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Implementation of trastuzumab in conjunction with adjuvant chemotherapy in the treatment of non-metastatic breast cancer in The Netherlands

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## Abstract

### Background.

Trastuzumab in conjunction with adjuvant chemotherapy markedly improves outcome. In the Netherlands, a national guideline was released in September 2005 stating that trastuzumab should be given in conjunction with adjuvant chemotherapy in women with HER2 positive breast cancer. Aim of this study was to identify the number of women with HER2-positive breast cancer and to evaluate the level of implementation of adjuvant trastuzumab in clinical practice nationwide.

### Patients and methods.

Women diagnosed with primary breast cancer between September 2005 - January 2007 were selected from the Netherlands Cancer Registry (NCR). HER2 status, adjuvant treatment and reasons to withhold trastuzumab were registered.

### Results.

14,934 Breast cancer patients were diagnosed in this period of whom 1,928 (13%) had a HER2-positive tumour. Of all HER2-positive women receiving adjuvant chemotherapy, 66 (6%) did not receive trastuzumab. This percentage decreased from 10% at the time of introduction of the guideline to 4% in the study period September 2005 - December 2006. Most common reasons to withhold trastuzumab were cardiovascular disease (29%) and patient refusal (21%).

### Conclusion.

Of all HER2-positive patients who received adjuvant chemotherapy, 94% received trastuzumab. The implementation of trastuzumab in clinical practice was realized within 8 months after introduction of the new guideline.

Keywords: adjuvant, breast cancer, guideline, HER2, trastuzumab,

## **Introduction**

Breast cancer is the most common cancer in women in the Netherlands, accounting for about one third of all female cancers [1]. Approximately 10-25% of breast cancers have overexpression of the human epidermal growth factor receptor 2 (HER2) protein and/or amplification of the HER2 gene [2-5]. In May 2005 the results of three large randomised studies were presented, revealing that in women with HER2-positive breast cancer, the risk of developing recurrences or distant metastases and the risk of death decreased by more than 30% by adding one year adjuvant treatment with trastuzumab [6,7]. Based on these results, recommendations for HER2-testing and the use of adjuvant trastuzumab were rapidly included in national and international guidelines [8].

The aim of this study was to evaluate the level of implementation of the Dutch guidelines for HER2-testing and the use of trastuzumab in clinical practice, analysing regional differences and reasons for withholding trastuzumab.

## **Patients and Methods**

### *Patients*

Patients were selected from the population-based Netherlands Cancer Registry (NCR) of the Association of Comprehensive Cancer Centres (CCCs) in the Netherlands, covering all 16 million inhabitants. The Association of CCCs consisted of 9 regional CCCs, which support the development and implementation of national guidelines by means of multidisciplinary working groups and consultancy services (on local, regional and national level), and monitor guideline compliance after their implementation using Cancer Registry data.

Main source of notification for the NCR is PALGA, the nationwide Dutch network and registry of histo- and cytological pathology, through which all newly diagnosed malignancies are reported to the cancer registry. Case ascertainment is completed by using the national hospital discharge database, which receives the diagnosis of admitted patients from all hospitals. After notification to the NCR, specially trained registrars of the CCCs visit the hospitals to collect information on patient and tumour characteristics, stage and treatment from patient files. Coding of the items is based on international coding rules (IACR). TNM classification was used for the staging of tumours [9]. Since 2005 HER2 status was recorded in the NCR on a routine basis. HER2-positivity was defined using a widely recommended testing algorithm [10,11]. An immunohistochemistry (IHC) score 3+ was considered positive. When IHC was inconclusive (2+), an additional fluorescent in situ hybridization (FISH) test was indicated. IHC score 3+ or a positive FISH test was considered indicative for HER2-positivity.

All women diagnosed with invasive breast cancer between September 2005 and January 2007 were selected (n=17,781). Women without surgery or with metastases at diagnosis, and women who received neo-adjuvant chemotherapy were excluded from analysis, leaving 14,934 women for analysis in this study.

