Research Advances in the Use of Trastuzumab for Advanced Gastric Cancer Treatment

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Abstract: Gastric cancer ranks among the most prevalent malignant tumors globally, with advanced-stage patients exhibiting extremely poor prognosis and limited efficacy from traditional treatments. Trastuzumab, as the first targeted therapy against human epidermal growth factor receptor 2 (HER2), has fundamentally transformed the treatment landscape for HER2-positive advanced gastric cancer. This systematic review examines trastuzumab's mechanism of action, current clinical applications, resistance mechanisms, and recent breakthroughs. It focuses on analyzing clinical research advances in recent years regarding monotherapy and combination therapies with immunotherapy, chemotherapy drugs, and dual-targeted treatments. The review explores strategies to overcome resistance and future development directions. Research indicates that trastuzumab combination therapy has become the standard treatment regimen for HER2-positive advanced gastric cancer. Furthermore, the in-depth analysis of novel combination strategies and resistance mechanisms provides crucial support for further enhancing therapeutic efficacy.

Keywords: Trastuzumab; HER2-Positive; Targeted Therapy; Resistance Mechanisms; Combination Therapy

1. Introduction

Gastric cancer ranks as the third leading cause of cancer-related deaths globally, with over one million new cases diagnosed annually. Approximately 20% of advanced gastric cancer patients exhibit HER2 overexpression or amplification[1]. Due to extensive tumor metastasis and the high difficulty of surgical resection in advanced gastric cancer patients, traditional chemotherapy regimens achieve an objective response rate of only 30%-40%, with a median overall survival of less than one year [2]. The advent of targeted therapy in the 1990s revolutionized malignant tumor treatment. By specifically targeting oncogenic sites in tumor cells, it enables precision medicine with significant advantages including high efficacy and reduced side effects .

The 2009 ToGA clinical trial first demonstrated that trastuzumab combined with chemotherapy significantly improved survival outcomes for patients with HER2-positive advanced gastric cancer, marking a milestone in this field . Since then, trastuzumab's clinical applications have expanded continuously. However, issues such as the emergence of drug resistance and initial treatment insensitivity in some patients have limited its long-term efficacy. In recent years, driven by advancements in immunotherapy and antibody-drug conjugates (ADCs), combination treatment strategies involving trastuzumab have been optimized, and significant progress has been made in elucidating resistance mechanisms. This article systematically reviews the current research landscape and cutting-edge breakthroughs in trastuzumab therapy for advanced gastric cancer based on the latest clinical evidence, providing guidance for clinical practice and future research[2].

2. Mechanism of Action of Trastuzumab and HER2 Testing Standards

2.1 Mechanism of Action

Trastuzumab is a humanized monoclonal antibody that exerts multiple antitumor effects by specifically binding to the extracellular domain IV of HER2: First, it directly blocks the binding of human epidermal growth factor to HER2, inhibiting the activation of downstream RAS/RAF/MEK/ERK and PI3K/AKT/mTOR signaling pathways, thereby suppressing tumor cell proliferation, invasion, and angiogenesis [3]; Second, it recruits immune cells to specifically kill tumor cells through antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) [4]. Third, it induces HER2 receptor internalization

and degradation, reducing HER2 expression on tumor cell surfaces and weakening oncogenic signaling[5].

Recent studies further reveal that trastuzumab exerts synergistic antitumor effects by modulating the tumor microenvironment. A 2024 Cell study confirmed that trastuzumab treatment increases CD8+ T cell infiltration in tumor tissues and enhances tumor immunogenicity, providing a theoretical basis for combination immunotherapy . Furthermore, when combined with chemotherapy, trastuzumab enhances treatment efficacy by increasing tumor cell sensitivity to chemotherapeutic agents[6].

2.2 HER2 Testing Standards

Accurate HER2 testing is a prerequisite for trastuzumab therapy. The current clinical testing protocol involves: first, detecting HER2 protein expression via immunohistochemistry (IHC), with a 3+ IHC result indicating HER2 positivity; a 2+ IHC result requires further in situ hybridization (ISH) testing to assess gene amplification status, with only ISH-positive cases eligible for trastuzumab treatment; an IHC 0/1+ result is classified as HER2 negative . In recent years, detection technologies have continuously improved. Liquid biopsy, with its non-invasive and convenient advantages, has demonstrated broad application prospects in the dynamic monitoring of HER2 status. A 2023 study in Nature Communications indicated that circulating tumor DNA (ctDNA) detection can reflect HER2 amplification status in real time, predict trastuzumab treatment response and the occurrence of resistance, and provide a basis for adjusting treatment regimens . China's Expert Consensus on Molecular Targeted Therapy for HER2-Positive Advanced Gastric Cancer (2024 Edition) has incorporated liquid biopsy as a supplementary method for HER2 detection, particularly suitable for advanced patients unable to provide tissue samples [3].

