HIGHLIGHT ARTICLE

Translational Research in Pancreatic Cancer

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Summary

The high mortality rate of pancreatic cancer places this uncommon malignancy quite high as a cause of cancer related deaths. Compared to other solid tumors, there is a lag in the development of new effective drugs and the actual clinical benefit remains poor over the last decade or so. The lack of therapeutic options necessitates the invention of the important molecules playing role in pancreatic carcinogenesis and the development of specific targeted therapies. Treatment advances have to be proven first in the bench before applying them at the bedside, thus why translational research is so needed. At the 2011 American Society of Clinical Oncology (ASCO) Gastrointestinal Cancers Symposium, preclinical evidence was presented regarding the efficacy of C4 compound against focal adhesion kinase (FAK) (Abstract #214), the role of the cyclooxygenase-2 (COX-2) inhibitor apricoxib in enhancing the efficacy of gemcitabine and erlotinib (Abstract #227) and the role of curcumin and ABT-888 (a poly-ADP ribose polymerase (PARP) inhibitor) as potent radiosensitizers (Abstracts #222 and #203). Interestingly, the invention of a novel monoclonal antibody (ensituximab) against the mucin epitope NPC-1C in pancreatic and colon cancer cell lines exhibited notable antibody-dependent cellular cytotoxicity (Abstract #235). Finally, enhanced selective targeting of pancreatic tumors was achieved by combining antibody-drug conjugates (ADC) with radioimmunotherapy (Abstract #206).

What Did We Know Before 2011 ASCO GI Cancer Symposium?

Antimetabolites, gemcitabine and to a lesser degree fluoropyrimidines, remain the most used therapeutics in pancreatic cancer for a long now time [1]. The only biological agent that showed some degree of activity is the epidermal growth factor inhibitor erlotinib [2]. Development of novel agents is needed in this highly lethal malignancy; therefore preclinical research is the basis for an orthologic approach in finding new treatments. Over the last few years, there have been presented preclinical evidence regarding new molecular targets and their treatments accordingly, requiring though further validation *in vivo* and in clinical trials [3].

What Did We Learnt from 2011 ASCO GI Cancer Symposium?

In this review, we present the most remarkable data regarding novel targets and drugs that may be proved useful in pancreatic cancer patients in future.

Targeting Focal Adhesion Kinase (FAK)

Over the last few years there have been efforts to develop drugs against FAK, as this protein seems to play a role in pancreatic cancer local growth and distal spread. FAK interacts between cancer cells and extracellular matrix, promoting tumor growth, survival and resistance to treatments [4]. The vascular endothelial growth factor receptor 3 (VEGFR3) binds to FAK in order to promote pancreatic cancer lymphangiogenesis. Dr. Kurenova *et al*. (Abstract #214) [5] screened at the Roswell Park Cancer Institute (Buffalo, NY, USA) thousands of small molecules *in silico* trying to find those which interact with the VEGFR/FAK binding site and are thus able to disrupt this signaling pathway. Of the screened small molecules they selected some compounds and tested those on pancreatic cancer cell lines (Miapaca-2 and Panc-1) for their ability to inhibit viability, motility, proliferation and apoptosis. They selected finally compound C4 as it showed evidence to affect and disrupt the VEGFR3/FAK complex to reduce cancer

cells viability, mobility and proliferation and decrease significantly (P=0.017) tumor growth *in vivo* especially in synergism with gemcitabine by about 80%. Therefore, the oral compound C4, similarly to other agents against FAK that have been reported in the last few years, needs further exploration and validation as a potential oral treatment in pancreatic cancer patients.

Inhibition of Cyclooxygenase-2

The role of cyclooxygenase (COX) in carcinogenesis has been suggested in various published papers. There are currently many clinical trials in progress testing the efficacy of COX inhibitors in pancreatic cancer patients. Dr. Kirane from the University of Texas Southwestern (Dallas, TX, USA) (Abstract #227) [6], determined the expression of COX-2 and epidermal growth factor receptor (EGFR) in pancreatic cancer cell lines and they then tested the treatment responses, by measuring alterations in phospho-EGFR and prostaglandin E2 (PGE2) production. The selected treatment was either the standard of care gemcitabine plus erlotinib or the standard of care along with oral apricoxib (a COX-2 inhibitor) at the dose of 10 or 30 mg/kg. After performing *in vitro* and *in vivo* on severe combined immune deficiency mice studies, the authors reported that though EGFR and COX-2 expression was present in all cell lines, it did not predict response to treatment. Nevertheless, addition of apricoxib to standard treatment significantly reduced cell growth and COX-2 activity *in vitro*, as well as primary tumor growth and metastases *in vivo*. The authors concluded that apricoxib enhances efficacy of standard treatment and therefore warrants further evaluation in clinical trials.

The Concept of Antibody-Drug Conjugates and Radio-Immunotherapy

Over the last few years, there have been data showing a potential role of radio-immunotherapy in combination with biological treatments or chemotherapy in pancreatic cancer models. The hypothesis of selective targeting pancreatic cancer mice xenografts by using antibody-drug conjugates alone or in combination with radio-immunotherapy was tested by Dr. Sharkey *et al.* (Abstract #206) [7]. Some groups of animals bearing pancreatic cancer xenografts were treated either with multiple antibody-drug conjugate doses, consisted of SN-38 (the irinotecan toxic metabolite) with an anti-TROP-2 antibody and an antimucin humanized IgG or appropriate controls. Other groups were treated with antibody-drug conjugates plus radio-immunotherapy at 60% or 100% of its maximum tolerated dose. The aforementioned treatments showed significant antitumor activity of antibody-drug conjugates alone or in combination with radio-immunotherapy, with mild additional toxicity. The combined antibody-drug conjugates/radio-immunotherapy treatment was more effective when given at the same time (±1-2 weeks), but delaying radio-immunotherapy by 2 weeks or longer after antibody-drug conjugates compromised treatment efficacy.

