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Pretreatment thrombocytosis in breast cancer and its prognostic implication: a review

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ABSTRACT

Thrombocytosis has been suggested to be a poor prognostic indicator in malignancies. Platelet granules contain a variety of growth factors which are secreted immediately after platelet activation which have been implicated in tumor progression and in the development of metastasis. Studies have shown that thrombocytosis is associated with a poor prognosis in various gyanecological and non gynaecological malignancies. This independent prognostic factor may provide a simple approach to improved risk stratification of patients in future clinical trials.

Keywords: Platelets, Thrombocytosis, Interleukin-6. breast cancer

Introduction

The association of thrombocytosis with malignancies has been known for more than 100 years [1].Studies have shown that thrombocytosis is associated with a poor prognosis in various gyanecological and non-gyanecological malignancies[2-8]. Recently, thrombocytosis was reported in patients with lung cancer,[2,3[colon,[3] renal cell carcinomas,[4]breast cancer[5] and gynecological malignancies such as cervical cancer[6]ovarian cancer[7] and vulvar cancer[8].We conducted MEDLINE and PUBMED search of the literature on the prognostic impact of thrombocytosis in breast cancer using the search term thrombocytosis in breast cancer, thrombocytosis , platelet count. References of all publication were also searched. We tried to analyse the impact of thrombocytosis on the prognosis of breast cancer, relationship between platelet count and the breast cancer. Thrombocytosis is defined as an elevated platelet counts above $4.5x10^9$/l. Difficulties in interpreting abnormalities of the platelet count in malignancy arise because several conditions may influence the platelet levels. Malignancy is often accompanied by disseminated intravascular coagulation and bone marrow involvement, which tend to lower peripheral platelet counts. Treatment with chemotherapy and radiation therapy also decreases platelet count. Platelets or thrombocytes are small, irregularly-shaped anuclear cell fragments which are derived from fragmentation of precursor megakaryocytes.[9] Megakaryocyte and platelet production is regulated by Thrombopoetin, a hormone usually produced by the liver and kidneys.[10, 11] Old platelets are destroyed by phagocytosis in the spleen and by Kupffer cells in the liver. A reserve of platelets is stored in the spleen and is released when needed by sympathetically-induced splenic contraction.

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Interaction of tumor cells and platelet

The steps involved in metastasis of tumor are entry of tumor cells in the bloodstream, an intravascular phase followed by extravasation of tumor cells from the capillaries resulting in metastasis at the distant site. Platelets participate in tumor progression by contributing to the metastatic cascade, protecting tumor cells from immune surveillance, regulating tumor cell invasion, and angiogenesis[12-16]Thrombin is being generated either by direct contact with platelets or indirectly by stimulating tissue factor-mediated activation of the coagulation system[17] In a study by Egan et al, the ovarian cancer induced platelet activation is mediated by adenosine 59-diphosphate released from tumor cells and can be blocked by adenosine 59-diphosphate receptor (P2Y12 and P2Y1) antagonists[18]. Certain studies have also shown that tumor cells could lead to secretion of dense granules

containing adenine nucleotides via the platelet Fcg receptor IIa[19].Platelet activation by tumors throughout all phases of the metastatic cascade leads to the release of platelet-derived factors stored in their granules leading to inflammatory, proliferative, and proangiogenic activities of platelets to promote tumor growth, tissue invasion, and metastasis[20,21].The platelets secrete thrombospondin-1 which facilitates the adhesion of tumor cells to the endothelium, promotes extravasations in the metastatic cascade[22,23]. The thrombospondin levels have found to be elevated in women with gynecologic malignancies. Once the tumor cells have exited circulation, factors derived from activated platelets are able to induce neoangiogenesis thereby enabling growth at the metastatic site[24].

