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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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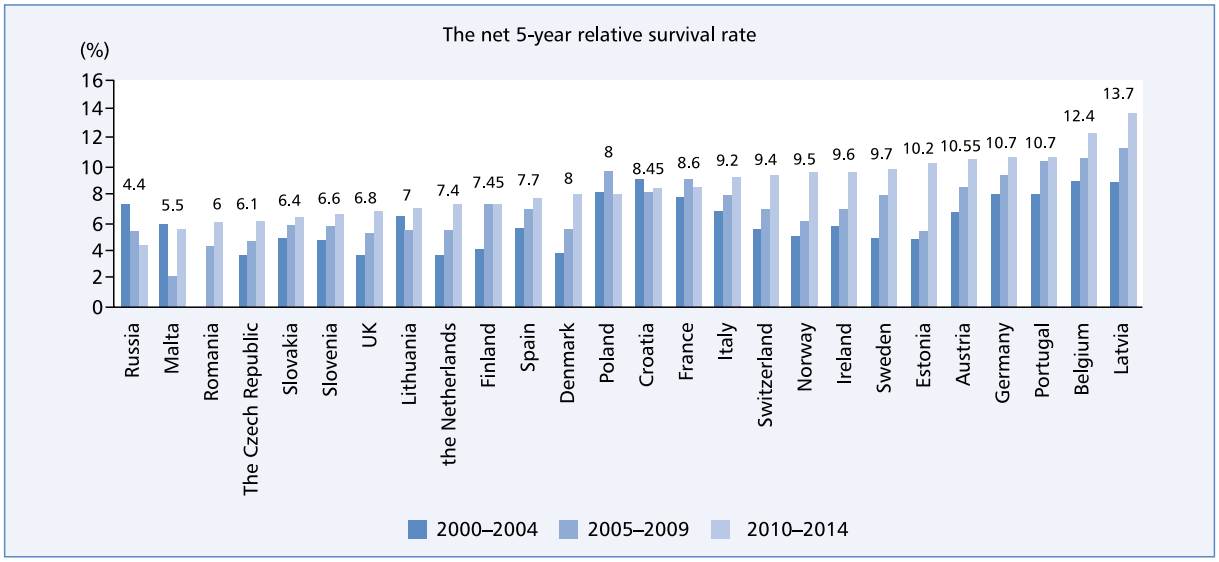

Figure 1. The net 5-year relative survival rates in Europe [10]

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

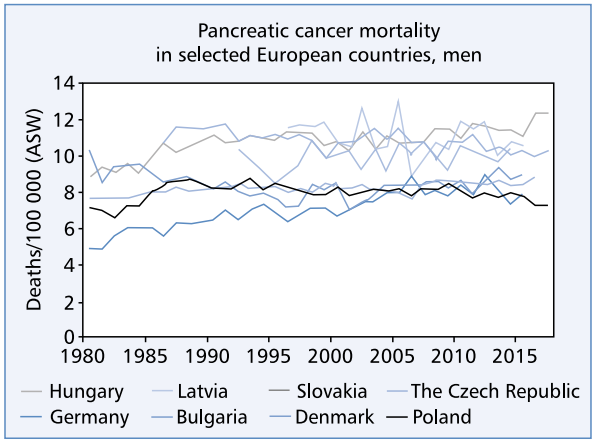

Figure 2. Pancreatic cancer mortality — men [11]

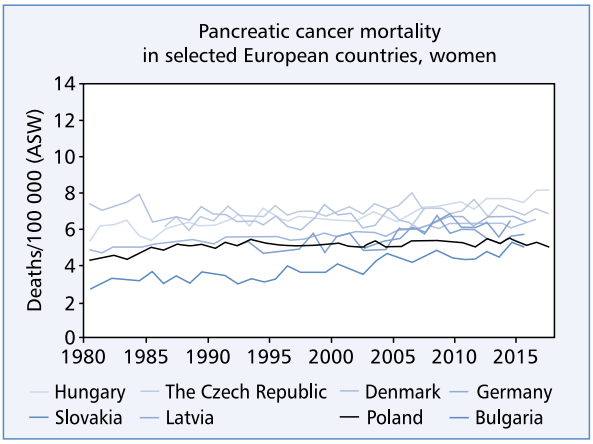

Figure 3. Pancreatic cancer mortality — women [11]

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].

