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CASE REPORT

A New Era of HER2 Directed Therapy –A Review of Cardiac Toxicities in Novel Anti-HER2 Agents

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ABSTRACT

Overexpression of human epidermal growth factor receptor 2 (HER2) has classically been associated with decreased overall survival. HER2-positive breast cancer makes up about 15-20% of breast cancers. Overall survival and progression-free survival of HER2 breast cancers have increased due to advancements in therapies. Trastuzumab, a humanized monoclonal antibody, targets HER2 in patients with overexpression. When combined with anthracyclines, which has been the treatment of choice for many years, there is increased cardiotoxicity. Since the discovery of trastuzumab, there have been a myriad of novel agents that target HER2 receptors, however little is known about the cardiotoxic effects of these novel agents. In this review, we describe clinical trials using novel anti-HER2 agents for the treatment of HER2-positive breast cancer and the frequency and severity of cardiotoxicity of these agents.

Introduction

Breast cancer remains the most prevalent cancer among females. In 2020, 2.3 million women were diagnosed with breast cancer and 685,000 women died globally.[1] Breast cancer treatment and prognosis is classified based on the type of receptor expression. Human epidermal growth factor receptor 2 (HER2) is a tyrosine kinase receptor on breast epithelial cells. The HER2 gene is located on the long arm of chromosome 17 and encodes a 185-kDa transmembrane protein. Classically, breast cancers that overexpress HER2 receptors are associated with a more aggressive cancer and decreased overall survival (OS).[2] The pharmacological inhibition of HER2 represents revolutionary progress in targeted therapy for breast cancer treatment by improving OS and disease-free survival rates in both early-stage and metastatic HER2-positive breast cancer.[3-4] With the advancements in overall survival, it is essential to examine long term toxicities, particularly cardiovascular risk, involved with the use of new HER2-targeted agents. In this review, we evaluate clinical trials using novel anti-HER2 agents for the treatment of HER2-positive breast cancer and the frequency and severity of cardiotoxicity of these agents, risk factors, and monitoring guidelines to minimize long-term effects.

OLDER AGENTS AND CARDIOVASCULAR RISK

Trastuzumab is a humanized IgG1 monoclonal antibody (MAB) that targets the extracellular domain of the HER2 protein by inhibiting homodimerization and preventing HER2 signaling. It was first FDA-approved in 1998 and quickly became recommended as first-line therapy with chemotherapy for patients that overexpress HER2 in metastatic breast cancer.[5] The HERA trial looked at trastuzumab in the adjuvant setting showing that one year of trastuzumab significantly reduced the risk of a disease-free survival event and death compared with observation. This led to FDA approval of trastuzumab in early breast cancer for its landmark improvements in outcomes. However, approximately 9% of patients experienced cardiovascular (CV) toxicity; these patients however had previous anthracycline exposure which can also cause cardiac toxicity. As a result of this trial, trastuzumab is not given in combination with anthracyclines but rather sequentially with a taxane. Cardiac toxicity rates are lower with taxane-based therapy but are still estimated to occur in 3-4% of patients.[6] This study, along with others, led to the FDA recommending cardiac monitoring every three months during trastuzumab therapy.

In 2007, lapatinib, in combination with capecitabine, became the first tyrosine kinase inhibitor (TKI) approved by the FDA for use in HER2+ metastatic breast cancer.[7] This approval was based on a phase III, randomized, open-label trial which showed that lapatinib with capecitabine was superior to monotherapy capecitabine in women with HER2+ advanced breast cancer who progressed on previous lines of therapy.[8] In this study, asymptomatic cardiac adverse events, defined as a relative decrease of 20% from baseline to below the lower limit of normal, were noted in four women in the combination therapy group. Still, these effects were transient and resolved upon reassessment.

NEWER AGENTS AND CARDIOVASCULAR RISK

Three types of novel anti-HER2 agents have been developed with increased OS and decreased adverse events. Newer MABs, like pertuzumab, inhibit HER2 signaling by preventing heterodimerization. TKIs bind to the intracellular domain of the HER receptors, inhibiting phosphorylation and downstream signaling pathways. Antibody drug conjugates (ADC) link specific monoclonal antibodies to potent chemotherapies allowing for targeted delivery to cancer. These novel drug classes have adverse effects that are still being studied. In the next section, we describe clinical trials involving novel agents and evaluate their frequency and severity of cardiotoxicity.

