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Clinical application status and development of TNBC (BC) monoclonal antibody

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Abstract. A particular subtype of breast cancer known as triple-negative breast cancer (TNBC) is distinguished by the lack of ER, PR, and HER2 expression, culminating in HER2-targeted therapy with a poor prognosis and inadequate conventional hormone therapy. With the growing comprehension of the biological traits of TNBC in recent years, treatment strategies have gradually developed, particularly the use of mAb medications, which has renewed optimism for the treatment of TNBC. Because of its high specificity and targeting, mAb drugs have shown remarkable efficacy and potential in cancer treatment. An extensive examination of the clinical usage of mAb medications in the treatment of TNBC is given in this review. summarizing clinical trial data on key drugs such as PD-1/PD-L1 and TROP-2-targeted drugs, demonstrating the significant effect of these drugs in prolonging PFS and OS in patients. At the same time, new therapeutic targets besides PD-1 and TROP-2 are discussed, as well as the potential advantages of combination therapy strategies. The clinical application of mAb medications in TNBC is thoroughly examined in this study., summarizing clinical trial data on key drugs such as PD-1/PD-L1 and TROP-2-targeted drugs, demonstrating the significant effect of these drugs in prolonging PFS and OS in patients. At the same time, new therapeutic targets besides PD-1 and TROP-2 are discussed, as well as the potential advantages of combination therapy strategies.

Keywords: TNBC; Monoclonal antibody; Clinical application; TROP-2; PD-1; CTLA-4.

1. Introduction

TNBC is a subtype of breast cancer defined by HER2, switching ER, and negative expression of the P [1]. Twelve percent of all cases of breast cancer identified in the US between 2012 and 2016 were TNBC, and its 5-year survival rate is eight to sixteen percent lower than that of hormone receptor-positive breast cancer [2]. Currently, immunotherapy, radiation, chemotherapy, and surgery are the major treatments for TNBC. However, unlike other forms of breast cancer, follow-up treatment is more complicated since there are no particular molecular targets, making it difficult to select chemotherapeutic drugs and construct treatment regimens [3]. With the extensive investigation of the biochemical traits associated with TNBC in recent years, treatment strategies for the disease are gradually developing, such as drugs targeting TNBC stem cell characteristics, drugs targeting tumor microenvironment, especially the application of monoclonal antibody (mAb) drugs, which brings new hope for the treatment of TNBC. Some mAb drugs targeting TNBC have entered the clinical trial stage, like PD-L1-targeting immune checkpoint inhibitors [4].

mAb drugs show remarkable efficacy and potential in the field of cancer therapy because of their high specificity and targeting. In the treatment of TNBC, mAbs primarily function by either influencing immune responses inside the tumor microenvironment or by targeting specific receptors on the surface of tumor cells to discover critical signaling pathways that inhibit tumor growth and metastasis. With the advent of more and more mAb drugs and positive results in clinical application, they have gradually become the core force in the field of TNBC treatment. These mAb drugs not only increase the treatment options of patients but also greatly enhance patients' quality of life, providing a new direction and hope for the comprehensive treatment of TNBC [4].

This review's main goal is to do a thorough analysis of TNBC mAb's use in clinical settings., and to prospectively predict its future development trend. To understand in detail the mechanism of how

these drugs inhibit tumor growth, metastasis and recurrence by acting on specific targets of tumor cells. In addition, the authors will evaluate their efficacy and demonstrated safety during treatment.

This review will also explore the main challenges facing current TNBC treatments, such as drug resistance, side effect management, and use in combination with other treatments. At the same time, the future research direction is summarized, encompassing the creation of novel medications, the enhancement of current medications, and the creation of customized treatment plans.

2. TNBC

2.1. Definition of TNBC

TNBC describes a subset of BCS that expresses neither HER2, PR, or ER. As a result, these tumors are resistant to hormone therapy (tamoxifen, aromatase inhibitors), as well as targeted medicines that specifically target HER2. (such as trastuzumab). For this kind of BC, conventional hormone therapy and HER2-targeted therapy are unsuccessful since these receptors are absent., and patients usually choose chemotherapy and surgery at the time of treatment. With more aggressive clinical behaviors, including faster tumor growth and higher recurrence rates, and poorer treatment status later, Particularly in the initial years following diagnosis, there is a higher chance of a distant recurrence and mortality [5].

