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Individualizing Chemotherapy using the Anti-Diabetic Drug, Metformin, as an “Adjuvant”: An Exploratory Study

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Abstract

Cancer remains one of the most challenging diseases to treat in this new millennium. In an attempt to increase tumor response rates and decrease patient toxicity to various chemotherapeutic agents, the efficacy of metformin as a chemosensitizer was investigated.

Preclinical and clinical evidence supports the use of metformin as a cancer therapeutic particularly in the treatment of cancers known to be associated with hyperinsulinemia, such as those of the breast and colon, as metformin has the ability to lower circulating insulin levels. Moreover, metformin may exhibit direct inhibitory effects on cancer cells by regulating cellular metabolism thereby reducing proliferation and inducing apoptosis.

A variety of solid tumor single-cell heterogenates were incubated with chemotherapeutic agents, plus/minus metformin, and analyzed for cell-death. A total of fourteen solid-tumors of various types were studied; ten of the fourteen tumors (71%) exhibited poor or modest sensitivity to the chemo agents tested, but when metformin was combined, a synergistic effect was observed resulting in high sensitivity (high cell kill); one of the fourteen tumors (7%) exhibited a marginal sensitivity to metformin employed as a single agent.

Our findings indicate a potential role for metformin in oncology therapeutics as a powerful adjuvant to chemotherapy in a wide range of cancer types. The diversity of the tumor specimens studied further validates the necessity to conduct clinical studies on the efficacy of metformin in the oncology setting. 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. Nonetheless, a randomized controlled clinical trial must be designed to further correlate and validate this preliminary pilot study and to fully appreciate the impact of metformin on cancer recurrence and survival.

Keywords: Metformin; Chemotherapy; Anti-diabetic; Solid tumors; Flow Cytometry

Abbreviations: CS/CR: Chemosensitivity/Chemoresistance; mTOR: Mammalian Target of Rapamycin; OCT 1: Organic Cation Transporter 1; SCH: Single-Cell Heterogenates; NSCLC: Non-Small Cell Lung Cancer; FSC: Forward Scatter Channel; SSC: Side Scatter Channel; DRUGS: 5FU: 5-Fluorouracil; ART: Artesunate; CIS: Cisplatin; DCA: Dichloroacetate; DOC: Docetaxel; DOX: Doxorubicin; ERL: Erlotinib; LET: Letrozole; LOM: Lomustine; MET: Metformin; MTX: Methotrexate; PEM: Pemetrexed; RAP: Rapamycin; RBV: Ribavirin; TAM: Tamoxifen; TAX: Taxotere; TAR: Tarceva; TMZ: Temozolomide

Introduction

Despite multiple advances in recent years, cancer remains one of the most challenging diseases to treat. Overall mortality has improved only marginally since the first cytotoxic chemotherapy was introduced at Roswell Park in 1950. In part, this is due to the inherent behavior of cancer. Basic research has firmly established that cancers are highly heterogeneous, resulting in wide inter-individual variations in response to therapy [1]. This divergence underscores the necessity of personalized medicine wherein the data garnered from a person's own cancer is utilized to develop a highly individualized therapeutic regimen.

Mammalian cell death can occur by several mechanisms: necrosis, apoptosis and autophagy. Autophagy is a catabolic process that results in degradation of bulk cytoplasmic contents, abnormal protein aggregates, and excess or damaged organelles. Autophagy is generally activated by starvation but has also been associated with physiologic

processes, pathologic processes (such as cancer), and is inhibited by the biochemical mTOR pathway. Inhibitors of mTOR such as the immune suppressant rapamycin and the antiviral ribavirin, strongly induce autophagy [2]. It has been shown that metformin can also induce autophagy and apoptosis in cancer cells [3]. Autophagy is the predominant pathway leading to cellular death in various tumors cells and leukemia cells because it is a simple process that is unaffected by mutations in p53 or the over expression of survival factors [4].