TYROSINE KINASE INHIBITORS

Newer agents, such as neratinib, tucatinib, and pyrotinib, are irreversible TKIs with varying binding sites and affinities to HER proteins that have overall low cardiac toxicities.

Neratinib is an irreversible oral TKI that inhibits HER1, HER2, and HER4. Based on the ExteNET trial, neratinib received FDA approval in 2017 for extended adjuvant treatment in early-stage HER2-overexpressed breast cancer following one year of adjuvant treatment of trastuzumab-based therapy.[9] Of the 11 clinical trials identified in Table 1, 10 of the neratinib studies reported decreased ejection fraction and three reported incidences of QT-prolongation.[10-20] Overall, the use of neratinib is not associated with an increase

in long term cardiotoxicity. Many of these effects were transient reductions in LVEF or QT-prolongation.

Tucatinib is an oral TKI that is highly selective for HER2. It was approved for use in 2022 in advanced, unresectable, or metastatic breast cancer in combination with trastuzumab and capecitabine based on the HER2CLIMB trial.[21] This study was a randomized, double-blinded, international clinical trial comparing the efficacy of tucatinib plus trastuzumab and capecitabine to placebo plus trastuzumab and capecitabine. The primary endpoint of PFS was 33.1% in the tucatinib-combination group vs 12.3% in the placebo-combination group.[22] Occurrence of cardiotoxicity was noted to be <1% in both groups of participants. The rate of cardiotoxicity was congruent in another tucatinib study. This was a phase 1b clinical trial combining tucatinib with ado-trastuzumab emtansine where only 4% of patients had grade I reduced LVEF.[23]

Based on a phase II trial, pyrotinib, a second-generation, irreversible TKI that inhibits HER1, HER2, and HER4 received conditional approval in 2018, in China, for use in patients with advanced or metastatic breast cancer in combination with capecitabine.[24] Subsequently, the PHOEBE trial, a phase 3, randomized, open-label, multicentre trial showed that pyrotinib plus capecitabine was superior to lapatinib plus capecitabine with PFS of 12.5 months vs 6.8 months, respectively.[25] Regarding adverse effects, both trials reported none to minimal cardiotoxicity with less than one percent of patients with cardiac adverse events. This is also congruent with the other two studies listed in Table 1 where one study, the PHEDRA trial, found that 2.2% of patients in the treatment arm had prolonged QTc, and the other study, PERMEATE, reported one patient with ventricular tachycardia.[26-27] Although pyrotinib is not currently approved by the FDA, it is a novel anti-HER2 agent that is widely used in Asia due to its efficacy and safety with marginal cardiac toxicity.

MONOCLONAL ANTIBODIES

The CLEOPATRA trial led to the approval of pertuzumab use with trastuzumab and docetaxel in HER2-positive metastatic breast cancer.[28] In 2013, pertuzumab was approved for use in the neoadjuvant setting for high-risk, early-stage breast cancer.[29] Afterwards, it was approved for use in the adjuvant setting based on the APHINITY trial for patients with locally advanced, inflammatory, or early-stage breast cancer.[30] All three trials demonstrated that adverse cardiovascular events were minimal with the use of pertuzumab.

Margetuximab is a human/mouse chimeric Fc-engineered IgG1 kappa monoclonal antibody. Margetuximab differs from trastuzumab in that its Fc region increases antibody-dependent cytotoxicity and immune function.[31] It was approved in 2020 as a third-line agent in HER2-positive metastatic breast cancer based on the SOPHIA trial.[32] This trial was a phase 3, randomized clinical trial evaluating the efficacy of margetuximab plus chemotherapy vs trastuzumab plus chemotherapy. The primary endpoint of PFS was met with PFS of 5.8 months vs 4.9 months of margetuximab vs trastuzumab, respectively. This study identified cardiotoxicity in some patients, but it was limited to 1.1% of patients treated with margetuximab

ANTIBODY-DRUG CONJUGATES

Trastuzumab emtansine is a HER2-targeted antibody-drug conjugate containing trastuzumab covalently linked to the microtubule inhibitory drug DM1. It first received FDA approval in 2013 for use in HER2+ metastatic breast cancer.[33] In 2019, it received approval for use in the adjuvant setting after remarkable results showed that there was a 50% lower risk of breast cancer recurrence or death compared to trastuzumab alone.[34] Total cardiac event rate was reported to be low at 3.37% in one retrospective study evaluating cardiotoxicity associated with trastuzumab emtansine treatment.[35]

