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Trastuzumab, a Monoclonal Antibody used to Treat Breast Cancer

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Abstract

The first HER2-targeted medication, the monoclonal antibody trastuzumab, was approved about 25 years ago as a result of the long-awaited identification of HER2 as an effective and highly sensitive therapeutic target. This marked a significant advancement in the treatment of extremely aggressive HER2-positive breast cancer. Since then, development of newer platforms and more specific therapeutics has accelerated due to the outstanding clinical activity seen in several trials using monoclonal antibodies, tyrosine kinase inhibitors, and antibody-drug conjugates that target HER2. The current guidelines for treating HER2-positive breast cancer are covered in this review, along with the processes underlying resistance to HER2-targeted therapy and novel therapeutic agents, such as immune system-boosting techniques.

Keywords: HER2; PI3K/AKT Pathway; MAPK Pathway; Trastuzumab; Breast Cancer

Abbreviations: BC: Breast Cancer; EGFR: Epidermal Growth Factor Receptor; EBC: Early Breast Cancer; IHC: Immune Histo Chemistry; FISH: Fluorescence in Situ Hybridization; ER: Estrogen Receptor; ASCO: American Society of Clinical Oncology; CHO: Chinese Hamster Ovary; LVEF: Left Ventricular Ejection Fraction.

Introduction

Pathology, molecular biology, and drug development advancements have made it possible for HER2-positive breast cancer (BC), a historically aggressive subtype, to achieve remarkable results. The first tyrosine kinas, epidermal growth factor receptor (EGFR), was identified in 1978, and the research was further energized in 1984 with the finding of the new or HER2 (also known as ERBB2) gene [1]. The development of a monoclonal antibody (mob) against HER2, trastuzumab [2], was ultimately prompted by the finding that amplification or over expression of HER2 was linked to incredibly low survival in BC.

Up until this moment, the most aggressive BC histologists with the worst prognoses were thought to be triple-negative and HER2-overexpressing diseases. Treatment for advanced BC was limited to palliative measures since it was deemed incurable. However, survival rates have significantly improved as a result of more recent and creative therapeutic approaches.

The tumour's HER2 reliance and the availability of potent HER2-targeted medications, including trastuzumab, pertuzumab, and most recently, tutunitinib and trastuzumab deruxtecan (T-Dud), have improved patient survival in those with HER2-positive (HER2+) BC [3]. When HER2+ early breast cancer (EBC) is treated with chemotherapy and dual antibody treatment, the survival rate currently exceeds 90% [4].

Further evidence that most patients presenting with early cancer are cured comes from the fact that over half of patients with metastatic HER2+ disease receive their diagnosis from scratch [5].

Notwithstanding this achievement, metastatic HER2+ tumours inevitably acquire resistance, resulting in the advancement of the illness. Therefore, increasing the number of patients treated in the early setting and preventing recurrence are the objectives of therapy for HER2+ BC. In those HER2+ cancers that do present with de novo stage IV disease or ultimately recur, development of novel therapies is needed as these tumours continue to be dependent on HER2 signalling. Therefore, extensive research is ongoing in the preclinical, translational and clinical arenas to develop original and more potent therapies for this exceptionally sensitive target, HER2 [6].

Two Decades of Clinical Experience: Historical context: the path towards practical application. A humanized monoclonal antibody called trastuzumab targets the extracellular domain of HER-2/ErbB2, a transmembrane receptor that belongs to the HER/Ebb group and has intracellular tyrosine kinas activity. Following HER-2's identification in 1985 and its identification in human breast cancer, the protein quickly become the subject of significant research. About 20–25% of all breast carcinomas were found to be poorly differentiated, rapidly growing tumours with a high potential for metastasis; these tumours were linked to it's over expression. Such breast cancer cells have been shown to be successfully inhibited in proliferating by Mobs against HER-2. This novel class of anticancer medication was prepared for clinical practice testing after the humanization of the marine anti-HER-2 mAb 4D5.

