Trastuzumab (Herceptin)

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Introduction

Monoclonal antibodies have revolutionized the treatment of many diseases by providing highly specific, targeted therapies. These biologic drugs are designed to recognize particular antigens, making them powerful tools in oncology where abnormal proteins drive cancer progression. One of the most successful and influential monoclonal antibodies is trastuzumab (Herceptin®), a humanized IgG1 antibody that targets the human epidermal growth factor receptor 2 (HER2). HER2 is a receptor tyrosine kinase that is overexpressed in approximately 15–20% of breast cancers, as well as a subset of gastric cancers. Tumors with HER2 amplification tend to be aggressive and associated with poor prognosis. Trastuzumab was developed to specifically target this receptor and interrupt its cancer-promoting signaling pathways. Trastuzumab has become a cornerstone of HER2-positive cancer therapy, dramatically improving patient outcomes (3).

Disease Indications

Trastuzumab is primarily indicated for the treatment of HER2-positive breast cancer, including early-stage, locally advanced, and metastatic disease. HER2-positive breast cancer is

characterized by increased HER2 gene copies and protein overexpression, which leads to excessive activation of cell growth and survival pathways. Before trastuzumab, this subtype was associated with a poor prognosis and high rates of recurrence. Clinical trials demonstrated that adding trastuzumab to chemotherapy significantly improved survival, making HER2-positive breast cancer one of the first examples where a targeted biologic therapy altered the natural course of the disease (3).

In addition to breast cancer, trastuzumab has been shown to benefit patients with HER2-positive gastric and gastroesophageal junction cancers. The ToGA trial, published in The Lancet in 2010, demonstrated that trastuzumab combined with chemotherapy extended survival compared to chemotherapy alone in this patient group (1). This finding expanded the use of trastuzumab beyond breast cancer and highlighted its broader potential in oncology.

Drug Information

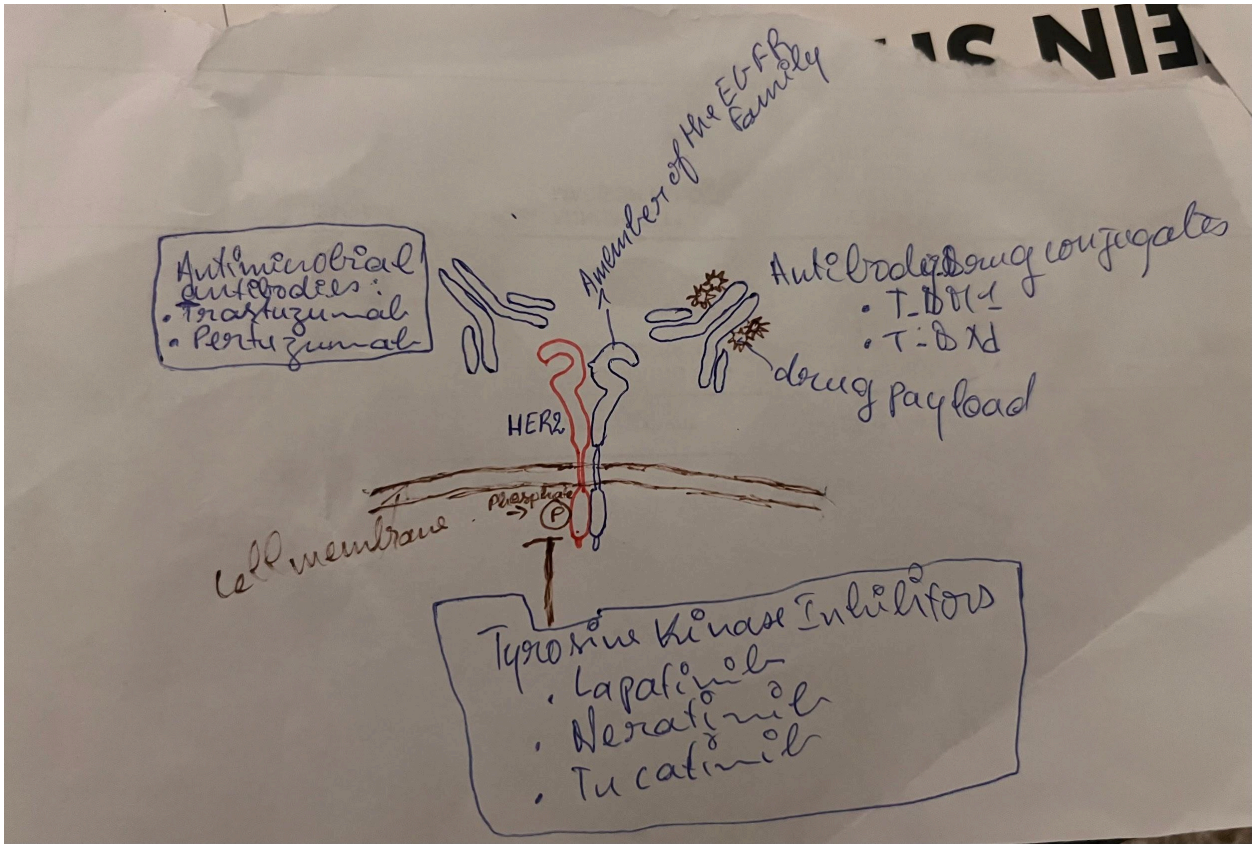
Trastuzumab is marketed by Genentech/Roche and was first approved in 1998 for metastatic HER2-positive breast cancer. Today, it is also approved for adjuvant and neoadjuvant treatment in early breast cancer, as well as for HER2-positive gastric cancer. The drug is administered primarily as an intravenous infusion. A common regimen includes a loading dose of 8 mg/kg followed by a maintenance dose of 6 mg/kg every three weeks (2). A subcutaneous formulation is also available, offering convenience for patients. Trastuzumab is frequently combined with chemotherapy agents such as paclitaxel, docetaxel, or platinum compounds, and in some regimens, it is combined with other targeted therapies like pertuzumab.

