Trastuzumab Adjuvant Chemotherapy and Cardiotoxicity in Real-World Women With Breast Cancer

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ABSTRACT

Background: Adjuvant trastuzumab therapy improves survival of human epidermal growth factor receptor 2 (HER2)−positive women with early breast cancer (EBC). A careful monitoring of cardiac function is needed due to potential trastuzumab cardiotoxicity (Tcardiotox). To date, the incidence, timing, and phenotype of patients with Tcardiotox in clinical practice are not well known.

Methods and Results: A total of 499 consecutive HER2-positive women (mean age 55 ± 11 years) with EBC treated with trastuzumab between January 2008 and June 2009 at 10 Italian institutions were followed for 1 year. We evaluated incidence, time of occurrence, and clinical features associated with Tcardiotox. Left ventricular ejection fraction (LVEF) was evaluated by echocardiography at baseline and at 3, 6, 9, and 12 months during trastuzumab therapy. Tcardiotox was recognized in 133 patients (27%): 102 (20%) showed asymptomatic reduction in LVEF of >10% but ≤20% (grade 1 Tcardiotox); 15 (3%) had asymptomatic decline of LVEF of >20% or <50% (grade 2); and 16 (3%) had symptomatic heart failure (grade 3). Trastuzumab was discontinued due to cardiotoxicity in 24 patients (5%) and restarted in 13 after LVEF recovery. Forty-one percent of Tcardiotox cases occurred within the first 3 months of follow-up, most prevalently in older patients with higher creatinine levels and in patients pretreated with doxorubicin and radiotherapy.

Conclusions: In clinical practice ,Tcardiotox is frequent in HER2-positive women with EBC and occurs in the first 3 months of therapy. Cardiac dysfunction is mild and asymptomatic in the majority of patients. The interruption of treatment is a rare event which occurs, however, in a significantly higher percentage than reported in randomized clinical trials. (*J Cardiac Fail 2012;18:113−119*)

Key Words: Breast cancer, trastuzumab, adjuvant chemotherapy, cardiotoxicity, heart failure.

In the past decades, a substantial improvement in survival of breast cancer patients has been observed as a result of new anticancer therapies.[1] Human epidermal growth factor receptor 2 (HER2) is overexpressed or amplified in ~20% of breast cancers and is associated with poor prognosis.[2−5] The introduction of trastuzumab (Herceptin; Genentech, South San Francisco, CA), a recombinant humanized monoclonal antibody that binds to the extracellular domain of HER2, in the adjuvant treatment of HER2-positive early breast cancer led to a significant improvement in disease-free survival and overall survival.[6−10]

Trastuzumab has documented cardiotoxic effects,[11] probably because it blocks the HER-2 receptor, which protects the adult cardiomyocytes exposed to the elevated stress or anthracycline.[12−14] The incidence of trastuzumab-induced cardiotoxicity ranges widely in randomized clinical trials but is usually overshadowed by the substantial improvements in disease-free and overall survival.[15,16] Therefore, this pharmacologic approach imposes a thorough cardiac assessment and stringent inclusion and exclusion criteria to minimize the occurrence of adverse cardiac effects.[6−10] Nevertheless, data from administrative databases[17] and

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Manuscript received July 7, 2011; revised manuscript received October 14, 2011; revised manuscript accepted October 19, 2011.

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1071-9164/$ - see front matter

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doi:10.1016/j.cardfail.2011.10.015

small single centers[18–24] report higher prevalences of cardiac dysfunction and heart failure and raise the concern that in ''real-world'' patients, the cardiac adverse effect could be more than trivial and uncommon.

Aims of the present study were to assess in a multicenter setting of community patients with early breast cancer treated with trastuzumab-based therapy: 1) the incidence of cardiac dysfunction and heart failure; 2) the distribution of cardiotoxic events during the time; and 3) the clinical variables associated with these adverse cardiac events.

