Heat-triggered delivery of synergistic chemotherapies in murine models of breast cancer

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INTRODUCTION

Doxorubicin (DOX) is among the most commonly used chemotherapy drugs in the treatment of breast cancer [1]. However, its use is limited due to cardiotoxicity [2]. Several formulation approaches have been developed to mitigate the off-target effects of DOX. Among these is a thermosensitive liposomal formulation of DOX (i.e., ThermoDox®) that has previously been evaluated in Phase III clinical trials. Despite the improvements in drug delivery to the tumor site afforded by this approach, a significant amount of free DOX can enter the systemic circulation potentially contributing to the observed normal tissue toxicity [3]. To reduce DOX doses and prevent adverse effects, our lab previously identified a highly synergistic drug combination of DOX with the heat shock protein 90 inhibitor alvespimycin (ALV). This combination has been previously developed into a heat-triggered drug delivery approach [4]. Here we investigate this drug combination together with localized mild hyperthermia (HT) in both immunocompromised and immunocompetent murine models of breast cancer.

METHODS

MDA-MB-231 tumor bearing SCID mice and 4T1 tumor bearing BALB/c mice were treated with thermosensitive liposomes (TSLs) in combination with mild HT, either in-house manufactured thermosensitive liposomes ThermoDox (3 or 5 mg/kg), a combination of ThermoDox and ThermoALV (3 and 15 mg/kg respectively), or with saline once per week for three weeks. Tumor volumes and animal weights were monitored to determine treatment efficacy and toxicity.

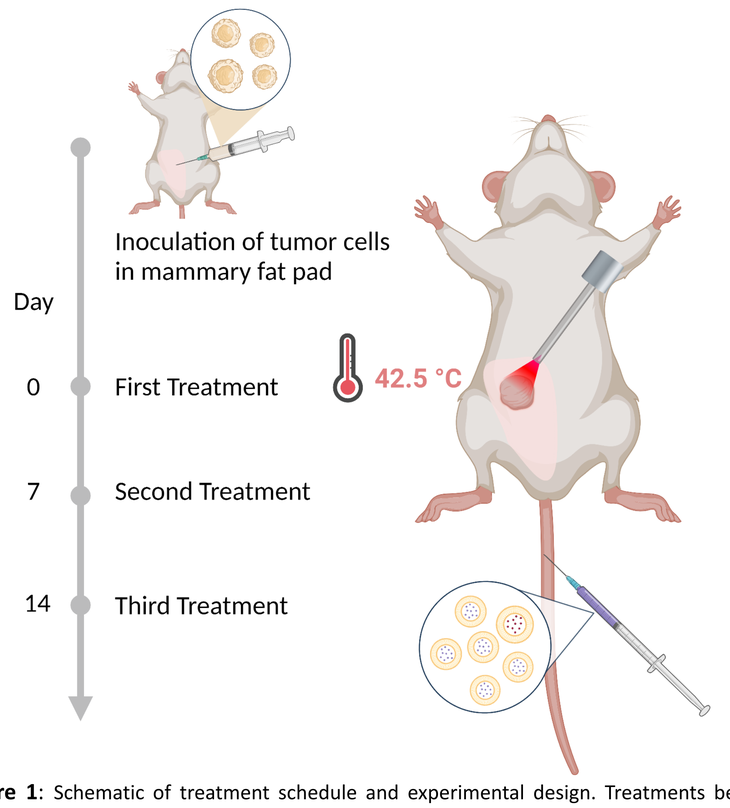

Figure 1: Schematic of treatment schedule and experimental design. Treatments began once tumor volumes reached >120 mm^3. Tumors were heated for 5 min at 42.5 °C using a laser-based system prior to liposome administration, and then maintained at the same temperature for 20 min post administration.

CONCLUSION

This work underscores the need for rational selection of chemotherapy regimens, even when advanced formulation approaches such triggered-release drug delivery are employed. In the MDA-MB-231 model, DOX and ALV at a synergistic ratio is able to improve treatment efficacy while lowering the DOX dose by 40%. Conversely, in the 4T1 model, adding ALV to DOX did not improve treatment outcomes. Efforts to explain the differences in therapeutic efficacy are currently underway.

