Proceedings of ICEGEE 2026 Symposuim: AI-Based Medicine and Biological Data Analysis
DOI: 10.54254/2753-8818/2026.AU33735

Trastuzumab for HER2-Positive Breast Cancer: From Clinical Trials to Real-World Practice

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Abstract. HER2-positive breast cancer is a highly aggressive subtype associated with high recurrence risk and poor prognosis. Trastuzumab is the standard targeted treatment and has achieved significant efficacy in clinical trials. However, its effectiveness in the real world remains inconsistent and is often affected by age, comorbidities, and treatment adherence. This study aimed to compare efficacy outcomes between clinical trials and real-world settings and to explore potential influencing factors. The results of this paper show that real-world efficacy was significantly poorer than that in controlled trials. Older age, multiple comorbidities, treatment interruption, and low adherence were the main causes. Elderly patients received less standardized treatment and had higher rates of discontinuation. The efficacy gap was not caused by the drug itself but by heterogeneity in patient characteristics and clinical practice. Individualized management and optimized treatment strategies are urgently needed to improve compliance and real-world outcomes. This study provides a reliable evidence basis for the clinical application of trastuzumab in HER2-positive breast cancer patients.

Keywords: HER2-positive breast cancer, trastuzumab, real-world evidence, clinical trials, treatment adherence.

1. Introduction

Approximately 99% of breast cancers occur in women, while men account for 0.5% to 1%. HER2 is a protein located on the surface of cancer cells and can promote the rapid proliferation of cancer cells. In recent years, the development of targeted therapy has brought new hope to patients with HER2-positive breast cancer.

Trastuzumab is a humanized monoclonal antibody targeting the HER2 protein. It can recognize and bind to the HER2 protein, block the growth signals of cancer cells, and help the immune system attack cancer cells at the same time. However, clinical trials have strict inclusion and exclusion criteria, and the enrolled patients are relatively homogeneous, which cannot fully reflect the real clinical population. Real-world patients include the elderly, those with comorbidities, and patients visiting hospitals at different levels. Therefore, real-world research can more accurately reflect the actual effects of drugs under different conditions. Multiple real-world studies have shown that the efficacy of trastuzumab in daily practice does not always reach the level of clinical trials. Study found based on the National Electronic Health Records Database in the United States that the real-

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world efficacy of patients with HER2-positive metastatic breast cancer was significantly worse than the clinical trial results [1]. The reasons for the differences are multifaceted: real-world patients are older, have poorer physical conditions, more comorbidities, and poorer treatment compliance. However, some studies offer positive perspectives. The global epidemiological modeling shows that HER2-targeted therapy has reduced the number of patients with distant recurrence of breast cancer worldwide by approximately 26% [2]. A real-world study on SONABRE reported that 26% of patients with HER2-positive metastatic breast cancer achieved complete remission after first-line pertuzumab and trastuzumab chemotherapy [3]. This indicates that the drug itself is effective. The problem lies in the different groups of patients who take the medicine.

The main purpose of this paper is to systematically analyze the key factors that lead to the gap in efficacy between clinical trials of trastuzumab and the real world. The structure of this article is as follows: The second part provides a detailed introduction to the design and key results of the HERA clinical trial; The third part presents real-world research data and compares them with clinical trials. The fourth part discusses the main factors influencing real-world efficacy (treatment interruption, insufficient treatment for elderly patients, economic factors, and concerns about cardiotoxicity). The fifth part summarizes the full text and puts forward suggestions.

2. Breast cancer and HER2

Breast can is the most common cancer detected among women, and with the progression of the disease, it causes a huge threat to women's health. About 99% of breast cancer happened in women, 0.5-1% of cancer happens among men [4]. HER2 is a protein that presents on the surface of cancer cells and promotes their rapid growth. According to the recent study, HER2 positive breast cancer accounts for approximately 15%-25% of all types of breast cancer [5]. In recent years, the development of target therapy has brought new hope to the patients diagnosed with the HER2 positive cancer. Trastuzumab is a kind of medicine that targets to the HER2 protein, it can recognize and combine with this protein and prevent the growth signals of cancer. It can also help the immune system attack cancer cells. Trastuzumab has a structure similar to that of human antibodies and is artificially synthesized through biotechnology, thus being classified as a humanized monoclonal antibody (hMab). However, clinical trials adopt strict inclusion and exclusion criteria, which means the enrolled patients are relatively homogeneous and do not fully reflect the actual clinical population. In real-world practice, patient cases are more complex (e.g., older age, more complications, and poorer treatment compliance), leading to potential differences between trial results and real-world effectiveness. The main purpose of this article is to identify the factors that influence the real-world efficacy of trastuzumab treatment.

