

ANGIOGENESIS AND TUMOR INITIATING CELLS AS THE TARGETS OF LOW DOSE METRONOMIC TOPOTECAN AND PAZOPANIB IN NEUROBLASTOMA MOUSE MODEL

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Purpose: Angiogenesis plays a critical role in Neuroblastoma (NB) growth and metastasis. Low Dose Metronomic (LDM) chemotherapy, combined with VEGF signalling pathway inhibitors is a highly effective strategy to inhibit angiogenesis and tumor growth in many preclinical models. Here we have tested the efficacies of three regimens: 1.0 mg/Kg LDM topotecan (TP), 150 mg/Kg pazopanib (PZ) and the combination of both (TP+PZ), as daily oral doses in a NB mouse model. Our hypothesis is that TP+PZ will have higher antitumor efficacy than either TP or PZ alone.

Methods: IC50s for both drugs using NB cell lines (SKN-BE2 and SH-SY5Y) and Tumor Initiating Cells (TICs) (NB12 and NB88R) were established in vitro. In vivo antitumor efficacies of the three regimens were tested on a SK-N-BE(2) subcutaneous xenograft model and BE(2)c metastatic model. Circulating Endothelial cells (CECs) and Circulating Endothelial Progenitor cells (CEPs) were employed as the surrogate markers of antiangiogenic efficacy. Pharmacokinetic (PK) study was conducted to test the drug interaction. Additionally, the in vivo efficacies of regimens against TICs were tested using NB12 subcutaneous xenograft model. Immunohistochemistry was conducted to study the effects of regimens on Hypoxia Inducible factors (HIFs) and stemness markers, e.g. Oct-4.

Results: TP caused a dose-dependent decrease in viabilities of cell lines and TICs, while PZ did not affect their viability. In both SK-N-BE(2) xenograft and BE(2)c metastatic models, all the three regimens showed antitumor efficacy, with TP+PZ showing significant enhancement in survival compared to the respective single agents. The reduction in CEC and/or CEP levels confirmed the antiangiogenic effects of the regimens. PK studies did not reveal any drug interaction between the two drugs. TP and TP+PZ, enhanced the survival of animals in NB12 xenograft model. Also, TP+PZ significantly reduced the levels of HIF-1 alpha and Oct-4 in NB 12 xenograft model.

Conclusion: TP+PZ showed significant antitumor efficacy, which was greater than the single agents in our NB mouse model. Anti-tumor activity was likely due to several independent mechanisms, which included antiangiogenesis, lowering of HIF-1 alpha levels and the reduction of the stemness phenotype of TICs.

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