej liczby limfocytów
NTRK	Neurotrophic Receptor Tyrosine Kinase	receptorowa kinaza tyrozynowa dla neurotrofin
ORR	Objectve Response Rate	obiektywny odsetek odpowiedzi
OS	Overall Survival	przeżycie całkowite
PARP	Poly-[ADP-Ribose]Polymerase	polimeraza poli-ADP-rybozy

PFS	Progression Free Survival	przeżycie wolne od progresji choroby
PLR	Platelet-to-Lymphocyte Ratio	stosunek bezwzględnej liczby płytek krwi do bezwzględnej liczby limfocytów
PS	Performance Status	stan sprawności
QoL	Quality of Life	jakość życia
SR	Short Responders	osoby z krótkotrwałą odpowiedzią
SII	Systemic Immune-Inflammation index	wskaźnik ogólnoustrojowej reakcji immunologiczno-zapalnej
TNM	Tumor, Nodules, Metastases.	guz, węzły chłonne, przerzuty

LISTA PUBLIKACJI ZAWARTYCH W ROZPRAWIE

1. **Quality of life of patients with advanced pancreatic cancer** (Tł. Jakość życia chorych na zaawansowanego raka trzustki)
   Autorzy: Raczyński I, Radecka B
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2. **Advanced pancreatic cancer: diagnosis and systemic treatment evolution over the last decades** (Tł. Zaawansowany rak trzustki — ewolucja w zakresie rozpoznawania i leczenia systemowego w ostatnich dziesięcioleciach)
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3. **Survival of pancreatic cancer patients treated with nab-paclitaxel (nab-P) in clinical practice: Analysis of National Health Fund data** (Tł. Przeżycie chorych na raka trzustki leczonych nab-paklitakselem (nab-P) w praktyce klinicznej: analiza danych NFZ)
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4. **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** (Tł. Systemowe leczenie chorych na zaawansowanego raka trzustki – czy nadal jest miejsce dla gemcytabiny w pierwszej linii? – doświadczenia polskich ośrodków)

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5. **Neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and systemic immune-infammation index as clinical predictive and prognostic markers in patients with advanced pancreatic cancer receiving gemcitabine monotherapy** (Tł. NLR, PLR, SII jako kliniczne markery predykcyjne i prognostyczne u chorych na zaawansowanego raka trzustki poddawanych monoterapii gemcytabiną)

   Autorzy: Raczyński I, Siedlaczek A, Streb J, Zając P, Czartoryska-Arłukowicz B, Chruściana-Bołtuć A, Talerczyk M, Wierzbicka K, Radecka W, Jurczyk M, Radecka B

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STRESZCZENIE

WSTĘP

Zachorowalność na gruczołowego raka trzustki systematycznie wzrasta. Obecnie jest to 10. najczęściej występujący nowotwór złośliwy w Europie i Stanach Zjednoczonych) [1,2]. W Polsce notuje się ok. 3500 nowych zachorowań rocznie [3]. Wśród nowotworowych przyczyn zgonu rak trzustki zajmuje 4. miejsce na świecie, a w Polsce 6. miejsce u mężczyzn (4,4%) i 5. miejsce u kobiet (5,4%) [3]. Ta dysproporcja pomiędzy zachorowalnością i umieralnością jest związana z rozpoznawaniem choroby w stadium rozsiewu u ponad połowy chorych oraz ograniczonymi możliwościami leczenia choroby zaawansowanej [1]. Szacuje się, że w 2030 roku rak trzustki będzie drugą najczęstszą przyczyną zgonów z powodów nowotworowych [1].

Na wczesnym etapie choroba przebiega bezobjawowo lub objawy są niespecyficzne. To powoduje, że zaledwie u około 10% chorych rak trzustki rozpoznawany jest we wczesnym, umożliwiającym radykalne leczenie chirurgiczne, stadium [4]. Niestety, niemal u 80% operowanych chorych w ciągu 2 lat dochodzi do nawrotu choroby, najczęściej w postaci odległych przerzutów [4]. Mediana czasu całkowitego przeżycia u chorych z przerzutami wynosi od 3 do 6 miesięcy, a 5 lat przeżywa jedynie od 0,5 do 9% chorych (w Polsce ok. 8%) [2,5].

Ważnym problemem klinicznym jest jakość życia chorych na zaawansowanego raka trzustki, która jest ogólnie zła z uwagi na rozbudowany obraz kliniczny (ból, wyniszczenie, przewlekłe zmęczenie) i niepożądane działania stosowanego leczenia. Co więcej, ocena tej jakości jest szczególnie trudna, m.in. z uwagi na ogólną świadomość złego rokowania. Temat jakości życia w tej grupie chorych jest podejmowany przez badaczy niezwykle rzadko [6]. Z nielicznych, jak dotąd, badań wynika, że QoL u chorych na raka trzustki jest obniżona już od początku choroby, a funkcjonowanie psychiczne chorych jest znacząco gorsze niż w przypadku innych nowotworów [7].

Standardowym leczeniem chorych na miejscowo zaawansowanego i uogólnionego raka trzustki jest chemioterapia. Pierwszym lekiem cytotoksycznym stosowanym w leczeniu chorych na raka trzustki był 5-fluorouracyl (5-FU).

Przez wiele lat lek stosowano w monoterapii, prowadząc również wiele badań klinicznych z użyciem wielolekowych schematów z 5-FU. Schematy takie były zazwyczaj bardziej aktywne, zapewniając ok. 20% odsetki odpowiedzi (ang. *objectve response rate*, ORR), jednak pozostawało to bez wpływu na całkowite przeżycie (ang. *overall survival*, OS) i kontrolę objawów zaawansowanej choroby, a wiązało się z wyższą toksycznością [8,9].

Pewien postęp odnotowano dopiero w 1997 roku, kiedy wykazano przewagę gemcytabiny w monoterapii nad 5-FU. Odnotowano wydłużenie mediany czasu OS oraz poprawę stanu sprawności, lepszą kontrolę bólu i poprawę jakości życia QoL (ang. *quality of life*, QoL) [10]. Na podstawie wyników powyższego badania gemcytabina stała się na wiele lat standardem leczenia chorych na zaawansowanego raka trzustki.

Na początku XXI w. przeprowadzono kilkanaście badań III fazy, w których oceniano skojarzenie gemcytabiny z innymi lekami o różnym mechanizmie działania. Tylko w jednym z tych badań (oceniającym połączenie gemcytabiny z erlotynibem) odnotowano przewagę leczenia skojarzonego nad gemcytabiną w monoterapii w zakresie OS i ORR, jednak leczenie skojarzone charakteryzowało się większą toksycznością [11].

Znaczący postęp w systemowym leczeniu pierwszej linii chorych na zaawansowanego (w tym z przerzutami) raka trzustki odnotowano dopiero w drugiej dekadzie XXI w., po przeprowadzeniu dwóch badań klinicznych III fazy: PRODIGE 4, w którym oceniano skuteczność i bezpieczeństwo schematu wielolekowego FOLFIRINOX oraz MPACT z paklitakselem w postaci nanocząsteczkowego kompleksu z albuminą (nab-P, nab-paklitaksel) w skojarzeniu z gemcytabiną [12,13]. Obie te terapie – FOLFIRINOX oraz nab-P z gemcytabiną – weszły do codziennej praktyki klinicznej, w której również potwierdzono ich wartość [14].

Obecnie wszystkie opisane schematy chemioterapii – gemcytabina w monoterapii, w skojarzeniu z nab-P oraz FOLFIRINOX – są stosowane w leczeniu pierwszej linii, a wybór schematu jest zazwyczaj podyktowany stanem sprawności chorych. Europejskie Towarzystwo Onkologii Klinicznej (*European Society for Medical Oncology*, ESMO) oraz Narodowa Sieć Pełnoprofilowych Ośrodków

Onkologicznych (*National Comprehensive Cancer Network*, NCCN) rekomendują zastosowanie schematów wielolekowych (FOLFIRINOX oraz nab-P z gemcytabiną czy innych, np.: gemcytabina z erlotynibem) u chorych w bardzo dobrym i dobrym stanie sprawności (stopień 0 lub 1 w skali ECOG). Chorzy w gorszym stanie sprawności (stopień 2 wg. ECOG) powinni otrzymywać monoterapię gemcytabiną, kapecytabiną lub fluorouracylem. Stan sprawności odpowiadający stopniom 3 i 4 w skali ECOG jest wskazaniem do zastosowania leczenia objawowego (ang. *symptom directed care)* [15,16].

Praktyka kliniczna w Polsce odzwierciedla wytyczne ESMO, przy czym nab-P z gemcytabiną jest stosowany w ramach programu lekowego, co jest czynnikiem ograniczającym jego zastosowanie. Nadal duża grupa chorych (pozostających w gorszym stanie sprawności lub niespełniających kryteriów włączenia do programu lekowego) otrzymuje gemcytabiną w monoterapii i w tej grupie także obserwuje się względnie długotrwałe korzyści z leczenia.

Postęp w zakresie systemowego leczenia pierwszej linii zwrócił uwagę na potrzebę określenia dalszego postępowania w przypadku niepowodzenia. Wyniki badań klinicznych wykazały uzasadnienie dla zastosowania w drugiej linii schematów opartych na 5- fluorouracylu [17].

U chorych na przerzutowego gruczolakoraka trzustki z mutacją germinalną w genie *BRCA1* i/lub *BRCA2* (g*BRCA*m) przeżycie wolne od progresji (ang. *progression free survival*, PFS) poprawia zastosowanie podtrzymującego (po wcześniejszej chemioterapii z pochodnymi platyny) leczenia inhibitorem polimerazy poli-ADP-rybozy (ang. *poly- [ADP-ribose] polymerase*, PARP), olaparybem [18]. W latach 2018 - 2019 możliwości leczenia chorych na przerzutowego raka trzustki zostały poszerzone w wyniku rejestracji przez FDA larotrektynibu i entrektynibu do leczenia guzów litych, które wykazują fuzję genu receptorowej kinazy tyrozynowej dla neurotrofin (ang. *neurotrophic receptor tyrosine kinase NTRK*) [19,20]. Prowadzone są też badania z wykorzystaniem immunoterapii [21,22].

W wielu badaniach podjęto próbę stworzenia modelu prognostycznego, umożliwiającego określenie rokowania u chorych na zaawansowanego raka trzustki. Jednym z częściej ocenianych parametrów jest stosunek bezwzględnej liczby neutrofili do bezwzględnej liczby limfocytów (ang. *neutrophil-to-lymphocyte ratio,*

NLR), którego wartość prognostyczna została potwierdzona w kilku badaniach, jednak nie zdefiniowano punktu odcięcia [23-28]. Wykazano również znaczący niekorzystny wpływ przedoperacyjnych ponadnormatywnych poziomów CA19-9 i CA125 na długoterminowe przeżycie chorych na raka trzustki [29]. Stosunek bezwzględnej liczby płytek krwi do bezwzględnej liczby limfocytów (ang. *platelet-to-lymphocyte ratio*, PLR) to kolejny wskaźnik niekorzystnego rokowania w odniesieniu do OS i PFS u chorych na zaawansowanego raka trzustki, aczkolwiek punkt odcięcia dla tego parametru też nie został zdefiniowany [30,31]. Względnie nowym narzędziem jest wskaźnik ogólnoustrojowej reakcji immunologiczno-zapalnej (ang. *systemic immune-inflammation index*, SII), kalkulowany w oparciu o liczbę płytek krwi, neutrofili i limfocytów. Wysoką ujemną wartość prognostyczną SII zaobserwowano u chorych na różne nowotwory [32,33] poddanych różnym metodom systemowego leczenia [34-36].

Rozpoznanie raka trzustki w zaawansowanym stadium, niska skuteczność leczenia zaawansowanej choroby, złe rokowanie i znaczne pogorszenie jakości życia chorych wskazują na potrzebę oceny tego problemu klinicznego nie tylko w ramach badań klinicznych, ale także w warunkach rzeczywistej praktyki.

CELE

Cel główny:

1) Przedstawienie aktualnej sytuacji epidemiologicznej dotyczącej raka trzustki, możliwości leczenia choroby zaawansowanej i badań nad jakością życia chorych na zaawansowanego raka trzustki.
2) Analiza wybranych opcji terapeutycznych oraz osiąganych wyników leczenia w codziennej praktyce klinicznej,

Cele szczegółowe:

1) Przedstawienie sytuacji epidemiologicznej dotyczącej raka trzustki w Polsce i na świecie określającej skalę problemu klinicznego.
2) Przedstawienie dotychczasowych oraz będących w fazie badań klinicznych możliwości systemowego leczenia u chorych na zaawansowanego nieoperacyjnego raka trzustki.

3) Przedstawienie aktualnego poziomu wiedzy nt. jakości życia chorych na raka trzustki w zależności od zastosowanego leczenia.
4) Analiza wyników leczenia chorych na przerzutowego raka gruczołowego trzustki w ramach programu lekowego „Leczenie pacjentów z gruczolakorakiem trzustki".
5) Ocena wyników leczenia gemcytabiną w monoterapii w warunkach praktyki klinicznej w Polsce oraz próba określenia cech wskazujących na możliwość uzyskania długotrwałych odpowiedzi pod wpływem tego leczenia.
6) Ocena wybranych klinicznych markerów predykcyjnych i prognostycznych u chorych na zaawansowanego raka trzustki poddawanych monoterapii gemcytabiną.

MATERIAŁ I METODY

Materiał*:*

1) Piśmiennictwo dotyczące epidemiologii, diagnostyki i leczenia chorych na raka trzustki.
2) Dane dotyczące chorych na gruczołowego raka trzustki leczonych nab-P w ramach programu lekowego B.85 LECZENIE PACJENTÓW Z GRUCZOLAKORAKIEM TRZUSTKI (ICD-10: C25.0, C25.1, C25.2, C25.3, C25.5, C25.6, C25.7, C25.8, C25.9) znajdujących się w bazie Narodowego Funduszu Zdrowia (NFZ).
3) Dane kliniczne chorych na gruczołowego raka trzustki leczonych w następujących ośrodkach onkologicznych:
   - Klinika Onkologii z Odcinkiem Dziennym, Opolskie Centrum Onkologii im. Prof. Tadeusza Koszarowskiego, Opole;
   - Oddział Kliniczny Onkologii, Szpital Uniwersytecki, Kraków;
   - Oddział Onkologii Klinicznej Zachodniopomorskie Centrum Onkologii, Szczecin;
   - Oddział Onkologii Klinicznej im. dr E. Pileckiej z pododdziałem Chemioterapii Dziennej, Białostockie Centrum Onkologii im. Marii Skłodowskiej-Curie, Białystok;

- Klinika Onkologii i Radioterapii, Oddział Chemioterapii Dziennej, Uniwersyteckie Centrum Kliniczne, Gdańsk;

Metody badawcze:

1) Analiza dostępnego piśmiennictwa;
2) Analiza rejestru NFZ obejmującego chorych na raka trzustki leczonych nab-P w latach 2014-2019;
3) Analiza danych klinicznych chorych na raka trzustki leczonych w okresie od stycznia 2017r. do grudnia 2021r. w 5 w/w ośrodkach onkologicznych w Polsce.

Metody statystyczne:

W ocenie wyników leczenia chorych w warunkach praktyki klinicznej w Polsce zastosowano metody analiz przeżycia, testy log-rank oraz metody statystyki opisowej. Przeprowadzono wieloczynnikową analizę w celu zidentyfikowania zmiennych wpływających na kwalifikację do leczenia oraz uzyskiwanie długotrwałych odpowiedzi.

W części dotyczącej analizy wybranych klinicznych czynników predykcyjnych i prognostycznych zastosowano testy Manna-Whitney'a-Wilcoxon'a dla danych ciągłych oraz testy Fishera i $\chi 2$ dla danych kategorycznych. Do sprawdzenia hipotez o normalności wykorzystano test Shapiro-Wilka. W analizie przeżycia wykorzystano estymator Kaplana-Meiera oraz zastosowano model nieparametryczny Coxa. Rozważano jedynie modele z każdą zmienną analizowaną indywidualnie ze względu na związki występujące między zmiennymi.

Elementy oryginalne pracy

1) Analiza wyników leczenia chorych na zaawansowanego raka trzustki w Polsce w warunkach praktyki klinicznej.
2) Określenie czynników umożliwiających uzyskanie długotrwałych odpowiedzi na monoterapię gemcytabiną.
3) Określenie wpływu na wyniki leczenia wybranych klinicznych czynników prognostycznych i predykcyjnych.

WYNIKI

W swojej pracy badawczej dokonałem szerokiej oceny problemu klinicznego jakim jest zaawansowany rak trzustki, sięgając po dane z badań klinicznych i codziennej praktyki. W cyklu publikacji poświęconych temu problemowi klinicznemu zebrałem informacje na temat epidemiologii, biologii, diagnostyki, kliniki, leczenia, rokowania oraz jakości życia chorych na zaawansowanego (w tym z przerzutami) raka trzustki. Oceniłem wybrane aspekty kliniczne dotyczące leczenia chorych na zaawansowanego raka trzustki w Polsce, łącznie z próbą zdefiniowania czynników klinicznych wpływających na prawdopodobieństwo uzyskania długotrwałych odpowiedzi na chemioterapię oraz oceną wybranych indeksów prognostycznych. Według mojej wiedzy nie publikowano jak dotąd tak obszernych analiz dotyczących chorych na zaawansowanego raka trzustki w polskiej populacji.

Pierwsza praca ma charakter poglądowy i stanowi przegląd piśmiennictwa nt.: jakości życia chorych na zaawansowanego raka trzustki.

W drugiej pracy przedstawiłem epidemiologię raka trzustki ze szczególnym uwzględnieniem danych z Krajowego Rejestru Nowotworów oraz dokonałem oceny ewolucji systemowego leczenia tego nowotworu w ostatnich dziesięcioleciach.

Trzecia praca jest pracą badawczą i stanowi retrospektywną analizę wyników leczenia nab-P w zakresie OS i PFS w warunkach praktyki klinicznej na podstawie danych pochodzących z bazy Narodowego Funduszu Zdrowia.

Kolejne dwie prace mają charakter badawczy i są efektem wieloośrodkowej współpracy, w ramach której oceniono retrospektywnie przebieg leczenia pierwszej linii gemcytabiną w monoterapii w pięciu ośrodkach onkologicznych w Polsce. W czwartej pracy podjąłem próbę opracowania modelu prognostycznego, umożliwiającego określenie profilu chorych mających szansę na uzyskanie co najmniej 6 miesięcznej odpowiedzi (obejmującej także stabilizację choroby). Do predykcji prawdopodobieństwa, że chory uzyska taką korzyść skonstruowałem równanie, które jest niewątpliwie innowacyjnym elementem moich analiz.

W piątej pracy oceniłem znaczenie rokownicze wskaźników NLR, PLR i SII u chorych na zaawansowanego raka trzustki leczonych w pierwszej linii gemcytabiną w monoterapii.

WNIOSKI

1) U większości chorych rozpoznanie raka trzustki ustala się w zaawansowanych stadiach, co w połączeniu z ograniczonymi możliwościami leczenia stwarza szczególnie niekorzystną sytuację epidemiologiczną w tej grupie chorych.
2) Mimo pojawienia się w ostatnich latach nowych możliwości systemowego leczenia chorych na zaawansowanego raka trzustki (wielolekowch schematów chemioterapii, leków ukierunkowanych molekularnie oraz immunoterapii), rzeczywista poprawa wyników leczenia jest niewielka.
3) Wykazano związek pomiędzy QoL i OS u chorych na zaawansowanego raka trzustki. Wyjściowy poziom QoL w skojarzeniu z wybranymi demograficznymi i klinicznymi danymi może mieć znaczenie prognostyczne. Optymalne leczenie objawowe u chorych na zaawansowanego raka trzustki poprawia komfort ich życia oraz przestrzeganie zaleceń. Podczas podejmowania decyzji terapeutycznych należy uwzględniać oceny QoL ponieważ koreluje ona z nasileniem objawów klinicznych.
4) Nab-P w skojarzeniu z gemcytabiną pozwala w warunkach praktyki klinicznej uzyskać podobne wyniki jak osiągnięte w badaniach klinicznych. Terapia ta ma uzasadnione miejsce w algorytmie terapeutycznym.
5) Gemcytabina w monoterapii nadal ma zastosowanie w leczeniu pierwszej linii. Odpowiedni dobór chorych do tego leczenia pozwala uzyskać długotrwałe odpowiedzi, aczkolwiek optymalny model predykcyjny nie jest znany. Zaproponowany model oparty o czynniki kliniczne i laboratoryjne (NLR = 2,5, płeć męską, brak przerzutów w wątrobie i prawidłowe stężenie hemoglobiny) wymaga potwierdzenia w dalszych prospektywnych badaniach z większą liczbą chorych.
6) Wskaźniki laboratoryjne - NLR i SII korelują z wynikami leczenia i mogą stanowić cenne uzupełnienie kryteriów klinicznych, wchodzących w skład modeli rokowniczych.

ABSTRACT

INTRODUCTION:

The incidence of pancreatic adenocarcinoma is systematically increasing. Currently, it is the 10th most common malignant tumor in Europe and the United States [1,2]. In Poland, approximately 3,500 new cases are reported annually [3]. Pancreatic cancer is 4th most common cause of cancer-related deaths worldwide, and in Poland it is 6th in men (4.4%) and 5th in women (5.4%) [3]. This disproportion of mortality vs morbidity rates is related to the diagnosis of disease in disseminated stage in more than half of patients and limited treatment options for advanced disease [1]. It is estimated that in 2030, pancreatic cancer will be the second most common cause of cancer-related deaths [1].

Initially the disease is asymptomatic, or the symptoms are non-specific. This means that only about 10% of patients are diagnosed with pancreatic cancer at an early stage, which allows for radical surgical treatment [4]. Unfortunately, almost 80% of operated patients experience recurrence of disease within 2 years, most often in the form of distant metastases [4]. The median overall survival in patients with metastases ranges between 3 and 6 months, and only 0.5 to 9% of patients survive 5 years (approx. 8% in Poland) [2,5].

It is worth emphasizing that the QoL of patients with advanced pancreatic cancer is generally poor due to the extensive clinical manifestations (pain, cachexia, chronic fatigue) and side effects of the treatment used. Assessing QoL is particularly difficult, among others due to the general awareness of the poor prognosis. The issue of quality of life in this group of patients is rare study objective [6]. The few studies so far show that QoL in patients with pancreatic cancer is deteriorated from the beginning of disease, and the mental functioning of patients is significantly worse than in other cancers [7].

Chemotherapy is the standard treatment for patients with locally advanced and metastatic pancreatic cancer. The first cytotoxic drug used in the treatment of pancreatic cancer patients was 5-fluorouracil (5-FU). For many years, the drug was used as monotherapy, and many clinical trials were conducted using multidrug regimens with 5-FU. Such regimens were usually more active, providing objective

response rate (ORR) of approximately 20%, but this had no impact on overall survival (OS) and control of advanced disease symptoms, and was associated with higher toxicity [8,9].

Some progress was noted only in 1997, when the superiority of gemcitabine in monotherapy over 5-FU was demonstrated. An increase in median OS and improvement in performance status, better pain control and improved quality of life (QoL) have been reported [10]. Based on the results of the above study, gemcitabine became the standard of treatment for patients with advanced pancreatic cancer for many years.

At the beginning of the 21st century, several phase III studies were conducted to evaluate the combination of gemcitabine with other drugs with different mechanisms of action. Only one of these studies (evaluating the combination of gemcitabine with erlotinib) showed an advantage of combined treatment over gemcitabine monotherapy in terms of OS and ORR, but at the cost of greater toxicity [11].

Significant progress in the first-line systemic treatment of patients with advanced (including metastatic) pancreatic cancer was noted only in the second decade of the 21st century, after two phase III clinical studies: PRODIGE 4, which assessed the effectiveness and safety of the multi-drug regimen FOLFIRINOX and MPACT with paclitaxel in the form of a nanoparticle complex with albumin (nab-P, nab-paclitaxel) in combination with gemcitabine [12,13]. Both of these therapies - FOLFIRINOX and nab-P with gemcitabine - have been introduced into daily clinical practice, where their value has also been confirmed [14].

Currently, all aforementioned chemotherapy regimens - gemcitabine in monotherapy, in combination with nab-P and FOLFIRINOX - are used in first-line treatment, and the choice of regimen is usually based on patients' performance status. The European Society of Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN) recommend the use of multidrug regimens (FOLFIRINOX and nab-P with gemcitabine or others, e.g., gemcitabine with erlotinib) in patients with very good and good performance status (ECOG grade 0 or 1). Patients with poorer performance status (ECOG grade 2) should receive gemcitabine, capecitabine or fluorouracil in monotherapy. Performance status

corresponding to ECOG grade 3 and 4 is an indication for symptom directed care [15,16].

