

Current Treatment Landscape and Emerging Therapies for Pancreatic Cancer

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Pancreatic cancer is a major challenge to patients, the public, and oncologists. In general, it is difficult to detect, most often presents at an advanced stage, and is resistant to therapy. Unfortunately, the treatment of pancreatic cancer has not benefited from recent gains in the molecular understanding of cancer seen with other types, such as non-small cell lung cancer. However, there has been considerable research and clinical trial activity in recent years. This article will evaluate the clinical data for current and emerging treatment strategies for patients with pancreatic adenocarcinoma.

Epidemiology and Prevalence

Approximately 1.6% of all people will develop pancreatic cancer at some point in their lives.¹ In 2018 in the United States, it was estimated that there would be 55,440 new cases of pancreatic cancer and 44,330 deaths, making pancreatic cancer the tenth most common cancer diagnosis, and the fourth most common cause of cancer-related death in both genders.² The 5-year survival for all patients diagnosed with pancreatic cancer is just 8.5%, but it varies tremendously by the stage at diagnosis (**Figure 1**).¹ These data include all pancreatic cancer subtypes, including the relatively uncommon pancreatic neuroendocrine tumors (PNETs), which have a much better prognosis.³

The number of new cases of pancreatic cancer is slightly higher for men and for blacks compared with whites and Asians/Pacific Islanders (16.9, 14.4, and 11.0 per 100,000 men and 14.3, 11.1, and 9.2 per 100,000 women, respectively).¹ It is typically diagnosed in older people, with a median age of onset of 70 years and median age of death of 72 years. The incidences of new disease and deaths have remained relatively constant since the National Cancer Institute started keeping records in 1975. However, beginning in the mid-2000s, the 5-year survival began to climb upward and is now 8.5% overall, as compared with less than 5% in 2000.¹

Standard of Care

The pancreas is a mixed glandular organ located behind the stomach, making palpation of this organ difficult, and detection not easy

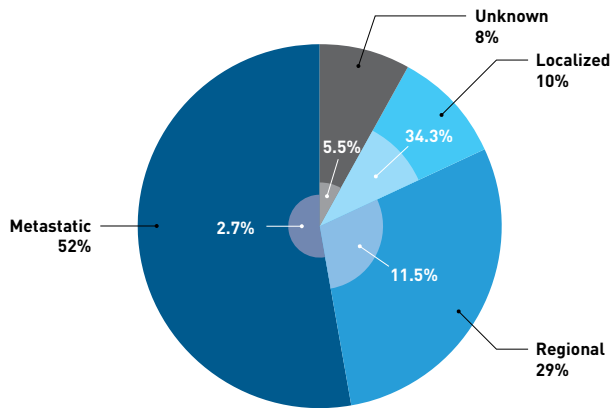
ABSTRACT

Pancreatic cancer remains a disease that is difficult to treat due to a typically late presentation, relatively high resistance to chemotherapy, and lack of effective targeted therapies. The standard of care relies on cytotoxic chemotherapy, primarily FOLFIRINOX and gemcitabine-based regimens. Dose modifications and/or the use of alternative combinations can reduce adverse effects, but these regimens remain highly toxic. As a result, long-term survival is low for patients with advanced or metastatic disease. There is a great need for novel anticancer agents that provide efficacy with minimal toxicity. Currently, inhibitors of immune tolerance and immune checkpoint inhibitors; PARP inhibitors; novel cytotoxic chemotherapies, such as trifluridine/tipiracil; and modifiers of the tumor microenvironment, such as pegylated hyaluronidase, are in clinical trials for the treatment of pancreatic cancer. This activity will review the current treatment landscape and preview emerging therapies for the treatment of advanced pancreatic cancer.

