The progress of Trastuzumab in the treatment of HER-2 breast cancer

Miao Hong[1, *, †], Peixuan Li[2, *, †], Mengxue Zhang[3, †]

[1]College of Pharmacy University of Cincinnati Ohio, USA

[2]Department of biopharmaceutical Huazhong Unversity of science and technology Wuhan, China

[3]Department of chemistry Chuangnam National University Deajeon, South Korea

[*]hongmo@mail.uc.edu, [*]u201812290.hust.edu.cn, [*]ZHANGMENGXUE960104@gmail.com

[†]These authors contributed equally

Keywords: human epidermal growth factor receptor (HER2), breast cancer, trastuzumab, pertuzumab, clinical trial.

Abstract: In 2020, 10 million individuals have died of cancer worldwide, with 11.7 % of those dying from breast cancer. Breast cancer is a very common disease in the worldwide. People have been looking for a cure for HER2 breast cancer for years. Surgery, radiation, chemotherapy, and immunotherapy are all options. However, the recurrence rate of tumors and the traumatic problems of surgery have not been resolved. Studies have shown that about 20%-30% is HER2 breast cancer and associated with poor prognosis. At the same time, HER2 also provides intervention points for the treatment of breast cancer. Molecular targeted therapy has gradually become a standard therapy and has achieved some success in clinical practice in the past 20 years. Phase II clinical data show that trastuzumab has good safety in the treatment of breast cancer patients with HER2 overexpression, is effective as a single treatment, and can cause a prolonged objective tumor response. Trastuzumab cannot, however, be used to treat all cases of HER2 overexpression. Therefore, drugs of the next generation have also been approved, such as pertuzumab and ado-trastuzumab emtansine. This review will focus on elucidating the mechanism and clinical effects of trastuzumab in the treatment of HER-2 breast cancer, and briefly describe its toxicity and drug resistance.

1. Introduction

Hormones and the presence or absence of the human epidermal growth factor receptor 2 (HER2/neu) receptor are prognostic and predictive factors in breast cancer (BC) and can help determine therapy options [1]. The HER2 receptor usually function in normal tissues, however, it is overexpressed or amplified in cancer cells, and is linked to clinically aggressive tumors and a poor prognosis [2].

Trastuzumab is a modified antibody that attacks the erythroblastic leukemia virus's gene homolog 2 (ErbB2), also known as human epidermal growth factor receptor-2 (HER-2). Overexpression of it has been associated to aggressive growth and a poor prognosis in 20% to 25% of human breast tumors. It's assumed to work in the etiology of HER2-positive cancers as well as their clinical aggressiveness. A murine antibody against the extracellular domain of HER2, 4D5, suppresses the growth of human breast cancer cells overexpressing HER2 in vitro and in xenograft models. To aid clinical research, the complementarity defining region of 4D5 was introduced into the framework of common human IgG1. According to phase II trial data from breast cancer women whose tumors overexpress HER2, trastuzumab has favorable safety qualities, is active as a single treatment, and can cause a prolonged objective tumor response.

In a multicenter phase III clinical trial, chemotherapy (based on doxorubicin or paclitaxel) combined with trastuzumab showed that chemotherapy has an effect on the time and response of disease progression when compared to chemotherapy alone. The drug's action greatly increased the rate of trastuzumab co-administration and survival, whereas overall serious adverse events did not rise. Myocardial dysfunction syndrome is comparable to that seen with anthracyclines, with

chemotherapy combined with trastuzumab being the most prevalent treatment. In October 1998, the United States approved trastuzumab for the treatment of individuals with metastatic breast cancer who overexpress HER2. This was based on the positive findings of clinical trials. MAb has also been listed in Switzerland and Canada since then [3].

The first HER-2 monoclonal antibody to be used in clinical trials was trastuzumab. The drug operates by physically blocking HER-2 molecules, forcing them to form dimers with other HER/ErbB family members and interrupting normal ErbB signaling. To provide a highly selective therapeutic alternative for patients with HER-2 positive breast cancer, ultimately using a chemical that produces fewer or no adverse effects than traditional chemotherapy.

This review briefly introduces HER-positive breast cancer, focusing on the clinical trials of trastuzumab properties and its treatment application of patients overexpressing HER2 receptors.

2. Background of The anti-HER2 antibody

2.1 The anti-HER2 antibody for HER2 breast cancer

Breast cancer cells that carry the HER2 protein receptor are referred to as HER2-positive. In general, this protein aids breast cells in their growth, division, and repair. However, there are situations when the gene that controls the HER2 protein malfunctions, and your body produces an excess of these receptors. This can cause your breast cells to divide and expand out of control. Cancer cells carry an extra copy of the gene that generates the HER2 protein in roughly 1 in 5 breast tumors. Breast cancer that is HER2-positive is more aggressive than other kinds of breast cancer [4].

The treatment for HER2 is successful and these medicines are so effective that HER2-positive breast cancer patients have a very excellent prognosis. Although these medications do not directly target the HER2 protein, certain regular chemotherapy treatments can be useful in treating HER2-positive breast cancer. HER2 testing is recommended for different invasive breast cancer, according to experts, because the results might have a substantial impact on treatment choices and decisions. Except as part of a clinical trial, detection of HER2 ductal carcinoma in situ is not commonly performed.