Clinical practice in Poland reflects ESMO guidelines, with nab-P with gemcitabine being used as part of a drug program, which is an additional limitation. There is still a large group of patients (who are in a worse performance status or do not meet the inclusion criteria of the drug program) receiving gemcitabine as monotherapy, and relatively long-term benefits of treatment are also observed in this group.

Progress in first-line systemic treatment have highlighted the need to define further management in failures. The results of clinical trials demonstrated the justification for the use of 5-fluorouracil-based regimens in the second line [17].

In patients with metastatic pancreatic adenocarcinoma with a germline mutation in the BRCA1 and/or BRCA2 (gBRCAm) gene, progression-free survival (PFS) is improved by the usage of maintenance treatment (after prior platinum-based chemotherapy) with olaparib, a poly-ADP-ribose polymerase (PARP) inhibitor [18]. In 2018 - 2019, treatment options for patients with metastatic pancreatic cancer were expanded as a result of the FDA registration of larotrectinib and entrectinib for the treatment of solid tumors with neurotrophic receptor tyrosine kinase (NTRK) gene fusions [19,20]. Studies with immunotherapy are also being conducted [21,22].

Many studies have attempted to create a prognostic model to determine the prognosis in patients with advanced pancreatic cancer. One of the most frequently assessed parameters is neutrophil-to-lymphocyte ratio (NLR), the prognostic value of which has been confirmed in several studies, but the cut-off point has not been defined [23-28]. A significant adverse effect of preoperative abnormal levels of CA19-9 and CA125 on the long-term survival of pancreatic cancer patients has also been demonstrated [29]. The platelet-to-lymphocyte ratio (PLR) is another indicator of poor prognosis in terms of OS and PFS in patients with advanced pancreatic cancer, although the cut-off point for this parameter has not been defined [30,31]. A relatively new tool is the systemic immune-inflammation index (SII), calculated based on the number of platelets, neutrophils and lymphocytes. A high negative prognostic value of SII has been observed in patients with various cancers [32,33] receiving various systemic treatments [34-36].

Diagnosis of pancreatic cancer at an advanced stage, low effectiveness of treatment for advanced disease, poor prognosis, and significant deterioration of patients' quality of life indicate the need to evaluate this clinical problem not only in clinical trials, but also in real-world conditions.

AIMS OF THE STUDY

Primary aim:

1) Presentation of the current epidemiological situation regarding pancreatic cancer, treatment options and QoL data for advanced disease.
2) Analysis of selected therapeutic options and achieved treatment results in daily clinical practice.

Specific objectives:

1) Presentation of the epidemiological situation regarding pancreatic cancer in Poland and worldwide, determining the scale of the clinical problem.
2) Presentation of current and being under clinical trial options for systemic treatment in patients with advanced, inoperable pancreatic cancer.
3) Presenting the current level of knowledge about the quality of life of pancreatic cancer patients depending on the treatment used.
4) Analysis of treatment results in patients with metastatic pancreatic adenocarcinoma under the drug program "Treatment of patients with pancreatic adenocarcinoma".
5) Assessment of the results of gemcitabine monotherapy treatment in daily clinical practice in Poland and an attempt to determine predictive factors of long-term responses.
6) Evaluation of selected clinical predictive and prognostic markers in patients with advanced pancreatic cancer undergoing gemcitabine monotherapy.

MATERIAL AND METHODS

Material:

1) Literature on epidemiology, diagnosis and treatment of pancreatic cancer patients.
2) Data on pancreatic adenocarcinoma patients treated with nab-P under the drug program B.85 TREATMENT OF PATIENTS WITH PANCREATIC ADENOCARCIMA (ICD-10: C25.0, C25.1, C25.2, C25.3, C25.5, C25. 6, C25.7, C25.8, C25.9) included in the National Health Fund (NFZ) database.
3) Clinical data of patients with pancreatic adenocarcinoma treated in the following oncology centers:
    - Oncology Clinic with the Day Chemotherapy subunit, Prof. Tadeusz Koszarowski Opole Oncology Center, Opole;
    - Clinical Department of Oncology, University Hospital, Krakow;
    - Department of Clinical Oncology, West Pomeranian Oncology Center, Szczecin;
    - Dr. E. Pilecka Department of Clinical Oncology with the Day Chemotherapy subunit, Maria Skłodowska-Curie Bialystok Oncology Center, Białystok;
    - Department of Oncology and Radiotherapy, Department of Day Chemotherapy, University Clinical Center, Gdańsk.

Research methods:

1) Analysis of available literature;
2) Analysis of the National Health Fund registry including pancreatic cancer patients treated with nab-P since in 2014-2019 years;
3) Analysis of clinical data of pancreatic cancer patients treated from January 2017 to December 2021 in the 5 above-mentioned oncology centers in Poland.

Statistical methods:

In analysis of treatment outcomes in daily clinical practice in Poland, log-rank tests and descriptive statistics methods were used. Multivariate analysis was performed to identify variables influencing treatment eligibility and long-term responses.

In the part concerning the analysis of selected clinical predictive and prognostic factors, the Mann-Whitney-Wilcoxon tests were used for continuous data and the Fisher and $\chi 2$ tests for categorical data. The Shapiro-Wilk test was used to test the normality hypotheses. The Kaplan-Meier estimator and the non-parametric Cox model were used in the survival analysis. Only models with each variable analyzed individually due to the relationships between the variables were considered.

Original elements of dissertation

1) Analysis of treatment outcomes in patients with advanced pancreatic cancer in daily clinical practice in Poland.
2) Determining predictive factors of long-term responses to gemcitabine monotherapy.
3) Determining the impact of selected clinical prognostic and predictive factors on treatment outcomes.

RESULTS

In my dissertation, I made a broad assessment of the clinical problem of advanced pancreatic cancer, based on clinical trials results and data from daily clinical practice. In a series of publications devoted to this clinical problem, I collected information on the epidemiology, biology, diagnostics, clinical characteristics, treatment, prognosis and quality of life in patients with advanced (including metastatic) pancreatic cancer. I assessed selected clinical aspects of the treatment of patients with advanced pancreatic cancer in Poland, including an attempt to define clinical factors influencing the probability of achieving long-term responses to chemotherapy and the assessment of selected prognostic factors. To my knowledge, such extensive analyzes of patients with advanced pancreatic cancer in the Polish population have not been published so far.

The first paper is of an illustrative nature and is a review of the literature on the quality of life of patients with advanced pancreatic cancer.

In the second paper, I presented the epidemiology of pancreatic cancer, with particular emphasis of data from the National Cancer Registry and assessed the evolution of systemic treatment of this cancer in recent decades.

The third paper is a research study presenting a retrospective analysis of the results of nab-P treatment in terms of overall survival and progression-free survival in clinical practice based on data from the National Health Fund database.

The next two studies are of a research nature and are the result of multicenter cooperation, which retrospectively assessed the course of first-line treatment with gemcitabine monotherapy in five oncology centers in Poland. In the fourth paper, I attempted to develop a prognostic model enabling the determination of the profile of patients who have a chance of achieving at least a 6-month response (including stabilization of the disease). To predict the probability that the patient will receive such a benefit, I constructed an equation, which is undoubtedly an innovative element of my analyses.

In the fifth paper, I assessed the prognostic significance of the NLR, PLR and SII indices in patients with advanced pancreatic cancer treated with gemcitabine monotherapy in the first line.

CONCLUSIONS

1) Pancreatic cancer diagnosed in advanced/metastatic stages in most of the patients, combined with a limited treatment option creates a particularly unfavorable epidemiological situation in this group of patients.
2) Despite the emergence of new options for systemic treatment for patients with advanced pancreatic cancer in recent years (multidrug chemotherapy regimens, molecularly targeted drugs and immunotherapy) the actual improvement in treatment results is relatively small.
3) A relationship between QoL and OS has been demonstrated in patients with advanced pancreatic cancer. Baseline QoL in combination with selected demographic and clinical data may have prognostic significance. Optimal symptomatic treatment in patients with advanced pancreatic cancer improves their quality of life and compliance. When making therapeutic decisions, QoL assessments should be taken into account because it correlates with the severity of clinical symptoms.

4) Nab-P in combination with gemcitabine allows obtaining results in clinical practice similar to those achieved in clinical trials. This therapy has a justified place in the therapeutic algorithm.
5) Gemcitabine monotherapy continues to be used in first-line treatment. Appropriate selection of patients for this treatment allows for long-term responses, although the optimal predictive model is unknown. The proposed model based on clinical and laboratory factors (NLR = 2.5, male gender, no liver metastases and normal hemoglobin concentration) requires confirmation in further prospective studies with a larger number of patients.
6) Laboratory indices - NLR and SII correlate with treatment results and can be a valuable complement to clinical criteria included in prognostic models.

OMÓWIENIE PRAC

Jakość życia chorych na zaawansowanego raka trzustki

Rak trzustki jest rozpoznawany zazwyczaj w zaawansowanym stadium. W obrazie klinicznym choroby miejscowo zaawansowanej lub uogólnionej dominuje ból oraz postępujące wyniszczenie, zmęczenie i bezsenność. Objawy te mają istotny wpływ na jakość życia (QoL), a jej pogorszenie obserwowane jest często już w chwili rozpoznania choroby.

Jakość życia jest metodą wielowymiarowej oceny samopoczucia i funkcjonowania chorych w różnych obszarach - czynności fizycznych, emocji, pełnionych ról społecznych, zdrowia psychicznego, sytuacji społeczno-ekonomicznej oraz życia seksualnego. Ocena jakości życia stała się w onkologii niezbędnym elementem badań III fazy. W opracowanych w 2013 roku przez Komitet ds. Badań nad Nowotworami Amerykańskiego Towarzystwa Onkologii Klinicznej (ang. American Society of Clinical Oncology, ASCO) wytycznych dotyczących oceny wyników badań klinicznych nad lekami przeciwnowotworowymi uznano, że istotna poprawa jakości życia jest jednym z ważniejszych wskaźników.

Ocena parametrów QoL chorych na raka trzustki była przedmiotem analizy już w latach 90. XX wieku. Z dotychczasowych nielicznych badań wynika, że QoL u chorych na raka trzustki jest obniżona już na początku choroby, a funkcjonowanie psychiczne chorych jest znacząco gorsze niż w przypadku innych nowotworów. Ocena QoL u chorych na raka trzustki jest jednak wyjątkowo trudna z uwagi na rozbudowany obraz kliniczny (ból, wyniszczenie, przewlekłe zmęczenie) i niepożądane działania stosowanego leczenia, a także ogólną świadomość złego rokowania.

W pracy dokonano przeglądu metod stosowanych w badaniach klinicznych do oceny QoL u chorych na raka trzustki. Starsze badania miały szereg ograniczeń, wynikających z niewielkiej liczebności badanych kohort, braku pełnej charakterystyki chorych oraz metodologii (np. stosowanie różnych, często niedostatecznie zwalidowanych narzędzi lub zróżnicowanie kryteriów wyboru danych do analizy, a także stosowanie wyłącznie statystyki opisowej, co praktycznie wyklucza wiarygodne porównania poszczególnych zmiennych i wskaźników).

Przedstawiono prace Guorgou i wsp., którzy w 2013 r. opublikowali pierwsze pełne badanie oceniające jakość życia 342 chorych na zaawansowanego raka trzustki otrzymujących chemioterapię według schematu FOLFIRINOX lub gemcytabinę w ramach badania PRODIGE 4. W badaniu zastosowano kwestionariusz EORTC-QLQ-C30, który chorzy wypełniali na początku badania (przed randomizacją), a następnie co 2 tygodnie do progresji choroby. Wykazano, że pomimo większej toksyczności chemioterapia według schematu FOLIRINOX korzystnie wpływała na wskaźniki QoL, zmniejszając względne ryzyko jej pogorszenia o 63% (HR 0,47; 95% Cl: 0,3–0,7; $p < 0,001$). Po 6 miesiącach do istotnego pogorszenia QoL doszło u 66% chorych otrzymujących gemcytabinę w porównaniu z 31% otrzymujących schemat wielolekowy.

Przedstawiono też wyniki badań dotyczących opiekunów, wykazując w ocenie jakościowej wysoki stopień negatywnych emocji u takich osób, a w badaniach ilościowych osiągnięcie przez 32% opiekunów progu rozpoznania klinicznej depresji. W niektórych badaniach wykazano też, że opiekunowie częściej doświadczają niepokoju niż sami chorzy.

Przeprowadzony przegląd piśmiennictwa wskazuje, że ocena QoL u chorych na zaawansowanego raka trzustki jest zagadnieniem wielowymiarowym, skomplikowanym i niedostatecznie opisanym. Ta szczególnie trudna choroba skutkuje pogorszeniem jakości życia nie tylko chorych, ale także ich opiekunów. Wskazane są dalsze badania w tym obszarze, w celu ilościowej oceny oraz określenia zależności pomiędzy jakością życia a cechami demograficznymi i klinicznymi chorych, jak również relacjami społecznymi i interpersonalnymi. Szczególną uwagę należy zwrócić na prawidłową metodologię badań oraz liczebność badanych grup.

Zaawansowany rak trzustki – ewolucja w zakresie rozpoznawania i leczenia systemowego w ostatnich dziesięcioleciach

Celem pracy było podsumowanie ogólnych informacji nt. epidemiologii i obrazu klinicznego raka trzustki oraz ewolucji strategii terapeutycznych i sposobów leczenia stosowanych obecnie w praktyce klinicznej.

Rak trzustki jest nowotworem charakteryzującym się coraz większą zachorowalnością i śmiertelnością. Z uwagi na skąpoobjawowy przebieg we wczesnej fazie najczęściej rozpoznaje się go w zaawansowanym stadium, co istotnie pogarsza rokowanie.

W pracy przedstawiono epidemiologię raka trzustki, podkreślając wysoki wskaźnik umieralność/zachorowalność, który w przypadku tego nowotworu wynosi 98%. To skutkuje wyższą pozycją raka trzustki wśród nowotworowych przyczyn zgonów niż wśród zachorowalności. Sytuacja epidemiologiczna raka trzustki w Polsce nie dobiega zasadniczo od danych odnotowywanych w krajach Europy Zachodniej i USA. W Polsce jednak brak pełnych danych dotyczących zachorowań na raka trzustki w Krajowym Rejestrze Nowotworów stąd wydaje się, że dobrym przybliżeniem rzeczywistej sytuacji epidemiologicznej są dane dotyczące zgonów.

Omówiono obraz kliniczny raka trzustki, podkreślając bezobjawowy lub skąpoobjawowy i niecharakterystyczny przebieg we wczesnej fazie. Szeroko przedstawiono objawy zaawansowanej choroby. Dokonano także przeglądu metod leczenia chorych na zaawansowanego raka trzustki z uwzględnieniem historii rozwoju oraz obecnych możliwości terapeutycznych.

Standardem leczenia systemowego pierwszej linii jest chemioterapia. W tym zakresie do połowy lat 90-tych XX w. panował praktyczny nihilizm, a sytuacja chorych zmieniła się nieco dopiero po wprowadzeniu gemcytabiny, która na wiele lat stała się standardem leczenia. Istotny postęp w leczeniu systemowym pierwszej linii odnotowano w drugiej dekadzie XXI w., po wprowadzeniu do leczenia chorych na raka trzustki chemioterapii wg schematów FOLFIRINOX oraz nab-P w skojarzeniu z gemcytabiną. Oba sposoby leczenia zostały uwzględnione w wytycznych towarzystw naukowych i weszły do praktyki klinicznej.

Wraz z postępem w leczeniu pierwszej linii coraz większą potrzebą stało się opracowanie możliwości leczenia drugiej linii. W wielu badaniach klinicznych

wykazano korzyści z takiego postępowania, zarówno po wcześniejszym zastosowaniu monoterapii jak i schematów skojarzonych.

W wybranych kohortach chorych możliwe jest także zastosowanie leków molekularnie ukierunkowanych (np. inhibitora PARP, olaparybu u chorych z mutacją germinalną w genie *BRCA1* i/lub *BRCA2* czy larotrektynibu i entrektynibu u chorych z fuzyjnym genem *NTRK*)) oraz immunoterapii.

Przeżycie chorych na raka trzustki leczonych nab-paklitakselem w praktyce klinicznej: analiza danych NFZ

Nab-paklitaksel (nab-P) jest nanocząsteczkową postacią paklitakselu opartą na nośniku albuminowym i wykazującą odmienne właściwości farmakologiczne od paklitakselu w tradycyjnej postaci. Lek jest zarejestrowany – między innymi – do leczenia pierwszej linii dorosłych chorych na przerzutowego gruczolakoraka trzustki w skojarzeniu z gemcytabiną. W badaniu MPACT wykazano, że skojarzenie obu leków w porównaniu z gemcytabiną w monoterapii poprawia OS (mediana 8,5 vs 6,7 miesiąca), PFS (mediana 5,5 vs 3,7 miesiąca oraz ORR (23% vs 7%).

Wartość leczenia nab-P w skojarzeniu z gemcytabiną potwierdzono na podstawie danych z rzeczywistej praktyki klinicznej. W Polsce leczenie takie jest objęte refundacją ze środków publicznych i realizowane w ramach programu lekowego.

Celem pracy była analiza wyników leczenia nab-P w skojarzeniu z gemcytabiną w zakresie OS i PFS w warunkach praktyki klinicznej w Polsce na podstawie danych pochodzących z bazy Narodowego Funduszu Zdrowia. Analizowano dane 873 chorych – 447 kobiet (51,2%) i 426 mężczyzn (48,8%), leczonych w latach 2014-2019 w ośrodkach onkologicznych w Polsce. Najwięcej chorych leczono w ośrodkach zlokalizowanych na terenie Mazowieckiego Oddziału Wojewódzkiego NFZ (n=193; 22,1%), a najmniej na terenie Opolskiego Oddziału Wojewódzkiego NFZ (n=13; 1,5%).

Mediana PFS w całej badanej grupie wynosiła 169 dni (95% CI 147-189). Nie odnotowano różnicy w przeżyciu kobiet i mężczyzn (p = 0,95). Wykazano natomiast dłuższą medianę PFS u młodszych chorych z grupy wiekowej 29-50 lat w porównaniu do chorych starszych (p = 0,41). Mediana OS w całej badanej grupie wyniosła 379 dni (95% CI 337-niemożliwe do obliczenia). Nie wykazano znamiennych różnic w zależności od płci (p = 0,76) i wieku (p = 0,65).

Analiza OS i PFS w zależności od roku rozpoznania choroby wykazała najlepsze wyniki w grupie chorych, u których rozpoznanie postawiono w latach 2014-2016. Ta dość zaskakująca obserwacja może być wynikiem z jednej strony niewielkiej (najmniejszej!) liczebności tej grupy, a z drugiej strony braku pełnych danych dotyczących PFS i OS w bazie danych NFZ dla chorych, których leczono

w późniejszych latach. Niemniej jednak nawet tak ograniczona analiza wskazuje, że zastosowanie nab-P w skojarzeniu z gemcytabiną w ramach leczenia systemowego chorych na gruczolaka trzustki pozwala na uzyskanie wyników PFS i OS zbliżonych do wyników badań klinicznych.

Analizując dane gromadzone w NFZ wydaje się, że ich słaba jakość, może wynikać z faktu, że rejestry te służą ocenie, wnioskowaniu i decyzjom podejmowanym raczej w obszarze administrowania i zarządzania zasobami, a nie są zbierane w celach związanych z praktyką kliniczną. To stało się największym ograniczeniem prezentowanej analizy, a jednocześnie podstawą do postulowania uzupełnienia rejestrów NFZ o dane medyczne, co znakomicie poprawiłoby ich użyteczność i przydatność, także dla urzędników i urzędów podejmujących decyzje organizacyjne czy finansowe odnośnie refundacji i stosowania różnych interwencji i technologii.

Systemowe leczenie chorych na zaawansowanego raka trzustki – czy nadal jest miejsce dla gemcytabiny w pierwszej linii? – doświadczenia polskich ośrodków

Rokowanie w raku trzustki niezmiennie pozostaje niepomyślne. Jest to nowotwór o wysokiej złośliwości, charakteryzujący się szybkim wzrostem miejscowym ze skłonnością do naciekania okolicznych tkanek oraz tworzeniem przerzutów, przede wszystkim w otrzewnej, węzłach chłonnych i wątrobie. Zastosowanie schematów wielolekowych oraz nowoczesnych leków ukierunkowanych molekularnie u chorych na raka trzustki nie wyeliminowało całkowicie stosowania gemcytabiny w monoterapii, która jest opcją terapeutyczną głównie u chorych w gorszym stanie sprawności, niekwalifikujących się do bardziej zaawansowanych terapii.

Celem pracy była ocena wyników leczenia gemcytabiną w monoterapii w warunkach praktyki klinicznej w Polsce oraz próba określenia cech wskazujących na możliwość uzyskania długotrwałych odpowiedzi pod wpływem tego leczenia. Przeprowadzono retrospektywną analizę 167 chorych na zaawansowanego raka trzustki leczonych gemcytabiną w monoterapii w pięciu ośrodkach onkologicznych w Polsce w latach 2017–2022 (Opolskie Centrum Onkologii w Opolu, Klinika Onkologii Uniwersytetu Jagiellońskiego w Krakowie, Białostockie Centrum Onkologii w Białymstoku, Zachodniopomorskie Centrum Onkologii w Szczecinie, Klinika Onkologii i Radioterapii Gdańskiego Uniwersytetu Medycznego w Gdańsku).

Gemcytabinę stosowano w monoterapii w początkowej dawce 1000 mg/m^2 p.c. co tydzień, 7 razy w cyklu 8-tygodniowym, a następnie 3 razy w cyklu 4-tygodniowym. Mediana OS w całej grupie chorych wynosiła 6,1 mies. (zakres 0,2 – 32,3 mies.), a mediana czasu PFS – 4,2 mies. (zakres 0,2-31,3 mies.).

Wyodrębniono grupę 60 chorych u których uzyskano odpowiedź (obejmująca także stabilizację choroby) utrzymującą się co najmniej 6 miesięcy (LR, *long responders*) oraz 107 osób z odpowiedzią trwającą mniej niż 6 miesięcy (SR, *short responders*). Kryterium czasowe ustalono w oparciu o medianę PFS uzyskaną pod wpływem skojarzonego leczenia pierwszej linii gemcytabiną i nab-P w badaniu klinicznym MPACT (*Metastatic Pancreatic Adenocarcinoma Clinical Trial*), wynoszącą 5,5 mies. Mediana PFS w grupie LR wyniosła 9,15 mies. (zakres 6,0 –

31,3 mies.), a w grupie SR – 3,2 mies. (zakres 0,2 – 5,8 mies.). Różnice odnotowano także w zakresie przeżycia całkowitego, którego mediana była 3-krotnie dłuższa w grupie LR w porównaniu do SR (odpowiednio 11,6 mies. [zakres 5,9-30,8] i 3,8 mies. [zakres 0,2 – 32,3 mies.]). W analizie wieloczynnikowej oceniano prawdopodobieństwo uzyskania co najmniej 6-miesięcznej odpowiedzi na leczenie za pomocą modelu regresji logistycznej. Wstępnej ocenie poddano różne modele (tworzone przez różne zmienne wybrane w oparciu o dane z piśmiennictwa oraz charakterystykę histokliniczną badanej grupy, jak wiek, BMI, NLR, płeć, wyjściowy stopień klinicznego zaawansowania wg klasyfikacji TNM, lokalizacja guza pierwotnego, lokalizacja przerzutów, PS wg ECOG, liczba leukocytów, stężenie hemoglobiny w ujęciu zmiennej kategorycznej). Do ostatecznej analizy wybrano model uwzględniający cztery zmienne: NLR (traktowany jako zmienna ciągła), przerzuty do wątroby (tak vs nie), płeć, stężenie hemoglobiny (w normie vs poniżej normy).

Wykazano, że wraz ze zwiększeniem wartości NLR o jedną jednostkę szansa, że chory znajdzie się w grupie LR zmniejsza się o 17% przy pozostałych parametrach niezmienionych. Nieobecność przerzutów w wątrobie zwiększa szansę na uzyskanie długotrwałej odpowiedzi o 368% w porównaniu do chorego, który ma przerzuty do wątroby przy pozostałych parametrach niezmienionych. Szansa na uzyskanie długotrwałej odpowiedzi przez chorego z prawidłowym stężeniem Hb jest o 112% większa niż w przypadku chorego ze stężeniem Hb poniżej normy przy pozostałych parametrach niezmienionych. Wykazano także, iż mężczyźni mają o 89% większą szansę na uzyskanie długotrwałej odpowiedzi niż kobiety o tych samych pozostałych parametrach. Do predykcji prawdopodobieństwa, że chory znajdzie się w grupie LR skonstruowano równanie, które przedstawiono w pracy.

