

The Risk of Toxicities from Trastuzumab, Alone or in Combination, in an Elderly Breast Cancer Population

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Key Words

Breast cancer · Elderly patients · Human epidermal growth factor receptor type 2 · Trastuzumab

Abstract

Background: Breast cancer in the elderly is associated with high recurrence and death rates, due mostly to undertreatment. Human epidermal growth factor receptor type 2 (HER2) overexpression is infrequent in older patients. Trastuzumab-based chemotherapy is often withheld from elderly patients because of its cardiotoxicity. **Patients and Methods:** Medical records of consecutive HER2-positive breast cancer patients aged ≥ 70 years old treated between 2005 and 2010 in the participating centers were retrospectively reviewed. All patients underwent multidimensional geriatric assessment (MGA). **Results:** Among 59 patients identified, 51 patients were evaluable (median age 76 years). The rate of any adverse event was 20% (10/51). The most relevant cardiac adverse event consisted of symptomatic congestive heart failure (CHF; $n = 1$, 2%) followed by asymptomatic decreases of left ventricular ejection fraction (LVEF; $n = 6$, 12%). Other toxicities included moderate hypersensitivity reac-

tions during trastuzumab infusions ($n = 3$, 6%). Hypertension, obesity, prior anthracyclines exposure and concurrent chemotherapy were associated with a higher incidence of toxic events. Previous radiotherapy, concurrent endocrine therapy and different trastuzumab-based regimens did not seem to influence toxicity. **Conclusions:** Our data suggest that trastuzumab has a good safety profile in nonfrail women aged 70 years and older. These favorable findings may be related to a limited number of anthracycline pretreatments, patient selection and a close cardiologic monitoring.

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Introduction

Increasing age represents the main risk factor for developing breast cancer (BC). In the USA, its incidence has been reported to rise from 1 in 209 for women younger than 40 years to 1 in 14 for women aged 70 years [1]. The number of breast cancers diagnosed in women >70 years old in the majority of Western countries has increased during the last decades [2, 3] with further growth expected in the forthcoming decades [4]. This is mostly attribut-

able to the population aging and to a larger use of screening mammography in elderly women [5]. A more frequent early detection, with consequent treatment of the disease at lower stages, has resulted in a progressive decline in mortality [3]. However, the survival gain has been slighter than in younger women [6], mainly due to undertreatment; therefore, to date, the death rates for breast cancer remain high in this age group, reaching 41.7% in very elderly patients [7].

The overexpression of the human epidermal growth factor receptor type 2 (HER2) has a negative impact on clinical outcomes [8]. The frequency of HER2 positivity decreases with age. In a retrospective study on 2,723 consecutive patients, HER2-positive disease declined from 27% in patients <40 years of age to 7% in patients >70 years of age [9].

Trastuzumab, a monoclonal antibody against the extracellular domain of HER2, has shown activity in metastatic BC as monotherapy [10] and remarkable efficacy in both metastatic and early-stage BC in combination with chemotherapy (CT), reducing relapse rates by 50% regardless of age and other relevant prognostic factors [11–15]. These results were confirmed in several large, randomized studies, which reported a significantly longer time to progression and overall survival with the combination of adjuvant trastuzumab plus CT, compared with CT alone [12, 13, 16, 17].

Although trastuzumab, either alone or combined with CT in a weekly or 3-weekly regimen, is a well-established standard treatment for early or advanced HER2-positive breast cancer, the risk-benefit ratio of trastuzumab-based regimens in the elderly has not yet been defined, as in clinical trials there are no sufficient safety data on women aged 70 years and older. Indeed, this age cohort has been poorly enrolled [18, 19] and mostly represented by healthy subjects. As a consequence, optimal treatment is controversial and, to date, the assessment of the same prognostic factors used for younger postmenopausal women drive the therapeutic choices made by physicians.

As chronologic and biologic age may differ, a multidimensional geriatric assessment (MGA) is increasingly being used to select patients according to functional and cognitive status, comorbidity and social and logistic limitations in order to identify frail subjects who should rather be treated only with supportive care [20].

The aim of this study was to retrospectively evaluate the safety of trastuzumab-based regimens in older women with early, locally advanced and/or metastatic HER2-positive breast cancer.

