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LETTER TO THE EDITOR

The potential role of neutrophil trogocytosis and G-CSF in the loss of HER2 expression

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In HER2-positive breast cancer (BC), the standard treatment consists of neoadjuvant sequential chemotherapy, HER2-targeted therapy, surgery, and, if indicated, radiotherapy and/or hormonal therapy. Trastuzumab, a recombinant antibody targeting HER2, has significantly extended the overall survival of BC patients and remains clinically reliable treatment. The 5-year survival, when following the standard treatment protocol, including HER2-targeted therapy, leads to a favorable prognosis with a 5-year survival rate around 75%. Improved overall survival (OS) was reported in BC patients when trastuzumab was administered in both the neoadjuvant and adjuvant period rather than in the adjuvant period alone. Thus, trastuzumab-containing neoadjuvant therapy is currently the standard of care [1].

A recent study performed by Ignatov et al. [2] investigated whether the loss of HER2 expression is related to trastuzumab treatment. The cohort consisted of 227 patients, in which second biopsy could be obtained after the oncologic treatment. 549 patients were excluded either because of the absence of resectable tumor after the neoadjuvant chemotherapy (NACT) or because of the absence of second biopsy. This well-conducted and valuable study showed that, in all of the patients, loss of HER2 has been observed rather than the gain of HER2 expression [2]. 93.7% of women with downgraded HER2 expression underwent anti-HER2 treatment and receiving the HER2 treatment was the only factor associated with change of the HER2 expression from positive to negative ($P < 0.0001$). Other clinical and pathological variables, including age, tumor type, Ki-67 expression, etc., were not related to any changes in HER2 expression. Ignatov et al. demonstrated that trastuzumab treatment alone changes HER2 positivity in 47.3% cases and, moreover, dual blockade with trastuzumab and pertuzumab caused in 63.2% of the patients the loss of HER2 positivity. The understanding of HER2 loss, however, is far from satisfactory and it has been proposed by the authors to conduct further investigations.

Regarding this matter, we would like to point out a recent finding that neutrophil trogocytosis causes a significant reduction in cancer cell cytoplasmic labeling in antibody-opsonized cancer cells. In the immunological study by Matlung et al., neutrophils directly interact with antibody-opsonized cancer cells and visibly phagocyte, the HER2-containing cancer cell membrane [3]. The specialized type of phagocytosis, called trogocytosis, was seen in breast cancer tissue after trastuzumab treatment and the positivity of HER2 was confirmed inside the neutrophils with intracellular staining [3]. The phenomenon of trogocytosis, originally thought to be mediated mostly by monocytes/macrophages, has recently been shown to largely depend on the presence and activity of neutrophils. Neutrophil trogocytosis is triggered by therapeutic antibodies, causing in the rituximab (anti-CD20) treatment a loss of CD20 molecule from the cell surface, but not death of the target cells [4].

In our opinion, similarly to rituximab treatment, the neutrophil trogocytosis might be one of the main factors responsible for the loss of HER2 after trastuzumab/pertuzumab treatment.

This is particularly important since the administration of recombinant granulocyte colony-stimulating factor (G-CSF) together with trastuzumab-containing neoadjuvant chemotherapy is an ongoing practice standard in the treatment of HER2-positive breast cancer [1]. It is beneficial to treat patients with G-CSF concomitantly to chemotherapy to prevent complications caused by chemotherapy-induced

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myelosuppression [1]. However, we aim to highlight that the concomitant administration of trastuzumab and G-CSF could contribute to increased neutrophil trogocytosis.

We suggest that it is reasonable to assume that the concomitant administration of G-CSF and trastuzumab should be reconsidered particularly in patients where trastuzumab resistance is attained. Nevertheless, this theory has not been considered so far, and to attest its relevance, extended research must be conducted.

Compliance with ethical standards

Conflict of interest The authors Zuzana Strizova, Jiri Vachtenheim Jr., and Jirina Bartunkova declare that there is no conflict of interest regarding the publication of this article. The manuscript has been approved for publication by all authors and is not currently under review or submitted to another journal.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors Zuzana Strizova, Jiri Vachtenheim Jr. and Jirina Bartunkova.

Research involving human and animal participants Humans were not involved in the study.

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