RESEARCH ARTICLE

Pre-treatment Elevated Platelet Count Associates with HER2 Overexpression and Prognosis in Patients with Breast Cancer

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Abstract

Purpose: To research the association between pre-treatment elevated platelet count and clinicopathologic characteristics in breast cancer (BC), as well as explore the relationship between pre-treatment elevated platelet count and HER2 status and prognosis of BC patients. Materials and Methods: A retrospective cohort of BC patients who were newly diagnosed or treated by surgery only and had pathological detection results and platelet values in the Department of Oncology, the First Affiliated Hospital of Liaoning Medical College were enrolled from 1/1/2008 until 31/12/2009, and followed up until 31/12/2014. Age, thrombocyte parameters before chemotherapy and/or radiotherapy, immunohistochemical (IHM) indexes, and regional lymph node (LN) involvement and progression-free survival (PFS) were recorded. Results: A total of 447 eligible subjects were included in this research. As we analyzed, for HER2, positive and negative, the incidence rates of elevated platelet count were 25.8% and 14.7% (P<0.05). In the Cox proportional hazards model both variables were independent risk factors for BC (for HER2, OR, 0.592, 95% confidence interval, CI, 0.355 to 0.985, P=0.044; for PLT, OR, 0.998, 95% CI, 0.996 to 1.000, P=0.042). For ER, PR, Ki67 and LN involvement, the differences were not statistically significant (P>0.05). Conclusions: In this research, pre-treatment elevated level of platelet count demonstrated a significant relationship with HER2 amplification/overexpression, and both variables significantly influenced the prognosis of BC. However, elevated platelet count did not exhibit any association with ER, PR, Ki67 and LN involvement.

Keywords: Breast cancer - platelet count - HER2 - correlation - prognosis

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Introduction

As a adverse prognostic factor, elevated level of platelet count has certain incidence in patients of a variety of solid cancers (Monreal et al., 1998; O’Byrne et al., 1999; Buergy et al., 2012; Stravodimou et al., 2013; Fang-Xuan Li et al., 2014; Yan Li et al., 2014; Ying Chen et al., 2015), whereas the reasons were not exactly clear (Taucher et al., 2003; Buergy et al., 2012). But evidence of the prognostic role of elevated platelet count is inadequate (Taucher et al., 2003; Buergy et al., 2012). However, elevated platelet count did not exhibit any association with ER, PR, Ki67 and LN involvement. We therefore performed a multivariate, retrospective cohort analysis in an attempt to assess the correlations between elevated platelet count with HER2 and BC prognosis.

Materials and Methods

Study subjects

The study was approved by The First Affiliated Hospital of Liaoning Medical University ethical committee, and all patients signed a written informed consent. We conducted this multivariate, retrospective cohort analysis by filtering 447 eligible subjects from 1372 BC patients from 1/1/2008 until 31/12/2009, and following up 6 years until 31/12/2014. These 447 cases were all newly diagnosed, and had detection results of IHM indexes and LN involvement, with the tissue samples were obtained by surgery or puncture, and had platelet parameters record detected before adjuvant therapy. Then large amounts of data statistics was taken to collect information such as: age, platelet counts, HER2, ER, PR, Ki67 and LN involvement.

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Classification of subgroups

On account of the normal reference ranges of platelet count was 100-300*10^9/L, the standard of the elevated was defined as a platelet count exceeding 350*10^9/L in this research, for purpose of minimizing the false positive rate. And in order to ensure the accuracy of the HER2 amplification/overexpression detection results, we selected those the IHM results were “3+” or those the FISH detection results were amplified or positive to be the HER2-positive group. In spite of the cut-off values to distinguish Ki67-high from Ki67-low in BC were uncertain, on the base of the highest Youden’s index (0.346) (Bewick et al., 2004), <10 and ≥10 were chosen to divide the Ki67 subgroups. The outcome factor was the untreated elevated platelet count (≥350*10^9/L) while the study factors were HER2 (positive or negative), ER (positive or negative), PR (positive or negative), LN (positive or negative), Ki67 (<10 or ≥10; or continuous).

Follow-up visits

All patients were followed up according to the National Comprehensive Cancer Network (NCCN) guidelines recommendations since the first visit to our department to 12/31/2014.
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Pedersen et al., 1996; Nakano et al., 1998; Eltabbakh et al., 1999; O’Byrn et al., 1999; Ikeda et al., 2002). The positive finding of the study was that the elevated platelet count and the HER2 status were statistically significant correlated, and both these two factors were significantly related to the prognosis of BC. Elevated platelet count remarkably influences the OS and PFS of BC patients, by affecting the metastatic potential of tumor cells. At the level of molecular biology, interaction between high platelet count and malignancy was a complicated network of signaling pathways via cytokines like vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), transforming growth factor β (TGF-β), interleukin 6 (IL-6), and others that have been implicated in phases of tumor growth and progression. Among these biochemical markers, VEGF played a critical role to connect elevated platelet value and HER2 together (Verheul et al., 1997; Laughner et al., 2001). As expected, our research demonstrated the

Discussion

From this retrospective research, the central insight is that the elevated platelet count had a statistical significant positive correlation with HER2 status. As the identification of the correlation, the author considered it has important implications to further study.

