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Clinical Significance of Immunoscore in Triple Negative Breast Cancer and Human Epidermal Growth Factor Receptor 2+ Breast Cancer

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Authors' contributions

This work was carried out in collaboration among all authors. Author PZT conceived the manuscript. All authors wrote and edited the manuscript and authors WWB and LWH approved its final version. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Breast cancer is one of the leading causes of death among women in the world. Advancements have been made in respect to the diagnosis and management of breast cancer. In this review we are going to look at immunoscore as an additional method of predicting prognosis as well as treatment for patients with TNBC and HER2+ breast cancer. At the moment the Immunoscore strategy has advanced in colon cancer but for breast cancer the TNM classification is the only standardized method for grading as well as predicting prognosis in breast cancer patients. Metastasis and growth of breast tumors are largely influenced by the immune contexture. In invasive breast cancer, response to chemotherapy and prognosis are predicted by a higher immune cell count. Tumor infiltrating lymphocytes (TILs) are immune cells that have migrated to the tumor tissue and the local microenvironment. This population is indicative of an immune response generated by the patient against the malignancy. In TNBC and HER2+ disease in particular, the presence of TILs has been shown to correlate with a good prognosis and good response to chemotherapy. Thus, an implementation of immunoscore in breast cancer could be a good tool in terms prognosis as well as a predictive tool.

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1. INTRODUCTION

The development of a scoring system called 'Immunoscore' derived from the immune context is a possible clinical parameter [1,2,3], As a clinically useful prognostic marker for breast cancer, and based on the amount of lymphocyte populations in the area within the borders of the invasive tumor [4]. A detailed overview of the immune contexture as opposed to Immunoscore has been stated before [2,5]. Immunoscore offers a score ranging from Immunoscore 0 (I0) when low lymphocyte population densities are found in both regions, to Immunoscore 4 (I4) when high densities are found in both regions [6]. Current immunohistochemistry technologies allow the use of such analyzes in routine diagnostic pathology. Therefore, given the possibly universal existence of immune regulation of tumors, it is important for patients to take the immune parameter as a prognostic factor into account and to incorporate Immunoscore as a component of cancer classification [7,8,2,9,10]. The Immunoscore classification, demonstrating the prevalence of immune infiltrates, has been shown to have a prognostic significance higher than that of the AJCC/UICC TNM classification system [6]. The field of immune regulation at the level of the tumor microenvironment has assumed a leading role in cancer research over the past few years in colorectal cancer [11,12,13,4,3], melanoma [14] and all other forms of cancer (Bindea G, 2010). Initially mentioned a few years ago [11] as a prognostic factor [12,4], the immunoscore may also play a role in predicting the response to biotherapy targeting immune check points [9,10]. In combination with protocol variability, the inherent uncertainty of immunohistochemistry leads to the variability of the findings obtained. A structured procedure for consensus is required. Large-scale harmonization attempts have already been witnessed in peripheral blood immune cell populations for widely used immunological assays [15,16]. To decrease these limitations, it is therefore necessary to seek assay uniformity. To achieve clinical applicability for individual patients, clinical validation of the immunoscore with standardized procedures is important.

2. THE IMMUNOSCORE AS A NEW APPROACH FOR THE CLASSIFICATION OF BREAST CANCER BASED ON THE TUMOR MICROENVIRONMENT

An increasing number of studies [1,4,9,12] have shown that host immune system influences development of cancer. The immunoscore defines densities of intratumoral immune infiltrates which determine poor or favorable prognosis depending on their quantity and quality in the tumor compartments that is tumor center and the invasive margin. In view of the important role of the host immune signature in regulating tumor progression, the integration of Immunoscore as a feature of cancer classification and a prognostic tool must now be initiated [4,12,13]. According to Salgado et al, the recommendations for assessing TILs in breast cancer are as follows;

