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Subcutaneous Trastuzumab: What About Cardiac Toxicity? Real Life Study in a Moroccan Medical Oncology Department

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KEYWORDS

Breast cancer, Trastuzumab, subcutaneous formulation, cardiac toxicity

ABSTRACT:

Introduction: Trastuzumab is a monoclonal antibody targeting the HER2 receptor. Initially, it was only administered intravenously. Since August 2013, the subcutaneous formulation has been introduced. The phase III HANNAH study demonstrated the non-inferiority of subcutaneous Trastuzumab compared to the IV in terms of efficacy and safety. At the medical oncology department of Souss Massa University Hospital, since 2019, Trastuzumab is only administered subcutaneously.

Objectives: The aim of our study is to report real-life data of cardiac toxicity of subcutaneous Trastuzumab.

Methods: We conducted a retrospective cohort study, performed at the Souss Massa University Hospital between January 2019 and December 2020. Our inclusion criteria were patients with HER2 positive localized breast cancer with good cardiac function. Cardiotoxicity was defined as a drop in LVEF below 50% or a 10-point drop from baseline EF or evidence of heart failure.

Results: Our study included 120 patients with a female predominance (99%). The average age was 49.81 years. Regarding cardiovascular risk factors, 1.66% of the patients were hypertensive, 5.83% were diabetic and 48.33% had a BMI>25. For tumour disease, the left breast was affected in 49.17% of the cases, 69.17% of the patients were hormone receptor positive. 4.16% were diagnosed with stage I, 47.5% with stage II and 48.33% with stage III. Therapeutically, 42.5% received neoadjuvant therapy. All patients underwent surgery but only 18.33% were able to benefit from conservative surgery. Sequential chemotherapy was used in all our patients except 5% who did not receive anthracyclines. Radiotherapy was indicated in 96.67% of cases. Initial LVEF was between 50 and 60% in 10%, between 60 and 70% in 62.5% and more than or equal to 70% in 27.5% of cases with an average of 66.28%. At the end of treatment, the average LVEF was 63% (49%-76%), a decrease in absolute value of 3.28% before and after using Trastuzumab. In 15 patients or 13.3%, subcutaneous trastuzumab had to be discontinued due to cardiotoxicity with a decrease in LVEF below 50% in 5 patients (4.16%), a decrease in LVEF of more than 10 points from baseline in 6 cases (5%) and more than 15 points in 3.33%. Subcutaneous injections were resumed in 11 patients (9.1%) after normalization of LVEF while it was permanently stopped in 4 patients (3.34%).

Conclusions: The use of subcutaneous Trastuzumab constitutes an indisputable progress in the treatment of breast cancer overexpressing HER2. Its cardiac safety in our real-life study is in line with that reported in the literature.

1. Introduction

Breast cancers are typically categorized according to their diversity, which aids in the selection of the most suitable therapies to achieve the best treatment results. The progress in chemotherapy and targeted gene therapy has significantly enhanced the efficacy of breast cancer treatment, leading to demonstrably improved survival rates.

Human epidermal growth factor receptor (HER2) operates as a transmembrane receptor tyrosine kinase,

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exerting a fundamental influence on the processes of cell growth and proliferation [1]. The main target of trastuzumab is the extracellular domain of the HER-2 receptor. It has become a milestone in early and advanced stage breast cancer treatment. The benefit of this revolutionary treatment has nonetheless, come with the potential downside of an increased risk of cardiotoxicity.

Four significant clinical trials (HERA, NSABP B31, Fin-HER, and BCIRG 006) have demonstrated that incorporating trastuzumab into adjuvant therapy substantially increases both disease-free survival (DFS) and overall survival (OS), with no significant impact on treatment related side effects, except for the occurrence of cardiotoxicity in patients receiving trastuzumab [2,3].

In contrast to the potential cardiac side effects associated with anthracycline treatment, the development of trastuzumab-induced cardiomyopathy is independent of the total dose of the medication administered [4]. Trastuzumab-induced cardiotoxicity (TIC) arises from the inhibition of HER2 signaling within cardiac myocytes [3]. The potential for cardiovascular events is heightened when therapy related subclinical damages coincide with comorbidities and unfavorable lifestyle factors such as decreased physical activity and obesity [5].

