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Function of ERbB2 in Cancer And The Development of Tailored Treatment For Gastric Cancer: Signaling Routes to Treatment Approaches

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SUMMARY

Introduction: Molecularly targeted therapies, such as those targeting erb-b2 receptor tyrosine kinase 2 (ERbB2) also known as human epidermal growth factor receptor 2 (HER2), are anticipated to improve the current status of systemic treatment beyond conventional cytotoxic therapy. Recent developments in molecular targeted treatments, particularly those that focus on human epidermal growth factor receptor 2, have significantly improved therapeutic potential for patients with gastric cancer. Human epidermal growth factor receptor receptors are the crucial factor in the development and progression of gastric cancer. A portion of gastric cancers exhibit rising levels or amplification of ERbB2 gene, which can stimulate tumor growth and the spread of cancer. The status of ERbB2 is also critical for managing treatment approaches, especially in recognizing patients who might be benefited from targeted therapies.

Methodology: PubMed, NIH, Scopus, Web of Science, and Google Scholar databases were used to do the literature search. Important information for this review was gathered through the analysis of case reports, retrospective research, clinical trials, clinical recommendations, narrative reviews, and online resources.

Topic: This article will discuss the complex molecular processes through which ERbB2 plays a role in cancer development, highlighting its impact on signaling pathways that promote gastric cancer and research progress within the realm of clinical trials. This review will also analyze the progress in ERbB2 targeted therapy and significance of ERbB2 as a target for advanced therapy.

Conclusion: Research is being conducted on targeted therapeutics for gastric cancer (GC). A considerable number of clinical investigations indicate that ERbB2 (HER2) may function as a great therapeutic target and biomarker in GC. Although GC treatment has advanced significantly, there are still numerous challenges to be solved.

Keywords: Gastric Cancer, ERbB2, EGF, Targeted Therapy, Clinical Trial

INTRODUCTION

Gastric cancer (GC), is a major global health concern, ranking fourth in cancer-related mortality and fifth in incidence worldwide [1]. In China alone, approximately 396,500 new cases are diagnosed annually, with over 80% identified at an advanced stage [2]. The prognosis for GC remains poor due to diverse traits and typically late diagnosis. Although tradi-

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tional chemotherapy has long been the standard treatment for advanced-stage GC, clinical outcomes remain suboptimal, with a 5-year survival rate of less than 10%. ERbB2 is a critical target for pharmacological therapy for GC that shows promising potential for future treatment strategies [3]. The human epidermal growth factor receptor 2 (HER2), which is also referred to as C-erbB-2 and ERbB2, is a proto-oncogene located on chromosome 17q21. It encodes a transmembrane protein that has tyrosine kinase activity and belongs to the HER receptor family, playing an important role in signal transduction pathways that promote cell growth and differentiation [4, 5].

HER2 does not directly bind with ligands but functions as a favored heterodimerization partner with other ERBB receptors, thereby amplifying downstream signaling [6]. It is particularly involved in key pathways such as PI3K/AKT, which guide cell survival and metabolism. Dysregulation of ERbB3 has been associated with resistance to targeted treatments in cancers that are ERbB2 positive. It is vital for neurodevelopment and tissue differentiation, and its dysregulation has been connected to specific cancers and neurological disorders [7]. These receptors are not only present in epithelial tissues; they can also be found in a variety of other cell types, each playing a role in different biological functions. ERbB2 and ERbB4 participate in synaptic plasticity and neurodevelopment, affecting cognitive and sensory processes in neuronal cells [8]. Epidermal Growth Factor Receptor (EGFR) and HER2 stimulate angiogenesis and vascular remodeling, mechanisms that are utilized in tumor development within endothelial cells. The presence of EGFR in macrophages and lymphocytes influences immune responses and inflammatory pathways in these immune cells. ERBB receptor family support tissue repair and fibrosis, highlighting their significance in wound healing and chronic inflammation within fibroblasts and mesenchymal cells [9].

Overexpression or amplification of the ERbB2 gene results in uncontrolled cell growth, increased survival rates, and is the potential for metastasis [10]. The amplification of the ERbB2 gene and the excessive production of its protein were initially identified in breast cancer and are closely linked to poorer prognosis. Numerous studies have shown that overexpression of ERbB2 gene is also found in various cancers, such as colorectal cancer, ovarian cancer, prostate cancer, lung cancer, and especially gastric and gastroesophageal cancers [11, 12]. These traits highlight the importance of targeting ERbB2 in cancer treatments. Therapies that target ERbB2, such as monoclonal antibodies (for instance, trastuzumab), tyrosine kinase inhibitors, and antibody-drug conjugates, have transformed the treatment options for ERbB2 positive cancers, leading to significant improvements in patient outcomes [13].

