

# Carbonic anhydrase inhibition boosts the antitumor effects of imatinib mesylate via potentiating the antiangiogenic and antimetastatic machineries.

Heba Darwish ,Amal A.Abd-El Fattah, NevineFathy, Samia A.Shouman

## Abstract

Carbonic anhydrase inhibitors have emerged in the past few years as an interesting candidate for the development of novel unconventional strategies. Despite their effect in tumor regression via inhibition of tumor acidification, their potential role is not yet fully elucidated. Herein, we investigated whether acetazolamide (AZ) could modulate imatinib (IM) anticancer activity, both in breast cancer cells (T47D) and in isolated tumor specimens of Ehrlich ascites carcinoma (EAC). The impact of this combination on angiogenesis was evidenced by decreasing PDGF-A expression and enhancing that of TSP-1. In the meantime, AZ significantly suppressed IM-induced attenuation of VEGF secretion in T47D cells, most probably due to NO inhibition. The combination also dramatically decreased the metastatic activity of T47D cells by mitigating the protein levels of MMP-2 and -9 and phosphorylation of p38 MAPK, while increasing the expression of TIMP-1 and -2. In addition, a strong proapoptotic effect was observed in T47D cells after combining AZ and IM in terms of increased caspase-9 and -3 activities. Interestingly, these results were confirmed by the reduction in the isolated tumor volume, MVD, Ki-67 and VEGF expression. Eventually, the study provides a new therapeutic strategy for treating cancer.

*Toxicology and Applied Pharmacology 2017, February*