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CASE REPORT/OLGU SUNUMU

RECURRENT SUPRAVENTRICULAR TACHYCARDIA ASSOCIATED WITH LAPATINIB: A CASE REPORT OF A PROBABLE CARDIAC ADVERSE EFFECT

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LAPATİNİB İLE İLİŞKİLİ TEKRARLAYICI SUPRAVENTRİKÜLER TAŞİKARDİ: OLASI KARDİYAK YAN ETKİ BİLDİRİMİ

ÖZET

Kanser tedavisinde kullanılan ilaçlar ile ilişkili kardiyak toksisite nadir görülür fakat önemli bir mortalite nedenidir. En sık görülen kardiyak toksisite miyokardiyal hücre hasarıdır ve özellikle antrasiklin ile oluşan sol ventrikül ejeksiyon fraksiyonundaki azalma irreversibl olarak konjestif kalp yetersizliğine ilerler. Halbuki, trastuzumab ile ortaya çıkan kardiyotoksisitede miyozitlerde kontraktilite disfonksiyonu oluşur ve hücre hasarı olmadığı için ejeksiyon fraksiyonunda reversibl olarak azalmaya neden olur. Trastuzumab ile ortaya çıkan bu kardiyak toksisite oldukça nadirdir ve benzer mekanizma ile daha da nadir olarak lapatinib kullanan hastalarda da gelişebilir. Buna rağmen, sol ventrikül disfonksiyonu olmaksızın ortaya çıkan kalp ritm bozukluğuna literatürde rastlanmamıştır. Biz bu yazıda, metastatik meme kanseri tanısı ile lapatinib tedavisi alan hastamızda ilk doz sonrasında gelişen ve elektrokardiyografi ile kanıtlanan supraventriküler taşikardi atağını sunmayı amaçladık. Öncesinde hipertansiyon, kardiyak hastalık öyküsü ve herhangi bir kardiyotoksisite bulgusu bulunmayan hastada sol ventrikül disfonksiyonu olmaksızın gelişen izole supraventriküler taşikardi atağı, literaturdeki kardiyotoksisite ile ilişkili bilgiler de kullanarak tartışılmak istenmiştir.

Anahtar sözcükler: lapatinib, trastuzumab, antiHer2 tedavi, kardiyotoksisite, aritmi, tirozin kinaz inhibitörleri

ABSTRACT

While cardiac toxicity due to chemotherapeutic agents is rare, it is a major cause of mortality. The most frequent cardiac toxicity is myocardial cell damage and particularly left ventricular ejection fraction reduction, which is due to anthracycline, progresses irreversibly to cardiac failure. However in trastuzumab associated cardiotoxicity, contractility dysfunction occurs in myocytes and the reduction of ejection fraction is reversible, since there is no cell damage. This cardiotoxicity which is due to transtuzumab is quite rare and although more rarely, it may also develop in patients using lapatinib through a similar mechanism. Nevertheless, cardiac arrhythmia without a left ventricular dysfunction is not reported in the literature. In this article, we aimed to present an electrocardiography confirmed supraventricular tachycardia attack which had developed after the first dose of lapatinib in a metastatic breast cancer patient. We want to discuss the development of an isolated supraventricular tachycardia, without a left ventricular dysfunction, in patients who do not have a history of hypertension, cardiac disease or any sign of cardiotoxicity, through using the cardiotoxicity related information in the literature.

Key words: lapatinib, trastuzumab, antiHer2 treatment, cardiotoxicity, arrhythmia, tyrosine kinase inhibitors

Introduction

Lapatinib is an oral tyrosine kinase inhibitor that effects both erbB1 (Her1, epidermal growth factor receptor) and erbB2 (Her-2) receptors (1,2). Clinical and preclinical studies showed that cardiac toxicities due to trastuzumab (anti- erbB2 inhibitor) and lapatinib had similar characteristics and cardiac signs were rare in patients treated with lapatinib (3,4). Trastuzumab related cardiac side effects occur frequently due to the contraction function loss of myocardial cells rather than a myocardial destruction (1, 5). This is called type 2 toxicity and it is commonly reversible. However, there are no result on the effect of trastuzumab and lapatinib on cardiac electrophysiology. Cardiac arrhythmias associated with bleomycin, etoposide, paclitaxel, interleukin-2, thalidomide is frequently observed as sinus bradycardia or atrioventricular block. It has been reported that, QT prolongation, Torsade de Point and lethal ventricular arrhythmias could occur in patients using arsenic trioxide (3). No serious and lethal cardiac arrhythmic side effects associated with lapatinib or any other tyrosine kinase inhibitors, except for asymptomatic QT prolongations, had been reported in the literature (6).

In this article, we aimed to present a patient who was diagnosed with a supraventricular tachycardia (SVT) attack in the first administration of lapatinib treatment because it was an example of a rare cardiac toxicity and reporting of adverse effects are important in determining the clinical approach.