HER2 has been used as marker in gastric cancer and trastuzumab has been evolved as a result. But resistance to trastuzumab has become a major drawback, necessitating the development of more potent second-line treatments. Antibodies that target particular ERbB2 domains or downstream signaling pathways like PI3K/AKT, as well as ERbB2 specific immune-based treatments such peptide vaccines and chimeric antigen receptor T cell therapies are among the strategies required to overcome resistance. Emerging strategies to overcome resistance include antibodies targeting specific ERbB2 domain. Review article targeting ERbB2 has been published with different cancers but limited number of article concentrated on gastric cancer. That is why an attempt has taken to review the potential of targeting ERbB2 against gastric cancer. This review will explore the molecular characteristics of the ERbB2 gene, the function of ERbB2 in gastric cancer, ERbB2 targeted therapies, major study and trials HER2 (ERbB2) targeted treatment in gastric cancer and the subsequent signaling pathways.

METHODOLOGY

A comprehensive computerized literature search was conducted using the PubMed, NIH, Scopus, Web of Science, and Google Scholar databases. The keywords used included: gastric cancer, ERbB2, EGF, targeted therapy, clinical trial, HER2, and signaling pathways related to HER2. The search included English-language studies and resources such as case reports, retrospective studies, clinical trials, clinical guidelines, narrative reviews, and relevant online sources. After screening for relevance and quality, a total of 98 articles were selected, reviewed, and included in this study.

TOPIC

Now there is an emerging need to find out newer therapeutics that can target ERbB2. It is also essential to explore the molecular characteristics of the ERbB2 gene, the function of ERbB2 in gastric cancer, ERbB2-targeted therapies, major studies and trials HER2 (ERbB2)-targeted treatment in gastric cancer and the subsequent signaling pathways.

Signaling pathways associated with HER2

HER2, which is encoded by the ERbB2 gene found on human chromosome 17 [14], is a receptor that spans the membrane and possesses intrinsic tyrosine kinase activity. As a part of the epidermal growth factor receptor (EGFR) family, HER2 is included in a group that consists of HER1 or EGFR, HER2, HER3, and HER4. Each receptor within this family consists of three essential components: an extracellular domain for ligand binding, a transmembrane domain spans the membrane, and an intracellular domain responsible for activation [15, 16]. The interaction of different ligands with the extracellular domain initiates a cascade of signal transduction pathways, which are crucial in controlling tumor cell proliferation, programmed cell death, attachment, movement, and differentiation [17, 26].

The HER2 monomer does not have ligand-binding capabilities and must undergo dimerization to achieve functional activity [18], leading to the formation of HER2-HER2 homodimers, HER2-HER3 heterodimers, and EGFR-HER2 heterodimers. Among these, the HER2-HER3 heterodimer is the most powerful HER signaling receptor and is crucial in the onset and advancement of cancer [19]. The HER2-HER2 homodimer facilitates cell adhesion, migration, growth, proliferation, and metastasis by activating signaling pathways such as SRC-FAK [20], GRB2-SOS-JAK2 [21], and RAS-MEK-MAPK [22] in gastric cancer (GC) cells. In addition, the HER2-HER3 heterodimer conveys signals via the RAS-MEK-MAPK and PI3K-AKT pathways, which further promotes tumor advancement [23]. After EGFR associates with HER2 to create EGFR-HER2 heterodimers, it initiates conformational alterations in the receptor, activates the intracellular domains of tyrosine kinases, significantly amplifies downstream signaling pathways (including MAPK and PI3K-AKT pathways), and encourages the proliferation, survival, and metastasis of tumor cells [24]. Furthermore, research has shown that increased levels of EGFR expression can facilitate the development of EGFR-HER2 heterodimers and hinder the internalization and effectiveness of antibody-drug conjugates (ADCs), but the internalization and effectiveness of ADCs can be recovered after knocking out or targeting EGFR with drugs [25].

