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The Oncologist 2012, 17:917-924.
doi: 10.1634/theoncologist.2011-0445 originally published online June 6, 2012

The Oncologist®

Breast Cancer

Administration of Angiotensin-Converting Enzyme Inhibitors and β-Blockers During Adjuvant Trastuzumab Chemotherapy for Nonmetastatic Breast Cancer: Marker of Risk or Cardioprotection in the Real World?

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Key Words. Cardiotoxicity • Trastuzumab • Breast cancer • Angiotensin-converting enzyme inhibitors • β-blockers

Disclosures: The authors indicated no financial relationships.

ABSTRACT

Background. **Adjuvant trastuzumab therapy improves the outcome of patients with early breast cancer (EBC) and overexpression of human epidermal growth factor receptor 2 (HER2). However, it is potentially cardiotoxic. This study aims to evaluate the relationship between the use of angiotensin-converting enzyme inhibitors/receptor blockers (ACEi/ARBs) and/or β-blockers and development of heart failure (HF) and/or left ventricular dysfunction during 1 year of adjuvant trastuzumab therapy.**

Methods. **A total of 499 women receiving adjuvant trastuzumab therapy for EBC entered in a multicenter registry and were divided into four subgroups according to treatment with ACEi/ARBs and/or β-blockers. Occurrence of HF and decrease of left ventricular ejection fraction (LVEF; minimum 10 percentage points) were recorded.**

Results. **HF occurred in 2% of patients who did not take either ACEi/ARBs or β-blockers, 8% of patients receiving ACEi/ARBs alone, 8% receiving β-blockers alone ($p = .03$), and 19% receiving both medications ($p < .01$). The prevalence of patients with LVEF that decreased by at least 10 percentage points was similar in all groups. Combined ACEi/ARBs and β-blocker therapy was independently associated with hypertension and a significant reduction of LVEF from baseline to 3-month evaluation. The use of ACEi/ARBs alone or β-blockers alone was predicted only by hypertension. Combined therapy of ACEi/ARBs plus β-blockers predicted LVEF recovery from the 3-month to 12-month evaluation.**

Conclusions. **In clinical practice, the degree of hypertension and decrease in LVEF during the first 3 months of adjuvant trastuzumab therapy for EBC are associated with the use of ACEi/ARBs and β-blockers. The combined use of these two medications is associated with a recovery of LVEF during months 3–12 of adjuvant trastuzumab therapy.** ***The Oncologist*** 2012;17:917–924

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1083-7159/2012/$20.00/0 http://dx.doi.org/10.1634/theoncologist.2011-0445

Introduction

In the last two decades, overall survival has increased for many patients with cancer because of new anticancer drugs, especially for patients with node-negative breast cancer [1]. However, these drugs are potentially cardiotoxic and may induce heart damage leading to heart failure (HF). The likelihood of cardiac side effects during adjuvant chemotherapy is related to the type of therapy, schedule of administration, and other well-known risk factors [2], including the timing of trastuzumab therapy [3]. It has been shown that the use of trastuzumab with standard chemotherapy (anthracycline and cyclophosphamide) significantly increases the risk of cardiac dysfunction in patients with epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer [4]. With adjuvant therapy, cardiac dysfunction is a relatively rare event [5–15]; however, in clinical practice, it is recognized quite frequently and seems to have a higher prevalence than what is reported in controlled trials [16, 17].

Angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptors blockers (ARBs), and β-blockers are effective treatments for cardiac complications from anthracycline chemotherapy; they increase the possibility of recovery from trastuzumab-related HF [18–20]. However, it is still unclear how, when, and for which patients these drugs should be used; their long-term effect on left ventricular (LV) function and toxicity-related cardiac symptoms are also unknown.

Accordingly, the aims of our study were to assess the prevalence of the use of ACEi/ARBs and/or β-blockers, as well as the relationship between the administration of ACEi/ARBs and β-blockers and changes in LV systolic function in a 12-month period for a large community population of unselected patients with nonmetastatic breast cancer treated with trastuzumab in the adjuvant setting.