Like many effective therapies, trastuzumab carries risks. The most serious side effect is cardiotoxicity, particularly when combined with anthracyclines. This can manifest as left

ventricular dysfunction or congestive heart failure. Although often reversible with discontinuation and medical management, this side effect requires close monitoring of cardiac function throughout treatment (4). Other adverse events include infusion-related reactions, diarrhea, fatigue, and neutropenia. Despite these risks, the survival benefits of trastuzumab generally outweigh the complications when carefully monitored.

Antibody Class and Structure

Trastuzumab is a humanized monoclonal antibody of the IgG1 subclass. Structurally, IgG1 antibodies consist of two heavy and two light chains forming a characteristic Y-shape. The Fab regions at the tips of the Y recognize and bind to the HER2 receptor, while the Fc region interacts with immune effector cells. This structural design is critical because it allows trastuzumab not only to block signaling pathways but also to recruit the immune system against tumor cells . A visual representation of this structure shows trastuzumab binding to the extracellular domain of HER2, thereby preventing receptor activation and downstream signaling.



Mechanism of Action

Trastuzumab works through multiple mechanisms. First, it binds to the extracellular domain (subdomain IV) of HER2, preventing receptor dimerization with other HER family members such as HER3. This inhibition blocks activation of downstream signaling cascades, including the PI3K/Akt and MAPK pathways, which are responsible for promoting tumor cell survival and proliferation . By interfering with these pathways, trastuzumab directly reduces tumor cell growth.

Second, trastuzumab exerts immune-mediated effects. Its Fc region engages natural killer (NK) cells through Fcγ receptors, triggering antibody-dependent cellular cytotoxicity (ADCC). This process leads immune cells to selectively kill tumor cells coated with trastuzumab. Evidence

from both preclinical and clinical studies supports ADCC as an important component of trastuzumab's efficacy .

Finally, trastuzumab has been associated with reduced shedding of the HER2 extracellular domain, a process that can produce a truncated receptor fragment (p95HER2) associated with drug resistance. By blocking this cleavage, trastuzumab may help maintain receptor integrity and reduce resistance mechanisms. In addition, some evidence suggests trastuzumab can inhibit angiogenesis by reducing vascular endothelial growth factor (VEGF) production, thereby limiting tumor blood supply.

Clinical Evidence

The clinical benefit of trastuzumab has been confirmed in multiple pivotal trials. Slamon and colleagues (2001) reported that the addition of trastuzumab to chemotherapy in metastatic breast cancer improved overall survival, response rates, and time to disease progression, although with an increased risk of cardiac dysfunction . This trial was one of the first to demonstrate the power of targeted antibody therapy in solid tumors.

Subsequent trials expanded its role to earlier stages of disease. The HERA trial, published in 2005, showed that one year of adjuvant trastuzumab after chemotherapy significantly improved disease-free survival in women with HER2-positive early breast cancer . This established trastuzumab as a standard component of curative therapy, rather than being limited to metastatic settings.

Beyond breast cancer, the ToGA trial in 2010 confirmed that trastuzumab improved survival in HER2-positive gastric cancer (1). This marked the first demonstration of targeted therapy

improving outcomes in gastric cancer and cemented trastuzumab's role as a versatile treatment option across multiple tumor types.

Together, these trials illustrate trastuzumab's evolution from an experimental therapy to a global standard of care. Its success has also paved the way for additional HER2-targeted agents, including pertuzumab, trastuzumab emtansine (T-DM1), and newer tyrosine kinase inhibitors.

Conclusion

Trastuzumab represents one of the most significant advances in targeted cancer therapy. By specifically binding HER2 and inhibiting both receptor signaling and promoting immune-mediated killing, it has transformed the outlook for patients with HER2-positive cancers. Its effectiveness in both breast and gastric cancers highlights the importance of precision medicine in oncology. Although cardiotoxicity remains a challenge, careful monitoring allows most patients to benefit safely from treatment. The development and success of trastuzumab also opened the door to an entire class of targeted therapies that continue to shape the future of cancer treatment. For these reasons, trastuzumab is widely regarded as a landmark drug in modern medicine.

References

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