NOVEL APPROACHES IN DEVELOPMENT FOR THE TREATMENT OF PANCREATIC CANCER

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1. ABSTRACT

Pancreatic adenocarcinomas are among the most resistant neoplasms to conventional chemotherapeutics. This has prompted intense investigations of novel non-cytotoxic agents based on new understandings of the molecular pathobiology of human malignancies. This review will focus on the potential uses of three new classes of agents: farnesyl transferase (FPTase) inhibitors, matrix metalloproteinase inhibitors (MMPI’s) and antibodies to the HER-2/neu oncogene. One of the first objectives in testing FPTase inhibitors was to ensure that these compounds were achieving their therapeutic benefit by inhibiting ras-mediated signal transduction events and not by another mechanism. In order to accomplish that, FPTase inhibitors should not have the capability of inhibiting raf oncogene transformed cells. Indeed, when tested in these cell lines, cells transformed by the ras-dependent tumor growth in nude mice and causes regression in Ha-ras transgenic animals (7-10). Moreover, FPTase inhibitors have not demonstrated toxicity to normal cells in culture or to normal tissues in mice. This observation is in sharp contrast to typical cytotoxic anti-cancer agents which often must be used at their maximally tolerated dose to obtain significant anti-tumor activity.

Enthusiasm grew for a possible Achilles’ heel of ras-dependent cell transformation when further studies showed that inhibition of FPTase by FPTase inhibitors causes reversal of ras-induced transformation of whole cells, inhibition of ras-dependent tumor growth in nude mice and causes regression in Ha-ras transgenic animals (7-10). Moreover, FPTase inhibitors have not demonstrated toxicity to normal cells in culture or to normal tissues in mice. This observation is in sharp contrast to typical cytotoxic anti-cancer agents which often must be used at their maximally tolerated dose to obtain significant anti-tumor activity.

One of the first objectives in testing FPTase inhibitors was to ensure that these compounds were achieving their therapeutic benefit by inhibiting ras-mediated signal transduction events and not by another mechanism. In order to accomplish that, FPTase inhibitors were tested on cells transformed by other oncogenes. For instance, FPTase inhibitors should not have the capability of inhibiting raf oncogene transformed cells. Indeed, when tested in these cell lines, cells transformed by the ras oncogene have been resistant to FPTase inhibitors when used at a similar dose to treat ras mediated transformed cells (6). However, recent studies suggest that FPTase inhibitors may also have activity in cell lines that do not have ras mutations. This suggests that the exact mechanism of FPTase inhibitors may still be unclear.

It is still not certain whether FPTase inhibitors will have cytostatic or cytotoxic effects. Preclinical models...
suggest that FTPase inhibitors may require chronic administration to be effective, as the tumors would grow back once the drug was discontinued (9). Thus a well tolerated oral formulation would have most promise. Clinical trials will need to be carefully designed to evaluate therapeutic efficacy. For example, while FTPase inhibitors may have little effect as a single agent for patients with metastatic disease it could prevent or delay regrowth of microscopic metastatic deposits in a patient who has undergone surgical resection. Phase I trials of FTPase inhibitors have been initiated.

3. MATRIX METALLOPROTEINASE INHIBITORS

Matrix metalloproteinases (MMP’s) are a family of Zn$^{2+}$ dependent endopeptidases with a broad spectrum of proteolytic activity for several components of the extracellular matrix (11). Tumor cells secrete MMP’s which destroy basement membranes and local connective tissue, allowing tumor cells to gain access to the lymphatic or blood circulation (12). Once established at a secondary site, tumor cells continues to secrete MMP’s that degrade connective tissue enhancing local growth (13). MMP’s also appear to promote the growth of new blood vessels that nourish metastatic deposits.

Though MMP’s are different in structure, molecular weight and substrate specificity, they all contain highly homologous zinc-binding active sites, hemopexin-like domains, and cleavable NH2-terminal sequences the removal of which results in activation of the enzymes (14). MMP’s are involved not only in pathologic tissue destruction by tumor cells. Their presence was documented during mouse embryogenesis (15). Collagenase activity was reported as important factor during wound healing and tissue remodeling (16). Several matrix metalloproteinases were identified to be secreted by rheumatoid synovial cells and thus contributing to joint destruction in rheumatoid arthritis (17).

In normal human tissues, MMP’s are in an inactive proenzyme form and their activity is regulated by its activators and inhibitors (18). A ubiquitous glycoprotein, TIMP, is considered to be a major inhibitor of metalloproteinase activity in tissues. This inhibitor is secreted by many cells in culture including fibroblasts, endothelial cells, chondrocytes and vascular smooth muscle cells. It is also present in bone, cartilage and amniotic fluid. TIMP inhibits MMP by forming irreversible 1:1 stoichiometric complex with the active enzyme (18). During tumor invasion the balance between MMP’s and their inhibitors is broken and number of MMP’s exceeds TIMP’s which contributes to the invasion and degradation of extracellular matrix (19-22).

Early studies on human cancer cell lines and animal models have demonstrated that inhibition of MMP’s inhibit the growth and spread of primary tumors and promote the formation of stroma causing encapsulation of the tumor. Some additional beneficial effects on inhibition of angiogenesis were demonstrated as well (23-27).

Many solid tumors, including pancreatic cancer, express high levels of matrix metalloproteinases (28-30). Synthetic inhibitors of MMP’s are therefore being developed to counteract the destructive and invasive nature of these enzymes (31,32).

