Cancer Genetics 209 (2016) 567–581

Cancer Genetics

Molecular targeted therapy for pancreatic adenocarcinoma: A review of completed and ongoing late phase clinical trials

Catalina Mosquera [a], Dino Maglic [b], Emmanuel E. Zervos [a,*]

[a] *Division of Surgical Oncology, Brody School of Medicine, East Carolina University, Greenville, NC, USA;* [b] *Brody School of Medicine, East Carolina University, Greenville, NC, USA*

Molecular targeted therapy is widely utilized and effective in a number of solid tumors. In pancreatic adenocarcinoma, targeted therapy has been extensively evaluated; however, survival improvement of this aggressive disease using a targeted strategy has been minimal. The purpose of this study is to review therapeutic molecular targets in completed and ongoing later phase (II and III) clinical trials to have a better understanding of the rationale and progress towards targeted molecular therapies for pancreatic cancer. The PubMed database and the NCDI clinical trial website (www.clinicaltrials.gov) were queried to identify phase II and III completed and published (PubMed) and ongoing (clinicaltrials.gov) trials using the keywords: pancreatic cancer and molecular targeted therapy. The search engines were further limited by adding Phase II or III, active enrollment and North American. A total of 14 completed and published phase II/III clinical trials and 17 ongoing trials were identified. Evaluated strategies included inhibition of growth factor receptors (EGFR, PDGFR, VGFR, IGF-1R), tyrosine kinase inhibitors, MEK1/2, mTOR blockade and PI3K and HER2-neu pathway inhibitors. Only one trial conducted by the National Cancer Institute of Canada and the PANTAR trial have demonstrated a survival improvement from EGFR inhibition using erlotinib. These trials ultimately led to FDA approval of erlotinib/Tarceva in advanced stage disease. It remains unclear whether new combinations of cytotoxic chemotherapy or immunotherapy plus molecular targeted therapy will be beneficial in management of pancreatic adenocarcinoma. Despite a number of phase II and III trials, to date, only erlotinib has emerged as an approved targeted therapy in pancreatic adenocarcinoma. There are several ongoing late phase trials evaluating a number of targets, the results of which will become available over the next 1 to 2 years.

Keywords Molecular targets, pancreatic cancer, clinical trials, phase II and III

Introduction

Pancreatic adenocarcinoma is a challenging disease believed to arise from multiple genetic mutations. It has a concerning increasing incidence (1). It currently represents the fourth leading cause of cancer related death in the U.S, and it is projected to become the second by 2030 (2–4). Surgical resection has been shown to provide survival improvement and is the only potential curative treatment for this generally treatment refractory disease (5–7). Most patients, however, are diagnosed at an unresectable stage thus underscoring the need to pursue novel alternatives or adjuncts to traditional cytotoxic chemotherapy regimens such as targeted therapy (8,9).

Molecular targets in cancer therapy were first approved in the U.S. by the Food and Drug Administration in February 2002 with the approval of imatinib mesylate (Gleevec) for the treatment of malignant metastatic and/or unresectable gastrointestinal stromal tumors (GIST). This Bcr-Abl tyrosine kinase inhibitor previously approved for chronic myelogenous leukemia in blast crisis, showed up to 43% tumor response rate in patients diagnosed with GIST (10). Since then, targeted therapies have been approved and widely utilized in renal, colorectal, gastroenteropancreatic neuroendocrine tumors, non-small cell lung cancer and malignant melanoma (11–15).

Received April 12, 2016; accepted July 21, 2016.