Metformin, a known mTOR inhibitor [5], is an oral antidiabetic drug used as a first-line therapy for the treatment of type 2 diabetes in obese patients with normal kidney function [6]. Recently, metformin has emerged as a potential anticancer agent. A large case-control study conducted at M.D. Anderson Cancer Center has suggested metformin may protect against pancreatic cancer [7]. Similarly, several epidemiological and case-controlled studies found diabetics using metformin have lower cancer risk in comparison to those using

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Received February 04, 2013; **Accepted** March 11, 2013; **Published** March 13, 2013

Citation: Bradford SA, Khan A (2013) Individualizing Chemotherapy using the Anti-Diabetic Drug, Metformin, as an “Adjuvant”: An Exploratory Study. J Cancer Sci Ther 5: 120-125. doi:[10.4172/1948-5956.1000197](http://dx.doi.org/10.4172/1948-5956.1000197)

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other anti-diabetic medications [8]. Further, it has been noted that combining statins and metformin is associated with reducing the risk for several cancers including hepatocellular, pancreatic, colorectal, gastric, and breast [9].

Metformin also displays significant growth inhibitory effects in several *in vitro* human and mouse tumor models [10]. In cell culture, metformin inhibits the proliferation of a range of cancer cells including breast, prostate, colon, endometrial, ovarian, and glioma [11]. These cellular studies were followed up with research showing a consistent antitumoral effect in various mouse models. Human clinical trials have confirmed the beneficial effect of metformin in breast and colon cancer [12].

Tumor cells often express high levels of insulin receptors, indicating a potential sensitivity to the growth promoting effects of insulin [13]. Thus, obesity and high insulin levels would be adverse prognostic factors for a number of cancers particularly those of the breast, prostate and colon, as noted above. Since metformin lowers blood insulin levels, it may diminish the negative effects of insulin on tumor development and growth. Therefore, to better appreciate the potential role of metformin as an anticancer vehicle and adjuvant to cytotoxic and targeted chemotherapy drugs, we tested its ability to augment response rates to these agents.

Materials and Methods

A variety of fresh solid-tumor specimens were obtained from

patients of a private clinic, Medicor Cancer Centres Inc. (Toronto, Ontario, Canada) The tumor specimens were either obtained from biopsies of superficial metastases, superficial lymph nodes infiltrated with metastases, or at the time of major cancer surgery. The tumor specimens were accredited by the attending pathologist to be comprised of tumor tissue. Patients provided written informed consent to CS/CR assay.

The live cell tumor fragments obtained were mechanically disaggregated to obtain single-cell heterogenates (SCH). The SCH were then incubated at 36°C/5% CO₂ for 48 hours in a humidified chamber to allow for equilibration. Following the incubation, the SCH were washed, counted, and a small aliquot stained with trypan blue to assess initial viability. Twenty thousand cells were added to each analysis vial. The vials of SCH were then exposed to the various chemotherapeutic agents at clinically achievable concentrations, singly and in combination with metformin (manufacturer: Ratiopharm Inc., metformin: 1,1-dimethylbiguanide, clinically achievable peak plasma concentration of 2.5 µg/ml) [14] and incubated at 36°C/5% CO₂ for 72 hours in a humidified chamber. SCH were also incubated without cytotoxic drug(s) as controls, without stain as auto controls and as reference for 100% tumor cell viability (data not shown).

The chemotherapeutic agents and combinations of agents used included those considered to be the current standard of care for each cancer type, according to the Ontario Ministry of Health and Cancer Care Ontario. In addition, specific off-protocol agents were used. Post

