Combinational Treatment for Pancreatic Cancer: Where Are We Standing?

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Pancreatic cancer has one of the highest mortality rates of all cancers, with an incredibly poor prognosis, aggressive metastasis, and limited choice of therapy. Of the estimated 43,920 new cases of pancreatic cancer diagnosed in 2012, only 5.8% are likely to survive beyond 5 years. Currently, surgical resection is the only effective treatment for this devastating disease. However, only around 15% of the patient population is eligible for surgery as most cases are diagnosed at a late stage when surgery is no longer an option. Even for resectable pancreatic cancer, the majority of patients are likely to relapse. Chemotherapy has not been successful in treating metastatic pancreatic cancer, and does not provide survival benefit [1]. As cases of chemoresistance become more prevalent, there is an increasing need for more effective and sensitive treatments and diagnostic tests. Targeted molecular therapy represents a new avenue of therapy, targeting deregulated signaling pathways in pancreatic cancer using specific molecules or inhibitors. Unfortunately, these treatment options are still in early phases of research and trials, and may represent a potential future standard of treatment as we learn more about the mechanisms behind this disease. The alarming lack of viable treatment methods raises an important question: Is there a way to put together all the available treatment regimens to fight against pancreatic cancer with our current knowledge and resources? Recent studies indicate a combinatorial effort of surgical resection, chemotherapy, and molecular targeted therapy may have a great potential and high impact on the treatment of pancreatic cancer [1].

Chemotherapy is the primary treatment option in those who are ineligible to surgical resection due to late-stage metastasis. Research into new chemotherapeutic avail is ongoing at major cancer centers and institutions, where the focus has been on seeking the most effective dose for combinational front-line chemo treatments. However, chemotherapeutic agents have become far less effective with the steady rise in chemo-resistant pancreatic cancer, and its monotherapeutic use is seen as palliative at best. Research into the causes of this resistance has demonstrated that a variety of cellular pathways are responsible [2]. Previous studies have demonstrated that aberrant expression of genes controlling the apoptotic pathways upon which chemotherapeutics such as gemcitabine and 5-FU act [2]. An important mechanism underlying resistance involves a lack of effective drug delivery [3]. The presence of stromal fibroblasts which block drug delivery as well as a decrease in angiogenesis leading to an ineffective perfusion of chemotherapeutic agents is also shown to be strongly associated with aggressive resistance to treatment [24].

A new direction of pancreatic cancer research has involved the use of specific molecules or inhibitors to target the aberrant signaling pathways in this disease. Of common interest are the chemoresistance-associated pathways, which represent potential alternative target sites for treatment using targeted molecular therapy. A common feature of many of these highly aggressive treatment-resistant cancer cells is the presence of stem-cell markers CD24, CD44, and esterase A. The hope is that by easing the ability to profile these populations, clinicians would be able to detect the presence of pancreatic cancer growth earlier [4]. Recently genomic profile studies have also been used to identify genes over-expressed in pancreatic cancer and to detect genetic mutations in oncogenes and tumor suppressor genes [5-9]. The identification of these over-expressed genes might lead to development of new diagnostic and prognostic markers and new gene therapy strategies. The ideal candidates are either genes which are specific in pancreatic cancer, or genes which are involved in multiple pathways such as survival, metabolism, and nutrition uptake. Surface ion transporters, and transcriptional factors might be good options for the above reasons. Ion transporters provide important ions for many biological processes, and are essential for the activities of many transcription factors and enzymes, which play important roles in cancer pathogenesis. Our previous studies have shown that a zinc transporter ZIP4 regulates pancreatic cancer growth and metastasis, and is overexpressed in majority of pancreatic adenocarcinoma [10]. The transcription factor PDX-1 appears to be overexpressed in the early stages of pancreatic cancer and is highly involved in the tumorigenesis [11]. Therefore those newly identified targets such as ZIP4 and PDX-1 are of great interest to pancreatic cancer research, as they not only represent potential avenues of targeted molecular treatment, but also have the potential to act as early diagnostic markers, which would further improve the patient outcome.

A more recent approach toward targeted molecular therapy utilizes specific microRNAs which have been aberrantly expressed in certain pancreatic cancers. Recent profiles of pancreatic ductal adenocarcinoma indicate the genes for microRNA expression lie in close proximity to potential oncogenes associated with pancreatic cancer. Their ability to closely regulate cellular activity makes them ideal for novel therapeutic targets by inhibition of oncogenic microRNAs via selective targeting by complementary anti-microRNA nucleases, or ribozymes. Alternatively, active administration of down-regulated tumor-suppressive microRNAs has been shown to inhibit tumor growth in mouse models [12]. This area of research is still in the early phase of testing in animal models, but may represent a promising direction in cancer treatment.

Partial or complete surgical resection is the only curative treatment for pancreatic cancer at this time, though only 15% of patients are eligible for the procedure. However, the surgical resection has not been included as part of the combinational therapy in experimental oncology, partially because of the lack for a reliable mouse model for surgical resection. Recently an imaging-guided surgical resection has
been performed in nude mouse with pancreatic cancer xenografts, and it has been showed the distal pancreatectomy at early stage improved the mean survival time and stabilized body weight and mobility in ASPC-1 xenograft mice when compared to sham controls [13]. Surgical intervention in cases of periampullar pancreatic cancer is proven to increase the 5-year survival rate from 5% to over 25% [14]. However, the impact of surgery greatly diminishes as the disease progresses, and thus importance should be placed on development of combination therapies utilizing early diagnostic methods and therapeutics that can slow the progression of the tumor, which would buy some time for surgical intervention.

The combinational therapy including surgery, chemotherapy, and targeted molecular therapy can not only improve patient outcome with better efficacy than any monotherapy, but can also be used to individualize patient treatment. As we learn more about the fundamental biology of pancreatic cancer, our ability to combine multiple treatment methods will allow us to customize treatment based on the specific markers, features, and progression of the individual patient’s disease. The synergistic effect of the combination of three different treatment strategies is the most promising avenue for greater patient survival and diminished chance of recurrence.

While no “magic bullet” monotherapy is on the horizon, a combined approach utilizing chemotherapy, adjuvant molecular targeting, and surgery is an incredibly promising avenue in curbing this deadly disease. The Journal of Clinical & Experimental Oncology allows the scientific community the tools needed to accurately and responsibly reflect, discuss, and review the most current and relevant progress in the field of oncology. This process ensures reliable collaboration and enables high quality translatable research. Published by SciTechnol, this journal is supported by an international team of editors and includes special features such as audio conversion enhancement, language translation, and digital distribution to ensure timely publication and ease of review processing.

References