Background

The erbB family of epidermal growth factor receptor tyrosine kinase includes HER-2.When it was discovered that the avian erythroblastosis tumour virus produced an oncogene that was extremely similar to the human epidermal growth factor receptor (HER-1, also known as ErbB1 and EGFR), the erbB receptor tyrosine kinases were linked to cancer in the early 1980s. Later on, a gene known as neu was discovered from a chemically produced rat neuroblastoma that could change fibroblast cell lines in culture. It was demonstrated to be connected to the HER-1 gene but different from it. Two other groups independently identified human erbB-related proto-oncogenes around the same time and gave them the names c-erbB2 and HER-2. It was later discovered that these genes were identical to neu. A human mammary cancer cell line was shown to overamplify an EGFR-related gene that King and colleagues also discovered to be identical to the HER-2/neu/erbB2 gene.

The HER-2 gene is found on chromosome 17, while the HER-1 gene is mapped to chromosome 7. Additionally, the HER-2 mRNA and protein have distinct sizes from the HER-1 gene products. These are just a few of the differences between HER-1 and HER-2. Two additional receptors, HER-3 and HER-4 (erbB3 and erbB4), are members of the erb B receptor tyrosine kinase family. All four receptors share an overall membrane-spanning structure made up of extracellular and transmembrane components as well as an intracellular region that contains a kinase domain flanked by tyrosine autophosphorylation sites. The various family members' domains differ from one another in a number of functional ways. For instance, HER-2 doesn't seem to have a direct ligand, and HER-3 doesn't seem to have intrinsic kinase activity. As a result, signaling requires a variety of intricate relationships including dimerization amongst the various family members. The HER-2 receptor can communicate by joining forces with other ligand-bound HER family members to create heterodimers, or by combining with two other HER-2 molecules to form a homodimer that possesses intrinsic kinase activity. Activated homo- and hetero-dimers are produced more frequently when HER-2 is overexpressed. Many adaptor proteins are drawn to the cytoplasmic domains by erbB receptor kinase activation, which in turn sets off a variety of downstream signaling cascades. Cell growth, division, differentiation, migration, and adhesion are all impacted by HER-2 activation.

HER-2 receptor overexpression was first observed in 20–30% of human breast cancers, according to research by Slamon and colleagues. The HER-2 gene is amplified in the great majority of instances, which results in overexpression. Increased quantities of mRNA are found by Northern blot and of the HER-2 receptor are found by immune histochemistry (IHC) or Western blot analysis when the HER-2 gene is amplified. Fluorescence in situ hybridization (FISH) provides the most convincing evidence of over-amplification of the gene when it reveals numerous copies of the HER-2 gene in the nuclei of afflicted cells. This method has proven to be effective in identifying HER-2 gene amplification in clinical specimens.

Early on in the development of invasive breast cancer, as well as in ductal carcinoma in situ, HER-2 gene amplification is observed. Overexpression a number of established poor histological prognostic characteristics, such as tumor size, high grade, a large proportion of S-phase cells, aneuploidy, and lack of steroid receptors, are correlated with HER-2 expression in breast cancer cells. A worse prognosis for breast cancer is correlated with overexpression of HER-2. Overamplification of the HER-2 gene was discovered to be a potent independent adverse prognostic factor in 1987 after Slamon and colleagues studied tumor samples from 86 patients who tested positive for lymph nodes. 526 of the 668 human breast cancer specimens that Slamon and colleagues gathered in 1989 had enough clinical data to investigate a potential relationship between HER-2 expression and outcome. HER-2 gene amplification was present in 27% of

the 345 no depositive individuals. In multivariate analysis, this was revealed to be a significant predictor of both disease-free and overall survival (P=0.006 and 0.045, respectively), outperforming all other prognostic markers with the exception of nodal status. Among the 181 node-negative patients in this initial investigation, there was no correlation discovered between gene amplification and the course of the disease. HER-2 overexpression was once more found to be prognostically significant in node-positive patients with breast cancer but not in node-negative patients, according to a retrospective series of 1506 patients from the Ludwig International Breast Cancer Study Group. More recent research, however, has shown that HER-2 gene amplification, even in patients without node, is an independent prognostic predictor.

