

## Use of Trastuzumab for Breast Cancer: The Role of Age

Walter Mazzucco<sup>1,3,4</sup>, Marta Rossi<sup>2,5,\*</sup>, Rosanna Cusimano<sup>4,6</sup>, Matteo Franchi<sup>2</sup>, Martina Bonifazi<sup>2</sup>, Alessandro Mistretta<sup>4</sup>, Francesco Vitale<sup>3,4</sup>, Walter Ricciardi<sup>1</sup>, Eva Negri<sup>2</sup>, Stefania Boccia<sup>1,7,\*</sup>, Carlo La Vecchia<sup>2,5</sup>

<sup>1</sup>Institute of Hygiene, Università Cattolica del Sacro Cuore, Rome, Italy; <sup>2</sup>Department of Epidemiology, IRCCS “Mario Negri” Institute for Pharmacological Research, Milan, Italy; <sup>3</sup>Sciences for health promotion Department, University of Palermo, Palermo, Italy; <sup>4</sup>Palermo District Cancer Registry, A.O.U.P. “Paolo Giaccone” di Palermo, Palermo, Italy; <sup>5</sup>Department of Clinical sciences and Community Health, University of Milan, Milan, Italy; <sup>6</sup>Public Health, Epidemiology and Preventive Medicine Unit, Local Health Agency, Palermo, Italy; <sup>7</sup>IRCCS San Raffaele Pisana, Rome, Italy

**Abstract:** Indication for the use of trastuzumab was given in Italy in 2000 for the treatment of HER-2 metastatic breast cancer and in 2006 for early stage breast cancer. Information on trastuzumab use and on its possible variation with age in Italy is however limited. Using health care administrative databases, we evaluated the prevalence of the use of trastuzumab, and the probability for administration since the first hospitalization for breast cancer in various age groups, in two series of Italian women diagnosed with breast cancer in the Lombardy region (2004-2009) and in the Palermo district. The rate between trastuzumab users and patients with a hospitalization for breast cancer increased from 2.9% in 2004 up to 17.2% in 2009 in Lombardy. Patients aged <65 years were more frequent users (9.6%) compared to those aged  $\geq 75$  years (1.3%). Similarly, in the Palermo district the proportion of users increased from 10.6% in 2006 to 28.5% in 2008, with subjects aged <65 years more frequently using trastuzumab (19.1%), than subjects aged  $\geq 75$  years (6.2%). The rate ratio between younger and older patients decreased over time in both settings (from 15 in 2004 to 10.2 in 2006, and 5.2 in 2009 in Lombardy, and from 4.0 in 2006 to 2.3 in 2009 in Palermo district). The proportion of breast cancer patients using trastuzumab increased over time both in Lombardy and in Palermo District, though geographical differences persisted. Younger breast cancer patients were more likely to receive a trastuzumab treatment than elderly ones.

**Keywords:** Trastuzumab, early breast cancer, metastatic breast cancer, breast cancer treatment, elderly.

### INTRODUCTION

Human epidermal growth factor receptor-2 (HER-2) gene (*her-2/neu* oncogene) is overexpressed/amplified in 15% to 25% of breast cancers [1,2], and this is usually associated with a poor prognosis and a worse response to treatment [3,4]. The adjuvant use of trastuzumab (Herceptin®), a humanized monoclonal antibody selectively targeting the extra-cellular domain of the HER2 receptor, improves disease free survival and overall survival in HER-2 positive breast cancer patients [5,6].

Initially used for the treatment of HER-2 late-stage breast cancer [7,8], nowadays trastuzumab represents a standard of care also for early stage disease in the adjuvant setting [9,10]. In Italy, trastuzumab was introduced for the treatment of HER-2 metastatic breast cancer in 2000 [11] and in 2006 the Italian Medicine Agency (Agenzia Italiana del Farmaco, AIFA) granted approval for trastuzumab in early breast cancer treatment, when administered “after breast surgery, chemotherapy (neoadjuvant/adiuvant) and radiotherapy (if applicable)” [12]. Information on the prevalence of trastuzumab use before and after AIFA guidelines implementation in Italy is however scanty. The inclusion criteria and the relatively small sample size of trials have limited information on the use of trastuzumab to specific groups of patients to date. This highlights the importance to investigate trastuzumab use in clinical practice in the general population, which also includes vulnerable subgroups of population - such as older patients and patients with comorbidities, taking into account the confidence of clinicians in managing trastuzumab also in these patients.