Patients and Methods

Data from 499 consecutive patients enrolled in 10 Italian hospitals and cancer institutes between January 2008 and June 2009 were retrospectively reviewed. All patients had previously been treated with chemotherapy (anthracyclines 88%, cyclophosphamide 89%, taxanes 44%, 5-fluorouracil 46%, neoadjuvant 25%). The trastuzumab treatment protocol as adjuvant chemotherapy for early breast cancer consisted of a loading dose of 8 mg per kilogram of body weight intravenously once, followed by maintenance doses of 6 mg/kg every 3 weeks for 1 year (18 doses in total). An available echocardiographic evaluation of left ventricular ejection fraction (LVEF) before starting trastuzumab was mandatory for inclusion in the study. Patients who showed a decline of >10 percentage points in LVEF before starting adjuvant trastuzumab therapy, compared with the assessment of LVEF before the previous anthracycline administration, were not included in the registry.

For each patient, we collected relevant comorbidities and baseline cardiovascular medications. Diabetes mellitus was diagnosed by World Health Organization criteria (fasting serum glucose ≥126 mg/dL or 2-hour postchallenge serum glucose ≥200 mg/dL or the use of hypoglycemic medication). Dyslipidemia was defined as total cholesterol > 190 mg/dL and or triglyceridemia >150 mg/dL. Hypertension was defined as pharmacologically treated high blood pressure and graded as mild if blood pressure before treatment was >140/90 but <160/95 mmHg, moderate if it was ≥160/95 but <180/105 mmHg, and severe if it was ≥180/105 mmHg [21]. In these patients, we considered and recorded the condition of well-controlled blood pressure, which was defined as blood pressure ≤140/90 mmHg. A state of increased cardiovascular risk was defined as a 10-year risk of cardiovascular death ≥5% according to the European Society of Cardiology guidelines on cardiovascular disease prevention in clinical practice [21].

Renal function was assessed by estimation of glomerular filtration rate with the simplified Modification of Diet in Renal Disease equation. For all patients, LVEF was taken up as the index of LV systolic function and measured at baseline and after 3, 6, 9, and 12 months with Simpson's method during standard two-dimensional echocardiography, according to Herceptin Adiuvant (HERA) Trial's results and as indicated in the drug package insert [22]. Trastuzumab-related cardiotoxicity was classified in five grades and defined as follows [23, 24]:

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

Before trastuzumab administration, no patients showed signs or symptoms of HF and all had normal LVEF (history of HF and/or abnormal baseline LV systolic function defined as LVEF ≤55% were considered to be exclusion criteria in our study). During trastuzumab treatment, diagnosis of HF was based on a comprehensive assessment based on modified Framingham criteria [25], clinical symptoms of HF, response to diuretic and vasodilators, and brain natriuretic peptide; it was confirmed by an echocardiographic evaluation of LV systolic and diastolic function. In presence of cardiotoxicity, the decision for interruption or rechallenge with trastuzumab was made by the clinical oncologist. The study protocol was approved by the local institutional review boards.

Statistics

Data are reported as means ± standard deviation. SPSS 11.0 (SPSS Inc., Chicago, IL) was used for statistical analysis. Unpaired Student's t test and χ^2 statistics were used for descriptive statistics. Between-group comparisons of continuous and normally distributed variables were performed by the analysis of variance. Multiple logistic regression analyses were carried out to individuate the variables independently related to β-blockers or ACEi/ARBs or combined β-blockers plus ACEi/ARB administration during the 12-month period of observation. Variables considered in the analyses were age, hypertension, degree of hypertension, dyslipidemia, diabetes, history of coronary artery disease, increased cardiovascular

risk, glomerular filtration rate, doxorubicin (percent and dose), epirubicin (percent and dose), baseline LVEF, and change in LVEF from baseline to 3-month evaluation. The same variables together with the pharmacological treatment with β-blocker plus ACEi/ARBs were included in a Cox regression analysis to assess whether β-blockers plus ACEi/ARB therapy was a marker of increased risk of trastuzumab-induced cardiotoxicity and a multiple linear regression model testing the variables associated with the changes in LVEF from 3-month to 12-month evaluation. Receiver operating characteristic (ROC) curve analysis was performed to assess the cutoff point of reduction in LVEF from baseline to 3-month evaluation prompting pharmacological treatment with β-blockers plus ACEi/ARBs. A two-tailed value of $p < .05$ was considered to be statistically significant.

