

Adjuvant trastuzumab cardiotoxicity in patients over 60 years of age with early breast cancer: a multicenter cohort analysis

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Background: Adjuvant Trastuzumab with chemotherapy is the gold standard for human epidermal growth factor receptor 2 (HER2)-positive early breast cancer (HER2+ EBC). Older patients have been largely under-represented in clinical trials, and few data on Trastuzumab cardiotoxicity have been reported in this subgroup.

Patients and methods: Four hundred and ninety-nine consecutive HER2+ EBC patients were treated with adjuvant trastuzumab and chemotherapy (*aTrastC*) at 10 Italian institutions. We evaluated disease prevalence and patient characteristics in the patients older than 60 years of age (over-60), prevalence of *aTrastC* cardiotoxicity and risk factors.

Results: There were 160 'over-60' patients (32%), in whom a higher prevalence of hypertension, diabetes, renal dysfunction, dyslipidemia and treatment with ACEi (40 versus 8%) and beta blockers (20 versus 8%) was found than in the younger patients (339 = 68%). Clinical heart failure occurred in 6% of the 'over-60' and in 2% of the younger patients. A reduction in left ventricular ejection fraction of >10 points was detected in 33% of the 'over-60' and in 23% of the younger patients (all $P < 0.05$). *aTrastC* was discontinued in 10% of the 'over-60' and in 4% of the younger patients ($P = 0.003$), restarted in 44% of the 'over-60' and in 58% of the younger women ($P = ns$).

Conclusion: In clinical practice, 32% of HER2+ EBC patients treated with *aTrastC* are 'over-60'.

These patients have an increased cardiovascular risk profile and develop *aTrastC* cardiotoxicity commonly.

Key words: cardiotoxicity, early HER2-positive breast cancer, left ventricular ejection fraction, trastuzumab

introduction

Human epidermal growth factor receptor 2 (HER2) has a significant role in cell growth and tissue proliferation. HER2 is overexpressed or amplified in about 15%–20% of breast cancers and is associated with poor prognosis [1–4]. The introduction of trastuzumab in the adjuvant treatment of HER2-positive early breast cancer (EBC) has led to significant improvements in disease-free survival and overall survival [5–10]. Trastuzumab, however, has documented cardiotoxic effects [11] probably due to the block of the HER-2 receptor which protects the adult cardiomyocytes exposed to the elevated stress or anthracycline [12–14].

Older women with EBC represent a fast-growing group of patients at higher risk of cardiovascular (CV) events and, thus, cardiotoxicity related to anthracycline-based therapy [15–18]. These patients are under-represented in adjuvant trastuzumab randomized clinical trials [5, 6, 9].

The aims of this study were to evaluate in a large multicenter registry: (i) the disease prevalence and clinical characteristics of patients older than 60 years of age (over-60) treated with adjuvant trastuzumab and chemotherapy in clinical practice, (ii) the feasibility of adjuvant trastuzumab and (iii) the prevalence and predictors of trastuzumab-induced cardiotoxicity in this setting of patients.

methods

Patients with HER2-positive EBC consecutively treated from January 2008 to June 2009 with adjuvant trastuzumab therapy at 10 Italian hospitals and cancer institutes were retrospectively reviewed. Patients with metastatic breast cancer and/or those who had experienced an episode of heart failure

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before trastuzumab administration were excluded. Trastuzumab was administered at all centers at a loading dose of 8 mg/kg of body weight i.v. once, followed by a maintenance dose of 6 mg/kg every 3 weeks for 1 year (18 total doses). The study protocol was approved by the local institutional review boards.