Methods

The records of all HER2-positive patients (ascertained with immunohistochemical staining for HER2 protein of 3+ intensity and/or amplification of the HER2 gene on fluorescence in situ hybridization) with early breast cancer consecutively treated with adjuvant trastuzumab therapy administered sequentially after the chemotherapy and/or radiotherapy in 10 Italian Hospitals and Cancer Institutes between January 2008 and June 2009 were retrospectively collected and reviewed, in each center, by 1 oncologist and 1 cardiologist. Two external cardiologists (G.C., L.T.) controlled the clinical data in each center. Two external cardiologists (G.C., L.T.) controlled the data on the ventricular function, and the patients were classified in accordance with the majority of ratings. The quality control was performed by an external panel of oncologists (S.G., F.T) and cardiologists (L.T., G.C., I.F., C.L., G.R), that, for each participating center, evaluated 25% of the records sampled randomly. Patients with metastatic breast cancer, who experienced an episode of heart failure before trastuzumab administration, or without an available echocardiographic evaluation before starting trastuzumab were excluded. Trastuzumab was administered in all centers at a loading dose of 8 mg/kg body weight intravenously once, followed by maintenance doses 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 cardiovascular medications and relevant comorbidities, such as hypertension (defined as blood pressure >140/90 mm Hg on different medical visits or being on pharmacologic treatment with antihypertensive drugs), dyslipidemia (defined as total plasmatic cholesterol >190 mg/dL, triglycerides >150 mg/dL, or current pharmacologic treatment with lipid-lowering medication), and diabetes mellitus (diagnosed by World Health Organization criteria as fasting serum glucose ≥126 mg/dL, 2-hour postchallenge serum glucose ≥200 mg/dL, or use of hypoglycemic medication). Cardiac evaluation other than a history of documented congestive heart failure included the evidence of coronary artery disease with previous myocardial infarction (Q-wave or ischemic ST segment on electrocardiogram and/or echocardiographic segmental wall motion abnormalities in absence of bundle branch block), angina pectoris requiring medication, valvular disease (defined as cardiac murmur with echocardiographic evidence of moderate to severe valvular regurgitation and/or stenosis of any grade), and arrhythmias requiring therapy. Finally, smoking habit was checked. In all patients, left ventricular ejection fraction (LVEF) was measured by the biplane disks method at baseline and after 3, 6, 9, and 12 months.

Trastuzumab-related cardiotoxicity was classified in 5 grades and defined as follows[2,5–7,25]:

Grade I: asymptomatic decline in LVEF of >10% from baseline evaluation.
Grade II: asymptomatic decrease in LVEF of <50% or ≥20% compared with baseline value.
Grade III: heart failure responsive to treatment.
Grade IV: severe or refractory heart failure or requiring intensive medical therapy and/or intubation.
Grade V: death related to cardiac toxicity.

The decision to interrupt or rechallenge with trastuzumab was given to the judgment of the clinical oncologist. The diagnosis of heart failure was based on modified Framingham criteria,[26] on documented new-onset fatigue and dyspnea, confirmed with cardiomegaly, congestion, or pleural effusions on chest X-ray, and response to diuretics. All of these findings were combined with evaluation of cardiac structure and function by echocardiography (performed in all patients) and B-type natriuretic peptide (not routinely performed in all participating centers).[27]

The condition of ''increased cardiovascular risk'' was defined as a 10-year risk of cardiovascular death ≥5% and recognized according with the European Society of Cardiology guidelines on cardiovascular disease prevention in clinical practice.[28]

Statistics

Data are reported as mean ± 1 SD. Unpaired Student test and χ^2 were used for descriptive statistics. Between-group comparisons of continuous and normally distributed variables were performed by the analysis of variance. Trastuzumab-related cardiotoxicity was classified in 5 grades and defined as reported in the methods section. Whereas a cardiotoxic event persisted over time and was diagnosed in more than one echocardiographic and clinical evaluation, we considered for each woman a single event timed when the highest grade of cardiotoxicity was detected. In case an LVEF measurement was missing at any time, we considered at that time the value detected in the previous echocardiographic evaluation. Multivariate logistic regression analysis was carried out to assess the independent predictors of transtuzumab-induced cardiotoxicity. The variables included in the model were age, estimated glomerular filtration rate, increased cardiovascular risk, radiotherapy, and pretreatment with doxorubicin. A subanalysis was made for comparing patients who had an increased cardiovascular risk with those who had not. A 2-tailed value of $P < .05$ was considered to be statistically significant. SPSS release 11.0 (SPSS, Chicago, IL) was used for statistical analysis.

Results

Between January 2008 and June 2009 we enrolled 499 women with ages ranging from 28 to 84 years (mean 55 ± 11 years). Their principal characteristics are reported in Table 1. Fifteen patients (3%) were previously excluded from the cohort owing to absence of echocardiographic evaluations (bad quality of images in all cases).