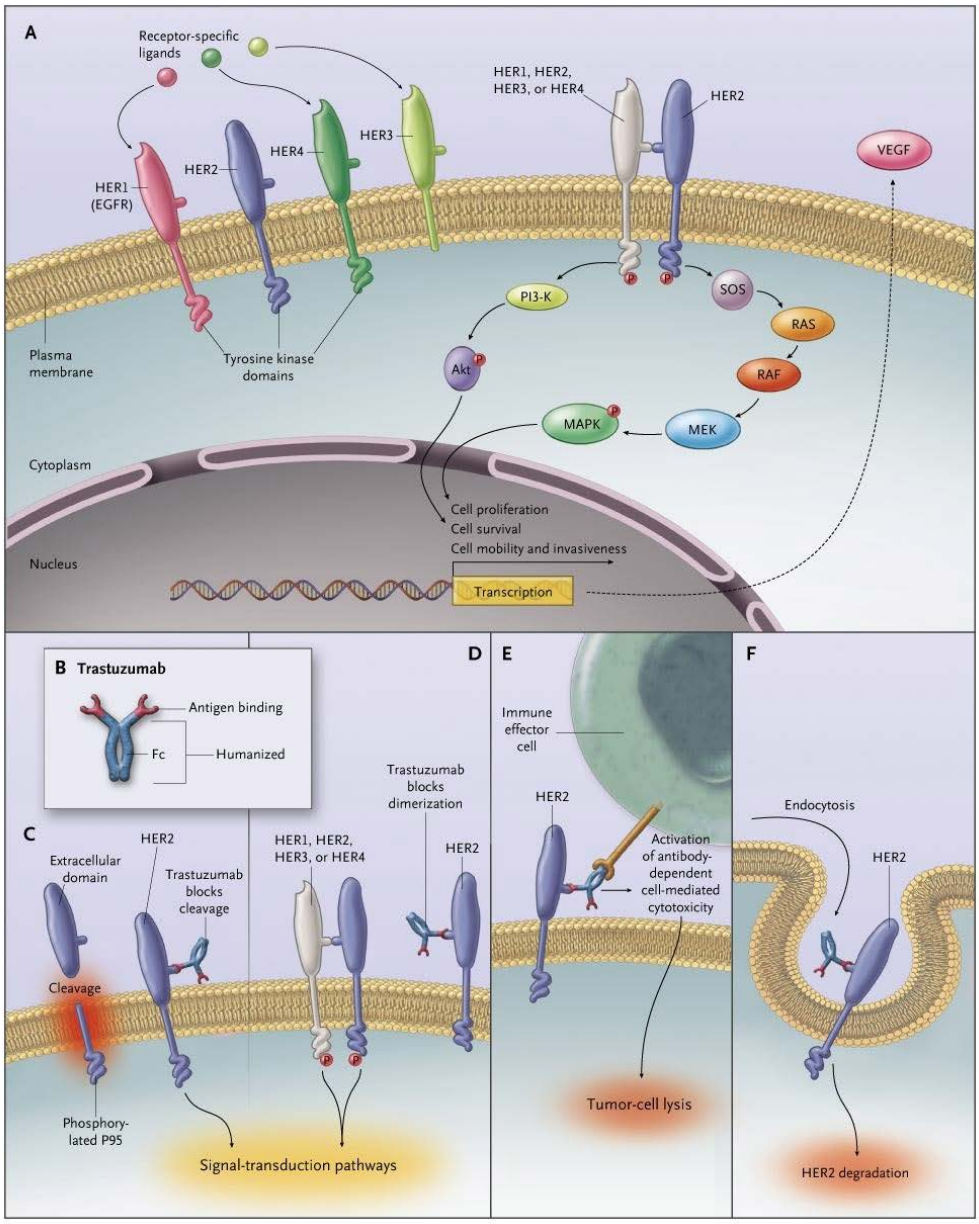

Figure 1. The signal transduction and potential mechanism of the HER family [Hudis, Clifford, & A. (2007). Trastuzumab — mechanism of action and use in clinical practice. New England Journal of Medicine, 357 (1), 39-51.]

Patients with HER2-positive breast cancer are living longer thanks to advances in HER2-targeted therapy. Chemotherapy plus a year of adjuvant HER2-targeted therapy, usually with the anti-HER2 antibody trastuzumab, have become the standard of care for localized illness (Figure 1).

2.2 Second generation and Third generation monoclonal antibodies used as HER2 breast cancer therapy

Kadcyla: ado-trastuzumab emtansine

Ado-trastuzumab emtansine (T-DM1) is an antibody medication that combines trastuzumab and emtansine. Due to improved progression-free and overall survival when compared to lapatinib with capecitabine, it was authorized in 2013 as a second-line therapy for metastatic BC. [3] T-DM1 is an antibody drug combination that is created when trastuzumab is chemically bonded to a potent microtubule inhibitor [5]. T-DM1 is ingested by HER2 cancer cells via endocytosis. The chemical connection is destroyed in the lysosome, and emtansine is released into the cell to hinder replication by binding to tubulin [6].