Case report

A mass was detected in the right breast of a 40-year-old premenopausal patient during her routine mammographic screening in 2005. Histopathological study of the biopsy samples indicated invasive ductal carcinoma and the patient underwent a right modified radical mastectomy. The patient was referred to our department for adjuvant therapy after the surgery. The immunohistochemical study revealed positive cerbB2, negative estrogen receptor and 2%

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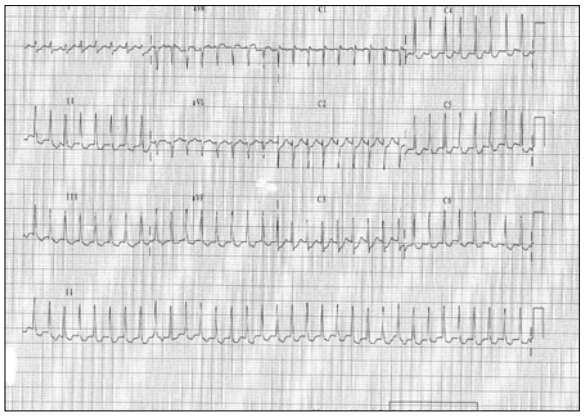

Figure 1. Supraventricular tachycardia (The ECG revealed that the heart rate was rhythmic with 197/min beats, QRS interval was <120 ms, RR and QT intervals were within the normal limits. No significant ST and T wave changes were observed).

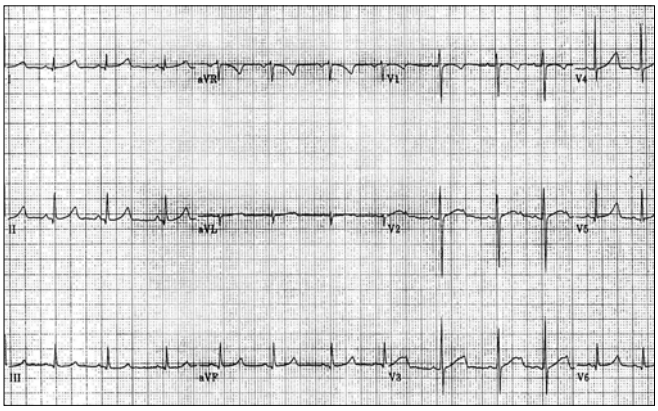

Figure 2. Normal rithym with QT dispersion (QTd=0.64 sn).

progesterone receptor in the patient who had 2 cm of tumor dimension and was node negative. The clinical and radiological evaluations did not reveal a metastatic lesion and four courses of adjuvant systematical treatment with epirubisin- cyclophosphamide was initiated which was followed by a hormone therapy with tamoxifen. Eighteen months after the first diagnosis, recurrent breast cancer and multiple metastatic nodules in both lungs were detected and a systemic treatment with trastuzumab + paclitaxel + carboplatin regimen was initiated. Following nine courses of the treatment a progression was not detected, and the treatment was maintained with only trastuzumab (345 mg/day in 21-day intervals). After 10 courses of this monotherapy, a lymph node metastasis developed in the right axillary region and a progression in the lung nodules was detected. Lapatinib (1250 mg / day) + capecitabine (1000 mg/m2) treatment was initiated. In the second day of the treatment, before the capecitabine intake, the patient was admitted to the emergency service with complaints of palpitation and weakness. The ECG revealed that the heart rate was rhythmic with 197/min beats, QRS interval was <120 ms, RR and QT intervals were within the normal limits. No significant ST and T wave changes were observed (Figure 1). Blood pressure was 90/60 mmHg and the body temperature was 36.4°C. The respiratory sounds were normal in both lungs and no cardiac murmur was detected. The patient was considered hemodynamically unstable and an episode of SVT was terminated with adenosine 6 mg by intravenous bolus injection. The echocardiography examination revealed that LVEF was 67%, cardiac wall movements were normal and pericardial fluid was not detected. The examinations and diagnostic tests did not indicate any cardiac (acute coronary syndrome, heart failure, pulmonary edema and pericardial effusion) or other symptoms associated with different etiological factors (fever, infection, anemia, thyrotoxicosis, hemorrhage, anxiety, and pulmonary embolism). There was no drug history other than fentanyl transdermal system 150 mcg/hr for day and tramadol retard tablets peroral 100 mg/day for pain control. The last 4 months, these doses were not changed. The patient had not used herbal therapy and other alternative medicine treatment. During the trastuzumab treatment, the cardiac assessments carried out once in every two months with echocardiography and ECG, did not indicate any cardiac toxicity, that was considered to be related with this drug (EF values before and after the lapatinib treatment were 67% and 65%, respectively). ECG was normal after the SVT episode. However, QT dispersion was found, but there was no P wave dispersion (Figure 2). Since the cardiac evaluation which was carried out after a couple of days did not reveal any pathology, lapatinib monotheraphy at a dose of 1000 mg/day was initiated. Following the second dose the patient was referred to the emergency service with palpitation and a feeling of syncope and her heart rate was as 192/min. Similar to her previous attack, the physical examination, ECG and laboratory findings of patient did not indicate any pathologic finding except the SVT. The SVT attack was considered to be associated with the lapatinib regimen and the treatment was stopped. In the second echocardiography, no change in the left ventricular ejection fraction (LVEF) values (EF 66%) was detected and the left ventricular wall movements were normal and no pericardial effusion was observed. Echocardiography and thoracic computed tomography did not have an image suggestive of metastasis. It was decided to stop the systemic treatment and monitor the patient with follow ups. The patient was followed starting with 50 mg of metoprolol per day. During the first month of follow up, the patient did not have any cardiac symptoms and her echocardiography and ECG were normal.

