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REVIEW ARTICLE

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Pancreatic adenocarcinoma — current trends in diagnosis and treatment

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ABSTRACT

Pancreatic cancer, despite significant medical advances, is still a significant clinical problem. This article focuses on discussing risk factors, diagnostic methods, and treatment options. These elements are crucial in making a prompt diagnosis and initiating treatment. On average, a physician in primary care sees a patient with undiagnosed pancreatic cancer once every few years. Knowing the underlying symptoms and referring the patient to an appropriate center can significantly increase survival. Diagnostic methods include physical examination, numerous imaging techniques, and determination of tumor markers in serum. Surgical treatment combined with adjuvant chemotherapy is the only chance of cure for pancreatic cancer patients qualified for surgery. However, most patients experience tumor recurrence. When a tumor recurs, treatment for these patients and patients with unresectable disease is palliative chemotherapy. Numerous studies are currently underway to improve diagnostic and treatment methods.

Key words: chemotherapy, palliative treatment, pancreatic cancer, new treatment trends

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Introduction

Pancreatic cancer is one of the most aggressive cancers with a poor prognosis. Symptoms in patients with pancreatic cancer often appear when the cancer is already advanced. There is no universal screening program to detect pancreatic cancer patients quickly. Only surgical resection offers a chance of a cure; however, the eligible patients are those with cancer localized in the pancreas and patients with resectable tumors and locoregional changes.

Epidemiology

Malignant neoplasm of the pancreas ranks 14th in the classification of tumors due to the incidence of malignant neoplasms [1]. According to a 2018 study, it is the seventh cause of cancer deaths worldwide [2]. The tumor is responsible for more than 200 000 deaths annually worldwide. The 5-year survival rate for people with pancreatic cancer remains at just 6% [3]. Pancreatic cancer is mainly diagnosed in people over the age of 55, and most commonly around the age of 75 [4]. The incidence for both sexes increases with age [5]. Men are more often affected [1]. Studies show that the incidence of pancreatic cancer is higher in developed countries compared to developing countries [6]. There is a steady increase in the incidence, which could make pancreatic cancer the third leading cause of cancer deaths in the European Union [7].

Histological types

The most common histological type of malignant tumor of the pancreas is adenocarcinoma arising from the epithelial cells lining the pancreatic ducts. It ac-

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Table 1. Tumor–node metastasis–metastases (TNM) clinical classification of pancreatic cancer according to the 8th edition of the American Joint Committee on Cancer (AJCC) [8]

T (primary tumor)	
Tx	Primary tumor cannot be evaluated
T0	No evidence of primary tumor
Tis	Pre-invasive cancer (carcinoma in situ; includes PanIN 3 classification)
T1	Tumor size less than 2 cm
T1a	Tumor size less than 0.5 cm
T1b	Tumor size of more than 0.5 cm in diameter, but less than 1 cm
T1c	Tumor size more than 1 cm in diameter, but less than 2 cm
T2	Tumor size more than 2 cm in diameter, but less than 4 cm
T3	Tumor size greater than 4 cm in diameter
T4	Tumor infiltrates the visceral trunk, superior mesenteric artery, and/or common hepatic artery
N (presence of lymph node metastasis)	
Nx	Regional LNs cannot be assessed
N0	No metastasis to regional LNs
N1	Metastasis in 1 to 3 regional LNs
N2	Metastasis in 4 or more regional LNs
M (presence of distant metastases)	
M0	No distant metastases
M1	Distant metastasis

Table 2. Clinical stages of pancreatic cancer according to the 8th edition of the American Joint Committee on Cancer (AJCC) [8]

0	Tis, N0, M0
IA	T1, N0, M0
IB	T2, N0, M0
IIA	T3, N0, M0
IIB	T1, N1, M0 T2, N1, M0 T3, N1, M0
III	T4, any classification N, M0
IV	Any classification T and N, M1

counts for 80% of all tumors and is usually located in the head, less commonly in the body, and most rarely in the tail of the pancreas. Pancreatic ductal adenocarcinomas usually arise from non-invasive precursor lesions of pancreatic intraepithelial neoplasia. Less commonly, carcinomas develop from intraductal papillary mucinous neoplasms or mucinous cystic neoplasms. Other types are lobular carcinoma and pseudopapillary carcinoma. This article focuses mainly on ductal adenocarcinoma because of its prevalence.

Classification

The classification is presented in Tables 1 and 2 [8].

Risk factors

Risk factors for the disease include smoking, chronic pancreatitis, obesity, diabetes mellitus, age over 70, blood type other than 0, alcohol consumption, diet rich in red meat and poor in fresh fruits, vegetables, and folic acid, *Helicobacter pylori* infection, genetic predisposition, exposure to chlorobenzene, nickel, or chromium.

