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Exploring the development prospects of TNBC and HER2+ BC treatment based on targeted therapy

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Abstract. Breast cancer (BC) is one of the most common cancers in women, and the number of patients is increasing year by year. TNBC (triple-negative breast cancer) and HER2+ BC, as the two most common subtypes, deserve more in-depth research. At present, there are many targeted therapies and immunotherapies for these two subtypes, using inhibitors or cancer vaccines to treat breast cancer more efficiently, and some research has achieved phased results. However, there are still many research gaps, such as the safety and immune mechanism of the vaccine are unclear, and only a few number of epitopes trigger an immune response. In this paper, three targeted therapies for TNBC (PARA inhibitors, CDK inhibitors and PI3K/AKT/mTOR signaling pathway inhibitors) were analyzed. Two types of immunotherapy (ICIs and CAR-T therapy), And four cancer vaccines for HER2+ BC (Peptide-based cancer vaccines, Protein-based cancer vaccines,DNA Based Anti-HER2 Vaccines and Dendritic Cell Vaccines), and summarized their respective advantages and disadvantages to provide more theories and case references for future studies. There are still many unanswered questions about drug resistance, and future research can focus on the immune microenvironment and drug resistance

Keywords: TNBC, Her2+BC, targeted therapy, immunotherapy.

1. Introduction

BC is a very common cancer with a high incidence in both men and women, and female breast cancer has exceeded lung cancer as the world's highest mortality cancer [1]. Therefore, the research on breast cancer is still a very meaningful and hot topic. Clinically, breast cancer is divided into four main subtypes based on the expression of hormone receptors, such as progesterone receptor (PR), estrogen receptor (ER), human epidermal growth receptor 2 (HER2), namely luminal subtype that expresses ER luminal subtype that expresses PR HER2-positive subtypes that overexpress HER2, and triple-negative breast cancer (TNBC) [2]. With the continuous progress at medical level, there have been many treatments for breast cancer, such as chemotherapy, endocrine therapy and HER2-targeted therapy, but the side effects of common therapies often make patients painful, and the recurrence and metastasis of cancer is still a relatively uncontrollable factor, so immunotherapy for breast cancer has gradually entered people's field of vision [3].Compared with previous therapies, it has a higher safety factor, fewer side effects and more significant therapeutic effects. Immunotherapy for cancer can be broadly divided into three basic types, namely adoptive immunotherapy, passive immunotherapy and active immunotherapy [2]. Adoptive immunotherapy involves taking immunoreactive cells or their products from a person who is immune

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to breast cancer cell antigens and giving them to a breast cancer patient so that the patient's lymphocytes acquire the same immunity against the tumor [2]. Passive immunotherapy is to directly inject various immune effector cells, cytokines or antibodies (trastuzumab and pertuzumab) with anti-tumor effects into breast cancer patients to kill tumors or stimulate anti-tumor response in the body, but it still cannot deal with the difficult problem that patients have resistance [2].

Active immunity is to activate the immune function of breast cancer patients so that they can actively control and kill tumor cells, this treatment can effectively deal with the recurrence and metastasis of cancer and other problems, higher safety, mainly refers to cancer vaccines [2]. Cancer vaccines can be further divided into cellular vaccines, peptide vaccines and nucleic acid vaccines. Targeted therapy and immunotherapy for TNBC are currently one of the hot topics in research. Targeted therapy includes PARA inhibitors with the nutations in the BRCA1/2 gene, CDK inhibitors that can effectively prevent cancer cell increase sharply, PI3K/AKT/mTOR signaling pathway inhibitors against PIK3CA mutations, etc [4]. Immunotherapy mainly includes ICIs (including PD-1 and PD-L1 inhibitors), CAR-T therapy and tumor vaccine [4]. At the same time, HER2+ BC takes up 15-20% of newly diagnosed invasive BC and is a very meaningful direction to study [5]. Peptide-based cancer vaccines currently under development, such as E75, GP2, AE37, etc. Protein-based cancer vaccines, such as CHP-HER2, which enables patients to develop specific CD4+ and/or CD8+ T cell responses to against the truncated HER2 protein; DNA Based Anti-HER2 Vaccines as well as Dendritic Cell Vaccines [6].