Similarly, in 2019, the FDA approved trastuzumab deruxtecan, another antibody-drug conjugate with humanized anti-HER2 MAB linked to a topoisomerase inhibitor. Patients who received treatment with this ADC had an average progression-free survival of 16.4 months as compared to the trastuzumab emtansine studies that showed PFS of 9.6 months.[36] While trastuzumab deruxtecan has been associated with many reports of interstitial lung disease, its association with cardiotoxicity is less discussed. Based on the literature reviewed, rates of decreased ejection fraction ranged from 1% to 2.6% for trastuzumab-deruxtecan-based regimens. Electrocardiogram prolonged QT-corrected interval was reported in 9% of studies for trastuzumab-deruxtecan regimens.[36-38]

Table 1: Studies using novel anti-HER2 agents with described cardiotoxic effects.

Drug Class	Drug Name	Source	Number of Patients	Cardiac Effects	Ref.
Tyrosine Kinase Inhibitor	Neratinib	Burstein et al. (2010)	127	4 patients with reduced LVEF measurement less than 50%. 1 had grade 3 cardiotoxicity and developed AV block and bradycardia, 1 patient had grade 4 acute left ventricular failure, which occurred 29 days after the last dose of neratinib.	10
		Awada et al. (2013)	79	Sinus rhythm abnormalities noted in 6 patients during treatment and 2 patients at the final visit. no clinically important changes in LVEF observed	11
		Chow et al. (2013)	102	1 patient with reduced LVEF. 5% of patients with prolonged QTc interval >500 ms and 17% of patients experienced a QTc interval increased >60 ms from baseline.	12
		Jankowitz et al. (2013)	21	2 patients with decreased LVEF >10% (both returned to baseline by 6 months)	13
		Martin et al. (2013)	116	3% of patients with reduced LVEF in neratinib arm	14
		Saura et al. (2014)	72	2 patients with 13% and 12% reduction in LVEF with neratinib. No congestive heart failure symptoms reported.	15
		Awada et al. (2016)	479	Grade 3 or higher cardiac events (ie, cardiac failure, decreased ejection fraction, left ventricular dysfunction and [peripheral] edema) reported in 3 patients (1.3%) in the neratinib-paclitaxel group and 7 patients (3.0%) in the trastuzumab-paclitaxel group.	16
		Freedman et al. (2016)	40	1 patient with grade 2 LVEF reduction, 1 patient with Grade 3 hypotension, 1 patient with grade 3 sinus tachycardia	17
		Park et al. (2016)	115	1 patient with grade 3 LVEF reduction. No congestive heart failure symptoms reported	18
		Chan et al. (2016)	2816	QT prolongation in 49 patients (3%) on Neratinib and 93 (7%) patients on placebo and decreased LVEF in 19 patients (1%) and 15 patients (1%) respectively. .	19
		Saura et al. (2020)	307	Cardiac arrhythmia was 3.3% for neratinib and 3.5% for control. Ischemic heart disease was 0.7% for neratinib and 0.6% for control. QT prolongation was 2.3% for neratinib and 3.9% for control. Left ventricular ejection fraction decrease was 4.3% for neratinib and 2.3% for control.	20
	Tucatinib	Murthy et al. (2020)	612	<1% in both groups of participants suffered cardiac arrest, cardiac failure, and myocardial infarction.	22
		Borges et al. (2018)	57	4% of patients with grade 1 LVEF	23
	Pyrotinib	Ma et al. (2019)	65	No grade 3 or higher severity cardiac events were reported	24
		Xu et al. (2021)	134	1 patient with grade 3 electrocardiogram QT prolonged and 1 patient with grade 4 supraventricular tachycardia	25
		Wu et al. (2022)	178	2.2% of patients in the pyrotinib group had a QTcF of 480 ms or more and a change of at least 60 ms from baseline	26
		Yan et al. (2022)	80	1 patient with ventricular tachycardia	27
Monoclonal Antibody	Margetuximab	Rugo et al. (2021)	266	1.1% of patients with grade 3 or higher reduced LVEF	32
Antibody Drug Conjugate	Trastuzumab-deruxtecan	Modi et al. (2020)	184	1% of patients with reduced LVEF	36
		Tamura et al. (2019)	115	9% of patients with QT prolongation	37
		Cortes et al. (2022)	524	2.3% of patients with reduced LVEF	38

RISK FACTORS

Novel anti-HER2 agents have revolutionized the management of HER2-positive breast cancer. However, these agents can be associated with cardiotoxicity, which can limit their clinical use. Therefore, understanding the risk factors with novel anti-HER2 agents is crucial for optimal patient management.