Results

We enrolled 499 women (age 55 ± 11 years). Of these, 128 patients (26%) had a history of arterial hypertension, 30 (6%) had a history of diabetes, and 75 (15%) had a history of dyslipidemia. A total of 59 patients (18%) were treated with β-blockers, 91 patients (12%) with ACEi/ARBs, and 26 patients (5%) with both ACEi/ARBs and β-blockers. In 50 cases, β-blockers were started before trastuzumab; in 9 cases, they were introduced at the 3-month evaluation. In 85 cases, ACEi/ARBs were started before transtuzumab; in 6 cases, they were introduced at the 3-month evaluation. The main clinical characteristics, oncological treatments, and pharmacological therapy for reducing the cardiovascular risk are shown in Table 1.

Patients treated with β-blockers and/or ACEi/ARBs were older, had a higher prevalence of hypertension and dyslipidemia, and were treated concurrently with diuretics, calcium antagonists, and statins compared with patients who did not receive β-blockers and/or ACEi/ARBs. Variables that differed between the groups of patients who received or did not receive β-blockers, ACEi/ARBs, and ACEi/ARB plus β-blockers are listed in Tables 2–4, respectively.

Considering the total study population, trastuzumab-related cardiotoxicity was recognized in 133 patients (27%). A total of 102 patients (20%) showed asymptomatic reduction in LVEF >10% but ≤20% (grade 1); 15 (3%) had asymptomatic decline of LVEF >20% or <50% (grade 2); 16 (3%) symptomatic heart failure (grade 3). No patient experienced a cardiotoxic event of grade IV or V. HF occurred in 2% of patients who did not take either ACEi/ARBs or β-blockers, in 8% of patients receiving ACEi/ARBs alone, in 8% receiving β-blockers alone (both $p = .03$) and in 19% receiving both medications ($p < .01$). The number of patients whose LVEF decreased by at least 10 percentage points was similar in all study subgroups (Fig. 1).

Kaplan-Meier curves showed a nonsignificant trend of increased cardiotoxic events in the subgroup of patients treated with combined therapy of β-blockers and ACEi/ARBs (Fig. 2). Cox regression analysis demonstrated that combined β-blocker and ACEi/ARB therapy was not associated with trastuzumab-induced cardiotoxicity (exponent $\beta = 1.89$, 95% confidence interval [CI]: 0.36–9.84; $p = .445$); it was predicted instead by a lower glomerular filtration rate (exponent $\beta = 0.98$, 95% CI: 0.96–0.98; $p = .039$) and treatment with doxorubicin (exponent $\beta = 2.72$, 95% CI: 1.42–5.20; $p = .003$). Even the trend of LVEF changes was similar in the study subgroups, but patients receiving combined β-blocker and ACEi/ARB therapy had a significant reduction in LVEF from

Table 1. Principal characteristic of 499 study patients

Variables	Total (n =499)
Age (yrs)	55 ± 11
History of hypertension (%)	26
Mild	14
Moderate	7
Severe	5
Well-controlled blood pressure[a] (%)	95
Systolic blood pressure (mmHg)	125 ± 12
Diabetes (%)	6
Dyslipidemia (%)	15
History of coronary artery disease (%)	2
Smoking habit (%)	15
Increased risk for cardiovascular events (%)	15
Hemoglobin (g/dL)	12.9 ± 1.2
Glomerular filtration rate (mL/min/1.73 m^2)	82 ± 19
LVEF (%)	65 ± 6
LVEF prior to anthracycline initiation (%)	66 ± 5
Therapy for managing cardiovascular risk factors (%)	
Angiotensin-converting enzyme inhibitors/receptor blockers	18
Diuretics	10
β-blockers	12
Calcium antagonists	3
Statins	7
Radiochemotherapy	
Radiotherapy (%)	60
Doxorubicin (%)	12
Dose (mg/m^2)	231 ± 46
Epirubicin (%)	76
Dose (mg/m^2)	339 ± 156
Cyclophosphamide (%)	89
Paclitaxel (%)	21
Docetaxel (%)	27
5-fluorouracil (%)	46
Neoadjuvant therapy	25
Trastuzumab (n of cycles)	17

Data are means ± standard deviations unless otherwise noted.
[a]Evaluated in the subgroup of patients with hypertension.
Abbreviation: LVEF, left ventricular ejection fraction.

