Immunomodulating Therapies in Breast Cancer

Subjects: Oncology

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Review of the role of the immune system in breast cancer. It covers the prognostic and predictive impact of tumor-infiltrating lymphocytes. Furthermore therapeutic advances ranging from immune checkpoint inhibitors and personalized vaccination strategies are highlighted.

Keywords: tumor infiltrating lymphocytes (TILs) ; immune checkpoint inhibitors (ICPis) ; mRNA vaccine ; tumor-associated antigens (TAA) ; neoantigens

1. Introduction

Breast cancer is the most common cancer and the leading cause of cancer death for women worldwide [1]. In 2015, breast vancer incidence was 2.4 million, with 523,000 breast cancer deaths. Invasive breast cancer can be divided in several molecular subgroups (e.g., luminal A, luminal B, HER2-positive, and triple-negative) which have different prognoses and different systemic therapeutic options (e.g., chemotherapy, endocrine therapy, anti-HER2 therapy) [2]. Early breast cancer has no distant metastases and is curable [2]. However, if distant metastases occur, the disease is treatable but incurable [3].

The role of the immune system in breast cancer has long been debated [4]. With the advent of modern techniques, such as mRNA sequencing data from The Cancer Genome Atlas (TCGA), it has been shown that high expression of T-cell and B-cell signatures predicts improved overall survival in many tumor types, including breast cancer [5]. In particular, triple-negative breast cancer (TNBC), which has a more pronounced immunogenic potential compared to other molecular subtypes, is of great interest. TNBC accounts for up to 20% of breast cancers and is associated with a significantly worse prognosis in the first 2 to 3 years after diagnosis compared with other breast cancer subtypes [6]. It is now generally accepted that TNBC is not a homogeneous disease. Instead, TNBC consists of multiple subtypes (e.g., basal-like 1 and 2, immunomodulatory, mesenchymal, mesenchymal stem-like, and luminal androgen receptor) [7]. In a comprehensive immunogenomic analysis of over 10,000 tumors using TCGA data, Thorsson and co-workers identified six stable and reproducible immune subtypes C1–C6 (i.e., wound-healing, IFN-γ-dominant, inflammatory, lymphocyte-depleted, immunologically quiet, and TGF-β-dominant) [8]. Interestingly, these immune subtypes include multiple tumor types, and are characterized by a dominance of either macrophage or lymphocyte signatures, T-helper phenotype, extent of intratumoral heterogeneity, and proliferative activity. Although these authors did not comment specifically on TNBC, it is likely that TNBC with a strong lymphocytic infiltrate belong to immune subtype C3. Using even more sophisticated techniques, such as single-cell sequencing, Wu and his collaborators have deconvoluted breast cancer cohorts and stratified them into nine clusters, called “ecotypes”, with unique cellular compositions and clinical outcomes that provide a comprehensive transcriptional atlas of breast cancer cellular architecture [9]. Significantly more somatic mutations and neoantigens are detected in TNBC than in other molecular subtypes, resulting in increased immunogenicity [10]. In a systematic review, Stanton and colleagues showed that the extent of tumor-infiltrating lymphocytes (TILs) varies within and between breast cancer subtypes, with TNBC having numerous TILs [11]. This may identify breast cancers that are more suitable for immunotherapy.

2. Prognostic and Predictive Significance of Tumor-Infiltrating Lymphocytes

Most studies that addressed the prognostic and/or predictive role of TILs in breast cancer focused on the cellular immune system, particularly cytotoxic T cells [12][13][14][15][16][17]. Overall, these studies showed that increased rates of tumor-infiltrating lymphocytes or T-cell transcripts were associated with improved prognosis in rapidly proliferating breast cancer such as TNBC.

In contrast, we primarily examined B cells and the humoral immune system and reported a strong positive prognostic impact of a B cell metagene on breast cancer prognosis [18]. This strong protective effect of a B cell/plasma cell signature was later confirmed by others [19][20]. Tumor-infiltrating plasma cells were identified by confocal microscopy as the source of immunoglobulin kappa C (IGKC) expression [21]. In this study, co-staining with anti-human IgG showed that IGKC was expressed in IgG-positive cells, a known feature of B-cell maturation and plasma cell differentiation after antigen contact. IGKC has been associated with favorable prognosis in untreated patients and with response to anthracycline-containing neoadjuvant chemotherapy in early breast cancer [21]. Indeed, in a comprehensive analysis of the prognostic landscape of genes and infiltrating immune cells in human cancers, Gentles et al. confirmed that plasma cell signatures, as well as plasma cells expressing IGKC, are associated with improved survival [20]. However, the strong dependence of the humoral immune system on T cells is examplified by C-X-C motif chemokine ligand 13 (CXCL13)-positive CD4+ follicular helper T (Tfh) cells, which are crucial for germinal center development and antigen-specific B cell maturation to high-affinity memory cells and antibody-secreting plasma cells [22]. In addition, CXCL13 has been associated with improved survival in TNBC [23].