Cigarette smoking is the most important modifiable risk factor for pancreatic cancer. The risk increases with both the duration of smoking and the number of cigarettes smoked. Studies have shown a 74% increased risk in smokers, a 20% increased risk in those who quit smoking compared to non-smokers [9]. It has also been found that at least 10–20 years must pass after smoking cessation for the risk level of the disease to be the same as that of a person who has never smoked [9, 10].

Another risk factor is excessive alcohol consumption. A daily amount of heavy alcohol in excess of 60 grams has been shown to significantly increase the risk of pancreatic cancer [11]. Alcohol is also a major cause of chronic pancreatitis. This condition, through a progressive inflammatory process, leads to fibrosis and loss of acinar and islet cells. Chronic pancreatitis increases the risk of cancer 13-fold.

A diet that includes red meat, animal fats, and processed foods increases the risk of pancreatic cancer. These foods contain carcinogens, nitrites, and N-nitroso compounds for food preservation [12]. Eating fruits and vegetables, including citrus containing antioxidants, reduces the risk of the disease by about 30% [13].

A meta-analysis showed that the risk of pancreatic cancer increases by 10% for every increase in body mass index (BMI) of 5 above normal BMI [14]. Adipose tissue surrounding pancreatic cells has also been shown to promote the formation of pancreatic intraepithelial neoplasia. The increase in obesity in populations of developed countries may be responsible for the increased incidence of this cancer.

Occupational exposure to toxic substances such as nickel, polychlorinated biphenyls, cadmium, arsenic, and pesticides increases the risk of pancreatic cancer by 12% [15–17].

An increased risk has also been observed in patients infected with *Helicobacter pylori* [18] or hepatitis C [19]. Therefore, studies are underway to prove whether *Helicobacter pylori* eradication can help reduce the risk of the disease [20].

In contrast, age, sex, ethnicity, blood group, microbial flora, genetic factors, and family history are among the non-modifiable factors.

Studies have shown that people with a blood type other than 0 are at higher risk of developing pancreatic cancer [21].

According to a study by Stevens and colleagues, people with type I diabetes have a double risk of pancreatic cancer compared to those without the disease [22]. It is important to remember that diabetes, although a risk factor, can also occur as a symptom of pancreatic malignancy. It has been shown that in 1% of patients over the age of 50 who developed diabetes, it was due to concurrent pancreatic cancer.

Familial pancreatic cancer accounts for 5–10% of new cases [23]. Several mutations and associated syndromes are known to predispose to the disease. These include Lynch syndrome (i.e., hereditary non-polyposis colon cancer), Peutz-Jeghers syndrome (caused by a mutation in the STK11 gene), hereditary chronic pancreatitis syndrome (germline mutation PRSS1), FAMMM (i.e., familial atypical nevus and melanoma syndrome), and mutations in the *BRCA1* or *BRCA2* genes.

Symptoms

The most common symptoms of pancreatic cancer are back pain, shoulder pain, dysphagia, constipation or diarrhea (mostly fatty), lethargy, weight loss (about 10% in 6 months), epigastric pain radiating to the back, and shoulder blade; nausea, vomiting, bloating, newly developed diabetes, pruritus, and jaundice. The first five of the above-mentioned symptoms occur in patients about six months before pancreatic cancer is diagnosed. Less common tumor symptoms include lethargy and newly diagnosed diabetes [24]. Other symptoms that may occur include Courvoisier's sign, palpable tumor in the intra-abdomen, ascites, paraneoplastic syndromes [recurrent thrombosis of superficial (Trousseau syndrome) or deep veins, hyperplasia, dermatomyositis and polymyositis, polyneuropathies, erythema nodosum].

Diagnostics

Diagnostic tests make it possible to classify a patient with pancreatic cancer into one of four categories in terms of the stage of the disease. The following types of tumors are distinguished: resectable, borderline resectable, locally advanced, and metastatic.

To diagnose pancreatic cancer, the following tests are helpful: Ultrasound, abdominal computed tomography (CT), endoscopic retrograde cholangiopancreatography (ERCP; when cholestasis is present, biliary drainage and prosthesis are necessary), magnetic resonance imaging (MRI), endoscopic ultrasound (EUS) with fine-needle biopsy (not performed if the patient is qualified for surgery), Positron emission tomography-computed tomography (PET-CT, to rule out the presence of metastases); determination of tumor markers in serum, mainly CA 19-9.

The most commonly used diagnostic method is abdominal ultrasonography. The sensitivity and specificity of the method depend, among other things, on the experience of the examiner and condition of the patient, his/her preparation for the examination, and range from 75% to 89% and 90% to 99%, respectively [25].

Computed tomography is a method routinely used in diagnosis. When pancreatic cancer is diagnosed, it helps determine whether resection is possible, whether vascular invasion has occurred and its extent, and whether metastasis is present [26].

