Pancreatic Cancer: Novel and Emerging Approaches to Early Detection and Treatment

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Overview

Advanced pancreatic cancer is a devastating disease with few available treatment options that yield very limited survival benefits. Research to improve the outcomes of these patients has resulted in a remarkable increase in the knowledge of the underlying molecular biology and mechanisms of therapy resistance of pancreatic adenocarcinoma. These insights have resulted in the rational development of new formulations of cytotoxic agents and the integration of targeted agents and immunotherapies into therapeutic regimens currently being evaluated in various clinical trials in this difficult to treat malignancy.

Given the limited therapeutic options for patients with advanced pancreatic cancer and the recent advances noted previously, it is important for community oncologists to be educated about these emerging treatments so that they can deliver optimal care to their patients.

Target Audience

This activity is directed toward medical oncologists and hematologists who treat patients with solid tumors and hematologic malignancies. Fellows, nurses, physician assistants, nurse practitioners, and other healthcare providers may also participate.

Learning Objectives

After participating in this CME activity, learners should be better prepared to:

- Describe molecular pathways and targeted therapies with clinical potential in advanced pancreatic cancer
- Review the safety, and efficacy data, and potential clinical role of novel treatment regimens with cytotoxic and/or targeted components
- Recognize and manage adverse events associated with established and novel therapies in pancreatic adenocarcinoma

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Pancreatic Cancer: Novel and Emerging Approaches to Early Detection and Treatment

Pancreatic cancer is the fourth leading cause of cancer-related death in the United States.[1] According to estimates from the National Cancer Institute, 46,420 new cases of pancreatic cancer will be diagnosed in the United States in 2014, and nearly 40,000 individuals will die of the disease.[2]

More than 90% of pancreatic malignancies are pancreatic ductal adenocarcinomas (PDACs).[3] These tumors originate in pancreatic ductal cells or from acinar cells that undergo acinar-to-ductal metaplasia.[3]

There has been little improvement in long-term survival among patients with PDAC over the past 40 years. The 5-year overall survival (OS) rate for patients with PDAC remains dismal—less than 5%. This is largely attributed to the fact that diagnosis is typically made after the disease has reached an advanced stage, a reflection of the asymptomatic nature of early pancreatic cancer.[3]

Other factors that confound PDAC diagnosis and treatment include a lack of biomarkers to aid in early identification; the anatomical location of the pancreas; the inability of current methods to detect small primary tumors prior to metastatic spread; the creation of dense fibrous tissue around the tumor (a result of interaction with stromal cells), which contributes to therapeutic resistance; and the small proportion of patients for whom potentially curative surgery is an option at diagnosis.[3]

Surgical resection offers the best chance for long-term survival, and 5-year survival rates for patients with resected PDAC have improved in this century. The risk of local and systemic recurrence is high, however, underlining the aggressive nature of this type of cancer. A recent study showed median survival among patients with resected PDAC to be 21.3 months, with a 5-year survival rate of 21%.[4]

These statistics highlight the urgent need for improved therapies and early detection modalities to combat this disease. This article is a concise review of new and emerging diagnostic and therapeutic modalities for improving care and enhancing outcomes for patients with PDAC.

Early Diagnosis: Novel Tools and Methodology

Endoscopic ultrasound is an established component of the diagnosis and treatment of pancreatic diseases, including pancreatic cancer. Recent innovations in endoscopic technology have emerged as a promising means of advancing progress in the early diagnosis and treatment of pancreatic cancer.

In a small pilot study (N = 29), researchers found that an optical blood oxygen sensor attached to an endoscope can identify pancreatic cancer with high rates of sensitivity and specificity in patients undergoing endoscopic procedures. The study was developed based on the field effect theory, which posits that detection of microvasculature changes, such as early increases in blood supply, in tissue surrounding lesions can be used to identify malignancies.[5]

The study comprised two arms: patients with pancreatic cancer (n = 14) and controls without pancreatic cancer (n = 15). Individuals with other known malignancies and gastroduodenal premalignant lesions were excluded from participation. Spectroscopic measurements of early increases in blood supply variables were obtained, including deoxyhemoglobin concentration (DHb) and mean blood vessel radius (BVR). The Mann-Whitney rank sum test was used for statistical analysis ($P \leq .05$).

