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A comprehensive evaluation of monoclonal antibody therapy for triple-negative breast cancer (TNBC)

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Abstract. TNBC is one of the subtypes of BC, Its cancer cells do not contain estrogen receptors or progesterone receptors, it does not contain HER2 receptors, or have a low content, which makes its therapeutic means limited and has a poor prognosis and is prone to tumor recurrence. Recently, Monoclonal antibody therapy, as one of the main forms of targeted therapy, has gradually gained attention and application in the treatment of TNBC. However, despite being a primary form of targeted therapy, monoclonal antibody treatment has only recently garnered attention and application in TNBC treatment. One significant challenge is the high incidence of side effects and associated symptoms, for which there is currently no effective solution. This article provides a comprehensive summary of the key landmark substances that are present in the pathological changes of TNBC, with particular emphasis on those substances that can impact prognosis. The review covers the mechanism, clinical effects, side effects, and combination therapy involving TNBC mAbs. At the conclusion of the article, new findings regarding TNBC research are presented, along with new opportunities for precision medicine for TNBC patients. This study concludes that monoclonal antibody therapy holds promise in the treatment of TNBC; however, further research is necessary to optimize treatment regimens and improve patient survival rates. This article's goal is to be a reference for future research on the side effects of TNBC, with a focus on improving patient prognosis and therapeutic outcomes.

Keywords: Triple-negative breast cancer, monoclonal antibody therapy, HER2.

1. Introduction

Due to the advancements in medicine and the enhancement of basic literacy, more and more individuals are beginning to pay attention to their own health concerns. The more harmful form of disease is cancer, which is why breast cancer (BC) is the most frequent cancer among women globally and accounts for one out of every ten new cases diagnosed annually in both developed and developing nations [1]. Additionally, it is the leading cause of cancer-related deaths among women worldwide [1]. Therefore, it is very important to study BC. BC is not a single disease, but rather is composed of distinct subtypes associated with different clinical outcomes [2]. Nowadays, BC can be divided into five categories, Luminal-A, Luminal-B(HER2 negative, HER2 positive), HER2 overexpression, TNBC. Endocrinotherapy and anti-HER2 targeted therapy are effective in treating Luminal-A, Luminal-B, and HER2 overexpression. But due to TNBC lacks a therapeutic target, the methods mentioned above are inappropriate for TNBC patients. Now Chemotherapy and adjuvant chemotherapy are major treatments,

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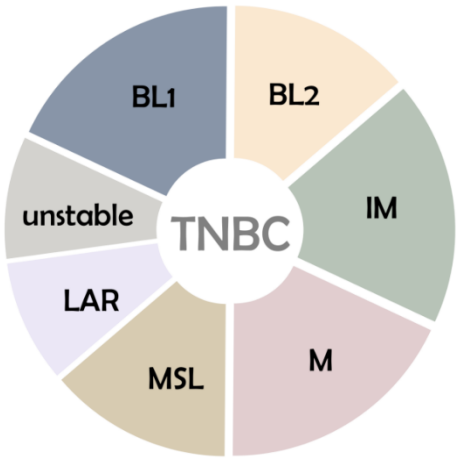
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however, these therapies are not very good for TNBC. Another important thing is that TNBC patients account for 12-17% of BC patients, and the prognosis is extremely poor, and they are prone to tumor recurrence [3]. So, finding effective treatments for TNBC has become one of the hotspots in oncology research. Recently, with the development of targeted therapy and immunotherapy, researchers are increasingly recognizing the potential value of monoclonal antibodies (mAbs) in TNBC. mAbs can directly inhibit tumor growth by specifically binding to antigens on the face of neoplasm cells and enhance anti-cancer influences by activating the body's immune system. This treatment not only can improve efficacy but also improve the quality of life of patients. However, Monoclonal antibody therapy against TNBC is in the exploratory phase, and there are some problems, such as identification of biomarkers, evaluation of efficacy, management of toxic side effects.

This paper will combine and analyze literature on monoclonal antibody therapy for TNBC, overview the research progress of TNBC monoclonal antibody therapy, key clinical trial results, and future research directions provide reference for further clinical practice and research.

