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Breast cancer immunotherapy and personalized medicine

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Abstract

Breast cancer response to immunotherapy is succussed; however, the evaluation of sensitive/resistant target treatment subpopulations based on stratification by tumor biomarkers may improve the predictiveness of response to immunotherapy. Treatment decisions which were based in the past predominantly on the anatomic extent of the disease are shifting to the underlying biological mechanisms. Gene array technology has led to the recognition that breast cancer is a heterogeneous disease composed of different biological subtypes, and genetic profiling enables response to chemotherapy to be predicted. Biological therapy has been developed to target HER2 receptor and combination of antibody drug conjugates linked cytotoxic therapy to HER2 antibodies. This review will give a general overview of the impact of breast cancer and the role of immunotherapy in breast cancer as well as studying tumor biomarkers that increase the likelihood of success with immunotherapy in breast cancer.

Keywords: Breast cancer; Immunotherapy; Sensitive/resistant target treatment

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Introduction

Breast cancer is a malignant tumor that occurs in breast cells, with an increasing trend in women in the modern world. Moreover, breast cancer is a multifactorial disease, and invasion can occur due to a combination of environmental and genetic factors. Meanwhile, there are still various therapeutic strategies available to treat breast cancer, and rapid technological advancements in the understanding of disease mechanisms have made possible other options and are characterized by their efficacy and fewer side complications. Currently, extensive research is investigating the development of the immune tool, immunotherapy, in cancer treatment. As a member of the team, particularly for the management of breast cancer, in addition, personalized medicine is a system of therapy that is maximum in vitro experimental treatment to be made with the help of some precise ways of diagnosis based on an individual's traits, religious beliefs, and level of mutation, as well as personalized medicine for body

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susceptibility to drug success, side effects, and level of hormone representation in the body, advancements in the treatment of breast cancer in modern days.

Immunotherapy in treating cancer has gained much knowledge or improvement and modified the immunotherapy aspects for past ages have been related to blocking distinctive cancer cells that provide antagonistic programmable facility, especially at the arrangement of interference prevention of proteins. In the era of modern technology, numerous growing immune therapies also use a microscopic medication system provided at the initial site of cancer to combine chemotherapeutics with the immune systems of priming. In its development, predictive biomarkers have been drafted to choose the population who are potentially nominees for specific treatment personalized medicine is preferable to referring for molecular research, focusing on the uniqueness of a patient's molecular and immune system profiling to receive specific constellations. A variety of predictive resistance tumors could develop with specifically distinct therapeutic anti-cancer agents to produce a more vigorous diagnostic examination.

Overview of Breast Cancer

Breast cancer is the most commonly diagnosed and leading cause of cancers for women worldwide. It is a heterogeneous disease and can be categorized into multiple subtypes based on clinical heterogeneity, genetic alterations, and molecular variations. Another criterion majorly classified it into hormone receptor positive (HR+) or negative, including human epidermal growth factor 2 receptor positive (HER2+), hormone receptor positive, and triple-negative cancer. Breast cancer also advances into various stages, including ductal carcinoma in situ (DCIS), invasive (or infiltrating), metastatic disease (or breast cancer that has spread to another part of the body). Breast cancer can be caused due to various factors, including genetic factors, molecular factors, unhealthy lifestyle, hormonal imbalance, environmental exposure, and metastasis in surrounding axillary lymph nodes, which is a major criterion for cancer's staging and prognosis.