A subcutaneous (s.c.) version of trastuzumab has been created to overcome the drawbacks associated with intravenous (i.v.) administration. These limitations include extended administration times and challenges for patients who rely on port-a-cath systems. S.c. trastuzumab injections can be administered more swiftly, typically taking 2–5 minutes as opposed to the 30–90 minutes required for i.v. infusion. This innovation is poised to enhance the overall treatment experience by increasing convenience for patients and promoting greater adherence to treatment plans [2].

In the initial analysis of the HannaH trial, it was determined that subcutaneous trastuzumab was just as effective as intravenous trastuzumab for patients with early breast cancer who tested positive for ERBB2 (HER2). This conclusion was drawn based on two primary criteria: achieving a pathologic complete response (meaning the absence of invasive cancer cells in the breast, with the acceptance of remaining ductal carcinoma in situ) and maintaining a certain level of serum through concentration prior to the eighth treatment cycle. Subsequent 2-year follow-up assessments revealed similar event-free survival rates over a 3-year period [6]. Additionally, the safety profiles of subcutaneous trastuzumab and intravenous trastuzumab remained consistent and comparable in the follow-up analysis [6].

2. Objectives

At the Souss Massa University Hospital, since 2019, Trastuzumab is only administered subcutaneously. The aim of our study is to report real-life data of cardiac toxicity of subcutaneous Trastuzumab.

3. Methods

We conducted a retrospective cohort study, performed at the medical oncology department of Souss Massa University Hospital.

Eligibility criteria:

Eligible patients were those with 18 years of age and older with histologically confirmed invasive breast cancer without evidence of metastatic disease (stage I to III), HER2-positive disease defined as 3 + overexpression by immunohistochemistry or HER2 amplification by fluorescence in situ hybridization and with known estrogen and progesterone hormone receptor status.

We excluded from our study patients having metastatic disease, or a cardiac disease at the time of diagnosis.

Administration method of trastuzumab:

The administrated dose for subcutaneous trastuzumab formulation is 600 mg irrespective of the patient's body weight. No loading dose was required. The 600 mg dose was administered as a subcutaneous injection only over 2-5 minutes every three weeks. The injection site was alternated between the left and right thigh. New injections were given at least 2.5 cm from the old site.

Data collection

We collected information, in respecting anonymity, regarding patient’s medical history (with Data on demographics, and cancer characteristics) and we also analyzed the cardiac risk factors.

For all our patients, a baseline cardiac assessment was performed: clinical examination and echocardiography with assessment of Left Ventricular Ejection Fraction

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(LVEF). Subsequent administrations were evaluated every 12 weeks throughout the course of treatment. Cardiotoxicity was defined as a LVEF decrease below normal values (50%) or an absolute decrease of >10 points below the baseline value or any symptoms or signs of heart failure.

Ethical approval

The study was conducted in compliance with the ethical standards of the responsible institution on human subjects as well as with the Helsinki Declaration.

Statistical analysis

A comprehensive analysis was conducted using the statistical software Jamovi. Statistical variables were described in terms of frequencies and percentages. Regarding survival analysis, we conducted a survival function using the Kaplan-Meier method and then compared the different survival functions using the Log Rank test. Notably, the significance level chosen for the findings was a p-value less than 0.05.

4. Results

During the study period, 120 new cases of early-stage breast cancer patients were considered as candidates to receive trastuzumab.

The mean age in the cohort was 49.81 ± 9.84 years. Concerning the cardiovascular risk factors, 1.66% had hypertension, 5.83% had diabetes, 48.33% had overweight or obesity and 46.67% of women were menopausal.

For tumor disease, the left breast was affected in 49.17% of the cases, and 69.17% of the patients were hormone receptor-positive. 4.16% were diagnosed with stage I, 47.5% with stage II, and 48.33% with stage III disease.

Regarding the treatment plan, 42.5% received neoadjuvant therapy. All patients underwent surgery, but only 18.33% were able to benefit from conservative surgery. Sequential chemotherapy was used in almost all our patients. There were only 5% who did not receive anthracyclines. Radiotherapy was indicated in 96.67% of cases.

