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Trastuzumab Deruxtecan Targets HER2 in the Treatment of Gastric Cancer

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Abstract. Gastric cancer presents high global mortality, and traditional chemotherapy and single-target agents are limited by frequent drug resistance and unsatisfactory tumor inhibition efficiency. This paper systematically sorts gastric cancer's Correa cascade carcinogenic process and core oncogenic signaling axes, then elaborates the complete structural composition and multi-layer anti-tumor mechanism of the novel antibody-drug conjugate trastuzumab deruxtecan (T-DXd). T-DXd binds HER2 specifically via monoclonal antibody fragments, releases topoisomerase inhibitor DXd after lysosomal cleavage of cleavable GGFG linkers, and eliminates adjacent HER-low/negative tumor cells through the bystander killing effect. Multiple DESTINY-Gastric Phase II trials confirm T-DXd achieves significantly higher objective response and longer overall survival than standard chemotherapy regimens in HER2-positive advanced gastric cancer, with controllable adverse reactions. Current clinical transformation obstacles mainly include interstitial lung disease risk and diverse acquired resistance subtypes. This paper provides systematic theoretical support for stratified clinical administration and novel ADC structural optimization for HER2-mutated gastric malignant tumors.

Keywords: Gastric cancer, Antibody-conjugate drugs, Detrastuzumab

1. Introduction

Gastric cancer remains a leading lethal digestive tumor worldwide. Advanced lesions feature strong molecular heterogeneity, and conventional chemo-targeted regimens often fail to achieve durable remission [1]. HER2 amplification drives persistent activation of RAS/MAPK and PI3K/Akt oncogenic cascades, becoming a key therapeutic target for gastric cancer. Traditional trastuzumab and first-generation ADC trastuzumab emtansine are restricted by limited anti-heterotumor capacity and easy acquired resistance. As a new-generation HER2-targeted antibody-drug conjugate, T-DXd exerts unique bystander anti-tumor activity and has been verified effective in multi-center Phase II trials, requiring systematic collation of its mechanism and clinical value.

Overseas teams completed serial DESTINY-Gastric trials and clarified two core resistance pathways including HER2 loss and drug efflux overexpression [2]. Foreign studies prioritize multi-omics analysis of its bystander effect and ILD risk stratification, while most reviews only discuss single clinical or mechanistic content without integrated sorting. Domestic research mainly focuses

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on cell and PDX animal verification, exploring H. pylori-HER2 correlation and combined medication schemes, yet large-sample real-world clinical data are insufficient globally.

Existing literatures are fragmented and lack a complete logic chain linking gastric cancer pathogenesis, HER2-driven signals and T-DXd targeted intervention. This paper firstly expounds Correa cascade and core tumor-promoting pathways, then analyzes T-DXd triple structure and dual killing mechanisms, summarizes preclinical and clinical evidence, sorts adverse reactions and resistance subtypes, and finally proposes optimized research directions to form a complete research system.2. Pathogenesis and Core Signaling Axes of Gastric CancerThe pathological evolution of gastric cancer follows the classical Correa cascade, which involves long-term superposition of infectious stimuli, chronic inflammation, epigenetic variation and gene mutation, and the whole progression covers normal gastric mucosa → superficial gastritis → atrophic gastritis → intestinal metaplasia → dysplasia → invasive carcinoma [1]. Four major categories of pathogenic factors jointly promote lesion deterioration: persistent Helicobacter pylori infection carrying CagA/VacA virulence factors, precancerous mucosal atrophy and intestinal metaplasia, long-term high-salt diet and alcohol-induced inflammatory stimulation, plus germline and somatic gene mutations such as APC, CDH1 and HER2 amplification [3].

