Cardiac monitoring during adjuvant trastuzumab therapy: Guideline adherence in clinical practice

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ABSTRACT

Background. Cardiotoxicity is an important adverse effect of adjuvant breast cancer treatment with trastuzumab and three monthly left ventricular ejection fraction (LVEF) monitoring is considered mandatory. The purpose of this study was to gain insight into LVEF monitoring during adjuvant trastuzumab treatment in clinical practice.

Material and methods. In a multicenter retrospective study encompassing 328 patients, of which 171 patients were actually treated with trastuzumab, we analyzed the frequency and mode of LVEF monitoring and compared it with LVEF monitoring guidelines.

Results. The results indicated poor guideline adherence. In 9% of patients trastuzumab was started in spite of a low LVEF (<55%). In 24% of patients no valid baseline LVEF value was available. LVEF measurements during treatment at three, six and 12 months were only performed in, respectively, 53%, 40% and 30% of patients.

Conclusion. A significant proportion of patients are treated with trastuzumab, while LVEF monitoring is not adequately performed. More attention should be paid to the implementation of (cardiac assessment) guidelines in clinical practice.

In approximately 15–25% of breast tumors the human epidermal growth factor receptor 2 (HER2) gene is amplified, over expressed, or both, which results in a poor prognosis [1]. During the past two decades the HER2 targeting antibody trastuzumab has become available for treatment of HER2 positive breast cancer [2]. Four large phase III adjuvant trials, including the Herceptin Adjuvant (HERA) study, have investigated the efficacy and safety of trastuzumab in combination with or after standard adjuvant chemotherapy. All four studies have shown a significant increased survival and a decreased recurrence risk [3–6]. However, trastuzumab treatment is also associated with side effects, most predominantly cardiac dysfunction. Studies evaluating adjuvant trastuzumab showed an asymptotically decreased left ventricular ejection fraction (LVEF) in 2–23% of patients [7–9]. In most cases (97%) the LVEF increased after (temporarily) discontinuation of trastuzumab treatment, spontaneously or through medical treatment [10]. Trastuzumab-related cardiac dysfunctioning is not dose-related or associated with histological changes and is usually transient and reversible [10,11]. The NSABP B-31 trial showed a recovered LVEF of ≥50% in
most patients during follow-up [12]. However, other follow-up studies showed a persistent decrease in LVEF or only a partial recovery [9,10,13–15]. Cardiotoxicity mainly occurs during the first three months of adjuvant trastuzumab treatment [8]. Additional risk factors are age, an LVEF of 50–54% at baseline, diabetes, hypertension, anthracycline treatment and radiotherapy [8,16].

Twenty percent of premature trastuzumab discontinuations can be attributed to cardiotoxicity [7–9]. Although trastuzumab cardiotoxicity occurs quite frequently, its clinical impact after discontinuation of treatment is modest [8]. The risk of unnecessary early discontinuation of treatment in patients with suspected cardiotoxicity should be minimized. However, continuation of treatment in patients with cardiotoxicity may in some patients result in more serious symptomatic heart failure. Consistent LVEF measures before, during and after trastuzumab treatment are necessary in each patient as the exact underlying mechanisms are not known and cardiotoxicity prediction models and cardiac prognosis of long-term survivors are still being studied [17].

In 2008 the Dutch guideline breast cancer included guidelines concerning LVEF monitoring during adjuvant trastuzumab treatment. This guideline states that the LVEF should be measured before start of trastuzumab (baseline) and every three months until the end of treatment. The baseline LVEF value should be at least 55%. A decline of ≥10% from baseline or an LVEF value below 50% requires a temporary discontinuation of trastuzumab [18]. If the LVEF value (partly) recovers (>50%), after repeated LVEF measurements within three weeks, trastuzumab can be resumed [19]. According to the trastuzumab drug label, which is equal to recommendations in the HERA protocol, also follow-up measures should be included at six and 12 months after completion [19,20].

Although many studies have underlined the importance of monitoring LVEF during trastuzumab treatment, little is known about the implementation of LVEF measurements and adherence to these guidelines in clinical practice. To the best of our knowledge, only a few studies measured cardiac monitoring in the course of trastuzumab treatment. One was conducted in the US, during adjuvant trastuzumab treatment [21] and one Australian study focussed on cardiac monitoring during treatment of metastatic breast cancer [22].

In this study we retrospectively analyzed the monitoring process and the role of cardiac function during trastuzumab treatment in one university hospital and two teaching hospitals.

