HIGHLIGHT ARTICLE

Utilizing Endoscopic Ultrasound-Guided Fine Needle Aspiration in Identifying Molecular Targets for Pancreatic Cancer

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Summary

Pancreatic cancer remains a devastating disease, with poor survival rates and high recurrence rates with current treatment regimens. Over the years we have come to understand the complex biology of this cancer, involving cross-talking signaling pathways that proffers resistance to current therapy. Several molecularly targeted agents remain in development. At the 2013 American Society of Clinical Oncology (ASCO) Annual Meeting, an abstract (#4051) was presented which explored using endoscopic ultrasound-guided fine needle aspiration of pancreatic cancer tissue to identify molecular targets, and argued for the feasibility of personalizing pancreatic cancer therapy based on the activated molecular pathways identified. We summarize their findings and discuss the possibility of utilizing this model to obtain a better understanding of pancreatic cancer at each stage of its metamorphosis and target therapy at these different levels

What Did We Know Before the 2013 ASCO Annual Meeting?

Pancreatic cancer remains an aggressive cancer with poor survival rates despite advances in research. It is estimated that 45,220 men and women will be diagnosed with the disease in 2013 and that 38,460 people will die from it [1]. Surgical resection remains the only potentially curable approach, but given the relatively late stage of diagnosis and high recurrent rates, adjuvant therapy remains practical [2]. Our improved understanding of the molecular bases of pancreatic cancer has led to extensive research on molecularly targeted therapy in the treatment of pancreatic cancer. Unfortunately, many of the agents that looked promising in pre-clinical studies haven't been successful in clinical trials with the exception of Erlotinib, the epidermal growth factor receptor (EGFR), which showed minimal improvement in survival when combined with Gemcitabine [3]. In the study published by Moore *et al*. [4, 5], 569 patients were recruited and treated with gemcitabine *versus* a combination of gemcitabine and erlotinib. The combinatorial arm of the study was noted to have a 6.24-month survival period compared to 5.91 months in the group treated with gemcitabine alone (P=0.038). Similarly, the 1-year survival rate was 24% in the combinatorial arm versus 17% in the group treated with only gemcitabine (P=0.023). Since 2006, erlotinib has been approved by the Food and Drug Administration to be used in the treatment of advanced pancreatic cancer [5]. Other agents targeting epidermal growth factor receptor (EGFR), vascular endothelial growth factor (VEGF), matrix metallo-proteases, and farnesyl transferase, among others, remain in development.

We now understand that the biology of pancreatic cancer is complex, with abundant cross-talk between cell proliferation signaling pathways, allowing for cancer cell survival even though some pathways have been blocked by targeted therapy [6]. Therefore, the pancreatic cancer cell becomes a "moving target" [6]. Pancreatic cancer also has different characteristics and targets at different stages of its development and may respond to therapy differently at different stages of its cycle [6]. It has been recommended that pancreatic cancer samples obtained from surgery or biopsy be utilized in genomic and proteomic studies to individualize tumor characters at different stages of its development and access responsiveness to different therapies at each stage so as to design a tailored therapy with minimal side effects [6].

Keywords Endoscopic Ultrasound-Guided Fine Needle Aspiration; Molecular Targeted Therapy; Pancreatic Neoplasms

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What Did We Learn at the 2013 ASCO Annual Meeting?

Identifying Targetable Pathways in Pancreatic Cancer from Endoscopic Ultrasound-Guided Fine-Needle Aspirates (EUS/FNA): Providing a Personalized Approach to Targeted Therapy (Abstract #4051 [7])

Wang-Gillam *et al*. presented an abstract on a personalized approach to targeted therapy in pancreatic cancer by identifying targetable pathways from endoscopic ultrasound-guided fine needle aspirates of pancreatic cancer tissue [7]. The rationale was that identifying the activated key signaling pathways from the cancer tissue will help in selecting the patients best suited for the kinase inhibitor trials. Molecular profiling (collaborative enzyme enhanced reactive immunoassay; CEER) was performed on pancreatic tissue obtained from patients who had undergone endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) for suspicious pancreatic lesions. Of the 61 patients with pancreatic cancer, 62% showed HER3 activation, and 52% showed activation of two or more HER pathways. Twenty-three percent of these patients with pancreatic cancer had both HER2 and HER3 activation. There was a high prevalence of HER, PI3K and AKT activation noted as well. The authors postulated that their findings proved the possibility of using pancreatic tissue obtained from FNA to identify targetable pathways as well as the possibility of personalized approach to therapy given the variability in pathway activation in pancreatic cancer patients.

Discussion

Epidermal growth factor receptor over-expression may be detected in up to 90% of pancreatic tumors [8], thus the development of targeted therapies against EGFR. Erlotinib is a tyrosine kinase inhibitor, which selectively binds EGFR, and is known to enhance tumor cell apoptosis when combined with gemcitabine [5]. Given that cancer cell lines which are sensitive to erlotinib express the HER3 receptor (which regulates the PI(3)K/Akt pathway) whereas those that are not sensitive to erlotinib do not, it has been postulated that erlotinib inhibits both EGFR and HER3, and that HER3 could be used as a biomarker of responsiveness to erlotinib [5]. The study presented by Wang-Gillam *et al*. at the ASCO 2013 Annual Meeting (Abstract #4051) showed high percentage of HER3 positivity in patients with pancreatic cancer, and a high prevalence of PI3K and AKT activation as well, suggesting responsiveness to erlotinib and validating the idea of targeting therapy based on molecular profiling which the authors postulate.

Pancreatic cancer is not a disease that is controlled by a single pathological process [6]. Several cell-signaling pathways are involved that cross-talk with each other, causing pancreatic cancer cells to develop resistance to treatment strategies. In light of this, given our knowledge of the tumor biology, targeting multiple pathways should be the next era in treatment of pancreatic cancer. In addition to preclinical studies, the role of molecular targets in treating pancreatic cancer should also be studied in clinical samples at different stages of the disease [6]. Given the expression of different characteristics by the cancer at different stages of its pathogenesis, maintenance, and pathogenesis, clinical samples should be obtained and drug sensitivity testing performed at these different stages to help guide therapy [6]. Endoscopic ultrasound-guided biopsies as described in Abstract #4051 should be utilized in clinical trials for identifying molecular targets. Information that would be obtained from this when analyzed with information collected from multiple pathways would be useful in developing novel therapeutics. The prospect of personalized therapy in the treatment of pancreatic cancer based on molecular profiling is one that is fascinating, and per Wang-Gillam *et al*. appears to be feasible.

Conflict of interest The authors have no potential conflicts of interest

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