Endoscopic retrograde cholangiopancreatography is used for drainage and biliary prosthesis. It also allows for the collection of material for histopathological examination. Brush cytology and aspiration cytology performed in this way increase the diagnostic accuracy of pancreatic tumor [27].

Another diagnostic test is MRI, which allows precise imaging of pancreatic lesions without exposing the patient to radiation. Magnetic resonance imaging cholangiopancreatography allows non-invasive evaluation of the pancreatic duct and bile ducts [28]. This method has applications including the presence of intraductal papillary mucinous neoplasm.

Endoscopic ultrasound with fine-needle biopsy is a method with more than 85% diagnostic accuracy for pancreatic cancer. Biopsy material is not necessary for surgical resection of the tumor if there is a reasonable suspicion of cancer. On the other hand, the time required to confirm the diagnosis can significantly delay the initiation of treatment. EUS has higher sensitivity in identifying lesions smaller than 2 cm compared to CT and MRI [29].

Positron emission tomography-computed tomography is a less commonly used diagnostic method. However, combining PET-CT with endoscopic ultrasound increases sensitivity and specificity of the test [30]. This test, although not routinely used, should be considered in patients with suspected adhesions that could not be visualized by other methods.

The CA 19-9 marker is not routinely used to diagnose pancreatic cancer. CA 19-9 [a sialylated Lewis blood group antigen with the sequence NeuNAcα2--3Ga1β1-3Glc (4-Fucα1) NAcβl-3Galβl-4Glc] [31–33] is mainly found in epithelial cells of the pancreatic ducts, biliary tract, gastric and prostate cells. Its levels increase in the presence of ovarian cysts, diverticular intestinal disease, and inflammatory diseases of the pancreas and biliary tract. Increased levels have also been

described in heat stroke, diabetes mellitus, idiopathic pulmonary fibrosis, endometriosis, and thyroiditis. This often results in false positives [34–37]. False-negative results occur in 10% of Caucasians because this population is not capable of producing CA 19-9. About 90% of patients fall into the Lewis (a– b+) or (a+ b–) blood group, in which CA 19-9 testing is possible [38–40]. False-negative results occur in patients with the Lewis (a– b–) blood group because the CA 19-9 antigen is fused to the blood group protein according to the Lewis system. The Lewis antigen of the MUC1 class of proteins is not expressed on the erythrocyte membrane in Lewis blood type-negative patients [41]. The half-life of CA 19-9 is about 1–3 days. The normal result is < 37 U/mL. Changes in the level of this marker are used to monitor treatment of the disease. An increase in the level of the marker may indicate a lack of response to the used treatment or a relapse of the disease [42]. Combining CA 19-9 antigen with CEA antigen increases specificity up to 84% compared to CA 19-9 alone [43]. A biomarker panel consisting of CA125, CA 19-9, and LAMC2 is also recommended, as it has been shown to significantly improve the detection of pancreatic cancer. The combination of these antigens increased sensitivity by 68% up to one year and by 53% up to two years before cancer diagnosis [44]

New diagnostic techniques are being researched, such as confocal laser needle endomicroscopy (which will allow real-time visualization of tissue at the microscopic level in pancreatic cysts during EUS, allowing optical biopsy) and confocal probe-based laser endomicroscopy (which might be used during ERCP for unspecified pancreatobiliary stenosis) [45, 46].

Treatment

Treatment options include surgery, neoadjuvant and adjuvant chemotherapy, chemoradiotherapy, targeted therapy, immunotherapy, and palliative treatment, among others.

A patient's response to treatment depends on many factors, including the biology of the tumor, patient's performance status, and rate of disease progression.

Surgical treatment

Radical surgery is the only method that offers a chance of a complete cure. From 10 to 15% of patients qualify for primary resection. However, the majority of patients who undergo resection experience recurrence. The 5-year survival rate after surgery is 20%. In the remaining 80–85% of patients, the disease is so advanced with generalized metastases that tumor resection is not possible.

Among pancreatic cancers, there are resectable tumors (no infiltration of major venous and arterial structures), borderline resectable tumors (varying degrees of involvement of the superior mesenteric vein or portal vein, coverage of the gastroduodenal artery up to the hepatic artery, and involvement of less than half the circumference of the superior mesenteric artery) [47], and locally advanced tumor. Even for borderline resectable tumors involving the portal vein or mesenteric vein, resection is possible. In cases of arterial involvement, surgical resection is often associated with the histopathological finding of tumor cells at the surgical incision line. Surgical advances and improvements in vein and artery reconstruction techniques have made it possible to operate on tumors that earlier were ineligible for surgical treatment. Whipple method surgery, or pancreatoduodenectomy, with removal of regional lymph nodes, is performed when the tumor is located in the head of the pancreas. The Whipple method includes resection of the pancreatic head, duodenum, proximal part of the jejunum, common bile duct, gallbladder, and part of the stomach. It is possible to later restore the continuity of the gastrointestinal tract by anastomosing the remnants of the pancreas to the stomach or jejunum. In the case of another location of the tumor, i.e. in the body or tail of the pancreas, the tumor undergoes partial resection or the entire pancreas is removed along with the spleen and regional lymph nodes. The goal of the operation is to achieve an R0 resection, as it offers better survival compared to an R1 resection [48]. The main complications that occur after Whipple surgery are leakage from the pancreatic anastomosis and formation of a pancreatic fistula [49].

