2016

New Platinum Agents, Triplatin and Triplatin NC, Suppress Advanced Breast and Pancreatic Cancer

Stephanie C. DeMasi
Virginia Commonwealth University, demasisc@vcu.edu

Kazuaki Takabe MD, Ph.D., FACS
Virginia Commonwealth University, kazuaki.takabe@vcuhealth.org

V I R G I N I A C O M M O N W E A L T H U N I V E R S I T Y

VCU Medical Center

New Platinum Agents, Triplatin and Triplatin NC, Suppress Advanced Breast and Pancreatic Cancer

Stephanie C. DeMasi, BS[1], Samantha J. Katner, BS[2], Eriko Katsuta, MD, PhD[1], Hiroaki Aoki, MD, PhD[1], Erica Peterson, BS[2], Nicholas P. Farrell, BS, PhD[2], Kazuaki Takabe, MD, PhD, FACS[1]

[1] Division of Surgical Oncology, Department of Surgery, Virginia Commonwealth University School of Medicine And Massey Cancer Center, Richmond, VA. [2] Department of Chemistry, Virginia Commonwealth University, Richmond, VA,.

Purpose

- To examine the efficacy of newly developed, polynuclear platinum agents, that work by a similar mechanism of damaging DNA cross-linking.

Background

- Recently, platinum agents are demonstrating to be an effective therapy against advanced metastatic cancer, though limited by the severe side effects.
- New platinum derivative compounds were developed to have less cytotoxicity, to overcome the severe dose dependent toxicities of the former platinum agents.

Methods

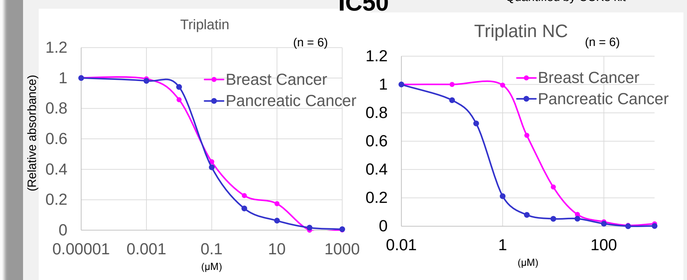
- ***In vitro***: Cell proliferations were quantified by CCK8 assay to determine IC50 and drug sensitivity of 4T1-luc2 cells as a murine breast cancer, and Panc02-luc cells as a murine pancreatic cancer.
- ***In vivo* 4T1 Implantation**: Female Balb/C mice were orthotopically implanted with murine 4T1-luc2 cells (1.0×10^4 cells suspended in 20 µL 1:9, PBS:Matrigel) into Rt #2 Mammary Fat Pad ODV. Mice were randomized 24-hours after implantation into 3 groups based on tumor size (defined as day 1). Animals were treated q4 days by I.P. injection with either Triplatin (0.3mg/kg), Triplatin NC (25mg/kg), or Saline. Primary tumor growth was monitored by direct caliper measurement and bioluminescent imaging by injecting D-Luciferin (0.2mL) and analysis of photon emission with Living Image Software.
- ***Ex vivo* 4T1 Lung Metastasis**: Mice were injected with I.P. luciferon and sacrificed 10 minutes after injection. The lungs were excised and placed in sterile 10cm petri dish. Lungs were imaged at a fixed time point (15 minutes) post injection.
- ***In vivo* Panc02 Carcinomatosis Implantation**: Generated by I.P. injection of 1×10^6 Panc02-luc cells into C57/Blk6 mice. Animals were randomized and treated q4 days with either Triplatin or saline by I.P. injection. Survival was monitored.