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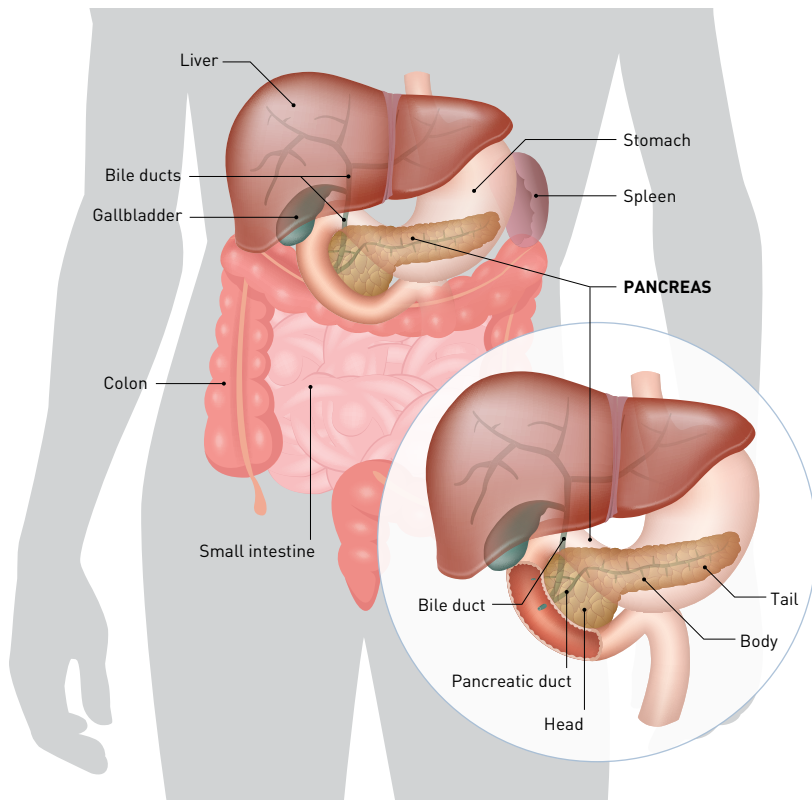
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FIGURE 1. Incidence and 5-Year Survival for Pancreatic Cancer by Stage at Diagnosis¹



The lighter colors represent the proportion of pancreatic cancers that are diagnosed at a localized, regional, metastatic, or unknown stage. The darker colors represent the 5-year relative survival of each group. Reprinted from the National Institutes of Health. SEER cancer stat facts: pancreatic cancer. National Cancer Institute. Bethesda, MD. www.seer.cancer.gov/statfacts/html/pancreas.html.

FIGURE 2. Anatomical Location of the Pancreas⁴



The pancreas lies behind the stomach in the left upper abdominal area. Reprinted from Terese Winslow © 2009 Terese Winslow; US Government has certain rights.

(see Figure 2⁴).⁵ It is mostly an exocrine gland that produces a mixture of bicarbonate and enzymes to aid in the digestion of complex molecules. The endocrine gland portion consists of discrete units, known as Islets of Langerhans, that secrete several important hormones, including insulin, glucagon, somatostatin, and pancreatic polypeptide. Structurally, the pancreas has a head and a tail, like a tadpole. The exocrine secretions drain through the main and accessory pancreatic ducts into the duodenum, and the endocrine hormones are released directly into the blood. The location of the tumor will dictate surgical options, which, unfortunately, are available to just 15% to 20% of patients at the time of diagnosis.⁶

Diagnosis

Risk factors associated with developing pancreatic cancer include a family history, smoking, obesity, sudden onset of diabetes, and chronic pancreatitis.^{3,7} Pancreatic cancer is a notoriously silent-growing tumor. Its retroperitoneal location and generalized symptoms make identification difficult. Symptoms typically do not manifest at an early stage. Rather, the cancer reveals itself when there is

anatomical obstruction of an organ function, and symptoms may include jaundice, light-colored stools or dark urine, pain in the upper or middle abdomen and back, weight loss for no known reason, loss of appetite, and fatigue.

There are various imaging tests that are performed on patients to help in the diagnosis of the disease and guide in surgical evaluation; these tests include computed tomographic (CT) scan, magnetic resonance imaging scan, and minimally invasive, laparoscopic techniques.^{3,7} There are no tumor-specific markers for pancreatic cancer, and other markers, such as serum cancer antigen (CA) 19-9, have low specificity (80%-90%).

The overwhelming majority (90%) of pancreatic cancers are referred to as pancreatic ductal adenocarcinoma (PDAC).^{3,7} PNETs account for 3% to 5% of pancreatic tumors, with the remainder being a variety of histologic types. Precancerous and small cancerous lesions are occasionally found incidental to another imaging procedure. These include high-grade pancreatic intraepithelial neoplasia (PanIn-3), intraductal papillary mucinous tumor, and mucinous cystic tumor.