Uzyskane wyniki potwierdzają, że gemcytabina w monoterapii nadal ma zastosowanie w leczeniu pierwszej linii chorych na zaawansowanego i przerzutowego gruczolakoraka trzustki. Odpowiedni dobór chorych do leczenia może umożliwić poprawę wyników przy zachowaniu mniejszej toksyczności w porównaniu z leczeniem skojarzonym.

NLR, PLR, SII jako kliniczne markery predykcyjne i prognostyczne u chorych na zaawansowanego raka trzustki leczonych gemcytabiną w monoterapii

W ostatnich latach pojawia się wiele danych na temat związku stanu zapalnego z kancerogeneza i progresją nowotworów, w tym raka trzustki. Komórki immunokompetentne oraz mediatory stanu zapalnego są obecne z mikrośrodowisku większości, jeśli nie wszystkich, nowotworów, niezależnie od czynnika wyzwalającego rozwój nowotworu. Mogą one odzwierciedlać stan odpowiedzi immunologicznej na proces nowotworowy. Uzasadnia to poszukiwanie markerów prognostycznych związanych ze wskaźnikami stanu zapalnego. W warunkach klinicznych od wielu lat ocenia się przydatność takich markerów i opartych na nich indeksów w ocenie rokowania w różnych kohortach chorych.

Celem pracy była ocena znaczenia rokowniczego NLR, PLR i SII u chorych na zaawansowanego raka trzustki leczonych gemcytabiną w monoterapii. Przeprowadzono retrospektywną analizę parametrów morfotycznych krwi u 167 chorych na zaawansowanego raka trzustki leczonych w pierwszej linii gemcytabiną w monoterapii w pięciu ośrodkach onkologicznych w Polsce w latach 2017–2022. Obliczono wskaźniki NLR, PLR i SII i zdefiniowano punkty odcięcia, stanowiące granicę między wartościami wysokimi i niskimi. Oceniono parametry kliniczne oraz ich rozkład w zależności od wartości OS równej i większej lub mniejszej od mediany OS. Oceniono rozkład liczbowy chorych z poszczególnymi przedziałami OS względem kategorii wskaźników stanu zapalnego.

W ocenianej kohorcie chorych z medianą wieku 71 lat przeważały kobiety (58%), chorzy w IV stopniu zaawansowania klinicznego (57%) z dominującą lokalizacją przerzutów odległych w wątrobie (42,5%). Mediana NLR wynosiła 2,69 (zakres 0,5 – 36,65), PLR 146,54 (zakres 18,53 – 1118,57), a SII 784,75 (zakres 79,86 – 10622,67). Punkty odcięcia zdefiniowano odpowiednio jako 4,5625 dla NLR (125 chorych [75,8%] z wartością mniejszą i 40 chorych [24,3%] z wartością równą lub większą), 150 dla PLR (87 chorych (52,7%) z wartością mniejszą i 78 [47,3%] z wartością równą lub większą) i 897,619 dla SII (96 chorych [58,2%] z wartością mniejszą i 69 [41,8%] z wartością równą lub większą). Porównując grupy z OS dłuższym lub równym medianie i OS krótszym od mediany wykazano statystycznie istotne różnice dotyczące BMI ($p = 0,02$), początkowego zaawansowania klinicznego

($p < 0,001$) i lokalizacji przerzutów ($p < 0,001$). U chorych uzyskujących przeżycie co najmniej równe medianie OS statystycznie istotnie częściej stwierdzano wartości NLR i SII poniżej punktów odcięcia. W odniesieniu do PLR nie stwierdzono statystycznie istotnych różnic pomiędzy grupami wyznaczonymi wartością OS.

Wykazano związek wskaźników obliczonych na podstawie parametrów morfologii krwi z wynikami leczenia, co może wskazywać na ich znaczenie predykcyjne i prognostyczne. Mogą one stanowić cenne uzupełnienie kryteriów klinicznych, wchodzących w skład modeli rokowniczych.

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REVIEW ARTICLE

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Quality of life of patients with advanced pancreatic cancer

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ABSTRACT

Pancreatic cancer is one of the most common malignancies with poor prognosis and high mortality. Advanced-stage disease at diagnosis and the dominant clinical symptoms significantly deteriorate the quality of life. The paper presents an analysis of the results of quality of life studies in patients with locally advanced and metastatic pancreatic cancer, as well as the relationship between therapeutic decisions and quality of life indicators. It has been shown that the initial assessment of life quality can have prognostic value. Appropriate symptomatic treatment of patients with advanced pancreatic cancer improves the quality of life, increases the compliance and prolongs survival. The assessment of the quality of life in patients with advanced pancreatic cancer has multivariable significance, which is not limited only to improving the quality of life.

Key words: health-related quality of life, advanced pancreatic cancer

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Introduction

The incidence of pancreatic cancer is systematically increasing and since the 1950s it has increased almost 3-fold [1]. Currently, it is the 10th most common neoplasm in both sexes in Europe as well as in the United States [1–3]. The fact that death due to pancreatic cancer is the 4th most common cause of death due to a neoplasm in the world is particularly worrying. The discrepancy between the two classifications is mainly due to the fact that in most patients this cancer is diagnosed in an advanced stage, resulting in poor prognosis. The ratio of mortality to morbidity in pancreatic cancer is 98%, and each year about 40,000 patients die due to this disease [1]. Projections indicate a further increase in incidence and assume that in 2030 pancreatic cancer will be the second most common cause of cancer-related deaths [4, 5].

In Poland, pancreatic cancer is the 11th most common neoplasm in men and the 14th in women. Currently in our country pancreatic cancer is diagnosed in about 3,500 patients per year [6]. Men are affected slightly more often and the peak of the incidence is noted in the range of 65–69 years. In terms of the number of deaths pancreatic cancer ranks the 6th in men (4.4%) and the 5th in women (5.4%) [6]. Deaths are in general noted in the same age group.

Pancreatic cancer is general diagnosed in the advanced stage. Early pancreatic cancer is asymptomatic or oligosymptomatic [7, 8]. The clinical picture of locally advanced or generalized disease is dominated by pain and progressive cachexia, fatigue and insomnia [4, 9]. These symptoms have a significant impact on the quality of life (QoL) and its deterioration is frequently observed already at diagnosis. Survival in this group of patients is short, median overall survival (OS) in the locally advanced stage does not exceed one year, and in generalized cases, it is 3–6 months [2, 10].

Early stage pancreatic cancer is diagnosed in only 10% of patients [11]. Radical treatment is possible only in this group. Surgical treatment (excision of the head of the pancreas with the duodenum, partial peripheral excision of the pancreas or complete excision of the pancreas and the duodenum) [3, 12]. Unfortunately, 80% of operated patients relapse within 2 years (most com-

monly because of metastases) is the standard procedure in this case [2]. In order to improve the results, surgical treatment is combined with adjuvant chemotherapy or radiotherapy.

In the treatment of patients with advanced pancreatic cancer chemotherapy is used as monotherapy or multidrug regimens, most commonly based on gemcitabine, fluoropyrimidine, nab-paclitaxel or irinotecan. However, the effectiveness of this treatment is limited, and the 5-year survival rate still does not exceed 5% [9, 13]. Because of clinical characteristics of pancreatic cancer, limited therapeutic options and poor prognosis, the assessment of the quality of life of the patients is of particular importance.

The aim of this analysis is to present the available quality of life outcomes in patients with locally advanced and metastatic pancreatic cancer and the particular role of quality of life in making therapeutic decisions in this group of patients.

The importance and methods of evaluating the quality of life in cancer patients

According to the position of the World Health Organization (WHO), quality of life (QoL) defines the individual perception of a person's life situation in the context of specific standards and values system in which he/she is living and in relation to his/her achievements, expectations and interests. In medicine QoL is considered as health-related (HRQoL) [14, 15]. This is a narrower topic than QoL in general, but in practice, HRQoL is replaced by QoL.

Quality of life is a method of multidimensional evaluation of patients' well-being and functioning in different areas — physical activities, emotions, social roles, mental health, the socio-economic situation and sexual life. A high value of the HRQoL index indicates that — in spite of the disease — the patient perceives himself as a well-functioning person; a low HRQoL value is a reflection of the limitations that the patient feels. Quality of life is important in clinical trials, where it is a very useful tool for evaluating the value of medical procedures in relation to treatment outcomes and survival of cancer patients [16]. It facilitates planning and organizing extemporary and long-term care, stratification of death risk or of additional hospitalizations which is of particular importance in the case of chronic diseases.

Methods of evaluation used in clinical trials are highly diverse, which often makes interpretation of the results difficult. This phenomenon is based on the fact that QoL is important and meaningful for patients, but it can be difficult to express in methodological categories. Until the 1980s QoL was evaluated in only 5% of clinical trials. In 1981 the European Organization for Research and Treatment of Cancer (EORTC) established the Quality of Life Group, which aim among others was to elaborate multidimensional instruments for evaluating QoL and standardizing of questionnaires. The basic questionnaire elaborated by the group (quality of life questionnaire C-30, QLQ-C30) is one of the most important tools in oncology [17]. It is a validated tool elaborated for cancer patients and intended for prospective analyses, which based on responses to 30 defined questions evaluates 5 domains of activity: physical, emotional, social, cognitive and intensity of symptoms (pain, fatigue, loss of appetite, nausea/vomiting, diarrhea, constipation, sleep disturbances) as well as total QoL. Full assessment in this questionnaire allows to obtaining score values in the range of 0–100, with more points indicating better functioning and less severe symptoms [18, 19].

The EQ-5D questionnaire (Euro QoL) is a tool used for the evaluation of the general health condition [20]. It contains 5 closed questions concerning the physical and mental functioning sphere (ability to move, self-care, daily activities, pain/discomfort and anxiety/depression). It allows to compare the quality of life of patients with the population norm. Thanks of this methodology, it is a tool recommended among others by NICE (National Institute for Care Excellence) for pharmacoeconomic evaluation, even though it is simpler than the EORTC scale

The evaluation of the quality of life has become an indispensable element in phase III clinical trials in oncology. The 2013 Cancer Research Committee of the American Society of Clinical Oncology (ASCO) guidelines for the evaluation of the results of clinical trials with anti-cancer drugs indicated a significant improvement in the quality of life — in addition to an improvement in overall survival — as one of the indicators which determine clinically significant trial results [21]. In 2013 the European Society of Medical Oncology (ESMO) also initiated work on a ESMO Magnitude of Clinical Benefit Scale (ESMO MCBS), in which the determination of QoL is one of the important parameters [22].

Systemic treatment of patients with advanced pancreatic cancer

Chemotherapy is the standard treatment of patients with locally advanced or metastatic pancreatic cancer. The first drug used for this indication was fluorouracil. Its administration allowed for about 10% of objective responses but did not improve QoL and OS [23]. Almost until the end of the 20th century in spite of a number of clinical trials no benefit was shown for multidrug combinations based on fluorouracil [24]. Some pro-

gress was only noted in 1997 when gemcitabine in monotherapy was shown to be superior to fluorouracil. Even though the OS benefit was minimal (the median still did not exceed 6 months), there was an improvement in performance status, better pain control and QoL improvement in patient treated with gemcitabine [25]. Gemcitabine became the standard of care in this indication for many years. In further phase III studies the combination of gemcitabine with a number of drugs with different mechanisms of action (e.g. capecitabine, irinotecan, oxaliplatin, vismodegib, sorafenib, masitinib) was investigated, but no significant improvement in OS was shown. The exception was a trial performed in 569 patients with unresectable, locally advanced or metastatic pancreatic cancer, in which erlotinib used in combination with gemcitabine significantly improved the outcomes — however, the median OS was only prolonged by 2 weeks (6.24 *vs.* 5.91 months, hazard ratio [HR] 0.82; P = 0.038), and progression-free survival (PFS) by a few days (3.75 *vs.* 3.55 months, HR 0.77; P = 0.004). The objective response rates (8.6% *vs.* 8%) and disease control rates (57.5% *vs.* 49.2%; P = 0.07) were comparable. Combined therapy led to increased toxicity, although it had no major impact on QoL [25]. The years 2000–2010 are therefore called a decade of failures.

For many years, the use of multidrug regimens in patients with metastatic pancreatic cancer was the subject of controversy. Progress has been made only in recent years when the results of two phase III trials were published showing a significant and clinically relevant benefit of the use of multidrug regimens in terms of overall survival.

In the academic PRODIGE 4 phase III trial performed in 342 patients with metastatic pancreatic cancer with a good performance status (0 or 1 in the Eastern Cooperative Oncology Group [ECOG] scale) the combined treatment according to the FOLFIRINOX regimen (oxaliplatin, irinotecan, leucovorin and fluorouracil) was compared with monotherapy with gemcitabine, showing a significant improvement in median PFS (6.4–3.3 months, P < 0.001) and OS (11.1–6.8 months, P < 0.001), albeit at the cost of higher toxicity [26]. Such treatment is currently recommended for patients with good and very good performance status.

In the MPACT phase III trial in 861 patients with metastatic pancreatic cancer, an innovative albumin-bound paclitaxel (nab-P, nab-paclitaxel) combined with gemcitabine was compared with gemcitabine alone. The combination arm showed a significant OS prolongation (8.5 months in comparison with 6.7 months in the group receiving gemcitabine alone) and a 28% reduction in the risk of death (HR 0.72, P < 0.001) [27]. The 12-month survival rate was significantly higher in the group receiving nab-P and gemcitabine (35% in comparison with 22% in the group receiving monotherapy; P = 0.0002). Median PFS in the group receiving combined treatment and gemcitabine alone was 5.5 months and 3.7 months, respectively (HR = 0.69, P = 0.000024), and the objective response rate (ORR) was 23% and 7%, respectively. Moderate toxicity was observed during combined treatment with nab-paclitaxel and gemcitabine with manageable adverse reactions. There have also been some data suggesting the possibility of nab-P dose reduction in the case of toxicity, which allows obtaining optimal treatment results with acceptable toxicity [3]. The combination of nab-paclitaxel with gemcitabine has become the new standard of systemic therapy in patients with advanced or metastatic pancreatic cancer.

Evaluation of quality of life in patients with advanced pancreatic cancer

The evaluation of QoL indices in pancreatic cancer patients was the subject of research as early as the 1990s. The so-far few studies on QoL in patients with pancreatic cancer indicate that it is reduced already at the beginning of the disease, and mental functioning is significantly worse than in patients with other cancers [16]. However, the assessment of QoL in pancreatic cancer patients is extremely difficult due to the nature of the disease, the high burden of morbidity and mortality, treatment complications and predominant clinical symptoms (pain, cachexia, fatigue), which have an additional negative impact on QoL [9]. Older studies had a number of limitations due to the small sample size, lack of a complete patients characteristic and methodology (e.g. using different — often not validated — tools or different criteria of selecting data for analysis and the use of descriptive statistics only, which practically excludes reliable comparison of individual parameters) [16].

The most recent studies use the EORTC-QLQ-C30 and EQ-5D questionnaires. In a study published in 2006, which included only 57 patients with pancreatic cancer on the basis of EQ-5D, a deterioration of QoL in comparison with the population norm was observed from the diagnosis [9]. In men, this deterioration affected all domains whereas in women a clear tendency for anxiety and depression was observed. The evaluation of QoL using the QLQ-C30 EORTC scale confirmed the deterioration of all five areas of the quality of life in men, whereas in women it mainly concerned physical functioning, social roles and cognitive functions [9]. The differences between two sexes in the areas of deteriorated functioning in pancreatic cancer patients are an important observation derived from this analysis; however, it requires further investigations.

In 2013 Guorgou et al. published the first complete analysis evaluating the quality of life of patients with

advanced pancreatic cancer receiving chemotherapy according to the FOLFIRINOX scheme or gemcitabine in the PRODIGE 4 trial [10]. Earlier, limited reports already indicated disorders of the global health status (GHS) and the occurrence of fatigue, pain and deterioration of physical, emotional and social functioning of pancreatic cancer patients receiving chemotherapy according to the FOLFIRINOX regimen [26]. In the trial, the EORTC-QLQ-C30 questionnaire was used which was completed by the patients at baseline (before randomization), and every 2 weeks thereafter until disease progression. Due to frequency of evaluation it was decided that both the percentage of patients completing the questionnaire and the responses obtained would be performed at baseline, after 15 and 30 days and then after 2, 4, 6, 8 and 10 months. At the beginning of the trial, the questionnaire was completed by 95% of patients treated according to the FOLFIRINOX scheme and 92% of patients receiving gemcitabine. During the trial, this percentage gradually decreased and after 10 months it was 40% and 67%, respectively.

The quality of life analysis included 342 patients with advanced pancreatic cancer — 171 patients each in the arm receiving FOLFIRINOX chemotherapy or gemcitabine alone. One of the inclusion criteria was the performance status (PS) of 0–1 in the ECOG scale, which seems understandable in patients receiving multidrug chemotherapy. It is therefore surprising, that 30 patients (1.4%) receiving FOLFIRINOX and 26 patients (16.6%) treated with gemcitabine alone stated during the initial QoL evaluation that they have to stay in bed or an armchair for "quite a lot`" or "a lot" of time. This observation confirms earlier observations of worse QoL in pancreatic cancer patients already at diagnosis. This also indicates the fact frequently described in the literature that QoL evaluation is subjective and variable. The initial QoL evaluation was similar in both arms. It indicated the intensification of symptoms such as anorexia, fatigue, pain, insomnia and constipation, but at the same time, it was high in the scope of the general functioning of the patients. No significant deterioration of QoL was noted during treatment in spite of the increase in diarrhea intensity especially in the group receiving FOLFIRINOX. GHS change during the trial was similar in both arms. In patients receiving FOLFIRINOX chemotherapy a significant improvement in physical functioning was observed ($P < 0.001$), and a significant improvement in emotional functioning was noted in both arms ($P < 0.001$). Moderate deterioration of GHS (≥ 10 points compared to baseline) occurred in 30.1% of patients receiving chemotherapy according to the FOLFIRINOX scheme and 18.5% of patients receiving gemcitabine.

In this analysis, the time until definitive deterioration (TUDD) of GHS and QoL was analyzed. Median TUDD (to deterioration by ≥ 10 points) was significantly longer in the group receiving FOLFIRINOX than in the group treated with gemcitabine in terms of GHS/QoL, all 5 domains of functioning and the severity of 6 main symptoms (fatigue, nausea/vomiting, pain, dyspnea, anorexia, constipation). The statistical significance was maintained for TUDD until deterioration by ≥ 20 points with the exception of emotional functioning and the median was also longer in the arm with combined therapy (not reached for GHS/QoL). A statistically significant correlation was also noted between the improvement of some analyzed parameters and a good treatment response. In the arm receiving FOLFIRINOX chemotherapy, these were GHS, pain and insomnia, whereas in both arms fatigue and dyspnea. Univariate Cox analysis indicated that in both arms particular QoL domains (physical functioning, social roles and severity of such symptoms as fatigue, constipation, dyspnea and anorexia) are significant prognostic factors for OS. After including these parameters in a model encompassing clinical and demographic data the statistical significance was confirmed for physical functioning and the severity of constipation and dyspnea [10].

In conclusion, despite greater toxicity, chemotherapy according to the FOLIRINOX scheme had a favorable effect on QoL, reducing the relative risk of its deterioration by 63% (HR 0.47; 95% Cl: 0.3–0.7; $P < 0.001$). After 6 months a significant deterioration of QoL occurred in 66% patients receiving gemcitabine alone in comparison with 31% receiving the multidrug scheme [26].

In 2016 a systematic review of trials evaluating QoL in pancreatic cancer patients was published [2]. Based on literature review until 2013 a total of 36 papers were found presenting the results of 30 trials, with a median sample size of 311 patients, range (103–832), mainly at the age of 58–66. There was a slight predominance of men (48–65%). The percentage of patients with a metastatic disease varied considerably (31–100%). The HRQoL scores were evaluated in 30 of these trials (comparison of gemcitabine with another drug in monotherapy — 4, comparison of gemcitabine with combination chemotherapy — 22, other treatment regimens — 4), and finally 23 trials were included in the analysis, of which in 19 no significant differences in QoL were found between the therapeutic arms, whereas in 4 (including the previously described PRODIGE 4 trial) differences were observed.

In a Canadian trial comparing the metalloproteinase inhibitor BAY12-9566 with gemcitabine, the superiority of gemcitabine for the evaluated survival parameters (OS, PFS) was demonstrated, including QoL evaluated with use of EORTC QLQ-30 questionnaire. General health status, physical functioning, cognitive functioning, social roles, and degree of fatigue was better in gemcitabine group [28]. In another trial evaluating the

value of metalloproteinase inhibitors in the treatment of pancreatic cancer patients , marimastat was used in combination with gemcitabine [29]. No benefit of this treatment has been demostrated over gemcitabine plus placebo in terms of survival. Quality of life was evaluated on the basis of a specific Functional Assessment of Cancer Therapy — Pancreas (FACT-Pa) questionnaire. By 2 months after treatment initiation there was an improvement in QoL in the gemcitabine/placebo group and a slight decrease in the gemcitabine/marimastat group ($P = 0.048$).

The authors of the cited review also pointed out certain limitations of the methodology used. First of all, the evaluated results most commonly concern patients remaining in the trial at a specific time point in which the QoL analysis was performed and not the entire population. A significant percentage of patients terminate participating in the trial (e.g. because of disease progression or death) and the evaluated population may not be representative, which has also been indicated by the authors of other studies [2, 13].

Pain was assessed in most analyses as a part of univariate analysis and in 7 out of 24 trials a statistically significant difference was demonstrated in the intensity of this symptom between the therapeutic arms. In patients treated with gemcitabine a decrease in pain intensity by 50% was noted and a decrease of the requirement for analgesics by 24%, whereas in the group treated with fluorouracil this was only 5%. Gemcitabine monotherapy was also superior to the metalloproteinase inhibitor BAY12-9566 in terms of pain relief. The results on neoplastic cachexia turned out to be inconclusive and both the severity and the mitigation or stabilization of the level of cachexia were observed.

In a meta-analysis of 91 clinical trials on pancreatic cancer published in 2015 by Carrato et al. [4] only in 5 studies the results of QoL analyses were presented. The small sizes of the analyzed groups and the heterogeneity of this population allowed only to demonstrate a significant decrease in QoL score using various validated EORTC questionnaires, and a higher incidence of anxiety and depression compared to population norm.

An interesting approach to the assessment of QoL in patients with pancreatic cancer was presented in an analysis published in 2018, where for the first time the assessment of the patients' caregivers were included [16]. The authors assumed that such a burdensome and poor prognosis neoplastic disease had an impact on the QoL of caregivers and their relations with patients. A total of 29 studies with qualitative assessment and 7 with quantitative assessment were included in the analysis. In assessment of different QoL domains, a tendency was found to deteriorate the indicators in pancreatic cancer patients compared to healthy people (population norm). Moreover, the results concerning the mental state of patients with pancreatic cancer were worse than in other neoplasms. The studies rarely analyzed in detail the factors contributing to the deterioration of mental functioning, but it was emphasized that unfavorable prognosis, difficult treatment and immunological and endocrine disorders are associated with a particular risk of disturbances in this area. The results of analyses in areas concerning physical and social functioning and overall QoL assessments varied and indicated different burdens and occurrence of symptoms (pain, fatigue or gastrointestinal dysfunction).

In analyses concerning caregivers, the qualitative assessment showed a high degree of negative emotions in caregivers, and quantitative studies found that 14% and 32% of caregivers, respectively, achieve the threshold for clinical depression diagnosis in the relevant questionnaires. Some studies have also found that caregivers are more likely to experience anxiety than patients themselves. The authors concluded that both patients and caregivers experience difficult situations that are important for QoL. At the same time, they indicated the validity of performing routine screening for psychophysical perturbances in patients with neoplastic disease, which is consistent with the position of the American College of Surgeons [16]. In terms of future trials, the authors of that analysis stressed out the need to collect a well-defined group, conduct longer observations with use of reliable statistical methods, and in this context the appropriate size of the analyzed cohort [16].

The first analysis comparing QoL of patients treated with gemcitabine in combination with nab-paclitaxel or gemcitabine in monotherapy was the phase II randomized trial published in 2020 in a group of 125 previously untreated patients with metastatic (102 — 81.6%) or locally advanced (23 — 18.4%) pancreatic cancer [13]. Patients were randomly assigned to both treatments in 1:1 ratio, and all treatment was outpatient. It should be emphasized that in the light of earlier comments on QoL deterioration in pancreatic cancer patients already at diagnosis, patients with factors negatively affecting the physical functioning (i.e. age over 76 years, serious cardiovascular diseases, severe organ failure, disorders which in the opinion of experts increased the risks associated with the therapy, expected survival less than 12 weeks, gastrointestinal dysfunctions, coagulopathies and neuropathy) were excluded. This approach considerably limited the patient population. Finally, the patients in the group receiving nab-paclitaxel with gemcitabine were significantly younger. Sex distribution was similar in both arms. The primary endpoint of the trial was the percentage of patients without deterioration of the QoL after 3 months. The time until definitive deterioration of QoL (TUDD), the time to decrease in the EORTC QLQ-C30 score by at least 10 points were also analyzed and QoL was compared between the arms. As in the

PRODIGE 4 trial the patients completed the EORTC QLQ-C30 questionnaire every 4 weeks, according to EORTC recommendations.