Discussion

Cardiac arrhythmias, due to chemotherapeutic agents are mostly asymptomatic and rare (3). To date the patophysiology of chemotherapeutic induced rhythm disorders by cytotoxic drugs remains to be clarified. The hypotheses are multiple and include direct and indirect pathways. Chemotherapeutic drugs can influence with sinoatrial conduction, but the pathophysiologic mechanism has yet to be determined (7).

SVT incidence is approximately 1- 3 cases per 1000 persons at normal population. However, it is also common in patients with ischemic heart disease, mitral valve prolapsed, rheumatic heart and valve diseases, pericarditis, pneumonia, pulmonary embolism, chronic lung disease, and alcohol consumption (8). Our patient had no previous history of symptomatic cardiac arrhythmias. Therefore, this episode was considered to be associated with lapatinib use.

The 12 lead ECG is the standard and safety measurement used in clinical trials to identify drug- related cardiac dysrhythmias (9). P

wave dispersion and Pmax value have been used to evaluate the discontinuous conduction of sinus impulses and the prolongation of atrial propagation time respectively. Therefore, P wave has been used to evaluate the heterogeneity of atrial continuous conduction and repolarisation (9). So P wave dispersion, QT dispersion and QT interval prolongation are usually used to show the effects of the drug association arrythmogenic potential. Prolonged P wave duration and P wave dispersion have been reported as representing increased risk for atrial fibrillation and other SVT types (9).

Due to the trastuzumab related cardiac toxicity, Perez et al. analyzed 18 phase I-III clinical trials and evaluated a total of 3558 patients who were treated with lapatinib (10). In ten of these trials, lapatinib was administrated as monotherapy and in eight of them lapatinib was administrated in combination with capecitabine, letrozole, paclitaxel, cisplatin or oxaliplatin / fluorouracil. In these 18 studies, among the 3558 patients, 2008 had breast cancer, while the rest 1550 had solid tumors other than breast cancer. It was reported that only 1.6% of the patients (58 of 3558) had LVEF reduction and most of those were asymptomatic (1.4 asymptomatic and 0.2% symptomatic). Concerning the LVEF, patients with or without breast cancer were similarly affected by the drug. It was noted that 598 patients had prior anthracycline treatment, 759 had anthracycline treatment after trastuzumab and 2201 patients received neither anthracycline nor trastuzumab treatment. In 588 patients, who had a prior anthracycline treatment but never received trastuzumab, LVEF reduction rate was 1.2% and 0.3% of those were reported as symptomatic. In 759 patients, who had received trastuzumab after anthracycline treatment, LVEF reduction rate was 1.7% and only 0.1% of those were reported as symptomatic. In 2201 patients who received neither trastuzumab nor anthracycline, the LVEF reduction rate was reported as 1.7% and 0.2% of those were asymptomatic (10). In the analysis conducted by Perez et al. it was reported that lapatinib associated symptomatic and asymptomatic LVEF reduction was very rare (1.4% and 0.2% respectively) (10). However, a predictive factor for LVEF reduction could not be determined (10). In this study, the low cardiotoxicity rate of lapatinib might be related to the heterogeneous characteristics of the patients and the longer time interval between the lapatinib and anthracycline treatments compared to the time interval between trastuzumab and anthracycline treatments. Therefore, it is necessary to maintain the analysis of clinical research results and to take into consideration even the rare side effects.

Cardiac metastases may lead to arrhythmia or myocardial infarction, cardiac tamponade, and congestive heart failure, which can manifest with dyspnea, cough, chest pain, or palpitation (11). Cardiac metastases are 20 to 40 times more common than primary tumors. Different studies have revealed an incidence of a 1, 6 to 20%. Lung cancer is responsibe for approximately 36% of cardiac metastases. Other malignancies that are most likely to spread to the heart are breast cancer, esophageal cancer, leukemia, lymphoma, and melanoma (11). Metastases to heart have to be distinguished from primary tumors like myxomas or from thrombi within the heart. Echocardiography allows for the rapid assessment of lesion location, size, and related hemodynamic changes. Additionally, magnetic resonance and computed tomography provide distinction between tumor, thrombus, or blood flow artifact (12). Our patient did not have cardiac metastasis.

However, arrhythmogenic effects of trastuzumab or lapatinib have not been clearly investigated. To the best of our knowledge there are few clinical studies to evaluate the effect of this agent on ECG related cardiac repolarization. When this drug to use, relevant measures should be taken with side effect was concluded.

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