### *Treatment guidelines*

In the Netherlands, guidelines are developed by the National Breast Cancer Organization of The Netherlands (NABON). They released the adapted national guideline in September 2005 indicating that for women with HER2-positive breast cancer trastuzumab should be given in conjunction with adjuvant chemotherapy. If women with HER2-positive tumours and chemotherapy did not receive adjuvant trastuzumab, reasons to withhold trastuzumab were documented by the registrars from the CCCs.

### *Statistical analysis*

Time of diagnosis was divided into 4 periods of 4 months. Regions in the Netherlands were defined according to the areas covered by the 9 CCCs [1]. Logistic regression was performed to study differences in the use of trastuzumab between regions. The region with the highest use of trastuzumab was coded as reference. Age (10-year categories)

and tumour stage (stage I, II and III) were included as covariates. The statistical significance level was set at a p-value  $<0.05$ . Analyses were performed using the STATA software package, version 10.1 for Windows (Stata Corporation LP, College Station, TX, USA).

## Results

### *HER2 status*

Between September 2005 and January 2007 14,934 women with invasive breast cancer were included in the study. Median age at diagnosis was 60 years (range 21-101, Table 1). Of these, 1,928 (13%) women were diagnosed with HER2-positive breast cancer. The percentage of HER2-positive tumours decreased with increasing age from 22% in women younger than 40 years to 10% in women 70 years or older (Figure 1,  $p < 0.001$ ). In 4% of women under 40 years of age HER2-status was unknown or not tested. This percentage increased to 8% in women over 70 (Figure 2). Both the percentage HER2-positive tumours (range 11%-15%,  $p = 0.008$ ) and the percentage with HER2-status unknown or not tested (range 3%-13%,  $p < 0.001$ ) varied between the CCC regions.

### *Use of trastuzumab*

Of all 1,928 women with HER2-positive breast cancer, 1,114 (58%) received adjuvant chemotherapy. This percentage decreased from 93% among women <40 years to 6% among women over 70 years of age (Figure 3). Of the 1,114 women with HER2-positive breast cancer who received adjuvant chemotherapy, 1,058 (94%) patients did receive trastuzumab as well. Only 6% (66 patients) did not receive trastuzumab; this percentage increased with age from 4% in women younger than 40 years to 11% in women aged 60-69 and varied between 3% and 16% between the CCC regions. Adjusted for age and stage there was a significant difference between CCC regions ( $p = 0.004$ ). The Odds Ratios for the CCC regions ranged from 0.17 to 0.97 compared to the reference region.

### *Implementation of trastuzumab*

At the time the recommendation for the use of trastuzumab was included in the national guideline (September 2005), 10% of the women with HER2 overexpression receiving adjuvant chemotherapy did not receive trastuzumab. This percentage decreased to 4% in the last study period (September-December 2006) (Figure 4,  $p < 0.001$ ). In the period May 2006 – December 2006 the variation between the regions in the proportion of patients receiving trastuzumab had disappeared, after adjusting for age and stage ( $p = 0.901$ ). The Odds Ratios for the CCC regions ranged from 0.32 to 1.56 compared to the reference region.

### *Reasons to withhold trastuzumab*

The most frequently reported reasons for doctors not to give trastuzumab were a history of cardiovascular disease, patient refusal and older age. In 36% no reason to withhold trastuzumab was reported in the patient files (Table 2).

## Discussion

Of women with HER2-positive breast cancer who received adjuvant chemotherapy, 94% actually received trastuzumab. For 64% of the women who did not receive trastuzumab, a legitimate reason was reported in the patient files. Keeping in mind that the guideline had only been made public in September 2005 and that the time period immediately after its release was also included in this study, we may conclude that the level and the speed of the implementation of trastuzumab in clinical practice was very satisfactory. The time needed to implement the new guideline in clinical practice varied between CCC regions, but within 8 months the differences between CCC regions had disappeared. These differences in time can partly be explained by different dates of meetings of the multidisciplinary working groups and consultancy services (on local, regional and national level).