The percentage of patients with no deterioration after 3 months was 34% in the group receiving gemcitabine in monotherapy and 58.3% in the group treated with nab-paclitaxel in combination with gemcitabine (P = 0.018), and after 6 months 27.3% and 36.6%, respectively (P = 0.357). The mean change in score in particular functional domains indicated a statistically significant advantage of combined therapy with the exception of physical functioning, in which the statistical significance was borderline (P = 0.051). In the group receiving gemcitabine alone an increase of all clinical symptoms intensity was observed, except for fatigue, (60.4 *vs.* 5.9, P = 0.027). After 6 months the trend of changes was similar, however, without statistical significance. The median TUDD was 5.36 months in the group receiving combined therapy and 3.68 months in the group treated with gemcitabine alone. The percentage of patients completing the questionnaire was similar in both arms with no significant differences throughout the study, thus did not affect the obtained results.

Summary

Multivariate analyses in cancer patients confirm the prognostic value of physical functioning and the severity of pain and anorexia, and also indicate a relationship between QoL and OS, although there have been no conclusive data for the homogeneous pancreatic cancer patients population.

In the described trials it was demonstrated that combining the initial QoL assessment with demographic and clinical data enables a more accurate evaluation of survival probability, which means that it can be of prognostic value. All studies showing differences in OS between treatment arms showed a parallel improvement in QoL and a reduction in pain intensity.

Appropriate methods of symptomatic treatment (including side effects management) in patients with advanced pancreatic cancer improve their comfort of life, increase the compliance and contribute to longer survival. Monitoring the quality of life and managing the disease symptoms has a positive effect on treatment outcomes.

The high degree of correlation between severity of clinical symptoms and the results of QoL evaluation indicates that the determination of the value of this parameter should be taken into consideration when making clinical decisions.

The above-mentioned observations indicate that QoL evaluation in patients with advanced pancreatic cancer has multidimensional significance and encompasses not only improvement of the patients' comfort but also their survival. It can be also hypothesized that it has an impact on the QoL of caregivers. Therefore, further investigations are necessary in this field, which would evaluate more accurately the quantitative relations between quality of life and demographic and clinical parameters of the analyzed patients, as well as social and interpersonal relations. Particular attention should be focused on proper methodology, the size of the analyzed groups and statistical analysis methods .

Conflict of interest

The authors have no conflict of interest to declare.

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VIA MEDICA

REVIEW ARTICLE

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Advanced pancreatic cancer: diagnosis and systemic treatment evolution over the last decades

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ABSTRACT

Pancreatic cancer is one of common malignant neoplasms. It is characterized by poor prognosis and high mortality, which is mainly due to detection in an advanced stage. This review presents epidemiological and clinical characteristics of pancreatic cancer, as well as current strategies of systemic treatment of advanced disease, including first- and second-line chemotherapy, as well as molecularly targeted therapies and immunotherapy.

Key words: advanced pancreatic cancer, systemic treatment, targeted therapy, immunotherapy

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Introduction

Pancreatic cancer (PC) is the 12th most common cancer worldwide and the 6th leading cause of cancer-related deaths. This disproportion is associated with the diagnosis that is made in advanced stages (in more than half of cases as disseminated disease) and with limited therapeutic options for advanced pancreatic cancer [1, 2]. Median overall survival (OS) in metastatic pancreatic cancer is 3-6 months, and the 5-year survival rate is only 0.5–9% (app. 3% on average) [3]. Although in early disease, allowing the use of surgical procedures with adjuvant therapy, the 5-year survival rate reaches 25%, this is still an unsatisfactory result [4]. Moreover, only one in ten patients with pancreatic cancer is diagnosed at an early-stage, and in three-quarters of such patients, disease relapses are observed despite radical primary treatment. Chemotherapy is a standard treatment for patients with locally advanced and metastatic (primary or relapsed) pancreatic cancer. For many years, no significant progress has been observed in the systemic treatment of patients with advanced pancreatic cancer. In the last decade, multi-drug regimens were introduced. They include FOLFIRINOX and gemcitabine in combination with paclitaxel in albumin-stabilized nanoparticle formulation (nab-P, nab-paclitaxel) in the first line, and a regimen containing nanoliposomal irinotecan (nal-IRI) in the second line. These regimens improved treatment outcomes, but their use is limited to patients with good performance status (PS) [5, 6]. The latest achievement in this area is the use of targeted drugs and immunotherapy in selected patient subgroups defined on the basis of molecular biomarkers.

Epidemiology

Approximately 459,000 people worldwide are diagnosed with pancreatic cancer each year (2.5% of all newly diagnosed cancers) and 432,000 people die from this disease (4.5% of all cancer deaths). This is predicted that in 2030 pancreatic can-

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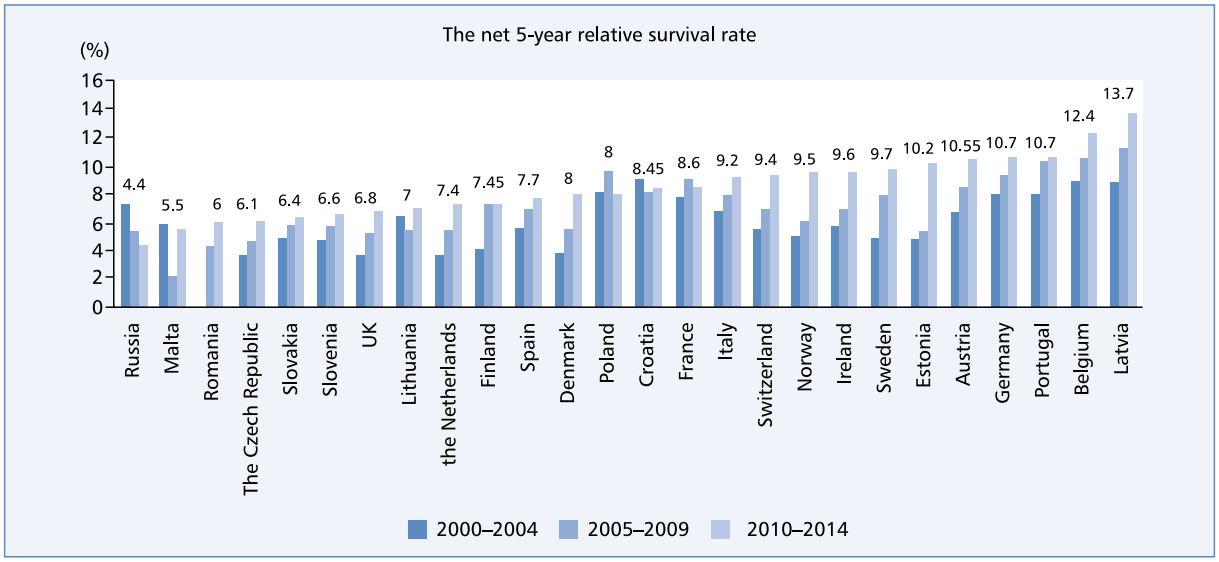

Figure 1. The net 5-year relative survival rates in Europe [10]

cer will be one of the most common and deadliest cancers [3, 7, 8]. Currently, the mortality/morbidity ratio for pancreatic cancer is very high, at up to 98% level [9].

Pancreatic cancer is 3–4 times more common in countries with a high human development index (HDI). The highest incidence rates (ASW, world age-standardized rate) are recorded in Western Europe (8.3/100,000), North America (7.6/100,000), Central and Eastern Europe (7.5/100,000), Northern (7.3/100,000) and South Europe (7.2/100,000). The fewest pancreatic cancers are found in East and Southeast Asia (< 1.5/100,000). Pancreatic tumors are about 1.3–1.4 times more common in men than in women.

Treatment options for pancreatic cancer patients are significantly limited, as evidenced by the 5-year net relative survival rates in European countries (Fig. 1) [10]. The survival rate of patients diagnosed in 2010–2014 ranges from 4.4% in Russia to 13.7% in Latvia. In Poland, only 8% of patients survive 5 years from diagnosis.

In Poland, in 2017, there were 1738 and 1770 cases reported to the National Cancer Registry (NCR) in male and female patients, respectively, and the total number of deaths due to pancreatic cancer was higher by about 1400 cases. Due to the lack of complete data on pancreatic cancer incidence in the National Cancer Registry and the very poor prognosis of this cancer, it seems that the data on deaths is a good approximation of the actual epidemiological situation.

For over 35 years, pancreatic cancer mortality in European countries has remained constant. Compared to other European countries, Poland is characterized by a low risk of death from pancreatic cancer, which is similar to that observed in Germany, Slovakia, or Denmark (Fig. 2, 3) [11]. An increase in mortality in both sexes was observed before the 1990s, followed by

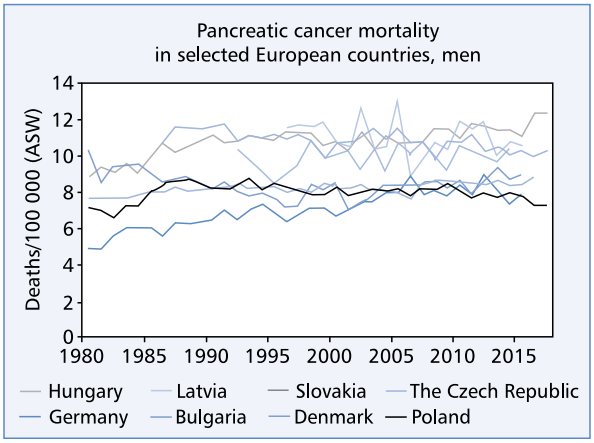

Figure 2. Pancreatic cancer mortality — men [11]

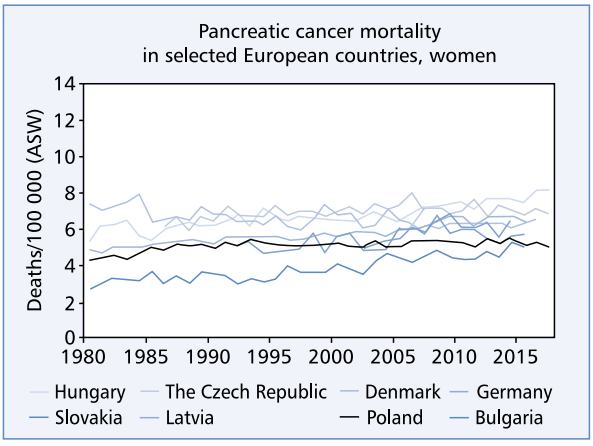

Figure 3. Pancreatic cancer mortality — women [11]

a long-lasting plateau. In the male population, since 2009, a decreasing trend has been observed while among women mortality rate does not change (Fig. 4). Over 95% of pancreatic tumors in the Polish population occur after the age of 50. The incidence of this neoplasm increases with age. Up to 50 years of age, mortality does not exceed 10/100,000. After age 50, the incidence increases by about 10 deaths for each decade of life, reaching 70–80/100,000 in the 9th decade (Fig. 5).

Clinical manifestation

The diagnosis of pancreatic cancer is usually made at locally advanced (almost 1/3 cases) or generalized stage of disease (> 50% cases) [1, 8, 12].

Only about 10% of patients are diagnosed at an early stage [1], and this is important because only such patients are eligible for radical treatment [12, 13]. In such cases, surgical treatment is the standard of care, usually consisting of pancreatoduodenectomy, partial peripheral pancreatectomy, or total pancreatoduodenectomy [12, 13]. Unfortunately, almost 80% of operated patients develop a relapse within 2 years, most often in the form of distant metastases [14]. In the vast majority of patients (80–90%), at diagnosis surgical treatment is not possible [8, 12, 15]. Median OS in patients with locally advanced PC does not exceed one year, and in systemic disease, it is only 3-6 months [14-16]. The introduction of modern imaging tests into clinical practice (ultrasonography, computed tomography, magnetic resonance imaging) slightly improved the prognosis in this group of patients [15].

Early-stage pancreatic cancer is asymptomatic or mildly symptomatic [13, 17, 18]. Symptoms are non-specific and may include back or shoulder pain, dysphagia, changes in bowel habits, somnolence, depressed mood, and depression [12, 17, 18]. It is worth emphasizing, however, that symptoms may appear even several months before the diagnosis, which confirms the importance of obtaining a proper medical history [17]. The clinical manifestation of locally advanced or generalized disease includes pain (back pain, epigastric pain), fatigue and insomnia, anorexia, nausea, early satiety, progressive cachexia, jaundice, and diabetes [3, 15, 19]. Many of these symptoms significantly impact the quality of life (QoL), leading to its impairment, often at diagnosis [14, 16].

Due to predominant PC detection at advanced stages, attempts are made to improve the diagnostics and to make a diagnosis at earlier stages. Population screening is not recommended. However, imaging in people with a family history of pancreatic cancer associated with disease-associated genetic variants is of increasing importance. It seems that regular imaging examinations performed in people over 50 with certain genetic abnormalities may contribute to earlier detection of suspicious lesions in the pancreas [12].

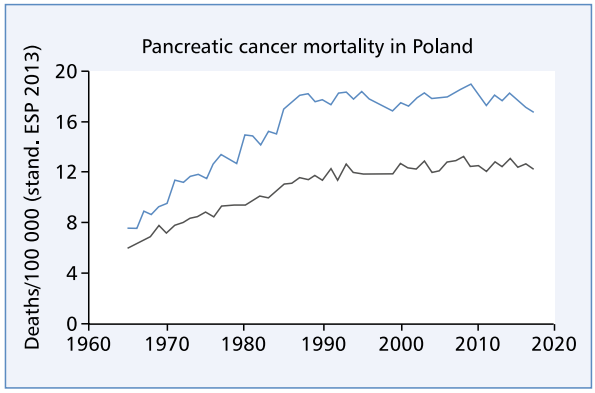

Figure 4. Pancreatic cancer mortality in Poland 1965–2017 [11]

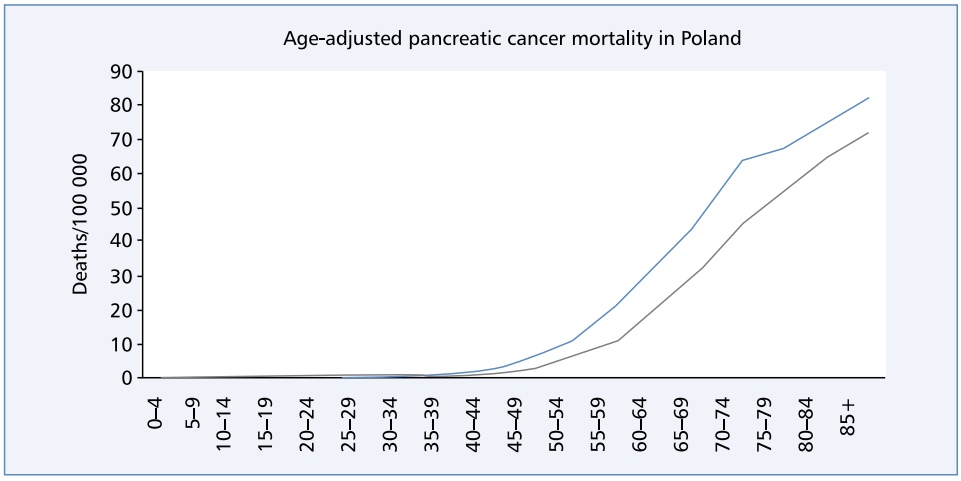

Figure 5. Age-adjusted pancreatic cancer mortality in Poland 2015–2017 [11]

Endoscopic ultrasonography (EUS) is a valuable imaging test, which allows the detection of tumors smaller than 2 cm. Magnetic resonance imaging with secretin administration and magnetic resonance cholangiopancreatography (MRCP) correlate well with EUS. Attempts have also been made to identify biomarkers associated with the early diagnosis of pancreatic cancer. The only one registered by the US Food and Drug Administration (FDA) is cancer antigen 19-9 (CA 19-9) serum level. Promising results (sensitivity and specificity of 100% and 84%, respectively) were obtained when determining volatile organic substances (VOCs) levels [12]. The value of this method, as well as the determination of the *p53* gene mutation in pancreatic juice, requires confirmation in further studies [12].

Systemic treatment of patients with advanced pancreatic cancer from the 1980s to the present day

First-line treatment

Fluorouracil was the first cytotoxic drug used in the treatment of pancreatic cancer patients. Until the end of the 20th century, many clinical trials were conducted using multi-drug regimens with fluorouracil, comparing them with best supportive care (BSC). However, they did not indicate the superiority of chemotherapy. Objective responses were obtained in about 20% of patients, but without the possibility of alleviating cancer symptoms (mostly pain) and – most of all – prolonging OS while the more active regimens were also more toxic [20–22].

Some progress was made only in 1997 when Burris et al. [22] demonstrated the advantage of gemcitabine monotherapy over fluorouracil. In total, 126 patients with advanced symptomatic pancreatic cancer were randomly assigned to the gemcitabine (1000 mg/m^2 once a week for 3 months and then maintenance therapy every 4 weeks) or fluorouracil (600 mg/m^2 every 7 days) groups. The primary endpoint was the so-called clinical benefit, including pain assessment (rescue analgesics use and pain intensity), Karnofsky performance status (KPS) score, and weight loss. Secondary endpoints included objective response rate (ORR), OS, and progression-free survival (PFS). Clinical benefit (improvement of at least one parameter without worsening the others for 4 weeks or more) was achieved by 23.8% of patients treated with gemcitabine compared with 4.8% of patients receiving fluorouracil ($p = 0.0022$), which was maintained for 18 weeks versus 13 weeks in the control group. The benefit in terms of OS was significant but the numerical difference was minimal (5.65 months in the gemcitabine group versus 4.41 months in the fluorouracil group; $p = 0.0025$). On the other hand, the 12-month survival rate was 18% and 2%, respectively. Improvement in performance status, better pain control, and improved QoL were observed in the gemcitabine group. The treatment was well tolerated. Patients treated with gemcitabine were slightly more likely to develop grade 3 or 4 neutropenia, but clinical manifestations of infection were not significant in the majority of patients [22]. Based on the results of this study, gemcitabine has for many years become the standard of care in pancreatic cancer patients.

In the first decade of the 21st century, several randomized phase III trials were conducted to evaluate the combination of gemcitabine and other drugs with different mechanisms of action (e.g. pemetrexed, capecitabine, irinotecan, oxaliplatin, and sorafenib). Moore et al.'s trial, published in 2007, was the only study that demonstrated the superiority of combination therapy over gemcitabine monotherapy in terms of OS [23]. In a group of 569 patients with advanced pancreatic cancer, a significant increase in median OS (but only by 2 weeks) and median PFS (only by a few days) was demonstrated after combined treatment with gemcitabine and erlotinib, as well as a significant reduction in the risk of death by 18% ($p = 0.038$) and the risk of progression by 23% ($p = 0.004$) (Tab. 1); however, combined treatment was more toxic [23].

In a phase III clinical trial comparing gemcitabine in monotherapy and in combination with capecitabine in patients with advanced pancreatic cancer, it has been shown that combination therapy significantly increases response rates and median PFS, which, however, does not translate into better overall survival (Tab. 1) [24]. On the other hand, a significant benefit in terms of OS was shown in a meta-analysis including two other studies conducted in smaller sample sizes (risk reduction of death by 14%; $p = 0.09$; Tab. 1) [24].

There was no significant progress in first-line systemic treatment of patients with advanced/metastatic pancreatic cancer until the second decade of the 21st century when two phase III clinical trials, PRODIGE-4 and MPACT, were conducted.

In the PRODIGE-4 study, 342 patients with disseminated pancreatic cancer and in good PS [e.g. 0 or 1 according to the ECOG (Eastern Cooperative Oncology Group) scale] were randomly assigned to receive FOLFIRINOX combination therapy (oxaliplatin, irinotecan, leucovorin, and fluorouracil) every 2 weeks or gemcitabine alone. Participants received chemotherapy for 6 months. Ultimately, the median number of cycles was 10 (range 1–47) in the FOLFIRINOX group and 6 (range 1–26) in the gemcitabine group ($p < 0.001$). Median OS, the primary endpoint of the study, and PFS were prolonged (11.1 *vs.* 6.8 months and 6.4 *vs.* 3.3 months, respectively) in the combination chemotherapy group, and a reduction in the risk of

Table 1. Phase III clinical studies with gemcitabine monotherapy in the first line in the control arm

Study publication	Studied regimen	ORR	DCR	PFS (months)	OS (months)
Moore 2007 [23]	G + erlotinib	8.6% *vs.* 8.0% p = NS	57.5% *vs.* 49.2% p = 0.07	3.75 *vs.* 3.55 HR = 0.77 p = 0.004	6.24 *vs.* 5.91 HR = 0.82 p = 0.038
Cunningham 2009 [24]	G + capecitabin	19.1% *vs.* 12.4% p = 0.034	–	5.3 *vs.* 3.8 HR = 0.78 p = 0.004	7.1 *vs.* 6.2 HR = 0.86 p = 0.08
Conroy 2011 [5]	FOLFIRINOX	31.6% *vs.* 9.4% p < 0.001	70.2% *vs.* 50.9% p < 0.001	6.4 *vs.* 3.3 HR = 0.47 p < 0.001	11.1 *vs.* 6.8 HR = 0.57 p < 0.001
Von Hoff 2013 [6]	G + nab-paclitaxel	23% *vs.* 7% p < 0.001	48% *vs.* 33% p < 0.001	5.5 *vs.* 3.7 HR = 0.69 p < 0.001	8.5 *vs.* 6.7 HR = 0.72 p < 0.001

DCR — disease control rate); G — gemcitabine; HR — hazard ratio; OS — overall survival; ORR — objective response rate; PFS — progression-free survival

death (by 43%; p < 0.001) and the risk of progression (by 53%; p < 0.001) was also observed (Tab. 1) [5]. Objective response rate was also improved (31.6% *vs.* 9.4%, respectively; p < 0.001). However, combination therapy was more toxic. Neutropenia and febrile neutropenia were reported in 45.7% and 5.4% of patients receiving FOLFIRINOX chemotherapy, respectively, and in 21.0% and 1.2% of patients receiving gemcitabine alone (p < 0.001 and p < 0.03), respectively [5]. The researchers highlighted the similarity of the results obtained in the group treated with gemcitabine to the results obtained in the study by Cunnigham et al. [24] and other phase III studies with this drug.

In the MPACT study, 861 patients with metastatic pancreatic cancer and KPS scores ≥ 70 were treated with nab-P in combination with gemcitabine or gemcitabine alone [6]. The primary endpoint was OS improvement after doublet chemotherapy (median 8.5 *vs.* 6.7 months in the gemcitabine group and relative risk of death reduction by 28%; p < 0.001; Tab. 1). Both the 12- and 24-month survival rates were significantly higher in the group receiving combination therapy compared to monotherapy (35% *vs.* 22%, respectively; p = 0.0002 and 9% *vs.* 4%, respectively; p = 0.02). There was also PFS (median 5.5 *vs.* 3.7 months, respectively, risk reduction 31%; p = 0.000024) and objective response rate (23% versus 7%, respectively; p < 0.001) improvement in patients receiving doublet chemotherapy. The most common grade ≥ 3 adverse reactions were neutropenia (38% in the nab-P and gemcitabine group *vs*. 27% in the gemcitabine monotherapy group), fatigue (17% *vs.* 7%, respectively), and neuropathy (17% *vs*. 1%, respectively). The study did not evaluate the quality of life [6].

