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Original article

CARDIAC SAFETY OF ADJUVANT SUBCUTANEOUS FIXED-DOSE PERTUZUMAB AND TRASTUZUMAB (PHESGO) IN HER2-POSITIVE BREAST CANCER: A PROSPECTIVE REAL-WORLD COHORT STUDY

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Abstract

Introduction: Fixed-dose subcutaneous pertuzumab and trastuzumab (Phesgo) reduces administration time in HER2-positive breast cancer while maintaining efficacy, though real-world cardiotoxicity data remain limited.

Objective: To evaluate the incidence, clinical features, and reversibility of cardiotoxicity in patients receiving adjuvant subcutaneous pertuzumab and trastuzumab in routine clinical practice.

Materials and methods: This prospective observational cohort study included 50 consecutive patients with HER2-positive early or locally advanced breast cancer treated with adjuvant subcutaneous Phesgo™. Left ventricular ejection fraction (LVEF) was assessed via transthoracic echocardiography at baseline and every three months during the one-year treatment. Cardiotoxicity was defined using Cardiac Review and Evaluation Committee (CREC) criteria.

Results: The median age was 54.5 years. Cardiotoxicity occurred in 3 of 50 patients (6.0%). One patient (2.0%) developed symptomatic NYHA class II heart failure, while two (4.0%) experienced asymptomatic LVEF declines exceeding 10 percentage points to below 50%. All cardiac events occurred in patients previously treated with anthracycline-based chemotherapy. Temporary Phesgo interruption and initiation of angiotensin-converting enzyme inhibitors and beta-blockers led to full cardiac recovery in all affected patients within 6–9 weeks, allowing successful completion of anti-HER2 therapy.

Conclusions: Adjuvant subcutaneous pertuzumab and trastuzumab showed a favorable real-world cardiac safety profile. Cardiotoxicity was uncommon, reversible, and effectively managed through regular cardiac monitoring and timely cardioprotective therapy.

Keywords: HER2-positive breast cancer, phesgo, pertuzumab, trastuzumab, cardiotoxicity, left ventricular ejection fraction, cardio-oncology

Introduction

HER2-positive breast cancer represents a biologically aggressive subtype of breast cancer and accounts for approximately 15-20% of all newly diagnosed cases[1,2]. Before the introduction of targeted anti-HER2 therapy, these tumors were associated with a higher risk of recurrence, more rapid disease progression, and shorter overall survival. The development of monoclonal antibodies targeting the HER2 receptor significantly improved patient outcomes, representing one of the greatest successes of modern oncological therapy.

Trastuzumab, the first anti-HER2 monoclonal antibody, dramatically improved survival in patients with HER2-positive breast cancer. The subsequent introduction of pertuzumab, which binds to a different domain of the HER2 receptor and inhibits its dimerization, enabled dual HER2 blockade with a synergistic effect. Clinical studies have shown that the combination of trastuzumab and pertuzumab results in higher pathological complete response rates, longer disease-free survival, and better long-term oncological outcomes compared with trastuzumab monotherapy[3,4].

The fixed-dose subcutaneous combination of pertuzumab and trastuzumab (Phesgo) represents a significant advance in the administration of anti-HER2 therapy. Compared with intravenous administration, subcutaneous administration substantially reduces the time required for treatment, decreases the burden on the healthcare system, and improves patient convenience and satisfaction without compromising efficacy or safety. The FeDeriCa study demonstrated that the fixed-dose subcutaneous combination was non-inferior to intravenous administration, with comparable pharmacokinetic parameters, efficacy, and safety profiles[5].

Despite significant therapeutic progress, cardiotoxicity remains one of the most important adverse reactions associated with anti-HER2 therapy. HER2 receptors are expressed not only in tumor cells but also in cardiomyocytes, where they participate in signaling pathways responsible for cell survival, regeneration, and adaptation to oxidative stress[9]. Inhibition of these pathways may lead to impaired left ventricular contractile function and a reduction in left ventricular ejection fraction (LVEF)[10]. Unlike anthracycline-induced cardiotoxicity, which is usually dose-dependent and results in structural, irreversible myocardial damage, cardiotoxicity caused by anti-HER2 therapy is generally functional, not dose-dependent, and potentially reversible if recognized and treated promptly[11].