Breast cancer is a highly diverse and fatal disease. Molecular technology has advanced the better understanding of its causative factors and genetic mutations that cause disease progression. A number of mutational genes have been spotted in breast cancer, including a hotspot mutational gene, P53, and other genes like HER2, PIK3CA, and ISO. All gene mutation profiles categorize breast cancer into broad phenotypes by comprehensive agreement by the World Health Organization as luminal subtypes (A and B), basal, and normal-like with respect to gene expression microarray that has discrete outcomes and unique treatment therapy. Breast cancer includes many phenotypes that differentiate how patients should be treated with respect to their genetic predisposition, hence the concept of personalized medicine may serve the better conversance of prescribed chemotherapy. Metastasis in breast cancer leads towards poor prognosis. Recurrence of breast cancer also results in severe poor prognosis. Chemotherapeutic drugs are based on genetic predisposition; however, the use of small molecule inhibitors is making progress in the advancement of breast cancer treatment, including Trastuzumab as an antibody preferred in the treatment of HER2+, Herceptin (and

more antibody). A cancer vaccine to fight against breast cancer, including Dendritic cell vaccine and Car-t cell therapy, is also in the pipeline.

Evolution of Immunotherapy in Cancer Treatment

In 1898, William Coley worked with a patient with an inoperable malignant tumor, as a result of infection with Streptococcus. In the next days, the patient turned well, leading to the complete disappearance of his sarcumamor. Thereafter, Coley attempted to treat other patients with the same approach he called bacterial vaccine therapy.

The celebrated case of a cervical cancer patient named Judy Perkins, who was completely free of this deadly disease after being treated with billions of her own immune cells in 2016, has rejuvenated the field of immunotherapy, the oldest in oncology. The aim of immunotherapy is to enhance or suppress the immune system's ability to recognize and destroy cancer cells, just as it does infections.

Today, cancer's relationship with the immune system remains central to the search for a cure for the 220 different diseases that make up the oncological stories. Multiple joint Nobel Prizes since the early 20th century and unprecedented immunotherapy awards from ASCO relive the tireless efforts of the pioneer cancer immunologists who first envisioned activating the patient's immune system, availing their own immune-win to treat the centrally-defining disease of cancer. In recent years, vast advancements in immunotherapy have been made, leading to incredible results for many tumors. So, how did medicine go from using its own immune system to destroy cancer cells, to effectively controlling and curing other, until then fatal, neoplastic diseases or at least controlling the progression and significantly improving the quality of life of patients with locally and/or disseminately advanced primary or recurrent cancers in numerous etiological contexts? For a more detailed explanation, it is imperative to consider different time pincer phases and time slots: then the 20th century until 1990, from 1990 to 2016, and the 21st century from now to 2021.

Concept of Personalized Medicine

Various difficulties arise when emphasizing the conventional approaches to cancer treatment, chemotherapy, and/or tyrosine kinase inhibitor (TKI's) utilized for treating cancer. Specific issues include low selectivity and drug efficacy, drug resistance, serious side effects, time taken in identifying the right drug, and off-target effects. To address the various issues, 'Personalized medicine' has arisen as a systematic and unique approach to tackle any kind of disease once detected. Personalized medicine (PM) has existed for decades, particularly with respect to tailoring lower-dose benztropine mesylate or carisoprodol meso 1, a drug for animals, but it has been more emphasized in developing personalized therapy to combat chronic diseases including cardiovascular diseases, mental illness, and cancer. The concept of personalized medicine (or precision medicine) evolved as elucidative knowledge of the disease at the molecular level began to increase. During treatment, personalized medicine is governed in tandem with genetic and genomic testing, understanding the underlying defect, or signaling pathway at the genetic, tumor, or protein level. In view of that, the clinician could consider the

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therapy plan by preventing, becoming sensitive to anticancer therapy, or accordingly deciding the dosage of the drug.

As breast cancer is the main cancer observed worldwide, various trials have sought a personalized therapeutic strategy to combat metastatic breast cancer (MBC) including hormone-sensitive ER+/PR+, HER2 positive, and TNBC subtypes. Additionally, the clinical application has raised various FDA-approved drugs for breast cancer treatment in contrast to conventional metastatic breast cancer therapies. This approval is governed based on the genetic constitution and inherited genetic susceptibility environment of patients. However, more investigations have indicated that transcriptomics, proteomics, epigenomics or a combination of these technologies are and are still beneficial for recognizing suitable treatments and more precisely predicting treatment efficacy in clinical cancer research.

