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Treatment of Pancreatic Cancer: Where Are We Now?

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Pancreatic adenocarcinoma was the 10th most common cause of cancer in 2010 with an estimated incidence of 43,140 in the United States. However, what is more striking is that estimated deaths reached 36,800, making it the 4th most common cause of cancer death in 2010¹. This disproportional mortality reflects treatment inefficacy for pancreatic cancer. In fact, compared to the other four major causes of cancer-related death—lung, colon, breast, and prostate—whose death rates are declining, pancreatic cancer death rates have remained relatively stable. What adds to this challenge is that less than 20% of patients with pancreatic cancer present with localized disease at the time of diagnosis². According to data from the Surveillance, Epidemiology, and End Results (SEER) registry, 8% are localized, 25.9% have regionally spread, 50.5% have metastatic disease, and 15.5% are unstaged at time of diagnosis³. With the advent of gemcitabine in 1996, five-year survival for pancreatic cancer patients has modestly improved from 3% to 6%. However, the prognosis remained poor with a median overall survival of 3.5 months and with only 5.3% of patients alive at the 3-year mark from 1998-2005³. However, there have been strides to improve treatment by focusing on the molecular pathogenesis of pancreatic adenocarcinoma.

It has become widely known that pancreatic cancer arises from a dynamic interplay between tumor epithelial cells and tumor stromal cells mediated by multiple signaling pathways. Such pathways include but are not limited to: KRAS, CDKN2A, TGF- β , TP53, EGFR, and NOTCH pathways⁴. Recently, gemcitabine has been supplemented by other therapies, such as EGFR inhibitors like erlotinib. Although the survival benefit was modest from this addition, it paved the way for the initiation of other clinical trials using this molecular approach. Concomitantly, studies are being undertaken to identify predictive markers to measure sensitivities to established drugs (gemcitabine and erlotinib) in order to stratify which patients will receive the most benefit from a given drug depending on their tumor profile.

This review will summarize the trials that have led to the current standard of therapy, highlight the most important signaling pathways along with the in vitro and in vivo trials that have attempted to target these pathways, and conclude by looking at the development of predictive markers with current treatment regimens.

Many clinical trials have been conducted to evaluate adjuvant treatment regimens for pancreatic cancer. In 1997, a phase III randomized control trial⁵ compared gemcitabine to 5-FU, demonstrating an increased overall median survival and increased 12-month survival rate in the gemcitabine group versus 5-FU group (5.7 months vs. 4.4 months and 18% vs. 2% respectively). This pivotal trial brought gemcitabine in the limelight as the standard of therapy over 5-FU in the adjuvant setting. Subsequently, in 2001-2004, the ESPAC-1 trial⁶ examined the efficacy of adjuvant 5-FU chemotherapy versus chemoradiotherapy versus observation alone. This multicenter trial showed a significant survival benefit for those who received adjuvant chemotherapy compared to those who did not—21% vs. 8% respectively. It also demonstrated a deleterious effect on survival in those patients who received chemoradiotherapy, conferring a five-year survival rate of 10% vs. 20% in the chemoradiotherapy group vs. control group, respectively.

The ESPAC-1 trial stimulated further study of adjuvant chemotherapy. In 2008, the CONKO-001 trial⁷ randomized 368 patients to receive adjuvant chemotherapy with gemcitabine vs. observation alone. The results showed a statistically significant difference in median disease free survival in the gemcitabine arm vs. observation arm (13.4 months vs. 6.9 months), longer median survival (22.8 mos vs. 20.2 mos), and overall 5-year survival (21% vs. 9%). Following this, two studies, the RTOG 97-04 and ESPAC-3 trial, sought to compare gemcitabine to 5-FU in order to confirm or negate the original 1997 clinical trial attesting to gemcitabine's superiority. In the RTOG 97-04 trial⁸, 451 patients were randomized to either 5-FU or gemcitabine for three weeks prior to chemoradiation and 12 weeks after chemoradiation

therapy. The results showed a median survival of 20.5 months and 3-year survival of 31% vs. a median survival of 16.9 months and 3-year survival of 22% in the gemcitabine arm vs. 5-FU arm, respectively ($p=.05$). Furthermore, in the ESPAC-3 trial⁹, 1,088 patients were randomized post-resection to receive gemcitabine or 5-FU. The median overall survival was 23.6 months vs. 23.0 months in the gemcitabine and 5-FU group, respectively and so, did not demonstrate a significant difference.