The risk of developing cardiotoxicity is higher in patients who have previously received anthracycline-based chemotherapy, as well as in those with pre-existing cardiovascular risk factors, including arterial hypertension, diabetes mellitus, older age, and previous left-sided chest radiotherapy. Therefore, current recommendations from the European Society of Cardiology (ESC) and the European Society for Medical Oncology (ESMO) recommend systematic cardiac monitoring with echocardiography before treatment initiation and at regular intervals during therapy, to enable early detection of subclinical or clinically manifest left ventricular dysfunction[6-8].

Although major randomized clinical trials, such as NeoSphere, APHINITY, and FeDeriCa, reported a relatively low incidence of severe cardiotoxicity, participants in these trials represent a highly selected population with limited comorbidities and carefully controlled treatment conditions[3-5]. In contrast, patients treated in everyday clinical practice often have more comorbidities and cardiovascular risk factors. Therefore, real-world evidence is particularly important for assessing the safety profile of this therapy.

The aim of this prospective observational study was to assess the incidence, clinical characteristics, time of onset, and reversibility of cardiotoxicity in a consecutive cohort of patients with HER2-positive early or locally advanced breast cancer treated with adjuvant subcutaneous fixed-dose pertuzumab and trastuzumab (Phesgo) in a real-world clinical setting.

Materials and methods

Study design and study population

This prospective observational cohort study included 50 consecutive patients with histopathologically confirmed HER2-positive early or locally advanced breast cancer who were treated at the University Clinic for Medical Oncology between 2024 and 2026. All patients

received adjuvant subcutaneous fixed-dose pertuzumab and trastuzumab (Phesgo), in accordance with current national and international recommendations for the treatment of HER2-positive breast cancer.

Inclusion criteria

Patients were included in the study if they met the following criteria:
- age ≥18 years;
- histologically confirmed invasive HER2-positive breast cancer;
- HER2-positive status confirmed by immunohistochemistry (IHC 3+) or FISH analysis;
- indication for adjuvant dual anti-HER2 therapy;
- baseline left ventricular ejection fraction (LVEF) ≥55%.

Exclusion criteria

- Patients with the following conditions were excluded:
- previously diagnosed congestive heart failure;
- unstable angina pectoris;
- acute myocardial infarction within the previous six months;
- uncontrolled arterial hypertension;
- other severe cardiovascular diseases that could affect the assessment of cardiac function.

Treatment protocol

All patients received the subcutaneous fixed-dose combination of pertuzumab and trastuzumab (Phesgo) according to the manufacturer's recommendations.

The loading dose was 1,200 mg pertuzumab and 600 mg trastuzumab in 15 mL of solution, administered subcutaneously.

The maintenance dose was 600 mg pertuzumab and 600 mg trastuzumab in 10 mL of solution, administered subcutaneously every three weeks.

The planned treatment regimen comprised a total of 18 cycles over one year.

Before initiation of anti-HER2 therapy, 38 patients (76.0%) had received a sequential anthracycline-taxane regimen (EC-T: epirubicin/cyclophosphamide followed by docetaxel), while 12 patients (24.0%) had received a non-anthracycline regimen (TCH: docetaxel, carboplatin, and trastuzumab).

Cardiac monitoring

All patients underwent standardized cardiac monitoring using transthoracic echocardiography.

LVEF was determined using the modified biplane Simpson method.

Echocardiographic examinations were performed:
- before treatment initiation (baseline);
- at 3 months;
- at 6 months;
- at 9 months;
- at the completion of the 12-month treatment period.

The occurrence of potential symptoms of heart failure, such as dyspnea, fatigue, and peripheral edema, was also monitored during treatment.

Definition and management of cardiotoxicity

Cardiotoxicity was defined according to the criteria of the Cardiac Review and Evaluation Committee (CREC)[12].

Symptomatic cardiotoxicity was defined as a decrease in LVEF accompanied by clinical signs and symptoms of NYHA class II-IV heart failure.

Asymptomatic cardiotoxicity was defined as a decrease in LVEF of ≥10 percentage points from baseline, with an absolute LVEF value of <50%.

If cardiotoxicity occurred, Phesgo treatment was temporarily interrupted, and patients were referred for a cardio-oncology assessment. In accordance with current cardiology recommendations, treatment with an angiotensin-converting enzyme (ACE) inhibitor (enalapril or ramipril) and a beta-blocker (carvedilol or bisoprolol) was initiated.

Cardiac assessments were repeated every three weeks. Anti-HER2 therapy could be resumed after LVEF had normalized to ≥50% and following an appropriate multidisciplinary team assessment.