Adjuvant anthracycline-based chemotherapy, with or without taxane, had been administered in 87% of patients and anthracycline- and taxane-based in 49%; 61% of patients had been treated with radiotherapy after chemotherapy and before trastuzumab (Table 2).

Patients who had an increased cardiovascular risk (77/499, 15%) were older (63 ± 8 vs 54 ± 11 years;

Table 1. Baseline Characteristics of 499 Patients Divided According to the Development of Cardiotoxicity (Any Grade) at Any Time During the Trastuzumab Chemotherapy

Variable	Total (n = 499)	Stable LVEF (n = 366)	Impaired LVEF (n = 133)	*P* Value
Age (y)	55 ± 11	55 ± 11	57 years ± 11	.03
Patients aged >60 y, n (%)	160 (32%)	105 (28%)	55 (41%)	.01
Hypertension, n (%)	130 (26%)	90 (25%)	40 (30%)	ns
Diabetes, n (%)	30 (6%)	22 (6%)	8 (5%)	ns
Dyslipidemia, n (%)	75 (15%)	53 (14%)	22 (16%)	ns
History of CAD, n (%)	10 (2%)	7 (2%)	3 (2%)	ns
Smoker, n (%)	76 (15%)	62 (17%)	14 (11%)	ns
Increased cardiovascular risk n (%)	77 (15%)	53 (14%)	24 (18%)	ns
Symptomatic arrhythmias, n (%)	20 (4%)	15 (4%)	5 (4%)	ns
Valvular disease, n (%)	40 (8%)	27 (7%)	13 (10%)	ns
LVEF (%)	64.8 ± 6.0	63.4 ± 5.3	68.7 ± 6.0	<.001
Hematocrit (%)	38 ± 3	38 ± 3	38 ± 3	ns
Hemoglobin (g/dL)	12.9 ± 1.2	12.9 ± 1.2	12.9 ± 1.1	ns
Creatinine (mg/dL)	0.81 ± 0.16	0.77 ± 0.14	0.86 ± 0.16	.003
eGFR (mL min^{-1} 1.73 m^{-2})	82 ± 19	83 ± 19	76 ± 15	.003
Baseline therapy				
ACEi/ARBn (%)	90 (18%)	61 (17%)	29 (22%)	ns
Diuretics n (%)	50 (10%)	34 (9%)	16 (12%)	ns
Beta-blockers n (%)	60 (12%)	42 (11%)	18 (13%)	ns
Calcium antagonists n (%)	15 (3%)	12 (3%)	3 (2%)	ns
Statins n (%)	35 (7%)	26 (7%)	9 (7%)	ns

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

$P < .01$), had a higher prevalence of hypertension (79% vs 17%; $P < .01$), diabetes (35% vs 0%; $P < .01$), dyslipidemia (66% vs 5%; $P < .01$), smoking habit (34% vs 12%; $P < .01$), and a history of coronary artery disease (10% vs 0%; $P < .01$) and more frequently received angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARBs) (53% vs 12%), beta-blockers (38% vs 7%), and statins (32% vs. 3%; all $P < .001$) than those who had not.

Trastuzumab-related cardiotoxicity was detected in 133 women (27%): grade I in 102 patients (20%), grade II in 15 patients (3%), and grade III in 16 patients (3%); all patients with symptomatic congestive heart failure were in New York Heart Association (NYHA) functional class II. In the whole cohort, no cardiac death occurred and no patient experienced grade IV or V cardiotoxicity. The episodes of cardiotoxicity occurred mainly during the first 3 months of therapy (11% of study population, 41% of the trastuzumab-related cardiotoxic events recorded during the 1-year follow up) with a stable trend thereafter (5% detected at 6-month evaluation, 5% at 9-month evaluation, and the remaining 6% at 12-month evaluation; $P = .04$ between the incidence at 3 months vs all other evaluations). LVEF measurements were missing in 50 patients at 3-month evaluation, in 44 at 6-month evaluation, in 55 at 9-month evaluation, and in 58 at 12-month evaluation.

