

Left Ventricular Dysfunction in Breast Cancer Patients Receiving Trastuzumab: An Observational Study in a Cohort of Iraqi Breast Cancer Patients

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Abstract

Background : Cardiotoxicity is a well recognized adverse event of trastuzumab. This study was designed to evaluate the frequency of decline in left ventricular ejection fraction (LVEF) to less than 50% in patients with breast cancer who have received trastuzumab in a daily practice setting.

Methods : Retrospective observational study of 116 patients with HER2 positive breast cancer treated with trastuzumab in one center between May 2012 and January 2017.

Results : Left ventricular ejection fraction decline to less than 50% was observed in 7 patients (6%). Patients above 70 years of age have the highest frequency of LVEF decline (33%). All events of LVEF decline was reported in the first six months of treatment. Prolonged administration of trastuzumab beyond one year was not associated with adverse cardiac events. Previous anthracycline exposure and chest irradiation was not found to be associated with LVEF decline.

Conclusions : Events of LVEF decline to less than 50% associated with trastuzumab use seems to be slightly higher in general daily practice than in clinical trial setting, especially in patients above 70 years, calling for better patient selection. First year of trastuzumab therapy carries the highest risk of cardiac events which necessitates a close cardiac monitoring, thereafter, periodic LVEF measurements can be reduced to reduce the costs.

Keywords : Breast cancer, Ejection fraction, Trastuzumab

Introduction

Overexpression of the HER2 protein (a transmembrane tyrosine kinase receptor involved in cell differentiation and proliferation), amplification of the HER2 gene, or both occur in approximately 15 to 20 percent of breast cancers [1,2]. Trastuzumab is a humanized

monoclonal antibody with specificity for the extracellular domain of HER-2 [3]. In 1998, trastuzumab was approved by the US Food and Drug Administration for the treatment of metastatic HER2-overexpressing invasive breast cancer when clinical trials confirmed that addition

of trastuzumab to standard chemotherapy improves disease-free survival (DFS) and overall survival (OS) in these patients [4-6]. Subsequent trials of trastuzumab in early breast cancer showed a reduction of the recurrence risk of about 50% and a 30% reduction in mortality [7-11]. This led to the approval of trastuzumab by the US Food and Drug Administration for the adjuvant treatment of early HER2-overexpressing invasive breast cancer [12]. Although trastuzumab was generally well-tolerated, its use in clinical trials was associated with increased risk of cardiotoxicity [7, 10, 13], which was attributed to the expression of HER2 by myocardial cells in response to stress [14]. In the clinical trial setting, two meta-analyses which included 11,991 patients with early breast cancer and 1497 patients with metastatic breast cancer treated with trastuzumab showed that the relative risk of congestive heart failure (CHF) was 5.11 (90% confidence interval [CI]: 3.00–8.72) in the adjuvant setting [15], and 3.49 (90% confidence interval [CI]: 1.88 to 6.47) in the metastatic setting [16]. As most clinical trials exclude patients with advanced age and pre-existing heart disease, the risk of trastuzumab related cardiotoxicity in daily practice may be higher and may be related to patients age, presence of cardiovascular risk factors or even to geographical variations [17-22]. In this study, a group of Iraqi breast cancer patients from single institution were studied for the incidence of trastuzumab related cardiotoxicity, timing, severity and risk factors.

Patients and Methods

A retrospective observational study of patients with HER2-positive breast cancer who have received trastuzumab between May 2012 and January 2017 in Thiqr medical oncology department.

A total of 116 patients with HER2-positive breast cancer have received trastuzumab during the study period, 79 patients (68%) as adjuvant therapy and 37 patients (32%) for metastatic breast cancer.

According to our policy for administration of trastuzumab, a baseline transthoracic echocardiography must be done before the first dose of trastuzumab and the LVEF determined. The LVEF had to be higher than 55% to allow patients to start treatment with trastuzumab. Thereafter, measurements had to be performed at least every 3 months until end of trastuzumab treatment. Also, patients with Uncontrolled severe hypertension, recent (less than 6 months) acute coronary syndrome, and, uncontrolled arrhythmia are considered not eligible for trastuzumab.

Trastuzumab was given every 21 days at a dose of 8 mg/kg for the first dose and 6 mg/kg for subsequent doses.

