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Original Research Article

Cardiotoxicity of Trastuzumab in Adjuvant Situation: A Prospective Study of 100 Cases

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Abstract: Breast cancer is the most common cancer of women in the world. Its mortality has decreased considerably due to the progression of cancer treatments. Trastuzumab is advancement in oncology but its cardiac toxicity remains a limiting factor in its use. To determine the incidence of this cardiotoxicity and to define the predictive factors of its occurrence in adjuvant situation. Material and methods: prospective study of 100 patients treated for adjuvant breast cancer at the Mohammed VI University Hospital Center in Marrakech - Morocco. Predictive factors for the occurrence of cardiotoxicity were studied. 39 patients had cardio toxicity (36 asymptomatic cases and 3 symptomatic patients) with an absolute decrease of 4.2% ($p < 0.001$). In multivariate analysis, a decreased left ventricular ejection fraction (LVEF) is the only significant risk factor ($p < 0.001$). The associated treatments (antracyclines and radiotherapy) do not represent a predictive factor of cardiotoxicity in our series ($p = 1$ and $p = 0.74$ respectively).Cardiac tolerance to trastuzumab in our series appears comparable with data from the literature. A decreased initial LVEF is a predictor of cardiotoxicity to trastuzumab.
Keywords: trastuzumab, cardiotoxicity, breast cancer, prospective study.

INTRODUCTION

Breast cancer is the most common cancer of women in the world. Its incidence is steadily increasing and more than one in 11 women is at risk of developing it [1, 2]. Since 1986, its mortality has decreased considerably with the progress of the different anticancer treatments.

Trastuzumab is a recombinant humanized monoclonal antibody directed against the extracellular portion of the transmembrane receptor of human epidermal growth factor HER2. It represents a real revolution in the management of breast cancer overexpressing HER2. Its use for one year as an adjuvant is an international standard, but its cardiotoxicity remains a limiting factor in its use.

The objective of this work was to determine the incidence of this cardiotoxicity and to define the predictive factors of its occurrence in adjuvant situation.

MATERIAL AND METHODS

A prospective cohort study of 100 patients treated for adjuvant breast cancer at the Department of Oncology at the Mohammed VI University Hospital Center of Marrakech between February 2012 and December 2014. We included all patients with preserved initial cardiac function defined by a left ventricular ejection fraction (LVEF) ≥55%. LVEF was measured by echocardiography before initiating treatment, then every three months and at the end of treatment. Predictive factors for the occurrence of cardiac toxicity were studied. The statistical analysis was carried out using the SPSS 20 software.

RESULTS

The average age in our series was 49.3 years. 53% of patients had obesity, 15% were hypertensive, 8% had diabetes, and 3% were valvular. 69% of the patients had a location in the left breast. Tumor classification was T2-T3 in 72% of cases and node

involvement was noted in 75% of cases. Antracycline adjuvant chemotherapy was performed in all cases (100%) and adjuvant radiotherapy was performed in 95% of cases. The clinical characteristics of our patients are shown in Table 1.

Table−1: Clinical Characteristics of Patients

Age		49.3 years [extremes between 21 and 69 years]
History	Obesity	53 %
	Arterial hypertension	15 %
	Diabetes	8 %
	Valvulopathy	3 %
Location	Left breast	69 %
	Right breast	31 %
Tumor status	T1	17 %
	T2	49 %
	T3	23 %
	T4	11 %
Lymph node status	N+	75 %
	N-	25 %
Antracycline chemotherapy		100 %
Radiotion therapy		95 %

The mean LVEF before the start of trastuzumab was 66.5% (55% -81%), during treatment was 63.5% (30% -77%) and at the end of treatment was 62.3% (36% -73%), an absolute decrease of 4.2% (p <0.001). 39 patients had cardiotoxicity including 36 asymptomatic cases and 3 symptomatic cases. Treatment was stopped provisionally in 8 cases and definitively in 4 cases. In multivariate analysis (Table 2), a low baseline LVEF was the only significant risk factor (p <0.001). The associated treatments (antracyclines and radiotherapy) do not represent a predictive factor of cardiotoxicity in our series (p = 1 and p = 0.74 respectively).

Table −2: Predictive factors of cardiotoxicity under trastuzumab

Risk Factors	Number of patients (N = 100)	Group with cardiotoxicity (N = 39)	Group without cardiotoxicity (N = 61)	p
Age ≥ 50 years	64	27	37	0.37
Obesity	53	18	35	0.24
Arterial hypertension	15	9	6	0.074
Diabetes	8	5	3	0.17
Valvulopathy	3	2	1	0.83
Initial LVEF decreased (55-60%)	34	22	12	0.001
Antracycline chemotherapy	100	39	61	1
Radiotion therapy	95	35	65	0.74

DISCUSSION

Trastuzumab is a humanized monoclonal antibody directed against HER2 oncoprotein with high affinity and specificity. It inhibits the activation of

HER2 signaling pathways responsible for an anti-tumor effect in patients with breast cancer overexpressing HER2. Inhibition of HER2 signaling by trastuzumab reduces the cardioprotective effects of HER2-mediated pathways leading to cardiotoxicity. This adverse event was reported for the first time in Slamon's pivotal trial of metastatic breast cancer [3]. It is of variable incidence and most often asymptomatic [4]. The results observed in our series in terms of rate of asymptomatic decrease of LVEF are similar to data from the literature [5-7] (Table 3).

Table−3: decrease in LVEF by studies

Study	Nomber of cases	Initial LVEF (%)	Decrease of LVEF (%)
HERA [5] Piccart-Gebhart 2005	5102	≥ 55	3,6
BCIRG [6] Slamon 2005	3200	≥ 50	18,4
NSABP + NCCTG [7] Romand 2005	4045	≥ 50	34
Our study	100	≥ 55	37

A review of the literature shows that there are different risk factors for cardiotoxicity in patients treated with trastuzumab. Old age and previous exposure to anthracyclines are the main factors reported. In the combined analysis of NSABP and NCTTG studies [7]; an age ≥ 50 years, previous exposure to anthracyclines and a baseline FEVG <55% significantly increased the risk of cardiotoxicity. In the HERA study [5], multivariate analysis found a statistically significant increase in cardiotoxicity in obese patients and those with a high cumulative dose of anthracyclines and a baseline LVEF of less than 60%. In our study, decreased initial LVEF was the only predictor of cardiotoxicity in patients treated with adjuvant trastuzumab.

CONCLUSION

The cardiac tolerance of trastuzumab in our series appears comparable with data from the literature. A decreased initial LVEF is a predictive factor in the occurrence of trastuzumab-related cardiotoxicity. A collaborative oncologist - cardiologist and the use of new diagnostic techniques are the best guarantors to offer ourpatients optimal care.

Conflicts of interest

The authors do not declare any conflict of interest.

Author contributions

All the authors contributed to the conduct of this work. All authors also declare that they have read and approved the final version of the manuscript.

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