Structural Characteristics of the ERbB2 Receptor

The four members of ERBB (also known as EGFR) proteins belong to subclass I of the receptor tyrosine kinase (RTK) superfamily; these include EGFR/ERbB1/HER1, ERbB2/HER2, ERbB3/HER3, and ERbB4/HER4. These receptors play a crucial role in numerous cellular functions, such as growth, proliferation, differentiation, and migration [27]. Each receptor consists of an extracellular domain (ECD) or ligand-binding region along with a single transmembrane domain (TMD). Furthermore, all receptors have a cytoplasmic/intracellular section that includes a juxtamembrane domain (JMD), a kinase domain, and a C-terminal tail domain [28, 29]. The ECD is made up of four subdomains (I–IV); domains II and IV take on an auto-inhibited tethered (closed) conformation when no ligand is present. The dimerization arm in domain II unhinges when ligands I and III interact, resulting in receptor homo- or heterodimerization, allosteric kinase activation, and phosphorylation of the C-terminal tail domain [29]. This activity involves downstream mediators to drive crucial cellular signaling pathways and attracts and activates a variety of downstream signaling proteins with phosphotyrosine binding structural domains or Src homologous structure-2 (SH2) [30]. EGF-activated ERbB2 binds Shc much less strongly than ERbB2 that has dimerized due to mutations in the transmembrane structural domain, even though the two proteins have similar levels of total phosphotyrosine [31]. Consequently, the signal generated by receptor heterodimers is unique; it reflects the characteristics of the heterodimers rather than being the simple sum of the signaling properties of the individual dimer partners.

Growth factors that bind to extracellular regions of the receptor and promote

receptor dimerization and/or oligomerization are examples of receptor-specific ligands that normally activate members of the ERBB family [32]. However, because it lacks high-affinity ligands and has an entirely distinct extracellular structural domain from other receptors, ERbB2 is a special member of the ERBB family. With an exposed dimerization loop in domain II and a missing domain III-V connection, ERbB2 has a stable conformation that resembles the ligand-activated state [33, 34]. ERbB2 does not bind to ligands is because structural domains I and III are close together in the „open" conformation, which inhibits ligand binding to EGF-related peptides [33].

Notably, ERbB2 cannot attach to any growth factor, which means that functional ERbB2/ERbB2 homodimers cannot be produced. Functional homodimers are only produced in response to non-physiological ERbB2 overexpression [35]. Every other member of the ERBB family has different signaling capacity and prefers ERbB2 as a dimer partner [36, 37]. In this regard, homodimers have less signaling continuity than heterodimers [38]. Kinase-deficient ERbB3 and ligand-free ERbB2 can be added to the signal transduction cascade by ERBB heterodimerization. This discovery suggests that this ERBB pair acts as an oncogenic unit; it is the most efficient in terms of downstream signaling, ligand-induced tyrosine phosphorylation, and contact strength [36, 39]. Research suggests that the presence of ERbB3 may be necessary for the carcinogenic activity of ERbB2 from tumor ERbB2 overexpression [40, 41].

It is interesting to note that ligand-induced ERBB receptor heterodimerization follows a strict hierarchy. ERbB2 may be involved in the lateral transmission of signals between other ERBB receptors, as evidenced by the fact that ERbB3 activation is inhibited in its absence. Furthermore, as an intramembrane regulator of ERbB2 activity, a member of the mucin family alters the location of ERbB2 (especially in a phosphorylated form) in the colorectum's epithelial cells, suggesting that it is especially crucial for controlling ERbB2 signaling [42]. Consequently, all of the EGF-related peptides induce heterodimerization and cross-phosphorylation, which ultimately results in tyrosine phosphorylation, even though none of them bind to ERbB2 directly. Phosphorylation cascades, which start with receptor modifications and end at the level of particular transcription factors, are how the signal flow is carried out.

The distinct role of ERbB2 in cancer biology and its clinical importance

ERbB2 (HER2), a member of the EGFR family, is notable for its distinct biological characteristics and its crucial role in the progression of cancer [43]. Unlike other members of the EGFR family, ERbB2 does not possess the ability to bind ligands directly. Instead, it serves as a favored partner for heterodimerization, increasing the signaling effectiveness of other ERBB receptors [44]. This trait enhances essential pathways such as PI3K-AKT and RAS-RAF-MEK-ERK, which are responsible for regulating cell growth, survival, and metabolism [45]. The overexpression or amplification of the ERbB2 gene is a defining feature of various aggressive cancers, such as breast and gastric cancers [46]. This abnormal activity of ERbB2 leads to uncontrolled cell growth, increased cell survival, and heightened metastasis, all of which result in poorer clinical outcomes. The significance of ERbB2 in a clinical setting is highlighted by its role as both a prognostic indicator and a target for therapy. In breast cancer, around 20–30% of cases show ERbB2 overexpression or gene amplification, which is linked to a more aggressive tumor profile characterized by rapid growth, greater metastatic potential, and a worse prognosis if left untreated [47]. Recognizing ERbB2 positive tumors allows healthcare providers to customize treatment plans, enhancing patient outcomes and overall quality of life. The widespread significance of ERbB2 in cancer care emphasizes its role as both a biomarker and a target for therapy in different types of cancer [48].