Perjeta: pertuzamab

The goal is to develop a recombinant humanized IgG1 monoclonal antibody that targets HER2's extracellular dimerization domain (subdomain II). Pertuzamab operates by blocking the formation of a distinction between HER2 and other members. Source dimerization, ADCC, and other immune mechanisms are examples of alternative immunological routes [7]. As clinical trials have shown that combining pertuzumab with trastuzumab-based therapy improves clinical outcomes, basic science research into the mechanisms underlying this synergy has become a hot issue in the quest to better understand HER2 biology [8].

3. Mechanism of action of Trastuzumab

Trastuzumab is a drug that is used to treat cancers of the breast, stomach, and esophagus. This medication is used to treat cancers that produce excessive quantities of the HER2 protein. Trastuzumab belongs to the monoclonal antibody class of medicines. Its job is to halt or stop cancer cells from growing [9].

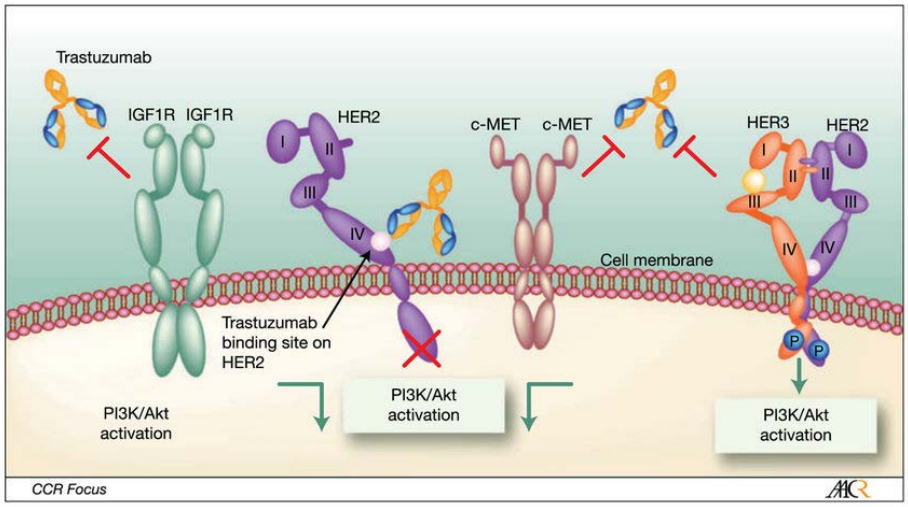

Figure 2. Trastuzumab mechanism of action [Pohlmann, P. R., Mayer, I. A., & Mernaugh, R. (2009). Resistance to trastuzumab in breast cancer. Clinical Cancer Research, 15(24), 7479–7491.].

Trastuzumab is a recombinant humanized IgG1 monoclonal antibody that targets the extracellular domain of the HER-2 receptor (ErbB-2). The HER-2 receptor is made up of an extracellular ligand binding domain, a transmembrane domain, and an intracellular or cytoplasmic tyrosine kinase domain. Trastuzumab binds to the HER-2 extracellular domain and inhibits it from being lyzed, preventing the receptor from being activated, impeding HER-2 dimerization, and facilitating antibody-dependent cell-mediated cells. Tumor cells lyse as a result of toxic activation, which enhances HER-2 internalization (Figure 2).

Trastuzumab's mechanism of action is thought to involve the suppression of constitutive HER2 signaling as well as the stimulation of immune effector cells. In HER2 amplified cells, trastuzumab impairs the ligand-independent HER2/HER3 interaction. This separation causes the PI3K-AKT signal to be uncoupled, which is linked to trastuzumab's anti-proliferative impact. Trastuzumab binds to FccRIII on immune effector cells as a humanized IgG1 and is an efficient mediator of antibody-dependent cell-mediated cytotoxicity (ADCC).

According to studies on animal models of breast cancer overexpressing HER2, trastuzumab inhibits angiogenesis and accelerates the normalization and degeneration of the vascular system through modulating pro-angiogenic and anti-angiogenic proteins. Heregulin (the ligand of HER3 and HER4) regulates the synthesis of vascular endothelial growth factor (VEGF), and blocking HER family receptors induces a decrease in VEGF [11]. Preliminary clinical trials utilizing a combination of trastuzumab and bevacizumab, which inhibits VEGF, have shown promise in HER2-positive aggressive breast cancer.

4. Pharmacokinetics, Pharmacodynamics, Dosage and preparation of trastuzumab

Trastuzumab has a dose-dependent pharmacokinetics when given as a 500 mg intravenous infusion for a short period of time per week. The standard dose is 0.004g/kg at first, followed by 0.002g/kg/wk for 20 weeks to achieve a steady-state blood concentration. The estimated average area under the concentration-time curve is about 580 mg/L day, and the average maximum serum concentration (Cmax) and average minimum serum concentration (Cmin) are about 0.11 and 0.066 g/L, respectively.

In patients with metastatic breast cancer, the weekly intravenous trastuzumab dose increases, the average serum elimination half-life (t1/2) increases, and the clearance rate decreases. At initial normal dosages of 0.004 g/kg and 0.002 g/kg/week, the usual t1/2 is around 30 days, with a washout period of up to 140 days. In clinical trials, the average clearance rate after the standard dose was 0.225 L/day [12].