Staging of Pancreatic Neoplasms

The American Joint Committee on Cancer (AJCC) has designated staging by tumor size,

involvement of the lymph nodes, and metastasis to other organs throughout the body, referred to as TNM classification (Table 1).⁸ N1 represents the presence of 1 to 3 regional nodes, and N2 represents the involvement of 4 or more regional lymph nodes; M1 represents the presence of distance metastasis. Changes to the seventh edition of the AJCC manual incorporated into the current (eighth) edition aid primarily in stratifying patients for surgery because the impact of pancreatic tumor stage on treatment is minimal.

Treatment Options

Although there are significant roles for radiation and chemoradiation, these are reserved for the resectable and adjuvant settings, where incorporation may decrease the potential for recurrence. Cytotoxic chemotherapy continues to form the backbone for the treatment of advanced pancreatic cancer. The FDA-approved treatment options for pancreatic cancer are limited to a small group of these agents⁹:

- Fluorinated pyrimidine antimetabolites: fluorouracil, gemcitabine (GEM)
- Topoisomerase I inhibition: irinotecan (metabolized to the active agent SN-38), liposomal irinotecan
- DNA crosslinking agents: oxaliplatin, cisplatin
- Tubulin inhibitors: paclitaxel, nab-paclitaxel (albumin-bound paclitaxel)

Guidelines

The main guidelines for the treatment of pancreatic cancer are published by the National Comprehensive Cancer Network (NCCN), American Society for Clinical Oncology (ASCO), and European Society for Medical Oncology (ESMO).^{7,10,11}

First-Line Therapy for Advanced-Stage Disease

Because most patients present with advanced disease, many of them also have deteriorating performance status due to the loss of appetite and weight. Performance status is a key component in determining which therapy can be tolerated by the patient. All 3 organizations recommend 5-fluorouracil (5FU), leucovorin (folinic acid; LV), irinotecan, and oxaliplatin (FOLFIRINOX) or nab-paclitaxel/GEM in patients with Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-1 (Table 2).^{7,10,11} For patients with PS 2, single-agent GEM remains the preferred option by all 3 groups. Single-agent GEM is additionally listed by ESMO as an option for patients with bilirubin levels greater than 1.5 times the upper limit of normal (ULN).¹⁰ At PS 3-4, all groups recommend palliative care, although the NCCN and ASCO recommend single-agent GEM for select patients.

Subsequent Lines of Therapy

The preferred regimen for the next line of therapy is whichever regimen was not administered in the first-line setting (ie, FOLFIRINOX

TABLE 1. Pancreatic Cancer Stages⁸

| | T | N | M |
|-----------|------------|-------|----|
| Stage 0 | Tis | N0 | M0 |
| Stage IA | T1(a,b,c) | N0 | M0 |
| Stage IB | T2 | N0 | M0 |
| Stage IIA | T3 | N0 | M0 |
| Stage IIB | T1, T2, T3 | N1 | M0 |
| Stage III | T1, T2, T3 | N2 | M0 |
| | T4 | Any N | M0 |
| Stage IV | Any T | Any N | M1 |

Primary tumor size (T)

TX - Primary tumor cannot be assessed

T0 - No evidence of primary tumor

Tis - Carcinoma in situ

T1 - Tumor ≤2 cm in greatest dimension (T1a: ≤0.5 cm; T1b: 0.5-1 cm; T1c: 1-2 cm)

T2 - Tumor 2-4 cm in greatest dimension

T3 - Tumor >4 cm in greatest dimension

T4 - Tumor involves the celiac axis, superior mesenteric artery, and/or common hepatic artery, regardless of size

Number of regional lymph nodes affected

NX - Regional lymph nodes cannot be assessed

N0 - No regional lymph node metastases

N1 - Metastasis in 1 to 3 regional lymph nodes

N2 - Metastasis in 4 or more regional lymph nodes

Presence of distant metastasis

M0 - No distant metastases

M1 - Distant metastasis

if nab-paclitaxel/GEM was administered first, and nab-paclitaxel/GEM if FOLFIRINOX was administered first).^{7,10,11} After this, the options are severely limited; choice of therapy is mainly dependent on the adverse effect profile of the regimen and the current status of the patient. Single-agent 5FU or capecitabine, 5FU/LV/irinotecan (FOLFIRI), 5FU/LV/liposomal irinotecan, and 5FU/LV/oxaliplatin (FOLFOX) are possibilities. Pembrolizumab is suggested for microsatellite instability-high (MSI-H) tumors, or those tumors with deficiencies in mismatch repair mechanisms (dMMR). Single-agent chemotherapy is usually a last option after exhausting this relatively short list. Beyond this, patients typically receive best supportive care.