However, the practical application of immunotherapy for breast cancer is not mature, and related studies need more application verification. This paper analyzes the latest progress in immunotherapy for breast cancer and the possibility of vaccine development to provide a feasible reference for further research.

2. Targeted therapy of TNBC

2.1. Introduction

For the past sixteen years, breast tumors have been categorized based on how ER, PR, and HER2 have expressed. In the middle of the 2000s, the term "triple-negative breast cancer" (TNBC) was first used. TNBC is a subtype of BC, which does not express the estrogen receptor (ER) or the progesterone receptor (PR), nor does it exhibit overexpression of the ERBB2 protein or amplification of the epidermal growth factor receptor 2 (ERBB2) gene [7,8].

2.2. PARP inhibitors

Malignant tumor cells are prone to BRCA gene mutation. BRCA1/2 gene mutations present in TNBC patients. As for homologous recombination repair of double-stranded DNA, BRCA1/2 plays an important role in it, and tumor cells with BRCA1/2 gene abnormalities have deficient DNA repair [4].PARP inhibitors work to reduce PARP activity and hinder DNA damage repair, resulting in an undue buildup of DNA damage and, finally, tumor cell death. PARP is an essential enzyme that repairs single-strand DNA damage [4]. PARP inhibitors in conjunction with immunotherapy have been studied deeper and have shown clearly better anticancer efficacy [9]. Niraparib with pembrolizumab led to a 47% (7/15) objective RR, an 80 percent (12/15) disease control rate, and an 8.3-month median PFS in patients with BRCA-mutated advanced or metastatic TNBC [9]. Despite the fact that PARP inhibitors are beneficial against TNBC, resistance in clinical trials cannot be disregarded; therefore, additional research into resistance mechanisms is necessary in order to create more effective and better treatment choices [4].

2.3. CDK inhibitors

A crucial enzyme called CDK controls changes in the cell cycle at every point, and prolonged activation of CDK promotes the growth of tumor cells [4]. Inhibitors of DK4/6 primarily block the G1-S phase, which in turn blocks the process of cellular DNA replication [4]. CDK4/6 inhibitors have strong sensitivity towards the LAR subtype [4]. As a result, treating the LAR subtype with CDK4/6 inhibitors may be an option [4]. The FDA has approved CDK4/6 inhibitors for the treatment of patients with TNBC

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[4]. In the PALOMA-2 study, palbociclib plus letrozole significantly increased PFS in ER+/HER2 breast cancer patients in the population of general and Asian [4]. As for patients with ER+/HER2 breast cancer, the PALOMA-3 study evaluated the effectiveness of palbociclib and fulvestrant combination therapy. Compared to controls, patients with palbociclib and fulvestrant had longer PFS and OS [4]. However, in ER+/HER2 breast cancer patients, the PALLAS study illustrated that palbociclib plus endocrine therapy did not increase PFS when compared to endocrine therapy alone [4]. Positive outcomes from a number of ongoing clinical trials involving CD4/6 inhibitors are anticipated in the near future.

