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The Toxicity Balance of Bispecific Antibodies in the Treatment of Breast Cancer

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Abstract. Breast cancer is a malignant tumor originating from uncontrolled proliferation of breast epithelial cells. The treatment of breast cancer such as chemotherapy, endocrine therapy, targeted therapy and immunotherapy has been improved recently, but the breast cancer is still the main cause of cancer-related mortality. Fortunately, the appearance of bispecific antibodies (BsAbs) has enhanced the treatment because it has two separate binding sites which could bridge the T cells and the surface of tumor targets. However, the toxicity of BsAbs have negative impacts on its clinical application since it increased inflammation triggering brain or nerves.This article illustrates mechanisms of how BsAbs treat breast cancer through it bridging mechanism and signal activation. Moreover, covering the source of toxicity that BsAbs against breast cancer, the method that help to reduce the toxicity, such as Fc-region engineering. Furthermore, the article discussed the improvement in outcome after modifying BsAbs's structure, hoping to provide a better reference basis for future diagnosis and treatment.

Keywords: Bispecific Antibodies, Breast Cancer, Treatment, Toxicity

1. Introduction

According to the World Health Organization (WHO), breast cancer is the most common cancer among women in the world. There is about 99% of breast cancer happening in women, reported by WHO 2026 [1]. And breast cancer is not a single disease. It encompasses multiple molecular subtypes. Including luminal A, liminal B, human epidermal growth factor receptor 2 (HER2)-enriched and triple negative, and each subtypes has different treatments. Although the combination use of surgery, chemotherapy, endocrine therapy and anti-HER2 treatment has significantly improved patients' outcomes, a proportion of patients still experience tumor recurrence and metastasis, due to traditional treatments have some limitations. For instance, while surgery serves as the primary option to resect solid tumors, it cannot guarantee the complete elimination of all cancer cells. Moreover, when patients who have obesity, heart disease and pulmonary disease will increase the risk of surgery. Similarly, the main challenging of chemotherapy, endocrine therapy and anti-HER2 treatment is drug resistance and toxicity resulting from lack of specificity [2].

The development of BsAbs is a next generation therapy with tremendous potential in the immunotherapy of breast cancer. BsAbs are manmade genetically engineered molecules capable of binding of two different targets simultaneously [3]. The structure of this antibody was about to

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enhance the synergistic effect of the therapy. Also, it is safer and more efficient alternative compared to the monoclonal antibodies (mAbs). Furthermore, the dual-targeting mechanism that BsAbs has is designed to enhance tumor specificity and promote immune mediated cytotoxicity, thereby overcoming the limitations of traditional mAbs. This article aims to systematically review the main mechanism of action of BsAbs in breast cancer, the representative clinical research progress, and the management of adverse reactions. It also analyzes the key obstacles that hinder its clinical application, with the expectation of providing references for further research and clinical practice in this field.

2. Mechanism of bispecific antibodies treatment

In breast cancer treatment, BsAbs work through several key mechanisms that help immune system fight tumor cells more effectively.

Firstly, BsAbs act as a "bridge" between immune cells and cancer cells. Each BsAb molecule has two arms: one arm attaches to a protein on the tumor cells such as HER2, Trop-2 or EGFR. And another arm connects to the immune cells. Typically, it is cluster of differentiation 3 (CD3) on T cells or cluster of differentiation 16 (CD16) on natural killer (NK) cells. This structure can physically connect the T cells or NK cells to breast cancer cells, which could stimulate the immune system to recognize and kill the tumor. Secondly, the bridging will lead to a formation of cytolytic immunological synapse. This connection could stimulate the activation, proliferation of T cells and release perforin and granzymes. Those of substances can penetrate and decompose the cell membrane of the cancer cells which could let the breast cancer cells die. In the research, experimental data has showed that effective membrane penetration and subsequent lysis often require a specific ratio. Scientists have used effectors-to-target (E:T) ratio to analysis the result. The data shows that E:T ratio 10:1 to observe significant cytolytic activity in breast cancer cell lines like BT-20 [4]. Thirdly, BsAbs could overcome the restriction of major histocompatibility complex (MHC) especially in bispecific T-cell engagers (BiTEs) style. During this style, antibodies can directly pass through CD3 and trigger T cells to attack cancer cells. Normally, T cells need to recognize the cancer cells through MHC, but many tumors evade detection by downregulating MHC8.-I expression. Finally, BsAbs are especially useful for specific breast cancer subtypes. For instance, zanidatamab (ZW25) can combine with the two different spots on HER2 protein. This dual binding is stronger than the traditional antibodies and at the same time it can work in HER2 low position or in patients who have developed resistance to standard therapies. During the clinical and empirical study, zenocutuzumab (MCLA-128), a BsAb targeting HER2 and HER3. Demonstrating a 45% disease control rate with favorable safety profile with enrolling patients with ER-positive, non-amplified HER2-low metastatic breast cancer in the research (Dillon et al., 2022). Furthermore, for the triple-negative breast cancer (TNBC). PD-1 x VEGF or TGF-β x PD-L1 has a high effect rate which could overcome the drug resistance of the single targeted drug [5].