We analyzed health care administrative databases in order to evaluate the prevalence of the use of trastuzumab in two different series of women diagnosed with breast cancer in the Lombardy

region and in the Palermo district. We estimated the prevalence overall and according to age, and evaluated whether the age of patients was a predictor of trastuzumab use with focus on differences in utilization in older versus younger subjects, independently of the duration and the compliance of trastuzumab therapy.

With 10 million resident inhabitants (51.2% females), Lombardy is the most populated region of Italy [13], located in the North-western part of the peninsula. As a high income per capita area, it has an elevated breast cancer incidence (rates 2010: <65 years = 78.18/100,000; 65-75 years = 345.00/100,000; >75 years = 464.33/100,000) [13]. With 5 million resident inhabitants (51.7% females), Sicily, an island located at the South of the peninsula, is the second most populated region of Italy [13] and has a lower breast cancer incidence than Lombardy (rates 2010: <65 years = 59.43/100,000; 65-75 years = 237.57/100,000; >75 years = 335.00/100,000). Palermo District is the greatest Sicilian province (about 1.25 million residents, 51.9% females) [13].

### METHODS

The data were retrieved from two regional health service databases of the Lombardy region and from the Palermo District Cancer Registry integrated database.

In Lombardy the first database is the “File F” (F stands for Farmaci, i.e. Drugs) registry 2004-2009, which includes all prescriptions of drugs administered directly in the outpatient setting and of selected novel high cost drugs administered in the outpatient setting or in Day Hospital (DH), and reimbursed by the National Health Service (NHS). It includes information on the date and the dosage of prescriptions, as well as the hospital and the physician administering the drugs [14]. The second source is the Regional hospital discharge forms (Scheda di Dimissione Ospedaliera, SDO) database 2003-2009. This is a computerized database which stores all Regional patient hospital discharge records and contains information about patients and their hospitalizations (both ordinary and DH), including demographic characteristics, admission and dis-

\*Address correspondence to this author at the Institute of Hygiene, Università Cattolica del Sacro Cuore di Roma, Largo F. Vito, 1, 00100 Roma; Tel/Fax: + 39 0635506224; E-mail: sboccia@rm.unicatt.it

charge dates, the main and five additional secondary diagnoses (coded according to the International Classification of Disease 9, ICD-9), date and type of interventions, and hospitalization-related diagnosis costs (coded according to the national diagnosis related group system - DRGs) [15]. From 2006, the SDOs referring to chemotherapy have also included information on whether the cost of the drug was compensated through the File F registry, or not [16].

The Palermo District Cancer Registry (Registro Tumori della Provincia di Palermo, RTPP) is an institution adhering to the Italian Cancer Registries Association (AIRTUM) network since 2006 [17]. From RTPP integrated database we extrapolated validated data generated by different flows, including the Palermo district hospital discharge form registry, deriving from the Regional one, the "File T" data flow, which included all prescriptions of drugs administered directly in the outpatient setting and of selected novel high cost drugs administered in the outpatient setting or in DH for the period 2006-2009, and reimbursed by the NHS [18,19].

### Study Population and Data Analysis

We identified all trastuzumab users through File F registry (2004-2009) in Lombardy, and File T data (2006-2009) in Palermo. The number of resident patients who have been admitted in a hospital per year was calculated by searching an SDO reporting a breast cancer diagnosis in the six assigned fields (ICD codes: 1740-6, 1748-49). These include patients who were admitted for both early stage breast cancers, including patients who underwent a surgery, and advanced breast cancers. In our databases, no information was available on HER2 positivity. Rates between trastuzumab users and patients with a hospitalization for breast cancer were calculated by age categories (<65, 65-74, ≥75 years) both among Lombardy residents, period 2004-2009, and Palermo district residents, period 2006-2009.