Other Treatment Options

Although the standard of care for stage III/IV pancreatic cancer includes regimens of FOLFIRINOX and nab-paclitaxel/GEM, other treatment options are available to patients, particularly, GEM-based regimens. These include GEM/docetaxel/capecitabine (GTX), GEM/oxaliplatin, and GEM/capecitabine.¹²⁻¹⁶ GEM/erlotinib is used often for patients with endothelial growth factor receptor-positive

TABLE 2. Comparison of Guideline Recommendations for the First-Line Treatment of Pancreatic Cancer Based on Performance Status^{7,10,11}

| Guideline | ECOG PS 0-1 | ECOG PS 2 | ECOG PS 3-4 |
|-----------|---|---|---|
| ESMO | <ul style="list-style-type: none"> FOLFIRINOX Nab-paclitaxel + GEM | <ul style="list-style-type: none"> PS 2 or bilirubin levels >1.5 ULN: GEM PS 2 as consequence of high tumor burden: nab-paclitaxel + GEM | <ul style="list-style-type: none"> Palliative care |
| NCCN | <ul style="list-style-type: none"> FOLFIRINOX Nab-paclitaxel + GEM | <ul style="list-style-type: none"> GEM KPS ≥70: Nab-paclitaxel + GEM | <ul style="list-style-type: none"> Palliative care GEM |
| ASCO | <ul style="list-style-type: none"> Favorable comorbidity profile: FOLFIRINOX Relatively favorable comorbidity: Nab-paclitaxel + GEM | <ul style="list-style-type: none"> PS 2 or a comorbidity profile that precludes more-aggressive regimens: <ul style="list-style-type: none"> > GEM > GEM + erlotinib > Capecitabine | <ul style="list-style-type: none"> PS ≥3 or with poorly controlled comorbid conditions: <ul style="list-style-type: none"> > Supportive care > Cancer-directed therapy only on a case-by-case basis |

ASCO indicates American Society of Clinical Oncology; ECOG, Eastern Cooperative Oncology Group; ESMO, European Society for Medical Oncology; FOLFIRINOX, 5-fluorouracil (5FU), leucovorin (folinic acid, LV), irinotecan, and oxaliplatin; GEM, gemcitabine; KPS, Karnofsky performance status; NCCN, National Comprehensive Cancer Network; PS, performance status; ULN, upper limit of normal.

(EGFR+) tumors, whereas GEM/cisplatin is used for patients with *BRCA1/2*-mutated tumors.⁷

Drug Resistance

Pancreatic cancer is characterized by a high resistance to traditional chemotherapies.^{17,18} Resistance can be intrinsic (*de novo*) and/or acquired in response to challenge with therapy. The most commonly used agents and regimens have modest clinical benefit and questionable impact on survival. Mechanisms of drug resistance in pancreatic cancer include aberrant gene expression, mutations, deregulation of key signaling pathways, support of stroma cells, presence of dense stroma, and presence of highly resistant stem cells. The effect of these mechanisms is to produce an environment that hinders drug penetration, expels the drug from tumor cells, and overcomes the toxic effects of chemotherapy.

Current Pharmacologic Treatment Options

Secondary to the progression of pancreatic cancer and poor prognosis, multiple trials have been completed to test different approaches and evaluate changes in quality of life (QOL). Select significant trials have helped to shape current treatment strategies. For very fit patients (PS 0-1), FOLFIRINOX is strongly recommended.^{7,10,11} A multicenter trial randomized 342 patients with metastatic pancreatic adenocarcinoma to receive FOLFIRINOX or single-agent GEM.¹⁹ The median overall survival (OS) was 11.1 months versus 6.8 months in the FOLFIRINOX and GEM groups, respectively ($P < .001$) (Table 3^{19,20}). FOLFIRINOX was more toxic than GEM, with 5.4% of patients experiencing febrile neutropenia, as compared with 1.2% in the GEM group. Other toxicities that occurred in greater than 10% of patients receiving FOLFIRINOX included neutropenia (46%), fatigue (24%), vomiting (15%), and diarrhea (13%) (Table 4^{19,20}). Sensory neuropathy, not seen with single-agent GEM, was experienced by 9% of the patients receiving FOLFIRINOX. QOL for these patients was

preserved with FOLFIRINOX; 31% of the patients in the FOLFIRINOX group experienced a definitive degradation of QOL at 6 months, as compared with 66% in the GEM group. Some institutions offer a reduced-intensity FOLFIRINOX regimen.^{21,22} At 80% dose intensity with growth factor support, toxicity was more tolerable, and the regimen still had therapeutic activity.²¹

