Journal of Drug Discovery, Development and Delivery

Austin Publishing Group

Open Access Full Text Article

Editorial

Research and Experimental Rational in the Development of Complementary Therapies as Potential Adjuvants in Chemotherapy: an Integrative Medicine Approach

Rachel Roberts, Rebekah Bradford, Chelsea Pittman, Fran Grappe, Lori Coward and Greg Gorman*

McWhorter School of Pharmacy, Samford University Birmingham AL, USA

***Corresponding author:** Greg Gorman, McWhorter School of Pharmacy, Samford University Birmingham AL. USA

Received: August 08, 2014; **Accepted:** August 15, 2014; **Published:** August 27, 2014

Editorial

It is well documented that the use of complementary medicines such as natural products, dietary supplements and herbal medicines has and continues to increase throughout the world. In contrast to this, the amount scientific data to support evidence-based decision making regarding the safe and effective concomitant use of these products with conventional therapeutic medications has lagged. Additionally, conventional "drug development" protocols often need to be modified due to the complex composition of these products. In an effort to expand this knowledge base, various academic laboratories, as well as the National Center for Complementary and Alternative Medicine (NCCAM) within the National Institutes of Health (NIH), have significantly increased scientific research on complementary and alternative medicines. Along those lines, the central theme of research in our laboratory is directed toward generating scientific data on the safety and efficacy of combining mainstream medical therapies (allopathic medicine) with complementary medicines through an integrative medicine approach. Specifically, we have been evaluating the potential of natural products to improve the efficacy of existing chemotherapeutic prodrugs through a variety of interactions as well as their ability to be active in alternative therapeutic pathways. Our multidimensional approach involves the application of various *in vitro* assays to study the potential multiple benefits of these complementary products with existing chemotherapeutic prodrugs. We have focused on three enzyme centered approaches to determine the potential for complementary medicines to achieve a multi-beneficial therapeutic effect: 1) bio-modulation of the metabolic activation pathway(s) of the prodrug, 2) selective or non-selective inhibition of cyclooxygenase1 and 2 (COX1, 2) and 3) aromatase inhibition. In using this approach we are able to classify combinations of complementary medicines with specific chemotherapeutic prodrugs (e.g. tamoxifen, irinotecan) in evaluating potential activity in one or more therapeutic pathways. Additionally, data from our studies also provides direction for combinations of complementary medicines and chemotherapeutic prodrugs which could be detrimental and result in sub-therapeutic exposure and decreased efficacy.

Bio-Modulation of Metabolic Activation Pathways

Targeted chemotherapeutic prodrugs are used to treat a variety of neoplastic indications. These prodrugs are catalyzed into one or more active metabolites through different pathways from interactions with a variety of enzymes (e.g. Cytochrome P450s, carboxyesterase, etc.). Likewise, inactive metabolites may also be formed from the prodrug as well. Concomitant administration of other medications can result in unfavorable interactions whereby the enzymes responsible for the activation of the chemo-prodrug may be less effective or unavailable to activate the prodrug. In contrast to this, it should also be possible to modulate the various metabolic enzymatic pathways using concomitantly administered natural products (i.e. complementary therapies) to maximize activation of the prodrug to its active metabolite(s) and minimize metabolism to inactive metabolites (i.e. metabolic bio-modulation). Additionally, the complementary therapy may also be metabolized by these enzymes potentially producing a variety of effects including positive or negative heterotrophic cooperativity, reduced enzyme activity and mechanism based inhibition. In our approach we begin with the natural product as it would be used as an over-the–counter supplement over a broad concentration range to evaluate its impact on the activation of the prodrug. Products which produce strong interactions are further evaluated to determine various characteristics such as type of interaction, $IC_{50,}$ $K_{i,}$ etc. Because natural products and herbal supplements are complex mixtures of many different classes of compounds, it is challenging to determine which compound(s) are contributing positively, negatively or have no impact with respect to metabolic activation. Compositional analyses of the active products are conducted such that individual compounds may be identified and evaluated.

Cyclooxygenase Inhibition

COX enzymes regulate the conversion of arachidonic acid to prostaglandins (PG), and two isoforms of the COX enzyme exist. COX-1 is constitutively expressed while COX-2 is an inducible form of the enzyme. Data shows that COX-2 is implicated in the role of apoptosis, angiogenesis and cell invasiveness all of which may contribute to its role in the formation of various solid tumors (i.e. colorectal and breast). Studies have shown an overexpression of COX-2 in malignant epithelial cells which can inhibit apoptosis by chemotherapeutic drugs. Likewise, COX-2 expression can increase cellular adhesion and invasiveness which will impact tumor metastasis. Research has shown that the use of both selective and non-selective COX inhibitors can reduce COX-2-catalyzed synthesis of PGs thereby reducing tumor growth from neoplastic epithelial cells, stromal cells, or both. By determining the ability of specific

Citation: Roberts R, Bradford R, Pittman C, Grappe F, Coward L and Gorman G. Research and Experimental Rational in the Development of Complementary Therapies as Potential Adjuvants in Chemotherapy: an Integrative Medicine Approach. J Drug Discov Develop and Deliv. 2014;1(2): 2.

natural products or their pharmacologically active components to selectively or non-selectively inhibit COX-1 and 2, we can identify complementary medicines that may be beneficial as adjunctive therapies to existing chemotherapy in the treatment of certain solid tumor cancers.

Aromatase Inhibition

The proliferation of hormone-receptor-positive cancer in breast and ovarian tissue is driven by the presence of estrogen. The *in vivo* synthesis of estrogen relies on aromatase enzymes to catalyze the conversion of hormones in the body into estrogen. Aromatase Inhibitors (AIs) work by blocking the enzyme aromatase which results in less estrogen being available to stimulate the growth of hormone-receptor-positive cancer cells. In post-menopausal women, the ability of complementary therapies to inhibit aromatase enzymes combined with traditional Selective Estrogen Receptor Modulator (SERM) chemotherapies offer a multi-pathway treatment approach potentially without common side effects (heart problems, osteoporosis and joint pain) often reported from existing synthetic AIs.

The goal of our research is to identify natural herbal products and/or active components in these products which contribute in a positive manner in one or more of the assays described above such that they may be further investigated and developed as chemotherapeutic prodrug adjuvants.

J Drug Discov Develop and Deliv - Volume 1 Issue 2 - 2014
ISSN : 2471-0288 | www.austinpublishinggroup.com

Citation: Roberts R, Bradford R, Pittman C, Grappe F, Coward L and Gorman G. Research and Experimental Rational in the Development of Complementary Therapies as Potential Adjuvants in Chemotherapy: an Integrative Medicine Approach. J Drug Discov Develop and Deliv. 2014;1(2): 2.