Overall, these and other findings suggest that humoral immunity may be as important as cellular immunity in eliminating cancer [24]. These, initially retrospective, results were later confirmed in exploratory studies using archival tissue from randomized trials [23][25][26], as well as by histological evidence of TILs in archival tissue from randomized trials [15][27][28]. Recently, in the neoadjuvant EXPRESSION trial, we demonstrated that genes with significantly higher expression in pathologically complete responders are primarily related to the immune response, including immunoglobulins [29]. These results also support the predictive role of the humoral immune system in early breast cancer.

This significant association of tumor-infiltrating immune cells and TNBC is not surprising, considering that the overall mutational burden is highest in TNBC [10]. In addition, these authors found that mutational burden was highly correlated with neoepitope load (R2 = 0.86). A comprehensive analysis of immunogenic signatures in TNBC based on two sets of large-scale breast cancer genomic data showed that TNBC has the strongest immunogenicity among breast cancer subtypes [30]. Furthermore, these authors confirmed that TNBC also has higher levels of immune cell infiltration and higher expression of genes encoding immune checkpoints than non-TNBC. However, mutational and neoantigen load appear to incompletely explain the immune response in TNBC, as other studies have described an inverse relationship between immune infiltration and somatic copy number alterations [31][32]. Obviously, the exact relationship between immune infiltration, mutation burden, and neoantigen burden has not been fully elucidated. Nevertheless, TILs are widely used, especially in TNBC. To improve reproducibility, a standardized method for the evaluation of TILs has been defined to integrate this parameter into standard histopathological practice [33][34].

3. Immune Checkpoint Inhibitors

Important target structures in the immune system are “immune checkpoints”. Immune checkpoint inhibitors (ICPis) block the interaction of certain cell surface proteins that serve as “brakes” on immune responses. Currently, the most important immune checkpoint in breast cancer is the PD-1/PD-L1 axis [35][36]. The interaction between PD-1 and its ligand PD-L1 functions as an immune checkpoint against unrestrained cytotoxic T effector cell activity. Furthermore, it promotes peripheral T effector cell exhaustion and conversion of T effector cells to immunosuppressive Tregs [37]. Immune checkpoint inhibitors that block the PD-1/PD-L1 axis and reactivate cytotoxic T effector cell function increase immune cell activity against tumor cells.

Phase I/II evidence for ICPis in advanced breast cancer.

Abbreviations: AE, adverse events; HR, hormine receptor; ICPis, immune checkpoint inhibitors; m, months; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TMBC, triple-negative breast cancer; vs., versus.

Indeed, the vast majority of randomized trials using ICPi in early or advanced TNBC showed significant benefits over standard therapy alone. When combined with an acceptable safety profile, immune checkpoint inhibitors are a promising new therapeutic option in TNBC. Recently, the Society for Immunotherapy of Cancer (SITC) published a clinical practice guideline on immunotherapy for breast cancer [38]. Recommendations in this clinical practice guideline include diagnostic testing, treatment planning, immune-related adverse events, and patient quality of life considerations to provide guidance to the oncology community treating breast cancer patients with immunotherapies.

4. Predictive Markers for Immune Checkpoint Inhibitors

Currently, the only established predictive biomarker for response to ICPi in advanced TNBC is PD-L1 status. Recent analyses have shown a potential role of TMB in response to durvalumab in early TNBC [39]. In a recently published comprehensive genomic analysis of 3831 consecutive breast cancer samples, potential biomarkers (e.g., TMB, microsatellite instability [MSI], BRCA mutations) were assessed to guide the use of ICPIs in these patients [40]. Interferon-γ (IFN-γ) plays a crucial role in the regulation of anti-tumor immunity [41]. Upon ligand binding, IFN-γ receptor 1 and 2 (IFNγR1 and IFNγR2) oligomerize and transphosphorylate, activating Janus-activated kinase (JAK) 1 and 2. Thereby, IFNγR1 is phosphorylated, creating a docking site for the signal transducer and activator of transcription (STAT) 1. Interferon-γ (IFN-γ) signaling signatures are associated with clinical response to treatment with ICPi [42]. Similarly, JAK/STAT pathways predict response to ICPi therapy [43]. In addition, cancer stem cells are a potential biomarker to predict the effectiviness of ICPis [44]. However, for all of these potential biomarkers, prospective randomized trials are needed to assess the predictive value in response to immune checkpoint inhibitors.

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