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EASTERN TIME [GMT-4]

Using Immunoadjuvants in Combination With Radiation Therapy in Single and boost doses in the Treatment of an Aggressive Pancreatic Mouse Cancer as an In-situ Cancer Vaccine.

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INTRODUCTION

In the fight against cancer, metastasis continuously poses a problem, causing almost 90% of cancer-related deaths.[1] In order to mitigate the metastatic burden, the abscopal effect is thought to be our answer. The problem, however, is knowing how to properly stimulate the immune response to create the abscopal effect to begin with. The **abscopal effect** refers to the treatment of disease at a distance from the treated site.

Using **Radiation Therapy** (RT), a known potent immune stimulator, it is proposed that multiple doses of radiation could potentially garner a stronger immune response.[2] To investigate this, a boost RT dose was given to some cohorts either at the site of initial treatment or at a secondary site to mimic treatment of a metastatic site, a schematic of which can be seen in the results section.

AIM

Investigating the anti-cancer effects in using an in-situ vaccine using various combinations of immunoadjuvants and radiation in varied dosing schedules. The immunoadjuvants used were Anti-CD40 and Anti-PDL1. Tumor volumes and survival percentages were monitored.

METHOD

Cell Culture/Tumor Inoculation:

- Murine pancreatic cancer cell line Panc02 was cultured in DMEM media supplemented with 10% FBS and 1% Penicillin-Streptomycin.
- C57BL/6 Male mice were inoculated withPanc02 cells suspended in PBS at concentrations of 300,000 cells/injection per each flank and 200,000 cells/injection on the dorsal to mimic primary and secondary treatment, and metastatic sites.

Cohort Scheme:

- Mice were separated into 8 cohorts, some receiving treatment to only the primary (**A**) tumor and some receiving treatment to both primary(**A**) and secondary(**C**) tumors.
  1. Anti-CD40 to **A**
  2. RT 6Gy to **A**
  3. Anti-CD40+RT 6Gy to **A**
  4. Anti-CD40+RT 6Gy to **A**+RT Boost to **C**
  5. Anti-CD40+Anti-PDL1+RT 6Gy **to A**
  6. Anti-CD40+Anti-PDL1+rt 6Gy to **A**+RT Boost to **C**
  7. Anti-CD40+Anti-PDL1+RT 6Gy to **A**+RT Boost to **A**
  8. Control

Treatment:

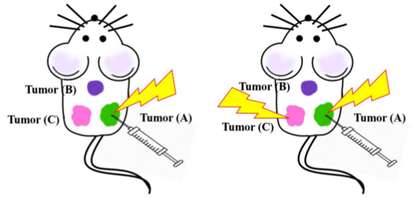
- Treatment began on day 0 with initial doses of RT and immunotherapy injections for treated mice and PBS injections for control mice.
  - RT was administered via the Small Animal Radiation Research Platform (SARRP) at 6 Gy
  - Immunomodulating Anti-CD40 and Anti-PDL1 were injected intratumorally (**IT**) at doses of 20µL and 200µL per dose respectively
- Subsequent Anti-PDL1was administered IT on day 4 and day 8
- A booster dose of 6 Gy RT was administered on day 8

RESULTS

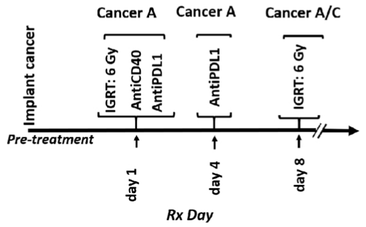
- The strongest tumor control is seen from two cohorts- both without RT boost doses. These are the RT+Anti-CD40 alone and the RT+Anti-CD40+Anti-PDL1 cohorts.
- Although provided graphs suggest that RT+Anti-CD40 alone are superior in tumor control, the cohort that had the additional treatment of Anti-PDL1 had a survival length of nearly twice as long (60 vs 34 days)

Observations and Obstacles:

- Nearly all mice used in this experiment suffered from high intratumoral pressure due to the nature of Panc02 causing ulceration of the tumor and adherence to the humane endpoints vs. study endpoints.

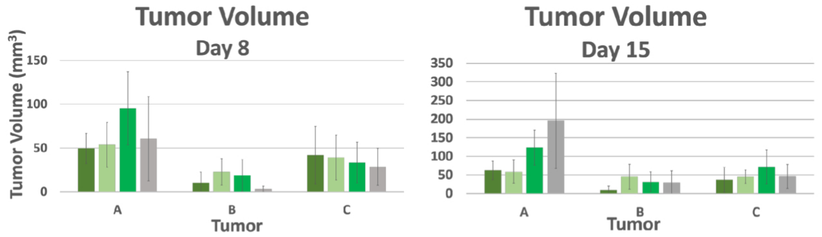


(Above)Diagram of treated mouse. Left: Mouse treated with only treatment to tumor A. Right: Mouse treated normally to tumor A and with boost shot to C.



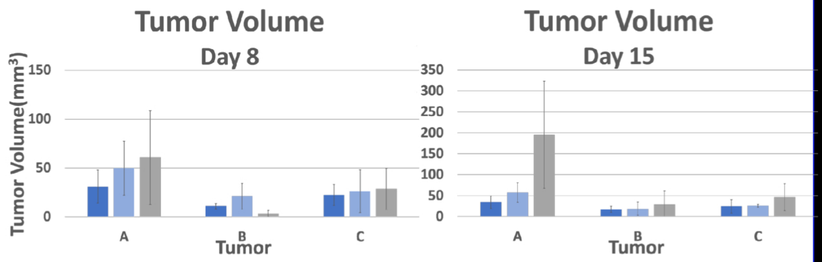
Timeline of treatment schedule.

Combination Treatment



- Anti-CD40+Anti-PDL1+RT 6Gy to A
- Anti-CD40+Anti-PDL1+rt 6Gy to Tumor A+RT Boost to Tumor C
- Anti-CD40+Anti-PDL1+RT 6Gy to Tumor A+RT Boost to A
- Control

Anti-CD40 Alone



- Anti-CD40+RT 6Gy to Tumor A
- Anti-CD40+RT 6Gy to Tumor A+RT Boost to Tumor C
- Control

***(Top) Left*:** Tumor volumes on days 8 (last Rx day) and day 15 for all cohorts using RT and both Anti-CD40 and Anti-PDL1 (both with and without RT boosts) vs. control. It can be seen that the cohort without a boost dose has the best tumor regression when Anti-PDL1 is added to the treatment. ***(Bottom) Right*:** Tumor volumes at same time points as left but with cohorts only treated with RT and Anti-CD40 (with and without RT boosts) vs control. It can be seen that the cohort that does not receive a boost dose shows better tumor control.

CONCLUSIONS

These preliminary data are promising despite the difficulties encountered during its execution. The strongest tumor control was seen from RT+Anti-CD40 alone and the RT+Anti-CD40+Anti-PDL1 cohorts, and the addition of Anti-PDL1 allowed for longer survival. In looking forward, a repeat study will be conducted with bigger cohort sizes and steps taken to alleviate the obstacles encountered. Additionally, optimizing the administration route of the Anti-PDL1 will be further investigated.

REFERENCES

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[2]Chuong M, Chang ET, Choi EY, et al. Exploring the Concept of Radiation "Booster Shot" in Combination with an Anti-PD-L1 mAb to Enhance Anti-Tumor Immune Effects in Mouse Pancreas Tumors. *J Clin Oncol Res*. 2017;5(2):1058.

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