For each patient, we collected baseline CV medications and relevant comorbidities. In all the patients, left ventricular ejection fraction (LVEF) was measured by the biplane method of disks at baseline and 3, 6, 9 and 12 months after the start of Trastuzumab. Trastuzumab-related cardiotoxicity was classified into five grades, which are defined as follows [2, 5–7, 19]:

- Grade I: asymptomatic decline in LVEF >10 points % from baseline evaluation.
- Grade II: asymptomatic decline in LVEF below 50% or ≥ 20 points % from baseline.
- Grade III: heart failure responsive to treatment.
- Grade IV: severe or refractory heart failure or requiring intubation.
- Grade V: death related to cardiac toxicity

The decision to interrupt or re-challenge with trastuzumab was left to the clinical oncologist. The diagnosis of heart failure was based on the modified Framingham criteria [20], chest X-ray, response to diuretics, the evaluation of cardiac structure and function by echocardiography and B-type natriuretic peptide. 'High cardiovascular risk' was defined according to

the European Society of Cardiology guidelines on CV disease prevention in clinical practice [21] and estimated to be a 10-year risk of CV death of >5%.

statistics

Data are reported as mean values ± 1 standard deviation. Continuous variables were compared by Student's *t*-test or by the Mann–Whitney *U* test, while categorical variables were compared by the χ^2 test. Between-group comparisons of continuous and normally distributed variables were carried out by analysis of variance. Receiver Operating Characteristic (ROC) curve analysis was carried out to assess the best cut-off point of age in the prediction of trastuzumab-related cardiotoxicity. Multivariate logistic regression analysis was carried out to test age as an independent predictor of trastuzumab-induced cardiotoxicity. The variables included in the model were age, hypertension, diabetes, estimated glomerular filtration rate, dyslipidemia, increased CV, taxanes (percentage of patients) and doxorubicin (percentage of patients and mean dose). Differences between the groups in related-trastuzumab cardiotoxicity-free survival were evaluated by Kaplan–Meier curves (log-rank test). Furthermore, K-means clustering analysis was carried out to split the population into four subgroups, using Euclidean distance metric, and the difference in the incidence of cardiotoxic events was compared between the groups. A two-tailed value of *P* of <0.05 was considered statistically significant.

Table 1. Baseline characteristics and adjuvant antitumor treatments of 499 patients divided by age

Variables	Total (n = 499)	Age ≤ 60 years (n = 339)	Age > 60 years (n = 160)	P
Age (years)	55 \pm 11	50 \pm 8	68 \pm 5	<0.001
Hypertension (%)	26	16	48	<0.001
Diabetes (%)	6	3	11	<0.001
Dyslipidemia (%)	15	10	26	<0.001
Increased CV risk (%)	15	10	29	<0.001
LVEF (%)	65 \pm 6	65 \pm 6	64 \pm 6	ns
Hemoglobin (g/dl)	13 \pm 1	13 \pm 1	13 \pm 1	ns
Creatinine (mg/dl)	0.81 \pm 0.16	0.80 \pm 0.16	0.85 \pm 0.16	0.003
eGFR (ml/min/1.73 m ²)	85 \pm 19	74 \pm 20	76 \pm 16	<0.001
eGFR < 60 (% of patients)	9	6	17	<0.001
Therapy for managing CV risk factors				
ACEi/ARB (%)	18	8	40	<0.001
Diuretics (%)	10	4	22	<0.001
Beta blockers (%)	12	8	20	<0.001
Calcium antagonists (%)	3	2	8	<0.001
Statins (%)	7	4	14	<0.001
Radiotherapy (%)	61	62	61	ns
Chemotherapy				
Anthracyclines (any) (%)	87	90	80	0.002
Doxorubicin (% of patients)	12	12	10	ns
Doxorubicin, mean dose (mg/m ²)	231 \pm 46	227 \pm 52	240 \pm 25	ns
Epirubicin (% of patients)	75	78	70	ns
Epirubicin, mean dose (mg/m ²)	339 \pm 156	343 \pm 158	328 \pm 153	ns
Taxanes (any) (%)	49	52	37	0.02
Paclitaxel (%)	22	21	21	ns
Docetaxel (%)	23	27	17	0.02
Others				
Cyclophosphamide (%)	89	90	87	ns
5-Fluorouracil (%)	46	48	44	ns

ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; CAD, coronary artery disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction.