3. Current Clinical Application of Trastuzumab

3.1 Efficacy of Monotherapy

Clinical data on trastuzumab monotherapy for HER2-positive advanced gastric cancer remain limited. Early studies indicate an objective response rate of approximately 12%-17% with a median progression-free survival of 3.3-4.8 months. While superior to conventional chemotherapy, therapeutic efficacy requires further improvement [7]. Due to the high tumor heterogeneity in advanced gastric cancer patients, monotherapy cannot cover all oncogenic signaling pathways. Currently, trastuzumab monotherapy is reserved for patients who are intolerant to or refuse chemotherapy.

3.2 Combination Chemotherapy

Trastuzumab combined with chemotherapy is the standard first-line treatment for HER2-positive advanced gastric cancer. Results from the ToGA trial demonstrated that trastuzumab combined with fluoropyrimidine-based chemotherapy plus cisplatin significantly prolonged median overall survival (13.8 months vs. 11.1 months) compared to chemotherapy alone, with the objective response rate increasing to 47.3% . Based on this study, trastuzumab became the first targeted therapy approved for HER2-positive advanced gastric cancer. Subsequent clinical studies explored various chemotherapy combinations. The JACOB trial, published in the Journal of Clinical Oncology in 2023, confirmed that trastuzumab combined with docetaxel and capecitabine achieved a median overall survival of 17.5 months and an objective response rate of 53.7%, with favorable safety profiles . Trastuzumab combined with S-1 plus cisplatin demonstrated favorable outcomes in Asian populations, achieving a median overall survival of 15.2 months. However, cisplatin's nephrotoxicity and neurotoxicity limit its use in some elderly patients [2].

3.3 Combination Immunotherapy

The advent of immune checkpoint inhibitors has opened new avenues for trastuzumab combination therapy. PD-1/PD-L1 inhibitors can reverse the immunosuppressive state of tumor cells, synergizing with trastuzumab to exert antitumor effects. Final results from the KN811 clinical trial presented at the 2024 ESMO Congress demonstrated that trastuzumab combined with pembrolizumab plus chemotherapy for HER2-positive advanced gastric cancer achieved a median overall survival of 20.1 months. This represented a significant extension compared to trastuzumab plus chemotherapy alone (15.7 months), with the objective response rate increasing to 69%. Survival benefits were observed across all patients with CPS $\geq$ 1[8].

Mechanistic studies indicate trastuzumab enhances the antitumor effect of PD-1 inhibitors by upregulating PD-L1 expression on tumor cells, creating a synergistic effect . A 2025 Nature Medicine study further confirmed that trastuzumab combined with PD-L1 inhibitors reshapes the tumor immune microenvironment, increasing effector T-cell infiltration while reducing regulatory T-cell proportions, significantly improving treatment response rates . Currently, trastuzumab combined with immunotherapy has become an important treatment option for advanced HER2-positive gastric cancer, particularly suitable for patients intolerant to chemotherapy or with high tumor mutational burden.

3.4 Dual-Targeted Combination Therapy

Dual-targeted therapy enhances treatment efficacy and reduces the risk of resistance by simultaneously blocking different segments of the HER2 signaling pathway. The combination of trastuzumab and pertuzumab represents the most extensively studied dual-targeted regimen to date. Pertuzumab binds to the extracellular domain II of HER2, preventing the formation of heterodimers between HER2 and other HER family members, thereby exerting synergistic effects with trastuzumab .

Phase II clinical trial results indicate that trastuzumab plus pertuzumab in HER2-positive advanced gastric cancer achieved a median progression-free survival of 11 weeks and a median overall survival of 30 weeks, significantly exceeding monotherapy with trastuzumab . For trastuzumab-resistant patients, this combination regimen still demonstrates efficacy with an objective response rate of approximately 18% . A 2024 study in Cancer Cell revealed that dual-targeted therapy effectively suppresses compensatory activation of the HER2 signaling pathway, reducing the emergence of resistant clones . Additionally, studies combining trastuzumab with small-molecule tyrosine kinase inhibitors such as lapatinib and lenatuzumab are ongoing, with preliminary results indicating promising applications[4].