Table 1: Patient demographics, tumor characteristics, and treatment delivered

Age[1]	49,81 ±9.84
Menopausal Status[2]	
Postmenopausal	56(46,67)
Premenopausal	64 (53,33)
Cardiovascular risk factors[2]	
BMI	
Normal	62 (51,66)
Overweight	38 (31,67)
Obesity	20 (16,67)
Hypertension	2 (1,66)
Diabetes	7 (5,83)
Breast[2]	
Right	61 (50,83)
Left	59 (49,17)
Tumor size[2]	
T1	9 (7,5)
T2	75 (62,5)
T3	14 (11,67)
T4	22 (18,34)
Ganglion involvement[2]	
Positive	82 (68,33)
Negative	38 (31,67)
Hormone receptor status[2]	
Positive	83 (69,17)
Negative	37 (30,83)
Surgery[2]	
Radical	99 (82,5)
Conservative	21 (17,5)
Systemic treatment[2]	
Neoadjuvant	51 (42,5)
Adjuvant	69 (57,5)
Chemotherapy[2]	
With anthracyclines	114 (95)
Without anthracyclines	6 (5)
Radiotherapy[2]	96,67%

[1] Expressed in mean ± standard deviation

[2] Expressed in frequencies (percentages)

The baseline cardiac assessment showed that initial LVEF was between 50 and 60% in 10%, between 60 and 70% in 62.5%, and more than or equal to 70% in 27.5% of cases with a median of 66.28%. At the end of treatment, the median LVEF was 63% (49%-76%), with an absolute value decrease of 3.28% between the start and the end of Trastuzumab use (Figure 1).

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13.3% of patients presented with cardiotoxicity according to the pre-established criteria (Table 2).

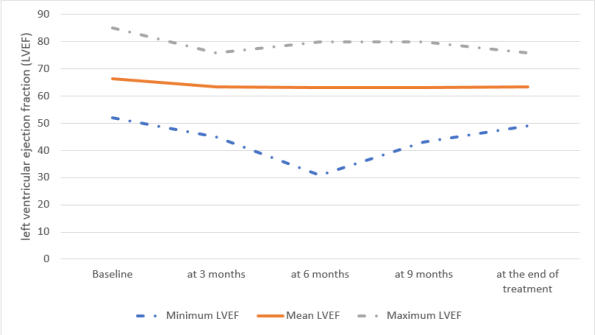

Figure 1: Mean LVEF from baseline to the end of treatment. Dashed lines represent the minimum and maximum values.

Table 2: Characteristics of the LVEF decrease in patients with cardiotoxicity (n =15)

Cardiotoxicity criteria	Patients(%)
LVEF decrease <50%	5 (4.16)
LVEF decrease >10 points below the baseline	6 (5)
LVEF decrease > 15 points below the baseline	4 (3.33)

In 15 patients or 12.5%, subcutaneous trastuzumab had to be discontinued due to cardiotoxicity with a decrease in LVEF below 50% in 5 patients (4.16%), a decrease of more than 10 points from baseline in 6 cases (5%) and more than 15 points in 3.33%. Subcutaneous injections were resumed in 11 patients (9.1%) after normalization of LVEF while it was permanently stopped in 4 patients (3.34%) due to persistent abnormal cardiac function.

The survival analysis did not demonstrate a statistically significant difference between patients who experienced cardiotoxicity and those who did not in terms of relapse-free survival (p=0.908) and overall survival (p=0.858) (figure 2).

5. Discussion

Over the recent decades, advancements in chemotherapy and targeted therapies have substantially improved the survival rates of cancer patients. However, these therapeutic gains have brought to light the long-term side effects of cancer treatment, particularly chemotherapy. Specific substances like anthracyclines and trastuzumab have been linked to a notable risk of cardiac complications, including left ventricular dysfunction and heart failure (HF), as well as thromboembolic events, hypertension, and arrhythmias. Remarkably, a significant number of breast cancer patients do not succumb to the cancer itself but rather to cardiovascular complications associated with cancer treatments. This underscores the critical importance of effectively managing cardiovascular risk factors for the ongoing care of individuals diagnosed with breast cancer [7].