Patients who developed cardiotoxicity had older age and reduced renal function compared with those who did not (Table 1) and received prior treatment with doxorubicin and radiotherapy more frequently (Table 2). Multivariate logistic regression analysis showed that lower glomerular filtration rate (odds ratio [OR] 0.96, 95% confidence interval [CI] 0.94−0.99) and doxorubicin treatment preceding trasuzumab (OR 3.03, 95% CI 1.05−6.81) were the independent predictors of trastuzumab-induced cardiotoxicity.

Comparing the groups of patients with and without increased cardiovascular risk, we found that LVEF was similar in the 2 study groups at baseline (65 ± 7% vs 65 ± 6%) and at 12-month evaluation (63 ± 6% vs 63 ± 6%; both P = ns), but its trend during the 1-year follow-up was significantly different, with a deeper drop in the first 3 months detected in the group at increased cardiovascular risk (Fig. 1). Such reduction in LVEF was generally asymptomatic, and we did not find any significant difference in the development of heart failure between the 2 study groups (Fig. 2).

Trastuzumab was discontinued in 28 patients (6%) owing to adverse events, in 24 of these 28 (86%) as consequence of cardiotoxicity: in 12 patients owing to a reduction in LVEF of >10%, in 11 patients owing to an impairment in NYHA functional class, and in 1 patient owing to a persistent tachycardia associated with a reduction in LVEF of >10% (Table 3). Among the patients who discontinued trastuzumab use, 37% of them discontinued within the first 3 months of therapy, 20% between the 3rd and 6th months, 18% between the 6th and 9th months, and 25% between the 9th and 12th months.Trastuzumab was restarted in 13 patients. None of these patients had any cardiotoxic event during the subsequent period of observation.

Discussion

The peculiarity of the present study is that it is the first multicenter investigation analyzing the real-life situation commonly encountered in oncology and cardiology clinical practice. In the present investigation we found that cardiac

Table 2. Adjuvant Antitumor Treatments, n (%)

	Total (n = 499)	No Cardiotoxicity (n = 366)	Cardiotoxicity (n = 133)	*P* Value
Radiotherapy	304 (61%)	212 (58%)	92 (69%)	0.05
Chemotherapy				
Anthracyclines (any)	434 (87%)	318 (87%)	116 (87%)	ns
Type of anthracycline:				
Doxorubicin	58 (12%)	34 (9%)	24 (18%)	0.01
Doxorubicin, mean dose (mg/m^2)	231 ± 46	232 ± 39	230 ± 56	ns
Epirubicin	376 (75%)	280 (77%)	96 (72%)	ns
Epirubicin, mean dose (mg/m^2)	339 ± 156	343 ± 155	324 ± 159	ns
Taxanes (any)	242 (49%)	185 (51%)	57 (43%)	ns
Type of taxane:				
Paclitaxel	108 (22%)	75 (20%)	33 (25%)	ns
Docetaxel	135 (27%)	106 (29%)	29 (22%)	ns
Cyclophosphamiden (%)	442 (89%)	319 (87%)	123 (92%)	ns
5-Fluoro uracil	232 (46%)	172 (47%)	60 (45%)	ns

toxicity developed in a relevant percentage (more than 1 out of 4) of women with early breast cancer when trastuzumab was administered after adjuvant chemotherapy. Our data definitively confirm the results reported in several single-center series[18–24] where the incidence of cardiotoxicity, ranging from 14% to 31%, was significantly higher than that observed in randomized clinical trials. Despite this relatively high incidence, trastuzumab-induced cardiotoxicity was limited to an asymptomatic (though significant) reduction in LVEF in the large majority of our patients. Thus, a first clinical implication from our results is that the cardiotoxicity in this setting of patients is quite frequent but has a modest clinical impact.

In our patients, the first 3 months of trastuzumab therapy represented the most critical period for the development of cardiotoxicity. Such observation confirms earlier studies,[18,29] including that by Cardinale et al[29] who monitored serial troponin blood levels in 251 women with early and metastatic breast cancer treated with trastuzumab and reported that >80% of troponin elevations were detected within the first 3 cycles of trastuzumab therapy. Thus, a second clinical implication is that the clinical and echocardiographic follow-up of these patients should be particularly careful and could be intensified during the first period of trastuzumab therapy and deescalated later, as the likelihood of cardiotoxicity becomes quite rare after the third month of treatment.