Researchers found that both DHb ($P = .001$) and BVR ($P = .03$) were higher in the cancer group than in the control arm. Although the findings are preliminary, they suggest that both DHb alone (92% sensitivity, 86% specificity) and DHb in combination with BVR (92% sensitivity, 79% specificity) can detect pancreatic cancer with high accuracy, without the need for an invasive procedure.[5] A larger multicenter study is currently under way to confirm these findings.[6]

The potential of circulating tumor cells as biomarkers to aid in the effective diagnosis and staging of pancreatic cancer has also garnered the attention of researchers. In a prospective analysis of 50 consecutive pretreatment patients who were either suspected to have or recently diagnosed with pancreatic cancer, circulating tumor cells were detected in 62.5% of patients with pancreatic cancer and in 5.5% of patients with benign pathology.[7]

Specificity of circulating tumor cells for a PDAC diagnosis was 94.4%; positive predictive value was 95.2%, and negative predictive value was 58.6%. The investigators found that in patients with PDAC diagnoses, circulating tumor cell numbers could be used to distinguish between stages 2, 3, and 4 cancer ($P = .013$), and the presence of two or more circulating tumor cells distinguished local/regional disease from metastatic disease ($P < .001$). These results suggest that circulating tumor cells could potentially serve as biomarkers to aid in earlier diagnosis and effective staging of pancreatic cancer.[7,8]

Novel Agents and Treatment Strategies

Data from the multicenter phase III NAPOLI-1 trial were presented at the European Society for Medical Oncology 16th World Congress. Patients in this trial had metastatic pancreatic cancer and had been treated previously with gemcitabine. Re-

sults showed that adding the novel agent MM-398, a nanoliposomal encapsulation of irinotecan, to second-line therapy with 5-fluorouracil (5-FU) and leucovorin significantly improved OS and progression-free survival (PFS). The addition of MM-398 to 5-FU and leucovorin conferred a 1.9-month survival advantage (6.1 months in the MM-398-plus-5-FU/leucovorin group vs 4.2 months in the 5FU/leucovorin group; hazard ratio [HR] = 0.67; *P* = .012). Given the lack of treatment options in this setting, this is a significant finding.[9]

The study's authors noted that drug delivery is one of the biggest challenges in pancreatic cancer treatment. The delivery system of MM-398 allows for longer drug exposure in the circulation and more accumulation of the drug and its active metabolite (SN38) at the tumor site. Thus, it generates higher antitumor activity and is more effective than conventional irinotecan alone.[9]

Although adverse events (AEs) were more common with the addition of MM-398, they were deemed acceptable (**Table 1**). Merrimack Pharmaceuticals is expected to file a New Drug Application for MM-398 in 2014.

TABLE 1. Adverse Events in NAPOLI-1

Adverse Event	MM-398 + 5-FU/ Leucovorin	MM-398	5-FU/ Leucovorin
Diarrhea	12.8%	21.1%	4.5%
Vomiting	11.1%	13.6%	3%
Fatigue	13.7%	6.1%	3.7%

In September 2013, the US Food and Drug Administration (FDA) approved the combination of *nab*-paclitaxel and gemcitabine as a first-line treatment for patients with metastatic adenocarcinoma of the pancreas.[10] This approval was based on results from the randomized phase III MPACT trial, which showed that adding *nab*-paclitaxel to gemcitabine significantly improved OS compared with gemcitabine alone (median 8.5 months vs 6.7 months; *P* <.001).[11]

Updated survival data from MPACT were presented at the 2014 Gastrointestinal Cancers Symposium. The extended analysis demonstrated superior OS with *nab*-paclitaxel plus gemcitabine compared with gemcitabine alone in patients with metastatic pancreatic cancer. Specifically, median OS was 8.7 months with the combination versus 6.6 months in patients who received gemcitabine alone (HR = 0.72; *P* <.0001).[11]

