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Commentary

Is it possible to predict the pCR with CBC? A commentary on "correlation analysis of lymphocyte-monocyte ratio with pathological complete response and clinical prognosis of neoadjuvant chemotherapy in patients with breast cancer" by Meng et al.

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Breast cancer (BC) is the most common cancer worldwide. It is possible to achieve significant improvements in disease-free and overall survivals with the addition of effective systemic treatments to curative surgery. Nowadays, in the management of operable BC, giving systemic therapy in the neoadjuvant setting is the preferred approach in many cases, starting from early-stage disease, due to its various advantages. The absence of invasive tumor in the primary tumor and regional lymph nodes after neoadjuvant therapy (NAT) in BC patients is defined as pathological complete response (pCR). The pCR is an important prognostic factor for survival [1]. This relationship is particularly evident in triple-negative, HER2-positive, and luminal-B disease [1]. Thus, obtaining pCR by NAT is currently a rational and important goal.

The pCR is taken as the primary endpoint in almost all NAT trials in BC patients. Therefore, it is important to identify markers that predict pCR. Moreover, it is possible to prolong the survival with additional treatments to be applied in adjuvant therapy in patients who cannot achieve pCR with NAT [2,3]. In the past couple of years, systemic treatment options for BC increased considerably. Treatment options have become more complex with the increase in studies of NAT and post-NAT adjuvant therapy. Hence, studies to determine the markers to be used to predict pCR is important. In this way, it may be possible to identify treatment strategies that indirectly improve survival and to individualize NAT.

In their study, Meng et al [4]. showed that the lymphocyte/monocyte ratio (LMR), which will initially be measured by complete blood count (CBC), plays an important role in predicting pCR in HER2-positive breast cancer. In HER2-positive patients with low- and high-LMR, the pCR rates were found to be 14.3% and 44.1%, respectively. Today, in HER2-positive BC, neoadjuvant chemotherapy + dual anti-HER2 blockade is the standard of care in many centers, if the tumor is larger than 2 cm in diameter and/or has positive axillary lymph nodes. Although the patients in this study were not on anti-HER2 blockers, we believe this significant difference (predictable in HER2-positive patients by LMR) is clinically meaningful. Whether LMR plays a predictive role in treatment regimens that include anti-HER2 agents in NAT should be evaluated in other widescale studies. If the predictive role of LMR is to be determined in patients receiving these treatment regimens, other studies can evaluate whether pCR rates can be increased by methods such as adding immunotherapy agents to NAT in patients with low-LMR. From the opposite perspective, it seems worth investigating whether similar pCR rates can be obtained with trastuzumab alone rather than dual anti-HER2 blockade in patients with high-LMR.

Although pCR was not available after NAT, a recently published meta-analysis demonstrated a correlation between the degree of

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pathological response and survival [5]. We believe that the relationship between LMR and the residual cancer burden (RCB) should be investigated, because it can predict RCB class before NAT. It will be possible in the future to escalate or de-escalate NAT through individualized treatment options. In this case, an easily assessable and (most probably) useful parameter could be used in deciding the most appropriate treatment for each patient.

The relationship of LMR with the prognosis has been studied previously in many solid tumor types, and high-LMR has been associated with poor prognosis in almost all of them [6]. There is little conflicting data regarding the role of LMR in predicting response to NAT in BC patients [7,8]. Meng et al [4]. found a remarkable connection between a certain molecular subtype (HER2-positive) and NAT response.

Traditionally, BC was thought to be not an immunogenic tumor. However, it has recently been found that immune activation in the tumor microenvironment plays an important role, especially in HER2-positive and triple-negative BCs. Immune activation plays an important role in achieving pathological and therapeutic outcomes in BC patients receiving NAT. One method used to detect immune activation is to assess tumor-infiltrating lymphocytes (TILs) based on the assessment of lymphocyte density in the tumor microenvironment. It has been refocused to TILs due to the recent success of immune checkpoint blockade therapy in many cancer types [9]. TILs increase plays a predictive role in the response to NAT in HER2-positive and triple-negative BCs and is associated with a good prognosis [10,11]. With the introduction of drugs such as pertuzumab, lapatinib, TDM-1, trastuzumab-deruxtecan, and tucatinib, which started with trastuzumab, major advances have been achieved in the management of HER2-positive BC. These advances were also reflected in NAT in HER2-positive BC. Today, when anti-HER2 drugs are combined with NAT, pCR can be achieved in approximately 65% of patients. However, there is a need for methods that can detect patients without pCR before treatment and strategies to ensure that pCR can be obtained in these patients. Data suggests that one of the main mechanisms by which anti-HER2 drugs increase tumor response is to increase immune responses in the tumor microenvironment [12]. Patients who fail to achieve pCR with chemotherapy combined with dual anti-HER2 therapy require additional strategies. Adding immunotherapy to the treatment of these patients may be a reasonable strategy. However, appropriate markers are needed to identify patients who will benefit from immuno-oncology therapy. TILs and PDL-1 are the most studied parameters in this context. However, the evaluation of both markers comes with technical equipment and additional costs. In some previous studies, it has been shown that there is a positive correlation between TILs and LMR [13]. In the study by Meng et al [4]., the role of LMR in predicting pCR in HER2-positive patients may be related to increased TILs and immune responses in the tumor microenvironment. The role of LMR in identifying patients for whom the addition of immunotherapy to treatment enhances the tumor response while determining the NAT strategy may be addressed in future studies.

By this study of Meng et al., it has been shown that a relatively understudied and an easily assessable parameter, LMR, may predict response to NAT in BC. This parameter, among others, may help physicians to escalate or de-escalate NAT with personalized treatment options, choosing the most appropriate treatment for each individual patient. The impact of this new prognostic tool on response rates and survival should also be further investigated in different settings with alternative treatment options including anti-HER2 antibodies and/or immune checkpoint inhibitors in the NAT of BC patients.

CRediT authorship contribution statement

Eda Tanrıkulu Şimşek: Conceptualization, Methodology, Investigation, Writing – original draft. **Batuhan Bayram:** Writing – original draft. **Alev Yıldırım:** Writing – original draft. **Ahmet Emre Eşkazan:** Conceptualization, Methodology, Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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