Risk factors for cardiotoxicity:

1. Age >65 years old: This may be due to pre-existing cardiac comorbidities, decreased cardiac reserve, and decreased ability to repair cardiac damage.

2. Obesity (BMI >30 kg/m2)

3. Hypertension: Either prior diagnosis or diagnosed at the time of treatment.

4. Diabetes

5. High dose radiation therapy: Defined as receiving RT ≥ 30 Gy where the heart is in the treatment field).

6. Prior treatment with a high dose of anthracyclines: Defined as having received doxorubicin ≥ 250 mg/m2 or epirubicin ≥ 600 mg/m2. The combination of anthracyclines and anti-HER2 agents can have a synergistic effect on cardiotoxicity.

7. Baseline left ventricular dysfunction: Decreased baseline left ventricular dysfunction is a significant risk factor for cardiotoxicity and should be closely monitored for signs of cardiotoxicity during treatment.

8. Treatment duration: Longer treatment duration has been associated with an increased risk of cardiotoxicity with anti-HER2 agents.[39-40]

MONITORING

With the advent of these novel anti-HER2 agents, monitoring for cardiotoxicity remains a critical aspect of patient care.

The American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) have provided guidelines for monitoring and managing cardiotoxicity in patients receiving anti-HER2 therapies.

The guidelines recommend baseline assessment of cardiac function using transesophageal echocardiogram (TTE) or multiple-gated acquisition (MUGA) scans and periodic monitoring throughout treatment.

For patients receiving HER2-targeted TKIs, electrocardiograms (ECGs) and monitoring of blood pressure and heart rate are also recommended.[39-40] Monitoring frequency is dependent on staging at diagnosis. According to the ESC 2022 Guidelines, biomarker assessment has been used to risk stratify patients but has not been commonly used as a marker to monitor CV toxicity.[25] Further data is needed to understand how to implement this information into clinical practice. For patients who are asymptomatic and with a normal assessment after three months, less frequent monitoring every six months may

be considered in those with low CV risk with early breast cancer. In patients with metastatic disease who have low to moderate CV risk, TTE assessment can be performed every 6 months after the first year in asymptomatic patients with normal cardiovascular evaluations. In those with high and very high-risk metastatic disease, TTE monitoring can occur every 2-3 cycles depending on the clinical scenario and availability of testing.[41]

In addition to regular monitoring, the guidelines suggest taking steps to minimize the risk of cardiotoxicity, including avoiding concomitant use of other cardiotoxic agents and managing cardiovascular risk factors such as hypertension and hyperlipidemia. If cardiotoxicity is detected, treatment should be interrupted or discontinued, and the patient should receive appropriate cardiovascular care.

Patients with significant cardiac histories were excluded from all clinical trial data, however, further studies looking into the use of anti-HER2 agents in patients with pre-existing reduced LVEF have shown them to be safe.[42] In asymptomatic patients with a reduced LVEF between 40-49%, regular cardiology visits in conjunction with close monitoring and the use of cardioprotective medications prevented cardiac events during the use of anti-HER2 therapy in the treatment of breast cancer in 90% of patients.[41] In symptomatic patients with reduced LVEF, close collaboration and consultation between cardio-oncology specialists and oncologists is recommended.

Conclusion

Novel HER2 agents have significantly reduced cardiac effects compared to traditional HER2 drugs. Based on this review, 1-4% of patients had notable cardiac effects from novel HER2 inhibitors. Certain risk factors predispose patients to increased cardiac toxicities. Patients with significant cardiac histories are excluded from all clinical trial data, but further studies, such as the SAFE-HEART trial, showed they can be safely used in patients who have asymptomatic heart failure with close monitoring and follow-up. Further studies are needed to evaluate the risk and degree of cardiotoxicity in patient populations with a significant cardiac history. Overall, the continued development of anti-HER2 agents represents a significant advancement in targeted therapy for breast cancer treatment, but continued research and monitoring of their cardiotoxic effects are necessary to ensure safe and effective use. Standardized reporting of cardiac events and improved analyses of at-risk populations are needed to better understand the cardiotoxicity of novel anti-HER2 agents.

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