Statistical Analysis

Categorical variables are presented as absolute numbers and percentages, while continuous variables are presented as medians and ranges.

Differences in the incidence of cardiotoxicity between patients treated with anthracycline and non-anthracycline regimens were analyzed using Fisher's exact test.

Statistical significance was defined as a two-sided p-value <0.05.

Results

Baseline demographic and clinical characteristics

A total of 50 patients with HER2-positive early or locally advanced breast cancer treated with adjuvant subcutaneous fixed-dose pertuzumab and trastuzumab (Phesgo™) were included in the study.

The median age was 54.5 years (range, 36-74 years). Arterial hypertension was present in 11 patients (22.0%), while diabetes mellitus was recorded in 4 patients (8.0%).

Table 1. Baseline demographic and clinical characteristics of the patients

Characteristic	Value
Total number of patients	50
Age, median (range), years	54.5(36-74)
Arterial hypertension, n (%)	11(22.0)
Diabetes mellitus, n (%)	4(8.0)
Anthracycline-based regimen (EC-T), n (%)	38(76.0)
Non-anthracycline-based regimen (TCH), n (%)	12(24.0)
Left-sided radiotherapy, n (%)	22(44.0)

Most patients (38; 76.0%) had previously received a sequential anthracycline-taxane regimen (EC-T), while 12 patients (24.0%) had received a non-anthracycline regimen (TCH). Left-sided adjuvant radiotherapy was administered to 22 patients (44.0%).

The baseline demographic and clinical characteristics of the study population are presented in Table 1.

Incidence and clinical characteristics of cardiotoxicity

During the 12-month follow-up period, cardiotoxicity according to the Cardiac Review and Evaluation Committee (CREC) criteria was recorded in 3 of the 50 patients, corresponding to an overall incidence of 6.0%.

One patient (2.0%) developed symptomatic NYHA class II heart failure, manifested by dyspnea on moderate exertion. Echocardiography showed a decrease in LVEF from 61% to 44%, representing a reduction of 17 percentage points.

Two patients (4.0%) experienced an asymptomatic decrease in LVEF of more than 10 percentage points, with final values of 47% and 48%, respectively.

The clinical characteristics of patients who developed cardiotoxicity are presented in Table 2.

Table 2. Clinical characteristics of patients with cardiotoxicity

Patient	Age	Previous anthracycline therapy	Baseline LVEF (%)	Lowest LVEF (%)	Clinical presentation
1	62	Yes	61	44	Symptomatic (NYHA II)
2	49	Yes	58	47	Asymptomatic
3	56	Yes	60	48	Asymptomatic

All cases of cardiotoxicity occurred in patients previously exposed to anthracycline chemotherapy. In the EC-T group, cardiotoxicity was observed in 3 of 38 patients (7.9%), whereas no cases were recorded in the TCH group (0/12).

Although the incidence was numerically higher among patients with previous anthracycline exposure, the difference did not reach statistical significance (Fisher's exact test, *p*=0.561).

Treatment and reversibility of cardiotoxicity

Phesgo treatment was temporarily interrupted in all three patients immediately after cardiotoxicity was diagnosed.

Standard cardioprotective treatment was initiated with an ACE inhibitor (ramipril 2.5 mg/ day) and a beta-blocker (carvedilol 6.25 mg twice daily), followed by regular echocardiographic monitoring.

All patients achieved complete recovery of left ventricular function, with LVEF returning to ≥50%. The median time to recovery was 7.5 weeks (range, 6-9 weeks).

After normalization of cardiac parameters, anti-HER2 therapy was restarted in all three patients. None experienced recurrent cardiotoxicity, and all successfully completed the planned 12-month treatment without permanent cardiac sequelae.

Discussion

This prospective observational cohort study assessed the cardiovascular safety and tolerability of adjuvant subcutaneous fixed-dose pertuzumab and trastuzumab (Phesgo) in patients with HER2-positive early or locally advanced breast cancer in real-world clinical conditions. Our results showed a low incidence of cardiotoxicity of 6.0% (3 of 50 patients), with most cardiac events being asymptomatic and fully reversible. Only one patient (2.0%) developed symptomatic left ventricular dysfunction (NYHA class II), while two patients (4.0%) were diagnosed with a subclinical decrease in LVEF. Contemporary cardio-oncology management, including temporary interruption of anti-HER2 therapy and timely initiation of standard neurohormonal blockade, enabled complete functional myocardial recovery in all affected patients.

