Therapeutic responses in a novel patient-derived xenograft model for rare pancreatic acinar cell carcinoma


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Abstract

Acinar cell carcinoma of the pancreas (PACC) is an uncommon malignancy, accounting for less than 1% of all pancreatic neoplasms. The disease accounts for ~1% of the pancreatic cancer malignancy, accounting for less than 1% of all pancreatic neoplasms. Our group was presented with a highly motivated patient who enrolled

Background

Pancreatic acinar cell carcinoma; (PACC) is an uncommon malignancy, accounting for <1% of all pancreatic neoplasms. Because of its rarity, only a few retrospective studies are available to help guide management. We previously reported the case of a patient with metastatic PACC who achieved prolonged survival with doxorubicin as a result of personalized treatment designed in part on the basis of molecular and in-vitro data collected on analysis of the tumor and primary cells in culture developed from the liver metastasis. We now report the characterization of a patient-derived xenograft (PDX) mouse model originating from this patient’s PACC liver metastasis. Antitumor activity of multiple drugs (SM-FL, irinotecan, oxaliplatin, gemcitabine, bevacizumab, erlotinib, doxorubicin) was used as a single agent therapy is demonstrated. Of the targeted and cytotoxic therapies used, oxaliplatin produced a dramatic and prolonged response to therapy even after withdrawal of treatment. The effective therapy induced tumor cell death, decreased serum lipase levels and the pancreatic tissue began expressing cytoplasmic amylase, an indication of healthy acinar cells. Thus, we have developed and characterized a PACC PDX model that may be used in drug discovery for the treatment of this rare cancer for which no standard-of-care exists.

Conclusions

Our studies show that we have established a reliable PDX model for PACC. This model is homogenous, as it is negative for markers of ductal carcinoma and neuroendocrine tumors. We tested nine separate cancer therapeutics to evaluate the benefits induced by each treatment. Overall, oxaliplatin yielded the best anti-tumor effect, without a toxic response. The PACC tumors’ killed serum lipase secretion and began to histologically appear like normal acinar cells. The therapy induced cell death, but did not stop proliferation. Since oxaliplatin induces DNA damage it may be worth understanding which DNA repair genes could be mutated in this model of PACC. Since previous research shows that DNA repair is an important component of PACC, we conclude that treatment with oxaliplatin may be a viable option for patients.

References


Figure 1: Characterization of PACC PDX mouse model

Figure 2. Therapeutic response in PA-018 PDX ACC mouse model

Figure 3. Evaluation of expression of pancreatic digestive enzymes

Figure 4. Oxaliplatin’s effects on proliferation and apoptosis in PACC

Table 1. Result summary of PA-018 therapeutic responses and toxicities

Table 1. The therapies used included DNA synthesis inhibitors (irinotecan), a DNA alkylating agent (temozolomide), a DNA intercalating agent (cisplatin), a Topoisomerase inhibitor (ovirubicin), an EGFR inhibitor (erlotinib), a c-kit inhibitor (imatinib) and an angiogenesis inhibitor (bevacizumab). Tumor growth was continually observed after treatment regimen ceased in order to determine time-to-endpoint (TTE) and difference between TTE medians (T-C). Body weight (BW) nadir was shown as percent change and deaths were divided into treatment-related deaths (TR) and non-treatment-related deaths (NTR).

Table 2. Amylase and lipase levels were examined via densitometry at 20X magnification.

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Figure 4. Oxaliplatin’s effects on proliferation and apoptosis in PACC

Immunohistochemistry (IHC) was examined for ki67 for proliferation index and cleaved caspase-3 (CC3) for apoptotic index. ki67 was scored by positive counts per core section and plotted as mean percent ± standard deviation. CC3 was scored by positive cells in distinct regions and plotted as percent n standard deviation. * indicates p < 0.05 for treatment group as compared to placebo, n = 5.