**Methods**

**Data collection**

All female patients diagnosed with a HER2 positive breast tumor between 2006 and 2011 in the three hospitals were selected from the population-based Netherlands Cancer Registry (NCR) managed by the Comprehensive Cancer Centre. In total 328 patients were included in this database. Over 50% (N = 171) of the patients had actually been treated with (neo)adjuvant chemotherapy and trastuzumab in one of the three hospitals.

Information concerning date of diagnosis, tumor grade and stage was retrieved from the NCR. Information on patient characteristics, type of surgical procedure, radiotherapy regimen, hormonal therapy, chemotherapy regimen and trastuzumab were extracted from medical records. Any deviations from treatment guidelines in doses or time between cycles were recorded. Also, frequency, mode and outcome of LVEF measurements were recorded. An LVEF test was considered to be a baseline measure when it was performed within 24 days prior to the first trastuzumab dose. If patients did not receive trastuzumab treatment, reasons were noted and categorized (Figure 1). LVEF measurements were primarily compared with the Dutch guidelines breast cancer 2008 and additionally with the HERA study measurement guidelines [15,18,19]. The HERA guidelines are also taken into account since a significant part of our study population was treated before the implementation of the national guidelines from 2008. Comorbidity was scored according to the Klabunde adaption of the Charlson index [23]. All collected data were anonymized and analyzed using SPSS 20.0. The study has been carried out in the Netherlands in accordance with the applicable rules concerning the review of research ethics committees.

**Analyses**

Descriptive analyses were performed to provide insight in patient characteristics, tumor characteristics, and adjuvant treatment. Imbalance for these factors between patients who did and patients who did not receive trastuzumab was tested by means of T-tests and χ²-tests.

Adherence to HERA protocol LVEF measurements was analyzed by the use of descriptive statics. LVEF measurement intervals and consequences of low LVEF values for trastuzumab treatment were described. Logistic regression analysis was performed to evaluate the effect of age and comorbidity on trastuzumab treatment among eligible patients. Using a similar test, we analyzed the effect of age and
comorbidity on discontinuation of trastuzumab treatment caused by a decreased LVEF.

Results

Description of the study population

Two hundred and fifteen of 328 included patients were eligible for treatment with (neo) adjuvant trastuzumab according to tumor and age criteria of the Dutch guideline breast cancer 2008 (Supplementary Table I, available online at: http://informahealthcare.com/doi/abs/10.3109/0284186X.2015.1068444) [18]. This guideline is to be taken up by all participating hospitals. Only motivated deviation from this guideline is permitted. One hundred and thirteen patients were not eligible for (neo)adjuvant trastuzumab treatment, majorly caused by primary tumor characteristics (n = 52) or age (n = 61). Among patients eligible for trastuzumab treatment, based on age and tumor criteria, 44 did not receive adjuvant trastuzumab because of several other reasons (Figure 1). An overview of the patient, tumor and treatment characteristics of both groups is shown in Supplementary Table II (available online at: http://informahealthcare.com/doi/abs/10.3109/0284186X.2015.1068444). Among the eligible patients, patients receiving trastuzumab were significantly younger (p < 0.001) and had a lower adapted Charlson comorbidity score (p = 0.01) compared to patients not receiving trastuzumab.

Methods of LVEF measures

In 81 patients all LVEF measurements were performed by a multiple-gated acquisition (MUGA) scan, ultrasounds were done in 63 patients and in 21 patients both procedures were performed alternating.

Start of trastuzumab treatment and related LVEF measures

In 79 patients (46%) the LVEF was measured before the start of chemotherapy (mean = 20.7 ± 21.0 days). In 130 patients (76.0%) an LVEF measurement was performed before trastuzumab therapy initiation (maximum 24 days in advance) (Table I).

In 15 patients (8.8%) trastuzumab treatment was started in spite of an LVEF value below 55% (LVEF mean = 51.7 ± 5.1). Three patients (1.8%) faced a delayed starting time due to a low LVEF. For the same reason seven patients never started trastuzumab treatment (LVEF mean = 45 ± 4.2).

LVEF during trastuzumab treatment

When looking at all measures during treatment, most patients underwent at least one (91.2%) or two (85.4%) LVEF measurements, irrespective of timing of these measurements. The proportion of patients receiving at least four measurements is 63.2%. In Table I these measurements are compared with the
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recommended time schedule of LVEF measurements from the Dutch guideline breast cancer and the HERA protocol (follow-up). Approximately 53% underwent LVEF measurement three months after treatment initiation. After six months LVEF measurement was limited to 40% of patients. For nine and 12 months the percentages were 32% and 30%, consecutively.

