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Article

Antiplatelet Therapy Combined with Anastrozole Induces Features of Partial EMT in Breast Cancer Cells and Fails to Mitigate Breast-Cancer Induced Hypercoagulation

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Abstract: Thromboembolic complications are a leading cause of morbidity and mortality in cancer patients. Cancer patients often present with an increased risk for thrombosis including hypercoagulation, so the application of antiplatelet strategies to oncology warrants further investigation. This study investigated the effects of anastrozole and antiplatelet therapy (aspirin/clopidogrel cocktail or atopaxar) treatment on the tumour responses of luminal phenotype breast cancer cells and induced hypercoagulation. Ethical clearance was obtained (M150263). Blood was co-cultured with breast cancer cell lines (MCF7 and T47D) pre-treated with anastrozole and/or antiplatelet drugs for 24 h. Hypercoagulation was indicated by thrombin production and platelet activation (morphological and molecular). Gene expression associated with the epithelial-to-mesenchymal transition (EMT) was assessed in breast cancer cells, and secreted cytokines associated with tumour progression were evaluated. Data were analysed with the PAST3 software. Our findings showed that antiplatelet therapies (aspirin/clopidogrel cocktail and atopaxar) combined with anastrozole failed to prevent hypercoagulation and induced evidence of a partial EMT. Differences in tumour responses that modulate tumour aggression were noted between breast cancer cell lines, and this may be an important consideration in the clinical management of subphenotypes of luminal phenotype breast cancer. Further investigation is needed before this treatment modality (combined hormone and antiplatelet therapy) can be considered for managing tumour associated-thromboembolic disorder.

Keywords: breast cancer; hypercoagulation; aspirin; clopidogrel; atopaxar; anastrozole; platelet activation; thrombin activity; tumour survival

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1. Introduction

The relationship between tumour cells and platelets is complex, reciprocal, and implicated in driving hypercoagulation as a factor of tumorigenesis. Cancer patients typically present with thrombocytosis and features associated with hypercoagulation, and they are thus are at risk for thromboembolic complications, a leading cause of morbidity and mortality [1,2]. In post-menopausal patients presenting with hormone-dependent breast cancer, anastrozole (a non-steroidal aromatase inhibitor) is typically a first line treatment; however, while this drug improves survival, it is associated with thrombotic risk [3–5]. The addition of antiplatelet therapy to the management of cancer has been suggested; however, there remains a dearth of information on the efficacy of combined antiplatelet and hormone therapy on hypercoagulation and reciprocal effects on cancer.

The pathophysiology of thrombosis is underpinned by the dysregulation of the coagulation cascade and activities of cellular constituents including endothelial cells and platelets. Platelets are anucleate derivatives of megakaryocytes, approximately 2–3 µm in diameter with an average lifespan of seven days within the circulation [6]. Platelets present with a range of bioactive molecules including various cytokines, chemokines, and

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