

ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

Section Editor: Clifford A. Hudis, MD

Pancreatic Cancer in Focus

Current and Emerging Treatment Options in Pancreatic Cancer



Ramesh K. Ramanathan, MD
Medical Director, Clinical Trials Program
Virginia G. Piper Cancer Center
Scottsdale Health Care
Scottsdale, Arizona
Clinical Professor of Medicine
Translational Genomics Research Institute
University of Arizona College of Medicine-Phoenix
Phoenix, Arizona

H&O What is the incidence of pancreatic cancer?

RR Each year in the United States, there are approximately 45,000 new cases of pancreatic cancer and 38,400 deaths from the disease. Worldwide, an estimated 300,000 cases of pancreatic cancer are diagnosed each year. There has been a slight increase in the annual number of estimated cases seen worldwide and—to a lesser extent—in the United States. Pancreatic cancer is a disease of the elderly, and the increased incidence is likely attributable to an aging population and increased life expectancy. The rising rate of smoking in the developing world is another likely contributor to the increase in pancreatic cancer diagnoses.

H&O What is the prognosis?

RR The prognosis varies. The best chance of a long-term cure is in patients who have early-stage disease that has not spread to the lymph nodes and who are candidates for surgery. Almost 20% of these patients will survive 5 years and hopefully achieve a cure. Unfortunately, few patients present at this stage. Most patients with pancreatic cancer present at an advanced stage when the disease has spread to the liver and other organs, and surgery is not an option. Overall, the 5-year survival in pancreatic cancer is only approximately 5%.

H&O What are the traditional treatment approaches to pancreatic cancer?

RR The traditional treatment approaches include surgery, radiation, and chemotherapy. Early-stage patients will undergo surgery, perhaps with chemotherapy and radiation afterward. Among patients with advanced disease who cannot undergo surgery, treatment consists mostly of chemotherapy, with occasional use of radiotherapy. For these patients, the standard of care for almost 20 years has been with gemcitabine (Gemzar, Lilly). Patients who receive gemcitabine have a median survival of 6 months and a 1-year survival of approximately 20%, which has been difficult to improve upon until recently.

H&O Could you please describe recent clinical trials examining novel treatment approaches in pancreatic cancer?

RR There have been approximately 30–40 large, phase III studies without a significant improvement in survival. In the past 2 years, however, improvements have been seen with 2 new therapies: the 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) regimen, developed in France, and the gemcitabine plus nab-paclitaxel (Abraxane, Celgene) regimen, developed in the United States at my institution (the Virginia G. Piper

Table. Data From the MPACT Trial

Intent-to-Treat	Nab-Paclitaxel plus Gemcitabine (n=431)	Gemcitabine (n=430)	Hazard Ratio (95% CI)	P-Value
OS, median (months)	8.5	6.7	0.72 (0.617–0.835)	.000015
1-year survival (%)	35	22		.000200
2-year survival (%)	9	4		.021234
PFS, median (months)	5.5	3.7	0.69 (0.581–0.821)	.000024
TTF, median (months)	5.1	3.6	0.70 (0.604–0.803)	<.0001

CI=confidence interval; MPACT=Metastatic Pancreatic Adenocarcinoma Clinical Trial; OS=overall survival; TTF=time to treatment failure.

Data from Von Hoff DD, et al. *J Clin Oncol* [Gastrointestinal Cancers Symposium, abstract LBA148]. 2013;31(suppl 4).

Cancer Center/TGen) and in collaboration with other programs. With these regimens, the barrier on overall survival of 6 months has been broken.

FOLFIRINOX was compared with gemcitabine in a randomized, phase II/III trial by Conroy and colleagues. Patients receiving the FOLFIRINOX regimen experienced increased overall survival (11.1 months vs 6.8 months) and progression-free survival (6.4 months vs 3.3 months) as compared with patients receiving gemcitabine. Rates of grade 3/4 neutropenia, febrile neutropenia, thrombocytopenia, diarrhea, and sensory neuropathy were significantly higher in the FOLFIRINOX group. Patients in the gemcitabine group had higher rates of grade 3/4 elevated alanine aminotransferase levels.

The phase III MPACT (Metastatic Pancreatic Adenocarcinoma Clinical Trial) study examined the addition of nab-paclitaxel to gemcitabine in 861 randomized patients. The primary endpoint of overall survival was significantly improved in the patients receiving nab-paclitaxel, as were progression-free survival (PFS) and time to treatment failure (Table). The overall response rate (ORR) was 23% in the nab-paclitaxel group and 7% in the gemcitabine group. The nab-paclitaxel/gemcitabine combination was well tolerated. The most common adverse events of grade 3 or higher in the combination arm and single-agent arm were neutropenia (38% vs 27%, respectively), fatigue (17% vs 7%, respectively), and neuropathy (17% vs 1%, respectively). Febrile neutropenia was more common in the combination group (3% vs 1%).

H&O Which patients are most likely to benefit from novel agents?

RR In contrast to malignancies such as breast cancer and colon cancer, pancreatic cancer currently lacks molecular markers. Therefore, which patients are most likely to benefit from novel agents is unknown. Research is under

way to identify molecular markers in pancreatic cancer. For nab-paclitaxel, secreted protein acidic and rich in cysteine (SPARC) may be an important biomarker. For the FOLFIRINOX regimen, thymidylate synthase (TS), topoisomerase (TOPO 1), and excision repair cross-complementation (ERCC) may be important. Hopefully, in the next few years, it will be possible to better select patients for certain therapies.

H&O Are there any other promising areas of research?

RR In the past 5 years, there has been an explosion of knowledge in pancreatic cancer, especially concerning the molecular biology of the disease. We are identifying targets that can be exploited and used for drug development. Several new targets are now being examined based on whole genome sequencing of pancreatic cancer cells. One of the biggest challenges in this disease is that pancreatic cancer cells develop a thick stroma around the tumor, which can be impenetrable to cancer drugs. Our group, which is part of the Stand Up To Cancer (SU2C) Consortium for Pancreatic Cancer, is working on understanding the genomic makeup of the cancer cells and is evaluating a number of new agents targeting the microenvironment and cancer cells. We are studying how cancer drugs are transported and metabolized within the cancer cells, as well as other approaches, including the metabolomics and the fuel supply, as we call it. Recent research has shed light on how pancreatic cancer cells preferentially take in nutrients like albumin and glucose (ie, the fuel supply) and ways to block this intake. In addition to the SU2C team, our clinical research consortium of 40 sites across the United States and Europe (The Pancreatic Cancer Research Team, www.PCRT.org) is actively engaged in a number of clinical trials for pancreatic cancer.

Another area of interest is molecular imaging with new agents. Positron emission tomography (PET) scans may be very helpful in pancreatic cancer. Preliminary evidence suggests that PET scans may predict which patients are likely to have a benefit very early. This technique is being examined in clinical trials. Another important focus of research in pancreatic cancer is KRAS targeting. Almost all pancreatic cancers have KRAS mutations, but it has been difficult to develop drugs against this target.

I would encourage patients and physicians to consider clinical trials. Very few cancer patients (3–5%) are

treated in clinical trials. All of the advances in pancreatic cancer in the past 20 years have been due to participation in clinical trials, which are crucial.

Suggested Readings

Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med*. 2011;364(19):1817-1825.

Von Hoff DD, Ervin TJ, Arena FP, et al. Randomized phase III study of weekly nab-paclitaxel plus gemcitabine versus gemcitabine alone in patients with metastatic adenocarcinoma of the pancreas (MPACT). *J Clin Oncol* [Gastrointestinal Cancers Symposium, abstract LBA148]. 2013;31(suppl 4).