The combination of nab-paclitaxel/GEM is also a standard-of-care regimen, but it is more often used for patients who are slightly less fit (ie, PS 0-2) or who have significant comorbidities.^{7,10,11} Nab-paclitaxel was investigated in an international trial that randomized 861 patients with metastatic pancreatic adenocarcinoma to receive nab-paclitaxel/GEM or single-agent GEM.²⁰ The median OS was 8.5 months versus 6.7 months in the nab-paclitaxel/GEM and GEM groups, respectively ($P < .001$) (Table 4^{19,20}). The most common grade 3 or greater toxicities associated with nab-paclitaxel/GEM use were neutropenia (38%), leukopenia (31%), thrombocytopenia (13%), anemia (13%), fatigue (17%), and neuropathy (17%). Febrile neutropenia occurred in 3% of the nab-paclitaxel group versus 1% in the GEM group. Among patients receiving nab-paclitaxel/GEM, neuropathy resolved to grade 1 or less within a median of 29 days, and 44% of patients were able to resume treatment at a reduced dose. FOLFIRINOX and nab-paclitaxel/GEM have not been compared in head-to-head trials. See Table 5¹⁹ for currently used FOLFIRINOX and nab-paclitaxel/gemcitabine regimens.¹⁹

Inclusion of drugs, such as irinotecan, in liposomes extends the serum half-life of the agent. Liposomal irinotecan is recommended by the NCCN based on the NAPOLI-1 trial of 417 patients randomized to receive liposomal irinotecan, 5FU/LV, or the combinations. The median progression-free survival (PFS) was significantly greater for patients who received liposomal irinotecan with 5FU/LV compared with patients who did not receive irinotecan (3.1 months vs 1.5 months; $P < .001$). Updated analyses demonstrated a median OS of 6.2 months versus 4.2 months ($P = .042$) for patients who

received 5FU/liposomal irinotecan compared with those who did not receive irinotecan.²³ Grade 3 or greater adverse effects that occurred most frequently with 5FU/liposomal irinotecan were lymphopenia (27%), neutropenia (20%), fatigue (21%), infection (17%), diarrhea (13%), and vomiting (11%).²⁴ Asian patients, in particular, were more sensitive to the neutropenic effects, with 55% experiencing grade 3 or greater neutropenia, as compared with 18% of whites. Febrile neutropenia was observed in 3% of patients receiving liposomal irinotecan, including death in 0.8%, versus none of the patients receiving 5FU/LV alone. This combination was approved for use as second-line treatment following GEM-based therapy in patients with metastatic disease. However, it should be noted that in the United Kingdom, the National Institute for Health and Care Excellence (NICE) did not recommend liposomal irinotecan based on a cost-effectiveness analysis.²⁵

Targeted Agents

Erlotinib continues to be the most widely used targeted oral agent in advanced pancreatic cancer. Erlotinib is an oral tyrosine kinase inhibitor that acts on the intracellular domain of the EGFR. The combination of erlotinib and GEM compared with placebo was associated with a median OS of 6.2 months versus 5.9 months ($P = .038$).¹³ The 1-year survival rate was 23% versus 17% for patients receiving erlotinib and placebo, respectively ($P = .023$). However, the data suggest that only a small fraction of patients actually benefited from the therapy.⁷

In addition to EGFR inhibition, other pathways have been studied in this disease, including the vascular endothelial growth factor receptor. This particular receptor is associated with angiogenesis, and any interruption to its activation may lead to tumor necrosis. Several monoclonal antibodies and oral tyrosine kinase inhibitors have been studied in phase 3 trials and include antiangiogenics (bevacizumab, axitinib, ziv-aflibercept, sunitinib, and kinase inhibitors rigosertib [polo-like kinase], dasatinib [Src kinase], and ganitumab [insulin-like growth factor-1 receptor]), and other agents such