The adjuvant or metastatic setting used in monotherapy and trastuzumab combination with chemotherapy is the recommended dose of trastuzumab (neo). The conventional dose schedule had no clear benefit at high doses or long dosing intervals. If substantial toxicity develops, there is no algorithm for reducing the trastuzumab dose [13].

Trastuzumab dosing schedule for surgical adjuvant therapy or metastatic disease. According to the official label, trastuzumab is administered via intravenous infusion at a dose dependent on body weight, once a week (metastatic, adjuvant) or once every three weeks (non-metastatic, adjuvant) (adjuvant). The regimen also includes the loading dose given at the start of treatment. Treatment is recommended for a year (adjuvant) or until the disease progresses (metastasis). In the auxiliary context, many dose regimens have been examined, but the optimal treatment period is uncertain.

Furthermore, by incorporating pharmacokinetic parameters into the dosing regimen, the dosing regimen can be improved. Due to the more favorable dynamics (no tumor penetration) in adjuvant therapy, a lower intensity dosage regimen compared to those utilized in metastatic disease may be appropriate. Furthermore, body weight has just a modest relationship with trastuzumab exposure and hasn't been found to have a major impact on clinical activity. In the short run, these pharmacokinetic factors may support the use of a set monthly dose to treat early breast cancer [14].

5. Clinical research

5.1 Early phase I single-agent trial

The higher dose of trastuzumab (intravenous 10-500mg single dose or once a week) did not result in greater toxicity, and its pharmacokinetics was dose-dependent, according to phase I trials. Tratuzumab is well tolerated and has no major side effects, but nausea and vomiting are common side effects, especially after the first dosage. The number and nature of adverse effects during co-administration with cisplatin were similar to those previously reported when cisplatin was used alone. In Phase II/III clinical studies, these tests were used to establish the best trastuzumab dose and schedule [15].

5.2 Phase II single-agent trial

Trastuzumab was studied in 222 HER2-positive women in a large-scale, multinational, and multicenter research. The overall response rate was the primary efficacy endpoint in this trial, with duration of reaction, TTP, QoL, 1-year survival rate, and treatment failure time as secondary endpoints. Intravenous trastuzumab was given to the patients in doses of 0.004 g/kg at first, then 0.002 g/kg every week. Patients have a wide range of disorders, according to patient demographics. In an IHC test, all patients showed double or overexpression of HER2, with the majority (78%) showing overexpression. Adjuvant chemotherapy (69 percent), single chemotherapy (2 percent), double chemotherapy (68 percent), or high-dose chemotherapy were among the previous therapies (26 percent). The overall response rate (evaluated by the independent response evaluation Committee) of patients treated with trastuzumab was 15% (95 percent CI, 11-21 percent), with 8 CR and 26 PR;

the median survival duration was one month. TTP was 0.1 months on average. The average time it took for a reaction was 9.1 months. Patients with objective tumor reaction after receiving trastuzumab have improved their physical and social functions, according to QoL data [16].

5.3 Phase III comparative trial

The efficacy and safety of adding trastuzumab to HER2 positive metastatic breast cancer patients. TTP and safety were the study's key efficacy objectives. Overall response rate, response duration, QoL, survival rate, and time to failure were the study's secondary objectives (TTF). Around 470 women were given adriamycin or epirubicin plus cyclophosphamide as first-line intravenous chemotherapy, or paclitaxel if they had previously had anthracycline adjuvant therapy. For a total of six cycles, all members were given the drug once every three weeks. Half of the patients were given intravenous trastuzumab (at first 4 mg/kg, then 2 mg/kg); 43 patients (30%) received anthracycline with trastuzumab; and 138 patients (29%) received only anthracycline. Paclitaxel plus trastuzumab was given to 92 percent of the patients, while paclitaxel alone was given to 96 percent.

The chemotherapeutic effect of patients taking trastuzumab was greatly improved, as measured by TTP, remission rate, and 1-year survival rate. TTP was significantly prolonged when Trazumab was paired with chemotherapy. The overall absolute rise in TTP of trastuzumab was similarly evident in the two therapy groupings, however the individuals receiving paclitaxel were greater. After adding trastuzumab to all patients with objective remission, the median duration of remission rose by several months (49 percent). 75% patients in the trastuzumab plus anthracycline subgroup and 4/6 patients who had trastuzumab plus paclitaxel and were completely alleviated had no disease progression at the conclusion of the data (follow-up for 29 months).

Table 1. Effacacy Of Trastuzumab Combined With Other Therapies [16].

	Trastuzumab+AC (n=143)	**AC alone (n=138)**	**Trastuzumab+paclitaxel (n=92)**	**Paclitaxel alone (n=96)**	**Trastuzumab+chemotherapy (n=235)**	**Chemotherapy Alone (n=234)**
Median TTP(month)	7.8	6.1	6.9	3.0	7.4	4.6
Response rate(%)	56	42	41	17	50	32
Median duration of reponse(months)	9.1	6.7	10.5	4.5	9.1	6.1
Median TTF(months)	7.2	5.6	5.8	2.9	6.9	4.5
1-Year survival(%)	83	72	72	60	79	68
Median survival(months)	26.8	22.8	22.1	18.4	25.4	20.3

Note: AC: anthracycline;TTP:time to disease progression;TTF:time to treatment failure

6. Safety evaluation

Chemotherapy-treated individuals with metastatic breast cancer frequently have side effects. The incidence of various mild to moderately severe side events increased in patients treated with trastuzumab. Patients have a higher incidence of transfusion-related signs and symptoms, as well as infection, as compared to chemotherapy alone. Trastuzumab was added to chemotherapy, however the findings of laboratory tests did not change significantly. Furthermore, patients who received trastuzumab in combination with chemotherapy had fewer abnormal liver function laboratory tests than those who received chemotherapy alone. Antibodies to trastuzumab were not generated in any of the participants in this research.