For each of the two settings a computerized record linkage between the two corresponding databases was carried out through a unique anonymous patient identification code, in order to analyze the clinical history of each subject. The date of admission of the

**Table 1. Rate between trastuzumab users (n) and patients with a hospitalization for breast cancer (N) among Lombardy residents, period 2004-2009, and Palermo district residents, Italy, 2006-2009, overall and by year.**

Lombardy	Age (yrs)	Overall	2004	2005	2006	2007	2008	2009
		% (n/N)	% (n/N)	% (n/N)	% (n/N)	% (n/N)	% (n/N)	% (n/N)
	<65	9.6 (3039/31 575)	4.5 (285/6278)	6.7 (410/6133)	13.2 (795/6010)	15.1 (901/5964)	21.0 (1313/6243)	23.7 (1447/6116)
	65-74	5.4 (823/15 307)	2.0 (65/3173)	3.1 (92/2981)	5.6 (164/2908)	7.0 (209/2984)	12.8 (381/2988)	16.0 (468/2916)
	≥75	1.3 (202/15 138)	0.3 (8/2840)	0.9 (26/2892)	1.3 (39/2932)	1.7 (48/2811)	3.7 (112/3015)	4.6 (131/2842)
	Total	6.6 (4064/62 020)	2.9 (358/12 291)	4.4 (528/12 006)	8.4 (998/11 850)	9.8 (1158/11 759)	14.7 (1806/12 246)	17.2 (2046/11 874)
	Rate ratio <65 Vs ≥75	7.4	15.0	7.4	10.2	8.9	5.7	5.2
Palermo district	Age (yrs)	Overall			2006	2007	2008	2009
		% (n/N)	-	-	% (n/N)	% (n/N)	% (n/N)	% (n/N)
	<65	19.1 (392/2050)	-	-	13.0 (81/624)	20.5 (167/814)	34.6 (233/673)	25.2 (164/652)
	65-74	15.7 (127/807)	-	-	10.0 (26/260)	13.8 (45/327)	27.9 (67/240)	23.8 (58/244)
	≥75	6.2 (43/698)	-	-	3.2 (6/185)	3.1 (7/227)	10.5 (23/219)	11.0 (23/210)
	Total	15.8 (562/3555)	-	-	10.6 (113/1069)	16.0 (219/1368)	28.5 (323/1132)	22.8 (252/1106)
	Rate ratio <65 Vs ≥75	3.1	-	-	4	6.7	3.3	2.3

first SDO reporting a diagnosis of breast cancer was considered as the date of the first hospitalization for breast cancer of each subject, and those patients who received a trastuzumab treatment after that date were identified. For this purpose, the SDOs from 2003 to 2008 for Lombardy, and from 2005 to 2008 for Palermo district were considered. This allowed us to look for possible hospitalization for breast cancer until one year before the beginning of trastuzumab use also for patients treated in 2004 in Lombardy and 2006 in Palermo district.

We also investigated whether trastuzumab was administered for an early or a metastatic breast cancer, by looking for diagnosis of metastasis in all SDOs previous to the trastuzumab treatment of each subject. We restricted these analyses to the years 2007-2009, considering that AIFA approval on early breast cancer treatment was granted in late 2006 [12].

A multiple logistic model was used to assess the association between the patient's age (at the first hospitalization for breast cancer) and the use of trastuzumab in terms of odds ratios (OR) and corresponding 95% confidence intervals (CI). The model included terms for age, year of first hospitalization for breast cancer and presence of metastasis. In order to avoid biases due to the introduction of the AIFA note in 2006, the ORs for the presence of metastasis were computed among cases diagnosed from august 2006.

The cumulative probability to receive a trastuzumab treatment after a hospitalization for breast cancer was estimated in the Lombardy region using Kaplan-Meier method among all trastuzumab users. Each subject accumulated person-years of follow-up from the date of admission of the first hospitalization reporting breast cancer until the first prescription of trastuzumab. Differences in the time of receiving a trastuzumab treatment after the first hospitalization by strata of age were assessed using the log-rank test.