Both aforementioned chemotherapy regimens — FOLFIRINOX and nab-P with gemcitabine — have been implemented in daily clinical practice. Their value was confirmed by the results of additional subgroup or real-world data (RWD) analyses aimed at identifying these groups of patients that benefit most from individual therapeutic options and conditions for their effective and safe use. The data from the PRODIGE-4 study show that the greatest benefit from FOLFIRINOX chemotherapy is achieved in patients below 76 years of age, with good performance status (ECOG 0 or 1), without signs of myocardial ischemia and with bilirubin levels close to the normal range [5]. In the MPACT study, the superiority of the nab-P/gemcitabine combination was seen in all predefined subgroups. Combination therapy significantly more often than monotherapy resulted in lowering baseline CA 19-9 levels (p < 0.001). Patients who had a reduced the level of this marker by at least 90% also achieved longer survival compared to patients with a reduction of less than 90% (median OS, 13.5 and 8.2 months, respectively, a reduction in the risk of death by 47%; p < 0.001) [6]. The analysis of treatment strength in the MPACT study showed worse outcomes in patients receiving unreduced nab-P dose compared to those who required a dose reduction (median, 6.9 *vs.11.4* months; p < 0.0001) and in patients with no delays in administering the next dose compared to patients with such delays (median 6.2 *vs.* 10.1; p < 0.0001) [13]. Patients requiring modified nab-P administration had also an improvement in PFS and the overall response rate. Importantly, a similar trend was also seen in the gemcitabine group. Multivariate analyzes confirmed a statistically significant association between the delayed administration and reduced dose of nab-P and OS. In the authors' opinion, modification of the drug dosage is an effective method of managing toxicity, allowing for an increase in drug exposure without adversely affecting its efficacy [13].

German RWD analysis based on the Tumorregister Pankreaskarzinom (TPK) registry data, collected

prospectively between 2014 and 2017 in 104 centers in Germany, allowed for evaluating treatment outcomes in1174 patients with locally advanced, inoperable, or generalized pancreatic ductal adenocarcinoma [25]. The most commonly used first-line therapy was nab-P in combination with gemcitabine (42%), followed by FOLFIRINOX (24%) and gemcitabine monotherapy (23%), and occasionally other regimens. Analysis of clinical data shows that patients receiving gemcitabine monotherapy were older (median 78 years) and in worse PS (73% of patients with ECOG PS ≥ 1) compared to those treated with nab-P in combination with gemcitabine (median age 71 years, 64% of patients with ECOG PS ≥ 1) or receiving chemotherapy according to the FOLFIRINOX regimen (median age 60 years, 52% of patients with ECOG PS ≥ 1). The disease control rate was 39% in the whole study group (30%, 41%, and 44% in the gemcitabine, nab-P plus gemcitabine, and FOLFIRINOX groups, respectively). Median PFS after first-line treatment was 4.6 months, 5.6 months, and 6.3 months, respectively; median OS was 6.8, 9.1, and 11.3 months, respectively, and the 6-month survival rate was 58%, 65%, and 80%, respectively [25]. In 280 patients (24%) the dose of drugs was reduced at the beginning or during therapy (34%, 21%, and 20% of patients in the FOLFIRINOX, nab-P with gemcitabine and gemcitabine monotherapy groups, respectively), and treatment was permanently discontinued due to toxicity in 17% of patients (23%, 16%, and 11% of patients, respectively). The analysis of TPK data showed that the most frequently chosen treatment regimens (gemcitabine, nab-P with gemcitabine, and FOLFIRINOX) were used in different patient populations.

These observations are consistent with the European Society for Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN) guidelines [26, 27]. The European Society of Clinical Oncology recommends the use of multi-drug regimens (FOLFIRINOX and nab-P with gemcitabine) in patients with good performance status (ECOG PS 0 or 1). Patients with poorer performance status (ECOG PS 2) or with bilirubin > 1.5X ULN should receive gemcitabine monotherapy. ECOG PS 3–4 and the presence of comorbidities is an indication for BSC [26]. The NCCN guidelines distinguish between two patient populations: with good and poor performance status. According to the guidelines, combination therapy (FOLFIRINOX, nab-P with gemcitabine and other regimens, e.g. gemcitabine with erlotinib) is recommended in the first group, while in the second group, monotherapy with gemcitabine, capecitabine or fluorouracil is recommended [27].

Second-line treatment

Progress in the field of systemic first-line treatment has highlighted the need to find options for further treatment lines after therapy failure. In the PRODIGE-4 and MPACT studies, approximately 40–50% of patients received second-line chemotherapy. In patients receiving first-line chemotherapy according to the FOLFIRINOX regimen in the PRODIGE-4 study, gemcitabine monotherapy was most often used as second-line therapy (in 82.5% of patients). In turn, for patients treated in the first line with gemcitabine, multi-drug chemotherapy (most often FOLFOX — 49.4%, much less often FOLFIRINOX — 4.7%) was used in the second line. Median OS did not differ in both groups; it was 4.4 months from the start of second-line treatment. In an exploratory analysis of MPACT study data, significantly longer survival was observed in patients receiving second-line treatment, median OS (from randomization to death) was 12.8 months in the nab-P/gemcitabine group and 9.9 months in the gemcitabine monotherapy group (p = 0.015), and 13.5 and 9.5 months, respectively (p = 0.012) in patients receiving fluoropyrimidine-based second-line chemotherapy, while in patients not receiving second-line treatment — 6.3 and 4.3 months, respectively (p < 0.001). Multivariate analysis showed that the factors of longer survival after first-line treatment included using nab-P with gemcitabine in first-line treatment, using second-line therapy, longer median PFS after first-line treatment, KPS ≥ 70, and the neutrophils-to-lymphocytes ratio at the end of first-line treatment ≤ 5. The authors of this analysis concluded that the results obtained justify the use of second-line treatment with fluoropyrimidine-containing regimens in patients with metastatic pancreatic cancer after failure of first-line treatment with nab-P with gemcitabine [8].

In the TPK analysis, 346 patients received second-line treatment. The most commonly used was nab-P with gemcitabine (28.9%) and chemotherapy according to the FOLFOX/OFF regimen (23.8%), much less frequently gemcitabine monotherapy (11.5%), FOLFIRINOX (7.9%), or fluorouracil (4.1%). In 111 patients, third-line chemotherapy was also used.

The efficacy and safety of second-line treatment in patients with advanced pancreatic cancer were also analyzed in randomized phase III trials. The CONKO-003 and the PANCREOX trials assessed the effect of adding oxaliplatin to fluorouracil (FU) with calcium folinate (leucovorin, LV) in patients after failure of gemcitabine-based chemotherapy (including in combination with nab-P). There were inconclusive results in terms of OS. In the CONKO-003 study, the addition of oxaliplatin was associated with a significant extension of median OS (5.9 *vs.* 3.3 months; risk of death reduction by 34%; p = 0.010), and the toxicity profile was similar to that seen with FU/LV [28]. In the PANCREOX study, median OS was significantly shorter in patients receiving the modified FOLFOX6 (mFOLFOX6) regimen

compared with FU/LV (6.1 *vs*. 9.9 months, p = 0.02). No benefit was demonstrated according to the primary endpoint of PFS (median 3.1 *vs*. 2.9 months, p = 0.99). The addition of oxaliplatin increased toxicity (grade 3 and 4 adverse reactions were reported in 63% of patients receiving mFOLFOX6 and 11% of patients receiving FU/LV) [29]. The results of these studies do not allow unequivocal confirmation of the benefits of adding oxaliplatin to FU in the second-line treatment. It should be noted, however, that in these studies different dosing of FU/LV was used (in the CONKO-003 study, the OFF regimen, and in the PANCREOX study, the modified mFOLFOX6 regimen).

In the NAPOLI-1 study, patients after failure of earlier gemcitabine-based therapy were randomized to nal-IRI monotherapy (151 patients), nal-IRI in combination with 5-FU/LV (117 patients), or 5-FU/LV (149 patients). The use of 5-FU/LV in the control arm has been criticized, but this regimen was also a comparator in the CONKO-003 study due to the lack of a generally accepted standard of care after failure of gemcitabine chemotherapy at that time. Irinotecan is not approved for the treatment of patients with pancreatic cancer, which justifies the choice of a treatment regimen. The FOLFIRI and FOLFIRI-3 regimens (different dosing of irinotecan, use before and after 5-FU/LV) were only evaluated in phase II studies and did not show any special benefit of irinotecan. Until the introduction of the FOLFIRINOX regimen, irinotecan-containing regimens were not standard practice, which explains the choice of 5FU/LV as the comparator in the NAPOLI-1 study.

Median OS was 6.1 months in the triplet-chemotherapy group and 4.2 months in the 5FU/LV group (P = 0.012) and 4.9 months in the nal-IRI monotherapy group (p = 0.94). Median OS in the control arm in the NAPOLI-1 study was longer than in the control arm in the CONKO-003 study (4.2 *vs.* 3.3 months, respectively) [28, 30]. Median PFS in the triplet-chemotherapy group was significantly longer than in the 5FU/LV group (3.1 *vs.* 1.5 months, risk reduction by 43%; p = 0.0001). In patients receiving nal-IRI monotherapy, median PFS was 2.7 months, and its extension compared to 5FU/LV was not significant (p = 0.1). When analyzing treatment response, interesting observations concerning the change in CA19-9 levels were noted. A reduction of abnormal baseline levels by ≥ 50% was observed in 29% of patients treated with nal-IRI + 5-FU/LV and only 9% of patients receiving 5-FU/LV (p = 0.0006). The most common grade 3 or 4 adverse reactions reported in the group receiving triplet chemotherapy were neutropenia (27%), diarrhea (13%), vomiting (11%), and fatigue (14%).

The authors concluded that treatment with nal-IRI in combination with calcium folinate-modulated fluorouracil prolongs survival of patients with metastatic pancreatic ductal adenocarcinoma after failure of prior gemcitabine-based treatment with manageable side effects, and, therefore, it may be a new therapeutic option for such patients [30]. This was reflected in the 2019 ESMO guidelines [26].

The benefit of second-line chemotherapy after failure of nab-P in combination with gemcitabine was also noted in a retrospective Italian analysis where median OS for patients receiving such treatment was significantly longer than in patients receiving BSC (13.5 *vs.* 6.8 months; p < 0.0001) [31]. Depending on the treatment regimen used in the second line, median OS was 12.9, 13.2, 13.8, and 12.3 months in patients receiving FOLFOX/XELOX, FOLFIRI, FOLFIRINOX (classic or modified), or other monotherapy drugs, respectively, with the differences not achieving the levels of statistical significance. The authors confirmed the legitimacy of the second-line treatment and indicated the possibility of obtaining therapeutic benefits in over 50% of patients after failure of first-line treatment with nab-P and gemcitabine [31].

Molecularly targeted therapy

In late 2019, the FDA, based on the results of the POLO study, approved the PARP [poly-(ADP-ribose) polymerase] inhibitor, olaparib, for the treatment of patients with generalized pancreatic adenocarcinoma with a germinal *BRCA1* and/or *BRCA2* genes mutations (gBRCAms). The POLO study was a double-blind, multicenter study in which 154 patients with metastatic pancreatic cancer with gBRCAm and no disease progression after first-line platinum-based chemotherapy were randomly assigned (3:2) to receive olaparib (300 mg twice daily) or placebo. Median PFS was significantly longer in patients receiving active treatment (7.4 *vs.* 3.8 months; p = 0.004). At the time of interim analysis (data maturity 46%), there was no difference between therapeutic arms in terms of OS. Based on the European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ), no significant difference was found between the study groups. The incidence of grade 3 or 4 adverse reactions was 40% in the olaparib group and 23% in the placebo group, and study treatment was discontinued due to adverse events in 5% and 2% of patients, respectively. Olaparib is an important therapeutic option that doubles the benefits of progression-free survival in patients with metastatic pancreatic cancer with gBRCAm [32].

At the turn of 2018 and 2019, treatment options for patients with metastatic pancreatic cancer were further expanded as a result of the FDA's approval of

larotrectinib and entrectinib for the treatment of solid neoplasms that display the fusion of the neurotrophic receptor tyrosine kinase (*NTRK*) gene [33]. Larotrectinib was registered on the basis of 3 studies involving a total of 55 patients previously receiving standard chemotherapy (if available for a specific type of cancer), including only 1 patient with pancreatic cancer. The overall response rate was 75% (13% of patients achieved a complete response and 62% of patients — including 1 patient with pancreatic cancer — partial response). Overall, 73% of patients had no disease progression after 6 months, and 55% of patients had no disease progression after 1 year [34]. In the group of over 50 patients with various cancers with *NTRK* gene fusion receiving entrectinib, 57.4% of patients achieved objective responses (including 4 complete responses), and 2 out of 3 pancreatic cancer patients achieved a partial response. Median PFS in the whole study group was 11.2 months, and median OS was 20.9 months [35]. It should be emphasized, however, that this innovative treatment strategy is indicated for a very limited number of patients with very precisely defined molecular abnormalities, and currently, nal-IRI is the drug of first choice in the second-line treatment of patients with metastatic pancreatic cancer after gemcitabine treatment.

Immunotherapy is also being assessed in the treatment of patients with pancreatic cancer. In the phase II KEYNOTE study, 158 study patients with various cancers with abnormalities in DNA repair genes *MSI-H* (high microsatellite instability)/*dMMR* (deficient in DNA mismatch repair), including 22 patients with pancreatic cancer, received pembrolizumab, a monoclonal antibody directed against programmed cell death-1 (PD-1). The objective response rate was 34.3%, median PFS was 4.1 months and median OS was 23.5 months. Treatment-related side effects occurred in 151 patients (64.8%) [36].

There is also some hope for T-cell immunotherapy targeting somatic mutations in tumor-specific peptide antigens, but the method is at an early-stage of research [37].

Conclusions

Progress in systemic treatment of patients with advanced pancreatic cancer is essential for prognosis improvement. In most patients, the diagnosis is made at advanced disease stages when systemic treatment is the only possible option. Until the mid-1990s, there was nihilism in practice in the field of systemic treatment, and the situation of patients changed only after gemcitabine use, which for many years became the standard of treatment even though its benefits were mainly related to the quality of life and cancer symptoms relief. Another significant step in first-line systemic treatment was noted in the second decade of the 21st century after the introduction of chemotherapy according to the FOLFIRINOX regimen and nab-P to the treatment of pancreatic cancer patients. Both methods of therapy have been included in the guidelines of scientific societies and implemented in clinical practice. As first-line treatment progressed, it became increasingly necessary to develop second-line treatment options. Many clinical trials have demonstrated the benefits of this approach, including monotherapy and multi-drug regimens. Research is underway to define predictive factors that will allow for the identification of the subpopulation of patients who benefit most from second-line treatment. As in many other areas of oncology, attempts have been made to apply molecularly targeted therapies in patients with advanced pancreatic cancer. Initial results are promising, and further studies on the use of immunotherapy raise hopes for patients and the medical community.

Conflict of interest

All authors declare no conflicts of interest.

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ORIGINAL ARTICLE

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Survival of pancreatic cancer patients treated with nab-paclitaxel (nab-P) in clinical practice: Analysis of National Health Fund data

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ABSTRACT

Introduction. Despite advances in the last few decades, pancreatic cancer is still characterized by systematically increasing morbidity and high mortality with a low survival rate. The introduction of nab-paclitaxel (nab-P) to the first-line treatment of patients with metastatic pancreatic adenocarcinoma in combination with gemcitabine resulted in improvements in overall survival (OS), progression-free survival (PFS) and objective response rate (ORR).

Material and methods. This study analyzes OS and PFS in pancreatic cancer patients treated with nab-P in the real world setting in Poland, based on data from the National Health Fund (NFZ) database.

Results. Data from 873 patients were found (2014–2019). PFS in the entire population was 169 days (95% CI 147–189) without difference between men and women, but significantly better in younger patients (29–50 years). OS in the entire population was 379 days (95% CI 337–non-assessable), with no difference between men and women. A statistically significant longer PFS and OS was demonstrated in the group of patients diagnosed in 2014–2016.

Conclusion. Nab-paclitaxel, when used in clinical practice, provides treatment results similar to those in clinical trials. Collecting and periodically analyzing demographic and clinical data could help to assess the place of nab-P in the treatment of patients with pancreatic cancer more accurately.

Key words: advanced pancreatic cancer; nab-paclitaxel; overall survival, progression-free survival

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Introduction

Adenocarcinoma accounts for over 90% of all primary pancreatic neoplasms, and its incidence systematically and significantly increases [1]. Pancreatic cancer is one of the leading causes of cancer-related mortality [2]. Based on data from 2017–2019, it has been estimated that approximately 1.7% of men and women will be diagnosed with pancreatic cancer at some point in their lives [3]. Currently, pancreatic cancer is the 12th most common cancer and the 7th leading cancer death worldwide [4, 5].

During the period from 1990 to 2017, the number of pancreatic cancers doubled worldwide (196 000 *vs.* 441 000). It is believed that the significantly increased incidence results from age structure changes in the world population (the risk of pancreatic cancer increases with age) and the improvement in diagnosis and detection of this disease in developed countries [2].

Europe is ranked second in terms of the incidence of pancreatic cancer after the Western Pacific region (9.3 per 100 000 men and 6.3 per 100 000 women). The highest number of cases is recorded in Germany, France,

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and Italy. Pancreatic cancer is the fourth leading cause of cancer death in Europe (8.8 deaths per 100 000 men and 5.7 per 100 000 women) after lung, colon, and breast cancer [6].

In Poland, 3852 cases were recorded in 2019 (incidence rate of 10.3%), and the number of deaths was 5068 (mortality rate of 13.2%) [7].

The survival rate of patients with pancreatic cancer is still very low, median overall survival (OS) in locally advanced stages does not exceed a year while it is 3–6 months in metastatic disease [8]. Although there has been an increase in the 5-year survival rate in the USA and Europe from less than 5% in the 1990s to 9% in 2019, the global mean rate is only about 3% [2, 9]. Unfavorable results are mainly related to late diagnosis. In most cases, the disease is diagnosed at either a locally advanced or metastatic stage, and only 15-20% of cases are diagnosed at early stages when radical surgery is possible [2].

Chemotherapy is used to treat patients with advanced pancreatic cancer, either as monotherapy or multidrug regimens with gemcitabine, fluoropyrimidine, nab-paclitaxel (nab-P), or irinotecan. The choice of the first-line treatment regimen should be adapted to the patient's general condition. Multidrug regimens (e.g. FOLFIRINOX — oxaliplatin, irinotecan, leucovorin, and fluorouracil) in the first line, and regimens with nanoliposomal irinotecan in the second line are more effective than monotherapy but should only be used in patients with good and very good performance status [10–13].

Nab-paclitaxel (nab-P) is a nanoparticle albumin-bound paclitaxel, showing pharmacological properties different from the conventional form of the drug. It is approved — among other indications – for the first-line treatment of adult patients with metastatic pancreatic adenocarcinoma in combination with gemcitabine [14]. The MPACT study showed that the combination of both drugs compared with gemcitabine alone improves OS, with a median of 8.5 *vs.* 6.7 months, progression-free survival (PFS), with a median of 5.5 *vs.* 3.7 months and objective response rate (23% *vs.* 7%) [13, 15].

The therapeutic value of nab-P in combination with gemcitabine was confirmed by real-world data (RWD), for example, the data from the German pancreatic cancer registry TPK collected prospectively in 104 centers between 2014 and 2017 [16].

Aim of study

This study aims to analyze the results of treatment with nab-P in daily clinical practice in Poland in terms of OS and PFS based on data from the National Health Fund (NHF) database.

Material and methods

The data of pancreatic adenocarcinoma patients treated with nab-paclitaxel (Abraxane®, Bristol-Myers Squibb Pharma EEIG, Ireland) from the NHF database were reviewed. The NHF data were collected after obtaining appropriate approval.

The analyzed data included the demographic characteristics of the patients and the results in terms of OS and PFS.

Overall survival was defined as the time to the last record in the database confirming that the patient was still alive. Progression-free survival was defined as the time to the last record in the database confirming the lack of disease progression in imaging tests and that the patient is still alive.

Statistical analysis

Statistical analysis was performed using survival assesement metods. Overall survival was calculated as the number of days from initiation of treatment to completion of observation or death. Progression-free survival was calculated as the number of days from initiation of treatment to completion of follow-up, disease progression, or death.

The significance of factors influencing OS and PFS was assessed using the log-rank test. The analysis was conducted using the R 4.0.5 software [17].

Results

Data from a total of 873 patients — 447 women (51.2%) and 426 men (48.8%) — treated between 2014 and 2019 were analyzed. The median age was 66 years [range 29–87 years; interquartile range (IQR) 61–70 years] with a predominance of patients over 60 years of age (80.0%).

Most patients were diagnosed in 2018 (n = 373; 42.7%) and 2019 (n = 198; 22.7%), and only 5.2% of patients were diagnosed in 2016 or earlier (n = 45).

Most patients were treated in centers located in the Masovian Provincial Department of the National Health Fund (n = 193; 22.1%), and the least in the Opole Provincial Department of the National Health Fund (n = 13; 1,5%),

The most common causes of treatment discontinuation were disease progression (n = 254; 43.4%) and death (n = 121; 20.7%). In 3 (0.5%) patients, treatment was discontinued due to a change of service provider. Detailed data on the analyzed group available in the NHF database are presented in Table 1.

Progression-free survival in the entire study group was 169 days (95% CI 147–189) (Fig. 1). There was

Table 1. Characteristics of pancreatic adenocarcinoma patients treated with nab-paclitaxel based on data from the National Health Fund database

Feature	Number of pts. n (%)
Sex	
Female	447 (51,2)
Male	426 (48,8)
Median age (years), (range) (IQR)	
66 (29–87) (61–70)	65.3 (8.2)
Age group	
29–50	39 (4.5)
50–60	135 (15.5)
60–70	429 (49.1)
70–87	270 (30.9)
Reason for treatment discontinuation	
Disease progression	254 (43.4)
Change of treatment	22 (3.8)
Patient withdrawal	38 (6.5)
Unacceptable side effects	56 (9.6)
Hypersensitivity to the active substance or excipient	18 (3.1)
Death	121 (20.7)
Another cause	73 (12.5)
Change of service provider	3 (0.5)
Year of diagnosis	
2014–2016	45 (5.2)
2017	257 (29.4)
2018	373 (42.7)
2019	198 (22.7)
Accounting Department of the National Health Fund	
Lower Silesia	40 (4.6)
Kuyavian-Pomeranian	24 (2.7)
Lublin	67 (7.7)
Lubuski	18 (2.1)
Lodzki	19 (2.2)
Lesser Poland	40 (4.6)
Masovian	193 (22.1)
Opole	13 (1.5)
Subcarpathian	49 (5.6)
Podlaski	31 (3.6)
Pomeranian	93 (10.7)
Silesian	107 (12.3)
Świętokrzyski	41 (4.7)
Warmia–Masuria	15 (1.7)
Greater Poland	61 (7.0)
West Pomeranian	62 (7.1)

IQR — interquartile range

no difference in survival between men and women ($p = 0.95$; Fig. 2). On the other side, a statistically significantly longer PFS was demonstrated in younger patients in the 29–50 age group ($p = 0.41$) (Fig. 3). A statistically significant difference ($p < 0.0001$) was demonstrated depending on the year of diagnosis with the highest median in the group patients diagnosed between 2014–2016 (Fig. 4).

Overall survival in the entire study group was 379 days (95% CI 337–not assessable) (Fig. 5). There were no statistically significant differences regarding sex ($p = 0.76$; Fig. 6) and age ($p = 0.65$; Fig. 7). On the other hand, a statistically significant difference ($p = 0.18$) was shown depending on the year of diagnosis with the highest median in the group of patients diagnosed between 2014–2016 (Fig. 8).

Discussion

Pancreatic cancer is still one of the major cancer-related threats to life and health. High mortality is primarily a consequence of the diagnosis at advanced disease stages. There has been some progress in the treatment of advanced disease in recent years, mainly with the introduction of multidrug regimens, but PFS and OS outcomes are still disappointing.

In the phase III PRODIGE 4 study, a statistically significant improvement in median PFS (6.4 *vs.* 3.3 months, $p < 0.001$) and OS (11.1 *vs.* 6.8 months, $p < 0.001$) with the FOLFIRINOX regimen (oxaliplatin, irinotecan, leucovorin, and fluorouracil) use was shown as compared to gemcitabine monotherapy, but the toxicity of the multidrug regimen was significantly greater [12]. In the MPACT study mentioned above, an increase in OS was achieved in patients with metastatic pancreatic cancer with a 28% reduction in the relative risk of death after adding nab-P to gemcitabine compared to gemcitabine alone. Multidrug regimens were moderately toxic with manageable side effects. The combination of nab-P with gemcitabine has become a new standard of systemic therapy in patients with advanced or metastatic pancreatic cancers [13].