Definition of Endpoints

We used an LVEF less than 50% as a cutoff to define patients with cardiotoxicity. Patients with LVEF decline > 10% from baseline (but NOT to less than 50%) were not defined as having cardiotoxicity

Results

| Table 1. Baeline Characteristics of Patients | |
|---|---------------|
| Characteristic | No (%) |
| Age at diagnosis (Years) | |
| < 35 | 12 (10.4) |
| 35 - 44 | 40 (34.5) |
| 45 - 54 | 38 (32.7) |
| 55- 64 | 16 (13.7) |
| 65 - 75 | 10 (8.7) |
| Sex | |
| Female | 116 (100) |
| Male | 0 (0) |
| Location of the tumor | |
| Right breast | 63 (54) |
| Left breast | 53 (46) |
| Hormone Receptor Status | |
| Hormone Receptor positive | 63 (54) |
| Hormone Receptor negative | 53 (46) |
| Chest wall Radiotherapy | |
| Yes | 65 (56) |
| No | 51 (44) |
| Trastuzumab therapy | |
| Adjuvant | 79 (68) |
| Metastatic disease | 37 (32) |
| Chemotherapy Received | |
| Anthracyclines without taxanes (A) | 20 (16.2) |
| Anthracyclines and taxanes (AT) | 80 (70.2) |
| Non-anthracyclines (Non-A) | 16 (13.6) |
| Duration of trastuzumab therapy | |
| < 6 months | 14 (12) |
| 6 months – 1 year | 76 (65.5) |
| 1 year – 2 year | 20 (17.2) |
| > 2 years | 6 (5.1) |
| Overall | 116 |

Table 1 lists the baseline characteristics of the patients. The median age of patients in the study was 46 (Range 25 – 74) years. More than 75 % of patients were less than 55 years of age and less than 5 % above 70 years. All patients were females. About 86% of the patients have received anthracyclines at some point, however, none of the patients have received concomitant anthracycline and trastuzumab.

From the total of 116 patients, Seven patients (6 %) developed decline of LVEF to less than 50%. Table 2 shows the characteristics of patients who develops LVEF decline.

Table 2. Characteristics of patients who develops LVEF decline to less than 50%

| Patient no. | Age (Year) | Timing of LVEF decline | Tumor location | Chest wall RT | Chemo received | Symptoms |
|-------------|------------|------------------------|----------------|---------------|----------------|----------|
| 1 | 53 | 2 months | R | Yes | A | Yes |
| 2 | 32 | 6 months | L | Yes | AT | No |
| 3 | 69 | 5 months | L | No | AT | Yes |
| 4 | 60 | 6 months | R | Yes | AT | No |
| 5 | 73 | 3 months | R | Yes | A | Yes |
| 6 | 74 | 6 months | L | Yes | AT | No |
| 7 | 52 | 4 months | L | No | NA | Yes |

Most events occurred in patients above 50 years of age. Only one patient below 50 years of age develops decline in LVEF. Two out of six patients (33.3%) above 70 years of age given trastuzumab develops decline in LVEF to less than 50%.

Most patients develops LVEF decline within the first 6 months with a mean of 4.5 months (Range 2 – 6 months). (2 patients within the first 3 months and 5 patients within the first 6 months). None of the patients who continued trastuzumab beyond 6 months develops decline in LVEF.

Four patients have left breast cancer, two of them have received chest wall irradiation, and three patients have right breast cancer all of them received chest wall irradiation.

Six patients have received anthracycline, four of them, with taxanes, while only one patient who have never received anthracycline develops LVEF decline.

Four patients (3.5%) have symptoms of LV dysfunction ranging from NYHA CLASS I to III, while three patients (2.5%) have asymptomatic LVEF decline to less than 50%.

Five patients discontinued trastuzumab permanently when LVEF decline < 50% observed, while two patients have been rechallenged with the drug after two months treatment of heart failure and improvement of LV function, but, both patients develops further decline in LV function after re-introduction of trastuzumab and discontinued treatment permanently.

Table 3 gives the occurrence of trastuzumab-related LVEF decline to less than 50% according to age and other selected baseline characteristics with the corresponding P value.

| Table 3 | | | |
|------------------------------------|-----------|----------------------------------|----------------|
| Characteristic | No | No (%) with LVEF < 50% | P value |
| Age at diagnosis (Years) | | | |
| < 50 | 72 | 1 (1.4) | < 0.05 |
| 50 - 70 | 38 | 4 (10.5) | |
| > 70 | 6 | 2 (33.3) | |
| Hormone Receptor Status | | | |
| Hormone Receptor positive | 63 | 3 (4.7) | > 0.05 |
| Hormone Receptor negative | 53 | 4 (7.5) | |
| Chest wall Radiotherapy | | | |
| Yes | 65 | 5 (7.6) | > 0.05 |
| No | 51 | 2 (3.9) | |
| Trastuzumab therapy | | | |
| Adjuvant | 79 | 4 | > 0.05 |
| Metastatic disease | 37 | 3 | |
| Chemotherapy Received | | | |
| Anthracyclines without taxanes (A) | 20 | 2 (10) | < 0.05 |
| Anthracyclines and Taxanes (AT) | 80 | 4 (5) | |
| Non-anthracyclines (NA) | 16 | 1 (6.2) | |