Agents Acting as Radiotherapy Sensitizers

Natural phytochemicals have long been studied for their anticancerous properties. One of the most studied phytochemicals is curcumin, the well known spice curry (turmeric), an agent which derives from the Asian plant *Curcuma Longa* [8]. The activity of curcumin along with gemcitabine is currently being tested in clinical trials on patients with advanced pancreatic cancer. Herein, Tuli *et al.* tested the potential activity of curcumin as a radiosensitizer in pancreatic cancer cell lines (Abstract #222) [9]. Cells were treated with radiotherapy, curcumin or combination therapy (radiotherapy 1 hour after treatment with curcumin) and were compared with untreated controls. Curcumin on its own showed low, dose dependent activity, but combined with radiotherapy resulted in a significant 70% reduction of cell proliferation and increase of caspase 3/7 activity (P<0.01). The radiotherapy dose enhancement factor was 2.5 at 100 µM of curcumin and 5 Gy radiotherapy. These findings if reproduced in *in vivo* models will allow appropriate testing of curcumin as radiosensitizer in clinical trials and may prove particularly useful in patients with locally advanced disease where radiotherapy may play a role.

In another study presented by Dr. Tuli *et al.* at the 2011 ASCO GI Cancer Symposium, the activity of a poly-ADP ribose polymerase (PARP) inhibitor as radiosensitizer was tested (Abstract #203) [10]. PARP inhibitors are already under evaluation in advanced clinical level (phase II-III trials) in familial breast cancer patients (BRCA1/2 carriers). In this abstract, pancreatic cancer cell lines were treated with PARP inhibitor ABT-888, gemcitabine and radiotherapy or their combinations. The addition of ABT-888 to radiotherapy significantly increased cell death, an effect further enhanced by concomitant use of gemcitabine. The radiotherapy dose enhancement factors for the 10 and 100 µM ABT-888 were 1.82 and 2.36, respectively. Therefore, the authors are currently performing an *in vivo* study of ABT-888 with gemcitabine and radiotherapy to validate their findings.

Ensituximab: A Novel Biological Agent

A novel chimeric antibody called ensituximab which targets the epitope NPC-1C was tested and presented by Dr. Diaz *et al.* (Abstract #235) [11]. NPC-1C has been found overexpressed in about half of colon and pancreatic cancer cell lines, but not in other tumor types. This protein belongs to the mucins (MUC) family. Treatment of colon and pancreatic cancer cell lines with ensituximab resulted in a consistent and reproducible *in vitro* and *in vivo* antitumor activity in both the colon and pancreatic cancer models. As a result of the preliminary activity, a phase I dose finding study was designed and is currently assessing safety

and toxicity in cancer patients, but also efficacy and immune responses to the NPC-1C antibody.

Discussion

Tackling one of the most aggressive and lethal malignancies, as pancreatic cancer, is always a tough task. The complexity of biological pathways, the plurality of molecular changes at various levels seems to set hurdles difficult to overcome in order to achieve real progress. In this review, we learnt about a new compound against FAK that has a potential role in preventing disease progression and drug resistance. It is not likely that this drug on its own will be able to make a difference in this complex disease, but will be interesting to see its clinical benefit when combined with drugs acting at a different molecular level. COX-2 inhibitors are already evaluated in various solid tumors as preventive, adjuvant or metastatic disease therapy alone or in combination with other drugs. So far, no conclusive evidence exists for their use at any level. Apricoxib is another COX-2 inhibitor the use of which really has to be validated prospectively and see whether this agent is any better from its counterparts. The use of radio-immunotherapy alone or in combination with biologicals seems to remain at the very investigational level at least in pancreatic cancer. In any case, unless the clinical results are excellent, the lack of special medical facilities will limit its application to a minority of cancer patients who have access to large cancer centers.

The use of radiosensitizing agents in pancreatic cancer has a role in locally advanced disease. Apart from gemcitabine and fluoropyrimidines, there is a potential for curcumin and the PARP inhibitor ABT-888 to play a radiotherapy sensitizing role. With regard to curcumin there are some concerns generally about the tolerance of the oral formulations at the therapeutic dose, mainly gastrointestinal symptoms. Furthermore, this natural compound does not attract the interest of pharmaceutical companies, and therefore well planned large trials are not funded. As far as PARP inhibitors are concerned, there is doubt how much benefit they can offer in this small pancreatic cancer subpopulation who requires chemoradiotherapy to be cost-effective. On the other hand, we really wish the novel antibody ensituximab show some surprising good efficacy and benefit our patients.

There is no doubt there is something we miss which prevents us from an effective management. The answer that is much sought will likely derive from translational research. For this reason investment on research is well justified. In conclusion, researchers should be congratulated for their timeless efforts and determination to understand and explain the causes, invent novel drugs and improve the current management of this disease

Conflict of interest The authors have no potential conflicts of interest

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