2.4. PI3K/AKT/mTOR signaling pathway inhibitors

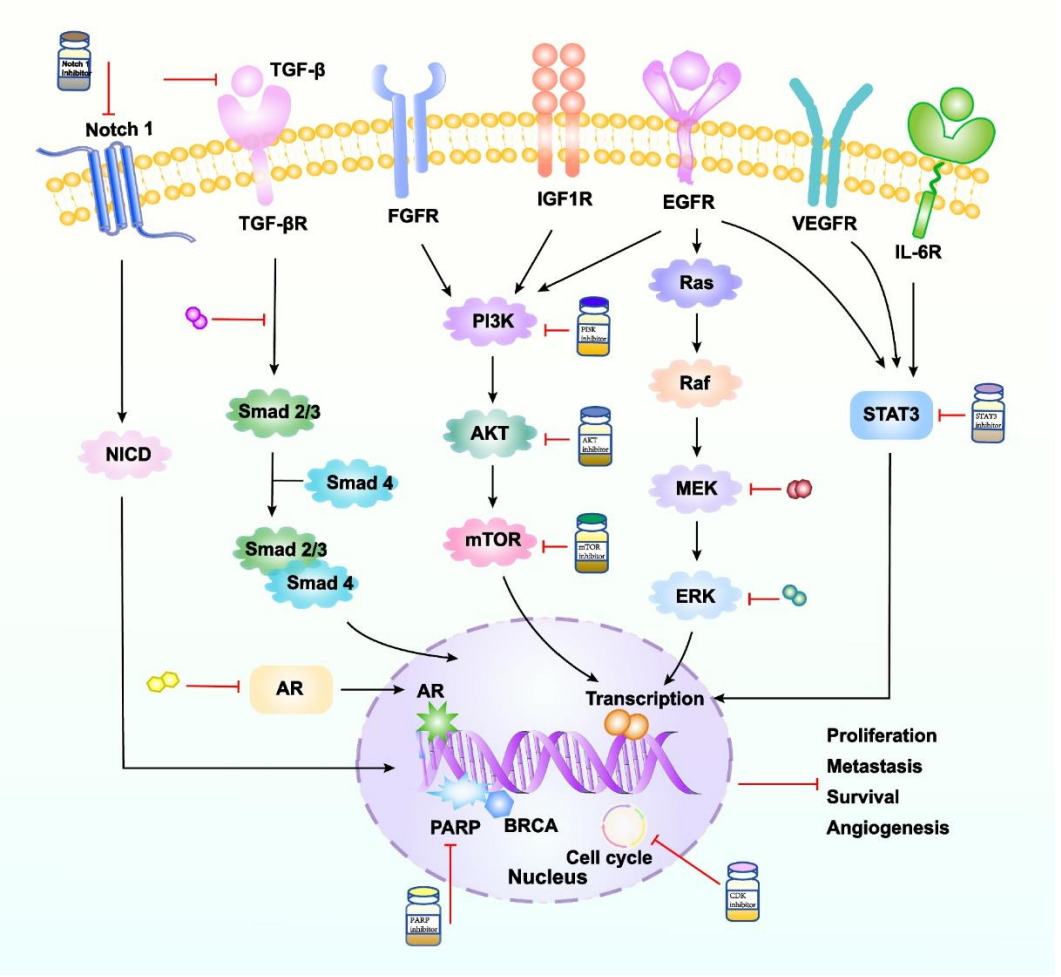

Figure 1. The signaling pathway and its inhibitors of TNBC [4].

The PI3K/AKT/mTOR signaling pathway is commonly active in carcinogenesis, cancer cell proliferation, survival, and anticancer therapy resistance [9]. Various genomic alterations activate PI3K pathways, such as PIK3CA and AKT, which operate as carcinogenic drivers to enhance tumor cell initiation, progression, apoptosis, and transformation [4]. Tumorigenesis is caused by PIK3CA mutations [4]. According to one study, PI3KCA mutations are detected in roughly 10% of TNBCs, suggesting that one intriguing treatment option for breast cancer may involve inhibiting the PI3K/AKT/mTOR signaling pathway [4]. Figure 1 depicts excitatory regulation with black arrows and inhibitory regulation with red arrows [4].The oncogenic signaling pathway PI3K/AKT/mTOR typically causes cancer and is linked to resistance to targeted anticancer therapy. More study on the efficacy of similar inhibitors is required [4].

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3. Immunotherapy of TNBC

CDK4/6 inhibitors has been agreed for use in treating TNBC patients by The FDA[4]. In the PALOMA-2 trial, PFS was significantly enhanced in ER+/HER2 BC patients in both the general and Asian populations when palbociclib plus letrozole was combined [4]. Palbociclib and fulvestrant combination therapy was assessed for efficacy in patients with ER+/HER2 BC in the PALOMA-3 trial. Patients receiving fulvestrant and palbociclib showed longer PFS and OS in comparison to controls [4].