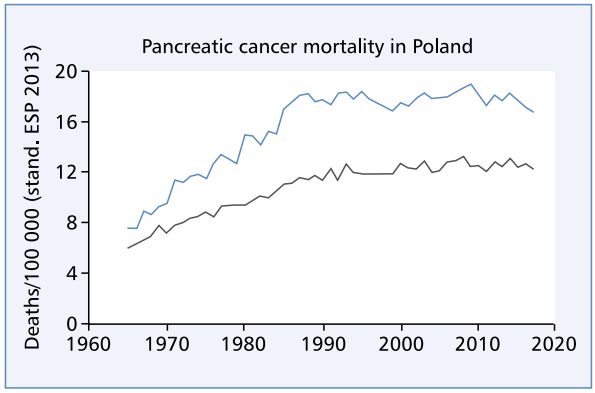

Figure 4. Pancreatic cancer mortality in Poland 1965–2017 [11]

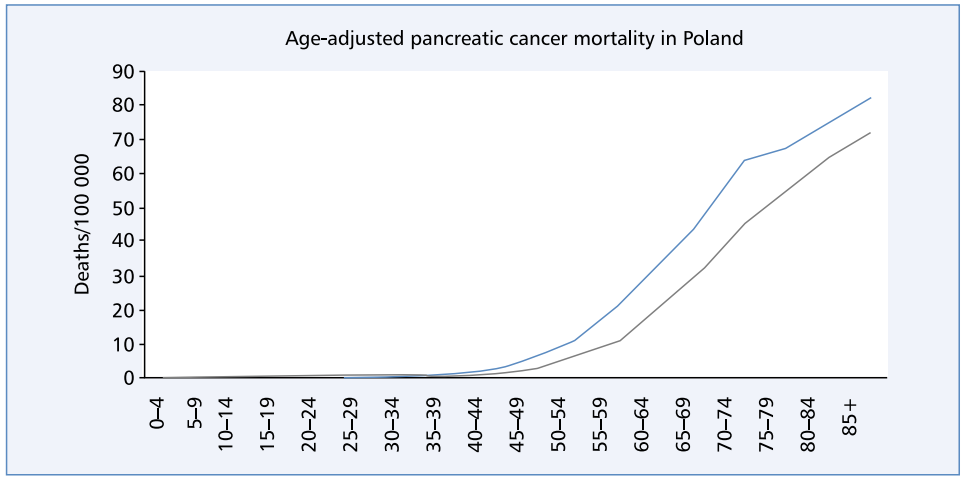

Figure 5. Age-adjusted pancreatic cancer mortality in Poland 2015–2017 [11]

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.

References

1. SEER cancer statistics. http://seer.cancer.gov/statfacts/html/pancreas (1.02.2021).
2. Ducreux M, Cuhna ASa, Caramella C, et al. ESMO Guidelines Committee. Cancer of the pancreas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015; 26 Suppl 5: v56–v68, doi: 10.1093/annonc/mdv295, indexed in Pubmed: 26314780.
3. Carrato A, Falcone A, Ducreux M, et al. A Systematic Review of the Burden of Pancreatic Cancer in Europe: Real-World Impact on Survival, Quality of Life and Costs. J Gastrointest Cancer. 2015; 46(3): 201–211, doi: 10.1007/s12029-015-9724-1, indexed in Pubmed: 25972062.
4. Mayo SC, Nathan H, Cameron JL, et al. Conditional survival in patients with pancreatic ductal adenocarcinoma resected with curative intent. Cancer. 2012; 118(10): 2674–2681, doi: 10.1002/cncr.26553, indexed in Pubmed: 21935914.
5. Conroy T, Desseigne F, Ychou M, et al. Groupe Tumeurs Digestives of Unicancer, PRODIGE Intergroup. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med. 2011; 364(19): 1817–1825, doi: 10.1056/NEJMoa1011923, indexed in Pubmed: 21561347.
6. Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med. 2013; 369(18): 1691–1703, doi: 10.1056/NEJMoa1304369, indexed in Pubmed: 24131140.
7. Mackay TM, Smits FJ, Latenstein AEJ, et al. Dutch Pancreatic Cancer Group. Impact of nationwide enhanced implementation of best practices in pancreatic cancer care (PACAP-1): a multicenter stepped-wedge cluster randomized controlled trial. Trials. 2020; 21(1): 334, doi: 10.1186/s13063-020-4180-z, indexed in Pubmed: 32299515.
8. Chiorean EG, Von Hoff DD, Tabernero J, et al. Second-line therapy after nab-paclitaxel plus gemcitabine or after gemcitabine for patients with metastatic pancreatic cancer. Br J Cancer. 2016; 115(2): 188–194, doi: 10.1038/bjc.2016.185, indexed in Pubmed: 27351217.
9. Yalcin S, Dane F, Oksuzoglu B, et al. Quality of life study of patients with unresectable locally advanced or metastatic pancreatic adenocarcinoma treated with gemcitabine+nab-paclitaxel versus gemcitabine alone: AX-PANC-SY001, a randomized phase-2 study. BMC Cancer. 2020; 20(1): 259, doi: 10.1186/s12885-020-06758-9, indexed in Pubmed: 32228512.

