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Review Article

Cardiac Toxicity of Trastuzumab in Patients Treated for Breast Cancer HER2 3+ An Algerian Study

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Abstract: Breast cancer is the most common cancer in women worldwide, its incidence is increasing but mortality has decreased in a huge way due to the growth of various cancer treatments. Patients with a contraindication for trastuzumab, an incomplete cardiographic echo record, and patients with already heart disease were excluded from the history. The means of cardiac monitoring was cardiac ultrasound or isotopic ventriculography, the toxicity criteria were those of the New York Heart Association (NYHA), a detailed operating sheet was made for each of our patients. The main objective of our study was to assess the incidence of cardiotoxicity in patients treated for breast cancer HER 2 3+ by trastuzumab.06% of our patients had had trastuzumab cardiotoxicity (i.e. 3 cases); two patients had an asymptomatic decrease in reversible LVEF and one patient had clinically significant heart failure requiring appropriate treatment for ICS and permanent discontinuation of trastuzumab. The protocols of targeted therapy with trastuzumab are an essential progress in oncology and cardiac toxicity is the major limiting factor for its use. Our work focuses on a retrospective study, conducted at the Department of Oncology and the Hospital Ahmida Ben adjila discussing cardiotoxicity of tarstuzumab in 50 patients with breast cancer HER2 3+ collected from january 2014 to december 2019.we have included in this study all patient with breast cancer overexpressing HER2 3+ treated by trastuzumab with an initial heart function and preserved LVEF ≥5 5%. We excluded patients contre to trastuzumab, incomplete echocardiographic folder, patients who received neoadjuvant trastuzumab and patients with metastatic breast cancer. Cardiotoxicity with trastuzumab is not common enough in our series but it does exist, which requires several careful preventive measures including monitoring by echocardiography.

Keywords: Tarstuzumab, breast cancer, HER2 3+, cardiotoxcity, targeted therapy, oncology.

INTRODUCTION

Epidemiology

Breast cancer is the most common malignant disease in women with more than a million cases worldwide each year. According to the literature, 9 to 30% of breast carcinomas are said to be HER2 3+ [1]. Although the incidence is increasing in most parts of the world, there are huge inequalities between rich and poor countries. Incidence rates remain highest in the most developed regions.

The Trastuzumab in the Breast Cancer

Trastuzumab has shown a benefit in terms of survival in HER2 3+ breast cancer whether in the metastatic phase or in adjuvant use [2]. However, this product revealed a significant cardiotoxic potential. These findings lead to a modification of practices. Indeed, the concomitant combination of chemotherapy with anthracycline and trastuzumab has been banned and at least quarterly cardiac monitoring has been established [3]. It is difficult to compare the incidence of trastuzumab cardiotoxicity from one study to another, because the methods and evaluation criteria are often different. Thus, some authors will only be interested in

the occurrence of clinical cardiac failure without taking into account ultrasound abnormalities. Our study is a retrospective study, conducted at the Department of Oncology and the Hospital Ahmida Ben adjila discussing cardiotoxicity of tarstuzumab in 50 patients with breast cancer HER2 3+ collected from january 2014 to december 2019.we have included in this study all patient with breast cancer overexpressing HER2 3+ treated by trastuzumab with an initial heart function and preserved LVEF ≥55%. We excluded patients contre to trastuzumab, incomplete echocardiographic folder, patients who received neoadjuvant trastuzumab and patients with metastatic breast cancer.

Different Studies

In the study by T. Genevée and B. Lortal; between October 1, 2007 and January 1, 2014, 188 patients were treated with trastuzumab for HER2-positive breast carcinoma [4]. In the study by Keddari. A and Djillat. K over one year (April 2014-April 2015) 90 patients treated for HER 3+ breast cancer in the medical oncology department and the pharmacy of the Sétif cancer center [5]. In the study by R. Tanz *et al.*, 53 patients were treated for HER2 3+ breast cancer during the year 2008-2009 at the medical oncology department of the Mohamed V military training hospital in Rabat [6]. In our series, the frequency was 16.55% or 50 patients of all breast cancers during the period January 2014-December 2019. This rate was significantly lower than the figures reported in other published national and international series. This could be explained by the late diagnosis due to the absence of a screening companion, the difficulty of accessing care and partly to a particular socio-cultural context (modesty, feeling of fear). In addition, health education and awareness still seem insufficient.

Table 1: Number of patients with HER2 3+ breast cancer in different studies.