Another surgical treatment is laparoscopic distal pancreatectomy. This is a minimally invasive technique. It has been shown to be as effective as traditional surgery [50]. It is also possible to use robotic techniques [51]. The success of pancreatoduodenectomy surgery also depends on the experience of the centers where it is performed. The use of adjuvant chemotherapy after surgery has shown a significant improvement in patient survival.

In some patients, biliary drainage is performed when jaundice is present before surgery. The presence of this symptom has been shown to increase the incidence of perioperative infectious complications and affect coagulopathy [52]. Drainage can be performed by the following methods: percutaneous transhepatic cholangiography, and endoscopic retrograde cholangiopancreatography (ERCP).

Adjuvant chemotherapy

The routinely used treatment is adjuvant chemotherapy. There are various treatment regimens. Initially, one of the standard regimens used was gemcitabine in

monotherapy for 6 months [53]. The Charite Onkologie (CONKO)-001 trial compared the use of six cycles of adjuvant gemcitabine treatment in patients with surgically removed pancreatic cancer with observation. (21 postoperative chemotherapy). Mean follow-up time was 136 months. Overall survival (OS) was 22.8 months with gemcitabine versus 20.2 months with observation (HR = 0.76; 95% CI 0.61–0.95; p = 0.01). The 5-year survival rate was 20.7% with gemcitabine and 10.4% with observation, and the 10-year survival rate was 12.2% and 7.7%, respectively [54].

Subsequently, capecitabine was added to the regimen, as it had a beneficial effect in patients undergoing R0 resection. The European Study for Pancreatic Cancer (ESPAC-4) trial compared the use of six cycles of gemcitabine alone (1000 mg/m^2 every week for 3 or 4 weeks) with administration of gemcitabine with orally administered capecitabine (one cycle: 1660 mg/m^2 for 21 days, followed by 7 days off) [55]. The median follow-up period was 43.2 months. OS was 28 months (95% CI 23.5–31.5) with combination therapy and 25.5 months (95% CI 22.7–27.9) with gemcitabine alone (HR = 0.82; p = 0.032). The use of gemcitabine-capecitabine combination therapy increased the 5-year OS rate from 16.3% (for gemcitabine alone) to 28.8% (gemcitabine-capecitabine combination). No significant difference in grade 3/4 toxicity rates was seen between groups. Treatment with capecitabine was associated with a higher incidence of third- or fourth-degree diarrhea (5% of cases *versus* 2% with gemcitabine alone), neutropenia (38% *versus* 24%), and hand-foot syndrome (7% *versus* 0% with gemcitabine alone).

Another treatment option is mFolfirinox (modified folinic acid, 5-fluorouracil, irinotecan, and oxaliplatin). The randomized PRODIGE-24 trial compared, in patients with R0/R1 resection, a treatment regimen of six cycles of gemcitabine [1000 mg/m^2 on days 1, 8, and 15 of the cycle (28 days)] with a regimen of twelve cycles of Folfirinox (oxaliplatin 85 mg/m2, leucovorin 400 mg/m^2, irinotecan 150 mg/m^2 and 5-FU 2400 mg/m^2 for 46 hours every 2 weeks) [56]. The median follow-up was 33.6 months. Disease-free survival (DFS) was 21.6 months with Folfirinox and 12.8 months with gemcitabine (HR = 0.58; 95% CI 0.46–0.73; p = 0.001). OS was 54.4 months with Folfirinox and 35.0 months with gemcitabine (HR = 0.64; 95% CI 0.48–0.86; p = 0.003). The majority (75.9%) of patients on the Folfirinox regimen experienced grade 3 or 4 toxicities compared to 52.9% of patients on gemcitabine.

A study comparing these two therapies showed that the mFolfirionox regimen had significantly better disease-free survival compared to gemcitabine. However, the administration of mFolfirionox is associated with increased risk of complications. The choice of treatment depends on the patient's postoperative fitness. In fit patients, mFolfirionox therapy is used, while in less fit patients, a regimen with gemcitabine and capecitabine is used [57]. For periampullary localized tumors, a single drug, mainly 5-FU, is used.