In 171 patients treated with trastuzumab a total of 991 LVEF measurements were performed. 514 of these measurements were performed during trastuzumab treatment, of which 9.3% (in 40 patients) showed an LVEF value $\leq 50\%$.

Trastuzumab treatment was interrupted in 24 patients, because of a low LVEF (mean $= 44.6 \pm 7.2$). In three patients the LVEF value showed only a small decrease (<10%) from baseline. In case of a low LVEF, the measurement was repeated in 95.8% of patients. Only 8.7% of these repeated measurements were performed within three weeks. Treatment was resumed in 18 patients at an average recovered LVEF level of 56.8 ± 4.4. In 7.0% (n = 12) trastuzumab treatment was discontinued early due to a low LVEF (mean = 43.1 ± 6.4).

Besides interrupted treatments and additional LVEF measures, other low LVEF outcomes during treatment were followed by no specific actions (n = 9) (LVEF mean = 44.6 ± 6.9), referral to a cardiologist (n = 5) (LVEF mean = 36.2 ± 8.2) or prescription of ACE-inhibitors (n = 2) (LVEF mean = 44.5 ± 3.5). Furthermore, pre-existing comorbidity and side effects from chemotherapy contributed to the decision to withhold treatment in three patients.

Follow-up measures of LVEF after end of treatment

Taking into account all LVEF measurements after completion of treatment, 70 patients (40.9%) had at least one follow-up measurement, irrespective of timing of these measurements. Follow-up measurements at six and 12 months after end of treatment, as recommend only in the HERA protocol, were performed in 8.8% and 0.6% of the patients (Table I).

Effect of age and comorbidity on outcomes

Results from logistic regression analyses indicate that older patients [OR 0.95; 95% confidence interval (CI) 0.91–0.99; p = 0.01] and patients with higher adapted Charlson scores (OR 0.72; 95% CI 0.56–0.91; p = 0.01) are treated less frequently with trastuzumab. Besides, trastuzumab treatment in older patients is discontinued more often caused by a low LVEF compared to younger patients (OR 1.04; 95% CI 1.00–1.08; p = 0.04), while adapted Charlson scores did not significantly affect discontinuation caused by a low LVEF (OR 0.90; 95% CI 0.61–1.31; p = 0.57).

Discussion

Our study is the first in Europe to provide insight into actual LVEF monitoring throughout adjuvant trastuzumab treatment in daily clinical practice. We have chosen to compare daily practice with the recommended measures from the Dutch guideline breast cancer. Guideline adherence concerning LVEF testing could be improved regarding three different issues: methods used for LVEF testing, timing of the LVEF measures, and actions taken after a low LVEF measurement.

Recommended methods for LVEF measurements are MUGA scans or ultrasounds. As the variation between these techniques is usually large, the methods are not interchangeable [24]. Nevertheless, in this study a proportion of patients both methods were interchanged.

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Table I. Adherence to timing of LVEF monitoring criteria from Dutch guideline breast cancer 2008 and HERA treatment protocol during and after trastuzumab treatment.

| Time between start trastuzumab and LVEF (months) | Patients to receive/receiving trastuzumab | Patients (%) undergoing LVEF assessment according to timing criteria from HERA protocol |
|-------------------------------------------------|------------------------------------------|--------------------------------------------------------------------------------------|
| Before trastuzumab                              | 171                                      | 76.0                                                                                 |
| During trastuzumab$^{\text{a,b}}$                | 161                                      | 52.8                                                                                 |
| 3                                               | 156                                      | 39.7                                                                                 |
| 6                                               | 144                                      | 31.9                                                                                 |
| 9                                               | 50                                       | 30.0                                                                                 |
| 12                                              |                                          |                                                                                     |

| Time between end trastuzumab and LVEF (months) | Patients having received trastuzumab | Patients (%) undergoing LVEF assessment according to timing criteria from HERA protocol |
|-------------------------------------------------|-------------------------------------|--------------------------------------------------------------------------------------|
| After trastuzumab$^\text{b}$                    | 171                                 | 8.8                                                                                  |
| 6                                               | 171                                 | 0.6                                                                                  |
| 12                                              |                                      |                                                                                     |

$^\text{a}$According to the Dutch guideline breast cancer 2008; $^\text{b}$According to the HERA treatment protocol.
Our results showed that most women on trastuzumab treatment underwent at least 1–3 LVEF measurements. However, when taking into account the timing of these measures in relation to the trastuzumab regimen, the results were rather disappointing. Also baseline LVEF values were lacking in many patients. Protocols from the large clinical trials and the Dutch guidelines suggested variable testing intervals [3,5,6,18–20]. However, baseline measures between the end of conventional chemotherapy and the start of trastuzumab therapy are essential, since subsequent measurement results should be compared with these baseline values. It should be noticed that in a minority of these patients the LVEF was measured a few days after start of therapy, which was probably used as baseline measure.