The most significant adverse event observed in the study of trastuzumab was cardiac dysfunction similar to that observed with anthracyclines. Signs and symptoms of patients with cardiac insufficiency include decreased ejection fraction, galloping horse rhythm, laboring dyspnea, cardiac hypertrophy, cough, tachycardia and peripheral edema, etc. Daniel Eiger et al. made a comprehensive analysis of the 12-month trial of auxiliary trastuzumab and the short-term trial, and reported the cardiac results of HER2-positive BC patients, using a random effect model weighted by inverse variance [17]. Three trials compared the results of the 9-week and 12-month auxiliary trastuzumab 3–5 schedules, while two trials (Short-HER and SOLD) compared the results of the 9-week and 12-month auxiliary trastuzumab 3–5 schedules [18]. As a result, clinical cardiac insufficiency was identified in five trials. 459 patients developed clinical cardiac dysfunction after receiving trastuzumab for 12 months, with a combined incidence of 8.2 percent (95 percent CI 7.5 percent to 8.9 percent), while 273 patients who received shorter treatment developed clinical cardiac dysfunction with a combined incidence of 4.8 percent (95 percent CI 4.3 percent to 8.9 percent).

Table 2. Pooled incidences of cardiac outcomes according to treatment arms [17].

Arm	Numbers of events	Incidence（95%CI）	Short regimens	Numbers of events	Incidence（95%CI）
Trastuzumab 12 months	459/5615	8.2%(7.5% to 8.9%)	-	-	-
Trastuzumab short regimen	273/5635	4.8%(4.3% to 5.4%)	Trastuzumab 6 months	224/3924	5.7%(5.0% to 6.5%)
-	-	-	Trastuzumab 9 weeks	49/1711	2.9%(2.2% to 3.8%)
Low LVEF					
Trastuzumab 12 months	323/3730	8.7%(7.8% to 9.6%)	-	-	-
Trastuzumab short regimen	234/3728	6.3%(5.5% to 7.1%)	Trastuzumab 6 months	234/3728	6.3%(5.5% to 7.1%)
CHF					
Trastuzumab 12 months	51/2896	1.8%(1.3% to 2.3%)	-	-	-
Trastuzumab short regimen	33/2892	1.1%(0.8% to 1.6%)	Trastuzumab 6 months	9/1690	0.5%(0.3% to 1.0%)
-	-		Trastuzumab 9-12 weeks	24/1202	2.0%(1.4% to 3.0%)
Premature Trastuzumab discontinuation					
Trastuzumab 12 months	249/3825	6.5%(5.8% to 7.3%)	-	-	-
Trastuzumab short regimen	95/3869	2.5%(2.0% to 3.0%)	Trastuzumab 6 months	95/3869	2.5%(2.0% to 3.0%)

Note: CHF: congestive heart failure; LVEF: left ventricular ejection fraction.

7. Data extraction and quality assessment

Sarah Cargnin et al. evaluated the effectiveness and safety of trastuzumab biosimilars compared with reference drugs through systematic evaluation and comprehensive analysis of randomized

controlled trials (RCT) [19]. The following inclusion criteria had to be met by eligible studies: (1) RCT comparing trastuzumab originator to any trastuzumab biosimilar in terms of efficacy or safety; (2) providing sufficient data for generating a risk ratio (RR) for dichotomous outcomes. Eight stage III RCTs were ruled out, and 3913 HER2+ breast cancer patients were found to meet the criteria for inclusion. The summary results of trastuzumab biosimilars showed that the objective response rate (ORR) and overall survival time were in the people who intended to treat and in accordance with the plan, when compared to reference drugs. Similarly, no significant difference was seen between any serious adverse responses during therapy and heart failure reported in at least three RCTs. This meta-analysis shows that trastuzumab biosimilars and the original product are clinically comparable.

8. Drug toxicity (IRRs)

Bone marrow suppression, nausea, and vomiting were uncommon when trastuzumab was administered alone, and no hair loss was noted. Antihistamines, anti-inflammatory medications, and corticosteroids can avoid acute allergic-like reactions, which occur in less than 10% of patients [20]. Although occasional cases of congestive heart failure were reported in early trastuzumab studies, the relationship between low left ventricular ejection fraction (LVEF) and trastuzumab was established during the aforementioned randomized study [21]. Cardiotoxicity was seen in 27% of patients who received trastuzumab and anthracyclines, 13% of patients who received trastuzumab and paclitaxel, and 5% of patients who received trastuzumab alone [22].

