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EDITORIAL

Targeted therapies for pancreatic adenocarcinoma: Where do we stand, how far can we go?

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Abstract

Pancreatic adenocarcinoma (usually referred to as pancreatic cancer) is a highly lethal and aggressive malignancy with a disease-related mortality almost equaling its incidence, and one of the most challenging cancers to treat. The notorious resistance of pancreatic cancer not only to conventional cytotoxic therapies but also to almost all targeted agents developed to date, continues to puzzle the oncological community and represents one of the biggest hurdles to reducing the death toll from this ominous disease. This editorial highlights the most important recent advances in preclinical and clinical research, with regards to targeted therapeutics for pancreatic cancer, outlines current challenges and provides an overview of potential future perspectives in this rapidly evolving field.

Key words: Clinical; Cytotoxic chemotherapy; Pancreatic cancer; Preclinical; Targeted agents

Core tip: Expansion of our knowledge regarding the molecular basis of pancreatic cancer has facilitated the development of a significant number of innovative targeted therapies for this lethal disease. Almost all these agents have, nevertheless, failed to produce statistically significant survival benefits when tested in clinical trial settings; therefore, successful clinical translation of preclinical advancements in pancreatic cancer research has yet to be materialized. Future treatment options might include multi-targeted and individualized molecular therapies, ideally guided by patient-specific genomic data, in combination with conventional cytotoxic or other regimens.

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INTRODUCTION

Despite recent advances in our understanding of the molecular mechanisms involved in the development and progression of pancreatic adenocarcinoma and an abundance of preclinical data suggesting the potential value of several targeted agents in treatment of this lethal disease, pancreatic cancer statistics remain grim and nearly the same as they were almost 30 years ago[1-3]. Pancreatic adenocarcinoma - usually referred to as "pancreatic cancer" - currently ranks as the fourth most frequent cause of cancer-related death among males and the fifth among females in the Western world, and is sadly expected to rise to the second leading position within the next decade[3,4]. Median survival is 4 to 6 mo following diagnosis while long term (5-year) survival rates do not exceed 4%-5%, for all stages combined[5]. The only treatment option with a curative potential is surgery, but less than 20% of patients are eligible for this approach, while the survival rates are poor (25%-30%) even among those with localized node-negative disease undergoing complete surgical resection and adjuvant chemotherapy[6].

This dismal clinical record inevitably leads to the following questions: Why have we failed thus far to reduce the death toll from this lethal disease? And, most importantly, what can we do to widen the range of available treatment options and improve their clinical effectiveness?

PRECLINICAL AND CLINICAL DATA: DISCREPANCY PREVAILS

In the preclinical arena of pancreatic cancer research the picture is much rosier; a significant and rather rapidly expanding number of different targeted agents have shown considerable efficacy in controlling growth of human pancreatic cancer cells, both *in vitro* and *in vivo*, and prolonging survival of pancreatic cancer models, as summarized in recent reviews on this topic[5-11]. This rather extensive armamentarium includes, among others, inhibitors of epidermal growth factor receptor (EGFR)[12,13], human epidermal growth factor receptor 2 (HER2)[14,15], vascular endothelial growth factor (VEGF) and VEGF receptors[16], insulin-like growth factor receptor[17-19], KRAS and its downstream effectors (mainly mitogen-activated protein kinase)[20,21], the developmental Wnt, Hedgehog and Notch signaling pathways[22-24], as well as reagents targeting the tumor extracellular matrix/stromal microenvironment or molecules overexpressed in the surface of pancreatic cancer cells (*i.e.,* mesothelin, carcinoembryonic antigen, epithelial cell adhesion molecule, MUC1)[25-29]. Dual-agent and multi-kinase molecular targeting represent additional exciting therapeutic possibilities and are gaining increasing research attention and popularity[30-34]. Alternative approaches, such as targeting the cellular process of autophagy - which plays a key role in the development and progression of malignancy or combined targeting of oncogene-driven signaling pathways and critical energy sources (such as mitochondrial respiration) of the subpopulation of dormant tumor cells surviving oncogene ablation, have also been studied as potential treatment options in pancreatic cancer, but are still in their infancy[7,35,36]. Interestingly, in accordance with increasing data suggesting potential preventive and therapeutic effects of aspirin and non-steroidal inflammatory drugs in gastrointestinal cancers, particularly colorectal cancer[37,38], aspirin is being explored as a targeted therapeutic agent for pancreatic cancer as well[39,40]. As shown in recent preclinical studies, aspirin, either alone or in combination with the antidiabetic drug metformin, may inhibit pancreatic cancer cell growth, counteract desmoplasia and cancer stem cell features and enhance the therapeutic efficacy of cytotoxic agents-such as gemcitabine- in pancreatic cancer by sensitizing pancreatic cancer cells to chemotherapy-mediated cytotoxicity[41-43].