"1. TILs should be reported for the stromal compartment (= % stromal TILs). The denominator used to determine the % stromal TILs is the area of stromal tissue (i.e., area occupied by mononuclear inflammatory cells over total intratumoral stromal area), not the number of stromal cells (i.e., fraction of total stromal nuclei that represent mononuclear inflammatory cell nuclei). 2. TILs should be evaluated within the borders of the invasive tumor. 3. Exclude TILs outside of the tumor borders, e.g., around DCIS and normal lobules.4. Exclude TILs in tumor zones with crush artefacts, necrosis, regressive hyalinization as well as in the previous core biopsy site. 5. All mononuclear cells (including lymphocytes and plasma cells) should be scored, but polymorphonuclear leukocytes are excluded.6. 1 section (4-5 μm, magnification 200-400x) per patient is currently considered to be sufficient. 7. Full sections are preferred over biopsies whenever possible. Cores can be used in the pre-therapeutic neoadjuvant setting; currently no validated methodology has been developed to score TILs after neo-adjuvant treatment. 8. A full assessment of average TILs in the tumor area by the pathologist should be used. Do not focus on hotspots.9. The working group's consensus is that TILs may provide more biological relevant information when scored as a continuous variable, since this will allow more accurate statistical analyses, which can later be

categorized around different thresholds. However, in daily practice most pathologists will rarely report for example 13.5% and will round up to the nearest 5-10%, in this example thus 15%. Pathologist should report their scores in as much detail as the pathologist feels comfortable with. 10. TILs should be assessed as a continuous parameter. The percentage of stromal TILs is a semiquantitative parameter for this assessment, for example, 80% stromal TILs means that 80% of the stromal area shows a dense mononuclear infiltrate. For assessment of percentage values, the dissociated growth pattern of lymphocytes needs to be taken into account. Lymphocytes typically do not form solid cellular aggregates; therefore, the designation “100% stromal TILs” would still allow some empty tissue space between the individual lymphocytes. 11. No formal recommendation for a clinically relevant TIL threshold(s) can be given at this stage. The consensus was that a valid methodology is currently more important than issues of thresholds for clinical use, which will be determined once a solid methodology is in place. LPBC (lymphocyte predominant breast cancer) can be used as a descriptive term for tumors that contain “more lymphocytes than tumor cells”. However, the thresholds vary between 50-60% stromal lymphocytes.” Following these guidelines, immunoscore can be determined by IHC paying attention to different TILs. Immunoscore strategy has a dual advantage: firstly, it appears to be the strongest prognostic factor for DFS and OS, especially in early-stage cancers, and secondly, it may indicate potential targets for novel therapeutic approaches, including immunotherapy [9]. More and more evidence indicate that cancer progression depends heavily on the complex tumor microenvironment (TME) in which it develops [17]. The TME contains a range of cell entities including fibroblasts, endothelial cells, blood vessels, lymph vessels and immune system cells [17]. Immunoscore is based upon the quantification of the lymphocyte populations especially CD3 and CD8-positive T cells in the tumor center (CT) and on the invasive margin (IM) In colorectal cancer [17]. Therefore, the same technique can be used to look at the Tumor Infiltrating Lymphocytes (TIL) in Triple Negative Breast Cancer (TNBC) and Human Epidermal Growth Factor Receptor 2 (HER2+) breast cancer. The TIL populations of breast cancer typically consist primarily of T-lymphocytes and CD8+ cytotoxic T-lymphocytes (CTLs). The role of T lymphocytes and cytotoxic T-cells having a significant influence on patient survival has been highlighted in several analyses and meta-analyses $$$. Since it represents an aggressive, adaptive immune response to neoantigens on the surface of the tumor cells and positively correlates with improved survival, this makes CD8+ a robust marker for the prognosis of patients with Breast Cancer and especially Triple Negative and HER2+ breast cancer [18]. CTLs have the ability to further differentiate into tissue-resident T-memory (TRM) cells that exist inside the breast tissue without systemic recirculation [19]. TRM cells release high levels of immune checkpoint molecules that lead to the removal of tumors and have been shown to be involved in immunosurveillance for breast cancer. TRM status has been shown to be an even higher prognosis marker than CD8+ cells alone and is substantially correlated with improved TNBC patient survival [20]. During acute inflammation, T helper cells are predominantly polarized T helper cell type 1 (Th1) and secrete cytokines such as IFN, TNF and IL-2 that function to restrict tumor development, promote antigen processing and presentation, and activate macrophages. During chronic inflammation and cancer, T helper cells are type 2 (Th2) polarized and express IL-4, IL-5, IL-6, IL-10 and IL-13, which inhibit cytotoxicity mediated by T cells [21]. T regulatory lymphocytes (Tregs) are characterized as T lymphocytes which are both CD4+ and FOXP3+ and have immunosuppressive functions. Tregs usually help defend against autoimmunity [22]. These immune cells are commonly known to contribute to the pro-tumor immune response and assist the tumor in subsequent immune escape in the case of breast carcinomas, so they are associated with poor prognosis [23,24]. These lymphocytes enable tumor progression by expressing inhibitory factors that inhibit the response of the anti-tumor Th1 [24]. There are many other types of immune cells which infiltrate breast cancers, including macrophages, NK cells and dendritic cells (DCs), in addition to T cells [25,26,27]. In short, CD4+ T helper, CD8+ CTLs, NK cells, M1 macrophages and DCs defend against the growth of tumor (LA, 2012). Conversely, tumor growth can be stimulated by CD4+ FOXP3+ Th2 cells, M2 macrophages, and myeloid-derived suppressor cells (MDSCs) [28]. These immune cells present In the TME of breast cancer can be studied further in an attempt to establish immunoscore based on the quality and quantity of these immune cells in the breast cancer microenvironment.