## RESULTS

Table 1 gives the rates between the number of trastuzumab users and the number of potential trastuzumab users per year, that is patients who were admitted for early stage breast cancers, including

patients who underwent a surgery, or advanced breast cancers from 2004 to 2009 in Lombardy, and from 2006 to 2009 in the Palermo district.

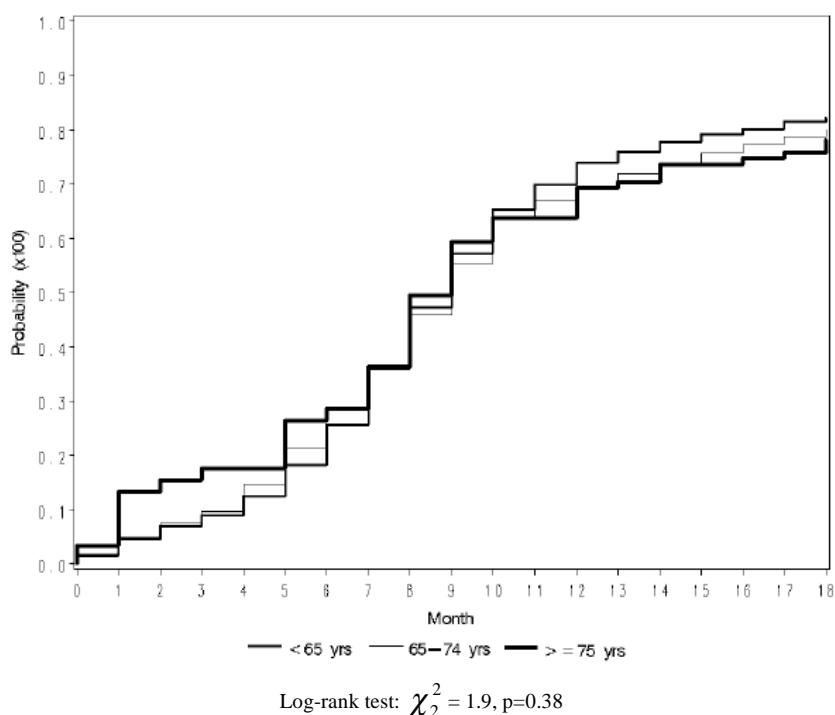
In Lombardy the rate increased from 2.9% in 2004 up to 17.2% in 2009 (overall of 6.6% during the whole study period). Subjects aged <65 years more frequently used trastuzumab (9.6%) than subjects aged  $\geq 75$  years (1.3%). The rate ratio between the younger and the elderly subjects was 7.4 overall, and showed a decreasing trend through the years: from 15 in 2004 to 5.2 in 2009.

Similarly, in Palermo district the rate increased from 10.6% in 2006 up to 28.5% in 2008, leveling off to 22.8% in 2009, with an overall use of 15.8% during the study period. Subjects aged <65 more frequently used trastuzumab (19.1%), than subjects aged  $\geq 75$  (6.2%). The rate ratio between the younger and the older subjects was 3.1 overall, and showed a decreasing trend starting from 2007, ranging from 6.7 to 2.3 in 2009.

Table 2 gives the adjusted ORs, and the corresponding 95% CI for trastuzumab treatment according to selected covariates among 59,316 and 4,015 subjects who were admitted in hospital for breast cancer between 2003 and 2008 in Lombardy and between 2005 and 2008 in Palermo, respectively. A younger age was a strong predictor of trastuzumab use. Subjects aged between 65-74 years and <65 had 6 and 14 times, and 3 and 4 times, the probability of receiving a trastuzumab treatment as compared to subjects aged  $\geq 75$  years in Lombardy and Palermo district, respectively.

When we restricted the analysis to the years 2007-2008 (when AIFA approval on early breast cancer treatment was already granted), we found that the presence of metastasis increased the probability to receive trastuzumab by 20% in Lombardy, while in the Sicilian district this result was not significant.

