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Combination of Trastuzumab and Radiotherapy in the Adjuvant Treatment of Breast Cancer: A Single Center Experience and Focus on the Cardiac Safety

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Abstract

Background: The main toxicity of trastuzumab, is the alteration of cardiac function. The objective of this study is to examine the acute cardiotoxicity of the combination of Radiotherapy (RT) and trastuzumab in the adjuvant treatment of breast cancer.

Materials and Methods: This is a retrospective study of 41 patients followed for localized breast cancer, treated by multimodal strategy combining chemotherapy, Radiotherapy and trastuzumab as adjuvant treatment in the medical oncology department at the Ibn Sina Military hospital of Marrakesh.

Results: All patients underwent adjuvant RT on the wall, including 17 on the left side. The median value of the Left Ventricular Ejection Fraction (LVEF) before starting treatment was 64%. The median value of the absolute decrease of LVEF, after the end of RT, was of the order of 4%. All patients received treatment with trastuzumab, during irradiation at usual doses for twelve months. Trastuzumab was stopped temporarily in seven patients, because of the fall in LVEF of more than 10%. After a median followup of 13 months, one patient developed congestive heart failure, imposing the definitive cessation of trastuzumab.

Conclusion: The association RT and trastuzumab, does not appear to increase the risk of acute cardiac toxicity, whatever the irradiated side.

Keywords: Breast cancer; Trastuzumab; Radiotherapy; Cardiac toxicity; Adjuvant treatment

Introduction

Adjuvant chemotherapy in breast cancer at an early stage significantly reduces the risk of disease recurrence and prolongs Overall Survival (OS) [1]. Many clinical trials and meta-analyzes have standardized the use of anthracyclines and Taxanes in the adjuvant setting [2-7]. Gene amplification "Human Epidermal Receptor" (HER2, HER2/neu or ErbB-2) is associated with a more aggressive phenotype and poor prognosis [8,9]. The analysis of clinical trial's datas have shown that common HER2 positivity predicts a benefit provided by the use of anthracyclines and paclitaxel [10,11]. The introduction of trastuzumab in adjuvant strategy has resulted in substantial improvements in survival, without increasing toxicity, except for the alteration of cardiac function [12]. This work attempts to assess retrospectively the impact of concomitant use of radiotherapy and trastuzumab on the Left Ventricle Ejection Fraction (LVEF).

Patients and methods

This is a retrospective study, based on the analysis of clinical records of patients followed for localized breast cancer, who underwent multimodal strategy involving adjuvant chemotherapy, trastuzumab and radiotherapy, during the period extending between January 2015 and December 2016. Eligible patients, had a malignant breast localized, resected, over-expressing the HER2 (3+ at immunohistochemistry or in situ hybridization positive). The evaluation of cardiac function, is made by echocardiography with assessment of LVEF before starting treatment with anthracyclines, prior to the introduction of trastuzumab (end of treatment with anthracyclines), and periodically after 3 cycles trastuzumab until the end of treatment by the latter. Trastuzumab was stopped at one of the following: clinical signs of congestive heart failure or a drop in LVEF of more than 10%. Radiotherapy was delivered to the tumor bed in cases of conservative treatment or on the chest wall in cases of radical surgery. Irradiation of axillary and Internal Mammary Chain (IMC), was performed after a histopathologic evidence of nodal involvement.

Results

Forty-one patients met the inclusion criteria. The clinical characteristics are summarized in Table 1. The median age of patients at baseline was 51 years. All patients received adjuvant chemotherapy regimen in the same way: 3 cycles of FEC100 (5FU 500 mg/m^2 ; Cyclophosphamide 500 mg/m^2; epirubicin 100 mg/m^2)-3 DOCETAXEL (100 mg/m^2)+trastuzumab (8 mg/m^2 the first injection and then 6 mg/m^2 every three weeks for twelve months). The median value of LVEF baseline was 64%. The median follow up was 13 months (range 3.4-15.3 months) from start of trastuzumab and 11.7 months (2.5-12 months) from start of RT. All patients had clinical evaluation

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Variable	Patients
Number	41
Age in years: median (range)	51 (23-75)
Pre-RT LVEF: median (range) (%)	64 (52-70)
Left-sided tumor: number (%)	17 (41,4)

Table 1: Démographic data.

and measurement of LVEF at the end of irradiation. RT was delivered to all patients. Twenty-six of these patients had regional lymph node irradiation which 12 had irradiation of the ipsilateral IMC. Seventeen patients had a tumor on the left. RT was delivered at a dose of 50 Gy in all patients. The initial value of LVEF before trastuzumab and RT divided by the value of LVEF at the end of irradiation showed a mean absolute reduction of 4%. This figure was not significantly different from the side of the tumor or if internal mammary nodes were irradiated. Only one case of congestive heart failure was listed. LVEF from baseline was 52% with clinical signs of heart failure, three weeks after starting treatment with RT. The patient was admitted to an intensive care unit, with a good evolution. The recovery of trastuzumab was not possible. An asymptomatic decline in LVEF was noted in 17% of patients requiring temporary discontinuation of trastuzumab, with rapid improvement of LVEF in the absence of any clinical signs of heart failure, allowing resumption of treatment.

Discussion

This study attempts to prove the safety of the combination RT and trastuzumab in the adjuvant treatment of localized breast cancer. The proportion of patients who experienced symptomatic cardiac toxicity was 2.4%. Asymptomatic fall in LVEF of more than 10% was recorded in 17% of our patients, prompting a temporary cessation of trastuzumab, with rapid recovery from the improvement in LVEF. These results are in the same direction as those noted in large series (NSABP-B31 trials, and HERA) [12,13]. Irradiation of the left side, and that of the internal mammary chain, did not influence the fall in LVEF. These results are in favor of the safety of the combination trastuzumab and RT, regardless of the irradiated side and even in case of irradiation of the IMC. However this is a retrospective study in small numbers and not randomized. In anticipation of large randomized studies, we must continue to actively monitor cardiac function in patients receiving RT combined with trastuzumab, and stop the treatment before clinical signs of severity or to the fall in LVEF of more than 10% relative to the reference value. It would also be interesting to evaluate late toxicity of this combination, and thus extend the monitoring of cardiac function as long as possible.

Conclusion

This work demonstrates the safety of the combination of radiotherapy and concurrent trastuzumab in the adjuvant treatment of breast cancer.

Competing interests

All authors declare that no financial or other potential conflicts of interest exist.

Author's contribution

IE was involved in collecting information regarding the cases. All authors participated in the treatment of patients. All authors read and approved the final manuscript.

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