2. Pathogenesis

Numerous examinations have confirmed that the numerous of these cancers are high-level infiltrative ductal carcinomas of no specific kind, known as IDCC-NSTs [4]. Extensive analyses of TNBCs have however demonstrated that certain distinct histologic types of BC, including metaplastic BCs, sarcomas with myeloid characteristics, and sarcomas with holocrine characteristics, are phenotypically predominantly triple-negative [4]. The methodical research of BCs with a triple-negative morphological type has shown that there is a subgroup of slow-growing tumors that often show slothful clinical conduct [4]. In the realm of breast pathology, these inferior variants of TNBC, though incredibly rare in the breast, are known as salivary gland-like breast cancers because they have analogues in the parotid glands. The focus of this section is on the features and pathogeny of each subdivision. Lehmann et al. have conducted additional research on TNBC heterogeneity [4]. Based on transcriptomic studies, they identified six subtypes in this group, including basal-like 1 (BL1), basal-like 2 (BL2), immunomodulatory (IM), and others, as shown in Figure 1.



Types	Characteristics	Cell lines
BL1	Cellular proliferation, cell cycle, DNA repair	HCC2157, MDA-MB-468, HCC38, HCC1937
BL2	Growth factor, myoepithelial markers	HCC1806, SUM149PT, CAL851
IM	Immune mediated signaling	HCC1187, DU4475
M	EMT and differentiation	BT549, CAL51, CAL-120
MSL	MET, angiogenesis, differentiation and stemness	MDA-MB-157, MDA-MB-436, MDA-MB-231, SUM159
LAR	Hormone signaling, luminal gene up-regulation	MDA-MB-453, SUM185, CAL148, MFM223

Figure 1. Association of different TNBC isoforms [5].

After discovering that the MSL and IM subtypes were derived from tumor-associated stromal cells and tumor-infiltrating lymphocytes (TILs), the four tumor-specific types that the research team ultimately narrowed down to were BL1, BL2, M, and LAR [4]. These four TNBC types have individual aspect models, and the immune-modulatory permeates vary within each subtype. It has been demonstrated that the BL1 type has an enhancement of genes linked to the cell cycle, cell division, and DNA damage response (DDR) pathways [4]. The distinct genetic profiles of the BL2 subtype included growth factor signaling, glycolysis and gluconeogenesis, and the expression of myoepithelial markers.

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Gene expression associated to cell motility is more prevalent in the M subtype [4]. Despite being ER negative, the LAR type was identified by androgenic hormone sensory organ sign, and its gene ontologies showed a substantial enrichment in pathways influenced by hormones, including porphyrin metabolism, androgen-estrogen metabolism as well as steroid synthesis [4]. Additionally, Burstein et al. identified four unique TNBC subtypes: BLIS, BLIA, MES, LAR. These results support the hypothesis that, at the transcriptome level, four strong subtypes of TNBC can be distinguished [4].

2.1. BRCA 1/2

Human tumor inhibitor genes BRCA1 and BRCA2, which are located on the long arms of chromosomes 17 and 13, separately, are known to be susceptible to BC induction when they are altered. Despite having different structures, BRCA1 and BRCA2 are connected and major players in the DNA fix course [6]. Recombinase regulation is directly impacted by BRCA2's binding to a single strand of DNA, while RAD51 localizes to DNA double-strand breaking and necessitates the development of the BRCA1–PALB2–BRCA2 complex. As a result, BRCA1/BRCA2 codes a protein that guards against mutant genes and preserves the stability of the human genome. It's crucial to reorganize [7, 8]. A crucial role for BRCA1/BRCA2 is played in the repair of DNA double-strand breaks. Part of the damage to DNA is repaired by BRCA1/BRCA2. Any possibly mutated cells will be eliminated through apoptosis, which is caused by inhibiting DNA repair. Tumor growth is accelerated when BRCA1/BRCA2 is mutated because DNA repair is not possible after that point [9].

2.2. ALDH1A1

When it comes to cancer, ALDH1A1 is thought to be a marker of BC stem cells. These cells are highly carcinogenic and capable of self-renewal, and they are crucial to tumorigenesis, progression, and outcome [10]. Tan et al. revealed that ALDH1A1 is abundantly convey within the BC tissues, however this is not linked with prognostic. 25% of cancers express ALDH1, and young patients have an almost 14-fold higher ALDH1-positive rate than do older patients.Although ALDH1A1 is thought to be a separate ER-negative element, this is not linked to the death and recurrence of BC [11]. Research implies that the presence of ALDH1A1 indicates a dismal outcome for BC [10,12]. Studies carried out in Japan have shown that 26% of sufferers with infiltrative ductal carcinoma exhibit ALDH1. Factors linked to its expression include bigger tumors, greater histological levels, later TNM stage, HER2 overexpression, and hormonal receptor negative status. Both the overall survival and recurrence-free survival times were shortened in the ALDH1A1 expression group compared to the non-expression group [13]. Moreover, ALDH1A1 expression is associated with a higher incidence of lymph node metastases, suggesting that ALDH1A1 is a tag of inferior tumour prognosis and progression [10].