Immune Checkpoint Inhibitors

Immune checkpoint inhibitors are some of the most successful cancer drugs to enter the clinic in the last decade, with their newfound success in treating a variety of aggressive, often untreatable cancers cementing them as a major player in the fight against this aggressive and dynamic disease. Immune checkpoint inhibitors are demonstrated to work by stimulating the immune system to attack cancer cells. Under normal conditions, T cells, a cell type involved in anti-tumor immune responses, are inhibited by proteins called immune checkpoints. Immune checkpoint inhibitors disable these proteins to enable the immune system to attack the cancer cells. Specifically, they block a suite of immune-inhibitory signaling molecules, including CTLA4, PD1, and PD-L1, in high-risk primary breast cancer and in metastatic disease.

Most recently, in the late-stage breast cancer setting, PD-1 immune checkpoint inhibitor, pembrolizumab, has demonstrated the highest efficacy of any immune checkpoint inhibitor in triple-negative breast cancer (cancer that doesn't have any or very low expression of the estrogen and progesterone hormone receptor or the HER2 protein). This is a clinically aggressive breast cancer where women are at high risk of their cancer spreading and for whom we did not have till now effective treatment with relatively moderate toxicity. There are also data showing the immunotherapy helps to treat cancer spread to the brain and that the benefit from immunotherapy continues for 12 months after stopping. However, response rates in clinical studies linking pembrolizumab with certain chemotherapies are around 9-23%. This indicates that while this approach has benefited many, it has also led to serious adverse events in others. Dacomitinib is an irreversible pan-human epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor that demonstrated superiority over gefitinib in terms of progression-free survival and overall survival in a large clinical unselected metastatic population and has similar efficacy in activating EGFR mutated breast cancer.

Mechanism of Action

Immune checkpoint inhibitors (ICIs) are important components of breast cancer immunotherapies. Tumor cells evade elimination by various mechanisms involving immune cells, inactivating negative immune checkpoint receptors expressed by T lymphocytes and

inducing the apoptosis of immune effector cells. When ICIs bind to their receptors, immune responses can be activated. At present, the most common ICIs are anti-cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) and anti-programmed cell death protein-1/programmed death-ligand 1 (PD-1/PD-L1). CTLA-4 has a co-stimulatory mechanism, which can be quickly mobilized to kill tumor cells, while PD-1/PD-L1 has a co-inhibitory mechanism of action that can inhibit the immune response between T lymphocytes and B lymphocytes.

ICIs exert their effect in distinct time frames. Anti-CTLA-4 and anti-PD-1 antibodies can promote a rapid cytotoxic effect on T and B cells and activate the immune system's "gas pedal". PD-1 is expressed earlier than CTLA-4 at the initial stage and anergizes naïve T cells encountering their specific antigen that is presented by a dendritic cell. During the priming phase of an immune response by antigens, molecules such as PD-1 are upregulated, and as the response matures, the induction of inhibitory surface molecules continues to increase, with the upregulation of CTLA-4 and PD-L1. These immune molecules are not only activated by the interaction of T and B cells with professional antigen-presenting cells (APCs); they are also involved in the interaction between T and non-professional APCs expressing Fc receptors (FcR) such as macrophages, mast cells, and eosinophils. The final result is the anergization of the already activated naïve T cells.

Clinical Efficacy in Breast Cancer

The most developed cancer type regarding FDA-approved immune checkpoint inhibitors is melanoma, followed by lung cancer, renal cell carcinoma, bladder cancer, and liver cancer. It took 8 years to achieve full-time FDA approval of ipilimumab, a CTLA-4 blocking drug, and pembrolizumab, an anticancer PD-1 drug for advanced melanoma. It took 12 years for full-time FDA approval of these drugs for non-small cell lung cancer. An immune checkpoint inhibitor developed for triple-negative breast cancer has not been FDA-approved for the front line even 8 years after the start of a clinical trial. Reality demonstrates that immunotherapy has just started in breast cancer. Whether the immune system can act as an anticancer defense mechanism was doubted until ipilimumab was approved for melanoma treatment.