Reactive or secondary thrombocytosis associated with malignancies has been established since the early 1870s, with an incidence of 10-57%.[23].Possible mechanisms include an overproduction of cytokines/growth factors stimulating megakaryocytes and their precursors. Serum IL-6 is increased in most patients with reactive thrombocytosis, and elevation of this cytokine has been detected in a significant number of patients with cancer. Bone marrow endothelial cells, kidney, and spleen are capable of Thrombopoetin (TPO) production. TPO is produced and released into the circulation at a constant rate by the liver.[10] Normal physiology of platelet production involves the clearance of TPO by high affinity TPO receptors on platelets and formation of a steady TPO concentration, thereby providing a basal stimulation of bone marrow megakaryocytes and normal rate of platelet production. However, in secondary thrombocytosis that can occur with malignancies, there can be up-regulation of TPO production by the liver, causing enhanced thrombopoiesis. Plasma TPO levels have also been shown to correlate with IL-6[25]. Platelets have capabilities to enhance sequestration, adherence, and penetration of malignant cells through the endothelial wall [22].They may also prevent the immune system from clearing tumor cells from the circulatory system. Thrombospondin, a platelet-secreted protein, is increased in patients with cancer, specifically in patients with metastasis, and may promote the adherence of tumor cells to the endothelial barrier, thus enhancing their escape from immune surveillance. Tumor growth is dependent on formation of new blood vessels from preexisting capillaries (i.e., angiogenesis)[26]. Tumor angiogenesis is dependent not only on endothelial cells and cancer cells but also on platelet-endothelium interactions. Platelets adhere to the tumor-related endothelium and release high concentrations of VEGF, which is a potent stimulator of angiogenesis. Platelet granules contain a variety of factors such as VEGF, basic fibroblast growth factor (bFGF), platelet-derived growth factor (PDGF), transforming growth factor beta (TGF-β), IL-6, thrombin, and fibrinogen [27]. These modulators are secreted immediately after platelet activation, and many have been implicated in various steps of tumor progression and in the development of metastasis. As one of the most significant proangiogenic cytokines, bFGF contributes to migration, proliferation, and differentiation of endothelial cells, and regulation of the expression of proangiogenic molecules. PDGF induces angiogenesis by means of stimulation of VEGF expression in tumor endothelial cells and by recruiting pericytes to new blood vessels. TGF-β has an active role in platelet aggregation and regulation of megakaryocyte activity[28]. This cytokine also regulates the activity of the VEGF system and enhances endothelial cell survival[29].

Table 1: summaries of studies of thrombocytosis in breast cancers

Cases (N)	Stage	Prevalence %	Thrombocytosis vs Normal platelet counts	Ref
165	Metastatic	18.2%	OS P=0.038 and PFS, p= 0.008	30
4300	Non metastatic	3.7%	OS P=0.0054 and PFS, p=0.0199	5
27	All stages	0.78%	No impact on OS and DFS	31

Thrombocytosis in breast cancer

Taucher *et al* studied the impact of pretreatment thrombocytosis on survival in primary breast cancer. They performed a retrospective, multivariate analysis of 4,300 patients with early-stage breast cancer. Pretreatment thrombocytosis was observed in 161 patients (3.7%). Patients with thrombocytosis were usually associated with younger age group (p=0.014), nodal positivity (p=0.035) and higher grade (p=0.005).

Estimated median OS, breast cancer-related survival and DFS for patients with versus those without thrombocytosis was 71.0 versus 99.5, 72.0 versus 100.9, and 80.4 versus 88.4 months, respectively (p = 0.0054, p = 0.0095, p = 0.0199). A multiple Cox regression model including tumor and nodal status, grading, age, hormone receptor status and pretreatment thrombocytosis identified pretreatment thrombocytosis as an independent predictive factor for OS (p = 0.0064) and breast cancer-related survival (p = 0.0162). Thus elevated platelet counts at time of diagnosis were associated with poor prognosis in breast cancer [5].

Stravodimou A et al in the study of 165 metastatic breast cancer showed that thrombocytosis is prevalent in 18.2% of the patients. The study concluded that a statistically significant difference in overall and progression free survival favouring the normal platelets group (Log Rank test *P* = 0.038 and 0.008, resp.). The multivariate Cox regression analysis showed that higher grade, ER/PR negativity, the presence of thrombocytosis were statistically and significantly associated with reduced progression free survival and Overall survival. It has been showed from the studies that pretreatment thrombocytosis is associated with reduced OS and DFS. Thrombocytosis is also associated with higher grade, young age, ER/PR negative tumor and more advanced cases. Further study is required to confirm these results and especially to test whether thrombocytosis can serve as a predictive marker of specific treatments. As it is already known that platelet contains VEGF resulting in an irreversible cascade and resulting in tumor progression. The role of anti-VEGF in the management of breast cancer with thrombocytosis is still unknown and further studies can be done to evaluate its use.

Conclusion

The prevalence of thrombocytosis associated with breast cancer portrays a worse survival, independent of other clinical or biochemical factors. With further studies, this single independent prognostic factor may provide a simple approach to improved risk stratification of patients in future clinical trial protocols.

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