Marimastat was one of the first MMPI’s to show significant oral bio-availability to enter clinical trials. It is a synthetic MMPI that mimics the substrate of the matrix metalloproteinases. This allows it to fit tightly in the active site of the enzyme. Its hydroxamate group binds to the zinc atom in the active site resulting in potent but reversible inhibition of the metalloproteinases MMP-1, MMP-2, MMP-3 and MMP-9.

Initial human trials occurred in normal volunteers, underscoring the fact that marimastat is not a cytotoxic agent. These studies did not indicate untoward toxicity, although some alteration of liver enzymes were noted. Following this, more than 1000 patients with metastatic ovarian, colorectal, pancreatic, prostatic, head and neck, breast, gastric, lung, and melanoma (33-38), have been treated on phase I/II trials to try to identify a biologically effective dose and to further to evaluate the safety profile and pharmacokinetics.

A phase I/II study of marimastat in patients with advanced, non-resectable pancreatic carcinoma has been reported (38). Patients received marimastat on a BID oral schedule for 28 days. One patient developed acute rash, fever, chills and muscle pains after marimastat. Otherwise there have been no significant drug-related toxicities. Seven of 19 patients demonstrated a reduction in the rate of rise of CA 19-9. Marimastat is also being tested by the Brown University Oncology Group in patients with locally advanced pancreatic cancer with stable or responding disease after paclitaxel and radiation. No significant toxicity from marimastat has been seen thus far in this study.

Since marimastat is not a cytotoxic agent, traditional endpoints of objective tumor response are anticipated. The evaluation of disease stabilization in a uncontrolled setting is hard to interpret. Carefully designed phase III trials are needed to determine the effectiveness of marimastat. Therefore a multicenter randomized placebo controlled trial is underway in the United States to evaluate whether marimastat can improve disease free and overall survival in patients with resected pancreatic cancer.

4. HER-2/NEU ANTIBODIES

The HER-2/neu proto-oncogene, located at Chromosome 17 p11- q21, encodes for a 185 kd membrane receptor protein (p185) that shares extensive homology with the epidermal growth factor receptor. Overexpression of HER-2/neu is thought to transform cells by constitutively stimulating signal transduction pathways and has been correlated with differentiation, aggressiveness and prognosis in breast, gastric and ovarian carcinomas.

In the pancreas there is increasing data regarding the incidence of HER-2/neu overexpression, demonstrated immunohistochemically, with reported figures ranging from 20%- 58 % in invasive ductal adenocarcinomas 39, 40, 41, 42, 43, 44, 45. Overexpression is more common in well and moderately differentiated tumors as compared to poorly differentiated and anaplastic tumors.
Novel Therapies for Pancreatic Cancer

While gene amplification is the predominant pathway of HER-2/neu overexpression in most tumors, in pancreatic cancers, increased transcription may play an important role. Elevated mRNA levels of HER-2/neu in the absence of gene amplification have been described in pancreatic cancer 39,41, 42, 44.

Herceptin, a human monoclonal antibody to the HER-2/neu receptor, has been synthesized by scientists at Genentech. Clinical trials have shown activity in breast carcinomas that overexpress the HER2/neu gene. Synergistic activity has been demonstrated in breast cancer with herceptin and paclitaxel. This suggests that studies in other malignancies that overexpress HER2/neu such as pancreatic cancer are warranted. The Brown University Oncology Group in collaboration with the M.D. Anderson Cancer Center is therefore initiating a phase II trial of gemcitabine and herceptin as first line therapy for metastatic pancreatic cancer.

5. REFERENCES


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Therefore, it is imperative that novel and targeted approaches are designed to facilitate the early detection and treatment of pancreatic cancer. Presently, there are numerous ongoing studies investigating the types of genomic variations in pancreatic cancer and their impact on tumor initiation and growth, as well as prognosis. This has led to the development of therapeutics to target these genetic variations for clinical benefit. @article{Lu2017GenomicVI, title={Genomic Variations in Pancreatic Cancer and Potential Opportunities for Development of New Approaches for Diagnosis and Treatment}, author={Shuangshuang Lu and T. Ahmed and P. Du and Yaohe Wang}, journal={International Journal of Molecular Sciences}, year={2017}, volume={18}} Pancreatic cancer is one of the most lethal solid tumors. The prognosis of metastatic pancreatic adenocarcinoma remains dismal, with a median survival of less than 1 year, due in large part to the fact that pancreatic adenocarcinoma is notoriously refractory to chemotherapy. However, there recently have been significant improvements in outcomes for patients with pancreatic adenocarcinoma: ongoing trials have shown promise, and these may lead to still further progress. Novel chemotherapeutic approaches. Many new therapies have emerged that offer promise for improving the treatment of metastatic pancreatic adenocarcinoma; among these are novel cytotoxic chemotherapies. The approach to pancreatic cysts continues to be problematic, due to the lack of good natural history data, few published studies with long-term follow-up data, and possible bias, since most of the reports are from centers that specialize in the treatment of pancreaticobiliary disorders. In general, patients with smaller lesions (< 2 cm) are less likely to be symptomatic, and. In addition, malignancy may develop in the remnant pancreas after partial pancreatic resection for a prior neoplastic lesion, since premalignant changes may be multifocal. There is a 2.8% risk of invasive cancer elsewhere in the pancreas in patients with IPMN, according to Lafemina et al. [39].