* Corresponding author.
E-mail address: zervose@ecu.edu

2210-7762/$ - see front matter © 2016 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.cancergen.2016.07.003

Table 1 Molecular pathways and potential therapeutic targets in pancreatic adenocarcinoma

Pathway	Molecular Targets	Molecular Pathophysiology
K Ras, MAP2K and MEK pathway	MAP2K MEK	Kras encodes for GTP-binding proteins that are activated by EGFR, resulting in activation of MAP2K, PI3K-Akt. With consequent initiation of cellular transcription, translation cell cycle progression, cell survival and motility
Tyrosine kinase receptor pathway	EGFR, VEGFR, IGFR-1, PDFR	Phosphorylation of tyrosine residues results in intracellular protein recruitment with consequent activation of Ras/Raf/MEK/MAPK, PI3K-AKT/STAT family proteins with subsequent cell proliferation, oncogenesis, angiogenesis, inhibition of apoptosis, and tumor metastasis
PI3K/Akt pathway	PI3K Akt	Signaling through tyrosine kinase receptors, (EGFR, IGF-1R) activates PI3K with consequent activation of Akt, and later induction of the mTOR pathway. PI3K/Akt are involved in cell proliferation, survival, resistance to apoptosis, and angiogenesis.
mTOR signaling pathway	mTOR	Serine/threonine kinase like Akt is activated by PIK3/Akt with consequent regulation of gene transcription and cell proliferation
STAT3 signaling pathway	STAT 3	Phosphorylated by a Janus kinase (JAK), STAT3 is involved in cell proliferation, survival, motility, invasion, angiogenesis and inflammation
Poly (ADP-ribose)polymerase pathway	PARP	Family of nuclear protein enzymes involved in mediating DNA manage response and apoptosis
RET pathway	RET GDNF	Through MAPK pathway RET is associated with proliferation and invasion of pancreatic adenocarcinoma.
TP53 tumors suppressor pathway		Tp53 mutations are associated with loss of cell cycle arrest, apoptosis and DNA damage repair

Targeted therapy has also been extensively evaluated in Phase I and Ib studies in pancreatic adenocarcinoma. Strategies in this disease have included: tyrosine kinase inhibition, growth factor receptor inhibition and proto-oncogene blockers (16–22). To date, these studies have not resulted in a change from current cytotoxic based regimens, though some have shown enough promise to move on to phase II and some phase III trials. The purpose of this manuscript is to review relevant and potential therapeutic molecular targets for pancreatic adenocarcinoma and the completed and ongoing trials evaluating experimental and approved agents aimed at these targets. The following paragraphs provide a brief review of relevant and targetable pathways in pancreatic cancer and are summarized in Table 1 and Figure 1.

K-Ras

As many as 90% of patients diagnosed with pancreatic adenocarcinoma are found to have a mutated oncogenic K-Ras gene (23). This gene is involved in the early phase of pancreatic tumorigenesis. K-Ras encodes membrane bound GTP binding proteins that are activated by signaling pathways such as Epidermal Growth Factor Receptor (EGFR). When mutated, K-Ras locks the protein in an activated state, resulting in a continuous induction of signaling cascades [Mitogen-Activated Protein Kinases (MAPK/MEK), and Phosphatidylinositol 3-Kinase/AKT (PI3K-Akt)] responsible for proliferative cellular processes including transcription, translation, inhibition of apoptosis, cell cycle progression and cellular motility (7). MAPK has also been found to promote proliferation and invasiveness of pancreatic adenocarcinoma when activated by the bond between glial derived neutrophilic factor (GDNF) and a proto-oncogene RET coded tyrosine kinase receptor (24).

Tyrosine kinase

Binding of growth factors to their respective receptors results in phosphorylation of tyrosine residues with consequent activation of signaling pathways [MAPK/MEK, PI3K-AKT, Ras, Raf, STAT]. Overexpression of EGFR, Vascular Endothelial Growth Factor Receptor (VEGFR), Platelet Derived Growth Factor Receptor (PDGFR) and the Insulin-Like Growth Factor Receptor (IGFR) due to mutations or loss of pathway regulation is associated with cellular proliferation, anti-apoptosis, anti-anoikis and angiogenesis (25). Overexpression of growth factor receptors has been documented in up to 90% of patients diagnosed with pancreatic adenocarcinoma (26,27). Growth factor receptors also play a significant role in activation of the Janus Kinase (JAK) pathway which in turn activates the STAT tyrosine phosphorylation pathway (JAK/STAT), which again promotes cell proliferation, invasion, angiogenesis and has been found to be associated with development of pancreatic metaplasia (28). HER2 is a related receptor tyrosine kinase encoded by proto-oncogenes that once activated