10. Allemani C, Matsuda T, Carlo VDi, et al. Global surveillance of trends in cancer survival 2000–14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. The Lancet. 2018; 391(10125): 1023–1075, doi: 10.1016/s0140-6736(17)33326-3.
11. Didkowska J, Wojciechowska U, Czaderny K, et al. Nowotwory złośliwe w Polsce w 2017 r. Krajowy Rejestr Nowotworów. MZ 2019. http://onkologia.org.pl/wp-content/uploads/Nowotwory_2017 (1.02.2021).
12. McGuigan A, Kelly P, Turkington RC, et al. Pancreatic cancer: A review of clinical diagnosis, epidemiology, treatment and outcomes. World J Gastroenterol. 2018; 24(43): 4846–4861, doi: 10.3748/wjg.v24.i43.4846, indexed in Pubmed: 30487695.
13. Scheithauer W, Ramanathan RK, Moore M, et al. Dose modification and efficacy of nab-paclitaxel plus gemcitabine vs. gemcitabine for patients with metastatic pancreatic cancer: phase III MPACT trial. J Gastrointest Oncol. 2016; 7(3): 469–478, doi: 10.21037/jgo.2016.01.03, indexed in Pubmed: 27284481.
14. Kristensen A, Vagnildhaug OM, Grønberg BH, et al. Does chemotherapy improve health-related quality of life in advanced pancreatic cancer? A systematic review. Crit Rev Oncol Hematol. 2016; 99: 286–298, doi: 10.1016/j.critrevonc.2016.01.006, indexed in Pubmed: 26819138.
15. Müller-Nordhorn J, Roll S, Böhmig M, et al. Health-related quality of life in patients with pancreatic cancer. Digestion. 2006; 74(2): 118–125, doi: 10.1159/000098177, indexed in Pubmed: 17191029.
16. Gourgou-Bourgade S, Bascoul-Mollevi C, Desseigne F, et al. Impact of FOLFIRINOX compared with gemcitabine on quality of life in patients with metastatic pancreatic cancer: results from the PRODIGE 4/ACCORD 11 randomized trial. J Clin Oncol. 2013; 31(1): 23–29, doi: 10.1200/JCO.2012.44.4869, indexed in Pubmed: 23213101.
17. Kamisawa T, Wood L, Itoi T, et al. Pancreatic cancer. The Lancet. 2016; 388(10039): 73–85, doi: 10.1016/s0140-6736(16)00141-0.
18. Wolfgang CL, Herman JM, Laheru DA, et al. Recent progress in pancreatic cancer. CA Cancer J Clin. 2013; 63(5): 318–348, doi: 10.3322/caac.21190, indexed in Pubmed: 23856911.
19. Sharma C, Eltawil KM, Renfrew PD, et al. Advances in diagnosis, treatment and palliation of pancreatic carcinoma: 1990-2010. World J Gastroenterol. 2011; 17(7): 867–897, doi: 10.3748/wjg.v17.i7.867, indexed in Pubmed: 21412497.
20. Auerbach M, Wampler GL, Lokich JJ, et al. Chemotherapy for pancreatic carcinoma. Cancer. 1996; 78(3 Suppl): 654–663, doi: 10.1002/(SICI)1097-0142(19960801)78:3<654::AID-CNCR46>3.0.CO;2-V, indexed in Pubmed: 8681304.
21. Pasetto LM, Jirillo A, Stefani M, et al. Old and new drugs in systemic therapy of pancreatic cancer. Crit Rev Oncol Hematol. 2004; 49(2): 135–151, doi: 10.1016/S1040-8428(03)00170-7, indexed in Pubmed: 15012974.
22. Burris HA, Moore MJ, Andersen J, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol. 1997; 15(6): 2403–2413, doi: 10.1200/JCO.1997.15.6.2403, indexed in Pubmed: 9196156.
23. Moore MJ, Goldstein D, Hamm J, et al. National Cancer Institute of Canada Clinical Trials Group. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol. 2007; 25(15): 1960–1966, doi: 10.1200/JCO.2006.07.9525, indexed in Pubmed: 17452677.
24. Cunningham D, Chau I, Stocken DD, et al. Phase III randomized comparison of gemcitabine versus gemcitabine plus capecitabine in patients with advanced pancreatic cancer. J Clin Oncol. 2009; 27(33): 5513–5518, doi: 10.1200/JCO.2009.24.2446, indexed in Pubmed: 19858379.