In a nutshell, BsAbs can force the immune cells to discover and kill the cancer cells. Simultaneously, overcoming the escape of tumor cells.

3. The representative clinical research progress of BsAbs in breast cancer

An open-label, multicenter, single-arm phase II clinical study published in Nature Medicine in 2026 systematically evaluated the safety and anti-tumor efficacy of the PD-1/VEGF bispecific antibody ivonescimab combined with taxane-based chemotherapy drugs as a first-line treatment regimen in female patients with locally advanced, unresectable or metastatic triple-negative breast cancer who

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had not received previous systemic treatment. Among 36 patients, the objective response rate (ORR) was 80.0%, and the median progression-free survival (PFS) was 15.2 months. The results of subgroup analysis revealed that patients benefited from this combined treatment regimen regardless of the level of PD-L1 expression. The objective response rate of the patient group with a PD-L1 combined positive score of ≥10 was 83.3%, and the median progression-free survival was 15.9 months; while the objective response rate of the patient group with a PD-L1 combined positive score <10 was also 79.3%, and the median progression-free survival was 13.0 months. These study results provided new treatment hope for the patient population with low or negative PD-L1 expression in triple-negative breast cancer [6]. In the Ib/II phase study reported at the 2024 ESMO conference, PM8002 combined with albumin paclitaxel was used as the first-line treatment for triple-negative breast cancer (TNBC), with an overall response rate (ORR) of 73.8%, a disease control rate (DCR) of 95.2%, and a median progression-free survival (PFS) of 13.3 months. Subgroup analysis showed that patients with PD-L1 CPS < 1 still achieved an ORR of 76.9%, further confirming the potential of this strategy in immunologically "cold" tumors [7].

The Ib/II phase study published in 2025 evaluated the efficacy of its combination with docetaxel as the first-line treatment for HER2-positive metastatic breast cancer. The study design was unique, aiming to explore the therapeutic potential for patients who had failed previous (new) adjuvant anti-HER2 treatment. The results showed that the confirmed objective response rate was 90.9%, the disease control rate was 97.0%, the median duration of response was 23.5 months, the median progression-free survival was 22.1 months, and the median overall survival was 36.9 months. In terms of safety, all patients experienced adverse events during treatment, with 71.1% being grade 3 or above. The most common ones were neutropenia, anemia, and diarrhea. The overall safety was controllable. The study suggested that this combined regimen has significant efficacy and tolerable safety for the first-line treatment of HER2-positive breast cancer [8].

4. Toxicity balance of bispecific antibodies in breast cancer treatment

While BsAbs are powerful to fight with the breast cancer, they carry notable adverse effects, with toxicity being a major limitation restricting their broad clinical application.

On-target/off-tumor toxicity represents another critical barrier for breast cancer BsAb therapy. After intravenous administration, CD3-recruiting BsAbs may engage T cells if their target TAA is also expressed on healthy mammary or epithelial tissues. The antibody forms a physical bridge between T cells and non-malignant host cells, triggering T cells to release cytotoxic perforin and granzymes and resulting in unintended damage to normal tissues [9]. This risk is especially relevant for breast cancer-associated antigens such as HER2, which are present at low levels in healthy breast epithelium. Multiple clinical trials of breast cancer-targeted BsAbs have reported such toxicities. For example, ertumaxomab (HER2 × CD3) and KN026 (dual HER2-targeting) have induced respiratory distress, acute renal failure, heart failure, fever, diarrhea and elevated transaminase levels in patients [7].