Trastuzumab has transformed the field by becoming a standard treatment for HER2-positive breast cancer. Since it was originally utilized, however, there have been concerns about its cardiac safety. Trastuzumab has the potential to produce cardiac toxicity, which could lead to medication discontinuation in rare cases. Cardiomyocytes have now proven to be an effective technique for assessing cardiotoxicity of therapeutically relevant drugs in people [24]. Biomarkers of cardiotoxicity caused by trastuzumab. According to new studies, trastuzumab toxicity can be detected early and avoided by using new chemotherapy regimens that use alternate anthracycline formulations or altogether skip anthracyclines [23]. According to the data above, the medicine still has a very low death rate in clinical use, but the overall treatment rate is relatively optimistic, so it can be utilized in clinical therapy (figure 3).

9. Drug Resistance

Resistance to HER2 medications must be improved, as well as their efficacy in treating HER2 breast cancer. According to experimental studies, 30% of patients will develop trastuzumab resistance, and the cause is thought to be connected to defective HER2 downregulation, dissociation from CBL, and impaired endocytosis.

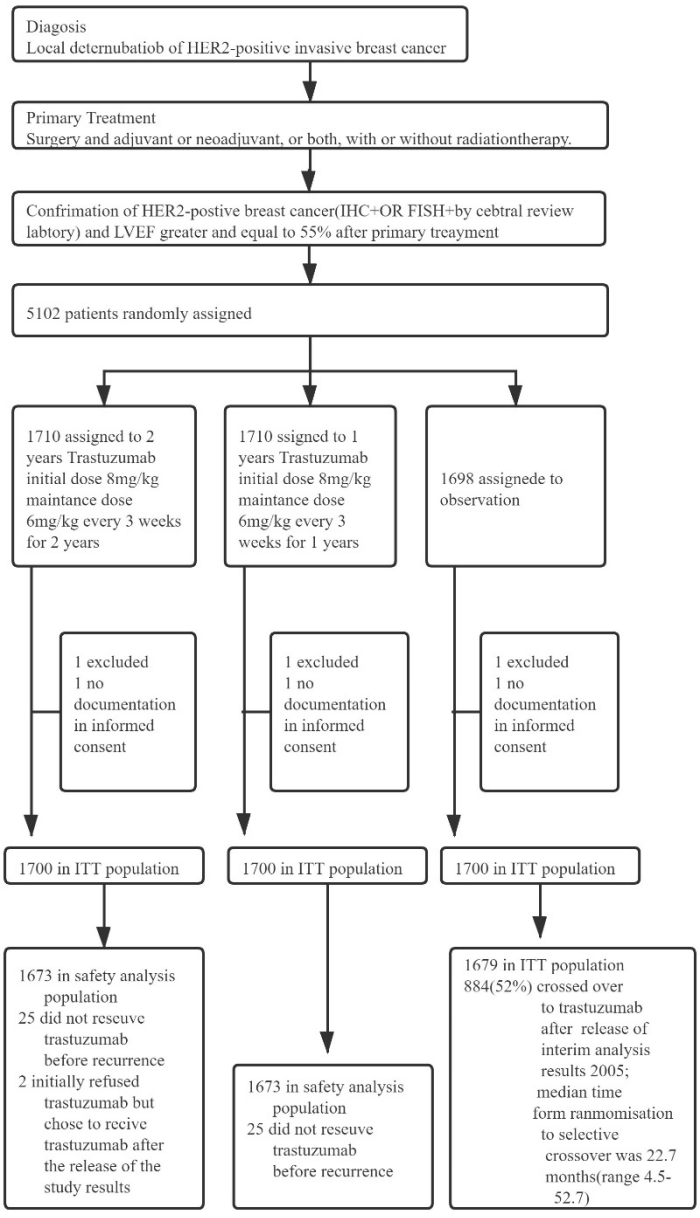

Figure 3. Clinical drug toxicity.

Patients developed resistance to trastuzumab as the research proceeded because it was identical to long noncoding RNAs (long Noncoding RNAs), which had no protein-coding ability over 200 nucleotides. In breast cancer, LNCRNA is a crucial regulator of trastuzumab resistance. By sponging Mir-18a causes it, leading in medication resistance [25, 27].

Understanding resistance pathways is critical for the development of T-DM1-targeted treatments in the future. Resistance mechanisms are unknown, although they could include processes that inhibit trastuzumab from binding to cancer cells. T-lethal DM1 activity may be limited by lysosomal degradation of trastuzumab or diminished intracellular trafficking of HER2, as well as poor internalization or increased circulation of the HER2-T-DM1 complex in cancer cells. Multidrug-resistant proteins that eject DM1 from cancer cells may also have an impact on its effectiveness. Aside from low HER2 expression in cancer, clinical, biological, and pharmacological features of T-poor DM1 effectiveness are unknown. T-DM1 resistance, on the other hand, may be influenced by characteristics associated to the mechanism of action of T-biological DM1. DM1 and its metabolite (lysine-MC-DM1) must accumulate in cancer cells at amounts above the threshold to trigger cell

death. We propose a set of settings that could change intracellular DM1 concentration and result in T-DM1 resistance.

Apart from low HER2 expression in cancer, clinical, biological, and pharmacological characteristics of T-poor DM1 effectiveness are unknown. T-DM1 resistance, on the other hand, may be influenced by characteristics associated to the mechanism of action of T-biological DM1. DM1 and its metabolite (lysine-MC-DM1) must accumulate in cancer cells at amounts above the threshold to trigger cell death [26].

