

When the Going Gets Tough . . .

Pancreatic cancer is a challenging disease. Despite advances in the understanding of its biology, improvements in diagnostic and staging tools, reduction in surgical mortality, and development of new active cytotoxic chemotherapy drugs and molecular targeting agents, the number of new cases per year remains disappointingly similar to the number of deaths per year in the United States — around 30,000. The reasons for this are many, including late diagnosis, the lack of effective preventive methods, poor understanding of the risk factors, and a lack of curative treatment modalities for patients with advanced and metastatic disease.

In this issue, which focuses on pancreatic cancer, Dr. Vimalachandran and colleagues discuss the genetics and prevention of this disease. Compared with breast and colorectal cancers, the study of familial pancreatic cancer (FPC) is in its infancy. Family history of hereditary pancreatitis, hereditary nonpolyposis colorectal cancer (mismatch repair genes), familial atypical multiple mole melanoma syndrome (CDKN2A/p16), and Peutz-Jeghers syndrome (STK11/LKB1) have been linked to FPC. Germline mutations of the CDKN2A, STK11/LKB1, and mismatch repair genes occur rarely in FPC. However, the germline BRCA2 mutations are found in up to 19% of patients with pancreatic adenocarcinoma who have at least one first-degree relative diagnosed with this neoplasia. In addition, the risk of pancreatic adenocarcinoma is increased in some families that segregate mutations of BRCA2. Among modifiable risk factors, cigarette smoking remains the No. 1 villain, responsible for about 30% of adenocarcinomas of the pancreas. Guidelines for genetic testing for FPC and screening of families with FPC are still in the early stages of development.

Diagnosis and staging of patients with pancreatic cancer are challenging tasks. Factors that impede the diagnosis and staging of pancreatic cancer include the retroperitoneal location of the pancreas, the limited possibilities of differentiating the tumor from normal surrounding tissue by routine radiology techniques, and the presence of abundant desmoplastic tissue into the pancreatic tumor. Dr. Varadarajulu and coauthors review the role of endoscopic ultrasonography for staging and diagnostic tissue sampling in patients with pancreatic cancer. The applications of this intervention in the delivery of localized therapy, either palliative (celiac plexus neurolysis) or antitumor (intra-lesional injections of anticancer treatments) are other potential management adjuncts.

Surgery is the only curative modality for pancreatic cancer, but only 20% to 25% of newly diagnosed patients are surgical candidates. In recent years, the mortality associated with pancreatic cancer surgery has decreased. Dr. Zervos and colleagues discuss the effect of experience among surgeons or surgical oncologists on the success and safety of surgical management of patients with pancreatic cancer. The benefits of experience in optimizing outcomes cannot be overestimated. However, in addition to technical expertise in pancreatic cancer surgery, the experienced surgeon is a key component of a multidisciplinary team that determines tumor resectability, assesses the need of tissue diagnosis prior to operation, and participates in the decisions regarding the need for neoadjuvant and adjuvant treatments.

The majority of patients with pancreatic cancer present with advanced and metastatic disease. In most cases, chemotherapy and radiotherapy are regarded as palliative interventions. In patients with locally advanced unresectable disease, the role of the addition of radiotherapy to chemotherapy in improving survival compared with chemotherapy alone has been challenged by a small ECOG randomized trial in which patients received either 5-fluorouracil (5-FU) plus radiotherapy or 5-FU alone. Both study arms had similar median survivals. A confirmatory trial from ECOG is underway that randomizes unresectable advanced pancreatic cancer patients to chemotherapy or chemoradiotherapy. In the adjuvant setting, the addition of radiotherapy after surgery has also been questioned. The results of the small randomized Gastrointestinal Study Group Trial favored the addition of 5-FU combined with radiotherapy followed by single-agent 5-FU compared with no treatment after curative pancreatic cancer surgery. A more recent randomized phase III trial (ESPAC 1) with more patients enrolled and more robust statistical power demonstrated no benefit to the addition of radiotherapy either as a single modality or combined with chemotherapy in the postoperative setting of patients undergoing surgical resection of pancreatic cancer with curative intent.

In patients with more advanced and metastatic disease, gemcitabine is the current standard of care. In a randomized pivotal phase III trial, single-agent gemcitabine resulted in longer median survival and better clinical benefit response (improvement in pain and/or Karnovsky performance status or lean body weight gain if a tie in the first two assessments occurred) compared to 5-FU. Several follow-up phase III trials adding 5-FU, cisplatin, oxaliplatin, or

irinotecan to gemcitabine compared to gemcitabine alone have not resulted in a survival improvement despite an increase in progression-free survival and/or response rates. Hopes were raised with the development and introduction of molecular targeting agents in clinical trials. Dr. Saad and Dr. Hoff review the so-far disappointing results with metalloproteinase inhibitors, epidermal growth factor receptor 1 and 2 blockers, and farnesyltransferase inhibitors in the management of advanced and metastatic pancreatic cancer.

In a disease with such difficult general outcomes, Dr. Brescia discusses the value of supportive care. Decision-making, always difficult in the management of any complex disease, is even more challenging in patients with cancer. The goals for a specific patient with cancer — curative intent, function, pain control, and improved quality of life — are highlighted. For patients with pancreatic cancer, Dr. Brescia provides guidance on symptom management for biliary obstruction, depression (highly prevalent but undertreated), pain control and the nuances of pain management, intestinal obstruction, fatigue, and terminal events.

To complete this issue, Dr. Shoemaker and coauthors describe a patient receiving 5-FU-based chemotherapy who had a coronary artery event resulting in vasospasm during the infusion of 5-FU. The patient had no critical lesions in the coronary arteries. Coronary artery spasm was the main pathophysiologic event. The different hypotheses for coronary artery events in patients on fluoropyrimidine therapy are summarized.

Working on this issue of *Cancer Control* provided me with the opportunity to learn from these authors who are leaders in their field. They thoroughly reviewed the data for their articles to provide us with guidance in meeting the many challenging situations that occur in our daily practice. I am sure that readers will enjoy this issue of *Cancer Control* as much as I did.

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