2.2. TNBC's Molecular Properties

The following features mostly display TNBC's molecular properties. ER, PR, and HER2 are not expressed by TNBC, to start. Hormone treatments that target these receptors are therapeutically unable to be utilized for TNBC due to this feature. Second, The gene expression profile of TNBC exhibited significant variability, resulting in many molecular subtypes. mesenchymal (M), mesenchymal stem cell-like (MSL), Immunomodulatory (IM), BL1, BL2, also intracellular androgen receptor (LAR) are six types of TNBC according to Lehmann et al., each with its own unique gene expression characteristics and potential therapeutic targets [6].

In addition, TNBC usually has a high gene mutation rate and copy number variation, and common gene mutations include TP53, BRCA1/2 and PTEN. Studies show that changes in these genes may cause dysregulation of the pathways responsible for DNA repair, apoptosis, and cell cycle regulation, which would encourage the growth of tumors [7]. Lastly, activation of the RAS/MAPK, Wnt/β-catenin, and PI3K/AKT/mTOR pathways are typical signaling anomalies in TNBC. Tumor growth, survival, and invasiveness are all strongly correlated with abnormal activation of these pathways [7].

2.3. Pathogenesis of TNBC

The pathogenesis of TNBC is complex and diverse, involving many aspects such as heredity, epigenetic inheritance, abnormal cell signaling pathway, tumor microenvironment and immune system interaction. First, a notable feature of TNBC is the high degree of genomic instability, resulting in a large number of gene copy number variations and a high mutation burden. Research has revealed that more than 80% of TNBC cases contain TP53 mutations [8].

Phosphatidylinositol 3-kinase (PI3K) pathway activation is a frequently seen signaling system aberration in TNBC. This activation is typically caused by mutations or amplification of genes, including PIK3CA, PIK3R1, and AKT1 [9]. Furthermore, the biological activity and responsiveness to treatment of TNBC are significantly influenced by its tumor microenvironment. It has been demonstrated that in patients with TNBC, tumor-infiltrating lymphocytes (TILs) enhance prognosis and response to neoadjuvant therapy [10].

Lastly, homologous recombinant DNA repair deficiency (HRD) is present in around 25% of TNBC cases and is frequently linked to somatic or germline mutations in the BRCA1/2 gene. HRD enhances genomic instability, causes a deficiency in the DNA double-strand break repair pathway, and encourages the growth of malignancies [11].

3. Target (Mechanism of action)

3.1. Basic Concepts of Monoclonal Drugs

To make monoclonal antibodies, a single B cell clone is utilized, a class of extremely selective antibodies that are able to identify and bind to a particular epitope. These antibodies' exceptional purity and specificity make them useful for a variety of biological studies and medicinal treatments [12].
The kinds and uses of mAbs are growing as a result of the advancements in antibody engineering technology and the generation of all-human antibodies. About 30 therapeutic mAbs were on the market in the US and Europe as of 2012; the US alone accounted for $18.5 billion in sales of these drugs [12].

Recently, there has been progress in the study of monoclonal antibodies, particularly in relation to breast cancer treatment. According to the EMILIA test, T-DM1 significantly greater overall and progression-free survival in HER2-positive metastatic breast cancer patients as compared to lapatinib with capecitabine [13]. The progression-free survival and overall survival of the tucatinib mAb group were considerably higher than those of the placebo group in a different HER2CLIMB test [14].

3.2. PD-1

The immunological checkpoint protein known as programmed death receptor 1, or PD-1, is mostly expressed on myeloid, activated T, B, and natural killer (NK) cells.
A sequence of intracellular signaling events is initiated when PD-1 binds to either PD-L1 or PD-L2. Although PD-L1 is extensively expressed on many different kinds of cells, PD-L2 expression is more limited and predominantly found on particular APCs and tumor cells. The PD-1 signaling pathway's main goal is to stop T cells from activating and serving as effectors [15].

TNBC is primarily treated with chemotherapy and PD-1/PD-L1 inhibitors, according to recent PD-1 correlations. The KEYNOTE-522 study was a critical clinical trial that assessed the benefits of continuing Pbolizumab monotherapy-adjuvant therapy following surgery, as well as the effects of PD-1 inhibitor paired with chemotherapy as neoadjuvant therapy. Study data showed that when coupled with chemotherapy, pabolizumab significantly compared to chemotherapy alone, enhanced patients' event-free survival (EFS) and pathological complete response (pCR) [16].

3.3. TROP-2

Trop-2 combines with IGF-1 to inhibit the signaling of the IGF-1R. The PI3K/AKT and MAPK pathways become less active as result of this mechanism, which stops tumor cells from growing and surviving. In breast cancer, especially TNBC, elevated Trop-2 expression is strongly associated with an unfavorable prognosis and an aggressive tumor.