As cardiotoxicity mainly occurs during the first three months of therapy [8], the LVEF measure after three months is of great importance. Nevertheless, in half of the patients this measure was not performed as recommended by the Dutch guidelines. Our findings were in line with a similar study performed in the US which also found low adherence rates to guidelines concerning the timing of LVEF measures at the start and during adjuvant trastuzumab treatment [21].

Low adherence numbers for further follow-up measures can partly be explained by the implementation of the Dutch guidelines in 2008, in which the follow-up measures were not included any longer. However a significant part of our study population was treated before 2008. In that period (2006–2011) less was known about the reversibility of cardiotoxicity, which suggests an even larger importance for guideline adherence.

A low LVEF level at baseline, as present in a proportion of this study population, is considered to be a risk factor for trastuzumab-related cardiotoxicity. We should note that the baseline value in the 2012 version of the Dutch guidelines has been lowered to 50%. Since patients in our study received trastuzumab treatment between 2006 and 2011 and the 2008 guidelines were applicable for most patients.

Besides continuing treatment in case of low LVEF results during the course of treatment, in other patients treatment was probably unnecessarily withheld from patients. Also notable is that in 5% of all patients no specific follow-up steps were taken after a low LVEF measure and trastuzumab therapy simply continued, even without extra monitoring of LVEF.

Clinicians often have to balance the well reported benefits of trastuzumab treatment against the cardiotoxic side effects of this treatment. Recent results questioning the reversibility of trastuzumab-related cardiotoxicity underscored the relevance of clinical guidelines regarding LVEF measures [14,16]. Guidelines are implemented to support clinicians in clinical decision making and the content of these guidelines reflect the best available knowledge at that moment. Certainly, guidelines are dynamic and are constantly being improved. Also the Dutch guidelines have been revised in 2012, leading to less restrictive LVEF starting levels based on progressive insight. This means that majority of patients who were treated with trastuzumab in conflict with the 2008 guidelines, were actually treated in line with the 2012 guidelines. In retrospect, we can conclude that patient safety was not an issue in these patients. However, non-adherence to guidelines of other newly implemented therapies can have more serious consequences.

Support from clinicians working with these guidelines, is essential for adherence. We may question the usefulness of strict guidelines which are not supported or acknowledged by a significant part of the clinicians. Therefore, future research should focus on reasons for non-adherence to clinical guidelines and on long-term consequences of non-adherence.

This study has several limitations. Due to the retrospective design of the study, the data collection was dependent on the registration in patient medical records, which might have been incomplete. For example, information regarding LVEF measurements was partly missing for some patients, which might have caused an underestimation of the actual performed measures. Also adequate registration of medical information is an important quality indicator of health care. Baseline characteristics on cardiovascular risk factors and cardiovascular clinical history were missing, while these factors could have influenced the development of cardiotoxicity during trastuzumab treatment. Information about the frequency of hospital admissions caused by heart failure after end of trastuzumab treatment were neither measured, because the time between end of treatment and data collection of this study was too short. However, it could be argued that the retrospective design would represent the compliance in daily practice more than a prospective one, in which the pre-existing awareness might overestimate the real awareness and the real adherence. Also, generalizability of results from this study may be limited by the fact that only three hospitals participated in the study. However, academic as well as general hospitals were included.
Conclusion

The results of this study indicated that the cardiac function during adjuvant trastuzumab is not routinely measured according to the national guidelines. Consequently, a significant part of patients received trastuzumab, while probably being exposed to an additional risk for cardiac failure. However, treatment appears to be withheld from a few patients in spite of adequate LVEF recovery. Based on progressive insights, we can conclude retrospectively that patients’ safety was not an issue. The effects of non-adherence to (LVEF monitoring) guidelines on clinical outcomes need attention in future studies. Most clinicians seemed to agree that some testing is required, since a majority of patients had at least a few measurements. However, the testing frequency, the intervals and the consequences of a low testing result are not as obvious in clinical practice as described in national guidelines. To improve cardiac monitoring during adjuvant trastuzumab, more attention is needed for the implementation of (cardiac assessment) guidelines in clinical practice.

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Supplementary material available online
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