In Poland, nab-P in the first-line treatment of patients with metastatic pancreatic adenocarcinoma has been used in combination with gemcitabine since 2017 as part of the Ministry of Health drug program only in patients non-eligible for more intensive chemotherapy according to the FOLFIRINOX regimen. The decision to use nab-P with gemcitabine was in line with the 2014 Polish Society of Clinical Oncology guidelines and the 2015 European Society of Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN) guidelines. No study has ever been conducted to directly compare the results

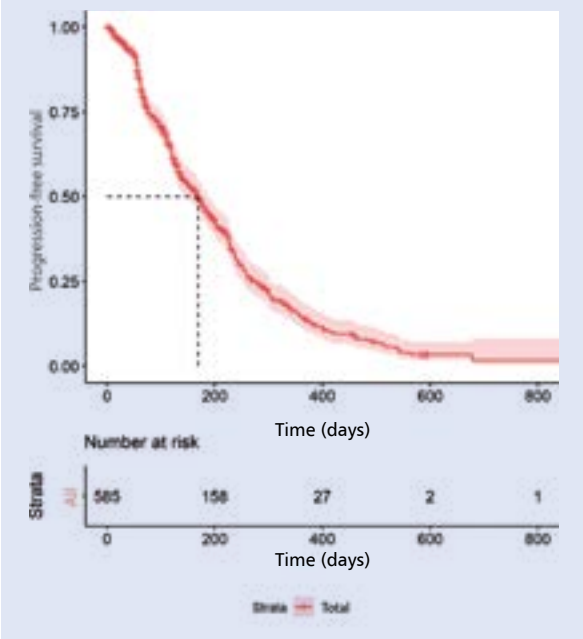

Figure 1. Progression-free survival in the entire group of patients

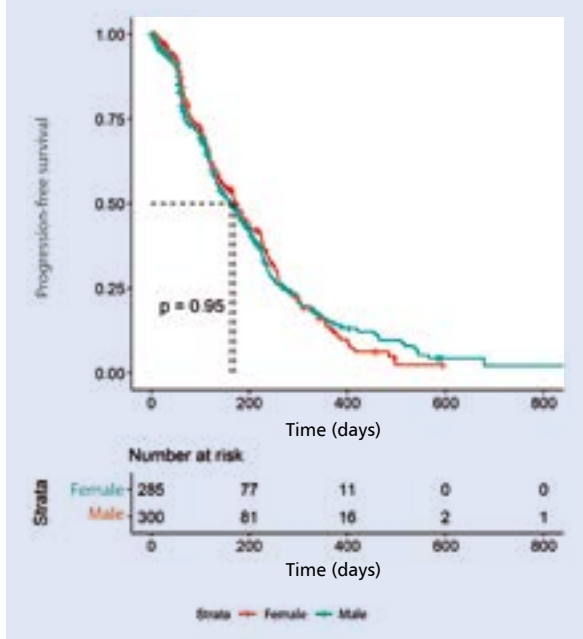

Figure 2. Progression-free survival depending on sex

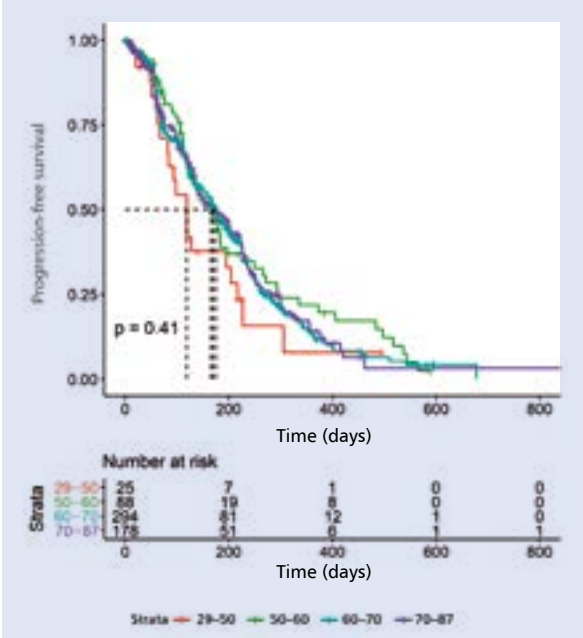

Figure 3. Progression-free survival depending on age

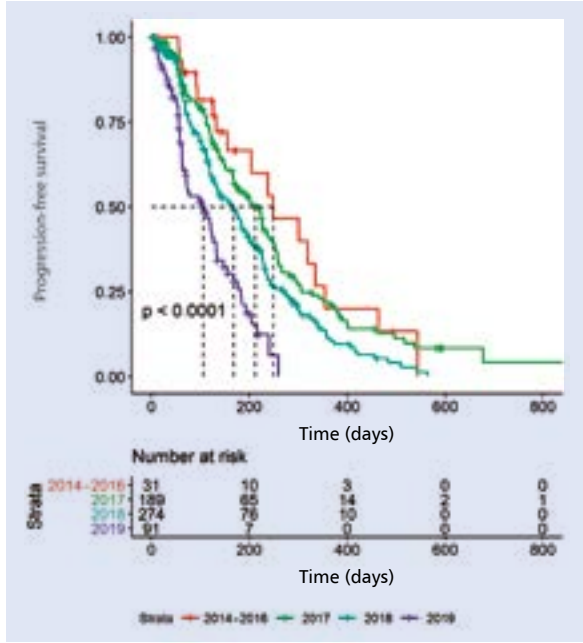

Figure 4. Progression-free survival depending on the year of diagnosis

of chemotherapy with the FOLFIRINOX regimen and the combination of nab-P with gemcitabine, which could help decide on the optimal treatment. However, when analyzing the studies comparing these two regimens with gemcitabine monotherapy (ACCORD 11 with FOLFIRINOX chemotherapy and MPACT with nab-P and gemcitabine) in first-line treatment, it can be noted that both studies included similar patient populations. This is evidenced not only by patient characteristics but also by almost identical results obtained in the control groups. The percentage of patients who received second-line treatment was similar (48% in

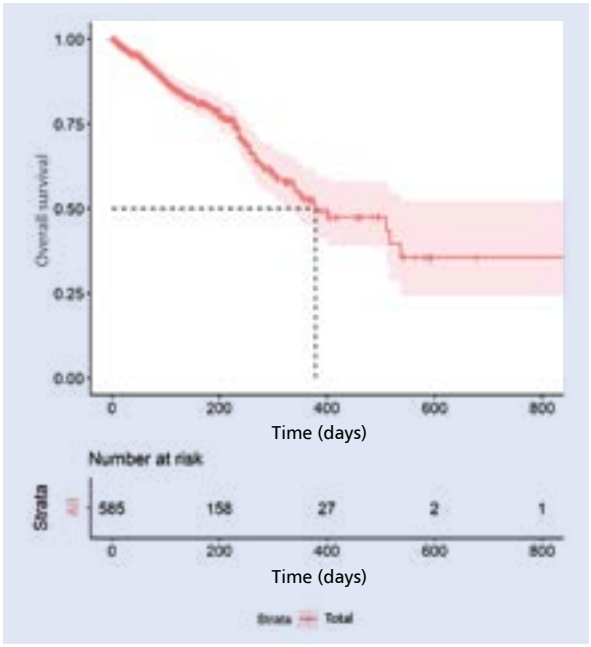

Figure 5. Overall survival in the entire group of patients

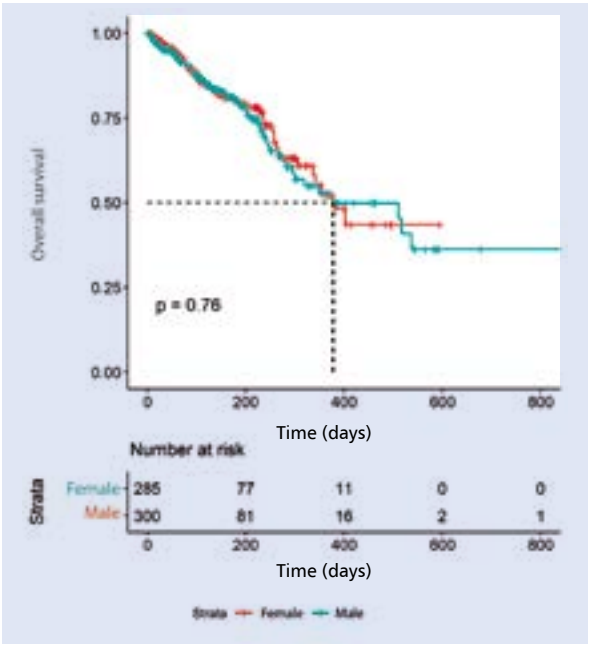

Figure 6. Overall survival depending on sex

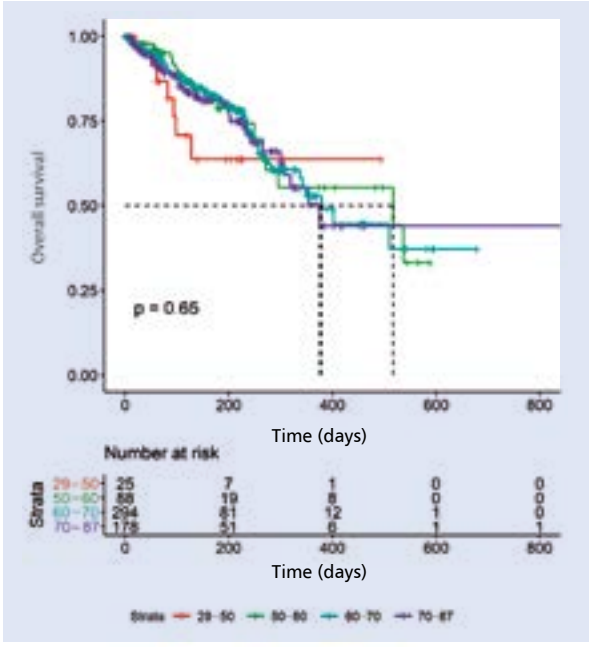

Figure 7. Overall survival depending on age

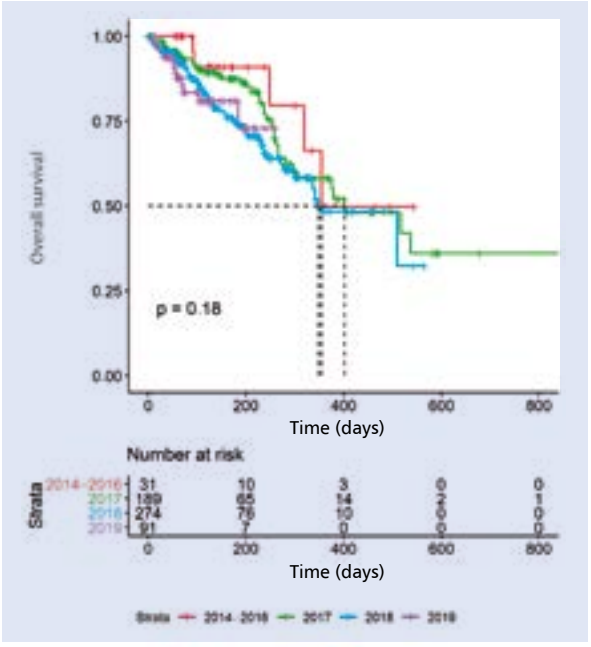

Figure 8. Overall survival depending on the year of diagnosis

ACCORD 11 and 40% in MPACT). Median OS, PFS, and objective response rates (ORR) were numerically better in ACCORD 11 than in the MPACT study (11.1 months, 6.4 months, and 32% *vs.* 8.5 months, 5.5 months, and 23%, respectively) [18]. An indirect comparison of the toxicity of both multidrug regimens indicates a higher incidence of adverse reactions during the FOLFIRINOX regimen, which could favor nab-P with gemcitabine, especially in patients with a worse performance status [19].

The European Society of Medical Oncology (ESMO) recommends the use of multidrug regimens (FOLFIRINOX and nab-P with gemcitabine) in patients with good or very good performance status,

which means scores 1 or 0 according to the Eastern Cooperative Oncology Group (ECOG) classification. Patients with reduced performance status (ECOG 2) should receive gemcitabine monotherapy. ECOG performance status 3-4 and the presence of comorbidities is an indication for the best supportive care [19]. The National Comprehensive Cancer Network (NCCN) guidelines distinguish between patient populations with good and poor performance status. According to the guidelines, combination therapy is recommended in the first group (FOLFIRINOX, nab-P with gemcitabine, and other regimens, e.g. gemcitabine with erlotinib) while monotherapy is recommended in the second group (gemcitabine, capecitabine or fluorouracil) [20].

This article presents the results of treatment with nab-P in the Polish population in daily clinical practice. In terms of sex and age, this population corresponds to patients treated in clinical trials. Unfortunately, the NHF databases do not include complete and detailed information on performance status or other clinical parameters and laboratory test results. This makes it impossible to compare the obtained results to the data from the subgroup analyses presented in individual prospective clinical trials and the current recommendations, taking into account patient performance status in the treatment eligibility criteria.

In the entire analyzed group of 873 patients, PFS was 169 days, and OS was 379 days. In both analyzes, no statistically significant differences were found depending on sex, and in the case of OS, also age. However, in both analyzes, a statistically significant difference was found depending on the year of diagnosis with the greatest benefit in the group of patients diagnosed in 2014–2016. On the one hand, this situation may be the result of the small (lowest!) size of this group, and, on the other hand, the lack of complete data on PFS and OS in the NHF database. The statistically significant improvement in PFS in patients in the youngest age group may be due to similar reasons. Nevertheless, even such a limited analysis shows that the use of nab-P in combination with gemcitabine in the systemic treatment of patients with pancreatic adenocarcinoma allows us to obtain PFS and OS similar to the results of clinical trials.

In 2019, an analysis of data from the pancreatic cancer registry collected prospectively in 104 centers between 2014 and 2017 was conducted in Germany, including a total of 1174 patients with locally advanced, inoperable, or metastatic pancreatic ductal adenocarcinoma. The median age of patients receiving nab-P with gemcitabine was 71 years, and in 64% of patients, ECOG performance status was ≥ 1. The corresponding values for patients receiving gemcitabine monotherapy or the FOLFIRINOX regimen were 78 years and 60 years, and 73% and 52%, respectively. Median PFS after first-line nab-P plus gemcitabine was 5.6 months (95% CI: 5.0–6.2) [for gemcitabine monotherapy and FOLFIRINOX: 4.6 months (95% CI: 3.7–5.2) and 6.3 months (95% CI: 5.5–6.9), respectively], and median OS was 9.1 (95% CI: 8.2–10.1) [for gemcitabine monotherapy and FOLFIRINOX: 6.8 (95% CI: 6.1–9.0) and 11.3 months (95% CI: 10.5–12.5), respectively]. The authors of the study concluded that the 3 most frequently chosen treatment regimens (gemcitabine, nab-P with gemcitabine, and FOLFIRINOX) were used in different patient populations, which confirms that all of them are applicable depending on the clinical situation [16].

In turn, according to the 2018 French guidelines for the diagnosis and treatment of patients with pancreatic cancer, both FOLFIRINOX and gemcitabine in combination with nab-P are the standard for first-line treatment in patients with good performance status [21].

Apart from clinical trials and research conducted in daily clinical practice, registers and databases are valuable sources of knowledge about the actual effectiveness and safety of various technologies. The prerequisite to such usefulness is a systematic, preferably prospective, supply of registers with complete, readable, and reliable data. Only then can the analyzes allow for correct conclusions useful in making therapeutic decisions.

When analyzing the data collected in the National Health Fund, it seems that their poor quality and quantitative value may result from the fact that these registers are used for evaluation, drawing inferences, and decision-making in the area of administration and management of resources rather than for purposes related to clinical practice. The above conditions were the greatest limitation of the presented analysis.

Conclusions

The results of treatment with nab-paclitaxel in daily clinical practice in patients with advanced pancreatic cancer are similar to those known from clinical trials. The drug has an established place in the therapeutic algorithm in the first-line of treatment. Collecting and periodically analyzing demographic and clinical data could further determine the role of nab-P in this still-difficult-to-treat population.

Conflict of interest

B.R.: advisory/consulting role & travel and accommodation support — Servier, Roche, AstraZeneca, BMS, MSD, Lilly, Pierre Fabre, Novartis.

M.K.: advisory/consulting role & travel and accommodation support — Servier, Roche, AstraZeneca, BMS.

I.R. declares no conflict of interest.

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VIA MEDICA

ORIGINAL ARTICLE

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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

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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)].

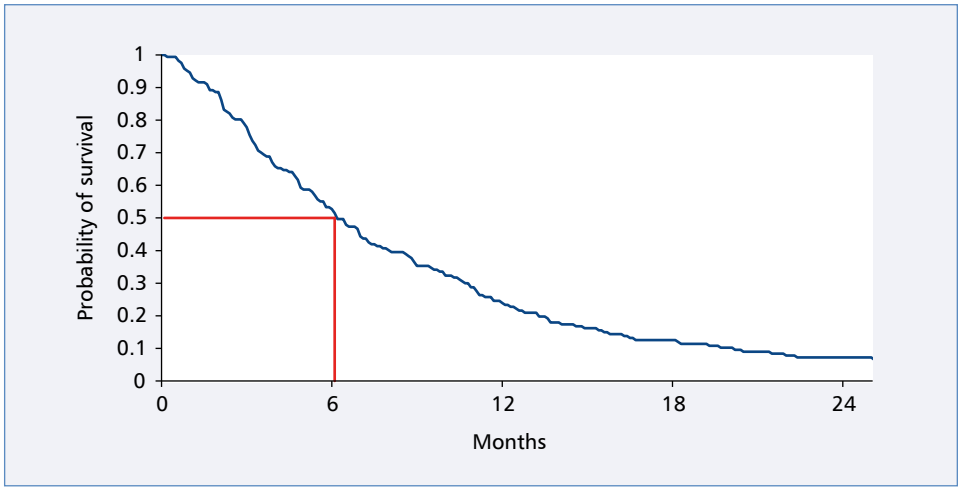

Figure 1. Overall survival in the entire study group

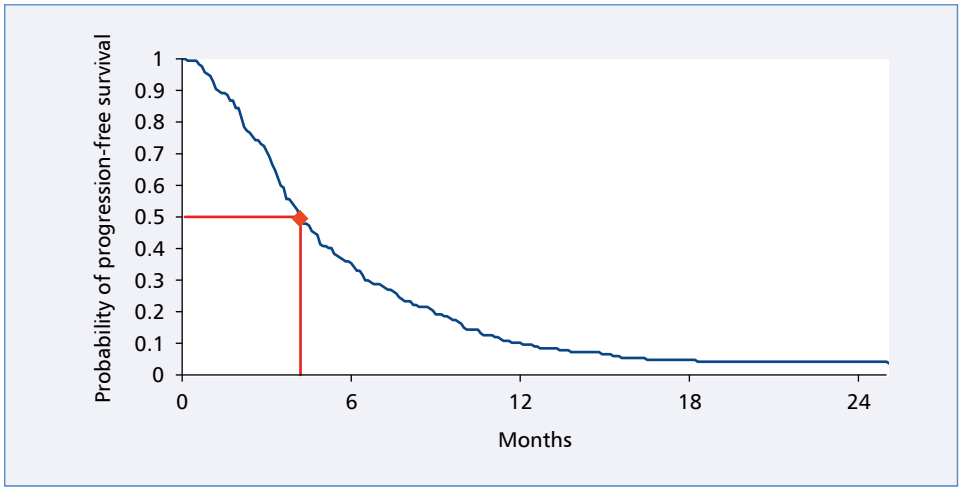

Figure 2. Progression-free survival in the entire study group

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

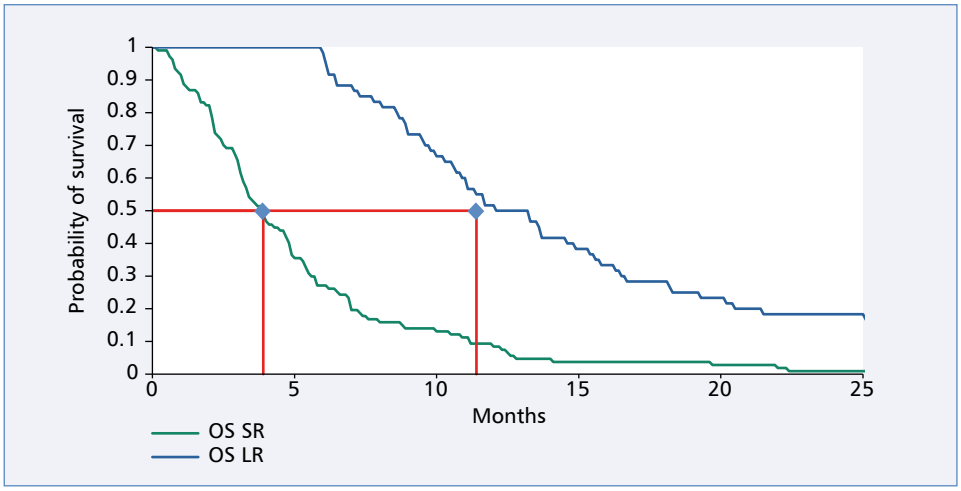

Figure 3. Overall survival (OS) in short (SR) and long-response (LR) subgroups

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:

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

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

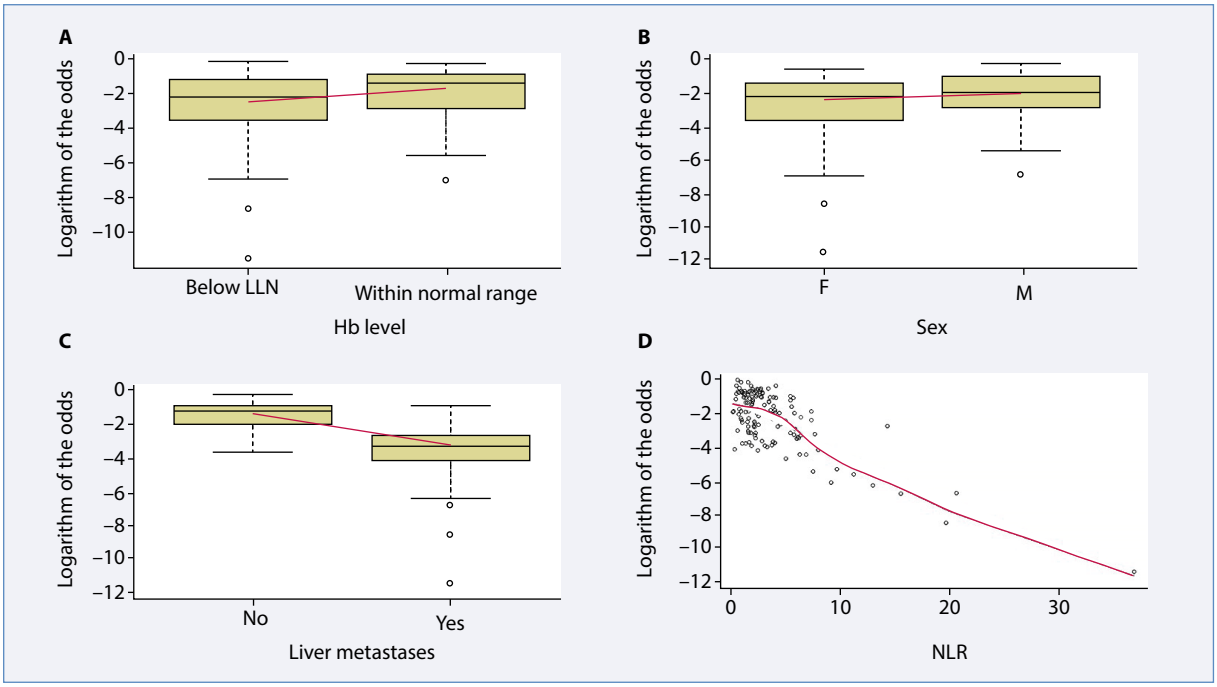

Figure 4. Box plots of logarithms of the odds depending on individual variables: hemoglobin (Hb) level (**A**), sex (**B**), presence of liver metastases (**C**) (median logarithms of the odds for individual values are connected by segments), and a plot of the dependence of the logarithm of the odds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

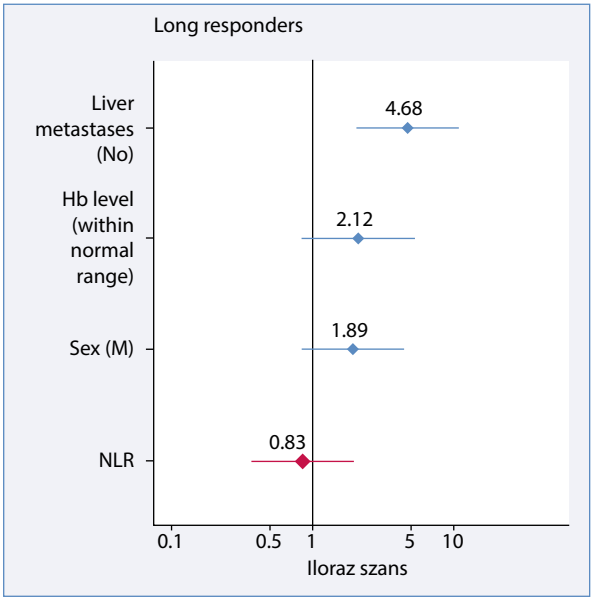

Figure 5. Forest plot for the selected model; Hb — hemoglobin; M — male; NLR — neutrophil/lymphocyte ratio

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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Neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and systemic immune-inflammation index as clinical predictive and prognostic markers in patients with advanced pancreatic cancer receiving gemcitabine monotherapy

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Abstract

Introduction. Pancreatic cancer is characterized by an increasing incidence and still poor prognosis despite the availability of various therapeutic options, currently including single- and multi-drug chemotherapy as well as molecularly targeted therapy. Therefore, appropriate qualification for particular therapies, based mainly on clinical and histological factors, is extremely important. Inflammatory status, associated with cancer development, justifies the search for prognostic markers related to the immune system, which could be additional factors facilitating selection of appropriate therapy.