Immune checkpoint inhibitors are in the position of real anticancer agents working well in the treatment of other cancer types in the biology of melanoma. Large-scale trials are in the process of blocking PD1, PD-L1, and CTLA-4, and combinations in the neoadjuvant, adjuvant, and metastatic settings in breast cancer to show clinical benefit and real-world activity. Recent evidence shows that, in advanced breast cancer, tesidolumab, an anti-PD-L1 antibody in combination with nab-paclitaxel, extensively significantly improved objective response rates (ORRs) (56.6% tesidolumab/nab-paclitaxel versus 45.6% placebo/nab-paclitaxel). Adverse events occurred at a greater frequency in cancers treated with immune checkpoint blockers. The natural antitumor defense mechanisms of the immune system are activated by immune checkpoint blockers. In clinical trials, nivolumab, pembrolizumab, atezolizumab, eribulin, and nab-paclitaxel were similarly combined with PD-L1+ and PD-L1- patients.

Biomarkers for Personalized Treatment

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Personalized medicine has been a buzzword for the last few years, but until now, the applications of this approach have been confined mainly to lung and melanoma cancers. However, in the breast cancer context, only germline mutations were long considered as the keys to directing treatment. Luckily, these grave discrepancies between advanced stages are now being addressed with updates in the field of immunotherapy, illustrating the importance of personalized medicine.

Immune cells work as a double-edged sword in cancer, which is counterintuitive as they attempt to both induce and eliminate diseases. A possible explanation for this duality is that not all immune cells present in the tumor microenvironment (TME) have antitumor activities. Therefore, determining the exact composition of immunostromal neo-etiologies can serve as an aid in tailoring immunotherapy-based courses. In the era of immunotherapy, a biomarker can be something that predicts an increased amount of good immunostromal factors in the TME such as CD8+ and CD45RO+ T cells. On the other hand, a biomarker could be something that suggests an inhibition of these good immunostromal factors. In the near future, we may shift towards the implementation of composite scores derived from both good and bad immunostromal variables to ascertain the ideal course of action. If one follows the good immunostromal biomarker course of action, immunotherapy will become more attainable and effective.

Types of Biomarkers

When and where to use a certain medicine, how a certain person will benefit from a medicine, and how not to pass on treatment hard for the person to bear are important statements of the need for personalized treatment that are mentioned frequently. Offering the most appropriate support to each individual both in the wake of being diagnosed and in the treatment path is aimed through individualized evaluations. In line with this information, the preferred treatment approach differs in parallel with the view that has been formed by examining other complementary elements while determining the type of treatment in breast cancer. The primary of these elements is the importance of distinguishing the cancer that has developed in the breast or armpit from many different types and designs.

Biomarkers indicate the biological features of healthy and/or abnormal cells and organs that they usually express after various physiological and/or biochemical stimuli. Ideally, biomarkers help to predict the movement of a disease or the patient's response to treatment, the optimal and/or most effective treatment, and the selection of a potentially effective drug, intervention, diagnostic test, follow-up schedule, and monitoring a patient's status and disease burden. They analyzed all possible biomarkers in order to get the maximum information with the least effort and cost of medicine in the early time period and followed an algorithmic treatment approach. The content of this article will examine these biomarkers distinguished by detailing in sub-groups. However, it is probable to determine a new sub-group on which a personalized approach is added with the ability to evaluate duplication and the 20Q deletion, both of which are an indication of B-cell clones in Hodgkin's lymphoma and were described in some patients.

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Role in Predicting Response to Immunotherapy

The development of drugs and their approval by the regulatory authorities is mainly based on the results of large randomized controlled trials (RCTs). However, findings from this study design may not always predict the performance of the drug in the 'real world' of clinical practice. In contrast, personalized medicine in this field, in the form of predicting the efficacy of a particular drug, has recently become an important issue. This is because, when an efficacious treatment for refractory disease is available, it is unethical not to use it, and to wait until large RCTs have fully proven its efficacy. So how can we predict that a particular therapy will work in an individual patient? What kind of differences between individual patients would allow us to predict the efficacy of a particular drug? To answer these questions, we need to establish the concept of biomarkers.