CagA toxin secreted by H. pylori can translocate into gastric epithelial cells and interfere with the normal function of SHP-2 phosphatase, which directly accelerates the abnormal activation of RAS signal and creates a pro-oncogenic intracellular environment at the early stage of lesion formation. Long-term intake of high-salt pickled food will destroy the protective mucus layer of gastric wall, increase the adhesion efficiency of H. pylori on epithelial surface, and amplify the damage effect of virulence factors [3]. Alcohol metabolites can induce oxidative stress of gastric mucosa, upregulate the expression of inflammatory mediators and accelerate the progression from simple inflammation to precancerous lesions. Multiple tumor-promoting signaling pathways are persistently activated in lesion tissues to mediate unlimited proliferation, anti-apoptosis and distant metastasis. The NF-κB axis sustains inflammatory cytokine secretion including IL-1β, IL-6 and TNF-α to maintain immune suppression; sustained inflammatory stimulation will further increase the mutation probability of epithelial cells and form a vicious cycle of inflammation-cancer transformation. Wnt/β-catenin disorder disrupts epithelial differentiation balance and promotes the accumulation of undifferentiated stem-like tumor cells, while the RAS/MAPK-PI3K/Akt cascade, the core downstream pathway of HER2, accelerates cell cycle progression and epithelial-mesenchymal transition (EMT) [4]. EMT can reduce intercellular adhesion by downregulating E-cadherin, and enhance the migration ability of tumor cells by upregulating N-cadherin and Vimentin. The tumor microenvironment is filled with M2-type macrophages, myeloid-derived suppressor cells (MDSCs) and cancer-associated fibroblasts (CAFs), which secrete TGF-β, VEGF and CXCL8 to construct an immunosuppressive microenvironment facilitating tumor invasion. HER2 gene amplification leads to spontaneous dimerization of membrane HER, continuous tyrosine kinase activation, and becomes a core driver of malignant progression in partial gastric cancer patients. In normal gastric epithelial cells, HER only forms heterodimers with other EGFR family proteins under ligand stimulation, while gene amplification causes excessive HER protein accumulation on cell membrane and triggers ligand-independent persistent activation of downstream signals [5].

2. Molecular structure and multi-target killing mechanism of T-DXd

Trastuzumab deruxtecan (T-DXd, DS-8201) consists of three modular components: humanized anti-HER2 trastuzumab antibody, cleavable GGFG tetrapeptide linker and cytotoxic topoisomerase I inhibitor DXd, each unit cooperates to realize precise tumor targeting and broad-spectrum lesion

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elimination. The drug-antibody ratio (DAR) of T-DXd is stably controlled at 8, which is significantly higher than the DAR value of traditional ADCs such as T-DM1 (3.5), laying a material foundation for its stronger single-dose cytotoxicity [2, 5].

2.1. Specific HER2 recognition and receptor downregulation

The trastuzumab moiety specifically binds domain IV of extracellular HER2 protein. Clinical immunohistochemistry (IHC) and in situ hybridization (ISH) are unified diagnostic criteria for HER status: IHC 0/1+ = HER2 negative, IHC 2+ requires ISH gene amplification verification, IHC 3+ confirms HER2 positivity [6]. The antibody adopts fully humanized IgG1 framework, which can also trigger antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) after binding tumor membrane HER2, and recruit peripheral immune cells to participate in tumor clearance besides direct signal blocking. After antibody binding, HER2 undergoes endocytosis and lysosomal degradation, reducing membrane HER abundance and blocking spontaneous dimerization, thereby inhibiting downstream RAS/MAPK and PI3K/Akt oncogenic signal transduction at the source. Even for IHC 2+ low-expression tumor cells with weak HER signal, trastuzumab can still complete effective specific capture to lay a prerequisite for subsequent payload release [7].

2.2. Controlled intracellular release of cytotoxic payload DXd

The linker adopts maleimide-hexyl-GGFG structure with dual advantages of plasma stability and tumor-specific cleavage. The maleimide alkyl chain can stably couple with cysteine residues on the antibody heavy chain without causing spontaneous detachment under physiological environment. The GGFG tetrapeptide cannot be hydrolyzed by plasma proteases under pH 7.4 physiological conditions, avoiding premature payload shedding and systemic off-target toxicity; after T-DXd enters tumor lysosomes via endocytosis, low pH (4.5–5.5) and high cathepsin B/L expression specifically cut the peptide bond between glycine and phenylalanine to release free DXd. DXd is a potent TOP1 inhibitor with 10-fold higher activity than SN-38; it traps TOP1-DNA cleavage complexes to induce irreversible DNA double-strand breaks, arresting tumor cells at G2/M phase and triggering endogenous apoptotic cascade.

Compared with non-lipophilic cytotoxic payloads used in traditional ADCs such as T-DM1, the moderate lipophilic property of DXd is the core structural basis of T-DXd's unique bystander effect, which cannot be replicated by earlier generations of HER antibody-drug conjugates. The lipophilic balance of DX is precisely designed: it can pass through phospholipid bilayers freely without being limited by cell membrane transporters, but will not diffuse infinitely into normal tissues at ultra-high concentration to cause wide-range organ damage [8].

