OMICS Group Conferences
Accelerating Scientific Discovery

3rd World Congress on
Cancer Science & Therapy

October 21-23, 2013 DoubleTree by Hilton Hotel San Francisco Airport, USA

Individualizing chemotherapy using the anti-diabetic drug, Metformin, as an "Adjuvant": An exploratory study

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Abstract

Cancer remains as one of the most challenging diseases to treat in this new millennium. In part, this is due to the inherent behavior of cancer. Basic research has firmly established that cancers are highly heterogeneous, resulting in wide interindividual variations in response to therapy. Mammalian cell death can occur by several mechanisms: necrosis, apoptosis and autophagy. Autophagy is generally activated by starvation but is also associated with pathologic processessuch as cancer. It can be inhibited by the biochemical mTOR pathway.mTOR inhibitors, such as the immune suppressant rapamycin and the antiviral ribavirin, strongly induce autophagy. It has been shown that metformin can also induce autophagy and apoptosis in cancer cells. Autophagy is the predominant death pathway in various tumors cells because it is a simple process that is unaffected by mutations in p53 or by the over expression of survival factors. Thus in an attempt to increase tumor response and patient sensitivity to various chemotherapeutic agents, we examined the supporting role of the biguanide mTOR inhibitor metformin, as an anticancer agent and potential adjuvant to cytotoxic chemotherapy.

Methods: Using flow cytometricmethods, a variety of solid tumor single-cell heterogenates were incubated with chemotherapeutic agents, plus/minus metformin, and analyzed for cell death. Fourteen solid-tumors were studied; thirteen of the fourteen tumors (93%) exhibited sensitivity to and or synergy to specific chemo agents when in combined with metformin; one of the fourteen tumors (7%) exhibited sensitivity to single agent metformin.

Conclusion: The emerging field of “theranostics” forms the basis of personalized medicine: the diagnostic information from a person’s own cancer is utilized to develop a highly individualized therapeutic protocol. Our novel, in vitromodel was developed as a clinically applicable tool to elucidate the live/death mechanism of action of metformin as a single treatment modality and as a chemosensitizer for treating various solid tumors. Fourteen solid-tumors were studied; thirteen of fourteen tumors (93%) exhibited sensitivity and or synergy to the specific chemo agent when combined with metformin. Not only did the 13 tumors exhibit “killing” but the range was in the 1st decade region delineated as “debris” indicating that the tumor SCSs were fragmented by the metformin combinations.

Only one of the fourteen tumors (7%) exhibited sensitivity to single agent metformin. However this sensitivity was moderate and fell into the 2nd decade, indicating that not all populations responded. It continues to be a concern when the SCSs fall into the 2nd decade region as this delineates apoptosis, but does not confirm that the drug’s message has reached the nucleus and hence induced ‘actual death’ and not merely ‘traveled the apoptotic pathway’ . Abnormalities in cell death regulation can be a significant component of diseases such as cancer; Cancer is an example where the normal mechanisms of cell cycle regulation are dysfunctional, featuring incomplete apoptosis or ‘insufficient ‘apoptosis with either an overproliferation of cells and/or decreased removal of cells.

Furthermore, albeit chemotherapeutic treatments for cancer can effectively reduce a tumor mass, the disease often relapses. This is due to cancer stem cells (CSC). Tumors contain a small number of tumor-forming, self-renewing stem cells thereby allowing for relapse. These CSCs are resistant to well-defined chemotherapy, and after treatment can regenerate all the cell types in the tumor.. For this reason, drugs that selectively target CSCs offer great promise for more complete cancer treatment. Metformin has been shown to inhibit the growth of breast cancer cell lines and inhibit tumor growth of xenografts in a triple-negative breast cancer cell line. The combination of metformin with existing chemotherapeutic drugs, which attack non-stem cancer cells, was shown to have a dramatic effect on reducing tumor mass and prolonging tumor remission.

The clinical safety, well characterized pharmacodynamic profile, and low cost of metformin make it an ideal candidate for development as an effective adjuvant anticancer agent. Albeit a small number of tumors were studied, these results indicate the potential for metformin in oncology therapeutics as an effective “adjuvant” chemotherapeutic agent. The identification and stratification of patients to predict metformin benefit and response can be performed successfully in a timely manner in vitro for initiation of first-line in vivo regimens. None-the-less a randomized controlled clinical trial must be designed to further correlate and validate this preliminary pilot study.