Therapeutic Approaches for Metastatic Pancreatic Adenocarcinoma

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KEYWORDS

• Pancreatic cancer • Metastatic disease • Gemcitabine • FOLFIRINOX
• Nab-paclitaxel • Targeted therapy

KEY POINTS

- Over 50% of patients with pancreatic cancer present with metastatic disease, when treatment is palliative and consists primarily of systemic chemotherapy.
- Recent studies have identified 2 combination chemotherapy programs that impart improved survival times compared with gemcitabine monotherapy for patients with adequate functional status: FOLFIRINOX (folinic acid, 5-fluorouracil, irinotecan, oxaliplatin) and gemcitabine plus nab-paclitaxel.
- New treatment approaches that leverage a growing understanding of pancreatic cancer biology are under development, including those that modify tumor-associated stroma, inhibit signaling from mutant *KRAS*, augment host immune response to the cancer, and exploit defects in tumor DNA repair mechanisms.

INTRODUCTION

Among 46,420 estimated new cases of pancreatic cancer in the United States in 2014, the majority of patients are diagnosed with metastatic disease at presentation.[1] Among the patients able to undergo a potentially curative resection, most experience disease relapse, necessitating palliative therapy. Thus, the 5-year survival rate among all patients diagnosed with pancreatic ductal adenocarcinoma (PDAC) remains estimated at 6.7%, with pancreatic cancer projected to become the second leading cause of cancer death in the United States by 2020.[2]

Since the US Food and Drug Administration (FDA) approval of gemcitabine monotherapy in 1996,[3] multiple randomized trials have failed to demonstrate improved

These authors have nothing to disclose.
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Hematol Oncol Clin N Am 29 (2015) 761–776
http://dx.doi.org/10.1016/j.hoc.2015.04.012 **hemonc.theclinics.com**
0889-8588/15/$ – see front matter

survival for combination chemotherapy programs in advanced PDAC. However, in the past several years, clinical trials of FOLFIRINOX[4] and gemcitabine plus nab-paclitaxel[5] have demonstrated improved outcomes compared with gemcitabine alone in patients with metastatic PDAC. Targeted therapies and immunotherapy building upon these new chemotherapy backbones hold great promise for future improvements in patient outcomes.

PATIENT EVALUATION AND PROGNOSTIC MARKERS

Suspicion for metastatic PDAC typically results from symptomatic complaints and the radiologic appearance of a pancreatic mass associated with a characteristic pattern of metastatic spread. Presenting symptoms relate either to the local effects of the primary pancreatic mass, such as with biliary obstruction, epigastric pain, and weight loss, or from symptoms due to metastatic deposits, which most commonly occur in the liver, peritoneum, and lungs. Initial evaluation consists of computed tomographic scan encompassing the chest, abdomen, and pelvis and biopsy of the primary tumor or a metastatic site to confirm invasive adenocarcinoma. Histologic evaluation is important because less-common malignancies can resemble metastatic PDAC but require distinct management. These malignancies include less-common pancreatic malignancies such as pancreatic neuroendocrine tumors and nonpancreatic malignancies such as high-grade lymphomas or metastatic implants to the pancreas.

Immunohistochemistry (IHC) of a metastatic biopsy can be helpful in confirming the diagnosis when the primary pancreatic mass is difficult to visualize on imaging studies. PDAC typically demonstrates reactivity against cytokeratin (CK) 7, CK19, and carcinoembryonic antigen (CEA) and often lacks reactivity to CK20.[6] IHC analysis for loss of Smad4 expression, which occurs in approximately 50% of PDAC tumors, as well as mutation analysis of the *KRAS* oncogene, which is mutated at codons 12 or 61 in 80% to 95% of tumors, can also be useful in defining a pancreatic origin when the primary site is radiologically indistinct.

The serum markers carbohydrate antigen 19-9 (CA19-9) and CEA should be assessed at diagnosis, and if their levels are elevated, they can be followed serially during therapy as a disease surrogate. CA19-9 is a sialylated Lewis blood group antigen that requires fucosyltransferase 3 (FUT3) activity for its production. Almost 10% of the population bears a germline polymorphism in *FUT3*, making them Lewis-antigen negative and incapable of producing CA19-9.[7] For individuals capable of CA19-9 production, low serum CA19-9 levels at diagnosis and declines in CA19-9 levels with initiation of chemotherapy are associated with improved outcomes.[8,9] Additional clinical, circulating, and histologic factors are associated with poorer prognosis in patients undergoing chemotherapy for metastatic PDAC, including older age, poor performance status, high serum C-reactive protein (CRP) levels, high metastatic burden, presence of peritoneal carcinomatosis, and high-grade histology.[10,11]

Molecular alterations have also been associated with prognosis in PDAC. Pancreatic cancers are typified by genetic alterations in *KRAS*, *TP53*, *CDKN2A*, and *SMAD4*, with approximately 40% of tumors possessing alterations in all 4 genes.[12] Initial studies have demonstrated a poorer prognosis for patients with tumors possessing a greater number of these alterations.[12] Furthermore, a comprehensive sequencing analysis of resected pancreatic cancers identified a survival disadvantage to the presence of somatic alterations in axon guidance genes.[13]