SPSS 11.0 Release (SPSS Inc., Chicago, IL) was used for statistical analysis.

results

patient characteristics

Patient characteristics are shown in Table 1. All the 499 patients had been previously treated with adjuvant chemotherapy. The patients were divided into two subgroups by the age (>60 and ≤60 years). This choice was supported by ROC analysis showing 60 years as the best cut-off point for predicting by age trastuzumab-related cardiotoxicity [area under the curve 0.56 [confidence interval (CI) 0.51–0.62], sensitivity 57%, specificity 52%]. There were 160 ‘over-60’s (32%): 68 (14%) between 60 and 65 years, 42 (8%) between 66 and 70 years, 34 (7%) between 71 and 75 years and 16 (3%) >75 years. As expected, the ‘over-60’s had comorbidities more frequently, were more frequently on treatment for managing risk factors and received anthracycline and taxanes before trastuzumab treatment less frequently than the younger patients (Table 1).

trastuzumab-related cardiotoxicity

Trastuzumab-related cardiotoxicity was reported in 133 patients (27%): cardiotoxicity was of grade I in 102 patients (20%), grade II in 15 patients (3%), and grade III in 16 patients (3%). In the whole cohort, no cardiac death occurred and no patient experienced grade IV or V cardiotoxicity.

Figure 1 shows the distribution of cardiotoxicity in the 499 study patients grouped by age by K-means cluster analysis. The prevalence of trastuzumab-related cardiotoxicity in the oldest group (age ≥68 years) was 38%. Trastuzumab-related cardiotoxicity occurred in 56 ‘over-60’ (35%) patients and 339 (23%) the younger patients ($P = 0.01$). Among these patients, heart failure syndrome was diagnosed in 6% of the ‘over-60’ and in 2% of the younger patients ($P = 0.003$). The Kaplan–Meier curves showed a reduced trastuzumab-related cardiotoxicity-free survival in the subgroup of ‘over-60’

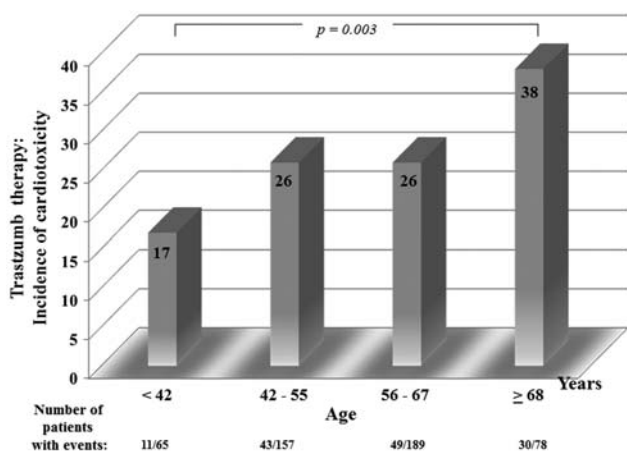


Figure 1 Distribution of cardiotoxicity in 499 women with early breast cancer treated with adjuvant trastuzumab therapy divided into four subgroups by age by K-means cluster analysis.

patients compared with those ≤60 years old (Figure 2). A similar trend was observed in the four subgroups of patients divided by age according to K-means cluster analysis (Figure 3). A multivariate logistic regression analysis showed that an age of >60 years [heart rate (HR) 1.76 (CI 1.15–2.70) $P = 0.009$] and prior adjuvant therapy with doxorubicin [HR 2.14 (CI 1.20–3.83), $P = 0.01$] are independent predictors of trastuzumab-related cardiotoxicity. The same predictors were identified when age was considered as a continuous variable [HR 1.02 (1.00–1.04), $P = 0.03$] or dichotomized for identifying four groups according to K-means cluster analysis [HR 1.28 (CI 1.02–1.61), $P = 0.03$].