The Role of Biomarkers in Predicting the Response to Immunotherapy

The word "biomarker" is a portmanteau made of "biological" and "marker", referring to biological (biochemical) molecules that can be found in blood, other body fluids or tissue and are linked to the presence or the rate of a disease, or chemical substances that can be listed as an indicator of an important change in the environment or in a biological system. The molecular targets that may be addressed by immunotherapy interventions, including myeloid cells, T cells, tumor cells, and the extracellular components of the TME, can be identified by using a variety of methods, including multiple omics (e.g., genomics, epigenomics, transcriptomics, proteomics, metabolomics, and radiomics), as well as staining and molecular imaging. In a broad sense, all of these markers can be termed "biomarkers". Beyond this definition, "predictive biomarker" refers to a patient's characteristics that are measured before the onset of immune-checkpoint inhibitors (ICIs) that can be used to predict its clinical benefit. Although there is no "universal" predictive biomarker of ICI therapy available, different types of predictive biomarkers, both including "host-related" biomarkers and TME-related markers have been investigated, these have been shown in Table 3. Thus, the evaluation of these markers may be important in breast cancer to consider its response to ICIs.

Future Directions

Given the current level of knowledge in the field and the activity of numerous ongoing basic, translational, and clinical studies in breast cancer immunotherapy, it seems preferable to focus on the future. Potential areas of development include the involvement of the gut microbiota in the immune response. Metabolomics approaches might potentially guide treatment decisions if they reveal the activation of specific metabolic pathways that could be counteracted by specific ICIs. Further development in the field of vaccine therapy associated with checkpoint blockade, as well as the choosing of patients to be treated with a personalized vaccine approach, are additional interesting fields of research that can be worth further investigation in the near future. Also, the synergistic activity of ICI with targeted agents could be further dissected and tailored

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to single patients. Finally, an area with strong potential for development is represented by new immune targets also in breast cancer.

A number of trials are ongoing with various anti-PD-1 or anti-PD-L1 agents and combinations. They will add data to this field to affirm the new standard of care of using immunotherapy in the treatment of advanced metastatic triple-negative breast cancer. After the presentation of this article, several chemotherapy-blind studies have been extensively proposed during several international oncology meetings. It is important to evaluate the benefit of immunotherapy in the first-line setting, mainly in the PD-L1 positive patient population, in combination with drugs that are commonly used in this specific evaluation. A proper response evaluation criteria need to be determined considering the risks of hyperprogression. Through these ongoing studies, we will elucidate whether the possibility of using atezolizumab in combination with nab-paclitaxel or paclitaxel or gemcitabine/carboplatin is a safe and effective option for first-line treatment. Furthermore, the potential benefit of frontline use of atezolizumab in combination with hazardous chemotherapeutic drugs is under discussion in a current phase III study. Progress in the study of molecular biology and genetic biomarkers in recent years is particularly likely to help us identify patients most likely to benefit from immunotherapy. In general, the development of research and successful therapies in the field of immuno-oncology is attracting the attention of experts, and there are extensive and in-depth investigations and clinical studies on the use of the medication or combination of these drugs in several tumor specimens.

Combination Therapies

The concept of combination therapies exists at the intersection of targeted therapy, tumor microenvironment modulation, and immune regulation. Scientists and clinicians are progressively understanding that no biological compartment of a cancer cell exists in isolation, and therefore, combinational strategies targeting multiple features are likely to be more efficacious. However, resistance barriers are likely to present in complicated, sophisticated combination strategies. Despite these challenges, chemotherapies, endocrine therapies, and anti-growth factor-mediated therapies have long been used in combinations in breast cancer treatment regimens.