2.1 Impact on Response to Chemotherapies

For patient clinical management, whether the immune background of the primary tumor predicts therapeutic responses is of vital importance [20]. Immune signature data showed that a strong immune component predicts a good chemotherapy response in breast cancer [29,30,31], a tumor in which a high lymphocyte infiltrate is associated with a higher neo-adjuvant therapy response rate [32,33]. A prospective retrospective research was performed to confirm the prognostic value of tumor-infiltrating lymphocytes (TILs) in triple-negative breast cancer (TNBC) using samples from the Fin HER adjuvant study and also to examine associations with trastuzumab benefits in HER2-over-expressing disease [34]. In TNBC and not in luminal or HER2+ subtypes, the authors found a strong correlation with a positive prognosis. They also found that the relationship between TILs as a continuous variable and treatment with trastuzumab was statistically important. Each 10 percent rise in lymphocytic infiltrate was associated with an 18 percent reduction in the relative risk of distant recurrence in patients receiving trastuzumab in addition to their chemotherapy for the primary end point of distant disease-free survival. Several facets of this analysis deserve careful review. The FinHER2 study enrolled 1010 early-stage breast cancer patients, and hematoxylin/eosin evaluation of TILs was performed by the researchers in about 92 percent of the cases. Of those, 134 were included in this study with triple-negative disease and 209 with HER2-amplified breast cancer; the number of events was 35 and 49 for TNBC and HER2+ disease, respectively. In addition, the 209 patients included in HER2+ were split into trastuzumab and non-trastuzumab arms. Therefore, the number of events for the prediction study of the value of trastuzumab is very small. The authors did not define the particular number of events for the trastuzumab and non-trastuzumab groups (or the numbers assigned to the different quartiles in each group), the numbers that are relevant to the perspective of the results. Another significant point to remember is that the 0.77 agreement between the two pathologists who analyzed the percentage of TILs in the stromal portion may not be sufficient and something to try to optimize in future studies [35]. The prognostic value of TILs in TNBC was shown in previous observations [36,37]. Better prognosis in patients with TNBC and higher TILs is also the result of a chemotherapy-induced 'immunoediting' process. The emerging hypothesis that the response to chemotherapy is at least partly based on an immunological reaction towards those tumor cells that are dying during the chemotherapy has been evaluated in cellular and animal models [38]. One of the pathways by which chemotherapy can activate the immune system to recognize and destroy malignant cells is usually referred to as immunogenic cell death (ICD). In reality, cancer cells that die from ICD are transformed into an anticancer vaccine and thus produce an adaptive immune response [38]. To determine the impact of the immunoscore as a predictive marker, it should be tested prospectively in randomized clinical trials.

3. CONCLUSION

Further studies are needed to determine the impact of the immunoscore in breast cancer as a prognostic tool as well for the management of breast cancer patients. Since in TNBC and HER2+ disease in particular, the presence of TILs has been shown to correlate with a good prognosis and good response to chemotherapy, adapting immunoscore focusing on the components of the TME could be the next step in the prognosis and management of patients with TNBC and HER2+ breast cancer.

CONSENT

It’s not appropriate.

ETHICAL APPROVAL

It’s not appropriate.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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