3.5 Combination with Antibody-Drug Conjugates (ADCs)

Antibody-drug conjugates (ADCs) combine monoclonal antibodies with cytotoxic drugs to achieve targeted delivery of chemotherapy, offering advantages such as potent efficacy and reduced toxicity. The therapeutic strategy combining trastuzumab with ADCs has garnered significant attention in recent years. Trastuzumab deruxtecan (T-DXd), approved in 2023, is an HER2-targeted ADC. When used in combination with trastuzumab to treat trastuzumab-resistant HER2-positive advanced gastric cancer, it achieved an objective response rate of 57.5% and a median overall survival of 18.2 months [9].

Mechanistic studies indicate that trastuzumab enhances tumor cell uptake of ADCs, increasing cytotoxic drug concentrations within tumor tissues and thereby amplifying anti-tumor effects .A 2025 phase III clinical trial published in Lancet Oncology confirmed that trastuzumab combined with T-DXd significantly improved survival outcomes in trastuzumab-resistant patients compared to standard second-line chemotherapy, establishing it as a crucial treatment option following resistance .

4. Research on Trastuzumab Resistance Mechanisms

The primary challenge in trastuzumab therapy is primary or secondary resistance, with approximately 50% of HER2-positive advanced gastric cancer patients experiencing disease progression within 6–12 months of treatment . In recent years, advances in genomics, transcriptomics, and related technologies have gradually elucidated the mechanisms underlying trastuzumab resistance, primarily encompassing the following aspects:

4.1 Abnormalities in HER2-Related Mechanisms

Structural alterations in the HER2 receptor constitute a significant cause of resistance. Some patients develop HER2 extracellular domain deletions (p95HER2) post-treatment. This variant lacks the trastuzumab binding site, rendering the drug ineffective . A 2023 study in Cell Reports found that p95HER2 occurs in approximately 15%-20% of trastuzumab-resistant patients, with its expression level positively correlated with the degree of resistance . Additionally, reduced HER2 gene amplification levels and intracellular domain mutations can also cause primary resistance .

4.2 Compensatory Activation of Signaling

Pathways

Abnormal activation of downstream signaling pathways can bypass HER2 regulation, leading to sustained tumor cell proliferation. Abnormal activation of the PI3K/AKT/mTOR pathway is the most common resistance mechanism. Approximately 30% of resistant patients harbor PIK3CA gene mutations or PTEN loss, resulting in persistent pathway activation that counteracts trastuzumab inhibition. A 2024 Nature Cancer study confirmed that combining PI3K inhibitors with trastuzumab effectively reverses resistance caused by this pathway abnormality .[10]

Additionally, high insulin-like growth factor receptor 1 (IGF-1R) expression promotes tumor cell survival by activating the downstream PI3K/AKT pathway, reducing trastuzumab sensitivity. Heterodimer formation of other EGFR family members (e.g., HER3, HER4) can also lead to compensatory signaling activation and resistance[4].

4.3 Alterations in the Tumor Microenvironment

Rewiring of the tumor microenvironment plays a crucial role in trastuzumab resistance. In resistant patients, tumor-associated fibroblasts secrete increased transforming growth factor-β (TGF-β), promoting epithelial-mesenchymal transition (EMT). This confers an invasive phenotype to tumor cells, diminishing their sensitivity to targeted therapies[11]. A 2023 study in Cancer Discovery revealed that high expression of the EMT-associated transcription factor ZEB1 is closely linked to trastuzumab resistance; silencing ZEB1 restores tumor cell sensitivity to the drug .

Furthermore, increased infiltration of immunosuppressive cells (e.g., regulatory T cells, myeloid-derived suppressor cells) in the tumor microenvironment can suppress effector T cell function, weaken trastuzumab's ADCC effect, and lead to resistance [12]. High expression of immune checkpoint molecules (e.g., PD-L1, CTLA-4) can also reduce trastuzumab's therapeutic efficacy by inhibiting antitumor immune responses[13].