3.1. ICIs

It has been reported that PD-1/PD-L1 is commonly overexpressed in BC, especially in TNBC [9]. In a research involving 53 instances of TNBC, PD-1 and PD-L1 amounts of expression were reported to be as high as 70% and 59%, respectively, with PD-L1 and PD-1 being expressed in 45 percent of the specimens [9]. PD-1 and PD-L1 are important ICB (Immune Checkpoint Blockade) molecules due to they allow cancer cells to more easily elude T-cell-mediated immune responses by integrating with PD-1 on T cells [9]. Consequently, reactivating TIL through inhibiting their association with monoclonal antibodies has beneficial therapeutic effects in several cancers [9]. These days, ICIs include PD-L1 and PD-1 inhibitors, which are widely used in clinical settings. Examples of these are pembrolizumab, atezolizumab, durvalumab, and nivolumab [4]. Inhibitor of PD-1 Pembrolizumab displayed antitumor efficacy and a tolerable safety profile in TNBC studies KEYNOTE-012 and KEYNOTE-086 [4]. When mTNBC patients were treated with pembrolizumab as opposed to chemotherapy, the KEYNOTE-119 trial revealed that OS (Overall Survival) did not improve. However, in the pembrolizumab study, medication efficacy rose with increased expression of PD-L1, indicating a potential link between high PD-L1 expression and pembrolizumab CBR (Clinical Benefit Rate) [4]. Combining chemotherapy with the KEYNOTE-173 study, I-SPY2 Phase II study, and KEYNOTE-522 Phase III trial greatly increased pCR (Pathological Complete Reaction) rates, prolonged event-free survival, and enhanced anti-tumor activity in patients with TNBC [4]. These studies verified the effectiveness of pembrolizumab as a neoadjuvant treatment for TNBC [4]. Pembrolizumab and nabutaxel together were shown to be effective in 59.3% of TNBC patients with pCR in the AGO-B-041 trial [4]. Pembrolizumab has been approved by the FDA for use as postoperative adjuvant therapy in patients with TNBC or as additional chemotherapy for patients with mTNBC with high PD-L1 expression or locally relapsed, unresectable tumors [4]. Additionally, medications targeting novel immunotherapeutic targets, such as TIM3, ICOS, and LAG3, are being developed [4].

3.2. CAR-T therapy

Chimeric antigen receptor (CAR) T cell treatment modifies a patient's peripheral T cells by genetic engineering, giving them the capacity to recognize and locate tumor cells [4]. The cells are transplanted into the quiet to completely destroy the tumor after formation and culture in vitro [4]. ROR1 and MUC1-focused CAR-T therapies are now considered viable restorative targets for TNBC [4]. Harrasser & Co. There is a CAR-T that targets ROR1, and it has demonstrated good antitumor activity in TNBC [4]. Clinical trials are being conducted [4]. BC can be treated using EGFRvIII-targeted natural killer (NK) CAR cells, and early research has shown that tissue-targeted CAR-NK cells administered as monotherapy in TNBC are effective [4].

4. HER2+ BC vaccines

4.1. Peptide-based cancer vaccines

Over the years, the significance of the immune microenvironment in influencing tumor treatment response has been widely researched, and vaccines have been a hot research direction for cancer immunotherapy [10]. Peptide-based antibodies have pulled in a parcel of consideration over the past decade for their potential utilize in battling cancer [6]. Peptide-based cancer antibodies offer a few conceivable preferences, counting ease of union, cost-effectiveness in comparison with other cancer-based antibodies, passable side impacts, and security [6]. E75, a 9-amino corrosive long peptide