This study aimed at assessing the prognostic value of the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII) in patients with advanced pancreatic cancer undergoing gemcitabine monotherapy.

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Material and methods. A retrospective analysis of blood morphological parameters was performed in 167 patients with advanced pancreatic cancer treated with gemcitabine monotherapy in the first line in five oncology centers in Poland in the years 2017–2022. The NLR, PLR, and SII were calculated, and cut-off points between high and low values were defined. Clinical parameters and their distribution were assessed depending on the overall survival (OS) value equal to or greater than or less than median OS. The distribution of patients within OS intervals in relation to the categories of inflammatory markers was assessed.

Results. The median age of patients was 71 years, the majority were women (58%), with clinical stage IV (57%), and with dominant location of metastases in the liver (42.5%). The median NLR was 2.69 (range 0.5–36.65), PLR 146.54 (range 18.53–1118.57), and SII 784.75 (range 79.86–10622.67). The cut-off points were defined as 4.5625 for the NLR [125 patients (75.8%) with a value less than and 40 patients (24.3%) with a value equal to or greater], 150 for the PLR [87 (52.7%)/ 78 (47.3%)], and 897.619 for the SII [96 (58.2%)/69 (41.8%)]. Comparing the groups with OS longer than or equal to the median and OS shorter than the median, statistically significant differences were found in relation to body mass index (BMI) ($p = 0.02$), baseline stage ($p < 0.001$), and location of metastases ($p < 0.001$). There were statistically significantly more NLR and SII values below the cut-off points in patients with survival at least equal to median OS. Concerning the PLR, no statistically significant differences were found between groups determined by OS value.

Conclusions. We demonstrated the relationship between indicators calculated on the basis of blood count parameters and treatment results. It may indicate the predictive and prognostic importance of indices reflecting immune system status, which can be a valuable addition to the clinical criteria included in prognostic models.

Keywords: advanced pancreatic cancer, gemcitabine, overall survival, progression-free survival

Introduction

Pancreatic cancer is one of the most aggressive malignant tumors associated with poor prognosis. The non-specific clinical manifestation and lack of characteristic symptoms at an early stage of disease limit the possibility of early diagnosis [1, 2].

Fewer than 20% of cases are diagnosed at the resection stage; 30–40% of cases are diagnosed at the locally advanced stage, and more than half at the dissemination stage [3]. Diagnosing the disease at a highly advanced stage and limited treatment options result in an unfavorable prognosis. The 5-year survival rates in the general population of pancreatic cancer patients do not exceed 10% [4, 5]. In Poland, only 8% of patients survive 5 years after diagnosis [6].

In the majority of patients, chemotherapy is the only treatment affecting the prognosis. Since the end of the 20th century, standard care for patients with advanced, inoperable pancreatic cancer has been gemcitabine monotherapy. Multidrug regimens introduced into treatment in the last decade — FOLFIRINOX and gemcitabine in combination with paclitaxel in the form of a nanoparticle complex with albumin (nab-P, nab-paclitaxel) in the first line and a regimen combining nanoliposomal irinotecan (nal-IRI) with fluoropyridines in the second line — allowed for extension of median overall survival (OS). However, it still does not exceed one year [7, 8]. Guidelines of the European Society for Medical Oncology (ESMO) and the National Network of Multispecialty Centers (NCCN) recommend adapting the chemotherapy regimen to the patient's performance status — for patients with good performance status, multidrug regimens are recommended, and for patients with worse performance status, gemcitabine (or capecitabine or fluorouracil) as monotherapy.

In recent years, there has been a lot of data on the relationship between inflammation, carcinogenesis, and progression of malignancies, including pancreatic cancer [9]. Immunocompetent cells and inflammatory mediators are present in the microenvironment of most, if not all, tumors, regardless of the triggering factor. They may reflect the state of the anti-cancer immune response. This justifies the search for prognostic markers related to inflammatory indices. The usefulness of such markers and indices based on them in establishing prognosis in various patient cohorts and clinical settings has been assessed for many years.

In the population of pancreatic cancer patients, the prognostic and/or predictive significance of the modified Glasgow Prognostic Score (GPS) [10, 11], neutrophil-to-lymphocyte ratio (NLR) [12–17],

platelet-to-lymphocyte ratio (PLR) [18, 19], C-reactive-protein-to-albumin ratio (CRP/Alb) [20, 21], and prognostic nutritional index (PNI) [22] has already been assessed. However, these studies mainly included patients qualified for surgery or postoperative chemotherapy.

The systemic immune-inflammation index (SII), calculated on the basis of the number of platelets, neutrophils, and lymphocytes, is a relatively new tool. It was first used to assess the prognosis in hepatocellular carcinoma (HCC) patients [23]. A standardized cut-off value has not been established and varies for different cancer types, but a high negative predictive value of the SII has been observed in many tumors [24, 25]. The predictive value of the SII in cancer patients undergoing various systemic treatment methods was also described [26–28].

This study aimed to assess the prognostic significance of the NLR, PLR, and SII in patients with advanced pancreatic cancer treated with gemcitabine in monotherapy. For this purpose, a retrospective analysis of laboratory parameters was performed.

Material and methods

The study included 167 patients with advanced pancreatic cancer treated with gemcitabine in monotherapy between 2017 and 2022 in five oncology centers in Poland (Opole Oncology Center in Opole, Oncology Clinic of the Jagiellonian University in Kraków, Białystok Oncology Center in Białystok, West Pomeranian Oncology Center in Szczecin, Department of Oncology and Radiotherapy, Medical University of Gdańsk). All patient data were anonymized after being extracted from individual files before analysis. The approval of the Bioethics Committee of the District Medical Chamber in Opole was obtained (resolution no. 347).

Gemcitabine was used as first-line treatment in all patients. In each of the centers involved in the study, it is possible to use nab-P in combination with gemcitabine as part of the drug program. In the majority of patients (80%) gemcitabine was used due to their failure to meet the drug program inclusion criteria [primarily due to the inability to confirm the presence of metastases and/or worse Eastern Cooperative Oncology Group (ECOG) performance status (PS)] (> 1). Gemcitabine was used as monotherapy at a starting dose of 1000 mg/m^2 of body surface (b.s.) every week, 7 times in an 8-week cycle, then 3 times in a 4-week cycle.

Several variables related to the patient's profile, biology, and disease stage were analyzed. Blood morphological parameters were analyzed in detail at the time of gemcitabine initiation, and the assessed parameters were calculated according to the following formulas [25]:

$$\text{NLR} = \frac{\text{number of neutrophils in peripheral blood per liter}}{\text{number of lymphocytes in peripheral blood per liter}}$$

$$\text{PLR} = \frac{\text{number of platelets in peripheral blood per liter}}{\text{number of lymphocytes in peripheral blood per liter}}$$

$$\text{SII} = \frac{\text{number of platelets in peripheral blood per liter} \times \text{number of neutrophils in peripheral blood per liter}}{\text{number of lymphocytes in peripheral blood per liter}}$$

Follow-up was completed on December 1, 2022. Due to the retrospective nature of the analysis, the cause of death was not determined. Overall survival was defined as the time from the treatment initiation to death, and progression-free survival as the time from treatment initiation to disease progression or death. Response to treatment was defined as no clinical and/or radiological evidence of disease progression.

Statistical methods

Mann-Whitney-Wilcoxon tests were used for continuous data and Fisher's and $\chi 2$ tests for categorical data. The Shapiro-Wilk test was used to test the normality hypotheses. The Kaplan-Meier estimator and the nonparametric Cox model were used in the survival analysis. Due to the relationships between the variables, only models with each variable analyzed individually were considered.

The optimal cut-off points for the NLR, PLR, and SII were 4.56, 150, and 897, respectively. They were determined based on receiver operating characteristic (ROC) curves and Youden's criterion. The analysis results showed that the area under the ROC curves (AUC) — AUROC for the NLR, PLR, and SII were 0.598 [95% confidence interval (CI) 0.509–0.688], 0.508 (95% CI 0.418–0.599), and 0.574 (95% CI 0.484–0.664), respectively, as shown in Figure 1.

Results

Clinical characteristics

The median age was 71 years (Tab. 1). Women predominated (almost 60%). More than half of the patients had a normal BMI, and one-third were overweight or obese. In the majority of patients (> 65%), the PS was assessed according to the ECOG score as good or very good. More than half were patients with clinical stage IV, and the liver was the most common location of metastases (42.5% of the study group).

Morphology parameters allowed for the assessment of white blood cell fraction disorders and the calculation of the NLR, PLR, and SII. The median NLR was 2.69 (range 0.5 — 36.65), PLR — 146.54 (range 18.53–1118.57), SII 784.75 (range 79.86–10622.67).

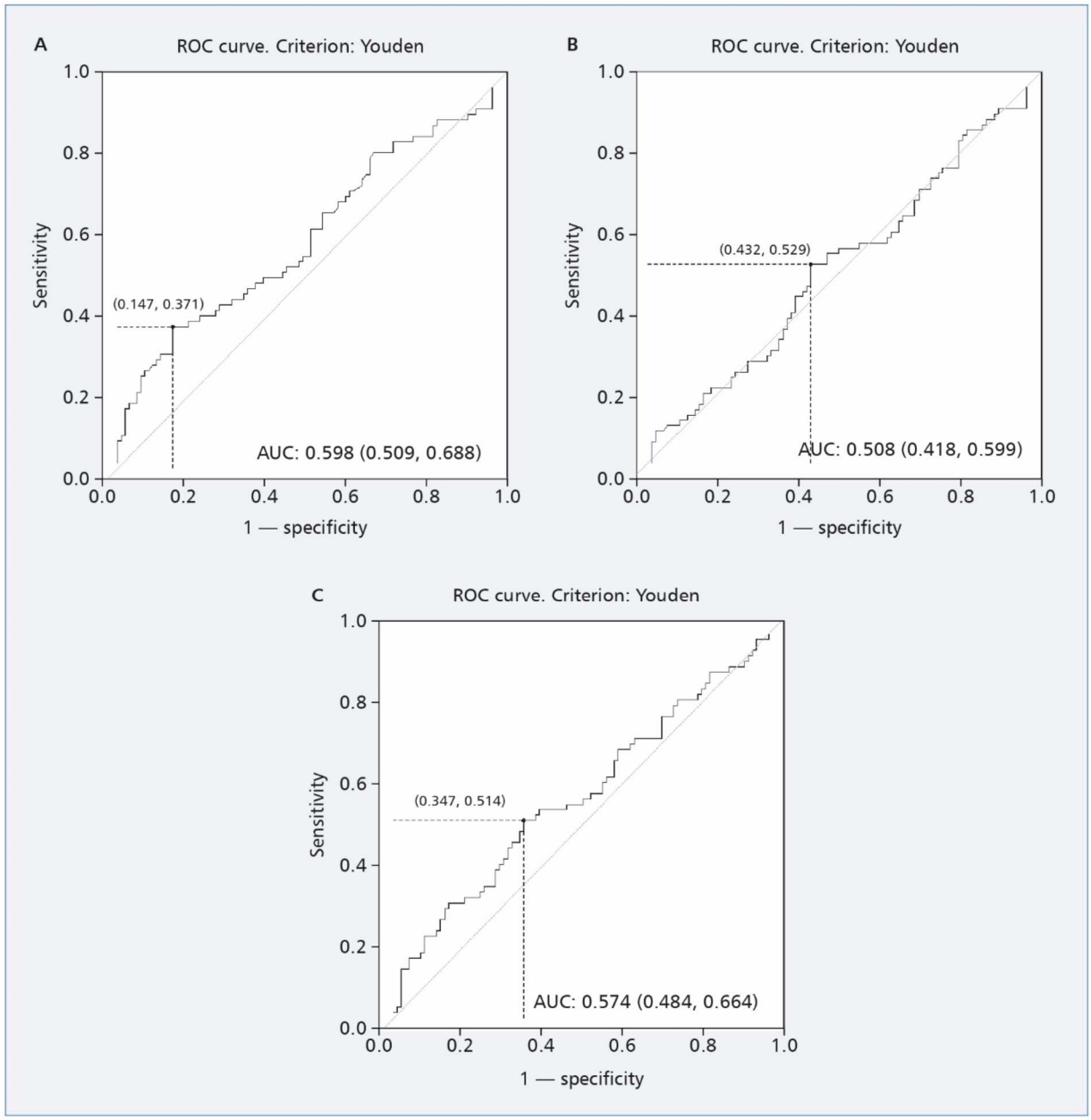

Figure 1. Receiver operating characteristic (ROC) curves; **A.** Neutrophil-to-lymphocyte ratio (PLR); **B.** Platelet-to-lymphocyte ratio (PLR); **C.** Systemic immune-inflammation index (SII); AUC — area under curve

In two patients, complete data on the percentage distribution of the white blood cell fraction were not obtained, and these patients were excluded from this part of the analysis.

Median overall survival was 6.48 months (range 5.75–8.45 months; Fig. 2), and the 6-, 12-, 18- and 24-month survival rates were 56%, 26%, 13%, and 8%, respectively.

The distribution of selected variables was assessed in patient subgroups defined based on median OS — in the group of patients with OS longer or equal to the median (OS ≥ median) and in the group with OS shorter than the median (OS < median; Tab. 2). There were no significant differences between the groups except for median BMI, clinical stage at baseline, and location of metastases ($p = 0.02$, $p < 0.001$ and $p < 0.001$, respectively).

Using predefined cut-off points for the NLR, PLR, and SII, patients were assigned to two groups according to each indicator: 125 patients (75.8%) presented the NLR < 4.5625 (hereinafter referred to as low), and 40 patients (24.3%) ≥ 4.5625 (referred to as high); 87 patients (52.7%) presented the PLR < 150 (low), and 78 patients (47.3%) ≥ 150 (high); 96 patients

Table 1. Patient characteristics

Feature	Number of patients n = 167 (%)
Age in years at diagnosis	
Median	71.24
Range	(47.44–85.87)
Sex	
Female	97 (58.08%)
Male	70 (41.92%)
BMI at initiation of gemcitabine treatment	
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 gemcitabine treatment initiation	
0	7 (4.19%)
1	102 (61.08%)
2	50 (29.94%)
3	7 (4.19%)
No data	1 (0.60%)
Clinical stage at baseline	
III	59 (35.33%)
IV	95 (56.89%)
No data	13 (7.78%)
Location of metastases at gemcitabine treatment initiation	
No metastases	60 (35.93%)
Liver and possibly other organs	71 (42.51%)
Other organs excluding the liver	36 (21.56%)
NLR at gemcitabine treatment initiation	
Median	2.69
Range	(0.5–36.65)
PLR at gemcitabine treatment initiation	
Median	146.54
Range	(18.53–1118.57)
SII at gemcitabine treatment initiation	
Median	784.75
Range	(79.86–10622.67)

BMI — body mass index; ECOG — Eastern Cooperative Oncology Group; NLR — neutrophil-to-lymphocyte ratio; PLR — platelet-to-lymphocyte ratio; PS — performance status; SII — systemic immune-inflammation index

(58.2%) presented the SII < 897.619 (low), and 69 patients (41.8%) ≥ 897.619 (high).

The numerical distribution of patients with OS ≥ median and OS < median was assessed in relation to the categories of the above indicators, and it was found that patients with survival at least equal to the median significantly more often had NLR and SII values below the cut-off points (Tab. 3). With regard to the PLR, no significant differences were found between the groups determined by the OS value.

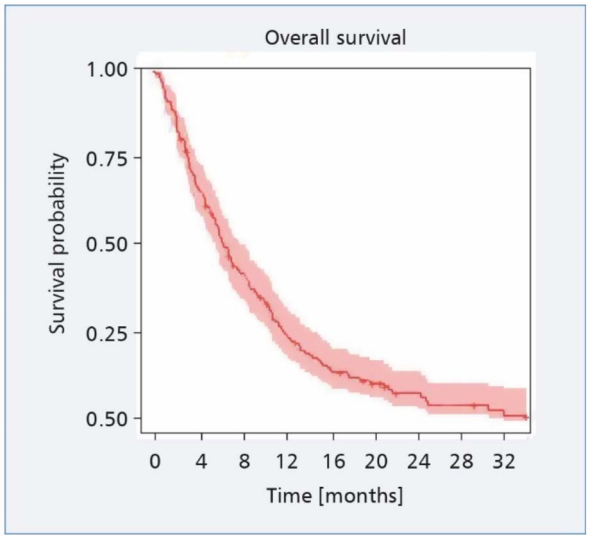

Figure 2. Overall survival in all patients

Table 2. Selected clinical and laboratory features in the subgroups with overall survival (OS) equal to or longer than the median and shorter than the median

Feature	OS ≥ median	OS < median	p value
Age at diagnosis [yrs.]			0.22
Median	71.9	70.5	
Range	(55.8–85.5)	(47.4–85.9)	
Sex			0.63
Female	48	48	
Male	31	38	
BMI at gemcitabine treatment initiation			**0.02**
Median	23.8	22.1	
Range	(15.4–34.1)	(14.9–33.6)	
ECOG PS at gemcitabine treatment initiation			0.96
0	3	4	
1	50	51	
2	23	27	
3	3	4	
Clinical stage at baseline			< **0.001**
III	38	21	
IV	33	61	
No data	8	4	
Location of metastases at gemcitabine treatment initiation			< **0.001**
No metastases	39	20	
Liver and possibly other organs	20	50	
Other organs excluding the liver	20	16	

BMI — body mass index; ECOG — Eastern Cooperative Oncology Group; PS — performance status

Table 3. Neutrophil-to-lymphocyte ratio (NLR), platelet-to--lymphocyte ratio (PLR), and systemic immune-inflammation index (SII) in the subgroups with overall survival (OS) equal to or longer than the median and shorter than the median

Feature	OS ≥ median	OS < median	p value
NLR value at gemcitabine treatment initiation			< **0.001**
< 4.5625	69	56	
≥ 4.5625	10	30	
PLR value at gemcitabine treatment initiation			0.21
< 150	46	41	
≥ 150	33	45	
SII value at gemcitabine treatment initiation			**0.01**
< 897.619	54	42	
≥ 897.619	25	44	

A significant relationship was demonstrated between the NLR, SII, and OS at the adopted cut-off points (Fig. 3, Tab. 4). Survival analysis using the Kaplan-Meier curve for all patients showed that a low SII (p = 0.0019) and NLR (p < 0.0001) were significantly associated with longer OS. Concerning the PLR index, no significance was demonstrated, although patients with a PLR value < 150 achieved longer survival than patients with a value ≥ 150.

Cox regression analysis was also performed to assess whether and how the category of each indicator affects the risk of death. It was shown that in patients with a high NLR, the risk of death was 2.5382 times higher than in patients with a low NLR. Similarly, in patients with a high SII, the risk of death was 1.6738 times higher than in patients with a low SII (Tab. 5). Similar to previous analyses regarding the PLR, the Cox regression model with this variable also turned out to be insignificant.

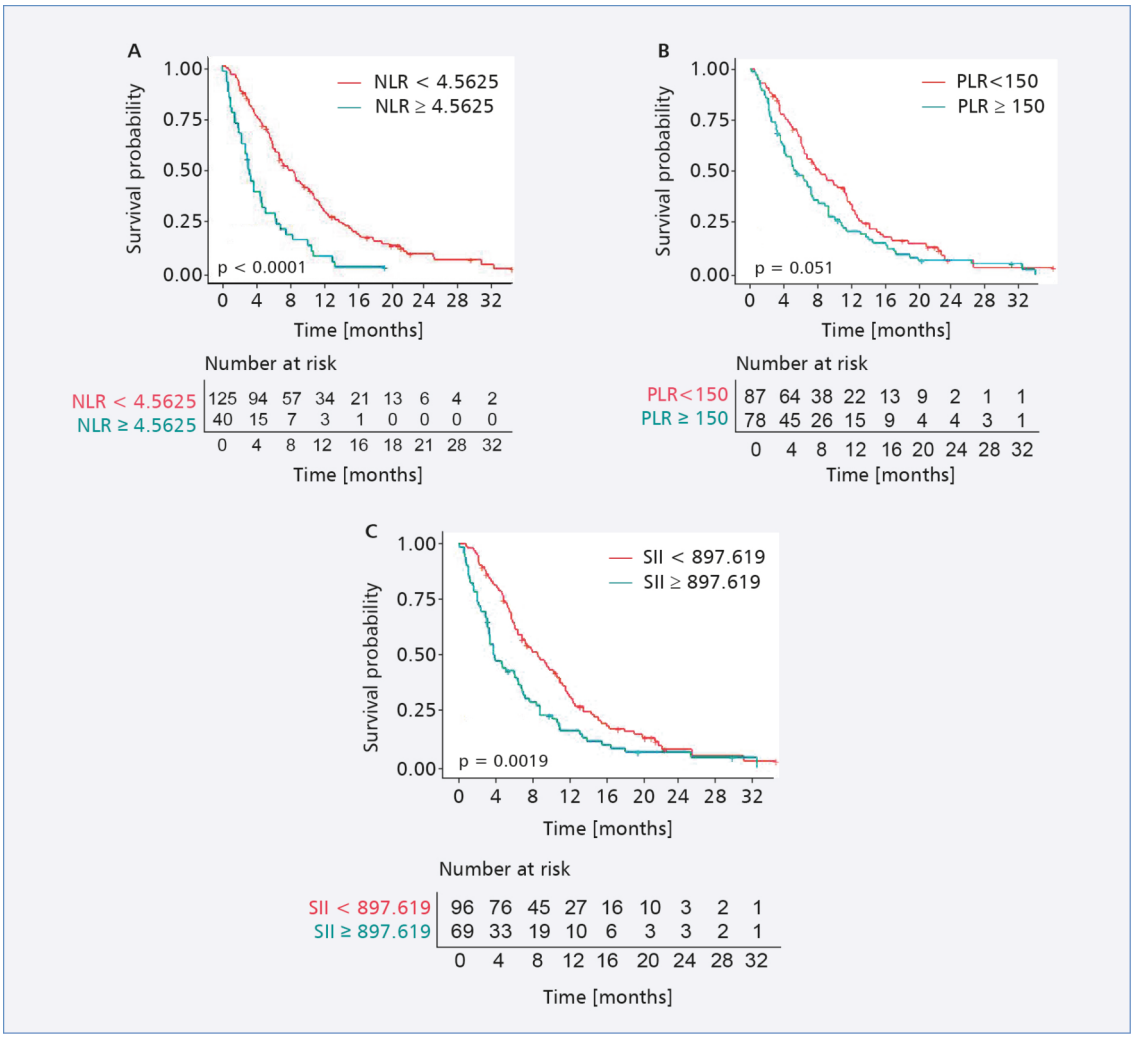

Figure 3. Overall survival according to the neutrophil-to-lymphocyte ratio (NLR) (**A**), platelet-to-lymphocyte ratio (PLR) (**B**), and systemic immune-inflammation index (SII) (**C**)

Table 4. Median overall survival (OS) for all patients and by the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII)

Index	Category	Median OS (95% CI) [months]	p value
NLR Cut-off point: 4.5625	< 4.5625 ≥ 4.5625	7.99 (6.84–10.32) 3.19 (2.43–5.19)	< **0.0001**
PLR Cut-off point: 150	< 150 ≥ 150	7.86 (6.12–11.01) 5.19 (3.85–7.20)	0.051
SII Cut-off point: 897.619	< 897.619 ≥ 897.619	8.68 (6.90–11.01) 3.94 (3.32–6.84)	**0.0019**
Total		6.48 (5.75–8.45)	

CI — confidence interval

Table 5. Univariate nonparametric Cox regression models

Index	HR	95% CI	p value
NLR Cut-off point: 4.5625	2.538	1.732–3.719	< **0.00001**
PLR Cut-off point: 150	1.38	0.9965–1.912	0.05
SII Cut-off point: 897.619	1.674	1.205–2.326	**0.003**

CI — confidence interval; HR — hazard ratio; NLR — neutrophil-to-lymphocyte ratio; PLR — platelet-to-lymphocyte ratio; SII — systemic immune-inflammation index

Discussion

Despite the introduction of new therapeutic methods in the last decade, advanced pancreatic adenocarcinoma is still associated with a poor prognosis [4–6]. The current treatment algorithm for advanced pancreatic cancer in patients with good or very good performance status includes multidrug chemotherapy regimens (FOLOFIRINOX, nab-P with gemcitabine), and in selected cohorts — olaparib (in patients with a BRCA1/2 mutation) or pembrolizumab [in patients with mismatch repair deficiency (dMMR) and high microsatellite instability (MSI-H)] [7, 8, 29]. In patients with poorer performance status, single-drug chemotherapy with gemcitabine is possible, and such treatment is still used in daily clinical practice [30].