Figure 1 is restricted to trastuzumab users, and considers time from the first hospitalization for breast cancer to trastuzumab use in different strata of age. Despite a greater frequency of trastuzumab use in younger patients, the time between first hospitalization and first trastuzumab use did not appreciably vary with age.



**Fig. (1).** Cumulative probability of trastuzumab use from the first hospitalization for breast cancer among 2787 patients with a hospitalization for breast cancer between 2003 and 2008 who received trastuzumab treatment between 2004 and 2009 by strata of age. Lombardy, Italy.

**Table 2.** Odds ratio and 95% confidence interval (95%CI) for trastuzumab use according to year of first hospitalization for breast cancer and age of patients at first hospitalization for breast cancer among 59,316 subjects (2787 trastuzumab and 56,529 non-trastuzumab users) with a hospitalization for breast cancer between 2003 and 2008 in Lombardy and among 4,015 subjects between 2005 and 2008 in the Palermo district, Italy.

	Lombardy			Palermo district		
	N	Trastuzumab use Vs. no trastuzumab use		N	Trastuzumab use Vs. no trastuzumab use	
		N (%) of users	OR* (95% CI)		N (%) of users	OR* (95% CI)
Year of first hospitalization						
2003	10672	278 (2.6)	1 <sup>^</sup>	-	-	-
2004	10063	262 (2.6)	1.1 (0.9-1.3)	-	-	-
2005	9784	361 (3.7)	1.6 (1.3-1.8)	1316	98 (7.4)	1 <sup>^</sup>
2006	9559	539 (5.6)	2.5 (2.2-3.0)	851	86 (10.1)	1.4 (1.0-1.9)
2007	9374	647 (6.9)	3.3 (2.8-3.8)	980	132 (13.5)	1.9 (1.5-2.5)
2008	9864	700 (7.1)	3.5 (3.0-4.0)	868	127 (14.6)	2.1 (1.6-2.8)
<i>p trend</i>			<0.001			<0.03
Age (yrs)						
≥75	14406	91 (0.6)	1 <sup>^</sup>	903	28 (3.8)	1 <sup>^</sup>
65-74	14498	484 (3.3)	5.7 (4.6-7.2)	1143	100 (10.4)	2.9 (1.9-4.5)
<65	30412	2212 (7.3)	13.8 (11.1-17.0)	2825	315 (13.6)	4.0 (2.7-5.9)
<i>p trend</i>			<0.001			<0.0001

<sup>^</sup> Reference category

\* Estimated by multiple regression model adjusted for year of first hospitalization for breast cancer, age and presence of metastasis.

## DISCUSSION

Our study indicates and quantifies that younger breast cancer patients were more likely than elderly ones to receive a trastuzumab treatment in Italy. The proportion of breast cancer patients treated with trastuzumab increased over time. Different proportions in the utilization of trastuzumab, however, were documented between Lombardy and Palermo, especially among the elderly.

The use of trastuzumab in HER-2 positive breast cancers is currently established both in the adjuvant setting for early stages and in the first-line approach for metastatic cases in Europe [20,21,22]. In the Netherlands, trastuzumab in conjunction with adjuvant chemotherapy in women with HER2-positive breast cancer was widely utilized within 8 months after introduction of a national guideline in September 2005: of all HER2-positive patients who received adjuvant chemotherapy, 94% received trastuzumab [23].

The more frequent use of trastuzumab in younger patients as compared to the elderly can be related to the higher prevalence of HER-2 positive breast cancers in younger women [24,25] and to the greater cardiotoxicity of trastuzumab in the elderly [26,27,28]. Although a systematic review of randomized controlled trials recommended the use of trastuzumab as a standard of care in the adjuvant therapy also for elderly patients [28], various studies documented high cardiotoxicity of trastuzumab in the elderly patients [28-33]. In a population-based study conducted in the USA between 1999 and 2007 on 12 500 women with incident breast cancer, of which 554 received trastuzumab, the 5-year cumulative incidence for heart failure and/or cardiomyopathy associated with trastuzumab and anthracycline use increased with increasing age. The cumulative incidence was 7.5% among age <55 years, 11.4% among 55-64 years, 35.6% among 65-74 years and 40.7% among ≥ 75 years. Women who received trastuzumab were younger (25 out of 2202 in

≥ 75 years versus 312 out of 4261 in <55 years, rate ratio=6.4) [28]. In a separate analysis of the Lombardy dataset [33], out of 2046 trastuzumab users, 53 (2.6%) experienced at least one hospitalization for a cardiac event, and there were two cardiac deaths. The risk was low (0.2%) below age 50, but was to approximately 10% at age ≥70.