3. Trastuzumab and the HERA clinical trial

This study draws on data from the HERA clinical trial. Launched in 2005, the HERA trial was a large-scale study that enrolled hundreds of women from different countries. The trial divided the participants into three groups to observe cancer recurrence: one group was treated with trastuzumab for one year, another for two years, and the third received no trastuzumab treatment as the control group. Trastuzumab was administered at an initial dose of 8mg/kg, followed by a maintenance dose of 6mg/kg every three weeks. The study found that two years of trastuzumab provided no additional benefit over one year, but slightly increased cardiotoxicity. Therefore, the study mainly reported data from the one-year group. The results showed that the recurrence rate of patients treated with trastuzumab was reduced by approximately 46% compared with the control group. This finding is

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supported by a hazard ratio (HR) of 0.54 (95% confidence interval [0.43, 0.67], p<0.0001), which means the reduction was not due to chance [6]. Two years later, the researchers calculated that the recurrence rate of those who received trastuzumab had decreased by more than 8 percentage points compared with the control group. The incidence of severe heart failure caused by cancer therapy-related cardiovascular toxicity was approximately 0.54% in the trastuzumab group, compared with 0% in the observation group, and symptomatic heart failure was 1.7%. The percentage of patients with a left ventricular ejection fraction decrease of about 10% but less than 50% was 7.1% versus 2.1% in the observation group. Other adverse events were slightly higher in the treatment group. The experiment proved that trastuzumab has a significant effect on treating HER2-positive breast cancer, and this effect was observed under ideal conditions that excluded patients with an LVEF lower than 55%, meaning the selected patients had no severe heart disease and strictly followed the treatment plan. It shows the best possible outcome of the treatment, but in the real world, patients' conditions cannot always be so ideal.

4. Real-world evidence and the difference between clinical trial and real world

Unlike clinical trials such as HERA, which are designed under controlled conditions, real-world evidence (RWE) is derived from routine clinical practice, including medical insurance databases, patient registration studies, and electronic medical records. Unlike clinical trials with strict inclusion and exclusion criteria, real-world research does not impose strict restrictions on patients, thus reflecting the actual treatment status of a more diverse patient population [1]. Real-world research does not have strict inclusion or exclusion criteria. It shows the real treatment situation of the patients. This patient group includes elderly people, patients with complications, and people visiting different levels of hospitals. Therefore, a real-world study can show how a treatment performs under different conditions. In some cases, data from real-world patients may differ significantly from that of clinical trials, with real-world therapeutic efficacy data being significantly worse than that observed in clinical trials. The reasons for this are diverse and depend on the actual age of the patients, their physical condition, and the fact that elderly patients are more likely to have complications. The administration of treatment to real-world patients is also not as strict as that to clinical trial patients. However, one study offers a more positive perspective. In a retrospective predictive analysis covering global populations, researchers divided patients into two groups: one group received 100% chemotherapy, and the other group consisted of women diagnosed with HER2-positive early breast cancer (HER2-eBC). This study was a retrospective predictive analysis covering global populations, and the sample size included 11.9 million patients diagnosed with breast cancer, of whom 7.5 million received HER2-targeted therapy, ensuring the reliability of the data [2]. The number of recurrent patients in the 100% chemotherapy group was 2.9 million, while that in the HER2-targeted therapy group was only 2.1 million, 26% of the patients achieved complete remission (CR) [3]. This shows that HER2-targeted therapy can indeed improve treatment efficacy and effectively avoid cancer recurrence. Overall, real-world trials and clinical trials differ in many aspects. The problem is not that the drug is ineffective, but rather the differences in the patient population. Patients in the real world are more complex and harder to manage, which is the main reason for the differences in treatment efficacy.

5. Factors affecting real-world therapy efficiency

If the treatment itself is not problematic, what exactly are the factors that cause the real-world efficacy to differ significantly from that of clinical trials? A real-world study based on the Japanese

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healthcare database found that a 6-month trastuzumab treatment course can reduce the incidence of CTR-CVT, but the prognostic outcome is not optimal [7]. However, if treatment is stopped prematurely—for example, when CTR-CVT occurs and significantly affects patients' health—cancer progression may occur due to incomplete treatment, even if the progression is not directly caused by CTR-CVT. A study from Brazil also pointed out that treatment interruption regardless of any reasons is significantly related to the disease free survival (DFS) and overall survival (OS) [8]. This study excluded patients who were within 6 months before or 8 months after treatment, patients with heart failure or metastatic/recurrent cancer, and those who did not receive trastuzumab. Besides treatment duration, insufficient treatment in elderly patients is another key factor. Between the ages of 70-74, approximately 70% of HER2-positive patients choose to receive trastuzumab [9]. There is a gap regarding the tolerance and efficacy of trastuzumab in an unselected real-world elderly patient population. However, among patients over 75 years old, this proportion suddenly decreases to 21%. A 2024 study based on the UK's national population data found that HER2-positive breast cancer patients over 70 years old who received trastuzumab treatment had a 43% lower risk of death [10]. Even the patients who only receive trastuzumab monotherapy will have a better prognosis than people who were not treated with trastuzumab [11].