According to available data, there might be a connection between HER-2 overexpression and therapeutic response. In endocrine therapy, for instance, a recent neoadjuvant trial suggests that in a small subset of patients with both HER-1 and/or HER-2 positive and estrogen receptor (ER) positive cancers, letrozole has a significantly higher response rate than tamoxifen (15/17 88% compared with 4/19 21%, odds ratio 28, P = 0.004). Anacyclines may also be a more effective chemotherapy drug than cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) regimens for patients with breast cancer that overexpresses HER-2. This is based on circumstantial data. Piccart, et al. recently reviewed this complex topic.

Despite the compelling evidence, there is not yet enough information to recommend that patients' HER-2 status be used to determine their course of treatment in addition to whether or not they would benefit from HER-2-directed medicines. The American Society of Clinical Oncology (ASCO) committee on the update of guidelines for the use of tumor markers in breast and colon cancer declared in 2000 that 'the use of c-erbB2 data to decide whether to prescribe endocrine therapy either in the adjuvant or metastatic setting is not recommended' and 'levels of c-erbB2 expression should not be used to exclude patients from anthracycline treatment'.

Development of Trastuzumab

The identification of HER-2 overexpression in a notable minority of human breast tumors, along with its unfavorable prognostic significance, led researchers to create therapeutic drugs that target HER-2.Raising murine monoclonal antibodies to the HER-2 extracellular domain was done by a number of organizations, including employees of Genentech Inc. It was demonstrated that some of these antibodies could stop the growth of cell lines that overexpressed the receptor. This effect was also observed in human breast cancer xenografts with overexpression of HER-2, where the antibody's effects were discovered to work in concert with anti-neoplastic drugs like cisplatin.

The most effective of the murine monoclonal antibodies that the Genentech researchers created was muMAb 4D5. These antibodies were able to suppress HER-2 + cell lines. According to Sarup, et al. this antibody was found to significantly suppress the growth of cell lines that overexpressed HER-2, while it had little to no effect on cells that did not express HER-2 at all. Based on its strong ability to prevent the growth of human breast cancer xenografts, 4D5 was chosen for additional clinical development.

To lessen the possibility of inducing an immunological reaction against mice in humans, the 4D5 murine monoclonal antibody was made human. Carter, et al. created a vector expressing a chimeric antibody by subcloning the antibody's hypervariable region into plasmids encoding an IgG1 constant region and a human κ light chain. Site-directed mutagenesis was subsequently used to further humanize the antibody. Chinese hamster ovary (CHO) cells were transduced with the vector, and the cells produce the antibody into the culture medium, where it is subsequently purified. Trastuzumab is a chimeric antibody that is 95% human and 5% murine, and it maintains the original antibody's strong affinity for the HER-2 epitope.

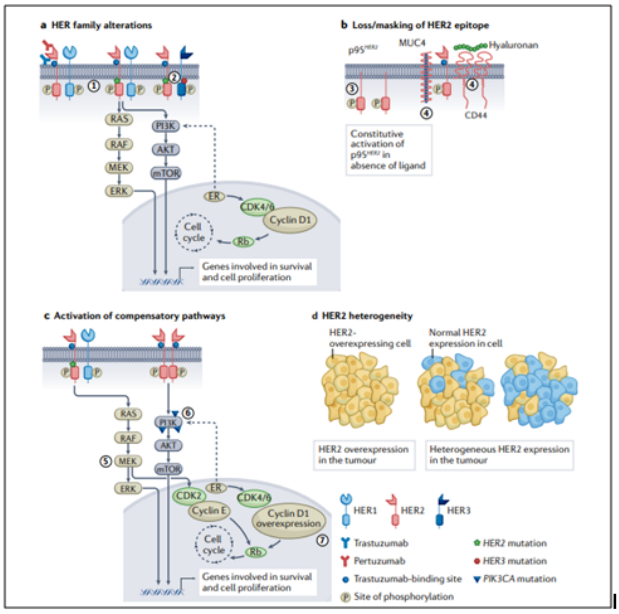

Figure 1: Choose HER2-targeted resistance methods.