3. Monoclonal antibody therapy

3.1. Atezolizumab in TNBC

3.1.1. Mechanism

Atezolizumab optionally goals PD-L1 to prevent interaction with acceptors PD-1 and B7-1, a costimulatory cell face protein, thereby reversing T cell inhibition and improving the body's immune answer to attack tumor cells.

3.1.2. Clinical and combination therapy

Emens et al. performed a phase I trial on 116 patients with advanced neoplasms who had received extensive pretreatment to evaluate the security and clinical curative effect of atezolizumab as a single-agent treatment [14]. While Adams et al. did not use atezolizumab as a single agent therapy, Emens and colleagues' trial did. Conduct an additional Ib experimental phase [15]. By exposing the immune system to increased amounts of TAA, combination therapy with checkpoint inhibitors and chemotherapy is expected to stimulate tumor-specific T-cell immunity. The study's main outcomes were the percentage

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of patients experiencing adverse events (AEs) and the utmost standed dose of atezolizumab, which measure safety and tolerability. The purpose of enrolling thirty-three patients was to assess tolerability and safety. Twenty-four sufferers (73%) had grade 3/4 AEs. There were no treatment-related fatalities. The clinical activity of the combined medication was the study's secondary aim. The ORR for the entire cohort was 39.4%. OS and PFS were found to be 14.7 and 5.5 months, respectively, on median. The study's findings show that atezolizumab plus nab-paclitaxel combination therapy is a effectual cure for sufferers with metastatic TNBC that has a manageable safety profile. [16]

3.1.3. Side effects

Atezolizumab monotherapy was observed to produce adverse events (AEs) in 63% of sufferers in the phase 1 trial. Grade 3 or 4 negative impacts were stated by 11% of the participants. Two percent of the cases had anemia; the other eight instances had arthralgia, myalgia, hyponatremia, neutropenia, fatigue, nausea, vomiting, diarrhea et al.

Notably, pulmonary hypertension claimed the lives of one patient, while an unrelated condition claimed the life of another. 10% of patients had dose interruption as a result of treatment-related adverse events (AEs), which accounted for just 3% of patients' therapy terminations. Most adverse events (aes) happened within one year of the start of therapy; just one AE, grade 3 or greater flat planus, occurred surpass that time [17].

3.2. Sacituzumab govitecan in TNBC

3.2.1. Mechanism of Treatment

Sacituzumab govitecan is an antibody–drug combination that is formed by attaching SN-38, the energetic metabolite of irinotecan, and topoisomerase I inhibitor to an antitrophoblast cell-surface antigen 2 (Trop-2) IgG1 kappa antibody using a proprietary hydrolysable link editor. Transmembrane calcium signal transducer Trop-2 is highly conveyed in a range of tumor types and is over 90% expressed in BC.The anti-Trop-2 mAb ties to Trop-2 conveyed on the face of treated tumor cells, enabling targeted delivery of SN-38 to tumor cells.12,16Free SN-38, because of its membrane permeability, can cause the "bystander effect"—an anticancer impact in neighboring tumor cells—either before the antibody-drug combination internalizes by linker hydrolysis or after internalization through intracellular release of SN-38 [18].

3.2.2. Clinical effects

Satumizumab has shown promising anti-tumor action in several clinical tests. For example, in the pivotal clinical trial ASCENT, The drug has shown important PFS and overall survival OS prolongation in patients with metastatic TNBC who have obtained previous chemotherapy. Compared to conventional chemotherapy, satuxizumab was able to provide better efficacy and tolerability, and also achieved significant results in terms of objective response rate (ORR).

3.2.3. Side effects

Although Satumizumab has very good efficacy, there are some side effects associated with treatment. Common side effects include neutropenia, which is the most ordinary side effect and can lead to a enhanced hazard of infection. Diarrhea: Due to the effects of SN-38 on the intestinal mucosa, diarrhea is another common side effect that can lead to dehydration and electrolyte imbalances. There are also some other side effects, such as atony、nausea and emesis.

