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Deep Venous Thrombosis in Breast Cancer Patients Using Tamoxifen, a Hypothesis

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ABSTRACT

Breast cancer is the most frequently diagnosed cancer in women and systematic therapy is an essential component of disease. Hormonal therapy, cytotoxic chemotherapy and the more recently introduced biological therapies are routinely employed in the vast majority of patients. Several pharmaceuticals that affect the estrogenic pathways have been studied as chemopreventive agents. Tamoxifen is an anti-estrogenic drug used in the treatment of estrogen receptor positive breast cancer patients. One of the important side-effects of tamoxifen is thromboembolic events like deep venous thrombosis. Tamoxifen also causes an increase in mean platelet volume. We hypothesize that thromboembolic effect of tamoxifen is via increase of mean platelet volume.

***Keywords*:** *Breast Cancer*, *Tamoxifen*, *Deep Venous Thrombosis*, *Hypothesis*

1. Introduction

Tamoxifen (TMX) is a non-steroidal anti-estrogenic agent with weak estrogen agonist effects and is used in palliative and adjunctive treatment of breast cancer, also reduces the incidence of breast cancer in women at high risk and the risk of invasive breast cancer in women with ductal carcinoma in situ. Because of the competition between estrogen and TMX for binding to estrogen receptors (ER) in the breast, TMX abolishes the augmentation effect of estrogen on breast cancer patients. Binding of TMX to ER leads to ER dimerization. The tamoxifen-bound ER dimmer is transported to the nucleus, where it binds to DNA sequences referred to as ER elements. This interaction results in inhibition of critical transcriptional processes and signal transduction pathways that are required for cellular growth and proliferation. Understanding the role of estrogen in breast cancer development and the effect of TMX in treatment has led the development of other pharmacological agents, e.g. anastrozole, letrozole, exemestane, toremifene and gosereline.

2. Side-Effects of Tamoxifen

Beside curative effect, TMX has some side-effects which restrict its usage. Thromboembolic events like deep venous thrombosis, and pulmonary embolism, hypercalcemia, endometrial hyperplasia, elevated risk of endometrial carcinoma, increase in liver function tests and erytematous skin lesions are some of the side-effects of TMX [1].

3. Deep Venous Thrombosis

Thrombosis is a pathological situation constituted with abnormal homeostasis. Deep venous thrombosis (DVT) definition is usually used for thrombosis of deep leg, mainly for ilio-femoral, veins. Advanced age, surgery (especially major surgical procedure), trauma, extended immobilization, malignant disease, neurological disease, central venous catheter, transvenous pacemaker, pregnancy and puerperium are acquired risk factors for DVT [2-8]. Some patients may have hereditary risk factors, e.g. antithrombin III deficiency, hiperhomocysteinemia, and antiphospholipid syndrome [9-11].

4. What Is MPV

Elevation of MPV (mean platelet volume) shows the presence of more reactive and larger thrombocytes, and this may be a risk factor for myocardial infarction (MI) [12]. As thrombocyte volume increases they became ac- tive in homeostasis [13]. It is known that MPV increases in acute coronary syndromes [14] and there is a relation between MPV and DVT [15].

5. Relation between MPV and Ischemic Events

Keskin *et al.* emphasized that there was no relation between risk factors of atherosclerosis and MPV, and MPV was not a risk factor for coronary artery disease but an important step in pathogenesis [14]. They also suggested that MPV increased in acute ischemic events, and became normal while ischemic events were recovering.

In another study thrombocytopenia and elevated MPV in acute phase of MI was determined as an indicator of prethrombotic situation and maintained that they could be risk factors for MI. It was suggested that MPV had an important role in MI formation via formation of occlusive thrombus and thrombotic embolism [16]. Thromboembolism and pulmonary embolism are important complications in patients with rheumatismal mitral stenosis and risk of complications increase in patients with elevated MPV [17].

6. Relation between Tamoxifen and MPV

TMX elevates vascular endothelial growth factor (VEGF) and thrombocyte activation [18]. Karagoz *et al*. randomized the breast cancer patients into two treatment groups and examined MPV values. An increase in MPV was determined in patients treated with TMX while patients treated with aromatase inhibitors showed no difference [19]. Exemestane, a steroidal aromatase inhibitor, caused less thromboembolic events than TMX [20].

7. Hypothesis

TMX is an important drug used in the adjuvant treatment of breast cancer patients and one of the serious side-effects is DVT. There are studies which show the relation between elevated MPV, DVT and MI. Upon these findings; we hypothesize that TMX causes DVT via elevating MPV.

8. Suggestion

History of DVT or thromboembolism must be interrogated carefully for the patients who will receive ho monotherapy for the adjuvant treatment of breast cancer. Patients with high risk of DVT or thromboembolism should use an aromatase inhibitor instead of TMX. Further studies are needed to determine the need, usage and timing of antiaggregant drugs if elevated MPV is found in patients using TMX.

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