The percentage of elevated platelet value in the total cohort appeared to be 15.21%, comparable to 10-63% in other solid cancers (Olesen et al., 1988; Gastl et al., 1993; BC (for HER2, OR: 0.592, 95% confidence intervals, CI: 0.355 to 0.985, \( P = 0.044 \); for PLT, OR: 0.998, 95% confidence intervals, CI: 0.996 to 1.000, \( P = 0.042 \)) which was in accord with previous research (Taucher et al., 2003; Burstein, 2005; Pathmanathan et al., 2014). Figure 6, 7 showed the survival functions.

Figure 2. Proportions of Patients in Different Platelet Count Value Intervals in the ER Cohort. The incidence rates of elevated platelet count in the ER+ group and the ER- group did not demonstrate any remarkable difference (\( P = 0.691 \))

Figure 3. Proportions of Patients in Different Platelet Count Value Intervals in the PR Cohort. The difference between incidence rates of elevated platelet count in the PR+ group and the PR- group is not significant (\( P = 0.197 \))

Figure 4. Proportions of Patients in Different Platelet Count Value Intervals in the Ki67 Cohort. The difference between incidence rates of elevated platelet count in the Ki67- low group and the Ki67- high group is not significant (\( P = 0.467 \))

Figure 5. Proportions of Patients in Different Platelet Count Value Intervals in the LN Cohort. The difference between incidence rates of elevated platelet count in the LN+ group and the LN- group is not significant (\( P = 0.361 \))

Figure 6. Association between Pre-treatment Platelet Count and Survival (PFS) of BC Patients

Figure 7. Association between HER2 and Survival (PFS) of BC Patients

Pedersen et al., 1996; Nakano et al., 1998; Eltabbakh et al., 1999; O’Byrn et al., 1999; Ikeda et al., 2002). The positive finding of the study was that the elevated platelet count and the HER2 status were statistically significant correlated, and both these two factors were significantly related to the prognosis of BC. Elevated platelet count remarkably influences the OS and PFS of BC patients, by affecting the metastatic potential of tumor cells. At the level of molecular biology, interaction between high platelet count and malignancy was a complicated network of signaling pathways via cytokines like vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), transforming growth factor β (TGF-β), interleukin 6 (IL-6), and others that have been implicated in phases of tumor growth and progression. Among these biochemical markers, VEGF played a critical role to connect elevated platelet value and HER2 together (Verheul et al., 1997; Laughner et al., 2001). As expected, our research demonstrated the
significant relevant between elevated platelet value and HER2 upregulation. But question remains unresolved as to how exactly the elevated platelet count is correlated with HER2 amplification/overexpression in BC patients. One explanation is that the HER2-positive BC triggers a upregulation of VEGF therefore lead to the elevated level of platelet count. Other possible perspectives are HER2-positive BC promotes a high level of platelet, platelets therefore release large doses of VEGF in the plasma.

In this research, due to the elimination of patients whose IHM results of HER2 were “2+”, the positive percentage of HER2 was 16.80%, which was not comparable to the 20-30% in previous study (Foy et al., 2012). However, the lower HER2 positive percentage minimized the false positive rate of elevated platelet count in the HER2-positive subgroup. HER2 was reported overexpressed in gastric cancer, and especially in BC. The upregulation of HER2 in BC promotes elevated risk of recurrence, poor prognosis, and even do harm to the efficacy of hormonal therapy (Puhalla et al., 2013), so the identification of its relevance to high platelet values in our research may help to provide synergism to the diagnose and adjuvant therapy targeting biochemical markers of BC.

Advantages of this research were a multivariate cohort analysis and a relatively big sample size. But some limitations should be mentioned. Firstly, our research was a hospital-based study in China, the subjects may not well represent the general population. Secondly, the results should be cautioned because of the differences of region and race. Thirdly, we need to further study the mechanisms of the correlation between elevated platelet count and HER2 amplification/overexpression, and large sample size multi-center prospective clinical trials were needed to confirm the effect of antiplatelet treatment in HER2-positive BC therapy.

In conclusion, the positive finding of the study was that pre-treatment elevated platelet count and the HER2 status were statistically significant associated, and both these two factors were significantly related to the prognosis of BC. Therefore, antiplatelet treatment maybe useful to improve therapeutic efficacy and prognosis of HER2-positive BC patients.

References


