Preclinical metronomic topotecan and pazopanib combination in primary or late stage metastatic triple-negative breast cancer

T. Di Desidero[1,2], P. Xu[1], S. Man[1], R.S. Kerbel[1,3], G. Bocci[2]

[1]Dept. of Medical Biophysics, Biological Sciences Platform, Sunnybrook Research Institute, University of Toronto, Toronto, Ontario, Canada
[2]Div. of Pharmacology, Dept. of Clinical and Experimental Medicine, University of Pisa, Italy
[3]Dept. of Medical Biophysics, University of Toronto, Toronto, Ontario, Canada

Introduction. Metronomic chemotherapy has shown promising activity in numerous preclinical studies (Jedeszko C et al., 2015) and also some phase II clinical studies involving various tumor types (Derosa L et al., 2014) and is currently undergoing phase III trial evaluation (Kerbel RS, 2014). Triple-negative breast cancer (TNBC) is an aggressive subtype with limited treatment options and very poorer survival than other types (Andre F et al., 2012). We evaluated the potential therapeutic impact and molecular mechanisms of topotecan administered in a continuous low-dose metronomic manner, alone or in concurrent combination with pazopanib on a triple-negative, primary and metastatic breast cancer model. **Methods.** Proliferation and apoptotic assays were performed on human umbilical vein endothelial cells (HUVECs) and 231/LM2-4, a serially selected metastatic variant of the triple negative MDA-MB-231 breast cancer-cell line, exposed to topotecan, pazopanib, sunitinib, alone or in combination, for 144h hours in hypoxic conditions. *VEGF*, *HIF1α* and *ABCG2* gene expression were performed with real-time PCR and topotecan intracellular concentrations were measured by high-performance liquid chromatography. Mice with primary tumors or advanced metastatic disease were treated with topotecan, in a standard (MTD) or in a low-dose metronomic manner (LDM), and pazopanib alone or in combination. **Results and discussion.** The combined treatment with metronomic topotecan and pazopanib significantly enhanced antitumor activity and prolonged survival with a significant decrease in tumor vascularity, proliferative index, and an induction of apoptosis. Metronomic topotecan determined a significant antiproliferative and proapoptotic activities on both endothelial and TNBC cells, enanched by pazopanib. Metronomic topotecan and pazopanib combination treatment greatly inhibited the expression of HIF1α, ABCG2 and VEGF genes in hypoxic TNBC cells, together with an increase in the intracellular concentration of the active form of topotecan. **Conclusions.** Our results suggest a potential novel therapeutic option for the treatment of metastatic triple-negative breast cancer patients.

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