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Carboxyamidotriazole-orotate inhibits the growth of imatinib-resistant chronic myeloid leukaemia cells and modulates exosomes-stimulated angiogenesis

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Chronic myelogenous leukemia is a myeloproliferative disorder characterized by the t(9:22)(q34:q11) reciprocal chromosomal translocation, resulting in the expression of the chimeric Bcr–Abl oncoprotein with constitutive tyrosine kinase activity. Deregulated Bcr–Abl induces the hyperactivation of various signalling pathways that promote cell growth, suppress apoptosis and alter cell adhesion. Bcr-Abl has also been involved in VEGF-mediated angiogenesis in CML and evidence indicates that the formation of new vessels plays an important role in the development and progression of CML. Imatinib mesylate (IM) is a selective well tolerated inhibitor of the Bcr–Abl tyrosine kinase that has significantly improved the prognosis of patients with chronic phase CML. Despite this remarkable progress, a major problem associated with the administration of imatinib is acquired resistance. Bcr-Abl gene amplification, increased expression of Bcr–Abl protein, point mutations in the Bcr–Abl tyrosine kinase domain have been reported as mechanisms of resistance to imatinib. Therefore, there is an urgent need for new anticancer agents and combinations that could improve responses and survival rates for CML. Recent studies from our laboratory have shown that addition of carboxyamidotriazole (CAI), an inhibitor of calcium-mediated signal transduction, to imatinib resistant human CML cells induces a marked decrease in cell viability and augmented apoptosis, events associated with downregulation of Bcr–Abl protein and inhibition of tyrosine phosphorylation of Bcr–Abl, STAT5, CrkL. Carboxyamidotriazole Orotate (CTO), is a derivate of CAI that has been developed at Tactical Therapeutics. CTO has a higher bioavailability and efficacy with respect to the parental compound. Exosomes are small vesicles of 40-100 nm diameter that are initially formed within the endosomal compartment and are secreted when a multivesicular body (MVB) fuses with the plasma membrane. These vesicles are released by many cell types including cancer cells and are considered messengers in intercellular communication. The exact function of exosomes in malignant cells has yet to be elucidated, but investigation has suggested roles in cell-to-cell communication, tumor-stroma interaction, and antigen presentation, thus potentially affecting cancer progression at different steps. Recent studies from our laboratory suggest that exosomes released from IM-sensitive CML cells directly affect endothelial cells modulating the process of neovascularization. Our data show that CTO is able to inhibit both *in vitro* and *in vivo* the growth of imatinib-resistant CML cells and to affect tumor microenvironment by modulating exosome-stimulated angiogenesis. CTO may be effective in targeting both cancer cell growth and the tumor microenvironment, thus suggesting a potential therapeutic utility in the treatment of leukemia patients.