Although the trials delineated above are inconsistent with respect to chemoradiotherapy and which chemotherapy is most effective, the National Comprehensive Cancer Network guidelines recommended that patients receive systemic gemcitabine followed by 5-FU chemoradiation or systemic chemotherapy alone with gemcitabine, 5-FU, or capecitabine⁷. However, in 2010, a phase III trial randomized 360 patients to gemcitabine vs. FOLFIRINOX (5FU/leucovorin, irinotecan, oxaliplatin) to assess overall survival in metastatic pancreatic patients. The FOLFIRINOX group displayed significantly longer overall survival, progression-free survival, better response rate, along with more treatment-related toxicity than the gemcitabine arm¹⁰. Although this trial demonstrated a treatment regimen more effective than gemcitabine, predictive markers are needed to determine which patients will benefit more from this aggressive approach.

Currently, the molecular pathogenesis of pancreatic adenocarcinoma has been a primary focus, leading to clinical trials involving targeted therapies. With the completion of genomic sequencing of pancreatic adenocarcinomas (sample size of 28), a total of 275 different genes have been found to be mutated. Of these 275 mutations, only 39 were repeated and only four of these genes (KRAS, CDKN2A, TP53, SMAD4) had a prevalence rate greater than 7%, posing a challenge to targeted therapies⁴. We know that pancreatic adenocarcinoma arises from ductal epithelium. However, it has been more recently emphasized that the invasive progression of this tumor is not solely due to the tumor cells alone; in fact, there is a dynamic interplay between the tumor cells and the surrounding stromal cells through multiple signaling pathways⁴. Understanding the dual compartment model of pancreatic cancer offers insight into alterations to the molecular framework that drive the tumor compartment, stromal compartment, or both.

We will focus on the following important signaling pathways and related *in vivo* and *in vitro* trials: KRAS, EGFR, TGF- β , CDKN2A, TP53, and NOTCH pathways. The KRAS oncogene is a membrane-bound protein with GTP-ase activity that affects multiple signaling pathways involved in cell-cycle progression, cytoskeletal alterations, and inhibition of apoptosis¹¹. Mutations in KRAS occur early on in pancreatic cancer and appear to be a key driver in tumorigenesis; in fact, about ninety percent of pancreatic adenocarcinomas have a mutation in the KRAS oncogene. Mouse models with mutant forms of KRAS¹² demonstrated an increase in number and grade of neoplastic lesions.

Unfortunately, attempts at targeting KRAS have been unsuccessful; however, it may be a predictive marker for other targeted therapies, which will be discussed below. The epidermal growth factor receptor (EGFR) family is a group of tyrosine kinase receptors—Her1 (ErbB-1), Her2 (ErbB-2), Her3 (ErbB-3), and Her4 (ErbB-4)—which bind ligands such as epidermal growth factor (EGF) and transforming growth factor- α (TGF- α). Binding of the ligands results in downstream signaling of multiple pathways, such as Ras, phosphoinositide-3 kinase, and phospholipase C. In pancreatic cancer cell lines, amplification of ErbB-1 and ErbB-2 genes occur most frequently, whereas there is little expression of this gene in normal pancreatic ductal epithelium¹³. It is thought that alterations in this receptor affect the tumor compartment, while overexpression of the ligands (EGF and TGF- α) affects the stromal compartment. In fact, it is not only the tumor cells that overproduce these ligands, it is also the desmoplastic cells in the stromal compartment¹⁴. From these findings, clinical trials were conducted with multiple EGFR inhibitors. In 2007, a phase III clinical trial investigated the efficacy of dual therapy with gemcitabine and cetuximab, an anti-EGFR monoclonal antibody used in the treatment of colon cancer, versus gemcitabine alone against locally advanced or metastatic pancreatic cancer¹⁵. The median survival was 6.5 months in the gemcitabine-cetuximab arm and 6 months in the gemcitabine arm, yielding no significant benefit in overall survival with the addition of cetuximab¹⁵. Similarly in 2007, another phase III trial was conducted to determine the efficacy of dual therapy with gemcitabine and erlotinib, an anti-ErbB-1/Her1 drug, versus gemcitabine alone. The patients in the gemcitabine-erlotinib arm had an increased overall survival, one-year survival (23% vs. 17%), and progression-free survival¹⁶. This study was groundbreaking, as it was the first to find adding an agent to gemcitabine improved survival. In 2011, a random-

ized phase II trial looked at the addition of yet another EGFR inhibitor panitumumab to the gemcitabine-erlotinib treatment regimen to examine whether it had superiority over the gemcitabine-erlotinib regimen.