Subgroup analysis found that patients with Karnofsky Performance Status (KPS) scores of 90 to 100 had greater median OS with *nab*-paclitaxel plus gemcitabine compared with gemcitabine monotherapy (median OS, 9.7 months vs 7.9 months, respectively; HR = 0.77; *P* = .0053). Patients with a KPS score of 70 to 80 also benefited, although not as much as did those with a higher KPS score (median OS, 7.6 months vs 4.3 months; HR = 0.59; *P* <.0001).[12]

Investigators also assessed the prognostic effects of cancer antigen (CA) 19-9 and neutrophil-to-lymphocyte ratio. Elevations in both were found to be significant predictors of reduced OS, whereas the number of metastases was not a predictor. Also of importance, treatment with *nab*-paclitaxel plus gemcitabine appeared to reduce the poor prognostic effect of CA19-9, as shown by similar OS being observed among patients receiving the combination regimen regardless of CA19-9 level.[12]

Two- and 3-year OS rates also favored the combination regimen (**Table 2**). MPACT is the first study in metastatic pancreatic cancer to report 3-year survival rates.[11]

Data presented by Cartwright and colleagues[13] at the 2014 Annual Meeting of the American Society of Clinical Oncology (ASCO) support uptake of FOLFIRINOX (oxaliplatin, irinotecan, leucovorin, fluorouracil) as standard of care for patients with advanced pancreatic cancer and good KPS. In this analysis, an update of data presented at ASCO 2013, OS was observed to be significantly better in patients treated with FOLFIRINOX than in those who received gemcitabine-based therapy in a large outpatient setting. An additional 700 patients were identified, increasing total enrollment to 2422. This is the largest study to date to report FOLFIRINOX data.[13]

Twenty-seven percent of patients received FOLFIRINOX (24% in 2013), and 73% received gemcitabine-based therapy (76% in 2013), which is the current standard for chemotherapy in this setting. The median age of all patients at diagnosis was 67 years, and 95% had KPS of 70% or greater.

TABLE 2. MPACT Updated Survival Outcomes

Overall Survival	*nab*-Paclitaxel + Gemcitabine	Gemcitabine Monotherapy
3-year, %	4	0
2-year, %	10	5
1-year, %	35	22

After controlling for age and KPS, the investigators found that OS was significantly longer in patients receiving FOLFIRINOX than in those in the gemcitabine arm (11.2 months vs 7.2 months, respectively; *P* <.0001).[13]

Another emerging approach to the treatment of advanced pancreatic cancer involves the use of high-intensity focused ultrasound (HIFU). Shen and colleagues[14] assessed the safety and efficacy of concurrent chemotherapy with or without HIFU for patients with local advanced or metastatic pancreatic cancer. In

TABLE 3. Selected Actively Recruiting Clinical Trials in Pancreatic Cancer

Study Type	Study Title	Primary Outcome(s)	NCT ID
Phase II	Phase II Study of Modified FOLFIRINOX in Advanced Pancreatic Cancer	Progression-free survival	NCT01523457
Phase II	Trial to Investigate Intensified Neoadjuvant Chemotherapy in Locally Advanced Pancreatic Cancer (NEOLAP)	To compare effect of intensified neoadjuvant chemotherapy on conversion rate to respectability	NCT02125136
Phase II	Combination Chemotherapy With or Without Metformin Hydrochloride in Treating Patients With Metastatic Pancreatic Cancer (PACT-17)	Progression-free survival	NCT01167738
Phase I/II	Gemcitabine + Nab-paclitaxel and FOLFIRINOX and Molecular Profiling for Patients With Advanced Pancreatic Cancer	Complete response rate	NCT01488552
Interventional	Vaccine Therapy With or Without Cyclophosphamide in Treating Patients Undergoing Chemotherapy and Radiation Therapy for Stage I or Stage II Pancreatic Cancer That Can Be Removed by Surgery	Safety, feasibility, immune response	NCT00727441
Phase II	Nab-paclitaxel Plus S-1 in Patients With Advanced Pancreatic Cancer (NAPSPAC)	Objective response rate	NCT02124317
Phase II pilot study	Gemcitabine and CT-011 for Resected Pancreatic Cancer	Safety, feasibility	NCT01313416
Phase III	Immunotherapy Study in Borderline Resectable or Locally Advanced Unresectable Pancreatic Cancer (PILLAR)	Safety/efficacy of FOLFIRINOX	NCT01836432
Phase III	Nab-paclitaxel and Gemcitabine vs Gemcitabine Alone as Adjuvant Therapy for Patients With Resected Pancreatic Cancer (the "APACT" Study)	Disease-free survival	NCT01964430