Modified cytotoxic agents, mainly including nab-paclitaxel (paclitaxel conjugated with albumin nano-particles) or other nanovector-based anticancer drugs, such as cationic liposome encapsulated paclitaxel (EndoTAGTM-1) or liposomal doxorubicin, cisplatin and irinotecan, have been recently developed using sophisticated nanotechnology and tested in preclinical studies of pancreatic cancer, with some encouraging results[7,44-49]. These selective drug formulations offer the advantage of improved drug delivery to the tumor tissue and selective targeting *via* binding to tumor-associated receptors or macromolecules, thus positively modulating the pharmacokinetics and therapeutic index of cytotoxic chemotherapy[44]. Nab-paclitaxel, in particular, can bind to SPARC (secreted protein acid and rich in cysteine), an extracellular matrix protein which is frequently overexpressed in pancreatic adenocarcinomas[10,50,51], and, presumably, result in depletion of desmoplastic tumor stroma and an increase in vascularization, thus enhancing transvascular transport and delivery of cytotoxic agents to tumor cells[52].

The overwhelming majority of the abovementioned targeted therapies have, nevertheless, failed to demonstrate any statistically significant efficacy in clinical trials of pancreatic cancer patients; the EGFR and VEGF monoclonal antibodies cetuximab and bevacizumab, respectively, and the multikinase inhibitor sorafenib are representative examples of once-promising targeted agents who failed to produce a statistically significant improvement of survival when used in combination with gemcitabine *vs* gemcitabine alone in phase III randomized trials[53-55]. Hence, successful translation of our otherwise encouraging preclinical achievements into tangible clinical benefit remains an elusive goal. Two notable exceptions, though, leave some room for optimism. Erlotinib, an EGFR tyrosine kinase inhibitor which was United States Food and Drug Administration (FDA)-approved in 2007 for the treatment of advanced pancreatic cancer, is the first targeted agent which

succeeded in producing a significant-albeit modest-survival benefit when administered as an adjunct to gemcitabine, especially among patients experiencing erlotinib-induced skin rash[7,56]; still, given the marginal effect of erlotinib on survival and its unclear therapeutic value in localized, resectable disease this drug has yet to be widely adopted as standard of care in routine clinical practice[8,10]. Based on the results of the recent phase Ⅲ Metastatic Pancreatic Adenocarcinoma Clinical Trial[57] of nab-paclitaxel and gemcitabine combination *vs* gemcitabine alone in 861 patients with metastatic pancreatic cancer, showing a statistically significant survival benefit (as regards overall, progression-free and 1-year survival) in the combinatorial arm, nab-paclitaxel was also approved by the FDA in 2013 to be administered in combination with gemcitabine as first-line therapy for metastatic pancreatic cancer.

CONCLUSION

Considering all available evidence, as summarized above, we should first acknowledge that, although some revolutionary progress has indeed been achieved on the theoretical front, preclinical enthusiasm has been severely tempered by clinical disappointment. The reasons behind this discrepancy remain largely unknown and can only be speculated upon at this point. Resistance of pancreatic cancer to anticancer drugs, including both standard cytotoxic and novel targeted agents, is often attributed to the abundant, dense, fibroinflammatory stroma surrounding pancreatic tumor tissue, which is believed to function as a barrier to efficient delivery of drug formulations to their target tumor cells by restricting blood supply and limiting diffusion of large molecules[10,58,59]. The high genetic heterogeneity and complexity of pancreatic cancer may also explain why targeting a specific mutation in a tumor containing 63 genetic alterations on average -as shown by previous genomic studies[22,60] - or "randomly combining drugs in the hope of achieving a better outcome in an unselected patient population"[10], may be doomed to fail.

Hopefully, the results of ongoing clinical trials on current and emerging targeted therapeutics, including, among others, the anti-EGFR and anti-HER2/neu monoclonal antibodies nimotuzumab (NCT02395016) and trastuzumab (NCT01204372), respectively, the hedgehog inhibitors vismodegib (NCT01195415) and LDE225 (NCT01485744) and agents targeting the Notch pathway, such as the gamma-secretase inhibitor MK-0752 (NCT01098344), may help bridge the gap between preclinical and clinical outcomes. The increasing advances in structural and functional genomics are also expected to further elucidate the key molecular events underlying pancreatic tumorigenesis and identify additional targets for novel agents. Based on data derived from global genomic analyses of pancreatic tumors, previous authors have suggested that agents broadly targeting downstream mediators of critical physiologic functions (such as neo-angiogenesis or cell cycle alterations) may be preferable to agents targeting specific mutated genes[60]. Most importantly, personalized genomic medicine, utilizing patient-specific genomic data for guidance of treatment selection in each individual patient, may not only significantly enhance the clinical efficacy of molecular targeted therapy but also reduce the burden of unnecessary - and potentially harmful-drugs.

As previously commented by Kleger *et al*[7], in a recent review article critically discussing current and future targeted therapies for pancreatic cancer, "smart drugs need smart applications". Indeed, most experts concur that the latter applications should include multi-targeted and, ideally, individualized molecular therapies, in combination with conventional cytotoxic agents or other regimens (such as immunotherapy)[61], guided by reliable biomarkers of treatment response. Increased toxicity resulting from these combinatorial approaches as well as their cost-effectiveness and socioeconomic implications should, nevertheless, be carefully considered and may represent major limiting factors for their widespread use. In a disease as aggressive and lethal as pancreatic cancer, maintaining the highest possible quality of life for as long as possible is the most important target, and expectations should always be based on realistic goals.

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