Discussion

In this study, which was carried out in a non-trial clinical practice setting, the incidence of LVEF decline to less than 50% was found to be 6.0 %, with 3.5% incidence of symptomatic heart failure. In the HERA trial, the largest trial of adjuvant trastuzumab, the incidence of symptomatic congestive heart failure was 1.73% [7]. In the B-31 trial, the incidence of decline in LVEF and congestive heart failure was 4.1% [10]. However, in a cohort of canadian patients received trastuzumab in a non-trial setting, the incidence of congestive

heart failure and LVEF decline to < 50% was 6.0% [23], which is exactly similar to our results. The BCIRG-006 trial have reported higher rates of cardiotoxicity, 18.6% for ACTH protocol and 9.4% for TCH protocol [13]. However, these results represents any decline in LVEF including subclinical loss of mean LVEF (defined as > 10% relative loss). In our study, we defined cardiotoxicity as a decline of LVEF to < 50%, and not included patients with a relative decline of LVEF.

Risk factors for trastuzumab cardiotoxicity have been studied by several investigators. Increasing age is

the most important risk factor for developing trastuzumab cardiotoxicity [24], although, other authors suggests that baseline LVEF [25], Obesity and Hypertension are also important [26]. In this study, we found a significant association between patient age and the development of cardiac toxicity with a significant P value. Decline in LVEF < 50% were reported in two out of six patients above 70 years of age, four out of thirty eight patients between 50 to 70 years, and, only one patient out of seventy two below 50 years of age. These data are in line with an Italian cohort study that included 681 women with breast cancer [18].

Studies suggest that the first 3 months of trastuzumab therapy account for most of the cardiotoxic events, and that cardiotoxicity occurring more than 6 months after start of trastuzumab is rare [32, 33]. A Dutch study which included 230 patients treated with trastuzumab found that 84.8% of the patients who discontinue the drug due to cardiotoxicity do so in the first six months, and that the first LVEF drop was seen at a median of 2.5 months (range: 0.7–10.3 months) [1]. Our results shows that all events of LV dysfunction occurred in the first 6 months, and none of the patients who continued trastuzumab develops decline in LVEF even after 3 years of continuous treatment suggesting that trastuzumab cardiotoxicity is not dose dependent, and that cardiac monitoring should focus on the first year of treatment.

Conclusions

In this observational study, we found that the frequency of decline in LVEF to less than 50% in patients receiving trastuzumab is 6%. Patients > 70 years of age are at the highest risk to develop this complication. Also, we found that all patients develops this complication in the first six months of trastuzumab treatment, necessitating a closer cardiac monitoring in this period.

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أنخفاض وظيفة البطين الأيسر لدى مرضى سرطان الثدي المعالجين بعقار التراستوزوماب

مصعب راجي البياتي

الخلاصة :

يعتبر هبوط وظيفة البطين الايسر من اهم الاعراض الجانبية المصاحبة لاستخدام عقار تراستوزوماب من قبل مرضى سرطان الثدي.

الهدف من هذه الدراسة هو تحديد نسبة حدوث انخفاض وظيفة البطين الايسر لدى مرضى سرطان الثدي الذين تتم معالجتهم بعقار تراستوزوماب من خلال العمل اليومي مع مقارنة هذه النسبة مع النسب المسجلة في الدراسات البحثية العالمية.

شملت الدراسة ١١٦ مريضة بسرطان الثدي تمت معالجتهم بعقار التراستوزوماب في وحدة الاورام السرطانية في الناصرية. حيث تمت متابعة وظيفة البطين الايسر من خلال فحص صدى القلب الذي اجري للمرضى كل ثلاثة اشهر وتحديد نسبة المرضى الذين اصيبوا بانخفاض وظيفة البطين الايسر الى اقل من ٥٠ بالمئة.

أظهرت النتائج أن ٧ مرضى (٦% من المجموع) من الذين استخدموا عقار تراستوزوماب حدث لديهم انخفاض في وظيفة البطين الايسر الى ما دون ٥٠%. اغلب المرضى الذين حدث لديهم هذا العارض الجانبي كانوا ممن تجاوزت اعمارهم ال ٧٠ عام. اغلب حالات انخفاض وظيفة البطين الايسر حصلت في الستة اشهر الاولى من العلاج ولم يتم تسجيل اي حالة عند الاستمرار بالعلاج لاكثر من سنة. لم يتم توثيق علاقة بين حالات انخفاض وظيفة البطين الايسر المرتبطة بعقار تراستوزوماب والاستخدام السابق لادوية الانثراسايكلين او للعلاج بالاشعة العميقة لجدار الصدر.

خلصت الدراسة أن نسب انخفاض وظيفة البطين الايسرى لدى المرضى المعالجين بعقار تراستوزوماب من خلال العمل اليومي هي اعلى بقليل من النسب المسجلة في الدراسات البحثية وهذا يعود الى الاختيار الدقيق للمرضى في الدراسات البحثية مقارنة بالعمل اليومي.