Conceptually, immune mediators of resistance and proliferative signaling are tumor cell-intrinsic resistances that can be targeted through immune modulating and targeted therapies, respectively. In addition, combinations with metabolic agents and signal transduction pathway inhibitors may prove promising. Above all, checkpoint blockade inhibitors are likely to lead to synergistic responses in combination with other immune modulating agents and not have overlapping toxicities, thereby improving therapeutic windows. Targeting resistance mechanisms to overcome prior resistance to immune therapies and make patients responsive may also lead to long-term trends in treatment paradigms especially if durable complete responses can be achieved.

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Emerging Technologies

Recent discoveries and new hypotheses regarding the complex processes governing the interactions between breast cancer cells and the host have led to new strategies that result in clinical benefit to patients. Other advances have been driven by emerging technologies, ranging from next-generation sequencing of the human genome to the high throughput screening of genetic material using gene arrays. Developing these breakthroughs into routine clinical applications will enable us to personalize care for tumor subtypes, including those that were previously thought to be untreatable, and to select the most appropriate therapy for each patient. The following sections review some of the most promising technical advances in these areas that are likely to form the basis of clinical practice in the years to come.

The Role of Tissue and Assay Development in the Transition of Breast Cancer Biomarkers

The transition of biomarkers from research settings to routine use can often be hindered by our choice of tissue for analysis and assay methodology. Invasive biopsies may not be justifiable in patient populations at low risk for the disease being tested for, and instead surrogate biomarkers must be identified to predict patient outcome and treatment response. For tissue-based biomarkers, the majority of work has focused on the development of assays to assess protein expression using immunohistochemistry and gene expression using in situ hybridization. However, the majority of gene expression studies validating the clinical relevance of the genomic assay in breast cancer have used paraffin-embedded blocks derived from surgical resection samples.

Conclusion

Immunotherapies will continue to advance in the upcoming years, and patients who previously had limited treatment options will greatly benefit from various combinations, resulting in improved response. These treatments can be used as first-line treatment or even in earlier phases. There are currently forty-two ongoing or upcoming clinical trials, among sixty-nine registered intervention studies, that are recruiting breast cancer patients. These trials will lead to significant improvements for patients who are resistant to currently approved immune checkpoint inhibitors.

Cancer has the ability to evade immune destruction, and accumulating evidence suggests that resistance to immunotherapy may be due to different mechanisms of immune escape by cancer cells. These mechanisms can be natural, such as a lack of mutation, or acquired, such as modulating the phenotype of cancer cells. Both types of mechanisms play a critical role in resistance to immune checkpoint inhibitors.

In conclusion, we have listed immune-mediated mechanisms of resistance to immunotherapy that are supported by pre-clinical and clinical evidence. These mechanisms have several implications and clinical utilities. These advances greatly improve the standing and vision for personalized breast cancer immunotherapy and open the door to the flourishing ability of

personalized medicine. They also provide new tools to clinicians to improve the management of breast cancer patients through multi-omics studies. These studies, along with the understanding of intra-tumor heterogeneity (ITH) of breast cancer, will allow for the design of efficient rational therapies. This idea aligns with the current trend of personalized medicine, which seeks to deliver therapeutics that are suited to the specific mutational landscape of every patient.

Competing interests

The authors declare no conflict of interest.

Ethics Statement

This study has been approved by the Ethical Review Committee of the Shanghai University of Sport (approval number: 312672411BN112). The publication of any potentially identifiable images or data contained in the article requires personal written informed consent. The research team will provide consultations for all subjects and their families to answer any research questions. Before signing the informed consent form, after the patients and their families fully understand the research process, our team members will organize the patients to sign the informed consent form or withdraw from the research. All subjects or their guardians will sign informed consent. Authors tend to submit research results to peer-reviewed journals or academic conferences for publication.

Authors' contributions

All authors shared in the conception and design and interpretation of data, drafting of the manuscript and critical revision of the case study for intellectual content and final approval of the version to be published. All authors read and approved the final manuscript.

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