Methods

We reviewed data between 2005 and 2010 of HER2-overexpressing breast cancer patients referred to two Sicilian oncology centers. Patients were eligible for this study if they met the following criteria: (1) female and aged ≥ 70 years, (2) a histological diagnosis of breast cancer (stage I–IV according to the TNM (tumor size, node, metastasis) American Joint Committee on Cancer version VI), (3) HER2-positive status determined using Hercept Test (DAKO) with a 3+ result on immunohistochemistry (IHC) or a 2+ IHC result and a positive result using fluorescence in situ hybridization (FISH), (4) patients had previously undergone surgery, radiation treatment of the chest wall, hormone therapy and CT (anthracycline-based or others), (5) availability of local staging and biological parameters: pT (tumor size), pN (nodal status), histological grade (G), ER (estrogen receptor), PgR (progesterone receptor) and Ki67 (proliferative index); the ER and PgR status was defined as positive if cell staining was $\geq 10\%$ by IHC, (6) patients were required to have adequate cardiac function evaluated by echocardiography (left ventricular ejection fraction, LVEF $\geq 50\%$), (7) an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, (8) adequate hematologic, hepatic and renal function and (9) MGA based on Balducci's criteria [20]. Patients were excluded if they had a prior history of uncontrolled arrhythmia and/or significant cardiac disease. Prior trastuzumab therapy was also not allowed. Each subject gave a written informed consent to the study, and the study was approved by the institutional ethical committee.

Trastuzumab was administered every 3 weeks (as a 8 mg/kg loading dose followed by 6 mg/kg) or weekly (as a 4 mg/kg loading dose followed by 2 mg/kg). In both regimens, trastuzumab was infused in 250 ml of normal saline, for over 90 min for the first dose and 60 min for the subsequent doses. Trastuzumab given in association with CT was administered on the first day of each cycle. Patients received corticosteroid premedication (dexamethasone, either 8 mg or 4 mg i.v.) for at least the first 3 weeks of trastuzumab administration.

Safety was assessed by changes in physical, hematologic and cardiologic findings.

A functional and cardiologic assessment by clinical history, physical examination, MGA, blood chemistry, electrocardiogram and echocardiogram-determined LVEF was performed before starting therapy and then every 3 months and with the occurrence of symptoms or signs suspicious for cardiac dysfunction. Adverse events were graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC). Cardiac dysfunction was defined as congestive heart failure (CHF), cardiomyopathy or a LVEF decrease of at least 10%.

Results

We examined 59 consecutive HER2-positive breast cancer patients aged ≥ 70 years and their main clinical-pathological characteristics are described in table 1. The mean age was 76 years (range 70–86 years). Histological types included 51 ductal, 5 lobular, 2 medullary and 1 mucinous invasive carcinoma. Determination of receptor

Table 1. The main characteristics of consecutive HER2-positive BC patients aged ≥ 70 years

BC	Number	%
Total	59	
Patients evaluable	51	86.4
Median age, years (range)	76 (70–86)	
Early-stage	18	35.3
Locally advanced	3	5.9
Metastatic	30	58.8
ECOG performance status		
0	27	45.8
1	20	33.9
2	12	20.3
MGA	48	81.3
Fit	20	41.7
Unfit	28	58.3
Comorbidities	46/59	77.9
Hypertension	19/46	41.3
Diabetes	12/46	26.08
Hypothyroidism	5/46	10.86
Obesity	3/46	6.52
Hypercholesterolemia	4/46	8.69
Depression	3/46	6.52
Thrombophlebitis	1/46	2.17
Rheumatoid arthritis	1/46	2.17
Osteoporosis	6/46	13.04

Table 2. Previous CT and/or radiotherapy and trastuzumab regimens in elderly BC patients

	Number	%
Trastuzumab monotherapy	9/51	17.6
Trastuzumab + hormonotherapy	19/51	37.3
Trastuzumab + CT	23/51	45.1
CT pretreatment	36/51	70.5
Anthracyclines	20/36	55.5
Non-anthracyclines	16/36	44.4
Previous RT (thoracic wall)	18/36	35.3

status showed ER-negative/PgR-negative disease in 25 patients (42.3%), ER-positive/PgR-positive disease in 19 patients (32.2%), ER-positive/PgR-negative disease in 12 patients (20.3%) and ER-negative/PgR-positive disease in 3 patients (5.0%). HER2 positivity was determined by IHC in 44 patients and by FISH in 15 patients.

ECOG performance status was 0 in 27 patients (45.8%), 1 in 20 patients (33.9%) and 2 in 12 patients (20.3%).