LVEF was similar in the two study subgroups at baseline (Table 1) and at 12-month evaluation ($63 \pm 5\%$ versus $63 \pm 6\%$ in ‘over-60’ women versus ≤60 years, respectively), but its

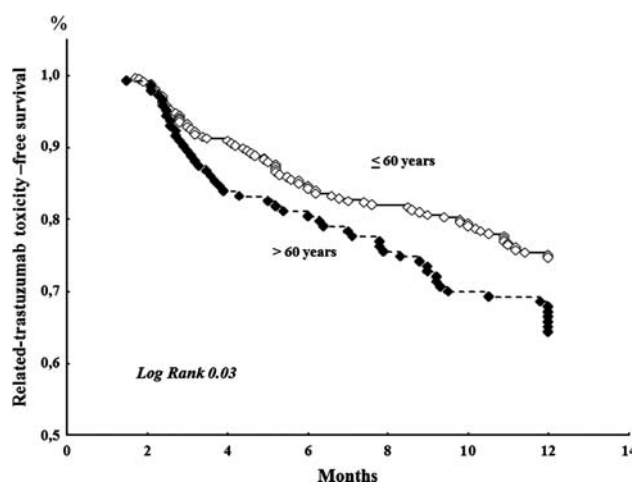


Figure 2 Related-trastuzumab cardiotoxicity-free survival (Kaplan–Meier curves) in patients older (black diamonds) and younger (white circles) than 60 years of age.

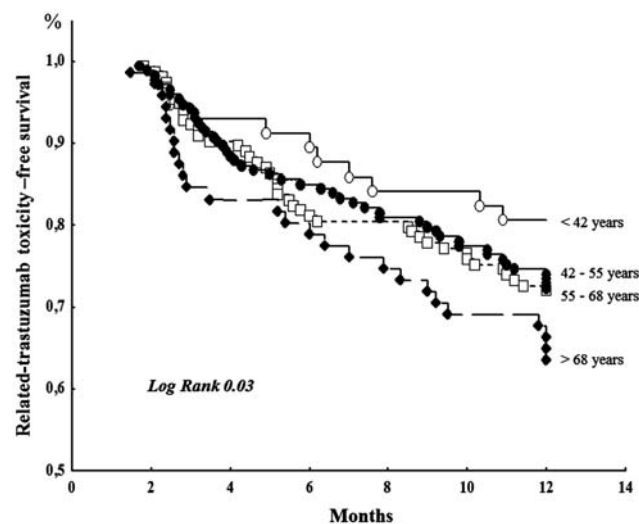


Figure 3 Related-trastuzumab cardiotoxicity-free survival (Kaplan–Meier curves) in patients divided into four subgroups by age by K-means cluster analysis.

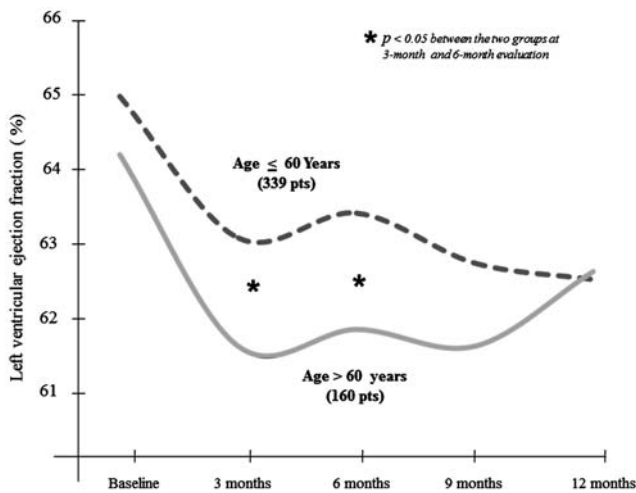


Figure 4 Trend in left ventricular ejection fraction (LVEF) during the 1-year follow-up in patients older (continuous gray line) and younger (dotted back) than 60 years of age. The older women had a significant early decrease in LVEF than the younger counterparts, which was evident at 3-month and 6-month evaluations, while no statistical difference between the two groups was observed later.

trend during the 1-year follow-up was significantly different with a deeper drop in the first 3 months detected in the 'over-60' group (Figure 4).