Table 2. Variables for patients who received and did not receive β-blockers

Variables	Did not receive β-blockers ($n = 440$)	Received β-blockers ($n = 59$)	p value
Age (yrs)	54 ± 11	63 ± 7	<.001
History of hypertension (%)	16	93	<.001
Mild	10	34	
Moderate	5	27	
Severe	1	32	
Dyslipidemia (%)	12	39	<.001
History of coronary artery disease (%)	1	8	<.001
Glomerular filtration rate (mL/min/1.73 m^2)	83 ± 19	70 ± 15	<.001
Left ventricular ejection fraction (%)	64.8 ± 6.0	64.9 ± 5.8	NS
Therapy (%)			
Angiotensin-converting enzyme inhibitors/receptor blockers	14	46	<.001
Diuretics	6	39	<.001
Calcium antagonists	2	15	<.001
Statins	5	24	<.001
Anthracyclines	89	75	.002
Cyclophosphamide	90	80	.02

Data are means ± standard deviations unless otherwise noted.
Abbreviation: NS, not significant.

Table 3. Variables for patients who received and did not receive angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers

Variable	Did not receive ACEi/ARBs ($n = 408$)	Received ACEi/ARBs ($n = 91$)	p value
Age (yrs)	53 ± 10	65 ± 8	<.001
History of hypertension (%)	10	96	<.001
Mild	7	41	
Moderate	2	30	
Severe	1	25	
Dyslipidemia (%)	11	32	<.001
Diabetes (%)	3	15	<.001
Left ventricular ejection fraction (%)	65.0 ± 5.8	64.0 ± 6.4	NS
Therapy (%)			
β-blockers	8	30	<.001
Diuretics	3	42	<.001
Calcium antagonists	1	13	<.001
Statins	5	18	<.001
Epirubicin	78	67	.02

Data are means ± standard deviations unless otherwise noted.
Abbreviations: ACEi/ARBs, angiotensin-converting enzyme inhibitors/receptor blockers; NS, not significant.

baseline to the 3-month evaluation in comparison with the other study groups (Fig. 3).

Multivariate logistic regression analysis showed that the administration of β-blockers alone and ACEi/ARBs alone depended only on the presence of hypertension. Patients receiving combined therapy of β-blockers and ACEi/ARBs were associated with the presence of hypertension and a greater reduction in LVEF from baseline to 3-month evaluation more than patients who did not receive the combined therapy (Table 5). The presence of a condition of increased cardiovascular risk

Table 4. Variables for patients who received and did not receive combination therapy of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers plus β-blockers

Variable	Did not receive combination therapy ($n = 473$)	Received combination therapy ($n = 26$)	p value
Age (yrs)	55 ± 11	65 ± 8	<.001
History of hypertension (%)	23	96	<.001
Mild	15	0	
Moderate	6	30	
Severe	2	66	
Dyslipidemia (%)	13	50	<.001
History of coronary artery disease (%)	1	8	.02
Left ventricular ejection fraction (%)	64.8 ± 6.0	64.5 ± 5.7	NS
Therapy (%)			
Diuretics	7	54	<.001
Calcium antagonists	3	19	<.001
Statins	6	31	.002
Radiotherapy	61	35	.008
Epirubicin	78	50	.001

Data are means ± standard deviations unless otherwise noted.
Abbreviation: NS, not significant.