this study, 248 patients were treated with concurrent chemotherapy with HIFU and 250 were treated with chemotherapy alone. The study demonstrated an objective response rate of 22.6% in the chemotherapy-plus-HIFU arm versus 16% in the chemotherapy-alone group. No significant differences in OS or AEs were noted.[14]

The role of chemoradiotherapy following resection for patients with pancreatic cancer is another area of ongoing investigation. A retrospective study by Khawaja and colleagues[15] sought to compare the efficacy of adjuvant gemcitabine plus gemcitabine-based chemoradiotherapy (n = 34) versus gemcitabine monotherapy (n = 19) following pancreaticoduodenectomy. The researchers found significantly higher median OS rates in patients who received adjuvant gemcitabine plus gemcitabine-based chemoradiotherapy than in those who received gemcitabine chemotherapy alone (20.4 months vs 16.6 months; HR = 2.42; 95% confidence interval [CI], 1.1-5.01). Subgroup analyses revealed superior OS and disease-free survival in patients who were younger than age 65 years, were at T3/T4 tumor stage, had negative resection margins, and had positive lymph node involvement.[15]

Immunotherapy

Novel immune-based strategies to detect and treat early- to late-stage pancreatic cancer have begun to show increasing promise. A combination treatment using two novel anticancer vaccines has emerged as one of the most promising developments to date. This treatment involves administering GVAX Pancreas vaccine followed by CRS-207. GVAX consists of genetically modified pancreatic cancer cells that secrete granulocyte-macrophage colony-stimulating factor (GM-CSF), an immune system stimulator. The vaccine is administered with low-dose cyclophosphamide, both to boost efficacy and to inhibit regulatory T cells. CRS-207 is composed of live attentuated *Listeria monocytogenes* that has been genetically modified to be safe for hu-

man use without losing its ability to trigger an immune response against mesothelin, a protein found on pancreatic tumor cells.[16]

A groundbreaking phase II study of this combination, reported at the 2014 Gastrointestinal Cancers Symposium, was the first to show efficacy of immunotherapy in pancreatic cancer.[17] These results prompted the FDA to grant Breakthrough Therapy status to CRS-207 and GVAX in July 2014 for use as combination treatment for metastatic pancreatic cancer.[18]

The study enrolled patients with metastatic pancreatic cancer who had refused or received at least one prior chemotherapy treatment. Patients were randomized 2:1 to receive either 2 doses of low-dose cyclophosphamide followed by GVAX followed by 4 doses of CRS-207 (Arm A, n = 61) or 6 doses of cyclophosphamide followed by GVAX (Arm B, n = 28) every 3 weeks. Repeated courses were permitted. The primary study endpoint was OS; secondary endpoints included safety and clinical and immune responses. Fifty-one percent of enrolled patients had received at least two prior chemotherapy regimens for metastatic pancreatic cancer. Median follow-up was 7.8 months.[17]

Median OS was 6.1 months in Arm A versus 3.9 months in Arm B (HR = 0.54; *P* = .011). Among patients who received 3 or more doses, median OS was 9.7 months versus 4.6 months, respectively (HR = 0.44; *P* = .0074). The treatment effect was especially evident in patients who had received at least two prior regimens for metastatic PDAC (median OS, 5.1 months in Arm A vs 3.7 months in Arm B; HR = 0.34; *P* = .001). Toxicities were manageable throughout; they included local reactions after GVAX administration and transient fevers, rigors, and lymphophenia after CRS-207 administration.[17]

These and other novel and emerging therapeutic strategies are the subjects of ongoing investigation **(Table 3)**.[19] As researchers continue to elucidate the mechanisms of pancreatic cancer and targeted therapies are developed, the medical and scientific communities inch closer to the goal of improving outcomes for patients with pancreatic cancer.

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