TABLE 3. Efficacy of Standard Treatments for Stage III/IV Pancreatic Cancer^{19,20}

| | Overall Survival | | Progression-Free Survival | |
|----------------|------------------|------------|---------------------------|------------|
| | FOLFIRINOX | GEM | FOLFIRINOX | GEM |
| Conroy et al | 11.1 months | 6.8 months | 6.4 months | 3.3 months |
| | $P < .001$ | | $P < .001$ | |
| | Nab-paclitaxel | GEM | Nab-paclitaxel | GEM |
| | FOLFIRINOX | GEM | FOLFIRINOX | GEM |
| Von Hoff et al | 8.5 months | 6.7 months | 5.5 months | 3.7 months |
| | $P < .001$ | | $P < .001$ | |

FOLFIRINOX indicates 5-fluorouracil (5FU), leucovorin (folinic acid, LV), irinotecan, and oxaliplatin; GEM, gemcitabine.

TABLE 4. Grade ≥3 Adverse Effects of FOLFIRINOX and Nab-paclitaxel/Gemcitabine^{19,20}

| | Conroy et al | | Von Hoff et al | |
|--|--------------|-----------|------------------------|-----------|
| | FOLFIRINOX | GEM alone | GEM/ Nab-paclitaxel | GEM alone |
| Neutropenia | 45.7% | 21% | 38% | 27% |
| Febrile neutropenia | 5.4% | 1.2% | 3% | 1% |
| Leukopenia | — | — | 31% | 16% |
| Thrombocytopenia | 9.1% | 3.6% | 13% | 9% |
| Anemia | 7.8% | 6% | 13% | 12% |
| Fatigue | 23.6% | 17.8% | 17% | 7% |
| Vomiting | 14.5% | 8.3% | — | — |
| Diarrhea | 12.7% | 1.8% | 6% | 1% |
| Neuropathy | 9% | — | 17% | 1% |
| Elevated level of alanine aminotransferase | 7.3% | 20.8% | — | — |
| Thromboembolism | 6.6% | 4.1% | — | — |

FOLFIRINOX indicates 5-fluorouracil (5FU), leucovorin (folinic acid, LV), irinotecan, and oxaliplatin; GEM, gemcitabine.

TABLE 5. Currently Used FOLFIRINOX and Nab-paclitaxel/Gemcitabine Regimens¹⁹

| FOLFIRINOX | Nab-paclitaxel/Gemcitabine |
|---|--|
| <ul style="list-style-type: none"> • Oxaliplatin: 85 mg/m² IV over 2 hours • Leucovorin: 400 mg/m² IV over 2 hours • Irinotecan: 180 mg/m² IV over 90 minutes • Fluorouracil: 400 mg/m² IV push, followed by 2400 mg/m² IV over 46 hours | <ul style="list-style-type: none"> • Nab-paclitaxel: 125 mg/m² IV over 30 minutes • Gemcitabine: 1000 mg/m² IV over 30 minutes |
| All agents given on day 1 of a 14-day cycle. | Both agents given on days, 1, 8, and 15 of a 28-day cycle. |
| Cycles are repeated until disease progression or unacceptable toxicity. | Cycles are repeated until disease progression or unacceptable toxicity. |

IV indicates intravenous.

as epacadostat (indoleamine 2,3-dioxygenase 1 [IDO1]) and vismodegib (sonic hedgehog pathway antagonist). All of these have failed to demonstrate clinically meaningful activity, except for sunitinib, which may have a role in maintenance therapy.²⁶ Sunitinib as maintenance after 6 months of progression-free disease management following standard-of-care guidelines was able to prolong 2-year survival (23% vs 7%).

Novel Subsequent-Line Treatment Options

Despite the failure of targeted agents to affect improved outcomes in patients with pancreatic cancer, or because of this failure, considerable effort is underway to identify novel therapies that can make meaningful differences to patients. Clinical research continues to focus on targeting specific mutations observed in patients with pancreatic cancer through oral small molecular inhibitors, monoclonal antibodies, immunotherapy, and alternative formulations of traditional cytotoxic agents.