The progression-free survival was 3.3 months in the panitumumab-gemcitabine-erlotinib arm vs. 2.0 months in the gemcitabine-erlotinib arm, demonstrating overall survival benefit with dual inhibition of the EGFR pathway³. Yet another signaling pathway involved in pancreatic cancer is the transforming growth factor-B (TGF-B) pathway. It is activated through binding of serine-threonine receptors, which in turn phosphorylate receptor-mediated SMADS (SMAD, SMAD2, SMAD3, SMAD4). These receptor-mediated SMADS translocate to the nucleus and transcribe genes involved in cell-cycle progression. The most common mutation is that of SMAD4 (DPC4), deleted in over fifty percent of pancreatic adeno-carcinomas^{17,18}. Loss of SMAD4 appears late in the progression of pancreatic cancer, facilitating the epithelial-to-mesenchymal transition which defines the more invasive and aggressive phenotype¹⁹⁻²⁰. The TGF-B pathway also classically fits into the dual compartment model of pancreatic cancer, having effects on both tumor epithelial cells and the stromal cells. In fact, a transgenic mouse model with TGF-B overexpression demonstrated increased collagen synthesis by pancreatic stromal cells, resulting in a desmoplastic reaction²¹.

Additionally, it appears that the loss of SMAD4 in combination with KRAS mutation results in tumorigenesis²². Bardeesy et al. created a mouse model with deletion of SMAD4 alone vs. deleted SMAD4 and KRAS mutation²². The model with deleted SMAD4 alone did not have carcinogenic properties; however, the deleted SMAD4 on KRAS mutation showed an accelerated growth of tumor both in the tumor and stromal compartments²². This study suggests that cross-talk occurs between these multiple signaling pathways, supporting a multi-targeted approach. In 2012, a mouse model was created to test this hypothesis by targeting both EGFR and TGF-B pathways, resulting in effective tumor inhibition and suggesting that this mechanism of treatment could be an upcoming therapeutic approach²³.

Furthermore, CDKN2A is a tumor suppressor gene that encodes p16; therefore, loss of CDKN2A results in cell-cycle progression through the phosphorylation of the Rb protein²⁴⁻²⁶. About ninety-five percent of pancreatic adeno-carcinomas have a loss of

CDKN2A and thus, p16¹⁹. A transgenic mouse model with loss of p16 on top of KRAS mutation demonstrated an earlier and more aggressive cancer phenotype than KRAS mutation alone²⁷. In vitro pancreatic cells treated with a CDK inhibitor plus gemcitabine showed considerable success by inhibiting tumor growth, sensitizing cells to gemcitabine-induced apoptosis, and down-regulating angiogenesis²⁸. TP53, another well-known tumor suppressor gene, encodes p53; loss of TP53 results in a cascade of events bypassing integral DNA checkpoints and apoptotic signals. TP53 mutations are found in fifty to seventy-five percent of pancreatic tumors, with missense point mutations being the most common type of mutation²⁹⁻³¹. Multiple in vivo mouse models³²⁻³³ demonstrated that mutations in both p53 and KRAS resulted in early and more progressive tumorigenesis, transforming preinvasive lesions induced by KRAS to invasive and metastatic carcinomas from the addition of the p53 mutation. Furthermore, the NOTCH pathway is an embryogenic pathway that prevents terminal differentiation of cells. When ligands bind to NOTCH receptors, the enzyme γ -secretase cleaves the receptor's intracellular domain so that it can translocate to the nucleus and transcribe its respective genes³⁴.