Mechanism of Action

A monoclonal antibody directed against the human epidermal growth factor receptor 2 (HER2) is called trastuzumab. By attaching itself to one of this receptor's extracellular

domains, trastuzumab prevents HER2 homodimerization and HER2-mediated signaling. Additionally, it may promote antibody-dependent cellular cytotoxicity, which kills HER2 expressing cells [7]. Its mode of action is marginally different from that of the more recent medication pertuzumab, which prevents HER2 from hetero-dimerizing with HER3, a similar growth factor receptor.

Trastuzumab-dkst, a biosimilar chemical, is marketed for sale in the United States. Ado-trastuzumab emtansine is a compound that combines trastuzumab, an anti-microtubule cytotoxic agent, with an antibody [8].

(a) Changes and/or mutations in the HER family of receptors that cause downstream signaling pathways to become active. (1) HER2 mutations that activate the RAS–MAPK and P13K–AKT pathways. (2) Co-occurring HER2 and HER3 mutations that activate the PI3K–AKT pathway. Cells overexpressing the p95HER2 receptor result in the loss of the HER2 extracellular domain (b) Masking of the trastuzumab-binding site on HER2 due to CD44-polymeric hyaluronan complex and mucin 4 (MUC4) overexpression. (3) Overexpression of p95HER2. (4) The CD44–polymeric hyaluronan complex and MUC4 overexpression.

(c) The pathways that compensate are activated. (5) CDK2 kinase is activated by MEK–ERK signaling, which is facilitated by mutations in HER2. (6) P13K–AKT pathway activation is caused by PIK3CA mutations. (7) Overexpression of the Cyclin D1 gene causes resistance to anti-HER2 treatments. (d) Variable expression of reduced sensitivity to HER2-targeted treatments that rely on HER2 overexpression is caused by the HER2 receptor in tumors. Estrogen receptor or ER [9].

Adverse Effect

It is well recognized that trastuzumab can cause cardiotoxicity, which often shows up as a reduction in left ventricular ejection fraction (LVEF). Although the precise etiology of this phenomenon is uncertain, it may be related to cardiac myocytes' reduced ability to remove reactive oxygen species [10].

Transtuzumab has an FDA boxed warning in the United States about both clinical and subclinical heart failure. As per the product label, up to 22% of patients have experienced a decline in LVEF of at least 10%; however, certain studies have indicated an incidence as high as 44% [11]. With an estimated frequency of 2% to 7%, symptomatic congestive heart failure following therapy is less common. Concurrent use of anthracyclines is the main risk factor for the development of cardiotoxicity; patients taking both trastuzumab and anthracyclines have a three to four times increased chance of developing severe cardiotoxicity [12]. A higher risk may also be attributed to advanced age, hypertension, coronary artery disease, and hyperlipidemia. When therapy is stopped, the majority of trastuzumab-induced cardiotoxicity instances in clinical practice seem to be reversible [13,14]. On the other hand, long-term echocardiographic evidence of myocardial dysfunction endures in certain patients [15].

Administering trastuzumab has been associated with severe infusion responses. Anaphylaxis, acute respiratory distress syndrome, interstitial pneumonitis, and edema are a few examples of these. To this end, there is an FDA boxed warning for trastuzumab. The majority of serious incidents happened 24 hours after the first infusion. If any of these occur, trastuzumab should be stopped. All patients should be watched for indications of angioedema, hypotension, or severe dyspnea. Re-treatment following pre-medication (e.g., with acetaminophen and/or diphenhydramine) has been tolerated by some patients, but not by all [16].

Trastuzumab has been linked to a small number of nephrotic syndrome instances, the most common of which are in patients with metastatic stomach cancer.

Other side effects of trastuzumab monotherapy that are frequently reported include: Headache, Chills, Gastrointestinal symptoms (nausea and vomiting; abdominal pain, diarrhea), Cough, Back pain, Upper respiratory symptoms (rhinitis, pharyngitis), Weakness and fatigue [17].