Inhibitors of Immune Tolerance

Numerous agents that affect the immune system are being explored. Immune checkpoint inhibitors are monoclonal antibodies (mAbs) that restore tumor immunogenicity. Tumors need to be able to evade the immune system and often express molecules on the cell surface that suppress the activity of cytotoxic T cells. MAbs, such as ipilimumab, tremelimumab, pembrolizumab, nivolumab, durvalumab, atezolizumab, and APX005M, are able to block tumor-mediated immune suppression, thereby allowing T cells to remain active and target the tumor.

The PD-1 inhibitor pembrolizumab is approved for microsatellite instability (MSI)-high or mismatch repair-deficient (MSI-H/dMMR) solid tumors. MSI refers to the hypermutable state of cells caused by impaired DNA mismatch repair (MMR), or dMMR. It consists of insertion and deletion mutations in stretches of short tandem DNA repeats (microsatellites) as well as nucleotide substitutions throughout the genome. In general, tumors are classified into 2 broad subgroups: (1) MSI-H and (2) MSI-negative (low or stable). In a study of multiple tumor types, pembrolizumab led to an objective response in 83% of patients with pancreatic cancer expressing MSI-H or dMMR ($n = 6$).²⁷ These data shed light on the future of this specific patient population that might benefit from this approach. Currently, immune checkpoint inhibitors are being studied both as single-agent options and in combination with other therapies.

Novel Cytotoxic Chemotherapy

Trifluridine/tipiracil (TAS-102) is a combination of a fluorinated thymidine analogue, trifluridine, and a thymidine phosphorylase inhibitor, tipiracil hydrochloride, at a molar ratio of 2:1.²⁸ The mechanism of action of trifluridine is similar to 5FU, and both interfere

with DNA synthesis and cell proliferation. Tipiracil is a potent inhibitor of thymidine phosphorylase, a key degradative enzyme, and allows for extended plasma levels of trifluridine. TAS-102 is approved in the United States for patients with refractory metastatic colon cancer and is currently being studied in combination with liposomal irinotecan in metastatic pancreatic cancer. Also, a cytidine analogue, fluorocyclopentenyl cytosine (RX-3117), is being studied in combination with nab-paclitaxel.

PARP Inhibitors

In many cell types, including some pancreatic tumors, dMMR is deficient due to *BRCA1/2* mutations. About 10% to 12% of patients with pancreatic cancer express *BRCA1* and/or *BRCA2* mutations.²⁹ In these cells, poly-ADP-ribose polymerase (PARP) is the major route for DNA repair. PARP inhibitors take advantage of this to create “a synthetically lethal” phenotype, in which DNA repair is severely inhibited. Theoretically, normal cells still possess non-PARP-mediated DNA repair mechanisms and should not be affected. Multiple PARP inhibitors are in clinical trials for pancreatic cancer (niraparib, veliparib, and rucaparib).

Single-agent olaparib was administered to 23 patients with germline *BRCA1/2* mutations and prior GEM treatment.³⁰ The response rate was 21.7% (4% complete response [CR], 17% partial response [PR]), and stable disease (SD) for 8 or more weeks was observed in 35% of patients. It is unclear how applicable these agents will be for the treatment of pancreatic cancer, given that the prevalence of *BRCA1/2* mutations in the general population is 1 in 300 to 800 people.³¹

Platelet-Derived Growth Factor Receptor Alpha (PDGFR- α)

Olaratumab is a human IgG1 antibody that binds PDGFR- α , a receptor tyrosine kinase, and has a role in cell growth, chemotaxis, and mesenchymal stem cell differentiation.³² PDGFR- α may be found on tumor and stromal cells. Olaratumab is being studied in combination with nab-paclitaxel/GEM for the first-line treatment of metastatic pancreatic cancer.

Pegylated Hyaluronidase

Pancreatic cancer often forms a dense stroma that impedes chemotherapy access to tumor cells.³³ The tumor-associated stroma is rich in hyaluronan. Pegylated hyaluronidase (PEGPH20) has been developed to degrade hyaluronan in order to facilitate delivery of chemotherapeutic agents to the cancer cells. The HALO 202 trial randomized 279 patients with untreated metastatic pancreatic adenocarcinoma to receive nab-paclitaxel/GEM with or without PEGPH20.³³ In the overall group, PFS was improved (HR, 0.73; 95% CI, 0.53-1.00; $P = .049$). In 84 (34%) patients with high hyaluronan content (HA-high), a similar increase in PFS was observed (HR, 0.51; 95% CI, 0.26-1.00; $P = .048$). Looking at just patients with HA-high

tumors, the objective response rate was 45% versus 31% in those receiving PEGPH20 plus chemotherapy versus chemotherapy alone; the median OS was 11.5 months versus 8.5 months, respectively. These data suggest that this may be a means to overcome drug resistance mediated by excessive stroma production, but just in patients with high hyaluronan content.