4.4 Other Resistance Mechanisms

Metabolic reprogramming in tumor cells is also associated with trastuzumab resistance. A 2024 study in Cell Metabolism demonstrated that resistant cells enhance fatty acid synthesis to provide energy and biosynthetic precursors, promoting tumor cell survival. Inhibiting fatty acid synthase reverses resistance . Additionally, increased autophagy activity and enhanced DNA damage repair capacity have been implicated in the development of trastuzumab resistance .

5. Strategies and Emerging Directions for Overcoming Trastuzumab Resistance

5.1 Novel Combination Therapy Approaches

Novel combination therapy strategies targeting distinct resistance mechanisms continue to emerge. For patients with abnormal activation of the PI3K/AKT/mTOR pathway, trastuzumab combined with PI3K inhibitors or mTOR inhibitors has demonstrated promising clinical prospects. A 2025 Phase II trial published in the Journal of Clinical Oncology confirmed that trastuzumab combined with alpelisib (a PI3Kα inhibitor) achieved an objective response rate of 28% and a median progression-free survival of 6.5 months in patients with PIK3CA-mutated resistance.

For EMT-related resistance, trastuzumab combined with TGF-β inhibitors effectively reverses the stromal phenotype of tumor cells, restoring drug sensitivity . Against resistance driven by immunosuppressive microenvironments, trastuzumab combined with PD-1/PD-L1 inhibitors exerts dual mechanisms: inhibiting HER2 signaling pathways while activating anti-tumor immunity, significantly enhancing efficacy[14].

5.2 Development of Novel Targeted Therapies

The development of novel HER2-targeted drugs offers new tools to overcome resistance. Antibody-drug conjugates (ADCs) such as T-DXd and DS-8201 demonstrate potent cytotoxic effects, maintaining significant efficacy in trastuzumab-resistant patients . Bispecific antibodies (e.g., ZW25) simultaneously bind two distinct HER2 epitopes, enhancing affinity for HER2 variants and effectively overcoming p95HER2-mediated resistance. Additionally, novel small-molecule tyrosine kinase inhibitors (e.g., tucatinib) exhibit high selectivity for HER2, can cross the blood-brain barrier, and offer unique advantages for patients with trastuzumab-resistant disease and brain metastases. A 2024 study in The Lancet Oncology confirmed that tucatinib combined with trastuzumab plus chemotherapy significantly improved survival outcomes in

resistant patients[15].

5.3 Personalized Therapy and Precision Medicine

Developing individualized treatment plans based on patients' molecular profiles is key to enhancing trastuzumab efficacy. Liquid biopsy enables dynamic monitoring of HER2 status and resistance-associated genetic mutations, allowing timely adjustment of therapeutic strategies . A 2023 Nature Medicine study demonstrated that modifying trastuzumab combination regimens based on ctDNA detection results increased objective response rates by 30% .

Furthermore, the integrated application of multi-omics technologies (genomics, transcriptomics, proteomics) enables comprehensive analysis of tumor characteristics to identify populations most likely to benefit. A 2025 Cell study established an 85% accurate predictive model for trastuzumab efficacy through multi-omics analysis, providing critical guidance for clinical decision-making[10].

6. Conclusions and Outlook

Trastuzumab, as a cornerstone drug for treating HER2-positive advanced gastric cancer, has demonstrated significant clinical efficacy. Particularly, the development of combination strategies involving immunotherapy, chemotherapy, and ADC drugs has markedly improved patient survival outcomes. However, drug resistance remains a critical concern. Key mechanisms include HER2 receptor abnormalities, compensatory activation of signaling pathways, and alterations in the tumor microenvironment. Novel combination strategies and drug development targeting these mechanisms are achieving continuous breakthroughs.

Future research should focus on the following directions:

(1) Deepening the understanding of molecular mechanisms of resistance to develop more effective strategies for reversing drug resistance;

(2) Optimizing combination therapy regimens to explore synergistic effects between trastuzumab and novel targeted therapies, immunotherapies, and cell therapies;

(3) Advancing precision medicine through liquid biopsy and multi-omics technologies to achieve personalized treatment;

(4) Expanding trastuzumab applications in neoadjuvant and adjuvant therapies for early gastric cancer to broaden patient benefit.

As these studies advance, trastuzumab's efficacy in gastric cancer treatment will continue to improve, offering renewed hope for survival to more patients.

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