Earlier studies identified several risk factors for the development of trastuzumab-related cardiac dysfunction.[13,17,18,30,31] These include older age, higher body mass index, hypertension, and antihypertensive therapy, in addition to cancer-related conditions such as anthracycline use and cumulative anthracycline dose administration. In our cohort, traditional cardiovascular risk factors (such as age, systemic hypertension, and diabetes) were not associated with the development of trastuzumab-induced cardiotoxicity. As also reported by Reynold et al,[32] our observations could be the result of the protective effect against heart failure and asymptomatic left ventricular dysfunction of cardiovascular pharmacologic therapy (ie, beta-blockers, ACE inhibitors/ARBs) used more frequently in women at increased cardiovascular risk. It is well known, indeed, that early ACE inhibitor/ARB and beta-blocker administration confers a substantial cardioprotective effect

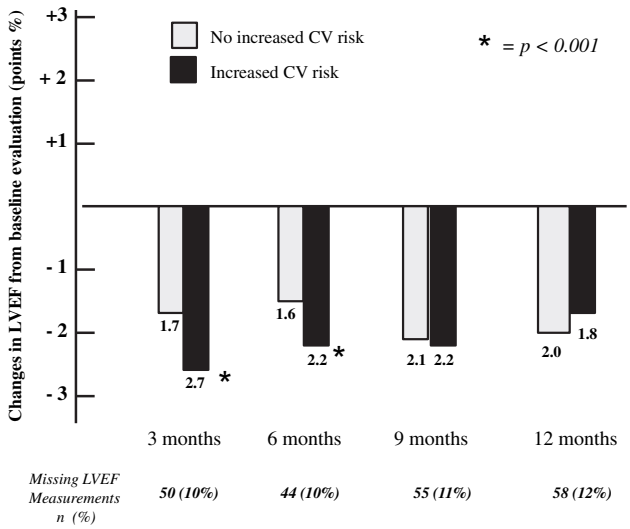

Fig. 1. Temporal trend of left ventricle ejection fraction (LVEF) in patients who had increased cardiovascular (CV) risk and those who had not.

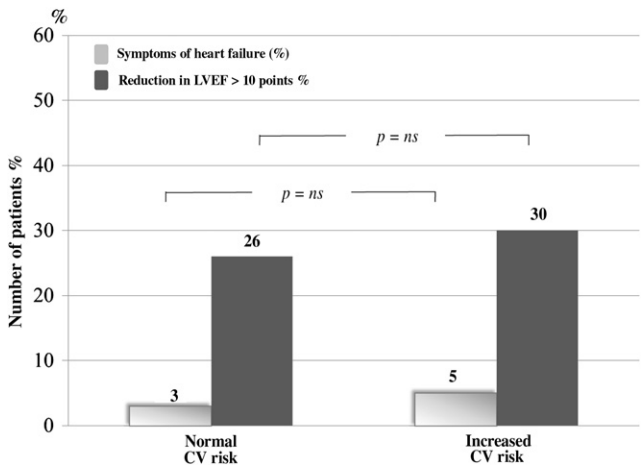

Fig. 2. Incidence of heart failure syndrome and asymptomatic cardiotoxicity in patients who had increased cardiovascular (CV) risk and in those who had not.

Table 3. Adverse Events, Trastuzumab Discontinuation, and Rechallenge Between Patients With and Without Cardiotoxicity

Variable	Total (n = 499)	No Cardiotoxicity (n = 366)	Cardiotoxicity (n = 133)	*P* Value
Cycles of trastuzumab, n	17	17	17	ns
Trastuzumab discontinuation, n (%)	28 (6%)	4 (1%)	24 (18%)	<.001
Trastuzumab restart, n (%)	13 (3%)	3 (1%)	10 (7%)	<.001
Cardiac events				
Heart failure syndrome, n (%)	16 (3%)	0	16 (12%)	.001

against the chemotherapy-induced cardiac damage.[33,34] Furthermore, trastuzumab-induced cardiac failure generally has a good response to drug therapy[31] and may be reversible.[13]

In our experience, anthracycline exposure (doxorubicin) predicted cardiotoxic events during subsequent trastuzumab administration. This was an expected finding, in line with the results of Perez et al,[35] who reported that in a population of 2,992 women with HER2-positive operable breast cancer, the cumulative incidence of postanthracycline cardiac events at 3 years was higher in the trastuzumab-containing arms versus the control arm. Similarly to our experience, Perez et al showed a low incidence of clinical events (<4%).