Administration

Management

An intravenous infusion of trastuzumab is given over a period of 30 to 90 minutes. It must not be given as a bolus and must not be given in conjunction with D5W. As mandated by the standards of the National Institute for Occupational Safety and Health (NIOSH), the administration of trastuzumab requires the use of closed-system transfer devices, double-gloves, and a gown because it is a potentially hazardous medicine. A maintenance dose of 2 mg/kg given once a week or 6 mg/kg administered once every three weeks is advised. Initial loading doses may be given at up to 8 mg/kg individuals with mild to severe renal insufficiency are advised to continue using trastuzumab; however, individuals with end-stage renal disease or hepatic impairment have not been investigated with this medication. Transtuzumab's estimated elimination half-life is 28 days; a higher tumor load may cause the elimination half-life to lengthen [7,8]. There is significant interpatient variability in medication clearance rates; higher body weight and lower serum albumin levels have been linked to higher clearance [9].

Dosage schedules for indications that are currently approved include

For HER2-overexpressing breast cancer, the recommended adjuvant treatment in addition to paclitaxel or docetaxel is 4 mg/kg/dose IV given as a single dose in week 1, 2 mg/kg/dose IV given weekly for weeks 2 through 12, and 6 mg/kg/dose IV given every three weeks for weeks 13 through 52. The first 12 weeks of treatment should include both paclitaxel and docetaxel [18].

When Combined with Either Carboplatin or Docetaxel: 4 mg/kg/dose IV given as a single dose in week 1, 2 mg/kg/dose IV given every week from week 2 to week 18, and 6 mg/kg/dose IV given every three weeks from week 19 to week 52; first 18 weeks of paclitaxel and docetaxel as monotherapy after a regimen based on anthracene [19].

Combination treatment with paclitaxel for metastatic breast cancer with overexpression of HER2: In week 1, start with a single IV dosage of 4 mg/kg/dose; starting in week 2, increase the dose to 2 mg/kg/dose each week [20].

Combination Therapy with Pertuzumab: begin with an IV dose of 8 mg/kg/dose on day one of a 21-day cycle for the first cycle, then start cycle 2 at 6 mg/kg/dose for a 21-day cycle. For recurrent disease, as a monotherapy, administer an IV dose of 4 mg/kg/dose for one week, followed by a dose of 2 mg/kg/dose in week two. For HER2-overexpressing metastatic stomach cancer, begin treatment with an IV single dosage of 8 mg/kg on day 1 of a 21-day cycle for the first cycle, and start cycle 2 with an IV single dose of 6 mg/kg on day 1 of a 21-day cycle [21].

Conclusion

Unprecedented improvements in survival have resulted from the amazing journey of HER2's identification as an oncogene, biomarker, and therapeutic target for a very aggressive form of breast cancer. This success can be attributed to the HER2 receptor's exceptional sensitivity to HER2-targeted therapy, which persists even after several treatment modalities. The 1,922 clinical studies for HER2+ BC demonstrate the intense interest in additional research and medication discovery for this specific subset of BCs. This accomplishment and ongoing passion genuinely reflect a great deal of work and collaboration amongst numerous basic and clinical experts to enhance the quality of life for patients. An essential component of the process is bridging the gap in drug development from academics to industry and vice versa. Targeting several pathways has been effective, and investigating resistance mechanisms could lead to the eventual treatment of HER2+ MBC. The addition of "enabling characteristics" to the most current update of the hallmarks of cancer serves as a helpful reminder of the ongoing discoveries being made in the field of cancer research as well as the evolving body of knowledge around the carcinogenic process207. Research is being conducted in many exciting areas; two examples are the use of the microbiome and the ongoing investigation of the gut's function in immunotherapy. Furthermore, a multitude of instruments have been identified and developed to augment the process of drug development. These include artificial intelligence, CRISPR–Cas9, single-cell sequencing, spatial transcriptomics, spatial proteomics, and theragnostic; the inventory continues to expand209–215. Future bispecific and other recently developed medication structures like ADCs will further enhance our capacity to safely target HER2+ cells, while reducing adverse events in our patients. Progress in treating patients with HER2-targeted therapy will be sustained by further research into these novel ideas and application of these techniques, building on previous successes [22-26].

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