These findings are consistent with data from landmark randomized clinical trials of dual HER2 blockade. In the APHINITY study, the incidence of primary cardiac events during adjuvant treatment with pertuzumab and trastuzumab remained low (0.7%)[4]. Similarly, the FeDeriCa study confirmed the non-inferiority and comparable cardiovascular safety profile of the subcutaneous combination relative to its intravenous formulation[5]. Our study extends these findings to everyday clinical practice, providing real-world validation in an unselected population that often presents with a broader range of cardiovascular risk factors and comorbidities.

An important clinical observation in our cohort was that all recorded cases of cardiotoxicity occurred in patients with previous anthracycline exposure (EC-T regimen). From a pathophysiological perspective, anthracyclines induce cumulative, dose-dependent cardiomyocyte damage through the generation of reactive oxygen species and inhibition of topoisomerase IIβ, thereby reducing myocardial functional reserve[9,10]. Further inhibition of the HER2/ErbB2 signaling pathway - which is essential for cardiomyocyte survival and endogenous adaptation to chemotherapy-induced stress - may increase the risk of secondary myocardial dysfunction.

Unlike type I cardiotoxicity induced by anthracyclines, which is associated with irreversible necrosis and ultrastructural damage, type II cardiotoxicity associated with anti-HER2 monoclonal antibodies is predominantly functional, non-dose-dependent, and reversible[11]. In our series, the median time to complete normalization of LVEF (≥50%) was 7.5 weeks after initiation of pharmacological treatment with ACE inhibitors and beta-blockers. This supports the effectiveness of targeted cardioprotection and allows anti-HER2 therapy to be rechallenged without compromising oncological outcomes.

The three-month echocardiographic monitoring protocol used in this study proved to be an effective strategy for early detection and prevention of progression to severe symptomatic heart failure. In accordance with current ESC cardio-oncology recommendations, future monitoring strategies should incorporate global longitudinal strain (GLS) and high-sensitivity cardiac biomarkers (hs-cTnI and NT-proBNP), which enable the detection of subclinical myocardial injury before a decline in LVEF becomes apparent[8,13].

An important strength of this study is its prospective design and the inclusion of consecutive patients from routine clinical practice, allowing a better assessment of the real-world safety of Phesgo. In addition, all patients were monitored using a standardized echocardiographic protocol and clearly defined cardiotoxicity criteria.

Although the study provides valuable real-world data, several methodological limitations should be acknowledged: the single-center design, the relatively small sample size (n=50), and the limited follow-up duration of 12 months. Future multicenter studies with longer follow-up and analysis of advanced echocardiographic parameters will enable further characterization of the long-term cardiovascular safety of this treatment.

Despite these limitations, the study indicates that adjuvant subcutaneous fixed-dose pertuzumab and trastuzumab has a favorable cardiovascular profile in routine oncology practice. Cardiotoxicity was characterized by a low incidence, favorable reversibility, and a high degree of manageability through a multidisciplinary cardio-oncology approach.

Conclusion

Adjuvant subcutaneous fixed-dose pertuzumab and trastuzumab (Phesgo) demonstrated a high level of cardiovascular safety and tolerability in patients with HER2-positive breast cancer in real-world clinical conditions.

The incidence of cardiotoxicity was low (6.0%), predominantly asymptomatic, and observed exclusively in patients previously treated with anthracycline chemotherapy, highlighting the need for increased cardiovascular vigilance in this subgroup.

The resulting left ventricular dysfunction proved to be fully reversible following temporary treatment interruption and timely administration of cardioprotective therapy with ACE inhibitors and beta-blockers, enabling safe rechallenge and completion of the planned oncological treatment.

Systematic cardio-oncology monitoring remains a key component of the timely identification and management of myocardial injury, ensuring an optimal balance between oncological efficacy and cardiovascular safety.

Although the results are limited by the small number of patients, this study provides additional real-world evidence that the subcutaneous fixed-dose combination of pertuzumab and trastuzumab is an effective and cardiac-safe therapeutic option for HER2-positive breast cancer. Further multicenter studies with longer follow-up and the use of advanced methods for early detection of cardiotoxicity, such as global longitudinal strain and cardiac biomarkers, are needed to further characterize the long-term cardiac safety of this therapy.

Conflict of interest statement. None declared.

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