The following comorbidities were identified in 46/59 (77.9%) patients: mild to moderate hypertension (n = 19,

Table 3. Type of toxicity in elderly BC patients treated with trastuzumab-based regimens

Type	Number	%
Hypersensitivity	3	5.9
Cardiotoxicity		
Reduction FEVS >10%	3	5.9
Reduction FEVS >15%	3	5.9
CHF	1	1.9
Median basal LVEF		61
Range		52–76
Median final LVEF		55
Range		40–65

41.3%), diabetes (n = 12, 26.08%), hypothyroidism (n = 5, 10.86%), osteoporosis (n = 6, 13.04%), obesity (n = 3, 6.52%), hypercholesterolemia (n = 4, 8.69%), depression (n = 3, 6.52%), rheumatoid arthritis (n = 1, 2.17%) and thrombophlebitis (n = 1, 2.17%). In 28 patients (60.89%) 1 comorbidity was identified, 2 were identified in 15 patients (32.60%) and 11 patients (23.91%) were found to have ≥ 3 concomitant comorbidities.

Among the 59 cases reviewed, baseline MGA was performed in 48 patients (81.3%), according to which 20 (41.7%) were classified as fit and 28 (58.3%) as unfit, 22 as vulnerable (22/28, 78.5%) and 6 as frail (6/28, 21.4%). Eleven patients were treated without a baseline MGA, but a careful evaluation of general conditions and comorbidities was taken into consideration. Trastuzumab was not administered in frail patients as well as in 2 patients who had not had an MGA but presented with important comorbidities.

Overall, 51 of the 59 patients received trastuzumab, alone or combined with cytotoxic or hormonal agents, and all were valuable for safety (table 2, 3). Eighteen patients presented with early-stage, 3 with locally advanced disease, and 30 with metastatic disease. Median treatment duration was 12.0 months with a range of 4–41 months. Thirty-six (70.5%) of 51 evaluable patients had been pretreated with CT, 16 (44.4%) had received non-anthracycline-containing regimens and 20 (55.5%) had received anthracyclines (11 received epirubicin and 9 received liposomal doxorubicin). Previous thoracic radiotherapy was performed in all patients presenting with early-stage disease. Trastuzumab as a single agent was administered to 9 patients (17.6%), 6 of whom had metastatic disease. Trastuzumab plus hormonotherapy (aromatase inhibitors) was administered to 19 patients

(37.3%), while trastuzumab in combination with CT was administered to 23 patients (45.1%): 8 received concomitant taxanes, 11 received vinorelbine and 4 received gemcitabine (table 2).

Mild to moderate hypersensitivity reactions associated with trastuzumab-containing infusions occurred in 3 patients (5.9%), including 2 cases of chills and fever that resolved after the administration of a 3-weekly trastuzumab loading dose, and 1 case of a chill.

No case of a severe reaction requiring the interruption of trastuzumab infusion was observed. These events were all of short duration (i.e. resolved by slowing the infusions) and did not reappear during the subsequent cycles.

In all patients, the median baseline LVEF was 61% (range 52–76%), and the median final LVEF was 55% (range 40–65%) (table 3). The majority cardiac events related to or likely to be ascribed to trastuzumab occurred in patients given concurrent CT: a total of 7 cases.

A case of symptomatic CHF occurred when navelbine given in combination with trastuzumab which required treatment withdrawal appeared during cycle 5 in a 78-year-old patient with a history of mild hypertension on therapy with an ACE inhibitor, who had had a recurrence after epirubicin-based adjuvant CT without radiotherapy. This woman experienced exertion dyspnea, tachycardia and peripheral edema. Her LVEF decreased from the basal value of 54 to 37%. All symptoms and signs improved on treatment with ACE inhibitors plus diuretics and β -blockers, and LVEF was partially recovered (up to 50%) within 17 weeks. No hospitalization was needed and her blood pressure was under control during this episode. Three patients who received aromatase inhibitors combined with trastuzumab developed asymptomatic >15% decreases in LVEF <50%. They discontinued trastuzumab-based treatment and initiated ACE inhibitors. After recovering the LVEF values, the same trastuzumab-based treatment was restarted, but 1 patient had a further 14% LVEF drop and therefore treatment was withdrawn. In the other 3 cases, there was a >10% LVEF decrease that did not reach 50%. These patients continued the same trastuzumab-based treatment with no further declines.

The median baseline LVEF of evaluated patients was 61%, with a range of 52–76%. The median final LVEF was 55%, with a range of 40–65% (table 3).

No substantial differences in the number or grade of adverse events were seen between patients who received trastuzumab once a week or every 3 weeks.

Discussion and Conclusions

The lack of guidelines for elderly HER2-positive breast cancer shows that there is a need for clinical trials to address the safety and efficacy of trastuzumab-based treatments in a population who may have a substantially long life expectancy (about 15 years for a 70-year-old woman with an average health status, declining to 7 years for an 85-year-old woman) [21] and, consequently, a high risk of recurrence and death for this aggressive form of BC.