Neoadjuvant treatment

Neoadjuvant chemotherapy is used for borderline resectable tumors, i.e. tumors without the presence of distant metastasis or metastasis to regional lymph nodes. These are patients whose infiltration covers less than 180 degrees of the circumference of the superior mesenteric artery or visceral trunk, or those with thrombosis of the superior mesenteric vein and/or the initial segment (less than 2 cm) of the portal vein when vascular reconstruction can be performed.

Neoadjuvant therapy consists of chemotherapy with or without radiation therapy. Retrospective studies from the Surveillance, Epidemiology, and End Results (SEER) and National Cancer databases show that neoadjuvant therapy is recommended in many guidelines for the management of patients with borderline resectable pancreatic cancers [58–60]. The phase III PREOPANC trial divided patients with resectable or borderline resectable pancreatic cancer into groups with diagnostic laparoscopy, neoadjuvant chemoradiotherapy, and surgical resection followed by four cycles of gemcitabine treatment, or with surgery followed by six cycles of gemcitabine treatment. Neoadjuvant treatment consisted of gemcitabine 1000 mg/m^2 on day 1 and day 8 in the first cycle (21 days), gemcitabine 1000 mg/m^2 on day 1, day 8, and day 15 in the second cycle (28 days) with simultaneous application of hypofractionated radiation at a dose of 36 Gy to the tumor and suspicious surrounding lymph nodes, gemcitabine 1000 mg/m2 on day 1 and day 8 in the third cycle (21 days) [61]. The percentage of 5-year OS was 20.5% (95% CI 14.2–29.8) for patients who received neoadjuvant chemotherapy and 6.5% (95% CI 3.1–13.7) for patients with primary surgery (HR = 0.73; 95% CI 0.56–0.96; p = 0.025). Mean OS was 15.7 months in patients in the group receiving neoadjuvant chemotherapy and 14.3 months in patients undergoing surgery. Sixty-one percent of patients treated with neoadjuvant chemotherapy underwent resection. Of these, 41% had negative margins (R0), and 65% of patients had disease without lymph node metastases. In the second group, the resection rate was 72%, resulting in R0 resection in 28% of patients and disease without lymph node metastases in 18% of patients. The optimal neoadjuvant therapy regimen has not been determined. Studies (ALLIANCE, PREOPANC-3, PANACHE-01-PRODIGE, NorPACT-01) evaluating other treatment regimens are ongoing.

Neoadjuvant treatment aims to eliminate micrometastases and shrink the primary tumor to minimize the possibility of tumor recurrence [62]. Postoperative therapy may

be less effective than preoperative therapy due to weaker drug delivery to the tumor locus and low radiation sensitivity caused by reduced oxygenation [63]. Not all patients benefit from preoperative treatment, as some patients have tumors that are not sensitive to chemoradiotherapy. This contributes to delaying surgical treatment or even prevents it. In addition, some patients develop fibrosis within the pancreas under treatment, which can increase the rate of pancreatectomy-related complications [64].

Chemoradiotherapy

Chemoradiotherapy has long been used in locally advanced pancreatic cancer. A study using gemcitabine or 54 Gy chemoradiation with capecitabine in patients with stable disease previously treated with 4 months of gemcitabine chemotherapy, showed no difference in OS between the two groups of patients [65]. Evidence is lacking on whether chemoradiotherapy should be used as an adjunct to chemotherapy [66]. Most available data from randomized clinical trials are insufficient [67–71]. The randomized LAP07 trial divided patients into two groups, the first of which was treated with gemcitabine and the second with gemcitabine with erlotinib for 4 cycles. Patients were then re-divided into a group treated with chemotherapy or chemoradiotherapy (a dose of 54 Gy in 30 daily fractions with capecitabine 800 mg/m2 twice daily on the days of radiation therapy) [72]. The study was stopped prematurely after the initial analysis. Median follow-up was 36.7 months. Overall survival (from the date of first allocation) was not significantly different between the two groups. Overall survival for chemotherapy was 16.5 months (95% CI 14.5–18.5) and 15.2 months for chemoradiotherapy (95% CI 13.9–17.3; p = 0.83). Overall survival for patients receiving gemcitabine was 13.6 months (95% CI 12.3–15.3) and for patients treated with demcitabine in combination with erlotinib was 11.9 months (95% CI 10.4–13.5; p = 0.09). The ECOG study compared a treatment regimen of gemcitabine alone with treatment with gemcitabine and radiotherapy, followed by gemcitabine alone [73]. The study evaluated survival, which was 9.2 months (95% CI 7.9–11.4) with gemcitabine monotherapy and 11.1 months (95% CI 7.6–15.5) with combination treatment) (p = 0.017). Grade 4 and 5 toxicity was more common with chemoradiotherapy (in 41%) than with chemotherapy (in 9% of cases). Chemoradiotherapy can be used when intensive chemotherapy is not possible.

