Novel chemotherapy agent appears to be a promising pancreatic cancer treatment

June 20 2012

A novel chemotherapeutic agent, the highly selective MEK1/2 inhibitor BAY 86-9766, may be a promising future treatment for pancreatic ductal adenocarcinoma (PDAC), according to preclinical results presented at the American Association for Cancer Research's Pancreatic Cancer: Progress and Challenges conference, held here June 18-21.

"We showed in our endogenous mouse model that our novel chemotherapeutic agent leads to dramatic tumor shrinkage after only one week of treatment," said Nicole Teichmann, Ph.D., of the Klinikum rechts der Isar at the Technische Universität München in Munich, Germany. "Moreover, the therapy was as effective in animals with advanced tumors and ascites, which is often the case if patients come to the clinic."

In this preclinical therapeutic study, BAY 86-9766 was evaluated in one of the most aggressive mouse models for PDAC, according to Teichmann. The researchers induced endogenous genetic alterations in these mice, and within eight weeks, the mice developed invasive, lethal PDAC. These genetic alterations closely mimic what is found in most human cases of the disease, she said.

"The mutations trigger the onset of a signaling cascade that is necessary for the survival and proliferation of the cancer cells," Teichmann said. "Our novel chemotherapeutic drug inhibits one essential protein of this cascade and therefore leads to the cascade's shutdown."

A daily treatment of 25 mg/kg with BAY 86-9766 prolonged the survival of the mice in the study compared to their 'placebo'-treated counterparts; median survival advantage was 20 days. The treatment caused dramatic tumor regression after only one week and was effective in animals with advanced tumors and ascites, which is often how patients present to the clinic.

"We were really surprised that the tumor load dramatically decreases after one week of therapy and also that the treatment conferred such a strong overall survival benefit," Teichmann said. "Previous studies with gemcitabine, the standard-of-care agent for PDAC since 1997, or other novel inhibitors tested in our lab with the same mouse model showed no or only very modest effects. In our hands, this is the first targeted drug to have shown such strong tumor effects in an endogenous mouse model of PDAC."

In most animals, the tumor relapsed after three weeks of treatment, which modeled the situation in humans. "Often patients respond to a therapy and after a while, the tumor relapses," she added. "We can exploit this same tumor relapse in the mouse to investigate the resistance mechanism to improve the therapeutic strategy."

These findings encourage testing in mouse models rather than xenograft models. "Our results support testing novel agents for pancreatic cancer in endogenous mouse models, rather than conventional xenograft models because they take into account the genetic and morphological heterogeneity of the disease and may be more predictive with regard to efficacy," Teichmann said.

More information:

Abstract

MEK1/2 inhibition with the novel chemotherapeutic agent BAY

86-9766 (RDEA119) – a promising treatment strategy for pancreatic cancer. Nicole Teichmann1, Marija Trajkovic-Arsic1, Arne Scholz2, Schmid M. Roland1, Braren Rickmer1, Jens T. Siveke1. 1Klinikum rechts der Isar, Technische Universität München, Munich, Germany, 2Bayer Schering Pharma AG, Berlin, Germany.

Introduction: Novel effective agents and improved mouse models for better prediction of clinical efficacy of new therapies for pancreatic cancer are urgently needed. In this study we used a genetically engineered mouse model of PDAC for preclinical evaluation of a novel highly selective MEK1/2 inhibitor BAY 86-9766.

Experimental design: To mimic molecular and morphological characteristics of human PDAC, we generated mice with pancreas specific activation of oncogenic Kras and concomitant deletion of p53 (Ptf1a+/Cre, Kras+/LSL-G12D, p53loxP/loxP; CKP) using a Cre/loxP approach. Those mice develop invasive PDAC and typically die at 8 weeks of age. To assess the in vivo efficacy of BAY 86-9766 CKP mice with a defined tumor burden were treated daily with 25 mg/kg of BAY 86-9766 from 40 days of age until death. Tumor progression was monitored by measurements of tumor volume via non-invasive T2-weighted magnetic resonance imaging on a clinical 1,5T MRI device.

Results: BAY 86-9766 prolonged the survival of CKP mice significantly with a median survival advantage of 20 days. Moreover, dramatic tumor regression was observed already after 1 week of treatment. This strong decrease of the tumor load was also seen when therapy was applied in mice with advanced tumors and ascites. Tumor shrinkage mainly results from an apoptosis induction via Bim upregulation and to a smaller extend from an impaired proliferation of the tumor cells. However, in most animals, tumors relapsed typically after 3 weeks of treatment. Indeed, relapsed tumors presented altered morphological features compared to their vehicle counterparts. To closer investigate the

underlying resistance mechanism primary mouse pancreatic tumor cell lines from vehicle and BAY 86-9766 treated PDACs were established and further characterized. Interestingly, in some cell lines isolated from MEK1/2 inhibitor treated mice and only one cell line isolated from vehicle treated controls an epithelial to mesenchymal transition (EMT) phenotype was observed. These data suggest that BAY 86-9766 treatment induced EMT, which coincides with the histological analysis and concomitant lower sensitivity to erlotinib treatment. Moreover, those cells exhibited higher protein levels of p-EGFR and p-ERK as well as higher mRNA and active GTP-bound levels of the driving oncogene Kras, which could be involved in triggering EMT.

Conclusions: These preclinical data provide compelling evidence that the novel MEK1/2 inhibitor BAY 86-9766 is a promising future therapeutic agent for the treatment of pancreatic cancer in clinical practice. The continuing profound examination of the escape mechanism of the relapsing tumor can then be exploited to develop an improved therapy strategy for this aggressive cancer type in the future.

Provided by American Association for Cancer Research