The occurrence of ERbB2 overexpression in gastric and gastroesophageal cancers varies between 4.4% and 53.4%, with mean at 17.9% [49, 50]. Numerous studies suggest that ERbB2 serves as a negative prognostic indicator, exhibiting more aggressive biological behavior and increased rates of recurrence in tumors that are ERbB2 positive [51-53]. However, additional research revealed no link between ERbB2 and prognosis in both early and advanced stages of cancer [54-57].

ERbB2 targeted molecular therapy

Trastuzumab is a monoclonal antibody that targets ERbB2. As one of the earliest drugs designed for molecular targeting, it was initially launched for the treatment of advanced breast cancer that is positive for ERbB2/HER2 [3]. There is no agreement on how trastuzumab functions within cancer cells, but the available evidence suggests that, besides blocking the dimerization of human epidermal growth factors with other members of this family and promoting endocytosis, it also appears to trigger cell-mediated immunity and curb angiogenesis [58].

In the trial involving trastuzumab for gastric cancer (ToGA), individuals with unresectable gastric and gastroesophageal tumors that expressed ERbB2 gene, were given either chemotherapy combined with trastuzumab or chemotherapy by itself. Patients who were administered trastuzumab demonstrated a statistically significant improvement in overall survival compared to those who only received chemotherapy [12].

Other molecular agents aimed at ERbB2 have been evaluated or are presently under investigation, including pertuzumab, lapatinib, and the antibody-drug conjugate trastuzumab-emtansine (TDM-1) [59-61]. Nonetheless, the effectiveness of these agents has been demonstrated to be either inadequate or slightly better than trastuzumab. Trastuzumab was the first targeted molecular agent authorized as a conventional treatment for gastric cancer, yet it is still being researched for more effective applications [61, 62]. Therefore, it is essential to assess the ERbB2 status in advanced gastric or gastroesophageal junction adenocarcinoma to identify patients who could gain from this potential treatment.

ERbB2 status

Either biopsy or surgical resection specimens can be tested to determine the ERbB2 status. Immunohistochemistry (IHC) assesses the expression of cancer cells' membrane proteins. Immunoreactive cancer cell intensity and proportion are evaluated using values ranging from 0 to 3+ (Table 1). In situ hybridization (ISH) determines whether gene amplification is present or not. It includes fluorescence in situ hybridization (FISH), chromogenic in situ hybridization (CISH), silver-enhanced in situ hybridization (SISH), and dual in situ hybridization (DISH). While most assays employ a chromosomal enumeration probe (CEP17) to measure the ratio of ERbB2 signals to copies of chromosome 17, other assays utilize a single ERbB2 probe to measure the number of ERbB2 gene copies present. ISH has been utilized to confirm instances that are IHC-equivocal [63]. In the United States and Japan, ERbB2 positive gastric cancer is classified as IHC 3+ or ISH positive, while in Europe, it is IHC 3+ or 2+ with ISH positivity [64, 65]. Using the ToGA trial's eligibility requirements, the FDA in the US has authorized trastuzumab in combination with chemotherapy for metastatic gastric cancer. This approval is restricted to patients who have an IHC score of 3+ or 2+ and ISH positive. Patients who were IHC 0 or 1+ and FISH positive did not significantly improve their chances of survival [66].