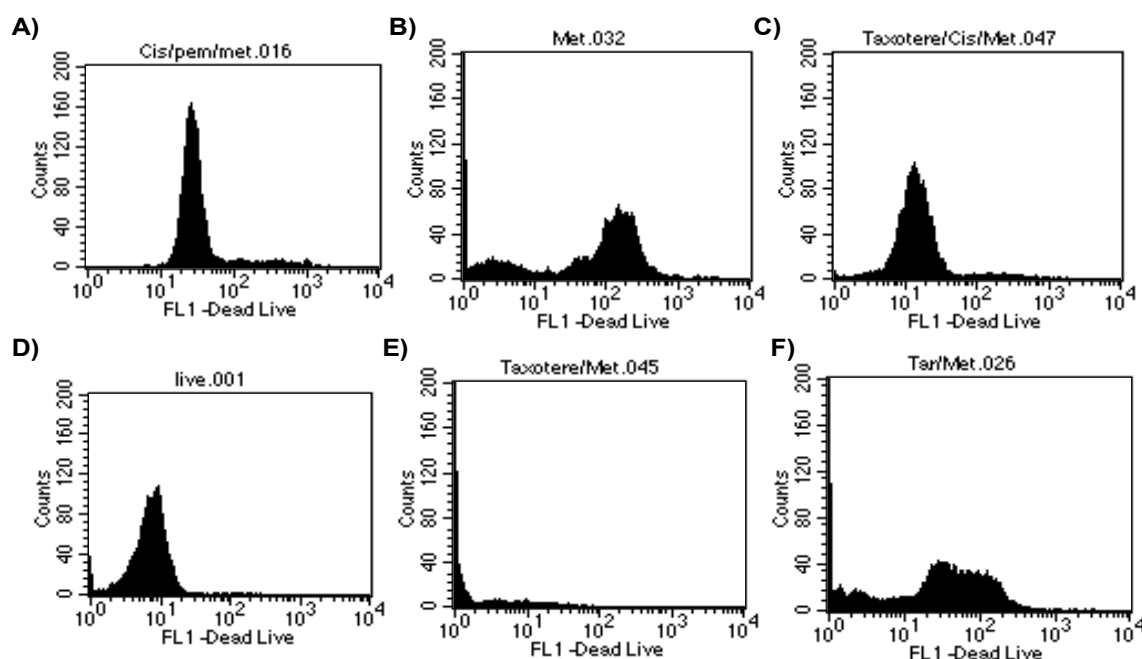


Figure 1: Flow Cytometry analysis of a non-small cell lung SCH (the histograms in this figure are for illustrative purposes - the lung tumor was not one of the fourteen in this study).

Legends:

- A. live (no exposure to drugs) indicates 98% viability; these cells have only picked up color on the outside of the cell.
- B. 95% shattered cells – debris ‘travels’ up the Y axis, the combination of MET and TAX have shattered the cells (made debris of the cells), reflecting no stain/no color.
- C. 69% dead cells, cells are in the 2nd decade designated dead, as the cell membrane has been compromised by the drug(s) and the stain has entered intracellularly, thus more color is exhibited.
- D. 63% dead cells, cells are in the 2nd decade designated dead.
- E. 79% of the tumor cell populations were killed by MET as a single agent.
- F. 9% dead cells (adding CIS to the combination of TAX/MET inhibited cell death).