Trastuzumab therapy plays a pivotal role in the management of both early and advanced breast cancer, a fact supported by numerous randomized trials. According to the metanalysis of Gustavo A Vian and al., using Trastuzumab as an adjuvant treatment in HER2 positive early breast cancer improves the rates of disease-free survival: 15.3% VS 8.2% and the overall mortality rates with 6% VS 8.5% [7]. Currently, the international standard of care for HER2-overexpressed localized breast cancer includes using trastuzumab as an adjuvant treatment for a period of one year. Importantly, this treatment is usually well-tolerated, with a minimal occurrence of adverse effects [8].

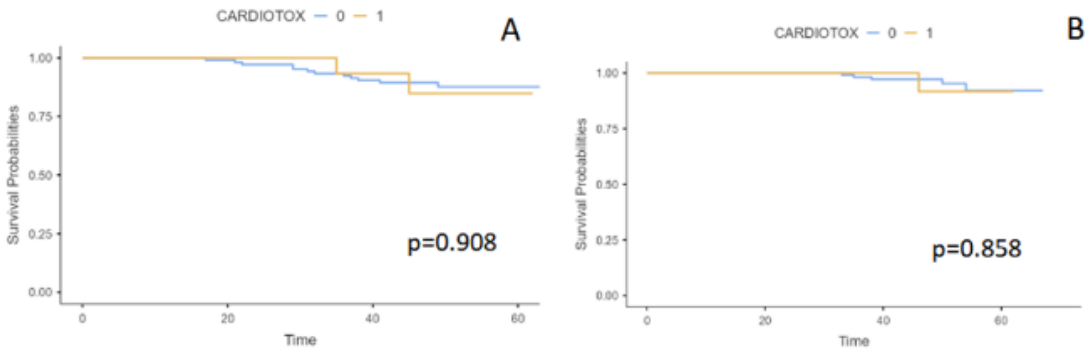

Figure 2: Kaplan–Meier Estimates of Event-free Survival (A) and overall Survival (B) based on cardiotoxicity.

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Subsequently, a subcutaneous formulation of trastuzumab has been created, presenting the possibility of enhancing patient convenience and optimizing resource utilization when compared to the conventional intravenous infusion method of administering the drug [9]. Patients receiving trastuzumab predominantly favored the subcutaneous (SC) formulation over the intravenous (IV) alternative, attributing a significant positive impact on their quality of life and markedly improving their overall experience. [10]

In the aim of proving the efficiency of the subcutaneous formulation comes the HannaH trial which stands as the most extensive randomized clinical study exploring the use of both subcutaneous and parenteral trastuzumab in individuals diagnosed with ERBB2-positive early breast cancer. After six years of follow-up, the results regarding event-free survival and overall survival continue to validate the comparable effectiveness of subcutaneous trastuzumab compared to parenteral trastuzumab, as initially noted in the primary assessment [11]. These event-free survival outcomes align with those seen in the HERA trial, which focused on adjuvant parenteral trastuzumab. [2]

For a better assessment of the safety profile of subcutaneous Trastuzumab, the Hermione study, a prospective non-interventional investigation, encompassed a cohort of 511 patients designated for treatment in both neoadjuvant and adjuvant contexts, with a maximum follow-up period of 12 months across 101 participating sites and focused on 505 patients, revealing that in a real-world clinical environment, the safety profile of subcutaneous (SC) trastuzumab administered to early-stage HER2-positive breast cancer aligns with the results reported in prior clinical trials. Importantly, these results did not reveal any previously unknown safety concerns and did not indicate any noticeable deterioration in patients' quality of life (QoL) [12].

Similarly, at the 6-year follow-up mark of the HANNAH trial the general safety and cardiac safety profiles of subcutaneous trastuzumab have shown ongoing consistency with those of intravenous trastuzumab. The incidence of cardiac AEs was low and was similar for patients treated with sc and iv trastuzumab formulation (44 of 297 (14.8%) vs 42 of 298 (14.1%) [11]. This alignment also extends to the results originally observed in the PrefHer and SafeHer studies [10, 13].