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determined from the HER2 receptor, is anticipated to tie to HLA-A2, in this manner actuating CTLS [6]. E75 is the foremost considered cancer antibody [6]. Several Phase I ponders were conducted by infusing peptides into immunizations by blending them with diverse resistant adjuvants [6].The comes about appeared that the immunization was secure and seem actuate peptid-specific CTL [6]. GP2 is an immunogenic peptide, a part of the HER2 (654-662) transmembrane space, and a 9-amino corrosive long peptide (IISAVVGIL) antibody [6]. It ties to the HLA-A2 atom, but with less fondness than E75, and actuates CTL [6]. According to stage I clinical trials, GP2 with GM-CSF is well tolerated and safe for patients with node-negative breast cancer [6]. Immunohistochemistry (IHC) 1+–3+ patients with node-positive, high-risk hub HER2 communicating malignancies who were clinically disease-free participated in the Stage II clinical trial [6].The results showed that there was absolutely no appreciable variation in the rate of recurrence between the control group and the vaccination group [6]. Nonetheless, the experiment suggests that the vaccination is safe to administer [6]. A peptide called AE37, which has fifteen amino acids, stimulates CD4+ T helper cell (Th) lymphocytes [6]. In Phase I clinical studies comprising patients with diverse HER2-expressed breast cancers at all stages and with IHC of 1+ to 3+, the vaccine did not significantly impact the disease-free survival (DFS) rates of patients with high levels of HER2-expressing receptors in breast tissue [6]. Peptide-based cancer vaccines have numerous benefits, but they also have a number of drawbacks, such as immune responses occurring on only a few epitopes. At the same time, different adjuvants are needed to enhance the immune response, and the selection of adjuvants needs to be further studied.

4.2. Protein-based cancer vaccines

Whereas peptide-based immunizations have numerous preferences in fortifying the resistant framework, they endure from numerous impediments [3]. As specified over, most peptide immunizations are HLA confined are epitopes particular to HLA Course I, and may require Th adjuvant to advance the determination of CTLs reaction [3]. Entire protein immunizations incorporate HLA Lesson I and Course II epitopes, which are too not HLA limited [3]. Creature tests have appeared that immunization with protein antibodies can initiate an immune response [3]. Kitano et al.utilized CHP-HER2, a protein immunization comprising of a truncated HER2 protein (amino corrosive 1-146 of HER2) and cholesterylpullulan (CHP) [3].

In response to the shortened HER2 protein, patients who received the CHP-HER2 vaccine subcutaneously developed particular CD4+ and/or CD8+ T cell responses [3]. Nine patients received the vaccination alone in phase two of this clinical trial, after which they received an injection of the adjuvant OK-432 or GM-CSF [3]. The remaining 6 patients underwent CHP-HER2 with GM-SCF treatment as part of an initial immunization regimen [3]. 14 patients produced 146 distinct HER2-specific antibodies; patients who received CHP-HER2 along with GM-CSF during the first immunization cycle showed signs of an immune response considerably sooner [3]. It indicates that GM-CSF may aid in accelerating the immune response in people who receive the CHP-HER2 vaccination at the beginning of immunization [3].

4.3. DNA Based Anti-HER2 Vaccines

In DNA (hereditary) immunizations, the DNA encoding the tumor antigen is displayed by a plasmid infused into the have [3]. DNA-based immunizations can be utilized to fortify antigen-specific selection and non-specific natural insusceptibility [3]. Due to its straightforwardness, security, solidness, and cost-effectiveness, this procedure is considered one of the foremost down to earth approaches to cancer immunotherapy [3]. DNA immunizations have the potential to actuate an anti-tumor safe reaction in breast cancer patients [6]. Different types of TAAs are used to design DNA-based vaccines, and TAAs are typically expressed overexpressed by oncogenes or transmitted in malignancies [6].Two overexpressed tumor proteins found in breast cancer are HER2/neu and mammaglobin-A (Mam-A), which have been employed to strengthen DNA antibodies as target antigens [6]. In a pilot treatment experiment, Norell et al. administered a DNA antibody expressing a full-length version of HER2/neu with a flag insufficiency and high doses of GM-CSF and IL-2 to eight patients with advanced/metastatic