2.3. Bystander effect for elimination of heterogeneous tumor lesions

DXd possesses moderate lipophilicity and can freely diffuse across cell membranes after release from HER2-positive tumor cells, generating a unique bystander killing effect on surrounding HER2-low or HER2-negative tumor cells which cannot be recognized by the antibody fragment. Gastric cancer tissues usually show obvious intratumoral heterogeneity: the same primary lesion often coexists with HER3+, HER2 2+ and HER negative cell clusters, and single targeted drugs cannot cover all tumor subpopulations. This mechanism overcomes tumor intralesional heterogeneity and effectively eradicates mixed metastatic lesions with heterogeneous HER expression, significantly

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expanding the anti-tumor coverage range compared with traditional ADCs lacking lipid-soluble payloads [9].

In parallel in vitro co-culture experiments of mixed HER-positive and HER-low tumor cells, only T-DXd treatment group showed obvious overall cell apoptosis, which intuitively verified the auxiliary tumor-killing role of its bystander effect. After DXd diffuses into adjacent tumor cells, it still acts on intracellular TOP1 protein to interfere with DNA replication cycle, so as to continuously suppress the proliferation of non-HER-amplified tumor subclones and reduce the risk of residual lesion recurrence after monotherapy [8].

3. Preclinical and clinical efficacy evidence of T-DXd

3.1. Preclinical verification in cell and PDX models

Multiple patient-derived xenograft (PDX) gastric tumor models covering IHC 1+, 2+, 3+ HER expression gradients are constructed to conduct head-to-head efficacy comparison among T-DXd, trastuzumab emtansine and single trastuzumab [10]. In vitro cell level, low-dose T-DXd can significantly inhibit the clone formation capacity of both HER-high and HER-low gastric cancer cell lines, while T-DM1 only produces weak inhibitory effect on fully amplified HER3+ strains and has no obvious activity on IHC 2+ cells. In subcutaneous xenograft nude mice, continuous intravenous administration of T-DXd achieves sustained tumor shrinkage, and the tumor inhibition rate shows obvious positive correlation with the dosage within the effective concentration window. Immunohistochemical detection of xenograft tissue after drug intervention shows the downregulation of proliferation marker Ki-67 and p-Akt protein, and the proportion of apoptotic tumor cells increases significantly.

Further orthotopic gastric cancer xenograft models with liver and lung metastasis are adopted to simulate clinical metastatic characteristics. Experimental results show that T-DXd can significantly reduce the number of distant metastatic nodules, which cannot be achieved by single trastuzumab or T-DM1, fully reflecting the unique anti-metastatic advantage brought by its bystander killing effect on heterogeneous metastatic lesions.

3.2. Destiny-gastric01 single-agent Phase II trial

This open-label, randomized controlled Phase II trial enrolled 187 HER-positive locally advanced or gastroesophageal junction cancer patients who failed at least one line of prior systemic therapy [2]. Subjects were randomly divided into two groups: 125 patients received T-DXd 6.4 mg/kg intravenous infusion every three weeks, and 62 patients received physician-selected chemotherapy (irinotecan or paclitaxel monotherapy). The primary study endpoint was objective response rate (ORR) assessed by independent imaging review committee. The ORR of T-DXd group reached 51%, far higher than 14% of the chemotherapy control group ($P < 0.001$); 10 patients in T-DXd group achieved complete tumor regression, while no complete response case appeared in the control cohort. More than 80% of patients treated with T-DXd achieved measurable lesion reduction, and the median duration of response was also significantly prolonged compared with chemotherapy. Subgroup analysis showed that patients with IHC 2+ HER low expression also obtained durable tumor remission, which provided direct pre-clinical and clinical basis for expanding T-DXd's applicable population.

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3.3. Combined target-chemotherapy Phase II clinical research

A total of 594 eligible HER-positive advanced gastric patients with newly diagnosed metastatic lesions were enrolled in this randomized Phase II study, with 1:1 random grouping to capecitabine plus cisplatin alone group and T-DXd combined double chemotherapy group [7]. The combination group received 5.4 mg/kg T-DXd every three weeks synchronously with standard platinum fluoropyrimidine regimen. The median follow-up time of all subjects was about 18 months. The median overall survival of the combination group was 13.8 months, while that of single chemotherapy group was 11.1 months (HR=0.74, P=0.0046). Stratified safety analysis showed that the incidence of grade 3–4 neutropenia, gastrointestinal reaction and cardiac adverse events had no statistical difference between two arms, which proved that adding T-DXd would not increase the toxic burden of standard chemotherapy. Subgroup survival data further indicated that patients with liver metastasis and peritoneal dissemination gained more prominent long-term survival benefit from combined therapy [11].