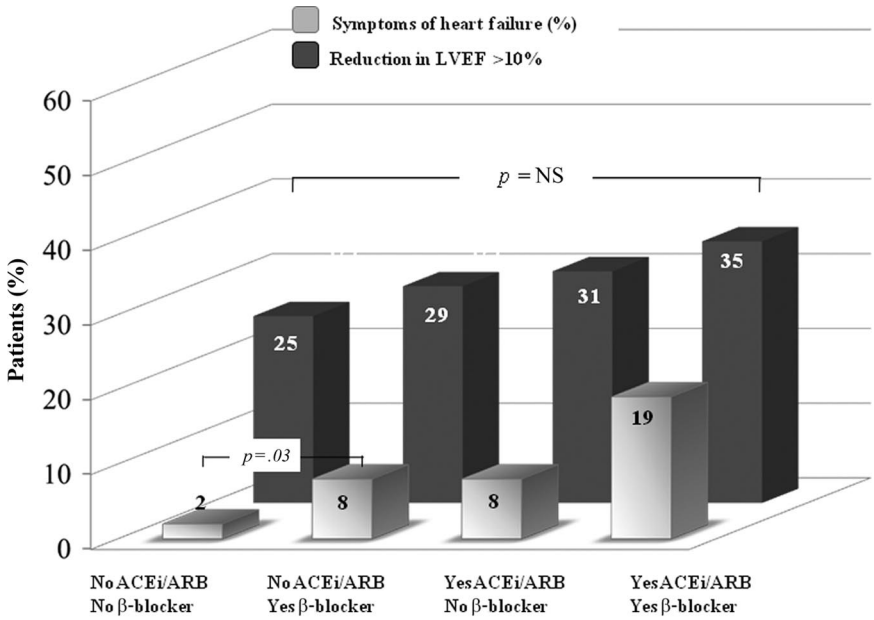

Figure 1. Prevalence of new-onset symptoms of heart failure and reduction in left ventricular ejection fraction >10 percentage points during 1-year follow-up according to the pharmacological treatment with β-blockers and/or angiotensin-converting enzyme inhibitors/angiotensin receptor blockers.

Abbreviations: ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; LVEF, left ventricular ejection fraction.

had no influence on the use of β-blockers and ACEi/ARBs, either administered alone or in combination. ROC curve analysis revealed that the best cutoff point for reduction in LVEF associated with the combined use of β-blockers and ACEi/ARBs was −3.5% (area under the curve = 0.78, 95% CI: 0.65–0.91, sensitivity = 75%, specificity = 82%).

Thus, we searched by a multiple linear regression model for the variables independently associated with the changes in LVEF from

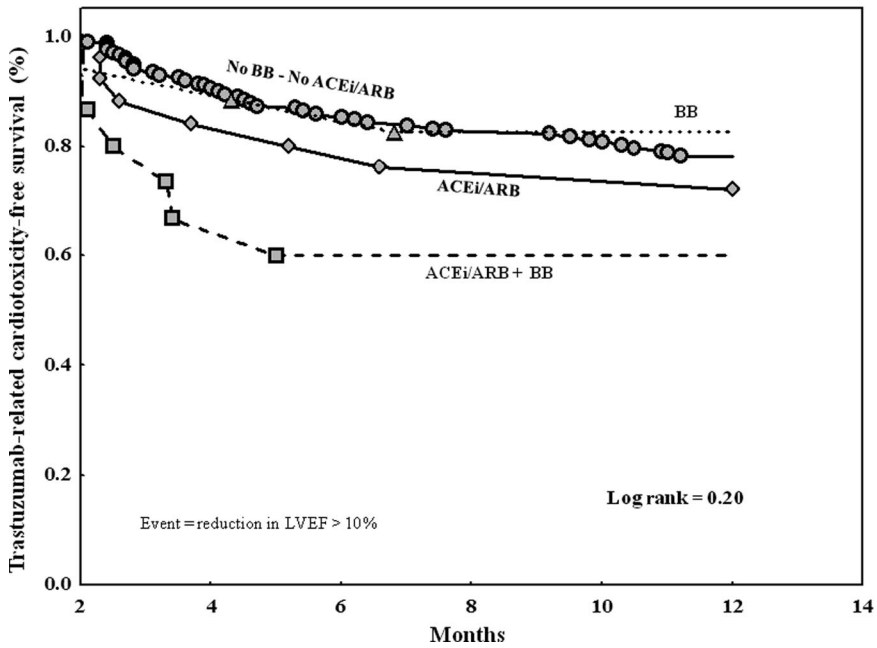

Figure 2. Kaplan-Meier plot of 1-year survival free from cardiotoxic events occurring at any time during the follow-up period according to medical treatment.

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, β-blocker.

