Treatment of Metastatic Pancreatic Adenocarcinoma: New Options and Promising Strategies

By Maeve A. Lowery, MD [4] and Eileen M. O'Reilly, MD [5]

All improvements in outcomes for patients with metastatic pancreatic adenocarcinoma have occurred with the use of cytotoxic agents, which will probably remain the mainstay of treatment for advanced pancreatic adenocarcinoma.

Pancreatic adenocarcinoma represents a rising public health challenge. The steady increase in diagnoses in the United States over the past several decades has occurred in the context of relatively flat mortality rates and modestly effective therapies.[1,2] While the past several years have seen the advent of several new therapies for advanced disease that offer some light for the future,[3,4] a major impact on patient survival in this disease is likely to be achieved only through advances in screening, early detection, and effective cancer prevention strategies. Thota and colleagues provide a comprehensive summary of the available treatment choices in 2014 for advanced pancreatic cancer, and by comparing the differences between treatments, they appear to conclude that FOLFIRINOX (leucovorin, fluorouracil, irinotecan, and oxaliplatin) represents the most active therapy for first-line treatment of advanced pancreatic adenocarcinoma for vigorous patients with a well-preserved performance status.[5] We concur with the authors' interpretation.

The past decade has provided substantial new insights into the molecular underpinnings and genomics of pancreatic adenocarcinoma. Although these observations have yet to be translated into meaningful improvements in outcome, we remain hopeful that an increased understanding of the disease at a molecular level will ultimately lead to the development of more effective and selective therapy.[6,7] To date, however, the major progress that has occurred in the therapeutic arena is in cytotoxic therapy for this disease. As Thota and colleagues point out, there is only one “targeted” therapy approved by the US Food and Drug Administration for the treatment of pancreatic adenocarcinoma: erlotinib. Its marginal impact on the natural history of advanced pancreatic adenocarcinoma when combined with gemcitabine remains a subject of much debate. The erlotinib/gemcitabine combination will probably be further displaced given the advent of FOLFIRINOX and albumin-bound paclitaxel and gemcitabine combinations, unless a subset of patients most likely to benefit can be clearly and prospectively identified.

New choices in the treatment of advanced pancreatic adenocarcinoma are welcomed. While one can clearly argue the merits and limitations of comparing FOLFIRINOX with albumin-bound paclitaxel and gemcitabine in cross-trial analyses, the fact is that we now have two reasonably active treatment options to recommend to patients. A prospective head-to-head comparison of the two combinations, although potentially worthwhile in some regards, is unlikely to be a well-justified use of resources from the patient, financial, and other perspectives. On an individual basis, considerations for choosing one regimen over another—in addition to performance status, major organ function, and comorbidities—include patient preference and the need for central venous access or home infusion; these are the topics of daily physician-patient discussions.

Albumin-bound paclitaxel was evaluated in patients with a wide range of performance status (70% to 100% on the Karnofsky scale), in a broad base of both community and academic settings, and in a globally conducted trial,[4] which suggests the results may apply to a large swath of patients. Moreover, the albumin-bound paclitaxel and gemcitabine combination may theoretically be an easier regimen than FOLFIRINOX to add novel therapeutic agents to; indeed, a series of phase Ib and randomized phase II studies evaluated early safety and dosing considerations for a variety of antistromal targeting agents, notch and stem cell targeting agents, and heat shock protein inhibitors, among others. To date, no targeted agents have been successfully combined with FOLFIRINOX, although a series of studies that add agents with non-overlapping toxicities are underway. The addition of other agents to this four-drug regimen is likely to remain challenging, however, at least for the “parent” version of the regimen. To reduce toxicity while maintaining antitumor activity and dose intensity, several modifications of the FOLFIRINOX regimen have been
suggested, which may prove easier to combine with targeted agents. At Memorial Sloan-Kettering Cancer Center (MSKCC) Yu and colleagues, in collaboration with investigators at CellPath Therapeutics and others, have developed an approach to improving patient-treatment selection by isolating and characterizing circulating tumor and invasive cells (CTICs).[8] Based on the use of an in vitro validated model system that analyzes these CTICs, a prediction tool has been generated for allocating which systemic regimen might be most appropriate for a given patient. In a small prospective study at MSKCC, in which investigators and patients were blinded to the results of the model prediction, patients who received therapy that the model indicated their tumor was sensitive to had more favorable outcomes than those who received therapy that the model indicated their tumor had either intermediate sensitivity or resistance to. An additional pilot study is underway, and a future goal is a randomized trial that compares the model prediction for allocation of therapy with investigator/empiric choice. Even without the approval of any new agents, such a predictive ability could meaningfully improve outcomes for patients by refining treatment selection. Results of correlative studies from the Metastatic Pancreatic Adenocarcinoma Clinical Trial (MPACT) are awaited and may provide prospective validation of tumor secreted protein acidic and rich in cysteine (SPARC) expression as a predictive biomarker for sensitivity to albumin-bound paclitaxel.

Pancreatic cancer is characterized by a highly immunosuppressive microenvironment that facilitates evasion of immune surveillance. Preclinical studies have identified immune defects even in preinvasive pancreatic lesions, with progressive accumulation of myeloid-derived suppressor cells in murine pancreatic tumors, which negatively correlates with the presence of tumor-infiltrating effector T cells.[9,10] These observations provide a strong rationale for the development of immunotherapy in pancreatic adenocarcinoma, and as the researchers in these studies note, a new wave of immunotherapeutic investigation with checkpoint inhibitors (programmed death 1 [PD-1], programmed death 1 ligand [PD-L1], and anti-cytotoxic T lymphocyte–associated antigen 4 [CTLA-4]) and other strategies, including chimeric antigen receptor targeting and a new generation of vaccines (eg, hyperacute vaccination using embryonic antigens [algenpantucel-L]), may hold promise. Investigation is underway for all these strategies. Nonetheless, Thota and colleagues acknowledge that all improvements in outcomes for patients with metastatic pancreatic adenocarcinoma have occurred with the use of cytotoxic agents. This observation is a sobering fact; thus, for now and the immediate future, cytotoxic therapies will probably remain the mainstay of treatment for advanced pancreatic adenocarcinoma.

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**References:**


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