The use of alternatives to irradiation, such as radiofrequency current ablation, irreversible electroporation, focused high-intensity ultrasound, microwave ablation, and local anti-KRAS therapy (using siG12D-LODER) are also under investigation. These treatments address local lesions and can be performed during laparotomy, percutaneously, or endosonographically [74]

Targeted treatment

Targeted treatment involving the use of monoclonal antibodies or small molecules has very high efficacy in many types of cancer. However, in the case of pancreatic cancer, only erlotinib, a small-molecule EGFR tyrosine kinase inhibitor, has proven effective in treatment [75]. Drugs such as cetuximab, bevacizumab, sorafenib, axitinib, and aflibercept have proven ineffective [76]. A study conducted by the National Cancer Institute of Canada (CAN-NCIC-PA3) compared treatment with gemcitabine alone with a regimen of gemcitabine plus erlotinib (100 mg/d) [77]. It showed that administration of erlotinib with gemcitabine slightly prolonged patient survival compared to gemcitabine monotherapy (HR = 0.81; 95% CI 0.69–0.99; p = 0.038). Median and one-year survival rates were 6.2 months and 23% in patients with the combination treatment and 5.9 months and 17% in patients treated with gemcitabine alone.

Patients who are treated with erlotinib with gemcitabine often develop a skin rash, which is a typical side effect of EGFR inhibition. Its occurrence indicates greater treatment efficacy and increases patient survival. If the rash does not appear until 8 weeks after the start of treatment, it is recommended to discontinue erlotinib, as no beneficial effect on survival length has been observed.

Another combination treatment regimen was a combination of gemcitabine with erlotinib followed by capecitabine therapy compared to a regimen of capecitabine with erlotinib followed by gemcitabine therapy achieving similar treatment efficacy [78]. The combination of the three drugs mentioned above had no effect on patient life expectancy [79]. Research is ongoing into the use of poly(ADP-ribose) polymerase (PARP) inhibitors, such as olaparib, as monotherapy or in combination with chemotherapy in pancreatic cancer patients with germline or somatic mutations in BRCA1, BRCA2, or PALB2 [80]. Olaparib is registered by the US Food and Drug Administration (FDA) for maintenance treatment in adult patients with metastatic pancreatic adenocarcinoma with the presence of a germline mutation in the BRCA gene. This mutation is detected through the use of an FDA-approved test. Its presence allows patients to receive a platinum derivative-based treatment regimen. In patients who do not experience disease progression within 16 weeks of starting the above therapy, further maintenance treatment with olaparib is possible. The POLO multicenter clinical trial showed that progression-free survival (PFS) for patients receiving olaparib averaged 7.4 months (95% CI 4.1–11) compared to 3.8 months (95% CI 3.5–4.9) for patients receiving placebo (HR = 0.53; 95% CI 0.35–0.81; p = 0.0035). Overall survival time for patients receiving olaparib was 18.9 months (95% CI 14.9–26.2) compared to 18.1 months (95% CI 12.6–26.1) for those receiving placebo (HR = 0.91; 95% CI 0.56–1.46; p = 0.683).

The overall response rate (ORR) was 23% for olaparib and 12% for placebo. During the study, olaparib was administered orally at 300 mg twice daily [81]. The following side effects may occur during the use of this drug: nausea, vomiting, abdominal pain, diarrhea, fatigue, headache and dizziness, leukopenia, anemia, thrombocytopenia, and others.

Palliative treatment

Treatment of unresectable metastatic pancreatic adenocarcinoma includes symptomatic treatment and palliative chemotherapy. Chemotherapy for patients with pancreatic cancer with current metastases involves combination therapy with Folfirinox or a regimen with gemcitabine and nab-paclitaxel (that is, albumin-bound paclitaxel). A study comparing the Folfirinox regimen [oxaliplatin, folinic acid (leucovorin), irinotecan, fluorouracil] with gemcitabine monotherapy, showed a better effect of Folfirinox treatment in terms of response and progression-free survival. However, the criteria for patient selection are specific. Therefore, Folfirinox treatment is recommended for patients younger than 75 years, with good performance status and no significant risk of cholestasis or cholangitis. This treatment is associated with increased risk of neutropenic fever, sensory neuropathy, and gastrointestinal toxicity. In a 2011 study, patients were randomly divided into two groups. The first received Folfirinox (oxaliplatin 85 mg/m^2, irinotecan 180 mg/m^2, leucovorin 400 mg/m^2, and 5-fluorouracil 400 mg/m^2 given as a bolus followed by 2400 mg/m^2 as a continuous infusion over 46 hours every 2 weeks), and the second group received gemcitabine (1000 mg/m^2 every week for 7 weeks followed by a week off and for 3 weeks and again a week off) [82]. Overall survival was 11.1 months with Folfirinox and 6.8 months with gemcitabine (HR = 0.57; 95% CI 0.45–0.73; $p < 0.001$). Progression-free survival was 6.4 months in the Folfirinox group and 3.3 months in the gemcitabine group (HR = 0.47; 95% CI 0.37–0.59; $p < 0.001$). Another study showed an advantage of gemcitabine treatment in combination with nab-paclitaxel over gemcitabine monotherapy in terms of response and progression-free survival.