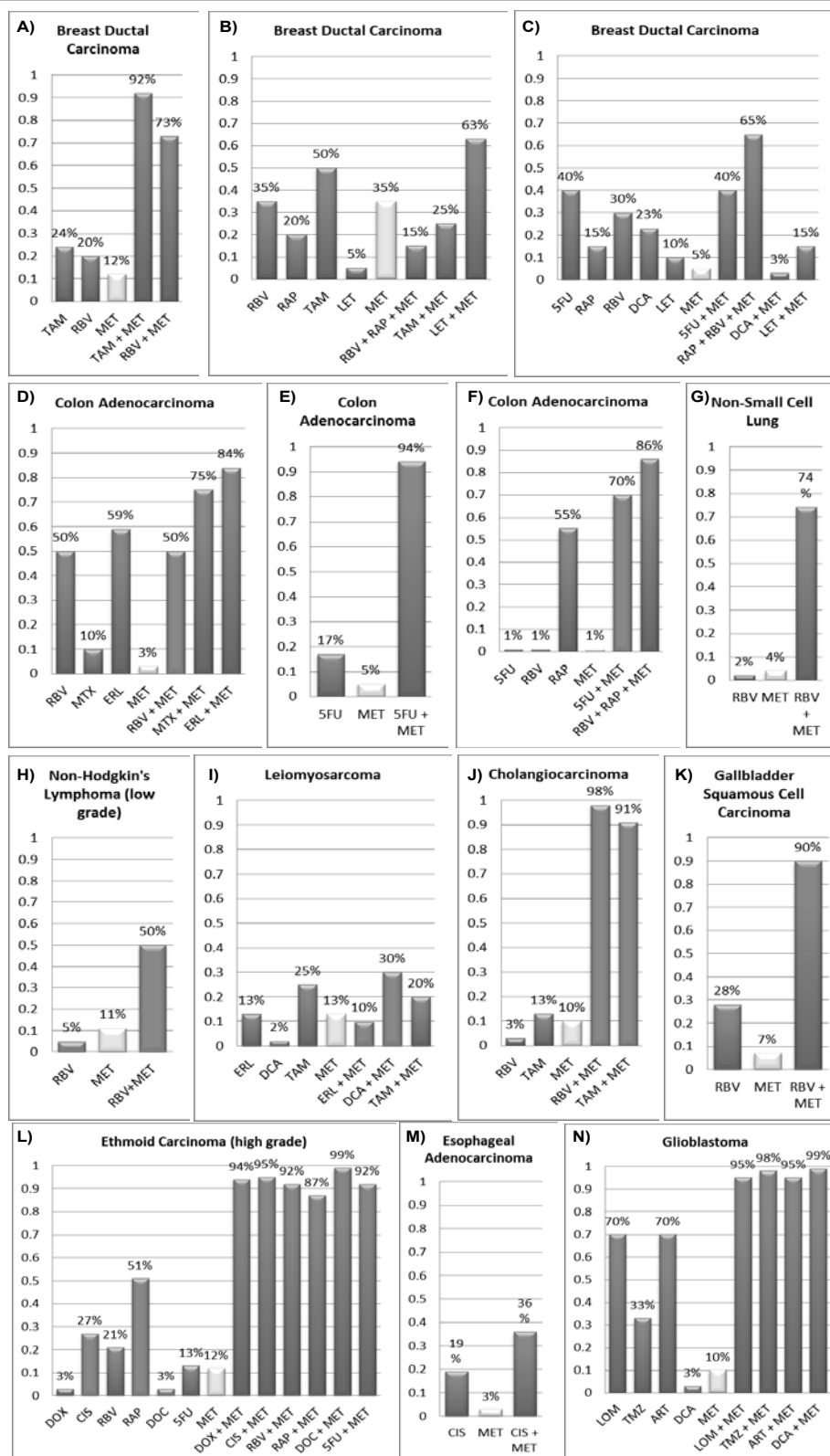


Figure 2: Illustrates the percentage of cell death (vertical axis) for single chemoagents, metformin, and combinations of chemoagents with metformin.

Legend: 5FU: 5-fluorouracil; ART: Artesunate; CIS: Cisplatin; DCA: Dichloroacetate; DOC: Docetaxel; DOX: Doxorubicin; ERL: Erlotinib; LET: Letrozole; LOM: Lomustine; MET: Metformin; MTX: Methotrexate; RAP: Rapamycin; RBV: Ribavirin; TAM: Tamoxifen; TMZ: Temozolomide

* All tumors were of high grade/metastatic potential unless noted; no tumor was naïve; no tumor was a primary; Flow Cytometer - 10,000 events were counted for each SCH.

incubation, SCH were washed and tagged with Molecular Probes LIVE/DEAD® Fixable Green Dead Cell Fluorescent Stain (Invitrogen, Molecular Probes – L23101 Kit) to evaluate SCH viability by Flow Cytometric methodologies. The reactive stain can permeate the compromised membranes of dead cells and react with free amines on the interior and exterior of the cell, whereas only membrane-exterior free amines of viable cells are available to react with the dye, resulting in intense or dim staining, respectively. *In vitro* SCH chemotherapy response was determined using a Becton Dickinson FAC Scan Flow Cytometer (BD, 1 Becton Drive Franklin Lakes, NJ USA 07417) and SCH were analyzed for percentage of live versus dead cell populations.

Accurate measurement by Flow Cytometry of LIVE/DEAD® stain can be obstructed by background ‘noise’ of other particles such as cell debris. Both FSC and SSC are unique for every particle, and a combination of the two may be used to differentiate various cell types in a heterogeneous sample (data not shown). The data acquired in each parameter are known as the ‘events’ and refer to the number of cells displaying the physical feature of interest. A histogram is generated based on the data acquired, which in this case represents the percentage of live and dead cell populations delineated by decades (Figure 1). The range 10^0 to 10^1 is defined as the live population and equates to >90% of the tumor mass. Resistant cells and the control SCH population (no cytotoxic drugs added) fall in this range. Beyond 10^1 is defined as ‘dead cells’ and between 10^0 and the first bar is the ‘shattered’/debris region (cells with low dye uptake).

Results

Fourteen solid-tumors were studied (Figure 2). Ten of the fourteen tumors (71%) exhibited poor or modest sensitivity to the chemo agents tested, but when metformin was combined, a synergistic effect was observed resulting in high sensitivity (high cell kill). Not only did the 10 tumors exhibit “killing” but the focus was concentrated in the 1st decade region of the Flow Cytometer generated histogram, delineated as “debris”. This indicated that the tumor cells were fragmented by the metformin combinations.