Researchers have demonstrated increased expression of NOTCH genes in early neoplastic lesions as well as in chronic inflammation from cancer or pancreatitis³⁵. NOTCH also appears to play a role in interacting with other signaling pathways such as EGFR and NF-kB³⁶. In vitro and in vivo studies have attempted to inhibit the NOTCH pathway by inhibiting γ -secretase, resulting in less progression to invasive carcinoma³⁷. Others have further investigated the role of the stromal component of pancreatic adenocarcinoma. Angiogenesis is vital to growth and progression of many tumors. Although microvessel density is fairly low in pancreatic adenocarcinoma, it has been established that angiogenesis plays a central role in the early parts of tumor progression³⁸⁻³⁹. Also, pancreatic cancer is associated with a significant desmoplastic reaction involving inflammatory cells; thus, it has been demonstrated that the number of macrophages and mast cells correlate with microvessel density⁴⁰⁻⁴². In 2010, a phase III trial by the Cancer and Leukemia Group B investigated the efficacy of bevacizumab (a VEGF inhibitor) plus gemcitabine vs. gemcitabine alone after encouraging results from a multicenter phase II trial. The median overall survival was 5.8 months vs. 5.9 months, the median progression-free survival, 3.8 months vs. 2.9 months and the overall response rates, 13% vs. 10%

in the gemcitabine-bevacizumab vs. gemcitabine-placebo group, respectively⁴³. In comparison to gemcitabine alone, the combination of gemcitabine-bevacizumab did not show a major benefit. A phase II study was soon underway in 2011 to investigate the efficacy of gemcitabine plus sorafenib, a multi-targeted tyrosine kinase inhibitor for receptors such as VEGF, PDGF, and RAF³. Although this was a well-tolerated regimen, it did not have promising results. In order to further elucidate these findings, the BAYPAN study, a double blind phase III randomized controlled trial, was conducted in 2012⁴⁴. Again, this trial confirmed that the addition of sorafenib to gemcitabine does not improve overall survival. Currently, a phase I/II study initiated in 2011 is examining the combination of gemcitabine and PCI-27483, a Factor VIIa inhibitor. The trial is still ongoing; however, animal models with this drug have demonstrated tumor growth inhibition at 2.5-3.0 times change in prothrombin time³. Clearly, understanding the molecular pathogenesis of pancreatic cancer has led to relevant clinical trials and discoveries; however, the challenge comes from finding the correct combination of systemic drugs and targeted therapies to control the progression of this highly malignant cancer.

With an understanding of molecular targets and the creation of novel drugs targeting these molecular hotspots, identifying predictive markers in individual tumors will help direct the most beneficial of these novel drugs. The development of predictive markers has been set on gemcitabine, as it has been standard therapy since 1996. In 2007, predictive markers for gemcitabine resistance were identified in human pancreatic cancer cell lines⁴⁵. It was discovered that the genes RRM1, RRM2, and hENT1 were increased in cells resistant to gemcitabine, whereas dCK was decreased⁴⁵.

Subsequently in 2010, these same four genes were analyzed as predictive markers to determine gemcitabine sensitivity in pancreatic cancer cell lines⁴⁶. Quantitative analysis revealed that high dCK, low RRM2, and high GEM score (the combined score) predicted a longer disease-free survival for those treated with gemcitabine⁴⁶. Multiple studies have also recently looked at the RNA binding protein, HuR, as a potential promising predictive marker for gemcitabine therapy⁴⁷⁻⁴⁸. HuR works by stabilizing dCK, which is responsible for phosphorylating gemcitabine into its active metabolites. Much like HER2/neu and herceptin, the presence of HuR is associated with a worse prognosis and stage for pancreatic cancer; however, its presence

is also associated with better outcomes when treated with gemcitabine⁴⁷⁻⁴⁸. In regards to erlotinib, a phase III trial in 2012 comparing two sequences—gemcitabine/erlotinib followed by capecitabine vs. capecitabine/erlotinib followed by gemcitabine—incidentally discovered that KRAS wildtype status correlated with improved overall survival⁴⁹. This sheds light on KRAS acting as a predictive marker for those treated with erlotinib, much as it is used for treatment with cetuximab.

Despite substantial improvements in systemic chemotherapy and a better understanding of the molecular pathogenesis of pancreatic cancer, it still remains one of the most aggressive and deadly cancers of all time. It is becoming apparent that a multi-targeted approach works best for pancreatic cancer to inhibit the multiple signaling pathways that enhance tumorigenesis. Predictive markers for the systemic or targeted therapies that have demonstrated improved overall survival in clinical trials are being identified. In this way, therapy can be individualized depending on the tumor profile, a paradigm shift that has occurred for other cancers that have shown a steady increase in survival rates. Rather than exposing a patient to a drug to merely experience its toxic side effects with limited improvement in survival time, we can stratify patients who will benefit and avoid treating those who will not. We are hopeful that improved insights and new technology will lead to a more promising future for pancreatic cancer, in which the diagnosis will one day be less of a death sentence and more of a chronic disease.

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