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BC [6]. HER2/neu immunization was associated with a robust humoral response, even though there was no discernible increase in T cell response [6]. Mam-A is a potential 93 amino acid corrosive secretoglobin protein that is a prime target antigen highly expressed in BC [6].In a Stage I clinical trial, Kim et al. injected 15 Mam-A+ patients with a DNA immunization containing Mam-A cDNA and watched for the development of a resistant response following inoculation [6]. Six months later, there was a decline in Foxp3C CD4C T cells and a rise in ICOSHiCD4+ T cells in the first seven patients chosen for the ponder [6]. It has been observed that activated ICOSHiCD4+ T cells specifically lyse MAMA-expressing breast cancer cells by producing IFN-γ instead of IL-10 [6]. This study demonstrates the viability of DNA antibodies in controlling BC.In any case, assist inquire about on the security and resistant instruments of DNA-based immunizations is required.

4.4. DC Vaccines

Dendritic cells (DC) are moreover known as "profession APCs" since of their work to control safe resistance and start anti-tumor impacts, and thus have a central part within the resistant framework [3]. By displaying the TAA to T lymphocytes via the MHC II and I pathways, DCs can trigger tumor-specific CTL responses in the context of microbial or viral contamination and cancer progression [3]. DC is essential for managing antibody-based reactions in expansion [3]. By stimulating the growth and maturation of CD4+ T cells, they can directly engage with B cells and support them, thereby enhancing specific humoral immunity [3]. All in all, DC may be the finest candidate for any helpful inoculation handle that produces a vigorous resistant reaction against cancer cells [3]. By fusing DCs with TNBC cells, Zhang et al. were able to deliver a complete antigen antibody against BC [6]. By promoting lymphocyte multiplication, the DC-TNBC crossovers have been shown to start anti-tumor susceptibility, and preclinical research on DC-based BC antibody is ongoing and has achieved some progress.

5. Conclusion

Targeted therapy and immunotherapy for the two most common types of breast cancer (TNBC and HER2+BC) are summarized and analyzed in this article.

At present, due to the lack of more effective therapies, chemotherapy is still the most important treatment method for TNBC patients, but with the continuous improvement of medical level and in-depth research on targeted therapy and immunotherapy, the treatment of TNBC will be more accurate. Inhibitors such as PARA inhibitors, CDK inhibitors and PI3K/AKT/mTOR signaling pathway inhibitors show promising prospects, and based on the characteristics of TNBC, patients with TNBC are anticipated to benefit from immunotherapy. TNBC immunizations as of now beneath advancement primarily incorporate dendritic cell antibodies, peptide antibodies and altered exosomal immunizations. GM-CSF could be a tumor immunization adjuvant in progressing clinical trials of BC immunotherapy. In expansion to the medicines specified over, there are combination treatments that can maximize the benefits of cancer immunotherapy, such as within the TNBC tumor demonstrate, when nilaparib was utilized with BioXCell RMP1-14, a synergistic tumor suppressive impact was found. For HER2+BC, the foremost utilized immunotherapy could be a cancer immunization, and dynamic immunotherapy has a few points of interest over inactive immunotherapy or chemotherapy and can be utilized as a combination of other modes. In inoculation, the acceptance of an resistant reaction is tumor-specific and as a rule well endured.The foremost imperative perspective of dynamic immunotherapy and anti-cancer inoculation is to supply solid resistance to tumor antigens, subsequently avoiding tumor repeat. The HER2 signaling network is a promising therapeutic target for HER2-positive cancers. Immunizations against cancer moreover have much to move forward, taking peptide-based antibodies as an illustration, due to the destitute immunogenicity of single peptide immunizations in actuating an fitting safe reaction, particularly in actuating cell-mediated resistance, significant consideration has been paid to enhancing the anti-tumor movement of peptide antibodies by consolidating distinctive adjuvants and conveyance vectors.

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