Results

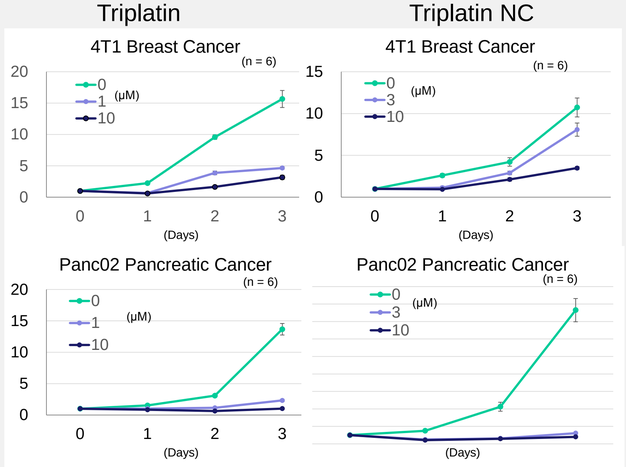
Triplatin and Triplatin NC suppressed cell growth of both **Breast Cancer** and **Pancreatic Cancer** in a dose dependent manner in vitro

IC50

Quantified by CCK8 kit

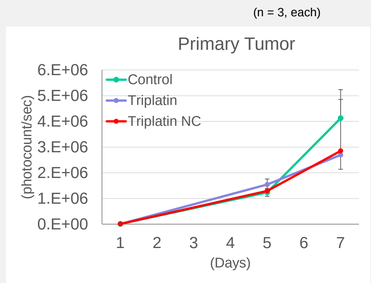


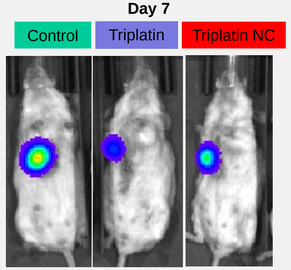
Cell Proliferation Assay



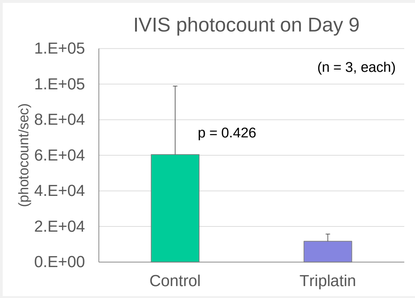
Triplatin and Triplatin NC suppressed **primary Breast Cancer tumor growth** and developing **lung metastasis** in vivo

Primary Tumor

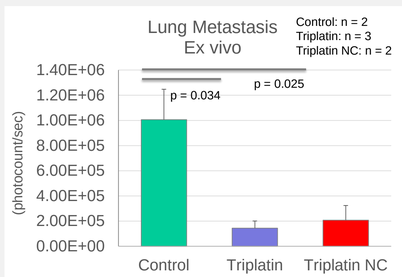


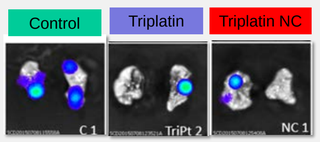


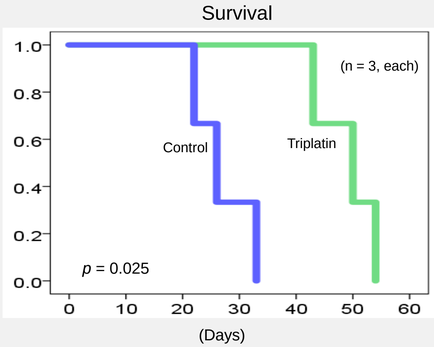
Triplatin treatment prolonged survival significantly in the **Pancreatic Cancer Carcinomatosis** model in vivo



Lung Metastasis







Conclusion & Recommendations

- Triplatin and Triplatin NC suppressed cell growth of both Breast Cancer and Pancreatic Cancer in a dose dependent manner in vitro.
- Both Triplatin and TriplatinNC demonstrated growth suppression of the primary breast tumor. A single animal (in the Triplatin NC group) was sacrificed due to weight loss.
- In the advanced ex vivo lung metastasis model our most striking results were observed, where the agents nearly prohibited lung metastasis from occurring.
- In the pancreatic cancer peritoneal carcinomatosis model, Triplatin reduced total tumor burden. Mouse survival was significantly enhanced by the Triplatin treatment group and no mouse developed weight loss more than 25% of body weight.
- The new platinum compounds with less cytotoxicity and favorable pharmacokinetics warrant further investigation to determine their role in advanced metastatic breast cancer and pancreatic carcinomatosis.