Dose response curves were not generated, since the clinical plan for the patients whose tumors were tested was to administer the maximum tolerated dose based on the therapeutic index of each drug. Thus the peak plasma concentration (C_{max}) was used for each drug as specified by the drug manufacturer.

Metformin adjuvant treatment of the two gallbladder cancers provoked high sensitivity to ribavirin and tamoxifen in one specimen and to ribavirin in the other specimen. Ribavirin is also an mTOR inhibitor and as such may have provided the impetus for the overt synergistic activity noted in these two specimens.

Metformin is known to inhibit glioma cell growth in low density cultures while promoting apoptosis in higher density cultures [15]. The glioblastoma phenotype tested in this study showed a significant potentiation of temozolomide (TMZ), artesunate (ART), lomustine (LOM) and dichloroacetate (DCA) by the addition of metformin.

Clinically, of the fourteen patients whose tumors were tested, not all could be followed to determine if the *in vivo* responses matched the *in vitro* results noted above. The reasons were:

a) the patient’s condition changed, and they were unable to take chemotherapy,

b) the patient’s oncologist refused to prescribe the assay-guided therapy,

c) the patient was lost to follow-up.

However, three patients who received a drug combination with metformin were tracked, and their responses correlated favorably with the assay findings. These were the patients with ethmoid carcinoma (responded to erlotinib + metformin), low grade non-Hodgkin’s lymphoma (responded to ribavirin + metformin) and glioblastoma (responded to lomustine + metformin).

Discussion

Although most cancers are monoclonal in origin, subsequent generations take on new characteristics because of the occurrence of innate genetic instability [16]. Thus, human cancers frequently display substantial intra-tumor heterogeneity in virtually all distinguishable phenotypic features, such as cellular morphology, gene expression (including the expression of cell surface markers, growth factor and hormonal receptors), metabolism, motility, angiogenesis, proliferation, immunogenicity and metastatic potential [17]. The clinical relevance is that tumor microenvironment heterogeneity will contribute significantly to the efficacy of drug therapy.

Metformin is an oral antidiabetic drug used as a first-line therapy for type 2 diabetes. Around 2006, the potential for the usage of metformin in the control and management of cancer was recognized [18,19]. Indeed, numerous observational studies reported decreased cancer incidence and cancer-related mortality in adult diabetics receiving pharmacologically relevant standard doses of metformin (1500 to 2250 mg/day) [19].

It has been shown that the potential sites of action of metformin are the insulin receptor, mTOR receptor and the glucose transporters. The ability of metformin to lower circulating insulin may be particularly important for the treatment of cancers known to be associated with hyperinsulinemia, such as those of the breast and colon [20]. It has been shown that metformin binds to the cell surface transporter OCT 1, which is required for drug entry into cells [21]. Once bound, metformin reduces ATP production thereby inhibiting mTOR activity resulting in a cytostatic effect. Tumor cells often express high levels of the OCT 1 receptor, indicating a potential role for metformin’s action in promoting entry of therapeutic agents into the tumor microenvironment [22]. Accordingly, this may explain the overwhelming response of the breast and colon cancers observed in this study.

Chemotherapy produces genotoxic stress and induces p53 activity, which can cross-react with the AMPK/mTOR pathway [23]. The combination of metformin and various chemotherapeutic agents showed a synergistic effect in various tumor types studied. These findings suggest that combined treatment is more effective in arresting cells in the cell cycle, decreasing tumor growth and increasing apoptosis, most likely through a signaling convergence of metformin and chemo agents at the level of AMPK, thereby inhibiting the ability of cancer cells to synthesize proteins.

Michael Pollak, MD, of McGill University in Montreal noted that contrary to popular belief glucose alone is not enough to stimulate cancer cell growth. “However, some tumors love high insulin levels. Some colon, prostate and breast cancers need insulin.” “Insulin also tells them to grow, multiply, divide. Some cancers see insulin as a growth signal.” Insulin makes cells grow, said Pollak, by helping glucose, their energy source, get through the cell membrane [24]. This indicates that since metformin mimics insulin mechanics, metformin may facilitate entry of the chemotherapeutic agents into the tumor microenvironment thereby allowing the agents to deliver their cytolytic activity into the cell.