After completing all primary therapy, patients were randomly randomized (1:1:1) to receive trastuzumab for 1 year (once at 8 mg/kg of bodyweight intravenously, then 6 mg/kg once every 3 weeks), 2 years (with the same dose schedule), or even to the observation group (including surgery, chemotherapy, and radiotherapy as indicated). In the intention-to-treat population, a total of 5099 patients were followed up on (1697 in observation, 1702 in 1-year trastuzumab, and 1700 in 2-years trastuzumab groups). After a median follow-up of 11 years (IQR 10.09–11.53), random assignment to 1 year of trastuzumab significantly reduced the risk of a disease-free survival event (HR 0.76, 95 percent CI 0.68–0.86) and death (0.74, 0.64–0.86) when compared to observation. Two years of adjuvant trastuzumab had no effect on disease-free survival when compared to one year of the drug (HR 1.02, 95 percent CI 0.89–1.17).Disease-free survival rates were 63 percent after observation, 69 percent after one year of trastuzumab, and 69 percent after two years of trastuzumab. Patients in the observation group crossed over to receive trastuzumab on a selective basis, accounting for 884 (52%) of the total. Cardiac toxicity was infrequent in all groups and mostly happened during treatment. Secondary cardiac endpoints were seen in 122 (7.3%) of the 2-year trastuzumab patients, 74 (4.4%) of the 1-year trastuzumab patients, and 15 (0.9%) of the observation patients. Adjuvant trastuzumab following chemotherapy for patients with HER2-positive early breast cancer improves long-term disease-free survival significantly when compared to observation [25]. According to the data above, the medicine still has a very low death rate in clinical use, but the overall treatment rate is relatively optimistic, so it can be utilized in clinical therapy.

10. The Future And Development

Trastuzumab is a humanized monoclonal antibody (mAb) that targets the extracellular region of the HER2 tyrosine kinase receptor. Trastuzumab was the first molecular target therapy medicine used to treat breast cancer, and it is a highly common condition. It does, however, have the potential to cause cardiotoxicity and medication resistance. This medicine has been successful in treating HER-2 breast cancer over the past two decades. Trastuzumab still has a number of issues to work out, such as its connection with drugs that target pathways, toxicity, and drug resistance. As a result, researchers can focus on these places in the future to alter the drug [28,29].

11. Conclusion

Breast cancer is a huge threat to the health of women around the world because of its high incidence. Conventional surgical treatment may be able to treat the disease, but with it, mental health and prognosis once again trouble patients and doctors. Under such circumstances, chemotherapy and small molecule targeted therapy have gradually become hot spots in this field. A large number of studies have shown that trastuzumab as a HER2 antibody has a significant therapeutic effect on breast cancer, greatly improving the cure rate of patients and reducing the risk of cancer recurrence after surgery. Trastuzumab combined with chemotherapy for the treatment of breast cancer patients with HER2 overexpression has good safety, and the single-agent therapy has a good effect, which can cause a prolonged objective tumor response. In clinical trials, trastuzumab has shown good therapeutic effects, and few patients have reported side effects. Through trastuzumab for the treatment of HER2-positive breast cancer, it may be possible to glimpse the future direction of disease treatment. In the future, for different types of breast cancer, it is still necessary to explore the mechanisms and find specific molecular tags to gradually explore targeted drugs for curing.

References

[1] Michel, A., Oppong, M. D., Rauschenbach, L., Pierscianek, D., Dinger, T. F., Schmidt, T., Hense, J., Pöttgen, C., Kimmig, R., Ahmadipour, Y., Özkan, N., Müller, O., Junker, A., Sure, U., Jabbarli, R., & El Hindy, N. (2021). HER2 receptor conversion is a strong survival predictor in patients with breast cancer brain metastases. World Neurosurgery, 152.

[2] Slamon DJ, Clark GM, Wong SG, Levin WJ, Ullrich A, McGuire WL (1987). Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. Science 235: 177–182.

[3] Albanell J, Baselga J. Trastuzumab, a humanized anti-HER2 monoclonal antibody, for the treatment of breast cancer. Drugs Today 1999; 35(12): 931–46

[4] Mayo Foundation for Medical Education and Research. (2020, April 7). What to know about her2-positive breast cancer. Mayo Clinic. Retrieved October 20, 2021, from https://www.mayoclinic.org/breast-cancer/expert-answers/faq-20058066.

[5] Konecny GE, Meng YG, Untch M, et al. Association between HER-2/neu and vascular endothelial growth factor expression predicts clinical outcome in primary breast cancer patients. Clin Cancer Res. 2004; 10(5):1706e1716.

[6] Olivier Jr KJ, Hurvitz SA. Antibody-Drug Conjugates: Fundamentals, Drug Development, and Clinical Outcomes to TargetCancer. John Wiley & Sons; 2016.

[7] Trastuzumab emtansine. In: Micromedex (Columbia Basin College Library ed.) [Electronic version]. Greenwood Village, CO: Truven Health Analytics; 2017.

[8] Hurvitz, S. A., & McCann, K. (2019). Her2-positive breast cancer. Elsevier.