The American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) 2013 guidelines define ERbB2

Table 1. Criteria used in the ToGA trial for scoring ERbB2 expression by immunohistochemistry (IHC) in gastric and gastroesophageal junction adenocarcinoma [66]

ERbB2 IHC Score	ERbB2 IHC pattern in surgical specimen	ERbB2 IHC pattern in biopsy specimen	ERbB2 expression assessment
0	Less than 10% of cancer cells exhibit either no response or membrane reactivity	No reactivity or no membranous reactivity in any cancer cell	Negative by IHC
1+	About 10% of cancer cells have weak or scarcely noticeable membrane reactivity; these cells are reactive only in a portion of their membrane	Cancer cell cluster* that exhibits weak or imperceptible membranous reactivity regardless of the proportion of positive cancer cells	Negative by IHC
2+	≥10% of tumor cells had weak to strong entire, basolateral, or lateral membrane reactivity	Regardless of the proportion of cancer cells that are positive, a cancer cell cluster* with mild to moderate complete, basolateral, or lateral membranous reactivity	Equivocal by IHC
3+	At least 10% of cancer cells have strong total, basolateral, or lateral membrane reactivity	Cancer cell cluster* with a strong complete basolateral, or lateral membranous reactivity irrespective of percentage of cancer cells positive	Positive

* - Cancer cell cluster consisting of ≥5 neoplastic cells

amplification as an ERbB2:CEP17 ratio of ≥2, which is consistent to the detection of ERbB2 gene amplification by FISH in breast cancer [67]. Hoffman et al. created a four-tiered IHC scoring system (Table 1) for gastric cancer based on the evaluation area limit of at least 10% stained tumor cells for resection specimens and a small cluster of cells (≥5 neoplastic cells) for biopsy specimens. This method was also utilized in the ToGA study [68]. For ERbB2 expression, a score of 0 or 1+ is considered negative. A score of 2+ is equivocal and requires confirmation with FISH or other ISH methods.

The progress in ERbB2-targeted therapies

The treatment of many tumors, especially HER2 (ERbB2)-positive breast cancer, has been entirely reshaped by the identification of ERbB2 as a prognostic marker. 15–20% of instances of breast cancer are ERbB2 positive tumors, which have historically been linked to poor outcomes due to their aggressive character, quick development, and high propensity for metastasis [69]. ERbB2 overexpression promotes cell proliferation, survival, and resistance to apoptosis by persistently activating important growth signaling pathways as PI3K/Akt and MAPK [70]. These pathways help ERbB2 positive cancers grow more quickly and have a higher chance of spreading. In addition to breast cancer, ERbB2 amplification is seen in 10–30% of esophageal and gastric malignancies, especially gastroesophageal junction adenocarcinomas, where it also negatively impacts prognosis and causes aggressive disease [71]. While less common, ERbB2 amplification can also be seen in other malignancies, including bladder, ovarian, and non-small cell lung cancer (NSCLC), where it is associated with worse clinical outcomes and more aggressive illness. However, with the introduction of ERbB2 targeted treatments, the outlook for ERbB2 positive tumors has improved, offering new therapeutic choices and better patient outcomes [72]. The first significant advancement in ERbB2 targeted treatment, trastuzumab (Herceptin), selectively binds to the extracellular region of the HER2 receptor to disrupt signaling and inhibit tumor growth. Trastuzumab uses antibody-dependent cellular cytotoxicity (ADCC) to mark tumor cells for immune system destruction [73]. It is now the accepted treatment for ERbB2 positive breast cancer, gastroesophageal junction adenocarcinoma, and ERbB2 positive metastatic gastric cancer. Since then, several ERbB2 targeted treatments have been developed, such as fam-trastuzumab deruxtecan-nxki (Enhertu), margetuximab (Margenza), trastuzumab deruxtecan (Enhertu), adotrastuzumab emtan-

Table 2. ERbB2 Targeted drugs

Drug	Class	Mechanism of action	Indications	References
Trastuzumab	Monoclonal antibody	Interacts with the extracellular domain of ERbB2 (HER2), blocking dimerization and signaling; enhances ADCC	ERbB2 positive breast cancer, gastric cancer	[46]
Pertuzumab	Monoclonal antibody	Interacts with an alternative site on ERbB2, blocking receptor dimerization with HER3	ERbB2 positive breast cancer, neoadjuvant and metastatic	[77]
Trastuzumab deruxtecan	Antibody drug conjugate	Trastuzumab is conjugated with deruxtecan, which is a topoisomerase inhibitor, specifically aimed at ERbB2 positive cells and providing a cytotoxic agent	ERbB2 positive breast cancer, gastric cancer, others	[78]
Margetuximab	Monoclonal antibody	Antibody designed with improved Fc receptor interaction, boosting the immune response against ERbB2 positive cells	ERbB2 positive breast cancer (advanced, refractory)	[79]
Fam-trastuzumab deruxtecan-nxki	Antibody drug conjugate	Targeted delivery of a topoisomerase inhibitor (deruxtecan) specifically to ERbB2 positive cells	ERbB2 positive breast cancer, gastric cancer, others	[80]
Neratinib	Small molecule inhibitor	Non-reversible pan-HER receptor inhibitor that focuses on HER1, HER2, and HER4, blocking signaling pathways	Extended adjuvant treatment of ERbB2 positive breast cancer	[81]
Tucatinib	Small molecule inhibitor	Targeted ERbB2 inhibitor, blocks ERbB2 signaling and prevents the proliferation of tumor cells	Breast cancer	[82]

