428

Development of an Oncolytic Adenovirus to Treat Metastatic Colorectal Cancer

Christopher J. LaRocca, Stacey Wilber, Eric Jensen, Subree Subramanian, Clifford Steer, Julia Davydova
University of Minnesota

OBJECTIVES/GOALS: Colorectal cancer (CRC) is a leading cause of cancer mortality, and many patients will develop metastatic disease at some point during their treatment course. Conventional therapies such as surgery, chemotherapy, and radiation are often of limited effectiveness in these advanced stages, which necessitates the development of novel therapies. METHODS/STUDY POPULATION: Our group has designed an oncolytic adenovirus backbone structure expressing the sodium iodide symporter (NIS) which can be used in conjunction with radioiodine to facilitate cancer imaging and therapy. Using multiple CRC cell lines, oncolytic adenoviruses with different fibers were tested in vitro to determine which of these modifications yielded the highest binding to the cancer cells. Additionally, multiple promoter structures are being tested to determine the impact on the replication and oncolytic effect of the virus. Furthermore, the potential of adenovirus-mediated NIS expression to facilitate PET/CT imaging and therapy with I-131 will be explored. RESULTS/ANTICIPATED RESULTS: The Ad5/3 chimeric fiber modification demonstrated the best binding in CRC cell lines. Additionally, tissue specific promoters are employed in oncolytic viruses to confer selective replication in cancer cells, while minimizing off target effects in nearby normal tissues. We have employed a Cox2 promoter, which has demonstrated an excellent oncolytic effect. In vitro NIS expression was shown in multiple CRC cell lines through immunostaining. Small animal PET/CT imaging demonstrated signal uptake in mice with subcutaneous CRC tumors after virus and radioiodine (I-124) administration. We anticipate that future studies employing radioactive iodine (I-131) in combination with our oncolytic virus will yield an augmented antitumor effect. DISCUSSION/SIGNIFICANCE: The NIS-expressing adenovirus has the ability to support radionuclide-based imaging and therapy for CRC. With additional pre-clinical testing, our adenovirus construct has the potential to bring NIS-based therapeutics to the bedside to positively impact CRC patient care outcomes.

429

Eribulin Synergizes with STING Agonists by Enhancing Type 1 Interferon Expression and Improves Antitumor Efficacy as Combination Treatment

Leila Takahashi-Ruiz, Charles S. Fermaintt, Nancy Wilkinson, Peter Y. Chan, Susan L. Mooberry, April L. Risinger
University of Texas Health San Antonio

OBJECTIVES/GOALS: Triple-negative breast cancer (TNBC) is a subtype of breast cancer that lacks effective targeted treatment options. TNBC's greater degree of immunogenicity than other breast tumors makes immunotherapy a viable strategy. Strategies to improve the immunotherapy response includes targeting the cGAS-STING innate immune pathway with STING agonists. METHODS/STUDY POPULATION: We have previously shown in vitro that eribulin, a microtubule destabilizer currently used in the treatment of TNBC, functions as an indirect STING agonist because it promotes the release of mitochondrial DNA into the cytoplasm. Separately, eribulin also significantly enhances type I interferon expression induced by STING agonists measured by qRT-PCR through a second TBK1-dependent mechanism downstream of STING activation through detecting higher amounts of phosphorylated IRF-3 by western blot protein analysis. Mechanisms of eribulin-mediated interferon expression occur in immune and TNBC cells and are shared with other microtubule destabilizers but not with the microtubule stabilizing agent paclitaxel. RESULTS/ANTICIPATED RESULTS: We determine that the enhancement of type I interferon expression by eribulin is pharmacologically synergistic with multiple STING agonists. The significant enhancement by eribulin led us to evaluate the antitumor efficacy of eribulin in combination the STING agonist ADU-S100 in a challenging spontaneous mammary tumor model MMTV-PyVT. We show that the combination treatment significantly decreased tumor growth which allowed for longer survival compared to other groups. This is particularly interesting because of our previous studies showing that eribulin alone, but not paclitaxel, promotes the activation of CD4+ T-cells in the spleen and draining lymph nodes of BALB/c mice with 4T1 tumors through flow cytometric analysis. DISCUSSION/SIGNIFICANCE: These data contribute to accumulating evidence that there are important mechanistic differences between the microtubule targeted chemotherapeutics currently used in the treatment of TNBC and suggest that eribulin can act as an immune adjuvant in addition to its anti-mitotic effect.

430

Etiology of Hepatocellular Carcinoma in the 27-County Rochester Epidemiology Project Catchment Area, 2010-2021

Caitlin VanLith[1], Aimee Uwilingiyimana[2], Lewis R Roberts[3]
[1]Mayo Clinic [2]Mayo Clinic Alix School of Medicine [3]Mayo Clinic Division of Gastroenterology and Hepatology

OBJECTIVES/GOALS: The goal of this study is to examine the incidence, etiology, and outcomes of hepatocellular carcinoma (HCC) in a 27-county region in SE Minnesota and W Wisconsin between 2010 and 2021. A comparison of the first to second half of the period will be made to look for possible trends. METHODS/STUDY POPULATION: The Rochester Epidemiology Project (REP) is a database of patient records across SE Minnesota and W Wisconsin. Starting in 2010, the REP opened to a 27-county catchment area, which includes over 1.3 million patients with a population coverage of approximately 64%. This study will use the expanded REP data to collect data on patients 20 years of age and older with a new diagnosis of HCC between Jan 1, 2010 and Dec 31, 2021â€"an estimated 1000 cases. Patients with a record of less than one year of residence in the catchment area will be excluded. Data on etiology, comorbidities, and outcomes of HCC will be extracted from medical records and analyzed for risk factors and changes over time. RESULTS/ANTICIPATED RESULTS: We anticipate that the overall incidence of HCC in the REP geographic area has increased over the period of 2010 to 2021. We anticipate that the prevalence of hepatitis C virus infection in patients with HCC has between 2010 and 2021, due to the widespread use and accessibility of hepatitis C-specific antiviral treatment over the past decade. We anticipate that the prevalence of NAFLD in patients with HCC has increased between 2010 and 2021. We do not anticipate significant changes in treatment modality or survival outcomes over this period. DISCUSSION/SIGNIFICANCE: This study will provide a comprehensive update on the state, etiology, and outcomes of HCC in the area surrounding

https://doi.org/10.1017/cts.2023.459 Published online by Cambridge University Press