The Studies	Countries	During	Number of cases
T. Genevée; B. Lortal	France/Bordeaux	(01/07/2007-01/01/2014)	180
Keddari. A; Djallat. K	Algérie/Sétif	(04/2014-04/2015)	90
R. Tanz *et al.*,	Maroc/Rabat	2008-2009	53
Our study	Algérie/Laghouat	(01/04/2014- 31/12/2019)	50

Risk Factors for Cardiotoxicity:

Risk factors for developing a cardiotoxicity due to trastuzumab have been evaluated in several studies which identified age greater than 55 years as well as reduced LVEF before trastuzumab administration as main factors. A body mass index of more than 25 kg/m2 has also been used as a risk factor in certain studies [7]. Women are more at risk than men, with a risk doubled compared to men. The determinism of this difference remains unknown.

Investigators in some studies have drawn the likelihood of developing cardiotoxicity in patients treated simultaneously with anthracyclines and trastuzumab increases after a cumulative dose of doxorubicin greater than 300 mg/m2 [8]. The sequence in which chemotherapeutic agents are administered appears to influence the development of cardiac dysfunction. When anthracyclines and trastuzumab were administered simultaneously, the frequency of symptomatic NYHA stage III and IV heart failure was 16%. Also, analyzes have shown a direct relationship between the occurrence of heart failure and the combination of radiotherapy with trastuzumab poses the problem of added toxicity, especially at the cardiac level [9]. We will analyze these factors in different studies as well as mine (table 2).

We note that all the risk factors for cardiotoxicity are present in the Chakib.B series while in our population there is only age with low frequency and sex (exclusion criteria). Concomitant radiotherapy was not a criterion because we don't have any service nearby.

Table 2: Analysis of the different risk factors for trastuzumab cardiotoxicity

The studies	Countries	Age upper than 55	female	Trastuzumab+anthracyclines (n)	Trastuzumab+radiotherapy (n)
F. Grudé	France	09	29	0	10
Kedari. A; Djallat	Algeria/ setif	60	103	0	/
Chakib. B	Morocco	63	90	103	109
Our study	Algeria /laghouat	08	50	0	0

Cardiac Ultrasound

In our study, the evaluation of cardiotoxicity of tarstusumab was done by cardiac ultrasound to measure LVEF for our patients before the start of treatment with trastuzumab and during treatment and even after treatment. According to the table below (table 3) the median value of LVEF before and after treatment for our population is the highest compared to other studies; with a decrease of less than 10 points.

This is explained on the one hand by the absence of underlying heart disease before treatment in our population and on the other hand by the minimal effect of trastuzumab on LVEF in our study.

Table 3: The value of LVEF in different studies

The studies	Countries	LVEF value before treatment	LVEF value after treatment
F. Grudé *et al.*,	France	61 %	48 %
Chakib. B.	Morocco	66.5 %	62.3 %
Our study	Algeria / Laghouat	71 %	67.5 %

CONCLUSION

Breast cancer remains a major public health issue. In recent years, in all age groups, a decrease in the mortality of patients with breast cancer has been observed. Its strategy is well codified; thanks to multidisciplinary care (surgeon, intensivist, pathologist, biologist, pharmacist and onco-radiotherapist). Scientific advances in molecular biology as well as the understanding of the oncogenesis of breast cancer have made it possible to develop molecules targeting receptors which regulate the tumor activity of cancer cells. They are called “targeted therapies”.

Trastuzumab or Herceptin is one of these therapies. The use of this molecule has shown an advantage in terms of survival and reduction in recurrences in patients with advanced HER2 3+-overexpressing breast cancer, then in patients with localized cancer. However, it turned out that trastuzumab has a strong cardiotoxic potential (heart failure and left ventricular dysfunction) due to its mechanism of action and its combination with different so-called traditional chemotherapies. This adverse effect is likely to affect survival or reduce the quality of life of treated patients. Cardiac dysfunction secondary to trastuzumab is not dose dependent and is reversible in the majority of cases.

Cardiotoxicity linked to the administration of trastuzumab appears in the form of dysfunction of left ventricular function, most often asymptomatic and reversible in the majority of patients. It must alert the medical profession and encourage them to do everything possible to try to reduce this risk. To do this, better knowledge of risk factors for this cardiotoxicity, adequate monitoring and preventive measures must be taken into account. The development of new diagnostic and therapeutic techniques is essential to reduce this cardiotoxicity.

According to the results of our study and despite its retrospective nature and the size of our sample, trastuzumab seems harmless for patients with HER2 3+ breast cancer. The use of trastuzumab constitutes indisputable progress in the treatment of HER2 3+rc overexpressed or amplified breast cancer. Its cardiac tolerance in our study matches that reported in the literature.

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