sine (Kadcyla), and pertuzumab (Perjeta) [74]. Monoclonal antibodies act by attaching to ERbB2, inhibiting receptor dimerization, and activating ADCC, which in turn inhibits tumor growth. Each of these treatment options marks a notable advancement in cancer therapy, allowing for more precise interventions that specifically obstruct ERbB2 signaling while minimizing off-target effects.

The advancement of these treatments has significantly changed the outlook for individuals with ERbB2 positive cancers, trans-

Table 3. Major clinical studies on ERbB2 targeted treatment in gastric cancer

CT - chemotherapy
DCR - disease control rate
FLOT - 5-fluorouracil, leucovorin, oxaliplatin, docetaxel
m - months
mPFS - median progression free survival
mOS - median overall survival
mpRR - major pathological response rate
ORR - objective response rate
pCR - pathological complete response
XELOX - oxaliplatin, capecitabine
***** - Associated treatment recommended by clinical guidelines

Anti-HER2 (ERbB2) drug	Key trial/NCT number	Phase	Design	Results	References
Trastuzumab	NEOHX	II	Trastuzumab + XELOX	R0 resection rate: 78%; pCR: 8%	[86]
	HER-FLOT	II	Trastuzumab + FLOT	R0 resection rate: 93%; pCR: 21.5%	[87]
	PETRARCA	II	Trastuzumab + pertuzumab + FLOT vs FLOT	pCR: 35% vs. 12%	[88]
	ToGA*	III	Trastuzumab + CT vs CT	ORR: 47% vs. 35%; mOS: 13.8 vs. 11.1 m; mPFS 6.7 vs. 5.5 m	[12]
	KEYNOTE811	III	Pembrolizumab + trastuzumab + CT vs Trastuzumab + CT	ORR: 74.4% vs. 51.9%; pCR 11.3% vs. 3.1%; mOS: 20.0 vs. 16.8 m; mPFS 10.0 vs. 8.1 m	[89]
	HER-RAM	Ib/II	Trastuzumab + ramucirumab + paclitaxel	ORR: 54%; DCR: 96%; mOS: 13.6 m; mPFS: 7.1 m	[90]
	JACOB	III	Trastuzumab + pertuzumab + CT vs. CT	mOS: 17.5 vs. 14.2 m mPFS: 8.5 vs. 7.2 m	-
Margetuximab	MAHOGANY	II/III	Margetuximab + retifanlimab	Cohort A (HER2 3+, PD-L1+) ORR: 53%; DCR: 73%	[91]
	CP-MGAH22-05	Ib/II	Margetuximab + pembrolizumab	HER2 3+, PD-1+ cohort; ORR: 44%	[92]
Lapatinib	LOGiC	III	Lapatinib + XELOX vs XELOX	ORR: 53% vs. 39%; mOS: 12.2 vs. 10.5 m; mPFS: 6.0 vs. 5.4 m	[93]
	TyTAN	III	Lapatinib + paclitaxel vs Paclitaxel	ORR: 27% vs. 9%; mOS: 11.0 vs. 8.9 m; mPFS: 5.4 vs. 4.4 m	[94]
Tucatinib	MOUNTAINEER02	II/III	Trastuzumab + tucatinib + ramucirumab + CT	Ongoing	-
Pertuzumab	JACOB	III	Pertuzumab + trastuzumab + CT vs Trastuzumab + CT	ORR: 56.7% vs. 48.3%; mOS: 17.5 vs. 14.2 m; mPFS 8.5 vs. 7.0 m	[95]
Trastuzumab deruxtecan (T-DXd)	Destiny-Gastric02*	II	T-DXd	ORR: 41.8%; mOS: 12.1 m; mPFS: 5.6 m	[96]
	Destiny-Gastric04	III	T-DXd vs Taxane + ramucirumab	Ongoing	-
Afatinib	LOGiC (NCT00680901)	III	Lapatinib + capecitabine + oxaliplatin vs placebo + capecitabine + oxaliplatin	mOS: 12.2 vs. 10.5 m mPFS: 6.0 vs.5.4 m	-

