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The acute effect of trastuzumab infusion on ECG parameters in metastatic breast cancer patients

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Summary

Objectives: Although trastuzumab therapy is known to be associated with congestive heart failure, its arrhythmogenic potential has not been studied in detail. The purpose of this study was to determine the acute influence of trastuzumab infusion on electrocardiogram (ECG) parameters in patients with metastatic breast cancer.

Patients and methods: Twenty patients with HER2 overexpressing metastatic breast cancer and normal cardiac function were enrolled in this single-centre prospective study. Standard 12-lead ECG recordings were performed at baseline and after trastuzumab infusion (2 mg/kg given over 30 min). P-wave durations, QT and RR intervals were measured and QT dispersion (QTd) and P-wave dispersion (Pd) were calculated.

Results: In comparison with baseline, no statistically significant change in any ECG parameters, including QT and RR intervals, P wave durations, Pd and QTd, was observed after infusion of trastuzumab.

Conclusion: In this study, no abnormality of atrial and ventricular depolarisation and repolarisation, indicated by Pd and QTd, was detected after infusion of trastuzumab. As Pd and QTd are both known to be associated with increased risk of serious arrhythmias and sudden death, it would appear that trastuzumab has no acute arrhythmogenic potential related to cardiac depolarisation and repolarisation.

Key words: herceptin; cardiotoxicity; arrhythmia

Introduction

Human epidermal growth factor receptor-2 (HER2) is a member of the epidermal growth factor receptor family regulating cell growth and proliferation [1]. The HER2 gene is amplified or the receptor protein is strongly overexpressed in approximately 15–25% of breast cancer cases [2, 3]. HER2 amplification/overexpression is associated with a poor prognosis, and is also predictive of response to hormonal therapy [4] and chemotherapy [5, 6]. Trastuzumab is a humanised murine monoclonal antibody against the extracellular domain of HER2 [7]. It is currently approved, in both the metastatic and the adjuvant setting, for breast cancer patients overexpressing HER2. It is used alone or in combination with standard chemotherapy [7].

The clinically most important side effect of herceptin is cardiotoxicity, which is reported in 2.6–4.5% of patients receiving trastuzumab alone and in as many as 27% of patients when trastuzumab is combined with an anthracycline in metastatic disease [8]. Cardiotoxicity may be manifested as asymptomatic decreases in left ventricular ejection fraction (LVEF) or symptomatic congestive heart failure (CHF) [9, 10]. The pathophysiology of this effect, which differs from the cardiotoxicity of anthracyclines, is still poorly understood [11].

To date the arrhythmogenic potential of trastuzumab has not been sufficiently investigated. The aim of the study was to determine the influence of trastuzumab infusion on ECG parameters in metastatic breast cancer patients. To the best of our knowledge this is the first clinical study to evaluate the effect of trastuzumab on ECG parameters related to cardiac repolarisation and depolarisation.

Material and methods

Study population

Twenty consecutive metastatic breast cancer patients with HER2 overexpressing tumours who had normal pretreatment cardiac physical, ECG and echocardiography findings were enrolled in this study. Patients with a history of and/or documented coronary artery disease, valvular or congenital heart diseases, congestive heart failure, cardiac rhythm disorders, and co-morbid diseases including uncon-

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trolled diabetes mellitus, hypertension and thyroid diseases, were excluded from this study. Ethics committee approval was obtained for the study.

HER2 status was assessed by immunohistochemical analysis (IHC) or by fluorescent in situ hybridisation (FISH) on fixed, paraffin-embedded tissues. A positive HER2 result was defined as IHC staining of 3+ or HER2 gene amplification in FISH. FISH was routinely performed if IHC staining was 2+.

Study protocol

Patients received trastuzumab alone or in combination with various types of chemotherapy. They were given a loading dose of 4 mg/kg intravenously, followed by a 2 mg/kg maintenance dose at weekly intervals. The study was done while patients were receiving trastuzumab alone and at the maintenance dose (2 mg/kg). Prior to trastuzumab infusion all patients were evaluated by clinical examination and vital signs including blood pressure and pulse. ECG recording was performed before and after trastuzumab infusion.

After a 20-min resting period in supine position all subjects underwent a 12-lead ECG recording at a paper speed of 50 mm/s and 2 mV/cm. All recordings were performed in the same quiet room during spontaneous breathing, following 10 minutes of adjustment in supine position. The ECGs were numbered and presented to the analysing investigator without name and date information.

P-wave duration, QT and RR intervals were measured. P-wave dispersion (Pd) and QT dispersion (QTd) were calculated. Mean differences between baseline and follow-up ECG parameters were compared.

The onset of the P wave was defined as the point of first visible upward slope from baseline for positive waveforms and as the point of first downward slope from baseline for negative waveforms. The return to the baseline was considered the end of the P wave. The maximum P wave duration (P max) measured in any of the 12 leads was used as the longest atrial conduction time. Pd was defined as the difference between the P max and the minimum P wave duration (P min).

QT interval was defined as the interval from the beginning of the QRS complex to the end of the T wave. QTd was defined as the difference between the maximum and minimum QT values.

