DEMONSTRATED TRIPLE NEGATIVE BREAST CANCER CHEMOTHERAPEUTIC VULNERABILITY TO A NOVEL AND LESS TOXIC NATURAL PRODUCT AGENT

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Abstract: Triple-negative breast cancers (TNBCs) with high mammary cancer stem cell (MCSC) content are inherently resistant to most available therapies. These insidious forms of breast cancer (BC) contribute to higher rates of BC mortality in young African-American (AA) women, a disparate group compared to White women. Though doctors combine surgery, radiation and chemotherapy using cytotoxic neoadjuvant treatment regimens, limited therapies have the potential to interact and reduce the proliferation of tumor relapse and recurrence promoting MCSCs. Therefore, developing novel approaches to selecting, and recommending dosing and administration of less toxic anti-TNBC agents that target MCSCs are paramount toward making better treatment options available against TNBC, a disease type with no approved targeted treatment currently. Having shown in vitro treatment with the African medicinal plant’s (Vernonia amygdalina’s) aqueous leaf extracts (VA extracts) inhibits proliferation of estrogen receptor positive cells, we hypothesized that treatment with VA extracts would decrease MCSC and TNBC cell proliferation in vitro and resultant chemotherapeutic vulnerabilities to VA extracts may involve apoptosis. To test our hypothesis, we used VA extracts alone or in combination with Paclitaxel (Taxol), one of the drugs administered as part of a preferred Standard of Care (SOC) regimen for invasive HER2-negative BC, in our in vitro and in vivo models wherein we have demonstrated feasibility. VA extracts arrested TNBC cell proliferation and induced apoptosis in vitro; and enriching for MCSCs from BC cell lines and human tumors by cell sorting and propagating as mammospheres, VA extracts decreased mammosphere initiating ability, surpassing Taxol’s efficacy. We also evaluated VA extracts’ ability to inhibit tumor growth of transplantable tumors derived from subcutaneously implanting HRAS and MDA-MB-468 TNBC cell MCSCs into nude mice. The most significant reduction in tumor volume was observed in the MDA-MB-468 MCSC-induced tumors following VA extract pretreatment as compared to those from HRAS MCSC implantation. We concluded that VA extracts are efficacious inducers of apoptosis by the mechanism of BAX cleavage due to oxidative stress-mediated calpain activation in vitro; and in vivo, treatment with VA extracts reduced initiation and progression of MCSC-induced xenografts and demonstrated chemo-preventive efficacy. Given these data and their low toxicity, particularly considering that they have safely been incorporated into the human diet for many centuries, VA extracts are highly attractive candidate agents to use as part of less toxic SOC drug combination regimens to treat patients with TNBC.

Key Words: Vernonia amygdalina, aqueous extracts, triple-negative breast cancer, chemo-preventive, chemotherapeutic, apoptosis

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