forming their previously grim prognosis into a more controllable situation with the potential for tailored treatment options. Consequently, ERbB2 status has emerged as an essential element in directing treatment decisions, enhancing therapeutic approaches, and boosting patient outcomes [75]. These therapies that target ERbB2 are frequently combined with other treatments to enhance their efficacy. For instance, trastuzumab is typically paired with chemotherapy in cases of ERbB2 positive breast cancer, whereas newer options like Trastuzumab deruxtecan (Enhertu) and pertuzumab are included in combination strategies to address resistance and boost effectiveness [76]. The ongoing advancement and enhancement of these treatments, backed by continuous clinical research and partnerships among biotechnology firms, have revolutionized the therapeutic environment, instilling optimism in patients and increasing survival probabilities. (Table 2) below categorizes these treatments by their type (monoclonal antibodies versus small molecule inhibitors), detailing their modes of action and uses, which offers a thorough summary of the existing and developing therapies for ERbB2 positive cancers.

Research progress and issues

In the era of precision oncology, the primary objective of personalized, patient-focused therapy is to identify the optimal timing and appropriate treatment mix for the suitable patient population. Years of research have led to the development of a comprehensive array of ERbB2 (HER-2) targeted therapies, such as monoclonal antibodies, antibody-drug conjugates (ADCs), and tyrosine kinase inhibitors (Table 3). Numerous therapy combinations are currently being researched. For example, in patients with ERbB2-positive gastric or gastroesophageal junction cancer, who have already received treatment, tucatinib, a highly selective ERbB2 targeted tyrosine kinase inhibitor with promissing anti-tumor efficacy in preclinical trials, has been investigated in combination with trastuzumab, ramucirumab, and paclitaxel. The bispecific antibody zanidatamab (ZW25) has shown greater anti-tumor effectiveness in both laboratory and animal studies compared to trastuzumab across different ERbB2 expression levels. In line with current standards, the combination of ZW25 with chemotherapy has yielded enhanced clinical responses, achieving an overall response rate of 75% as a first-line treatment for gastroesophageal adenocarcinoma, and it has received orphan drug designation for gastric cancer from the FDA [83]. A limited number of clinical trials assessing ERbB2 targeted therapeutics in advanced GC have yielded statistically and clinically meaningful results, such as the ToGA study, KEYNOTE-811, and DESTINY-Gastric02*. Additional study and more consistent results in larger demographic groups are needed, as seen by other studies that have had little to no positive influence despite offering useful information.

Alongside clinical trials, fundamental and translational research such as genomics, proteomics, transcriptomics, and immunogenomics plays a crucial role in advancing targeted oncology [84]. A comprehensive understanding of the broad molecular landscape can guide clinical practice, including selecting patients, developing combination treatment strategies, and addressing treatment resistance. Recent technological advancements, such as next-generation sequencing (NGS), big data analytics, and bioinformatics methods, have significantly enhanced our understanding of the molecular characteristics of ERbB2 positive gastric cancer (GC). For instance, in the JACOB trial, while no significant overall survival benefit was observed, a post hoc translational analysis revealed that high ERbB2 copy number variation (CNV), measured through NGS, was linked to improved clinical outcomes; this suggests that more targeted patient selection will be crucial in future research. Additionally, a study by Xu et al. that utilized whole exome sequencing on paired tumor samples taken before and after trastuzumab treatment demonstrated a positive relationship between increased chromosomal instability and extended survival [85]. Key insights into ERbB2 are summarized in Table 4 (Table 4). Since tumor heterogeneity poses a significant challenge to precision medicine in gastric cancer (GC), a more thorough and detailed understanding of the molecular characteristics of ERbB2 positive GC would greatly enhance clinical application.