Furthermore, reason is cytokine-release syndrome (CRS). CRS always classifies as on-target toxicity or on-tumor toxicity. When CD3-based T-cell engagers such as BiTEs bind simultaneously to a tumor associated antigen (TAA) on breast tumor cells and the CDε chain T cells, an artificial cytotoxic immunological synapse formed [4]. This combination can bypass the restriction of MHC and activates the T cell receptor (TCR) signaling pathway, including massive T cell activation, proliferation, and cytokine secretion independent of MHC presentation [10]. Once activated, T cells secrete abundant effector molecules and pro-inflammatory responses. In breast cancer patients, this widespread inflammation can extend to the central nervous system, impairing neural function.

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Accumulated inflammation may cause memory impairment, delayed responses and confusion, symptoms define as immune effector cell-associates neurotoxicity syndrome (ICANS).

To mitigate these safety liabilities in breast cancer therapy, researchers apply fragment crystallizable (Fc) engineering to modify the antibody Fc domain, refining pharmacological profiles, safety and manufacturability. Promoting heavy chain heterodimerization is one core strategy. The knobs-into-holes (KiH) technology introduces a bulky amino acid mutation in one CH3 domain to create a "knob", and smaller amino acid substitutions in the paired CH3 domain to form a complementary "hole" [4]. This complementary structural design drives correct pairing of two distinct heavy chains. For asymmetric breast cancer BsAbs, mutation sets including Y349C, T366S, L368A, Y407V paired with S354C, T366W are commonly adopted to achieve accurate heterodimer assembly [9]. Salt bridges and charge interactions are further incorporated to stabilize heterodimer formation. Beyond chain pairing, Fc engineering can tune binding affinity between the Fc region and immune cell Fc gamma receptors (FcγRs), enabling either enhancement or attenuation of downstream immune effector functions. For breast cancer BsAbs, Fc-silencing mutations such as L234F, L235E and N297G are frequently introduced to reduce FcγR engagement, minimizing off-target immune activation and lowering the risk of severe CRS and ICANS without disrupting the core T-cell redirection function.

5. Future development

BsAbs are a new and exciting way to treat breast cancer. They help the immune system find and attack cancer cells. However, they still have problems. Some patients get serious side effects, and not every patient responds to the treatment. So, scientists still have a lot of work to do.

One big goal is to make BsAbs safer. Right now, these drugs can cause side effects like fever and inflammation. Scientists are working on new designs that only activate inside the tumor. This means the drug attacks cancer cells but leaves healthy cells alone. That would cause much fewer side effects. Another goal is to combine BsAbs with other treatments. For example, doctors can use BsAbs together with chemotherapy or immunotherapy. This combination might work better and help patients who stopped responding to older drugs. Ivonescimab (an anti-PD-1/anti-VEGF bispecific antibody) combined with taxane chemotherapy is used as the first-line treatment for locally advanced, unresectable or metastatic TNBC. As of July 2025, the median follow-up of the Phase II study (N=36) was 22.1 months. The overall population achieved an ORR of 80.0%, DCR of 100%, and mPFS of 15.2 months. Among the population with PD-L1 CPS < 10 (accounting for 83.3%), the ORR was 79.3%, mPFS was 13.0 months, and the 12-month PFS rate was 54.3%. The Phase III study of this regimen (HARMONi-BC1) is currently underway [8]. Scientists also want to find biomarkers. A biomarker is a sign in the blood or tissue that tells doctors how a patient will respond. With biomarkers, doctors could choose the right treatment for the right patient. This is called personalized medicine. Finally, scientists hope to make BsAbs easier to take. Most current drugs are given through a needle in the hospital. In the future, some might be given as a simple injection under the skin. This would be more convenient for patients.

6. Conclusion

Bispecific antibodies bring promising new hope for breast cancer treatment. Unlike traditional therapies, BsAbs use their special dual-binding structure to connect immune cells and tumor cells. They help the immune system recognize and kill breast cancer cells, even overcoming some tumor escape tricks such as MHC downregulation. Different BsAbs have shown encouraging results for

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several breast cancer subtypes, including HER2-low and triple-negative breast cancer. However, safety problems limit their wide use. Toxic reactions like CRS and ICANS, as well as damage to healthy tissues, remain important risks. Fc engineering, such as the knobs-into-holes technique and Fc-silencing mutations, offers useful ways to balance treatment power and safety. These changes help lower unwanted side effects while keeping the anti-tumor ability of BsAbs. In the future, improved antibody design, combination therapy and personalized treatment will make BsAbs safer and more effective. Although more research and clinical trials are still needed, bispecific antibodies will likely become a valuable tool to fight breast cancer and help more patients.

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