[9] Petit AM, Rak J, Hung MC, et al. Neutralizing antibodies against epidermal growth factor and ErbB-2/neu receptor tyrosine kinases down-regulate vascular endothelial growth factor production by tumor cells in vitro and in vivo: angiogenic implications for signal transduction therapy of solid tumors. Am J Pathol 1997;151:1523-1530

[10] Kumar R, Yarmand-Bagheri R. The role of HER2 in angiogenesis. Semin Oncol 2001;28:Suppl 16:27-32

[11] Fuentes G, Scaltriti M, Baselga J, Verma CS. Synergy between trastuzumab and pertuzumab for human epidermal growth factor 2 (Her2) from colocalization: an in silico-based mechanism. Breast Cancer Res. 2011; 13(3).

[12] McKeage, K., Perry, C.M. Trastuzumab. Drugs 62, 209–243 (2002).

[13] Boekhout, A. H., Beijnen, J. H., & Schellens, J. H. (2011). Trastuzumab. The oncologist, 16(6), 800–810.

[14] Levêque D, Gigou L, Bergerat JP. Clinical pharmacology of trastuzumab. Curr Clin Pharmacol. 2008 Jan; 3 (1): 51-5.

[15] Shak S, for the Herceptin Multinational Investigator Study Group. Overview of the trastuzumab (Herceptin1) anti-HER2 monoclonal antibody clinical program in HER2-overexpressing metastatic breast cancer. Semin Oncol 1999, 26(Suppl. 12)

[16] Baselga J. Clinical trials of Herceptin (trastuzumab). Eur J Cancer. 2001 Jan; 37 Suppl 1:S18-24. PMID: 11167087.

[17] Eiger D, Franzoi MA, Pondé N, Brandão M, de Angelis C, Schmitt Nogueira M, de Hemptinne Q, de Azambuja E. Cardiotoxicity of trastuzumab given for 12 months compared to shorter treatment periods: a systematic review and meta-analysis of six clinical trials. ESMO Open. 2020 Feb; 5(1):e000659.

[18] Pivot X, Romieu G, Debled M, et al. 6 months versus 12 months of adjuvant trastuzumab in early breast cancer (PHARE): final analysis of a multicentre, open-label, phase 3 randomised trial. Lancet 2019; 393: 2591–8.

[19] Cargnin S, Shin JI, Genazzani AA, Nottegar A, Terrazzino S. Comparative efficacy and safety of trastuzumab biosimilars to the reference drug: a systematic review and meta-analysis of randomized clinical trials. Cancer Chemother Pharmacol. 2020 Nov;86(5):577-588. doi: 10.1007/s00280-020-04156-3. Epub 2020 Oct 1. PMID: 33005979.

[20] Herceptin (trastuzumab): full prescribing information. South San Francisco, CA: Genentech, 2004. (Accessed June 11, 2007)

[21] Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med 2001;344:783-792

[22] Seidman A, Hudis C, Pierri MK, et al. Cardiac dysfunction in the trastuzumab clinical trials experience. J Clin Oncol 2002;20:1215-1221

[23] Brian M. Necela , Bianca C. Axenfeld, Daniel J. Serie, Jennifer M. Kachergus , Edith A. Perez , E. Aubrey Thompson and Nadine Norton The antineoplastic drug, trastuzumab, dysregulates metabolism in iPSC-derived cardiomyocytes Dec2017, Vol. 6 Issue 1, p1-13. 13p.

[24] Giacomo Bregni , Giulia Galli , Arpine Gevorgyan , Filippo de Braud , Serena Di Cosimo Trastuzumab cardiac toxicity: a problem we put our heart into Jan-Feb 2016;102(1):1-5

[25] David Cameron, Martine J Piccart-Gebhart, Richard D Gelber, Marion Procter, Aron Goldhirsch, Evandro de Azambuja, Gilberto Castro, Jr, Michael Untch, Ian Smith, Luca Gianni, Jose Baselga, Nedal Al-Sakaff, Sabine Lauer, Eleanor McFadden, Brian Leyland-Jones, Richard Bell, Mitch Dowsett, and Christian Jackisch, for the Herceptin Adjuvant (HERA) Trial Study Team 11 years' follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer: final analysis of the HERceptin Adjuvant (HERA) trial 2017 Mar 25; 389(10075): 1195–1205.

[26] Mark Barok, Heikki Joensuu, and Jorma Isola Trastuzumab emtansine: mechanisms of action and drug resistance. 2014; 16(2): 209.

[27] Mingli Han, Yuanting Gu, Pengwei Lu , Jingyi Li , Hui Cao , Xiangke Li, Xueke Qian, Chao Yu , Yunqing Yang , Xue Yang , Na Han , Dongwei Dou , Jianguo Hu , Huaying Dong Exosome-mediated lncRNA AFAP1-AS1 promotes trastuzumab resistance through binding with AUF1 and activating ERBB2 translationMol Cancer. 2020 Feb 5;19(1):26

[28] G. Valabrega, F. Montemurro & M. Aglietta Trastuzumab: mechanism of action, resistance and future perspectives in HER2-overexpressing breast cancer Annals of Oncology 18: 977–984, 2007 Sofia Maximiano,Paulo Magalhães, Mara Pereira Guerreiro,Manuel Morgado Trastuzumab in the Treatment of Breast CancerBioDrugs. 2016 Apr;30(2):75-86