Trastuzumab was discontinued in 16 patients (10%) of the older and 14 patients (4%) of the younger patients ($P = 0.003$) and restarted in 44% of the older and 58% of the younger women ($P = ns$). It was discontinued in 3 patients in both the groups because of adverse events, and in 13 and 11 patients as a consequence of cardiotoxicity, respectively: in 7 and 6 patients because of a reduction in LVEF of >10 points %, respectively, and in the remaining 6 and 5 patients, respectively, because of an impairment in the New York Heart Association functional class.

discussion

Our multicenter investigation analyzed the real-life state commonly encountered in oncological and cardiological clinical practice. In this context, 'over-60' women represent one-third of the patients treated with adjuvant trastuzumab after adjuvant chemotherapy for EBC. This percentage is significantly higher than the 16% reported by Romond in N-31 and N9831 Trials [5] and by Piccart-Gebhart in a HERceptin Adjuvant (HERA) trial [6], suggesting a large under-representation in randomized clinical studies. There is an increasing incidence of breast cancer [18] in older women and their epidemiological burden will become increasingly important over the next decades because of aging of the 'baby boom' generation. Their marginalization in the randomized clinical trials [22, 23] produces uncertainties on what might be considered the optimal therapy for improving the clinical outcomes minimizing the risk of cardiotoxicity.

87% of our patients received an anthracycline-based chemotherapy before trastuzumab, a high percentage similar to the HERA Trial [6] and other 'real world' series such as those published by Guglin et al. and Wadhwa et al. [24, 25]. This

finding confirms the evidence that the use of adjuvant chemotherapy with anthracycline-based regimens tends to rise compared with the early 2000s [26], both in middle-aged and older women [27]. More recently, however, a new strategy has been successfully tested in some important clinical trials in which the therapeutic approach was to combine two HER2-targeted agents with nonoverlapping mechanisms of action, so that, for many patients, chemotherapy could be eliminated entirely [28]. Thus, there is still opportunity for improvement in this field, by way of both further reduction in recurrence and decrease in the toxic effects of the treatment.

Previous studies have identified several risk factors for the development of trastuzumab-related cardiotoxicity [16, 24, 26, 27], including anthracycline use and cumulative anthracycline dose administration, higher body mass index, hypertension, antihypertensive therapy and older age. In this study, older age was the only clinical variable associated with trastuzumab-related cardiotoxicity, probably as a result of the protective effect of therapy for other CV risk factors [29–31]. Our older patients, indeed, very commonly had hypertension, diabetes, dyslipidemia and reduced renal function, all favoring myocardial oxidative stress and related-anthracycline cardiotoxicity. Evidently, older age may give expression to these unfavorable conditions summarizing the state of frailty predisposing to cardiotoxicity. Such an impression is reinforced by analyses of temporal trend of LVEF. Unlike younger women, the 'over-60' group presented a greater incidence of cardiotoxicity, and this risk was not limited in the early stage of treatment, when probably the cardioprotective therapy was not optimized, but persisted throughout the period of treatment. Furthermore, we observed an overall incidence of cardiac events (26%) substantially higher than that reported in the trastuzumab randomized trials, [5–9] possibly because of the higher prevalence in older patients in our series. In this study, one of three 'over-60' woman had cardiotoxicity with a threefold higher risk of developing clinical heart failure compared with the younger patients. As expected, the rate of trastuzumab discontinuation was significantly higher in older women. Nevertheless, trastuzumab chemotherapy was resumed effectively in nearly 50% of patients. All these findings suggest that older women, representing a group of patients who would probably benefit from a strategy for monitoring early cardiac damage with biomarkers [32], require specific attention during treatment, including a careful evaluation of LVEF and an aggressive treatment of CV risk factors.