Age itself seems to become a barrier that excludes elderly patients, leading to worse survival outcomes for elderly cancer patients and causing many elderly patients who would benefit from the treatment to be excluded. In addition to patient-related factors, economic factors also affect real-world efficacy. Economic factors also pose a significant barrier. As an artificially synthesized therapeutic antibody, trastuzumab is relatively expensive. In regions with limited medical resources, economic constraints often prevent patients from accessing standard trastuzumab treatment, leading to incomplete treatment courses and reduced efficacy. Although some biosimilars have been launched to potentially reduce costs, price remains a major obstacle to treatment accessibility in many areas. Cardiotoxicity is also a concern for many people. In the HERA trial report, although the incidence of severe heart failure is only 0.5%, many doctors are often more cautious in their actual work than in trials. Patients are also concerned about the effects of cardiotoxicity, leading many doctors to avoid HER2 treatment for patients with slight heart risk factors, or patients may discontinue treatment too early. However, many studies have shown that cardiotoxicity associated with trastuzumab is usually reversible with appropriate intervention, and researchers are now exploring methods to complete therapy and continue the drug even when cardiotoxicity occurs.

The HERA trial has shown that under the ideal conditions of strict patient screening, trastuzumab can significantly reduce the recurrence risk of HER2-positive breast cancer, with an HR of 0.54. This clearly demonstrates the efficacy of trastuzumab. Additionally, data from real-world research indicates that in real-world settings, the efficacy of trastuzumab does not always reach the level observed in clinical trials. The reason for this discrepancy is not the ineffectiveness of the drug itself, but the complexity of the real-world patient population. These patients are older, have more comorbidities, poorer treatment compliance, and are also influenced by economic factors and doctors' decision-making preferences. These findings indicate that clinical trial results cannot be simply applied to real-world practice. Doctors need to make choices based on the specific conditions of each patient. For example, for elderly patients, treatment should not be abandoned merely because of their age. For patients with heart failure risk factors, drugs can be used under standardized monitoring, as severe cardiotoxicity is controllable, it is suggested that specialized prospective studies be conducted on elderly patients over 75 years old. It is also recommended that cardiotoxicity monitoring be incorporated into the routine follow-up process. To narrow the gap between clinical trial results and real-world effectiveness, several measures should be taken: first,

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strengthen standardized treatment guidance for clinicians, especially for elderly patients and those with cardiac risk factors, to avoid unnecessary treatment abandonment; second, optimize medical resource allocation and promote the accessibility of trastuzumab and its biosimilars to reduce economic barriers; third, establish long-term monitoring systems for cardiotoxicity, enabling early intervention and ensuring treatment completion; finally, conduct more large-scale, multi-center real-world studies to clarify the efficacy and safety of trastuzumab in diverse populations. In summary, trastuzumab is efficacious in the treatment of HER2-positive breast cancer, but its efficacy is reduced in real-world settings. This reduction is not due to the ineffectiveness of the drug, but rather to the fact that optimal utilization of the drug has not yet been achieved in clinical practice. To narrow the gap between clinical trials and the real world, it is important to ensure that all patients can complete standardized treatment, reduce unnecessary treatment interruptions, and control side effects effectively.

6. Conclusion

This paper compared the efficacy of trastuzumab in clinical trials and real-world practice, identified the main reasons that influence the real-world outcomes. The HERA trial demonstrated that trastuzumab is highly effective under ideal, controlled conditions. However, real-world evidence consistently shows that the actual effectiveness of trastuzumab does not always match the results from clinical trials. This gap is not because of the drug itself being ineffective, but rather due to the complexity of real-world patient populations and healthcare systems.

Patients in real-world settings are generally older, have more comorbidities, and more uncontrollable compared to the clinical trial. Older patients are less likely to receive trastuzumab, and treatment interruption for various reasons significantly decreases the survival outcomes. Economic barriers is also a limited factor to trastuzumab, especially in less developed regions with poorer medical equipment. Additionally, doctors and patients' concerns about cardiotoxicity often lead to treatment interruption and will worsen the symptoms, even though the side effects are usually manageable.

These findings suggest that clinical trial results cannot be directly applied to everyday practice without considering patient diversity and real-world affects. To make the gap between clinical trials and real-world effectiveness smaller, several measures are recommended. Standardized treatment guidance should be strengthened, especially for elderly patients and those with cardiac risk factors. Medical resource should allocate more efficient, and the research of using the biosimilars will contribute to reduce the economic barriers. People should set up a long-term cardiotoxicity monitoring system to invent early and make sure the therapy would be completed successfully. Finally, a large scale and multi-center worldwide research is necessary to find the real impact on people in the real world. Overall, trastuzumab is a useful and valuable drug, but due to a series of factors related to patients and the system, it hasn't fully showed its potential in the real-world practice.

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