4. Clinical challenges and future research directions

4.1. Common adverse reactions and clinical management strategies

Gastrointestinal discomfort and neutropenia are the most frequent treatment-emergent adverse events of T-DXd, while interstitial lung disease (ILD) is a rare but life-threatening specific adverse reaction requiring whole-cycle close monitoring [12]. Nausea, vomiting and mild diarrhea mostly occur within the first two treatment cycles, and most can be relieved by routine symptomatic antiemetic and antidiarrheal intervention without drug withdrawal. Neutropenia usually appears in the second or third week after medication, and regular blood routine monitoring is required; for grade 3–4 neutropenia, dose delay or reduction combined with granulocyte-stimulating factor can effectively recover blood cell level.

Interstitial lung disease has unique pathogenic characteristics: moderate lipophilic DXd can diffuse out of HER-positive tumor cells and infiltrate normal lung interstitial tissue, while alveolar epithelial cells express almost no HER protein and cannot capture ADC to block payload damage. Free DXd induces alveolar DNA double-strand breaks, triggers epithelial apoptosis and inflammatory exudation, and severe cases progress to acute respiratory failure. Clinical risk factors for ILD include age over 65 years, previous chronic obstructive pulmonary disease, long-term smoking history and concurrent thoracic radiotherapy. Standardized management specifications recommend baseline chest high-resolution CT and blood oxygen detection before administration, and regular imaging review every two treatment cycles; once suspected ILD occurs, T-DXd should be suspended immediately, and glucocorticoid anti-inflammatory intervention should be given as early as possible according to severity grading [6].

4.2. Multi-type acquired drug resistance mechanisms

After continuous T-DXd monotherapy for 6–12 months, a considerable proportion of patients will develop secondary drug resistance, which can be classified into four core molecular subtypes according to sequencing data. First, HER2 extracellular domain mutation or overall protein downregulation leads to reduced ADC binding efficiency and insufficient endocytic uptake of drug complexes. Second, intracellular drug efflux transporters such as ABCG2 and ABCB1 are highly overexpressed, which pump free DXd out of tumor cytoplasm and reduce intratumoral effective

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cytotoxic concentration. Third, lysosomal protease expression disorder blocks the complete cleavage of GGFG linker, resulting in insufficient release of active payload inside tumor cells. Fourth, tumor microenvironment remodeling occurs: massive infiltration of MDSCs and M2 macrophages upregulate multiple anti-apoptotic cytokines, making tumor cells insensitive to DNA damage-induced apoptosis signals.

Current basic laboratory research has preliminarily explored targeted reversal strategies for different resistance subtypes: for HER2 loss mutation, combined small-molecule EGFR family inhibitors can partially compensate target deficiency; for efflux transporter overexpression, co-administration of ABC pump antagonists can improve intratumoral DXd accumulation [7, 13].

4.3. Multi-dimensional future development directions

Follow-up translational research can be expanded from four systematic dimensions. First, optimize ADC molecular structure: design low-lipophilic modified linkers to weaken the pulmonary diffusion capacity of DXd payload, reduce the incidence of ILD adverse reactions on the premise of retaining partial bystander anti-tumor activity. Second, carry out large-scale multi-center stratified clinical trials specially for IHC 2+ HER-low gastric cancer populations, formulate unified graded dosage adjustment standards according to patient physical status and metastatic site types, and build long-term real-world follow-up cohorts to supplement high-level evidence. Third, explore multi-modal combined treatment schemes: match T-DXd with PD-1/PD-L1 immune checkpoint inhibitors or anti-angiogenic drugs, clarify the administration sequence and cycle interval of combined regimen, and excavate synergistic anti-tumor effects on immunosuppressive microenvironment. Fourth, develop targeted resistance reversal agents: screen small-molecule inhibitors against ABC efflux pumps and mutant HER extracellular fragments, form standardized sequential treatment schemes for resistant patients after T-DXd failure, and prolong overall survival time of advanced gastric cancer patients [9].

5. Conclusion

This paper systematically sorts the Correa cascade pathological progression of gastric cancer, HER-driven oncogenic signaling axes and triple modular structure of T-DXd. T-DXd exerts dual anti-tumor activity through specific HER2 binding and lipophilic DXd-mediated bystander effect. Landmark DESTINY-Gastric trials verify its superior objective response and overall survival compared with traditional chemotherapy, while interstitial lung disease and diverse acquired resistance limit its wide clinical application. Further structural optimization of ADC linkers, stratified large-sample clinical trials and resistance reversal combination regimens will promote the popularization of T-DXd in precise gastric cancer treatment. The integrated summary of drug structure, multi-layer killing mechanism and clinical evidence provides systematic theoretical support for subsequent HER-targeted ADC research and individualized gastric cancer intervention.

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