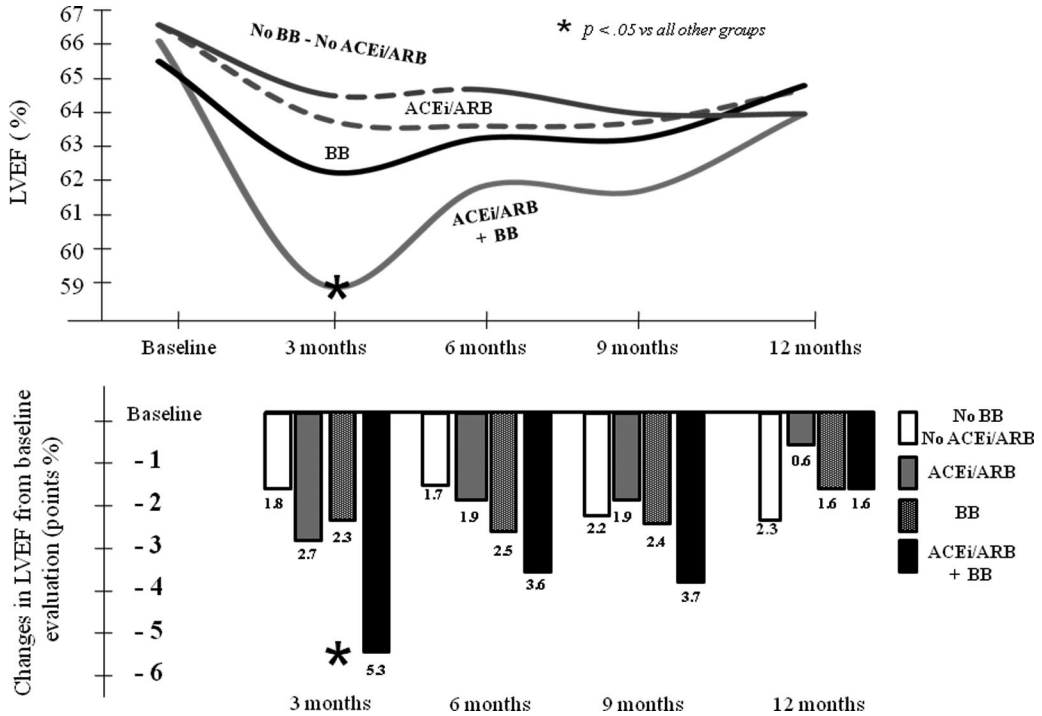

Figure 3. Trend of left ventricular ejection fraction in the study subgroups during 1-year trastuzumab therapy expressed as mean absolute values (upper panel) and change from baseline echocardiographic evaluation (bottom panel).

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, β-blocker; LVEF, left ventricular ejection fraction.

the 3-month to 12-month evaluation: combined therapy of β-blockers plus ACEi/ARBs (β coefficient = 0.16, $p = .03$, tolerance = 0.94) and changes in LVEF from baseline to the 3-month evaluation (β coefficient = 0.37, $p < .001$, tolerance = 0.94).

Discussion

The prognosis for nonmetastatic early breast cancer at 10 years is excellent; the probability of death is less for cancer-related causes than for other reasons, including cardiac complications

Table 5. Variables independently associated with the use of β-blockers and/or angiotensin-converting enzyme inhibitors/angiotensin receptor blockers: Multivariate models (multiple logistic regression analysis)

Variables	Odds ratio	95% confidence interval	*p* value
β-Blockers			
Hypertension	11.20	2.61–48.22	.001
Degree of hypertension	3.4	2.00–5.62	<.0001
Increased cardiovascular risk	0.89	0.44–2.35	NS
Change in LVEF from baseline to 3-month evaluation	0.98	0.92–1.08	NS
ACEi/ARBs			
Hypertension	18.12	4.52–70.11	<.001
Degree of hypertension	5.91	2.94–11.70	<.001
Increased cardiovascular risk	0.83	0.35–2.11	NS
Change in LVEF from baseline to 3-month evaluation	0.95	0.90–1.04	NS
β-Blockers plus ACEi/ARBs			
Hypertension	0.61	0.12–18.70	NS
Degree of hypertension	15.8	5.6–44.7	<.0001
Increased cardiovascular risk	2.5	0.55–11.40	NS
Change in LVEF from baseline to 3-month evaluation	0.88	0.79–0.98	.02

Abbreviations: ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; LVEF, left ventricular ejection fraction; NS, not significant.

