Accepted Manuscript

Sorafenib improves alkylating therapy by blocking induced inflammation, invasion and angiogenesis in breast cancer cells

Alfeu Zanotto-Filho, Subapriya Rajamanickam, Eva Loranc, Pragathi Masamsetti, Aparna Gorthi, July Carolina Romero, Sonal Tonapi, Rosangela Mayer Gonçalves, Robert L. Reddick, Raymond Benavides, John Kuhn, Yidong Chen, Alexander J.R. Bishop

PII: S0304-3835(18)30240-4

DOI: 10.1016/j.canlet.2018.03.037

Reference: CAN 13827

To appear in: *Cancer Letters*

Received Date: 12 July 2017

Revised Date: 21 March 2018

Accepted Date: 23 March 2018

Please cite this article as: A. Zanotto-Filho, S. Rajamanickam, E. Loranc, P. Masamsetti, A. Gorthi, J.C. Romero, S. Tonapi, R.M. Gonçalves, R.L. Reddick, R. Benavides, J. Kuhn, Y. Chen, A.J.R. Bishop, Sorafenib improves alkylating therapy by blocking induced inflammation, invasion and angiogenesis in breast cancer cells, *Cancer Letters* (2018), doi: 10.1016/j.canlet.2018.03.037.

Abstract

Molecular targeted compounds are emerging as a strategy to improve classical chemotherapy. Herein, we describe that using low dose of the multikinase inhibitor sorafenib improves cyclophosphamide antitumor activity by inhibiting angiogenesis, metastasis and promoting tumor healing in MDA-MB231 xenografts and the 4T1-12B syngeneic breast cancer metastasis model. Mechanistic studies in MDA-MB231 cells revealed that alkylation upregulates inflammatory genes/proteins such as COX-2, IL8, CXCL2 and MMP1 in a MEK1/2-ERK1/2-dependent manner. These proteins enrich the secretome of cancer cells, stimulating cell invasion and angiogenesis via autocrine and paracrine mechanisms. Sorafenib inhibits MEK1/2-ERK1/2 pathway thereby decreasing inflammatory genes and mitigating cell invasion and angiogenesis at basal and alkylation-induced conditions whereas NRF2 and ER stress pathways involved in alkylation survival are not affected. In non-invasive/non-angiogenic breast cancer cells (SKBR3 and MCF7), alkylation did not elicit inflammatory responses with the only sorafenib effect being ERK1/2-independent ROS-dependent cytotoxicity when using higher drug concentrations. In summary, our data show that alkylating agents may elicit inflammatory responses that seems to contribute to malignant progression in specific breast cancer cells. Identifying and targeting drivers of this phenotype may offer opportunities to optimize combined drug regimens between classical chemotherapeutics and targeted agents.