3.2.4. Joint use

Compared to standard-of-care chemotherapy, sacituzumab, a first-in-class Trop-2–directed antibody–drug conjugate, shown a major advance in advancement-free and general subsistence [19]. Sacituzumab was associated with a higher frequency of toxic effects than chemotherapy, specifically myelosuppression and diarrhea. Sacituzumab is being studied in a number of BC patient trials. These

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include evaluating the medication in the beginning stages of TNBC as adjuvant and neoadjuvant therapy in the changing setting in combination with immunotherapy-based methods, in the later stages of TNBC, in conjunction of a PARP inhibitor, and for hormonal receptor-positive and HER2-negative metastasis BC. [20]

4. Future

4.1. New targets MARCO-TST

In recent years, because transcriptional variations in TNBC are yet unknown, some researchers have methodically examined RNA splicing. The macrophage receptor versus collagen structure-tumor-specific transcript (MARCO-TST), which is exclusively conveyed in TNBC cancerous cells and triggers the anoxia path, was found to be an oncogenic transcript. Additionally, they demonstrated how BRD4-bound superenhancer drives MARCO-TST transcription. BET inhibitors cause transcriptional activity and MARCO-TST function to be persistently inhibited. Their research offers a possible TNBC therapy plan to block MARCO-TST activity. Researchers identified a splicing variation of macrophage receptor with MARCO-TST that is specific to tumors, as opposed to the wild-type MARCO that is specific to myeloid cells. MARCO-TST expression may accelerate tumor increase in vivo and in vitro and has been linked to unfavorable outcomes in TNBC patients. MARCO-TST enhanced HIF-1α permanence by mechanically cooperating with PLOD2, which leaded to metabolic disequilibrium of TNBC and the development of a anoxic tumor microhabitat. A de novo substituted transcription beginning site that was superenhancer-activated served as the starting point for MARCO-TST. Increased knowledge of extraterminal protein inhibitors and bromodomain inhibitors was observed in tumors that expressed MARCO-TST. Organoids made by patients were used to further demonstrate this treatment approach. [21] This remarkable discovery is intrinsically connected to another exceptional achievement. To evaluate the potential for RNA stitching in TNBC, they gathered RNA-seq information from 360 TNBC sufferers in the TNBC (FUSCCTNBC) cohort of Shanghai Cancer Center at Fudan University [21].

4.2. TNBC tumor-specific transcripts profile

Upon discovering that there are numerous "tumor-specific transcripts" in the cells of TNBC, the teams led by Professors Shao Zhimin and Jiang Yizhou from Fudan University Cancer Hospital and Professor Huang Shenglin's group were able to create the first "tumor-specific transcript" map of TNBC nationwide. The findings of the study were published in the prestigious, worldwide Proceedings of the National Academy of Sciences journal. The once "incurable" TNBC has almost tripled in efficacy under the guidance of the "Fudan classification" precision therapy approach.

5. Conclusion

First of all, through a brief introduction to the pathogenesis of TNBC, as well as its classification and changes in the pathogenesis of special landmark substances, understanding the peculiarities of TNBC and the degree of difficulty in treating it. Although the TNBC mAb therapy mentioned in the next step has reached different degrees of link to the symptoms of patients, it is not difficult to see from the article that there is an important problem in these therapies: a variety of side effects, and these side effects have a high incidence, so it will be a pressing problem to be solved. In the last part, the future of TNBC, the emergence of the new target MARCO-TST and the "tumor-specific transcript" map of TNBC, which has made great contributions to the development of BC in recent years, may be the answer to solve this problem. This medical conundrum will surely be overcome, and a good treatment for TNBC will be available to the public. This article contains several sections that lack sufficient detail and comprehensiveness. For instance, the discussion on pathogenesis overlooks additional significant marker substances and the current monoclonal antibody therapies for TNBC extend beyond the two mentioned herein. Furthermore, the section addressing future directions is deficient in content regarding precision treatment strategies for TNBC. Nonetheless, This paper remains optimistic that this article will inspire readers regarding monoclonal antibody therapies for TNBC. Furthermore, the ongoing research

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into TNBC will yield additional treatment options, ultimately enhancing patient outcomes and improving the therapeutic efficacy for individuals diagnosed with this condition.

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