Moving into the future, several promising developments may help the treatment of ERbB2-positive GC [97]. Identifying new predictive biomarkers will be essential for choosing patients who will benefit from ERbB2- targeted therapy and for tailoring treatments to

Table 4. Key points of ERbB2 in gastric cancer

Aspect	Key points
Prevalence	ERbB2 amplification/overexpression in 10-20% of gastric & gastroesophageal junction cancers; more common in intestinal-type than diffuse-type
Biological role	Member of EGFR family; activated via heterodimerization; drives proliferation, angiogenesis, invasion, and survival through PI3K/AKT, MAPK/ERK, JAK/STAT pathways
Clinical significance	Linked with aggressive disease, poor prognosis and determines eligibility for ERbB2-targeted therapy
Testing methods	Usually gene amplification; gastric cancer requires different scoring criteria vs breast cancer
Emerging therapies	Lapatinib (limited benefit); Margetuximab (engineered antibody); HER2 + immunotherapy (checkpoint inhibitors under trial)
Future promise	Liquid biopsy for real-time monitoring and molecular profiling for personalized medicine

each patient's unique molecular and genetic profile [98]. Additionally, a more sophisticated and customized approach to therapy is anticipated as personalized medicine continues to advance, considering factors such as immune status, tumor heterogeneity, and genetic background. Designing clinical trials that are more precise, innovative, and logically structured will be essential in light of historical phenomena, which, include both successes and failures. In the context of precision medicine, selecting the appropriate populations, timing, and combination tactics remain major challenges. Future advancement will depend on combining multiomics-driven clinical trials with extensive translational and preclinical research.

CONCLUSION

Research into targeted therapies for gastric cancer (GC) is currently progressing rapidly. Although adverse effects are infrequently reported, a significant number of clinical trials suggest that ERbB2 (HER2) may serve as both a promising therapeutic target and biomarker in GC. There has been a lot of progress in treating GC, but there are still many obstacles to overcome, including drug resistance, the limited effectiveness of current treatments following trastuzumab failure, and the requirement for more accurate prognostic biomarkers. However, with the advent of novel therapeutic modalities like as improved ADCs, bi-specific antibodies, immune checkpoint inhibitors, and liquid biopsies, the treatment landscape for ERbB2-positive GC has potential for revolutionary advancements. It is anticipated that highly effective ERbB2-targeted therapies will become available for GC soon due to extensive research.

CONFLICT OF INTEREST

All authors declare no conflict of interest.

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Funkcija gena ERbB2 u kanceru i razvoju prilagođenog lečenja raka želuca: signalni putevi u pristupu lečenja

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KRATAK SADRŽAJ

Uvod: Molekularno ciljane terapije, poput onih usmerenih na receptor tirozinkinazu erb-b2 (ERbB2), poznat i kao receptor ljudskog epidermalnog faktora rasta 2 (HER2), očekuje se da značajno unaprede trenutni sistemski tretman u odnosu na konvencionalnu citotoksičnu terapiju. Najnoviji napreci u molekularno ciljanim terapijama, posebno one koje su usmerene na HER2, značajno su poboljšali terapijski potencijal kod pacijenata sa karcinomom želuca. Receptori ljudskog epidermalnog faktora rasta predstavljaju ključni faktor u nastanku i progresiji karcinoma želuca. Deo karcinoma želuca karakteriše povećana ekspresija ili amplifikacija gena ERbB2, što može stimulisati rast tumora i metastatsko širenje. Status ERbB2 ima ključnu ulogu u definisanju terapijskih strategija, posebno u identifikaciji pacijenata koji mogu imati koristi od ciljane terapije.

Metodologija: Za pretragu literature korišćene su baze podataka PubMed, NIH, Scopus, Web of Science i Google Scholar. Relevantni podaci prikupljeni su analizom kliničkih slučajeva, retrospektivnih studija, kliničkih ispitivanja, kliničkih smernica, narativnih pregleda i dostupnih online izvora.

Tema: Rad će detaljno prikazati složene molekularne mehanizme putem kojih ERbB2 utiče na razvoj karcinoma, sa posebnim osvrtom na signalne puteve koji doprinose progresiji karcinoma želuca, kao i najnovija dostignuća u okviru kliničkih ispitivanja. Takođe će biti analiziran napredak u terapiji usmerenoj na ERbB2 i značaj ovog receptora kao potencijalnog cilja u savremenim terapijskim pristupima.

Zaključak: Istraživanja u oblasti ciljane terapije karcinoma želuca su intenzivna i obimna. Brojna klinička ispitivanja ukazuju da ERbB2 (HER2) predstavlja važan terapijski cilj i biomarker u ovom malignitetu. Iako su terapijski pristupi znatno unapređeni, i dalje postoje brojni izazovi koje je potrebno prevazići.

Ključne reči: karcinom želuca, ERbB2, EGF, ciljana terapija, klinička studija

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