Kevin Struhl of Harvard Medical School believes the answer lies in metformin's ability to suppress cancer stem cells that fuel new tumors throughout the body [25]. Cancer stem cells are generally very resistant to chemotherapy, and thus if it is substantiated that metformin indeed delivers an unmitigated death knell eradicating the stem cells, it would then also prevent metastasis and recurrence. This phenomenon of cancer stem cells relates to the EMT genetic program which is known to be sufficient to drive the ontogeny of the breast cancer stem cell molecular signature. Javier Menendez illustrated that non-cytotoxic concentrations of metformin efficiently impedes the generation of the stem cell phenotype by transcriptionally repressing the stem cell epithelial-mesenchymal transition. Metformin treatment dynamically regulated the breast cancer stem cell immunophenotype, transcriptionally reprogramming cells through decreased expression of key drivers of the EMT machinery including the transcription factors ZEB1, TWIST1 and SNAI2 (Slug) and the pleiotrophic cytokines TGFβs states [26].

Moreover, Liu and colleagues recently reported that metformin exhibited a unique biological and molecular effect against triple-negative breast cancer cells [27]. In this study, metformin suppressed the generation of the breast cancer stem cell phenotype by regulating stem cell properties including the epithelial-mesenchymal transition status.

Our novel, physiologically relevant *in vitro* model was developed as a clinically applicable tool to exploit the efficacy of chemotherapeutic agent in treating various solid tumors using a Flow Cytometer. However, it continues to be a concern when the SCH fall into the 2nd decade region of the Flow Cytometer generated histogram. There is a possibility that the cells may begin undergoing apoptosis but the signal has not reached the nucleus yet, thus indicating the agent in question was merely cytotoxic rather than cytolytic. Our preliminary data as well as others [28] indicates that the cell populations in this region may be merely “knocked out”, and as such, circumventing irrefutable death (autophagy, necrosis, apoptotic DNA modification). Cancer is an example where the normal mechanisms of cell cycle regulation are dysfunctional, featuring incomplete apoptosis with either an over proliferation of cells and/or decreased removal of cells [28].

In our hands, metformin, as a single agent, had limited efficacy with the various tumor types analyzed. Only one of the fourteen tumors (7%) exhibited sensitivity to single agent metformin (breast ductal carcinoma, Figure 2B). However this sensitivity was modest, indicating incomplete apoptosis (not all cell populations responded). When combined with other chemo agents used in this study, a dramatic increase in efficacy was observed. This was evident in a diverse group of tumor types.

The primary focus of this study was to show that metformin has a potential role in cancer therapy. We noted that metformin primarily acted as a chemo sensitizer to a variety of chemotherapeutic agents and exhibited limited efficacy as a single agent. The efficacy as a single agent was limited to one of three breast tumors. As acknowledged in the literature, these tumor types are associated with hyperinsulinemia. Yet metformin alone did not demonstrate efficacy in any of the colon cancers which are also categorized as hyperinsulinemic. These points to the innate heterogeneity of tumor response profiles, regardless of histological similarity.

A further advantage of using metformin is its ability to target cancer stem cells, which are known to impede total eradication of the

tumor mass. Finally, metformin is cost effective, safe and well tolerated. Metformin's ability to potentiate other anti-cancer drugs could allow dose reduction and therefore diminished toxicity, and endow the cancer patient with a proper quality-of-life continuum. Although considered very safe, there are potential risks with taking metformin such as gastrointestinal upset, allergic reaction, hypoglycaemia, malabsorption of vitamin B12, and a risk of lactic acidosis if the patient has renal or hepatic failure [29].

Due to the small number of tumors studied, statistical significance was difficult to assess. Our results indicate the potential for metformin in oncology therapeutics as an effective “adjuvant” chemotherapeutic agent. The diversity of the tumor specimens studied further validates the necessity to conduct clinical studies on the efficacy of metformin in the oncology setting. 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. Nonetheless, a randomized controlled clinical trial must be designed to further correlate and validate this preliminary pilot study and to fully appreciate the impact of metformin on cancer recurrence and survival.

Acknowledgments

The authors declare they have no competing interests.

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Citation: Bradford SA, Khan A (2013) Individualizing Chemotherapy using the Anti-Diabetic Drug, Metformin, as an “Adjuvant”: An Exploratory Study. *J Cancer Sci Ther* 5: 120-125. doi:[10.4172/1948-5956.1000197](https://doi.org/10.4172/1948-5956.1000197)

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