25. Hegewisch-Becker S, Aldaoud A, Wolf T, et al. TPK-Group (Tumour Registry Pancreatic Cancer). Results from the prospective German TPK clinical cohort study: Treatment algorithms and survival of 1,174 patients with locally advanced, inoperable, or metastatic pancreatic ductal adenocarcinoma. Int J Cancer. 2019; 144(5): 981–990, doi: 10.1002/ijc.31751, indexed in Pubmed: 30006989.
26. ESMO Guidelines Committee. Ann Oncol. 2017; 28(suppl 4): iv157. http://www.esmo.org/Guidelines/Gastrointestinal-Cancers/Cancer-of--the-Pancreas/eUpdate-Treatment-Recommendations (1.02.2021).
27. https://www.nccn.org/. https://www.nccn. (1.02.2021).
28. Oettle H, Riess H, Stieler JM, et al. Second-line oxaliplatin, folinic acid, and fluorouracil versus folinic acid and fluorouracil alone for gemcitabine-refractory pancreatic cancer: outcomes from the CONKO-003 trial. J Clin Oncol. 2014; 32(23): 2423–2429, doi: 10.1200/JCO.2013.53.6995, indexed in Pubmed: 24982456.
29. Gill S, Ko YJ, Cripps C, et al. PANCREOX: A Randomized Phase III Study of Fluorouracil/Leucovorin With or Without Oxaliplatin for Second-Line Advanced Pancreatic Cancer in Patients Who Have Received Gemcitabine-Based Chemotherapy. J Clin Oncol. 2016; 34(32): 3914–3920, doi: 10.1200/JCO.2016.68.5776, indexed in Pubmed: 27621395.
30. Wang-Gillam A, Li CP, Bodoky G, et al. NAPOLI-1 Study Group. Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): a global, randomised, open-label, phase 3 trial. Lancet. 2016; 387(10018): 545–557, doi: 10.1016/S0140-6736(15)00986-1, indexed in Pubmed: 26615328.
31. Giordano G, Febbraro A, Milella M, et al. Impact of second-line treatment (2L T) in advanced pancreatic cancer (APDAC) patients (pts) receiving first line Nab-Paclitaxel (nab-P) + Gemcitabine (G): An Italian multicentre real life experience. Journal of Clinical Oncology. 2016; 34(15_suppl): 4124–4124, doi: 10.1200/jco.2016.34.15_suppl.4124.
32. Golan T, Hammel P, Reni M, et al. Maintenance Olaparib for Germline -Mutated Metastatic Pancreatic Cancer. N Engl J Med. 2019; 381(4): 317–327, doi: 10.1056/NEJMoa1903387, indexed in Pubmed: 31157963.
33. Fink J. Genomic Testing Makes Inroads After First-Line Therapy in Metastatic Pancreatic Cancer. Targeted Therapies in Oncology. 2020; 9: 72.
34. Drilon A, Laetsch TW, Kummar S, et al. Efficacy of Larotrectinib in TRK Fusion-Positive Cancers in Adults and Children. N Engl J Med. 2018; 378(8): 731–739, doi: 10.1056/NEJMoa1714448, indexed in Pubmed: 29466156.
35. Doebele R, Paz-Ares L, Farago A, et al. Abstract CT131: Entrectinib inNTRK-fusion positive (NTRK-FP) non-small cell lung cancer (NSCLC): Integrated analysis of patients enrolled in three trials (STARTRK-2, STARTRK-1 and ALKA-372-001). Clinical Trials. 2019, doi: 10.1158/1538-7445.am2019-ct131.
36. Marabelle A, Le DT, Ascierto PA, et al. Efficacy of Pembrolizumab in Patients With Noncolorectal High Microsatellite Instability/Mismatch Repair-Deficient Cancer: Results From the Phase II KEYNOTE-158 Study. J Clin Oncol. 2020; 38(1): 1–10, doi: 10.1200/JCO.19.02105, indexed in Pubmed: 31682550.
37. Poschke I, Faryna M, Bergmann F, et al. Identification of a tumor-reactive T-cell repertoire in the immune infiltrate of patients with resectable pancreatic ductal adenocarcinoma. Oncoimmunology. 2016; 5(12): e1240859, doi: 10.1080/2162402X.2016.1240859, indexed in Pubmed: 28123878.