Dietary Considerations Effecting Lung Metastatic Therapeutic Responsiveness and Co-Morbidities

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Breast cancer is the most frequently diagnosed cancer in women; with approximately 246,000 new cases diagnosed each year. A specific subtype of breast cancer, triple negative breast cancer (TNBC), are highly aggressive, highly metastatic, and have a high rate of recurrence. Several studies have demonstrated a strong link between obesity (body mass index of over 30) and a greater risk of developing TNBC. Moreover, some studies have reported an increase in breast cancer mortality in obese women at diagnoses suggesting obesity promotes metastases and/or reduces therapeutic effectiveness. Patients with TNBC are particularly susceptible to off-target effects of chemotherapy, because their tumors respond only to systemic cytotoxic chemotherapy, such as doxorubicin (DOX). DOX is a type of anthracyclines-based therapeutics and are used to treat several cancer types. DOX is the standard approach for adjuvant treatment of breast cancer because they result in improved outcomes compared to other modalities. However, high cumulative doses of DOX raise the risk of congestive heart failure in those TNBC patients, limiting overall survival and quality of life in women surviving tumor metastasis.

In this study, we plan to determine whether varying diet modulates TNBC metastatic lung tumor growth and therapeutic responsiveness. We propose that differing dietary consumption while treating metastatic lung tumors with doxorubicin may potentiate or ameliorate therapeutic off target effects such as DOX-induced cardiac damage which would affect the quality of life in surviving metastatic breast cancer patients. In Aim 1, we will determine the effect of diet on TNBC lung metastatic growth and metastatic tumor therapeutic responsiveness. In this aim, we will use a mouse breast cancer model that develops lung metastasis within 4 weeks. The primary tumor will be surgically removed after 4 weeks and mice bearing lung metastases only will be treated. After surgery, mice will be placed on a high fat (from milk fat)/high sugar Western diet, a Western diet supplemented with fish oil, or a standard mouse chow diet (low fat/low sugar). Mice on different diets will then treated with doxorubicin for 5-weeks. We will monitor lung metastases growth and DOX drug responsiveness. In Aim 2, we will investigate how diet affects doxorubicin-induced cardiac toxicities and quality of life in breast cancer lung metastases model. Using the above described model, we will determine the effect of diet on doxorubicin-mediated cardiac damage. Since doxorubicin treatment causes acute cardiac damage with durable effects we will determine how the diet may either potentiate or reduce dox-mediated cardiac dysfunction. Results from this Metavivor Young Investigator Award project could have high translational value and will determine whether fish oil supplements during chemotherapy may enhance metastatic lesion drug responsiveness while concurrently decreasing off target dose limiting cardiac toxicities. These data may lead to practice-changing improvements in therapy that are critically needed to reduce TNBC deaths for the increasing numbers of breast cancer survivors facing serious cardiovascular side effects from their successful treatment.