[26]. The new targeted drugs appear to have increased the risk of cardiac dysfunction, even when administered in the adjuvant setting, although some studies do not agree [27, 28]. The incidence of cardiotoxicity induced by trastuzumab adjuvant therapy for patients with breast cancer varies widely in individual randomized clinical trials according to the definition of cardiac toxicity, eligibility criteria, and chemotherapy regimens [29–31]. Limited data exist regarding the clinical use of ACEi/ARBs and β-blockers in community patients receiving trastuzumab adjuvant therapy.

Our results clearly show that the degree of hypertension and the decrease in LVEF during the first 3 months of trastuzumab treatment are the two conditions associated with the combined therapy of ACEi/ARBs plus β-blockers. When the two classes of drugs are singly given, they are only associated with the presence of hypertension and degree of hypertension. In this study, one of five patients receiving the two medications experienced HF and one of three patients receiving the two medications had a significant decline in LVEF. The incidence of HF was much lower in the other three subgroups of patients, whose decline in LVEF during the first 3 months of trastuzumab therapy was less steep. By this point of view, therapy with ACEi/ARBs and/or β-blockers (which was mainly started before trastuzumab and in the remaining cases after the 3-month echocardiographic evaluation) seems to be a marker of risk for cardiac disease more than an attempt of cardioprotection. One clinical implication of our study is that it could be particularly useful to schedule the first echocardiographic evaluation during the trastuzumab treatment after the second dose of the drug (about 42 days from the start).

A second original finding of our study is that LVEF recovery from the 3-month to 12-month evaluation was independently associated with the combined therapy of ACEi/ARBs plus β-blockers, suggesting a cardioprotective role for the combination of these two drugs. This behavior is in line with the observations of Ewer et al. [32], who also showed that the heart damage could be reversible and "healed" by trastuzumab discontinuation and HF standard therapy with ACEi and β-blockers; this damage has been called "type II" to distinguish it from the "type I" doxorubicin-induced damage [33]. Therefore, patients with cancer who are treated with potentially cardiotoxic chemotherapy regimens represent a high-risk group for the development of HF. These patients, who have no cardiac damage but have risk factors that clearly predispose them to the development of HF, should be aggressively treated in accordance with the American Heart Association Guidelines for the treatment of stage A HF [34]. Thus, ACEi and β-blockers are two medications that should be strongly indicated to improve morbidity and mortality related to HF in patients with cancer [34]. Furthermore, in a recent manuscript approved by the European Society for Medical Oncology Guidelines Working Group, ACEi and β-blocker therapy has been defined as mandatory for patients, even if asymptomatic, who show left ventricular dysfunction on standard Doppler echocardiogram [35].

Conclusions

Our registry study shows that, in a real-world population of unselected patients with nonmetastatic breast cancer receiving trastuzumab in the adjuvant setting, treatment with ACEi/ARBs and/or β-blockers is prescribed in about one-third of patients and is essentially related to the presence of hypertension. Combined therapy with ACEi/ARBs and β-blockers is rarely prescribed before

starting treatment with trastuzumab and is mostly used in patients with severe hypertension whose LVEF significantly declines within the first 3 months of trastuzumab treatment. This therapeutic approach allows the recovery of left ventricular systolic function and the prosecution of trastuzumab adjuvant therapy in a sizeable percentage of patients. Thus, to date, the use of ACEi/ARBs and β-blockers seems to be a marker of risk for trastuzumab-related cardiotoxicity more than a challenge of cardioprotection. According to our findings, we speculate that combined therapy with ACEi/ARBs and β-blockers should be given to patients with lower glomerular filtration rates who were previously treated with doxorubicin, the two conditions predisposing patients to cardiotoxicity during trastuzumab treatment. Further prospective studies are needed to verify if this precautionary methodology may prevent trastuzumab-related cardiotoxicity in these patients.

Acknowledgments

We thank all the participants in the Italian Cardioncological Network.

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