The NCT00844649 multicenter trial compared treatment with gemcitabine and nab-paclitaxel with treatment with gemcitabine alone [83]. Overall survival was 8.5 months in the combined gemcitabine and nab-paclitaxel treatment group versus 6.7 months with gemcitabine monotherapy (HR = 0.72; 95% CI 0.62–0.83; $p < 0.001$). Progression-free survival was 5.5 months with combination treatment and 3.7 months with gemcitabine alone (HR = 0.69; 95% CI 0.58–0.82; $p < 0.001$). The combination of gemcitabine and nab-paclitaxel was associated with greater toxicity than gemcitabine treatment. Grade 3 toxicities occurred in the following proportion of patients treated with the combined regimen: neutropenia in 38%, fatigue in 17%, neuropathy in 17%, and neutropenic fever in 3%. When treated with gemcitabine alone, neutropenia occurred in 27% of patients, fatigue in 1%, neuropathy in 1%, and neutropenic fever in 1%. Several patients who participated in the study were not qualified for treatment with Folfirinox. Therefore, gemcitabine in combination with nab-paclitaxel compared to Folfirinox can be used in a wider group of patients, and side effects that may occur during treatment are easier to manage. Gemcitabine in combination with nab-paclitaxel is preferred in older patients or patients with poorer performance status. It is also possible to use gemcitabine monotherapy in patients in poor general condition.

Nanoliposomal irinotecan with 5-FU, which has been approved by the FDA and the European Medicines Agency, is a possible second-line chemotherapy option. The NAPOLI-1 trial compared nanoliposomal irinotecan monotherapy with treatment with nanoliposomal irinotecan in combination with 5-FU and folinic acid and with treatment with 5-FU and folinic acid [84]. Overall survival was 6.1 months (95% CI 4.8–8.9) for patients treated with nanoliposomal irinotecan with 5-FU and folinic acid and 4.2 months (95% CI 3.6–4.9) for patients treated with 5-FU and folinic acid ($p = 0.012$). Overall survival for patients treated with nanoliposomal irinotecan alone was 4.9 months (95% CI 4.2–5.6) and 4.2 months (95% CI 3.6–4.9) for patients treated with 5-FU and folinic acid (HR = 0.99; $p = 0.94$). Nanoliposomal irinotecan in combination with 5-FU and folinic acid was associated with improved OS (HR = 0.58; 95% CI 0.42–0.81). However, combination therapy was associated with more grade 3 and 4 adverse events. Neutropenia occurred in 27% of patients, diarrhea in 13%, vomiting in 11%, and fatigue in 14%. Oxaliplatin and nanoliposomal irinotecan are also used. The American Society of Clinical Oncology Clinical Practice Guidelines for metastatic pancreatic cancer include the use of gemcitabine plus nab-paclitaxel or gemcitabine monotherapy as second-line chemotherapy [85].

The prospective PANCREOX trial evaluated the efficacy of treatment with the FOLFOX regimen (calcium leucovorin, 5-FU, and oxaliplatin) compared to treatment with 5-FU with leucovorin in patients after chemotherapy with gemcitabine [86]. Median follow-up was 8.8 months. Progression-free survival was 3.1 months for FOLFOX and 2.9 months for 5-FU with leucovorin (HR = 1.00; 95% CI 0.66–1.53; $p = 0.989$). Grade 3 and 4 toxicity occurred in 63% of patients with FOLFOX and in 11% of patients with 5-FU plus leucovorin. No benefit was found with the addition of oxaliplatin to 5-FU and leucovorin.

Palliative care is also an important part of patient treatment, as it is common for this group of patients to develop obstructive jaundice and duodenal obstruction. These abnormalities require surgical, endoscopic, or radiological interventions. Due to the development of treatment methods, percutaneous biliary drainage has been mainly replaced by endoscopic techniques. A large-diameter metal stent is usually used. This prolongs the patency period of the stent and reduces the incidence of cholangitis [87]. When gastric outlet obstruction occurs, surgical gastrojejunostomy and endoscopic duodenal stents are applicable. The latter method is recommended for patients with short life expectancy and/or poor performance status.

Screening tests

Universal screening for pancreatic cancer in adults is not recommended [88].