study limitations

First, our study has a retrospective nature. Second, it was carried out between January 2008 and June 2009, when trastuzumab could be started only after anthracycline-based chemotherapy. This state might not be suitable for assessing the pure cardiotoxic effect of trastuzumab, which could have been favored by previous anthracycline administration in some patients. Third, the decision on how and when to start angiotensin-converting enzyme inhibitors (ACEi)/angiotensin receptor blockers (ARBs) and/or beta blockers therapy and the relative dosage of such drugs was left to the discretion of the attending physicians. The administration of these drugs in

some cases may have influenced the results, leading to an underestimation of trastuzumab-related cardiotoxicity.

In conclusion, in clinical practice, older women with HER2-positive EBC represent a growing group of patients receiving trastuzumab. In this setting, cardiotoxicity is relatively common and higher than reported in randomized clinical trials. Although the cardiac damage in the majority of cases is mild and elapses asymptomatic in most of patients, this group of patients frequently is affected by other CV risk factors (often undervalued because of the coexistence of the cancer) that may enhance the detrimental effect of the trastuzumab on the heart. The most relevant clinical implication deduced from our finding is that the recommended pharmacological and nonpharmacological interventions for heart failure or hypertension including the use of Ace-I/ARB and/or beta blocker should be greatly considered to protect these patients against the progression of cardiac damage possibly favored by trastuzumab therapy.

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disclosure

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Multifocality and multicentricity in breast cancer and survival outcomes

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Background: The clinicopathological characteristics and the prognostic significance of multifocal (MF) and multicentric (MC) breast cancers are not well established.

Patients and Methods: MF and MC were defined as more than one lesion in the same quadrant or in separate quadrants, respectively. The Kaplan–Meier product limit was used to calculate recurrence-free survival (RFS), breast cancer-specific survival (BCSS), and overall survival (OS). Cox proportional hazards models were fit to determine independent associations of MF/MC disease with survival outcomes.

Results: Of 3924 patients, 942 (24%) had MF ($n = 695$) or MC ($n = 247$) disease. MF/MC disease was associated with higher T stages (T2: 26% versus 21.6%; T3: 7.4% versus 2.3%, $P < 0.001$), grade 3 disease (44% versus 38.2%, $P < 0.001$), lymphovascular invasion (26.2% versus 19.3%, $P < 0.001$), and lymph node metastases (43.1% versus 27.3%, $P < 0.001$). MC, but not MF, breast cancers were associated with a worse 5-year RFS (90% versus 95%, $P = 0.02$) and BCSS (95% versus 97%, $P = 0.01$). Multivariate analysis shows that MF or MC did not have an independent impact on RFS, BCSS, or OS.

Conclusions: MF/MC breast cancers were associated with poor prognostic factors, but were not independent predictors of worse survival outcomes. Our findings support the current TNM staging system of using the diameter of the largest lesion to assign T stage.

Key words: breast cancer, multifocal, multicentric, outcomes

introduction

Although multifocal (MF) and multicentric (MC) breast tumors are a common entity, their clinical behavior is not well characterized. The incidence of MF and MC tumors in the

literature ranges from 6% to 60%, with the large variability due to differences in definitions used, inclusion or exclusion of *in situ* disease, and method of pathologic sampling [1, 2]. As advances in preoperative imaging continue, the number of MF and MC tumors identified increases [3–5], and better guidelines for their management are needed. The tumor size has long been recognized as an independent predictor for worse overall survival (OS) [6]. Intuitively, it would seem that the presence of more than one synchronous unilateral tumor

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