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CLR1404, A TUMOR-SELECTIVE ALKYL PHOSPHOCOLINE ANALOG INCREASES RADIATION SENSITIVITY IN SOLID TUMORS

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Background:
Drugs that radiosensitize tumor cells while sparing normal tissues could have a significant impact on the efficacy of cancer radiotherapy. CLR1404 is a novel alkyl phosphocholine analog and belongs to the family of synthetic anti-tumor alkyl phospholipid compounds, some of which have demonstrated radiosensitizing capabilities. CLR1404 shows tumor-selective uptake in a wide variety of malignant tissues, and therefore we hypothesized that CLR1404 could be used as a tumor-targeted radiosensitizer to augment radiation response in a variety of solid tumors.

Objectives:
To examine the capabilities of CLR1404 as tumor-targeted radiosensitizer to augment radiation response in a variety of solid tumors.

Design/Method:
We examined the radiosensitizing effect of CLR1404 on several pediatric and adult solid tumor-derived human cell lines in vitro and in vivo. The selective uptake of CLR1404 in cancer cells versus normal cells was evaluated by flow cytometry, using a CLR1404-Bodipy fluorescent derivative. The in vitro radiosensitization of cancer cells was evaluated by clonogenic survival assay using CLR1404 at different concentrations with or without external beam radiation (XRT). Tumor growth rate after radiosensitization with CLR1404 followed by XRT was examined in vivo in xenograft-bearing athymic nude mice.

Results:
CLR1404 demonstrated significantly higher uptake and retention in all cancer lines tested (neuroblastoma: CHLA20, NB-1691, SK-N-AS; rhabdomyosarcoma: RD, Rh-30, Rh-41; Ewing sarcoma: TC-71, TC-106; and prostate carcinoma: PC3) when compared to uptake in normal human fibroblasts ($p<0.05$). CLR1404 significantly reduced clonogenic survival in a dose dependent manner when combined with XRT (CHLA20, Rh-30 and PC3; $p<0.01$). Treatment of human tumor xenografts with fractionated external beam radiation combined with CLR1404 revealed a significant increase in tumor growth delay compared with CLR1404 or radiation treatment alone (Rh-30, TC-

71, PC3; $p<0.01$). There was no observable toxicity during or after the treatment.

Conclusion:
We conclude that tumor targeted CLR1404 has the capacity to augment the therapeutic response to external beam radiation in a variety of solid tumors. Given the importance of radiotherapy in pediatric cancer treatment strategies, our data warrant further pre-clinical testing with the goal to translate our findings into future clinical trials.

Category:
Solid Tumors