Researchers Look to the Future for Breakthroughs in PC

Written by Muriel Cunningham

Several experts gathered to review the current state of pancreatic cancer (PC) research and treatment. Margaret Tempero, MD, University of California, San Francisco, San Francisco, California, USA, gave an overview of PC and hereditary subtypes. PC is a difficult disease to treat, because 80% of patients have advanced unresectable disease at diagnosis and 80% of patients who undergo surgical resection relapse. The cure rate is approximately 5% to 6%, and patients with metastases who are not treated live for a median of only 3 months. "Of all the epithelial malignancies, this is probably the most aggressive," noted Dr. Tempero. Whereas deaths due to cancers such as lung, breast, and colorectal have been falling, deaths from PC are increasing. The aging population combined with inadequate treatments and a lack of early detection methods are expected to result in further increases in PC in the next 2 decades. Should current trends continue, PC could become the second leading cause of cancer death by 2030 [Rahib L et al. *J Can Res* 2014], exceeding breast and colorectal cancer.

Risk factors for developing PC include age, cigarette smoking, heavy alcohol consumption (> 9 drinks/day), diabetes for > 10 years, higher body mass index and waist-to-hip ratios, and chronic pancreatitis. Five percent to 10% of PC cases are related to hereditary PC, of which there are 2 types. The first type is composed of families with recognized genetic syndromes with a germline mutation linked to an increased risk of PC (Table 1). The second type is familial pancreatic cancer, which is defined as families in which 2 or more members have had PC without a recognized mutation. Benign neoplasms are often detected in familial screening programs, and when cancer is diagnosed, it is not at an early stage. "This is very troubling right now for the entire community. Understanding which of these premalignant lesions are at highest risk is becoming a higher and higher priority," noted Dr. Tempero.

Christophe Louvet, MD, Institut Mutualiste Montsouris, Paris, France, gave an overview of the treatment of locally advanced pancreatic cancer (LAPC). The role of chemoradiation therapy (CRT) in the treatment of LAPC is currently debated because conflicting results have been obtained in clinical trials. CRT combined with chemotherapy remains a promising strategy, and its potential has been demonstrated in several studies. In the LAP-07 study [NCT00634725, Huguet F et al. *ASCO* 2014 (abstract 4001^)], the goal was to determine if CRT would increase overall survival (OS) in LAPC patients with tumors controlled after 4 months of chemotherapy. No difference in OS was seen by adding CRT. As a secondary end point, however, the local progression rate of 32% was significantly lower in the CRT group compared with the chemotherapy-alone group (46%; p = .035). In addition, the time of treatment-free survival was longer with CRT (median, 6.1 months) compared with chemotherapy (median, 3.7 months; log-rank, p = .017).

Dr. Louvet offered several different ideas for building on the results obtained in LAP-07. The first is to improve systemic chemotherapy by following up on positive results seen in studies with leucovorin calcium–fluorouracil–irinotecan hydrochloride–oxaliplatin (FOLFIRINOX), nanoparticle albumin–bound (nab)-paclitaxel plus gemcitabine, and nab-paclitaxel plus leucovorin calcium–fluorouracil–oxaliplatin (FOLFOX). The use of personalized medicine and further refining chemotherapy, surgery, and CRT protocols are also areas that may lead to improved outcomes. Two upcoming studies, RTOG 1201 [NCT01921751] and SCALOP 2 [NCT02024009], will hopefully answer some of these questions.

Eileen M. O'Reilly MD, Memorial Sloan Kettering Cancer Center, New York, New York, USA gave an overview of treatment options for metastatic PC. In the PRODIGE 4/ACCORD 11 study [Conroy T et al. *N Engl J Med* 2011], FOLFIRINOX was superior to gemcitabine, with a median OS of 11.1 months vs 6.8 months for gemcitabine (HR, 0.57; 95% CI, 0.45 to 0.73; p < .001). Controlling the disease with FOLFIRINOX also preserves quality of life for a longer period of time

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Table 1. Syndromes Associated With Pancreatic Adenocarcinoma