In this study, population-based data from the NCR, covering the whole of the Netherlands were used. Of all included women with primary breast cancer, 13% was diagnosed with HER2-positive cancer. In a meta analysis by Dendukuri et al.[5] about 16% of primary breast cancers was HER2-positive, which is comparable to the percentage found in this study. Other studies have shown a percentage of around 25% [3,4,12]. However, those were studies performed in the initial period of HER2 testing, or studies with selected groups of patients, e.g. only including metastatic breast cancer or hormone receptor negative patients. At present, the most widely accepted and well established algorithm to determine HER2 status is to start with IHC, followed by FISH when IHC proves to be inconclusive. HER2 testing was introduced in Dutch reference pathology laboratories before this guideline was issued, as trastuzumab was already common practice for the treatment of metastatic breast cancer. However, in the beginning the quality of HER2 testing varied between laboratories. A number of variables (e.g. tissue handling and fixation) can affect the accuracy of the results and comparative studies were published about the discordance rates between laboratories and tests [10,11,13,14]. The pathologists realised that differences in determining HER2 status existed and updated guidelines for HER2 testing were added to the national guideline [8]. Viewing the results of our study in this light, part of the differences between CCC regions could be explained by the differences in pathology laboratories.

IHC and/or FISH-tests are somewhat less often performed in the older patients. The guideline is clear about the conjunction of trastuzumab with chemotherapy in women under 70 [8]. For women above the age of 70 the guideline does not give standard advice for adjuvant chemotherapy due to insufficient data. For these women other factors (e.g. hormone sensitivity, co-morbidity and frailty) play an important role in supplying chemotherapy (and trastuzumab). Therefore, determining HER2 status is of limited relevance in this age group.

Because this study investigated the timelines and the rate of implementation of the new guideline for the use of trastuzumab, patients with metastases or receiving neo-adjuvant chemotherapy were excluded. The use of trastuzumab is coded when treatment with trastuzumab started, but no information was gathered about its duration or if it was temporary interrupted, e.g. for cardiotoxicity. However, the aim of the current study was to study the proportion of patients starting with trastuzumab. Any premature termination of treatment for cardiotoxicity or other reasons and its impact on morbidity, recurrence and survival should be part of another study.

This study is unique because of the setting in which it has been performed. The collaboration between the National Breast Cancer Organization of The Netherlands (NABON), the CCCs and the NCR has resulted in a quality system in which the development, implementation, monitoring and evaluation of the guideline is covered as a whole. This study proves that new tumour characteristics and treatments can be registered by the NCR within reasonable time. The registry clerks of all CCCs use the same strict definitions and coding rules, which enhances the quality of the data and thus the reliability of the results.

In conclusion, our study shows that of all Dutch women with non-metastatic invasive breast cancer, 13% has HER2 overexpression and this percentage markedly decreases with age. Of the women with HER2-positive breast cancer who received adjuvant chemotherapy, 94% actually received trastuzumab. The implementation of trastuzumab in clinical practice was realized within 8 months after introduction of the new guideline. This study shows that a population-based cancer registry can be of great value when evaluating the implementation of new treatment policies.

#### **Conflict of interest statement**

None declared.

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**Table 1** - Patient characteristics

All patients (n=14,934)		N	%
Age	median	60	
	range	21-101	
	<40	785	5
	40-49	2,806	19
	50-59	4,006	27
	60-69	3,599	24
	70-79	2,448	16
	80+	1,290	9
HER2 status (IHC and/or FISH)	negative	11,574	77
	IHC 2+	486	3
	positive	1,928	13
	unknown	946	6
HER2 positive patients (n=1,928) (IHC and or FISH)			
Chemotherapy	no	814	42
	yes	1,114	58
Trastuzumab	no	871	45
	yes	1,057	55

**Table 2** - Reasons for withholding trastuzumab (n=66)

	N	%
Cardio toxicity	19	29
Patient refusal	14	21
Age	7	11
Other	2	3
No reason given (for withholding)	24	36

**Fig. 1** Percentage of patients with a HER2-positive tumour, by age, in the period September 2005 - December 2006.

The vertical lines show the range between CCC regions.

**Fig. 2** Percentage of patients with a HER2 status unknown or not tested, by age, in the period September 2005 -

December 2006. The vertical lines show the range between CCC regions.

**Fig. 3** Percentage of patients with HER2-positive breast cancer receiving chemotherapy.

**Fig. 4** Percentage of patients with HER2-positive tumours and adjuvant chemotherapy, receiving trastuzumab, by period. The symbols represent the different CCC regions.