Trop-2's involvement in cell adhesion and cell cycle progression increases tumor growth, and its coordinated expression with AKT affects the treatment response. Thus, in therapeutic trials, antibo-drug couplings (ADCs) targeting Trop-2, including sacituzumab Govitecan (SG), have demonstrated notable anticancer efficacy [17].

According to the ASCENT research results, the goxtuzumab treatment group (a monoclonal antibody that targets the Trop-2 site) had a median progression-free survival (PFS) of 5.6 months, while the chemotherapy group's was just 1.7 months. Additionally, the goxtuzumab group had an objective response rate (ORR) of 35% while the chemotherapy group had an ORR of 5%. These results support the effectiveness of TROP-2 in the treatment of TNBC [17].

3.4. CTLA-4

By attaching to its ligands, the immunological checkpoint molecule CTLA-4, often referred to as Cytotoxic T lymphocyte-associated Antigen 4, prevents T cell activation hence aiding cancers in evading immune system attack.CD80 and CD86. CTLA-4 inhibitors are thought to be viable

treatment options for TNBC since the expression of CTLA-4 may be connected to the tumor's immune escape [18].
Corning & Jerry's presented the findings of their most recent Phase I/II clinical study, which combined PD-L1/CTLA-4 double anti-KN046 with albumin-binding paclitaxel, to treat patients with advanced triple negative breast cancer, at the 45th Annual SAN Antonio Breast Cancer Symposium (SABCS). According to this trial, patients with advanced TNBC had positive responses to the KN046 combination therapy, with an ORR of 44% and a disease control rate (DCR) of 96%.

4. Summary Application status of MAB drugs

According to the above inference, It is clear that monoclonal antibodies are crucial to the management of TNBC, particularly when it comes to immunotherapy and targeted therapy. Nowadays, the mainstays of TNBC therapy include antibodies that target certain tumor antigens and PD-1/PD-L1. For example, pabolizumab and Attillizumab have shown therapeutic benefits in patients with TNBC in certain clinical trials [19].

Goxstuzumab, an antibody drug combination (ADC) that targets Trop-2, was just granted approval. Individuals with locally advanced or metastatic triple negative breast cancer who have received at least two prior systemic therapies but are not responsive.Goxstuzumab has proven to be more effective than existing therapeutic alternatives. Furthermore, tirellizumab, a PD-1 inhibitor, exhibits promise in the management of TNBC, particularly in the Chinese market where self-developed medications are sold [20]. In this session, the clinical application data will be analyzed using the drugs terrellimab and goxaltobizumab as examples.

4.1. Clinical Data Analysis of Terrellimab

A PD-1 mAb is called triplimab. By preventing PD-1 from interacting with PD-L1,It activates immunological responses against tumors mediated by T cells. Treatment with triplelizumab has demonstrated potential for certain malignancies, such as small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC).

When EGFR/ALK mutations were absent in NSCLC individuals,the CHOICE-01 study assessed the safety and effectiveness of triplelizumab in conjunction with chemotherapy. The trial's findings indicated that triplelizumab combined with chemotherapy was superior to placebo combination chemotherapy. chemotherapy significantly improved OS, with an HR of 0.69, and PFS, with a median PFS of 8.4 months against 5.6 months [21].
Moreover, the EXTENTORCH trial assessed the effectiveness of triplelizumab with chemotherapy as a first treatment for advanced stage ES-SCLC. This multicenter, randomized, double-blind, placebo-controlled Phase III study was conducted. Giving triplelizumab in addition to chemotherapy significantly improved PFS and OS, according to the study's data. Compared to 5.6 months and a median HR of 0.667, The median OS was 14.6 months, with a median HR of 0.798 and a median PFS of 5.8 months, respectively [22].

4.2. Clinical Data Analysis of Goxaltobzumab

Goxstuzumab is an ADC that targets Trop-2 and works by delivering the cytotoxic drug SN-38 directly to TROP-2-expressing cancer cells. Goxatuzumab has been approved specifically for TNBC and has demonstrated therapeutic potential in a number of solid cancers.

Exhibited at ESMO 2023, the TROPiCS-03 study's findings revealed goxtuzumab exhibited anticancer activity in solid tumors, including mUC, SCLC, and NSCLC. Goxstuzumab's ORR in second-line treatment of ES-SCLC was 37%, its CBR was 40%, and its DOR was 6.3 months. When used to treat recurrent/refractory head and neck squamous cell carcinoma, goxtuzumab had a median progression-free survival of 4.1 months; its ORR and CBR were 16% and 28%, respectively [17].