Supportive Care

Pancreatic cancer is characterized by a high symptom burden at the time of diagnosis with a short survival expectancy.^{7,11,34,35} Palliative care plays a critical role in the management of patients with pancreatic cancer throughout the continuum of care and should be provided as soon as a diagnosis is confirmed. Complications associated with pancreatic cancer are due to tumor growth and infiltration of adjacent structures (biliary obstruction, duodenal obstruction, pancreatic insufficiency, pain) and systemic phenomena (cachexia, thromboembolic events). Patients should undergo a comprehensive palliative care assessment by their primary oncology team, which includes:

- Benefits and burdens of anticancer therapy
- Physical symptoms
- Psychosocial or spiritual distress
- Personal goals, values, and expectations
- Educational and informational needs
- Cultural factors affecting care

Unfortunately, many physicians and patients are reluctant to seek out palliative care, believing that palliative care is associated with imminent death.³⁴ On the contrary, palliative care supports the patient and provides important symptom management. Patients receiving palliative care have a better QOL throughout all stages of their disease with lower cost of care.^{36,37} The MD Anderson Cancer Center found that, when they switched the service name to “Supportive Care,” there were more and earlier patient referrals for palliative care service.³⁸

Quality of Life

QOL should be stabilized at the highest possible level with chemotherapy to postpone deterioration in functional/performance status.³⁹ Pain and fatigue are 2 very common problems that are independent survival prognostic indicators for patients with pancreatic cancer.⁴⁰ Among patients with pancreatic cancer, 83% and 32% experience fatigue or have upper gastrointestinal symptoms, respectively; these were highest among all cancer subtypes in a recent survey of 922 patients who had been referred to a palliative care program.

Two decades ago, GEM was the first therapeutic agent to substantially improve QOL for patients with pancreatic cancer. GEM monotherapy provided greater clinical benefit (defined by pain control, Karnofsky performance status, and weight gain) in 23.8%

of GEM-treated patients, as compared with 4.8% of those patients treated with 5FU monotherapy ($P = .0022$).⁴¹ FOLFIRINOX preserved QOL to a greater degree than GEM monotherapy. In the PRODIGE study, 31% of patients receiving FOLFIRINOX experienced degradation of QOL, as compared with 66% of those receiving GEM ($P < .001$).¹⁹ More recently, modifications to the use of FOLFIRINOX (elimination of bolus 5FU) resulted in a higher preservation of QOL and reduced toxicity, as compared with the original dosing schedule.²² Still, FOLFIRINOX is an aggressive regimen, and many patients cannot tolerate it. For these patients, nab-paclitaxel/GEM is a reasonable option.^{7,10,11}

Patients with pancreatic cancer experience frequent pain, fatigue, and depression. Pain is most often caused by the growing cancer and invasion into other tissues.⁴² Control of pain with medication is important for maintaining QOL. As the end of life approaches for these patients, opioid use can be aggressively titrated.³⁴ Patients with fatigue should try to schedule activities for times of the day when they are more likely to have energy. Depression and psychological distress are very common among patients with pancreatic cancer. Psychosocial support is important to the patients and caregivers.

End-of-Life Considerations

Patients and family should prepare for the end of the patient's life.³⁴ The values and preferences of the patient should be of utmost priority. Patients and caregivers should be educated on the dying process and create an advanced care plan. Additional guidance can be found in the ASCO booklet, “Advanced Cancer Care Planning.”⁴³

Conclusions

Pancreatic cancer remains a difficult-to-treat disease with poor outcomes. While awaiting the identification of additional actionable molecular targets and the ongoing development of targeted therapies, cytotoxic chemotherapy will continue to be the mainstay of treatment. Current therapy primarily relies on FOLFIRINOX and GEM-based regimens. Modification to these regimens can reduce toxicity and provide some efficacy. Unfortunately, patients and families must grapple with the stress and anxiety that accompany the diagnosis and treatment. It is hoped that, in the near future, additional agents will be approved that can substantially improve survival and QOL for these patients. ■

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