The International Cancer of the Pancreas (CAPS) Consortium recommends starting screening of patients in high-risk groups at age 50, with repeat screening every year if pancreatic lesions are not detected [89]. High-risk groups for pancreatic cancer include a family history of pancreatic cancer (at least two first-degree relatives diagnosed with pancreatic cancer), hereditary pancreatic syndromes (Peutz-Jeghers syndrome, familial atypical polycystic melanoma syndrome, hereditary pancreatitis, PALB2 mutation, BRCA2 mutation, Lynch syndrome) [90]. The imaging modalities of choice are EUS and MRI, as they are sensitive and specific enough for small lesions and carry no risk of exposure to ionizing radiation. The ability to detect premalignant and malignant lesions with both methods is about 20%.

Future plans

Immune checkpoint inhibitors are currently used in several types of cancer. However, pancreatic cancer is a poorly immunogenic tumor, and an immunosuppressive environment is created at the site, which is a barrier to effective immunotherapy. Using monoclonal antibodies, inhibition of cytotoxic T-Lymphocyte-associated Antigen 4 (CTLA-4), programmed cell death protein-1 (PD-1), and programmed death ligand-1 (PD-L1) ligand is researched [91]. Research is underway on the use of CTLA-4 or PD1 inhibitors in combination with chemotherapy, radiation, or cytokine antagonists [92]. Anti-CTLA-4, anti-PD-1, or anti-PD-L1 drugs cause T-cell activation [93]. Ipilimumab is a monoclonal anti-CTLA-4 IgG1 antibody that can be used in combination with gemcitabine treatment in patients with pancreatic cancer [94, 95]. The NCT01473940 clinical trial showed that treatment with ipilimumab plus gemcitabine achieves PFS of 2.5 months (95% CI 0.8–4.8) and OS of 8.5 months (95% CI 2.2–10.3) [96, 97]. The most common toxic complications were hematologic manifestations [97]. The NCT01928394 trial is evaluating the efficacy of combining ipilimumab with nivolumab, which is an anti-PD-1 antibody [98]. The NCT02527434 trial of tremelimumab (anti-CTLA-4 IgG2 antibody) used as monotherapy was unsuccessful. Eighteen of 20 patients experienced disease progression. OS was 4 months (95% CI 2.83–5.42) [99]. However, the combination of tremelimumab with gemcitabine in the NCT00556023 trial produced OS of 7.4 months (95% CI 5.8–9.4) [100]. The combination of tremelimumab with durvalumab (anti-PD-L1 antibody) after 5-FU or gemcitabine-based chemotherapy was also studied. With the drug combination, the ORR was 3.1% (95% CI 0.08–16.22) [101]. A small group of patients with microsatellite instabilities in their tumors can be treated with pembrolizumab, as it has been approved by the FDA [102]. Eighty-three percent of pancreatic cancer patients achieved a response to pembrolizumab immunotherapy within a time range of 2.6 months to 9.2 months (assessed using RECIST) [103]. The Keynote-158 trial demonstrated the efficacy of pembrolizumab treatment in dMMR/MSI-H pancreatic cancer. OS was 4.0 months (95% CI 2.1–9.8), and PFS was 2.1 months (95% CI 1.9–3.4) [104]. The NCT02331251 trial evaluated the combination of pembrolizumab with gemcitabine and nab-paclitaxel chemotherapy [105]. Progression-free survival was 9.1 months, and OS was 15.0 months [105, 106]. A dose escalation study of atezolizumab (mAb IgG1 antibody against PD-L1) showed dose tolerance up to 20 mg/kg every 3 weeks [107]. The NCT03829501 study is ongoing [108].

CPI-613 is an inhibitor of two important enzymes of the tricarboxylic acid cycle, pyruvate dehydrogenase and alpha-ketoglutarate. A phase I study of combining CPI-613 with Folfirinox showed a response rate of 61%, prompting continued research into the efficacy of adding this drug to Folfirinox [109]. Losartan, which is among the angiotensin receptor blockers, reduces collagen and hyaluronan production within the stroma of pancreatic cancer, resulting in reduced shear stress and contributing to better drug delivery [110].

There are emerging hopes for techniques to link genetic changes to clinically relevant characteristics such as the pattern of recurrence and response to chemotherapy to create tests used in clinical practice [111]. Another goal is to further improve the identification of specific mutations to individualize therapy [112].

Summary

Pancreatic cancer belongs to a group of cancers with a high mortality rate. It is important to know the risk

factors of this cancer and to be aware of modern diagnostic options. Due to the limited possibilities of surgical intervention, other management options for patients with advanced pancreatic cancer are presented.

Author contributions

A.G.: prepared the first draft of the manuscript, manuscript revision and literature review.

K.K., A.M.: reviewed the literature and translated the manuscript.

K.H.: final preparation of the manuscript and substantive supervision.

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Conflict of interest

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