Safety analysis of goxaltuzumab demonstrated that all patients experienced unfavorable incidents at any level during treatment, The most frequent side effects across all grades were neutropenia and

diarrhea. Among these the incidence of grade 3 and above TEAEs was 60% in the ES-SCLC cohort, and no adverse events resulting in the trial treatment being stopped were documented. No deaths due to adverse reactions have been reported.

5. Future Outlook

5.1. Current Challenges

Despite advances in the treatment of TNBC with mAbs, several challenges remain:

Selecting the biomarkers is the first step. While not a perfect predictor, the level of PD-L1 expression is a significant biomarker for predicting the effectiveness of PD-1/PD-L1 inhibitors. Only a tiny percentage of PD-L1-negative individuals may benefit from treatment, and not all PD-L1-positive patients may respond to it.

Second is the treatment response rate, the ORR of MAB drugs is usually not very high, meaning that many patients may not experience significant tumor shrinkage after treatment.

Also important is the development of drug resistance,because tumor resistance might eventually emerge in patients who initially react to mAb therapy, thus restricting its long-term efficacy.

Finally, there is the issue of financial burden, as Mabs are often expensive, which limits their widespread use, especially in resource-limited areas.

5.2. New Target

In addition to PD-1 and Trop-2, researchers are also exploring other new therapeutic targets for TNBC treatment. One new target is protein phosphatase 1 regulatory subunit 14B (PPP1R14B). Research conducted by Professor Zhimin Shao and Daqiang Li at Fudan University Affiliated Cancer Hospital indicates that PPP1R14B contributes significantly to the development of TNBC and paclitaxel resistance, pointing to PPP1R14B as a potential therapeutic target for TNBC. Studies have revealed that aberrant expression of PPP1R14B in TNBC can predict poor patient survival and promote TNBC progression and drug resistance by regulating microtubule instability and cell cycle division process [23]. Furthermore, research indicates suggests a potential treatment target for TNBC could be ROR1 [24].

5.3. Exploration of Combined Treatment Strategies

The combination treatment strategy has shown potential advantages in the treatment of TNBC, which can improve the therapeutic effect and overcome the limitations of single treatment.

The first is the most traditional palizumab plus chemotherapy regimen. A sizable phase 3 clinical trial called KEYNOTE-522 aims to assess palizumab used as a neoadjuvant therapy with chemotherapy for early TNBC. Some study's findings demonstrated that adding palizumab to neoadjuvant therapy considerably increased the pCR rate when it compared to chemotherapy and continued use of palizumab in subsequent adjuvant therapy significantly improved EFS [25].

And then there's the possibility that the newer triplizumab combined with chemotherapy will be tried. In metastatic or recurring triple-negative breast cancer, the Phase III TORCHLIGHT research compares the effects of triplizumab or placebo with NAB-paclitaxel. It is randomized, double-blind, and controlled. Based on the study, the combination treatment with triplizumab significantly increased PFS in the subgroup that is positive for PD-L1. The people in ITT also exhibited a similar pattern [20].

At last, medication delivery and nanosystems can be combined for targeted therapy. A new tumor-targeted nanodrug delivery system has been created by researchers from the First Affiliated Hospital of Nanjing Medical University houses the Oncology Department. They have also released a study investigating the synergistic effect of enzalutamine in TNBC.

This study confirmed the synergistic anti-tumor effects of the two drugs through a combined screening method and provided a potential treatment for TNBC [26].

6. Conclusion

Through an in-depth analysis of the clinical application of mAb in TNBC and its future development trends, this review reveals the great potential of this treatment strategy in improving patient outcomes and quality of life. The definition, molecular characteristics and pathogenesis of TNBC were reviewed, and the importance of mAb in cancer therapy was emphasized due to its high specificity and targeting. By analyzing clinical trial data on key mAb drugs such with TROP-2-targeted medications and PD-1/PD-L1 inhibitors, we summarized the significant effects of these drugs in prolonging PFS and OS in patients.

This review's objective is not limited to offering new treatment options for TNBC patients, but also to provide a valuable reference for future research. We highlight the potential value of mAb drugs in personalized treatment strategies and their advantages in overcoming the limitations of traditional treatment approaches. However, it can be realized that there are some limitations in this study. For example, although mAb drugs have shown good efficacy and safety, not all patients benefit from them, and long-term efficacy and drug resistance issues still need further research. In addition, drug cost and accessibility issues are also important factors limiting the widespread use of mAb drugs.

As the technology continues to evolve, researchers will continue to explore new mAb drug targets, or improve the delivery system of existing drugs, and develop more precise personalized treatment regimens. Simultaneously, investigating methods to lower the cost and increase the accessibility of medications helps support the mAb medications' resistance and long-term efficacy.

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