In pancreatic adenocarcinoma, as in many other cancers, more and more data indicate a close relationship between inflammation and carcinogenesis, tumor progression, and metastasizing [31, 32]. The main prognostic impact of inflammatory markers can be attributed to the cytokine-driven immunogenic tumor microenvironment [31, 33]. In recent years, inflammatory markers and indices based on them have been frequently used to assess prognosis and predict treatment outcomes in daily clinical practice. One of the recently evaluated prognostic indicators is the SII, which is a combination of NLR and PLR, whose importance has been evaluated in many cancers [34–38].

This study aimed to assess the prognostic value of the NLR, PLR, and SII in patients with advanced pancreatic cancer treated with gemcitabine in monotherapy. For this purpose, a retrospective analysis of laboratory parameters was performed.

It was shown that low SII and NLR values are significantly associated with prolonged OS ($p = 0.0019$ and $p < 0.0001$, respectively). No such relationship was found in the case of the PLR; however, patients with PLR values < 150 had numerically longer survival than patients with values ≥ 150.

The majority of the study cohort were women (58%), patients with clinical stage IV (57%) and distant metastases predominantly in the liver (42.5%). Taking into account the clinically based model for assessing long response (LR) probability in patients treated with gemcitabine in monotherapy, which was proposed in a previous study, the majority of patients in the current cohort belonged to the group with a lower probability of LR (women, with the presence of liver metastases and with an NLR value > 8) [30].

The median OS rate in the study group was 6.48 months (range 5.75–8.45 months), and the 6-, 12-, 18-, and 24-month survival rates were 56%, 26%, 13%, and 8%, respectively. Despite the presence of the worse predictive factors defined in the above-mentioned model [30], these results were better than those obtained in the study by Burris et al. [39], comparing gemcitabine monotherapy and 5-fluorouracil, in which a median OS rate of 5.65 months and 12-month survival rate of 18% were achieved in the gemcitabine arm. It should be emphasized that the summary of these data is only indicative and does not meet the formal requirements for comparison.

Selected clinical variables were analyzed depending on the OS value (≤ or > median). In such subgroups, statistically significant differences were found in terms of the median BMI ($p = 0.02$), clinical stage at gemcitabine treatment initiation ($p < 0.001$), and location of metastases ($p < 0.001$). This means that in the analyzed group, OS equal to or longer than the median was achieved mainly by patients with a higher BMI, with lower clinical stage, and without liver metastases. It could be assumed that these features contributed to a slightly better general condition of the patients, but this was not reflected in the assessment of ECOG performance status ($p = 0.96$).

The medians of the NLR, PLR, and SII calculated on the basis of blood counts were 2.69 (range 0.5–36.65), 146.54 (range 18.53–1118.57), and 784.75 (range 79.86–10622.67), respectively.

Two patients were excluded from the analysis due to a lack of data on white blood cell percentage distribution. Additionally, based on appropriate statistical methods, cut-off values for each indicator were determined, which were 4.5625, 150, and 897.619 for the NLR, PLR, and SII, respectively. These values are similar to those adopted in the meta-analysis by Oh D et al. [40], in which high NLR and PLR values were considered to be 2.0–5.0 and 150–200, respectively. In turn, in the work of Jomrich et al. [41], the optimal cut-off values for the SII, PLR, and NLR were set at 873, 179, and 225, respectively.

Comparing subgroups of patients defined in terms of median OS and taking into account the cut-off points of individual indicators, it was shown that in the group with OS $\geq$ median, the NLR and SII values below the cut-off points were found significantly more often ($p < 0.001$ and $p = 0.01$, respectively). With regard to the PLR, this difference was only numerical and without statistical significance ($p = 0.21$). The data we obtained are consistent with other studies. The meta-analysis by Yang et al. [42] showed that a higher NLR value is associated with worse survival in pancreatic cancer patients. Subgroup analysis showed that the worsening of OS occurred mainly in patients with metastases, poor tumor differentiation, poorer performance status, high CA-19.9 and CRP levels, and low albumin levels. The meta-analysis by Oh et al. [40] confirmed the above observations regarding the NLR and demonstrated the prognostic significance of the PLR. Significant correlations have been reported between high NLR and PLR values and worsened survival [40]. Jomrich et al. [41] showed that the preoperative SII value is an independent and stronger prognostic factor for OS in patients with resected pancreatic cancer than the NLR and PLR. The authors additionally concluded that SII measurement is easy to use and cheap, and patients with elevated SIIs before surgery may benefit from anti-inflammatory treatment [41].

Conclusions

The results of our analysis show the relationship between indicators calculated on the basis of blood count parameters and treatment outcomes, which may indicate their predictive and prognostic importance. They can be a valuable addition to the clinical criteria included in prognostic models. Further research is necessary to confirm the prognostic values of the analyzed indicators to determine their possible relationships with the clinical and biological tumor characteristics and develop more comprehensive prognostic and predictive criteria for individual therapies.

Article Information and Declarations

Data availability statement

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

Ethics

The 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 primary author; concept, methods, research, data analysis, literature review, preparation of the original manuscript, data collection, final acceptance of manuscript; A.S.: statistical analysis, final acceptance of manuscript; J.S., B.Cz.-A., A.Ch.-B., M.T., K.W., W.R., M.J.: data collection, final acceptance of manuscript; P.Z.: data collection, statistical analysis, final acceptance of manuscript; B.R.: should be considered the primary author; concept, methods, research, data analysis, literature review, preparation of the original manuscript, data collection, final acceptance of manuscript.

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Conflict of interest

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

Supplementary material

None.

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KOMISJA BIOETYCZNA OPOLSKIEJ IZBY LEKARSKIEJ W OPOLU
45-054 OPOLE, ul. GRUNWALDZKA 23; Tel:0-77 4545939, Fax 774546709

UCHWAŁA Nr 347 z dnia 17 marca 2023r.

Komisja Bioetyczna Opolskiej Izby Lekarskiej w Opolu, działając na podstawie rozporządzenia Ministra Zdrowia i Opieki Społecznej z dnia 11 maja 1999 r. w sprawie szczegółowych zasad powoływania i finansowania oraz trybu działania komisji bioetycznej (Dz.U.Nr 47, poz.480), Kodeksu Etyki Lekarskiej z uwzględnieniem zasad Deklaracji Helsińskiej (Declaration of Helsinki) oraz Zasad Prawidłowego Prowadzenia Badań Klinicznych (Good Clinical Practice) i Międzynarodowej Konferencji na Rzecz Harmonizacji Wymogów Technicznych dla Rejestracji Środków Farmaceutycznych (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceutical of Human Use (ICH) – na posiedzeniu w dniu **17 marca 2023r.** zapoznała się z wnioskiem o wyrażenie opinii o projekcie badania medycznego złożonym przez kierownika tematu:

prof. dr n. med. Barbara Radecka

Zatrudniony: Opolskie Centrum Onkologii w Opolu im. prof. Tadeusza Koszarowskiego Oddział Onkologii Klinicznej
45-061 Opole, ul. Katowicka 66a

Badanie nosi tytuł:

"Systemowe leczenie chorych na zaawansowanego raka trzustki - czy nadal jest miejsce dla gemcytabiny w pierwszej linii? - doświadczenia polskich ośrodków."

do badania dołączone zostały następujące dokumenty:

1. Opis projektu
2. Karta rejestracyjna
3. Wniosek o zwolnienie z opłaty
4. Zgoda Dyrektora Opolskiego Centrum Onkologii
5. Curriculum vitae

Komisja Bioetyczna po wysłuchaniu opinii o projekcie złożonej przez dr n. med. Jacek Miarka **postanowiła dopuścić projekt badania medycznego do realizacji.**

...ODNICZĄCY
Komisji Bioetycznej
Opolskiej Izby Lekarskiej
w Opolu
Dr n. med. Jacek Miarka

KOMISJA BIOETYCZNA
Opolskiej Izby Lekarskiej
w Opolu
45-054 Opole, ul. Grunwaldzka 23
tel. 454-59-39; fax 454-67-09

LISTA OBECNOŚCI

członków Komisji Bioetycznej Opolskiej Izby Lekarskiej w Opolu

na posiedzeniu w dniu **17 marca 2023r.**

Nazwisko i imię	Zawód	Miejsce pracy	podpis
Przewodniczący 1. dr n. med. Miarka Jacek	Lekarz kardiolog	SP ZOZ W Nysie	
2. dr n. med. Wojtyłko Aleksander	Lekarz chirurg dziecięcy	NZOZ AW Med. w Opolu	
3. dr n. med. Feusette Piotr	Lekarz kardiolog	Uniwersytecki Szpital Kliniczny w Opolu	
4. dr n. med. Kossowska Agnieszka	Psycholog	Pracownia Badań Psychologicznych DIAGNOZIS	
5. mgr Pospiech Anna	Prawnik	Urząd Miasta Opola	
6. mgr Szczegielniak Barbara	Farmaceuta	Apteka " Przyjazna" Opole	
7. Prof. dr hab. Morciniec Piotr	Teolog	Uniwersytet Opolski	
8. doktor hab. n. med. Czarnik Tomasz	Lekarz anestezjolog	Uniwersytecki Szpital Kliniczny w Opolu	
9. lek. Żurawel Robert	Lekarz chirurg ogólny, naczyniowy	Uniwersytecki Szpital Kliniczny w Opolu	

dr hab. n. med. Barbara Radecka

(tytuł zawodowy, imię i nazwisko)

Opole, dnia 15 listopada 2023 r.

OŚWIADCZENIE

Jako współautor pracy pt. ***Quality of life of patients with advanced pancreatic cancer (Jakość życia chorych na zaawansowanego raka trzustki)*** oświadczam, iż mój merytoryczny wkład jako senior autora w przygotowanie pracy oraz jej przedstawienie w formie publikacji polegał na współtworzeniu koncepcji, przeglądzie literatury, współtworzeniu manuskryptu oraz ostatecznej akceptacji artykułu.

Jednocześnie wyrażam zgodę na przedłożenie ww. pracy przez lek. Ireneusza Raczyńskiego jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

Barbara Radecka

.....

(podpis współautora)

dr hab. n. med. Barbara Radecka

(tytuł zawodowy, imię i nazwisko)

Opole, dnia 15 listopada 2023 r.

OŚWIADCZENIE

Jako współautor pracy pt. ***Advanced pancreatic cancer: diagnosis and systemic treatment evolution over the last decades (Zaawansowany rak trzustki — ewolucja w zakresie rozpoznawania i leczenia systemowego chorych w ostatnich dziesięcioleciach)*** oświadczam, iż mój merytoryczny wkład jako senior autora w przygotowanie pracy oraz jej przedstawienie w formie publikacji polegał na współtworzeniu koncepcji, przeglądzie literatury, współtworzeniu manuskryptu oraz ostatecznej akceptacji artykułu.

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Barbara Radecka

.....

(podpis współautora)

Warszawa, dnia 22.11.2023

dr hab. n. med. Joanna Didkowska

(tytuł zawodowy, imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. ***Advanced pancreatic cancer:diagnosis and systemic treatment evolution over the last decades (Zaawansowany rak trzustki — ewolucja w zakresie rozpoznawania i leczenia systemowego chorych w ostatnich dziesięcioleciach)*** oświadczam, iż mój wkład merytoryczny w przygotowanie pracy oraz jej przedstawienie w formie publikacji polegał na stworzeniu koncepcji części epidemiologicznej, przeglądzie literatury, współtworzeniu manuskryptu oraz ostatecznej akceptacji artykułu.

Jednocześnie wyrażam zgodę na przedłożenie ww. pracy przez lek. Ireneusza Raczyńskiego jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

Didkowska

Signed by / Podpisano przez:
Joanna Aleksandra Didkowska
Date / Data: 2023-11-22 09:55

.....
Narodowy Instytut Onkologii

(podpis współautora)

dr hab. n. med. Barbara Radecka

(tytuł zawodowy, imię i nazwisko)

Opole, dnia 15 listopada 2023 r.

OŚWIADCZENIE

Jako współautor pracy pt. ***Survival of pancreatic cancer patients treated with nab-paclitaxel (nab-P) in clinical practice: Analysis of National Health Fund data (Przeżycie chorych na raka trzustki leczonych nab-paklitakselem w warunkach praktyki klinicznej: analiza danych Narodowego Funduszu Zdrowia)*** oświadczam, iż mój merytoryczny wkład w przygotowanie pracy oraz jej przedstawienie w formie publikacji polegał na współtworzeniu koncepcji, analizie danych, przeglądzie literatury, współtworzeniu manuskryptu oraz ostatecznej akceptacji artykułu.

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Barbara Radecka

.....

(podpis współautora)

Warszawa, dnia 14/11/2023

Prof. dr hab. n. med. Maciej Krzakowski

(tytuł zawodowy, imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. ***Survival of pancreatic cancer patients treated with nab-paclitaxel (nab-P) in clinical practice: Analysis of National Health Fund data (Przeżycie chorych na raka trzustki leczonych nab-paklitakselem w warunkach praktyki klinicznej: analiza danych Narodowego Funduszu Zdrowia)*** oświadczam, iż mój wkład merytoryczny jako senior autora w przygotowanie pracy oraz jej przedstawienie w formie publikacji polegał na tworzeniu koncepcji, współtworzeniu manuskryptu oraz ostatecznej akceptacji artykułu.

Jednocześnie wyrażam zgodę na przedłożenie ww. pracy przez lek. Ireneusza Raczyńskiego jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

Prof. dr hab. med. Maciej Krzakowski
specjalista
onkologii klinicznej i radioterapii
8564781

.....

(podpis współautora)

dr hab. n. med. Barbara Radecka

(tytuł zawodowy, imię i nazwisko)

Opole, dnia 15 listopada 2023 r.

OŚWIADCZENIE

Jako współautor pracy pt. ***Systemic treatment of patients with advanced pancreatic cancer — is there still a place for gemcitabine in the first line? Experiences of Polish centers (Systemowe leczenie chorych na zaawansowanego raka trzustki — czy nadal jest miejsce dla gemcytabiny w pierwszej linii? Doświadczenia polskich ośrodków)*** oświadczam, iż mój merytoryczny wkład jako senior autora w przygotowanie, przeprowadzenie badań oraz przedstawienie w formie publikacji polegał na współtworzeniu koncepcji i metodyki badania, przeglądzie literatury, współtworzeniu manuskryptu oraz ostatecznej akceptacji artykułu.

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Barbara Radecka

.....

(podpis współautora)

mgr biotech. Patryk Zając

(tytuł zawodowy, imię i nazwisko)

Opole, dnia 15 listopada 2023 r.

OŚWIADCZENIE

Jako współautor pracy pt. ***Systemic treatment of patients with advanced pancreatic cancer — is there still a place for gemcitabine in the first line? Experiences of Polish centers (Systemowe leczenie chorych na zaawansowanego raka trzustki — czy nadal jest miejsce dla gemcytabiny w pierwszej linii? Doświadczenia polskich ośrodków)*** oświadczam, iż mój wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie w formie publikacji to: zbieranie danych, analiza statystyczna oraz zatwierdzenie ostatecznej wersji artykułu.

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Patryk Zając

.....

(podpis współautora)

Kraków, dnia 13.11.2023

Dr n. med. Joanna Streb

(tytuł zawodowy, imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. ***Systemic treatment of patients with advanced pancreatic cancer — is there still a place for gemcitabine in the first line? Experiences of Polish centers (Systemowe leczenie chorych na zaawansowanego raka trzustki — czy nadal jest miejsce dla gemcytabiny w I linii? Doświadczenia polskich ośrodków)*** oświadczam, iż mój wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie w formie publikacji to: zbieranie danych oraz zatwierdzenie ostatecznej wersji artykułu.

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dr n. med. JOANNA STREB
specjalista onkologii klinicznej
specjalista medycyny rodzinnej
5172961

.....

(podpis współautora)

Białystok, dnia 13.11.23

Dr n. med. Bogumiła Czartoryska-Arłukowicz

(tytuł zawodowy, imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. ***Systemic treatment of patients with advanced pancreatic cancer — is there still a place for gemcitabine in the first line? Experiences of Polish centers (Systemowe leczenie chorych na zaawansowanego raka trzustki — czy nadal jest miejsce dla gemcytabiny w I linii? Doświadczenia polskich ośrodków)*** oświadczam, iż mój wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie w formie publikacji to: zbieranie danych oraz zatwierdzenie ostatecznej wersji artykułu.

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Bogumiła Czartoryska-Arłukowicz
Dr n. med.
specjalista onkolog kliniczny
chorób wewnętrznych

(podpis współautora)

Szczecin , dnia 09. 11. 2015

Lek. Aleksandra Chruściana-Bołtuć

(tytuł zawodowy, imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. ***Systemic treatment of patients with advanced pancreatic cancer — is there still a place for gemcitabine in the first line? Experiences of Polish centers (Systemowe leczenie chorych na zaawansowanego raka trzustki — czy nadal jest miejsce dla gemcytabiny w pierwszej linii? Doświadczenia polskich ośrodków)*** oświadczam, iż mój wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie w formie publikacji to: zbieranie danych oraz zatwierdzenie ostatecznej wersji artykułu.

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A. Chruściana-Bołtuć

(podpis współautora)

Szczecin , dnia 13.11.2023

Lek. Małgorzata Talerczyk

OŚWIADCZENIE

Jako współautor pracy pt. ***Systemic treatment of patients with advanced pancreatic cancer — is there still a place for gemcitabine in the first line? Experiences of Polish centers (Systemowe leczenie chorych na zaawansowanego raka trzustki — czy nadal jest miejsce dla gemcytabiny w I linii? Doświadczenia polskich ośrodków)*** oświadczam, iż mój wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie w formie publikacji to: zbieranie danych oraz zatwierdzenie ostatecznej wersji artykułu.

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Małgorzata Talerczyk

Małgorzata M. Talerczyk
lekarz chorób wewnętrznych
specjalista onkologii klinicznej
2040845

Gdańsk, dnia 18.11.2023

Lek. Katarzyna Wierzbicka

(tytuł zawodowy, imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. ***Systemic treatment of patients with advanced pancreatic cancer — is there still a place for gemcitabine in the first line? Experiences of Polish centers (Systemowe leczenie chorych na zaawansowanego raka trzustki — czy nadal jest miejsce dla gemcytabiny w I linii? Doświadczenia polskich ośrodków)*** oświadczam, iż mój wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie w formie publikacji to: zbieranie danych oraz zatwierdzenie ostatecznej wersji artykułu.

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K. Wierzbicka

(podpis współautora)

dr inż. Agnieszka Siedlaczek

(tytuł zawodowy, imię i nazwisko)

Opole, dnia 15 listopada 2023 r.

OŚWIADCZENIE

Jako współautor pracy pt. ***Systemic treatment of patients with advanced pancreatic cancer — is there still a place for gemcitabine in the first line? Experiences of Polish centers (Systemowe leczenie chorych na zaawansowanego raka trzustki — czy nadal jest miejsce dla gemcytabiny w pierwszej linii? Doświadczenia polskich ośrodków)*** oświadczam, iż mój wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie w formie publikacji to: analiza statystyczna oraz zatwierdzenie ostatecznej wersji artykułu.

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Agnieszka Siedlaczek

.....

(podpis współautora)

Lek. Weronika Radecka

(tytuł zawodowy, imię i nazwisko)

Opole, dnia 15 listopada 2023 r.

OŚWIADCZENIE

Jako współautor pracy pt. ***Systemic treatment of patients with advanced pancreatic cancer — is there still a place for gemcitabine in the first line? Experiences of Polish centers (Systemowe leczenie chorych na zaawansowanego raka trzustki — czy nadal jest miejsce dla gemcytabiny w pierwszej linii? Doświadczenia polskich ośrodków)*** oświadczam, iż mój wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie w formie publikacji to: zbieranie danych oraz zatwierdzenie ostatecznej wersji artykułu.

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Weronika Radecka

(podpis współautora)

Kraków, dnia 10.11.2023

Lek. Michał Jurczyk

(tytuł zawodowy, imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. ***Systemic treatment of patients with advanced pancreatic cancer — is there still a place for gemcitabine in the first line? Experiences of Polish centers (Systemowe leczenie chorych na zaawansowanego raka trzustki — czy nadal jest miejsce dla gemcytabiny w I linii? Doświadczenia polskich ośrodków)*** oświadczam, iż mój wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie w formie publikacji to: zbieranie danych oraz zatwierdzenie ostatecznej wersji artykułu.

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Michał Jurczyk

(podpis współautora)

Michał Jurczyk
LEKARZ
3749786

dr hab. n. med. Barbara Radecka

(tytuł zawodowy, imię i nazwisko)

Opole, dnia 15 listopada 2023 r.

OŚWIADCZENIE

Jako współautor pracy pt. ***NLR, PLR, SII as clinical predictive and prognostic markers in patients with advanced pancreatic cancer receiving gemcitabine monotherapy (NLR, PLR, SII jako kliniczne markery predykcyjne i prognostyczne u chorych na zaawansowanego raka trzustki poddawanych monoterapii gemcytabiną)*** oświadczam, iż mój merytoryczny wkład jako senior autora w przygotowanie, przeprowadzenie badań oraz przedstawienie w formie publikacji polegał na współtworzeniu koncepcji i metodyki badania, przeglądzie literatury, współtworzeniu manuskryptu oraz ostatecznej akceptacji artykułu.

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Barbara Radecka

(podpis współautora)

dr inż. Agnieszka Siedlaczek

(tytuł zawodowy, imię i nazwisko)

Opole, dnia 15 listopada 2023 r.

OŚWIADCZENIE

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Jednocześnie wyrażam zgodę na przedłożenie ww. pracy przez lek. Ireneusza Raczyńskiego jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

Agnieszka Siedlaczek

(podpis współautora)

Kraków, dnia 13.11.2023

Dr n. med. Joanna Streb

(tytuł zawodowy, imię i nazwisko)

OŚWIADCZENIE

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specjalista onkologii klinicznej
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(podpis współautora)

mgr biotech. Patryk Zając

(tytuł zawodowy, imię i nazwisko)

Opole, dnia 15 listopada 2023 r.

OŚWIADCZENIE

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(podpis współautora)

Białystok, dnia 13.11.23

Dr n. med. Bogumiła Czartoryska-Arłukowicz

(tytuł zawodowy, imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. ***NLR, PLR, SII as clinical predictive and prognostic markers in patients with advanced pancreatic cancer receiving gemcitabine monotherapy (NLR, PLR, SII jako kliniczne markery predykcyjne i prognostyczne u chorych na zaawansowanego raka trzustki poddawanych monoterapii gemcytabiną)*** oświadczam, iż mój wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie w formie publikacji to: zbieranie danych oraz zatwierdzenie ostatecznej wersji artykułu.

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Szczecin , dnia 09. 11. 2023

Lek. Aleksandra Chruściana-Bołtuć

(tytuł zawodowy, imię i nazwisko)

OŚWIADCZENIE

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A. Chruściana-Bołtuć

(podpis współautora)

Szczecin , dnia 13.11.2023

Lek. med. Małgorzata Talerczyk

OŚWIADCZENIE

Jako współautor pracy pt. ***NLR, PLR, SII as clinical predictive and prognostic markers in patients with advanced pancreatic cancer receiving gemcitabine monotherapy (NLR, PLR, SII jako kliniczne markery predykcyjne i prognostyczne u chorych na zaawansowanego raka trzustki poddawanych monoterapii gemcytabiną)*** oświadczam, iż mój wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie w formie publikacji to: zbieranie danych oraz zatwierdzenie ostatecznej wersji artykułu.

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Małgorzata M. Talerczyk
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Gdańsk, dnia 18. 11. 2023

Lek. Katarzyna Wierzbicka

(tytuł zawodowy, imię i nazwisko)

OŚWIADCZENIE

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K. Wierzbicka

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Lek. Weronika Radecka

(tytuł zawodowy, imię i nazwisko)

Opole, dnia 15 listopada 2023 r.

OŚWIADCZENIE

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Weronika Radecka

(podpis współautora)

Kraków, dnia 10.11.2023

Lek. Michał Jurczyk

(tytuł zawodowy, imię i nazwisko)

OŚWIADCZENIE

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