Syndrome	Relative Risk of Pancreatic Cancer
Familial atypical multiple mole melanoma (FAMMM)	13- to 22-fold
Familial breast and ovarian cancer	< 5-fold
Fanconi anemia, breast cancer	Unknown
Familial adenomatous polyposis	5-fold
Hereditary nonpolyposis colon cancer (HNPCC)	1.5- to 9-fold
Peutz–Jeghers syndrome	Up to 100-fold
Hereditary pancreatitis	53-fold
Cystic fibrosis	2.6- to 32-fold
Ataxia telangiectasia	Unknown

Adapted from Brand RE et al. *Gut* 2007.

Table 2. Systemic Treatment Options

Patient Category	First Line	Second Line
PS 0–1, younger, good liver function	▪ Clinical trial ▪ FOLFIRINOX ▪ Gemcitabine + nab-paclitaxel	▪ Clinical trial ▪ Gemcitabine-based regimen (if prior 5-FU) ▪ mFOLFIRINOX or mFOLFOX6? (if prior gemcitabine) ▪ FOLFIRI ▪ MM-398 + 5-FU/LV? ▪ Capecitabine (if prior gemcitabine)
PS 1–2, older, adequate liver function including good albumin	▪ Clinical trial ▪ Gemcitabine + nab-paclitaxel ▪ Gemcitabine ± erlotinib	
PS 2–3 ± major liver dysfunction/ poor albumin	Gemcitabine ± erlotinib	▪ Capecitabine ▪ Supportive care

nab=nanoparticle albumin–bound; PS=performance status.

Source: National Comprehensive Cancer Network (NCCN) Clinical Guidelines in Oncology. Pancreatic Adenocarcinoma. Version 1. 2014.

Tempero MA et al. *J Natl Compr Canc Netw* 2014.

[Gourgou-Bourgade S et al. *J Clin Oncol* 2013]. "This is, I think, a key point that we need to remember when we are treating patients, as quality of life is such a critical component in any state of pancreas cancer, particularly in the advanced disease setting," Dr. O'Reilly noted.

The other frontline choice is nab-paclitaxel plus gemcitabine, which was superior to gemcitabine alone in the MPACT trial (8.5 vs 6.7 months; HR, 0.72; 95% CI, 0.62 to 0.83; p < .001) [Von Hoff DD et al. *N Engl J Med* 2013]. Several modifications to FOLFIRINOX have been published, but no consensus currently exists regarding the best approach. "Options are good. Our challenge will be trying to select the right option for a given patient rather than saying that one is better than another," said Dr. O'Reilly. A treatment algorithm based on patient age and performance status is presented in Table 2.

Many Phase 3 PC studies have yielded disappointing results, but Malcolm J. Moore, MD, Princess Margaret Cancer Center, University of Toronto, Toronto, Ontario, Canada, believes that new agents in development provide hope for the future of PC treatment. Agents that have been unsuccessful in the past include vascular endothelial growth factor inhibitors, metformin, epidermal growth factor receptor inhibitors, oxaliplatin in second-line therapy, insulin-like growth factor receptor targeting, stromal disruption, and human equilibrative nucleoside transporter 1 expression with gemcitabine. "We really should be going into Phase 3 only when we have very strong signals in Phase 2," emphasized Dr. Moore.

PC is a genetically complex disease, with abnormalities occurring in a variety of different pathways that have become potential targets of pharmacological agents. New drugs in later phases of development focus on areas such as hypoxia (TH-302), DNA repair inhibition (poly adenosine diphosphate ribose polymerase inhibitors), mitogen-activated protein kinase pathways (MEK 1/2 inhibitors), and embryonic signaling pathways (gamma secretase inhibitors). Immunotherapeutic strategies are also being tested, including vaccines, T-cell activation via the CD40 pathway, targeting programmed cell death 1 and programmed death ligand 1, and targeting cytotoxic T-lymphocyte-associated protein 4. "I think we have made some progress in the last few years, thankfully, but when you look at all these new approaches the best is yet to come," concluded Dr. Moore.