As shown by the comparison of the time trend of ventricular function between the patients with or without high cardiovascular risk, the former had a significantly deeper drop in cardiac function than the latter during the early phase of transtuzumab administration, with a reduction of the gap between the 3th and the 12th month of treatment. However, they had the same incidence of adverse events of patients who did not have an increased risk. This finding may seem incomprehensible if we do not consider that patients who had increased cardiovascular risk were more frequently receiving ACE inhibitors/ARBs, beta-blockers, and statins than patients who had not, at a dosage frequently modulated during the course of the chemotherapy as a consequence of the evaluation of left ventricular function.[33,34] This observation suggests that the computation of the cardiovascular risk with the Chart Risk Table Score may be a useful tool to identify the patients with higher probability of cardiotoxicity before trastuzumab administration.

In our experience, trastuzumab was interrupted in very few patients (6%) and, as reported by others,[30] successfully restarted in one-half of them. It would be reasonable to draw a conclusion that rechallenge with trastuzumab should be encouraged in greater number of patients because of safety of such practice and survival benefit offered by the drug administration.

Study Limitations

Several limitations of our study have to be emphasized. First, almost all patients, according to recommendations between January 2008 and June 2009,[30] initiated treatment with trastuzumab after completion of adjuvant chemotherapy as well as anthracycline-based therapy. This approach would not allow to precisely weigh the cardiotoxic effect purely of trastuzumab therapy, which could be favored, in some case, by previous anthracycline administration. Second, the choice of how and when to start ACE inhibitors/ARBs and/or beta-blockers and of the relative dosage of such drugs was left to the discretion of the attending physicians. This approach, in some cases, may have influenced the results, leading to an underestimation of the trastuzumab-related cardiotoxicity owing to the protective effects on the myocardium of these medications. Third, in this study, the baseline LVEF was higher in women with cardiotoxicity than women without: This unexpected difference, which was irrelevant from the clinical point of view, could be due to an overestimation of baseline LVEF in some women, leading to a possible false diagnosis of trastuzumab-related cardiotoxicity during the follow-up. Finally, we did not present data on cardiotoxicity within a comparison group of women who did not receive trastuzumab. This could be an important limitation if we not consider that since the Herceptin Adjuvant (HERA) trial, it is quite difficult to obtain a reliable control group for the women with HER2-positive early breast cancer, because this condition has a bad prognosis and trastuzumab represents the gold standard therapy in the absence of contraindications. Accordingly, in all centers participating in our registry, trastuzumab was systematically administered to all women in whom it was indicated.

Generalizability of the Study Findings

In our experience, the women receiving trastuzumab were less frequently exposed to anthracycline (87%) than those participating to the HERA trial (94%),[7] and in other ''real-world'' single-center series published after the completion of HERA trial, such as those of Guglin et al (93%) and Wadhwa et al (100%).[18,19] Nevertheless, our multicenter Registry confirm that in community settings the majority of patients with early breast cancer receive trastuzumab after anthracyclines. The lower rate of permanent discontinuation of trastuzumab therapy that we found in our patients is also different from some randomized clinical trials. We think that such findings may be the result of both a ''more inflexible'' interpretation of the exclusion criteria for trastuzumab therapy and a ''more flexible'' propensity to restart the drug applied in clinical practice than in the randomized trials.

Conclusion

In clinical practice, trastuzumab-induced cardiotoxicity in HER2-positive early breast cancer patients is relatively

frequent. However, the cardiac damage is mild and elapses asymptomatically in most patients. It occurs early, in the first 3 months of therapy, and is a reversible phenomenon associated with older age, reduced renal function, and treatment with doxorubicin and radiotherapy. The women with increased cardiovascular risk have a deeper drop of LVEF during the first 3 months of treatment. The recommended therapy for heart failure or hypertension with ACE inhibitors/ARBs and/or beta-blockers seems to protect these patients against the progression of the cardiac damage and trastuzumab therapy usually may be completed safely. Such women are frequently >60 years of age and represent the subgroup of subjects with the highest incidence of breast cancer,[36] who are usually not enrolled or are largely underrepresented in randomized clinical trials and for whom some substantial differences in adjuvant use seems to exist[36] and trastuzumab is not infrequently denied.[37]

Disclosures

None.

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Appendix 1

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