Our data documented an increasing use of trastuzumab over time. In particular, we found a gap from 2005 to 2006 that can be largely due to the inclusion of early breast cancer in the AIFA indication in 2006. Thereafter, the use of trastuzumab has been increasing, possibly because of a greater confidence of clinicians in weighing up efficacy and possible cardiac adverse events of this drug also in early breast cancer patients [33]. The use of trastuzumab was less frequent in Lombardy as compared to Palermo district. This might be attributable to a different approach in the two clinical settings. In particular, in Lombardy various trials had been ongoing during the study period and a larger subgroup of breast cancer patients in Lombardy than in Palermo has received trastuzumab as neoadjuvant chemotherapy [34] or other chemotherapies in the context of experimental studies [35,36,37]. The trials were carried out in the major oncological research institutes of Lombardy and sponsored by drug manufacturer, making consequently information on drug use not available in our health administrative sources of data such as the File F registry. This, however, can only in part explain the high use of trastuzumab in Sicily, particularly in 2008, since over-expression of HER-2 gene was around 21% among breast cancers in Palermo district in those years [38]. The decline in trastuzumab use in 2009 in the Palermo district, on the contrary, is likely to be attributed to economical restrictions [39].

No differences in the period between the first hospitalization for breast cancer and the beginning of trastuzumab treatment appeared according to strata of age among trastuzumab users. When we restricted the analyses to the Lombardy region between 2007 and

2009 - a period in which the trastuzumab use for early breast cancer was already approved, we found that metastatic patients were more likely to receive trastuzumab as compared to early breast cancer.

Our study has some limitations related to the use of healthcare databases for epidemiological researches, including the absence of information on some potential confounders [40-41]. The administrative purpose, for which these datasets were primarily instituted, may also limit the completeness and accuracies of medical information reported [42]. On the other hand, the main advantages of these datasets are the representativeness of routine clinical practice in large populations, the high numbers of observations and the coverage of all age groups.

## CONCLUSION

We reported and quantified an increase in the use of trastuzumab among breast cancers over the past few years. In our study a younger age of patients was a strong predictor of trastuzumab use while use was relatively limited in the elderly. This could be explained by a higher risk of trastuzumab-related adverse events in older women.

## CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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Conception and design of the study: Carlo La Vecchia, Stefania Boccia

Generation and analysis of data: Matteo Franchi, Alessandro Mistretta

Interpretation of data: Walter Mazzucco, Marta Rossi, Rosanna Cusimano, Eva Negri

Manuscript writing and drafting: Walter Mazzucco, Marta Rossi

Revision of the manuscript: Carlo La Vecchia, Stefania Boccia, Walter Ricciardi, Francesco Vitale, Rosanna Cusimano, Martina Bonifazi, Eva Negri

Approval of the final version of the manuscript: Walter Mazzucco, Marta Rossi, Rosanna Cusimano, Matteo Franchi, Alessandro Mistretta, Francesco Vitale, Walter Ricciardi, Stefania Boccia, Carlo La Vecchia, Eva Negri

## ABBREVIATIONS

HER-2	= Human epidermal growth factor receptor-2
Vs	= Versus
AIFA	= Agenzia Italiana del Farmaco (Italian Medicine Agency)
DH	= Day hospital
NHS	= National Health Service
SDO	= Scheda di Dimissione Ospedaliera (Hospital discharge forms)
ICD	= International Classification of Disease
DRG	= Diagnosis related group system
RTPP	= Palermo District Cancer Registry
AIRTUM	= Italian Cancer Registries Association

OR	= Odds ratio
CI	= Confidence interval

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