RESULTS

In the immunocompromised MDA-MB-231 model, the combination treatment was able to reduce toxicity (i.e., less bodyweight loss) while simultaneously prolonging median survival times compared to the high dose ThermoDox treatment (Figure 2B and 2C). Similarly, primary tumor growth was significantly inhibited compared to control animals in the immunocompetent 4T1 model (Figure 2A). However, due to the aggressive metastatic spread observed in this model, no difference in median survival times was observed. Future work will focus on exploring a better therapeutic approach to control the spontaneous metastasis in 4T1 model.

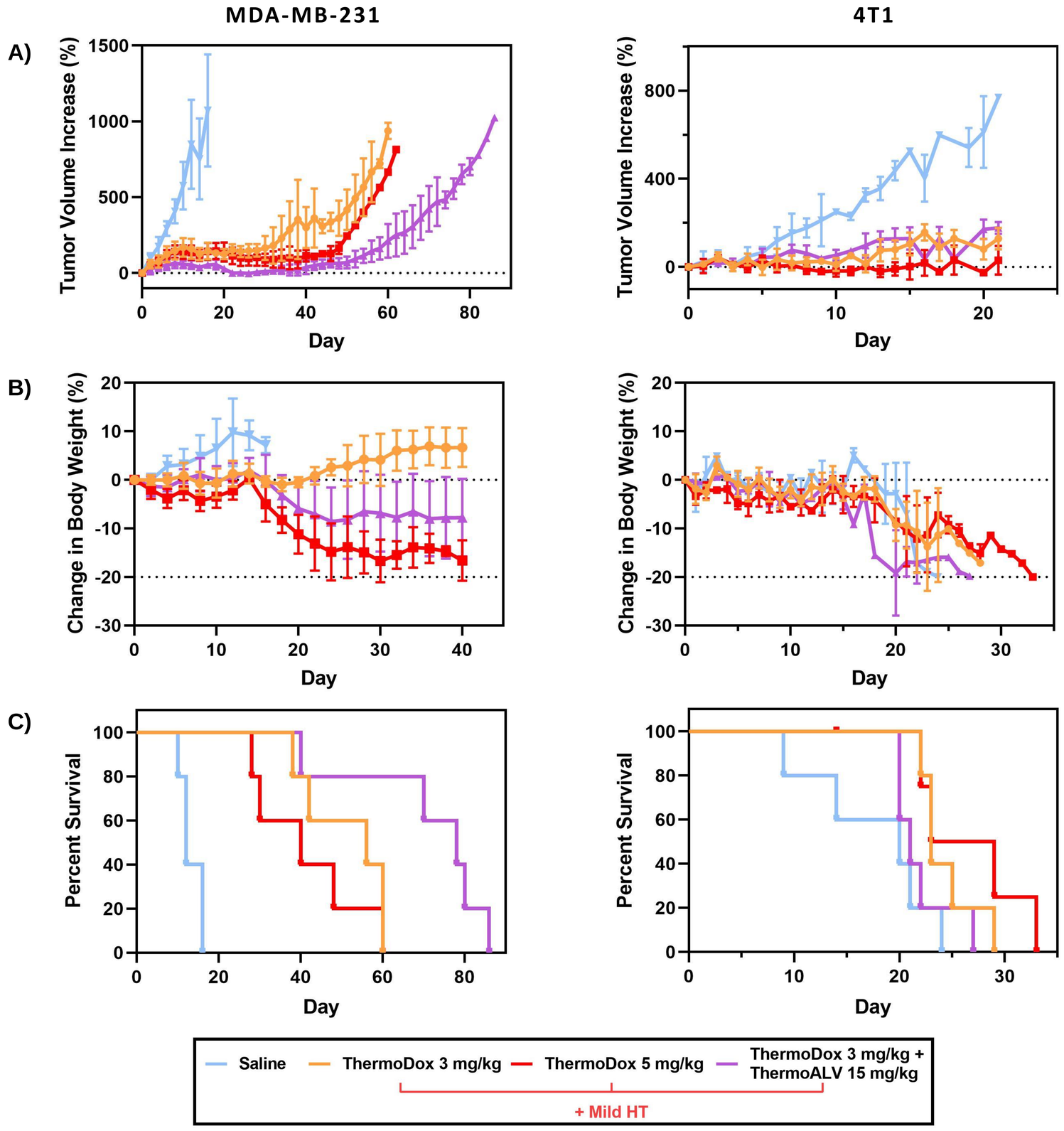

Figure 2: A) Tumor volumes, B) percent change in animal weight, and C) survival as a function of time. Animals were euthanized when the tumor diameter reached >15 mm or animals lost more than 20% body weight.

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