The objective of this study was to evaluate the safety of trastuzumab as a monotherapy or in addition to CT or endocrine therapy in a 5-year series of consecutive HER2-positive breast cancer patients aged ≥ 70 .

The retrospective nature of the study limits our analysis, but the collection of this large case-series with HER2-overexpression is nevertheless one of the few studies aimed to assess the safety profile in elderly patients treated with trastuzumab-based regimens.

Our results show that trastuzumab-based treatments were well-tolerated and adverse events were mild to moderate in severity, with only 2 treatment withdrawals.

Either mild or no side effects were observed in patients given trastuzumab alone or in combination with hormone therapy. Hypertension and obesity as comorbidities, previous anthracycline treatment and CT combined with trastuzumab are associated with a higher incidence of development of various-grade cardiac toxicity. Infusion-related side effects occurred mostly during the first trastuzumab administration, and their frequency and degree were comparable with those described in various other studies [22].

Advanced age is an important risk factor for cardiac events, as well as pre-existing cardiac dysfunction, baseline LVEF $\leq 50\%$, poorly controlled hypertension, anthracycline pretreatment and previous radiotherapy to the left thoracic wall [8]. Older patients with numerous associated chronic diseases are at higher risk of cardiotoxicity. Its severity varies from asymptomatic LVEF decreases to symptomatic CHF, which may be life-threatening [23].

In about 80% of cases, it is reversible and responds to trastuzumab withdrawal and standard therapies for CHF [24, 25]. In a multivariate analysis of two large studies, NSABP-B31 and NCCTG N-9831, age appeared to be a significant predictor for CHF in the combination arms [13, 20, 21]. An analysis of the Herceptin Adjuvant (HERA) trial also showed a higher rate of age-related cardiac events in the arm receiving trastuzumab plus CT, compared with CT alone (3.64 and 0.59%, respectively) [12]. Subsequent to the introduction of trastuzumab-

based treatments in the clinical practice, a certain liberalization of the strict selection criteria utilized in the clinical trials has led to an increase of cardiotoxicity incidence, with 28% of patients being reported to experience a cardiac event [26, 27]. Cardiac events were seen in 2.6–4.5% of the patients treated with trastuzumab monotherapy, in 13% of those on trastuzumab plus paclitaxel and in 27% in those on trastuzumab plus anthracyclines [28, 29].

In our case-series, the incidence rate of CHF was 1 case in 51 patients (1.9%), below the cut-off of 4% that has been considered acceptable in clinical trials [28, 29]. Furthermore, cardiac adverse events were not affected by the number of trastuzumab administrations, consistent with the cardiotoxicity data generally reported for this drug [22]. Moreover, when trastuzumab was combined with CT, it showed a manageable toxicity, with an incidence rate that did not exceed the ranges observed in studies on women <70 years old [27].

Several observations need to be expressed about our favorable safety results. First, the reduced number of anthracycline-containing pretreatments (n = 20, 55.5%) as well as the frequent employment of liposomal formulations might have resulted in a lesser incidence of cardiac events. Secondly, a substantial percentage of patients were selected on the basis of MGA; this tool spares frail patients from receiving potentially toxic drugs and, in our case, it allowed physicians to offer trastuzumab-based treatments to more than three quarters of the patients. Finally, close patient monitoring allowed precocious therapeutic interventions in the cases of cardiac dysfunction. So our data

found a good correlation with some recent reports where the patients were treated with trastuzumab as an adjuvant modality and in other limited cases [8, 30–32].

Our results are consistent with those of a recent paper published by Serrano et al. [33]. In older patients, cardiovascular risk factors and previous CT treatments are the most important factors in the development of trastuzumab-related cardiotoxicity. So age does not exclude trastuzumab-based therapy in this class of patients.

A recent paper published by Brollo et al. [34] analyzed the role of trastuzumab in elderly patients in an adjuvant setting. However, these data can not be compared with our results because this work included patients >60 years old whereas we refer to a population of >70 years old. They also analyzed the role of trastuzumab-based therapy only in an adjuvant setting whereas we evaluated the safety of trastuzumab in an adjuvant and a metastatic setting.

In conclusion, our data show a good safety profile of trastuzumab in nonfrail women aged ≥ 70 years. Future multicenter prospective trials should address both the early and metastatic stages in this high-risk age group and include selection criteria such as a geriatric assessment. Such trials should provide algorithms of optimal risk-benefit for trastuzumab-based treatments [7, 35, 36].

Disclosure Statement

The authors do not have any potential or actual personal, political or financial interest in the material, information or techniques described in the paper.

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