Statistical analysis

All calculations were carried out with SPSS program (version 13.0, SPSS, Chicago, Illinois, USA). All data were presented as median and interquartile range (25–75%). Statistical comparison of quantitative data was by Wilcoxon test. P value of <0.05 was considered to be statistically significant.

Results

The median age of the 20 patients was 57.5 years (range: 35–70). All patients had already received anthracyline-based chemotherapy.

There were no significant differences in pre- and post-infusion values for systolic blood presure, diastolic blood pressure and heart rates (table 1). In comparison with baseline, there was no statistically significant change in any ECG parameters, including QT and RR intervals, P wave durations, Pd and QTd, after infusion of trastuzumab (table 2).

Discussion

The 12-lead ECG is the standard safety measurement used in clinical trials to identify drug-induced cardiac adverse effects [12]. In general, Pd, QT-interval prolongation and QT dispersion, which are accurate predictors of the effect of drugs on cardiac repolarisation, are used for measuring the arrhythmogenic potential of a drug [13]. The correlation with increased dispersion of myocardial repolarisation and depolarisation and the genesis of cardiac arrhythmia has been extensively studied.

Table 1

Clinical parameters before and after trastuzumab infusion*.

	Before trastuzumab (n = 20) Median IQR (25–75%)	After trastuzumab (n = 20) Median IQR (25–75%)	P value	95% CI of the difference Mean
HR (beats/min)	96 (80–106.75)	96.5 (83–107)	0.397	–1.6 (–6.62; 3.42)
SBP (mm Hg)	130 (120–140)	125 (120–140)	0.66	1.0 (–3.78; 5.78)
DBP (mm Hg)	80 (70–80)	80 (72.5–80)	0.18	–1.5 (–3.8; 0.80)

* HR: heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure.

Table 2

ECG parameters before and after trastuzumab infusion*.

ms	Before trastuzumab (n = 20) Median IQR (25–75%)	After trastuzumab (n = 20) Median IQR (25–75%)	P value	95% CI of the difference Mean
P max	105 (95–118.75)	105 (96.25–110)	0.440	1.25 (–5.28; 7.78)
P min	65 (56.25–70)	60 (60–68.75)	0.222	2.25 (–1.88; 6.35)
P dispersion	40 (30–45)	40 (30–50)	0.819	–0.75 (–8.00; 6.50)
QT max	365 (340–400)	375 (352.5–383.75)	0.402	–4.00 (–3.65; 5.65)
QT min	305 (290–338.75)	317.5 (296.25–327.5)	0.600	–4.50 (–6.76; 7.76)
QT dispersion	52.5 (40–63.75)	50 (42.5–65)	0.835	–0.50 (–7.49; 6.49)
RR interval	620 (540–747.5)	645 (542.5–710)	0.575	11.75 (–22.28; 45.78)

* ms: millisecond; P max: maximum P wave duration; P min: minimum P wave duration; P dispersion: (P max – P min); QT max: maximum QT interval; QT min: minimal QT interval; QT dispersion: (QT max – QT min).

The QT interval represents the period of global ventricular depolarisation and subsequent repolarisation [14]. Prolongation of the QT interval due to inherited ion channel abnormalities or due to drugs or metabolic abnormalities has been associated with an increased incidence of ventricular arrhythmias [15]. In addition, experimental studies have demonstrated that regional differences in repolarisation facilitate reentry and development of ventricular arrhythmias. QTd has been shown to provide an indirect measure of the inhomogeneity of myocardial repolarisation and is known to be associated with an increased risk of serious ventricular arrhythmias and sudden death [16, 17]. Reported values of QT dispersion vary widely, ranging from 10 to 71 ms in normal subjects.

Pd and P max have been used to evaluate the discontinuous propagation of sinus impulses and the prolongation of atrial conduction time respectively [18]. In other words, dispersion of P wave has been used to evaluate the heterogeneity of atrial repolarisation [18, 19]. Prolonged P-wave duration and Pd have been reported as representing increased risk for atrial fibrillation (AF) [20].

With more efficient therapeutic options, the long-term prognosis of many cancer patients has improved dramatically. In consequence, toxicities of chemotherapy such as cardiac dysfunction and arrhythmias assume prognostic importance. Trastuzumab is now standard therapy, either alone or in combination with chemotherapy, in breast cancer patients overexpressing HER2, both in the adjuvant and metastatic setting [21]. However, its use is limited by cardiotoxicity. Trastuzumab-induced cardiotoxicity mainly affects the mechanical function of the heart. Cardiomyopathy, or a decrease in LVEF (>10%) has been shown to be 3–7% with trastuzumab alone, 13% with concurrent paclitaxel, and 27% with concurrent anthracyclines [22]. However, there are no data on the effect of trastuzumab on cardiac electrophysiology.

The results of this study showed that trastuzumab infusion was not associated with a significant difference in ECG parameters, including QT interval, QTd and Pd, which are commonly used to predict supraventricular and ventricular arrhythmia. However, this study is subject to a number of limitations: although it shows that trastuzumab has no acute arrhythmogenic effect in relation to cardiac depolarisation and repolarisation, it does not rule out the potential for arrhythmia of prolonged use after reaching a certain cumulative dose. Moreover, the results are limited by small sample size and require confirmation from larger studies with a longer follow-up.

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