Treatment with Trastuzumab has been linked to cardiotoxicity, which is characterized by a decline in left ventricular ejection fraction (LVEF) and may or may not be accompanied by clinical signs and symptoms of heart failure (HF) [14,15]. Importantly, it's worth noting that this cardiotoxicity is typically reversible [15].

In our study, 13.3% of patients presented cardiotoxicity in accordance with the pre-established criteria, which is similar to the results found in the HannaH trial [11], and also similar to Breast Cancer International Research Group (BCIRG) 006 trial results (18%) [16], less than what the joint study of National surgical adjuvant breast and bowel project describes (NSABP) B-31 (34%) [17], and higher than in the Herceptin Adjuvant (HERA) trial (7.1%) [2].

Close monitoring of the left ventricular ejection fraction (LVEF) is necessary before and throughout the course of treatment by regular echocardiography. It identifies the initial signs of myocardial damage through the detection of anomalies in right ventricular contractility, ventricular dilation, and deviations in left ventricular contractility. If clinical indications of heart failure emerge, it is imperative to cease therapy. Additionally, patients experiencing an asymptomatic decline in their left ventricular ejection fraction (LVEF) of 15% (or 10% if the acceptable lower LVEF threshold is set at 50%) should also discontinue trastuzumab treatment [18].

Trastuzumab discontinuation rate, primarily due to cardiotoxicity, varies between 8.5% and 31.4% [19]. Trastuzumab-associated cardiotoxicity has been characterized as not dependent on dosage and is notably reversible, even when the medication is continued [20]. In the McArthur and Chia study, the rate of treatment suspension due to cardiac dysfunction was 21.6% [21]. Nonetheless, the same study indicates that the majority of patients who ceased their treatment due to cardiac issues were able to resume it once they had regained their cardiac function.

In our study, 16 patients (13.3%) had to discontinue the s.c trastuzumab due to cardiotoxicity. Injections were resumed in 12 patients after normalization of LVEF while it was permanently stopped in 4 patients (3.34%)

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due to the non-recovery of their ventricular function. These results were compatible with prior studies.

While analyzing the safety profile of the s.c trastuzumab, many risk factors for Trastuzumab induced cardiotoxicity have been studied by different groups, but results have been inconsistent [22]. Notably, factors such as a history of hypertension, smoking, a family history of coronary artery diseases, and a low baseline left ventricular ejection fraction (LVEF) have been identified as significant predictors for the occurrence of TIC in some of these studies [1,23].

Other researches have pointed to factors such as age, hypertension, preexisting cardiac dysfunction, a less than 50 % LVEF baseline, and prior anthracycline treatment or radiotherapy to the left chest wall combined with chemotherapy as contributing to an increased risk of cardiotoxicity [24, 25].

In the HERA trial, several cardiotoxicity risk factors were identified. These included a lower baseline LVEF (ranging from 55% to 60%), a higher BMI (greater than 25), the presence of hyperlipidemia, and an increased cumulative dose of anthracycline (exceeding 287 mg/m2). Conversely, diabetes, a history of cardiac diseases, and hypertension were found to have no notable influence on the occurrence of cardiotoxicity [2, 26].

According to Seidman A and al., the combination of trastuzumab with chemotherapy regimens containing anthracycline led to a notable rise in the occurrence of cardiac side effects, with the incidence increasing up to 27% [27].

In our study, hypertension, diabetes, overweight or obesity, menopausal status and sequential chemotherapy use were not identified as significant cardiovascular risk factors.

S.c trastuzumab administration represents an undeniable advancement in the treatment of HER2-positive breast cancer. Cardiac tolerance observed in our study aligns with that reported in the literature.

Since treatment strategies for breast cancer patients typically involve multiple modalities, it can be challenging to isolate the specific cardiotoxic effects of each regimen. These treatments have the potential to interact with one another, potentially compounding their impact on the cardiovascular system.

Hence, it is of paramount importance for healthcare providers to acknowledge the risk factors and pinpoint patients with an elevated susceptibility to cardiotoxicity. This proactive approach is vital for implementing preventive measures and offering tailored treatments to optimize therapeutic results. Therefore, it is strongly advisable to maintain ongoing surveillance of cardiac function, as this can effectively address any emerging cardiac issues and enhance the outcomes of adjuvant treatment for these patients.

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