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HSP90 and tyrosine kinase inhibitors: A synergistic combination for combating cancer?

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The merging of knowledge from genomics, cellular signal transduction and molecular evolution is producing a new paradigm of cancer analysis. Tyrosine kinases have long been understood to initiate and promote malignant cell growth. Targeting tyrosine kinases to fight cancer has been a major strategy for the pharmaceutical industry for almost 3 decades. Despite the initial success of tyrosine kinase inhibitors, the ability of cancer to evolve resistance and switch between oncogenic signals has made the effective use of tyrosine kinase inhibitors difficult. The molecular chaperone HSP90 physically supports global tyrosine kinase function while also acting as an evolutionary capacitor. The Cancer Genome Atlas has compiled a trove of data that indicates a number of cancers over-express or possess mutant tyrosine kinases that depend on HSP90 and its cohorts. Targeting HSP90 function could therefore complement tyrosine kinase inhibitors for treating cancer by inhibiting cancer evolution and preventing oncogenic switching. Based on this hypothesis our work has focused on the interplay between tyrosine kinases and the HSP90 molecular chaperone machine with the aim of developing synergistic combinations of molecular therapies to combat cancer.

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Dichloroacetate (DCA) as an oncology chemotherapeutic agent? What's all the hype and is it warranted? Complete with clinical outcomes

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Background: Chemotherapeutic treatment regimens tend to be deleterious and toxic to cancer patients. Thus, today many clinicians are changing their clinical practices opting for targeted and/or ancillary drug treatments that kill the tumor cell populations while sparing healthy cells. Greater than 70% of all cancer types rely on cytosolic aerobic glycolysis for energy production, an inefficient means of generating ATP rather than mitochondrial oxidative phosphorylation resulting in an acidic microenvironment conducive to their growth and proliferation. DCA inhibits Pyruvate Dehydrogenase Kinase (PDK) thereby increasing influx of pyruvate into the mitochondria, promoting glucose oxidation, reversing the suppressed mitochondria thus promoting apoptosis in cancer cells. Thus, it would be reasonable to propose that cancer cells would likely be sensitive DCA. Therefore, a prospective study of the efficacy of DCA as a potential chemotherapeutic agent was conducted.

Results: 27 solid-tumors were studied; 3 of 27 exhibited high*/intermediate sensitivity to DCA as a single agent; 7 of 27 exhibited high*/intermediate sensitivity to DCA in combination with chemotherapeutic agent(s). 9 of 27 exhibited no sensitivity to DCA as a single agent or in combination. Clinical outcomes further validated the in vitro data.

Conclusion: Our findings indicate a potential role for DCA in oncology therapeutics in a wide range of cancer types. Moreover, it is stimulating to propose that autophagy may be the focus rather than apoptosis since cancer cells circumvent this pathway and are sensitive to autophaghic communicants. Nonetheless, randomized controlled clinical trials must be designed to further correlate and validate this preliminary pilot study on DCA.

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