Cardiotoxicity with adjuvant trastuzumab use in breast cancer: A single institution’s experience

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Abstract  Background: Trastuzumab use in Her-2-neu positive breast cancer patients is the current standard of care. Trastuzumab is known to result in cardiotoxicity. The toxicity seems to be dose-dependent, and serial cardiology assessment with echocardiography is advised. In spite of this, patients do develop cardiotoxicity and identification of patients at high risk and, if possible, any preventive means is of paramount importance.

Methods: We performed a retrospective analysis of medical records of all breast cancer patients presenting at King Khalid University Hospital from 02/2006 to 06/2009 and receiving adjuvant trastuzumab on the basis of either immunohistochemistry showing Her-2-neu (3+) or FISH positive Her-2-neu receptor status. Patients received adjuvant trastuzumab at an 8 mg/kg loading dose over 90 min, followed by 6 mg/kg every 3 weeks. A repeat multigated acquisition scan/echocardiogram was done after every 4 courses. Patient characteristics, such as age, menopausal status, tumor size, lymph nodal status, distant metastasis at presentation, grade of tumor, estrogen and progesterone receptor status, comorbid conditions (diabetes, hypertension, ischemic heart diseases), chemotherapy received, total dose of trastuzumab, timing of cardiotoxicity, and number of patients having cardiotoxicity, were recorded. A patient was said to have cardiotoxicity if the ejection fraction dropped by 10% of the original value or if there was a drop in the ejection fraction below the normal value.

Results: A total number of 98 breast cancer patient records were analyzed in this study. A total of 11 patients developed cardiotoxicity, evident by a drop in the ejection fraction on an echocardiogram. Seven patients out of 11 had a drop in ejection fraction below 10% of the baseline value,
1. Introduction

The human epidermal growth factor receptor 2 (Her-2-neu/erb-B-2) is expressed in the adult myocardium and plays an important role in the modulation of anthracycline-associated cardiotoxicity (Suter et al., 2007; Tripathy and Burstein, 1998; Guglin et al., 2008). Trastuzumab is an antibody against the Her-2-neu (c-erb-B-2) protein. This product has received considerable attention of late, based on its apparently modest toxicity and its efficacy in treating Her-2-expressing metastatic breast cancer. Several large multicenter trials have been conducted studying trastuzumab as either a single agent or in combination with chemotherapy. The toxicity profile of trastuzumab was also characterized. A common side effect included infusion reactions consisting of transient fever and chills, which occur in 25–30% of patients and are more likely to be seen with the first cycle of administration only. Other side effects include possible exacerbation of some chemotherapy-related side effects, including GI toxicity and myelosuppression. However, most attention has focused on the possible cardiac side effects of trastuzumab therapy, particularly in combination with chemotherapy (Montemurro et al., 2008). Cardiac dysfunction (CD) is defined as the onset of cardiac symptoms or an asymptomatic decrease in EF of 10% or more. The mechanisms for CD remain unclear. Trastuzumab benefits patients with metastatic breast cancer and improves disease-free and overall survival after adjuvant chemotherapy (Montemurro et al., 2008; Telli et al., 2007) and BCIRG 006 clinical overview. However, trastuzumab treatment is also associated with congestive heart failure and cardiac dysfunction. Patients receiving trastuzumab should undergo monitoring for deteriorating left ventricular function prior to trastuzumab treatment, and frequently during and after trastuzumab treatment. Discontinue trastuzumab for clinically significant decreases in left ventricular function (CHF). In patients with asymptomatic declines in LVEF, trastuzumab may be held and resumed up to 3 times. When trastuzumab is withheld, it may be resumed if, within 4–8 weeks, (1) the LVEF returns to normal limits and (2) the absolute decrease from baseline is <15% points. Trastuzumab should be permanently discontinued if (1) a persistent (>8 weeks) LVEF decline is observed or (2) trastuzumab dosing is withheld on more than 3 occasions for cardiomyopathy (Telli et al., 2007).

The objectives of this retrospective study were to evaluate cardiotoxicity with trastuzumab in breast cancer patients and to determine the long-term safety of this drug.

2. Methods

We performed a retrospective analysis of the medical records of all breast cancer patients presenting at King Khalid University Hospital from 1993 to 2008 and receiving trastuzumab (Herceptin, Genentech) on the basis of either immunohistochemistry showing Her-2-neu (3+) or FISH positive Her-2-neu receptor status. Patients characteristics, such as age, menopausal status, tumor size, lymph nodal status, distant metastasis at presentation, grade of tumor, estrogen and progesterone receptor status, comorbid conditions (diabetes, hypertension, and ischemic heart diseases), chemotherapy received, total dose of trastuzumab, timing of cardiotoxicity, and number of patients having cardiotoxicity, were recorded. Patients on trastuzumab therapy were evaluated before each course for subjective symptoms of heart failure and for objective examination to rule it out. A MUGA/echoangiogram was repeated after 4 courses of trastuzumab to look for a drop in the EF. A patient was said to have cardiotoxicity if the ejection fraction (EF) dropped by 10% of the original value or if there was a drop in the EF below the normal value 16.

3. Results

Total number of patients included were 98 age ranged between 20–80 years. 28% were diabetic, 33% were hypertensive and 24% had dyslipidemia. 58% of patients had their lesion on the right side. None of the patients had coronary artery disease at the start of therapy. Most patients had received doxorubicin-based chemotherapy either in the form of the TAC chemotherapy protocol (docetaxol, cyclophosphamide, F-FU) or the AC (doxorubicin, cyclophosphamide) chemotherapy protocol, followed by taxotere. Total cumulative dose of doxorubicin was calculated for each patient before starting trastuzumab therapy. Eighty-nine percent of patients received <300 mg/m^2 of doxorubicin before trastuzumab. Baseline multigated acquisition scan (MUGA)/echocardiogram showed EF within normal limits (Fig. 1).

It was observed that cardiotoxicity was dose-dependent as most of the patients had a drop in the EF after receiving a >60 mg/kg dose (after the 10th course of therapy), and none of the patients had idiosyncratic cardiotoxicity. Symptomatic cardiotoxicity developed late in the course of treatment (Fig. 2) (Tan-Chiu and Piccart, 2002). Seventeen percent of patients discontinued trastuzumab during treatment, 11 because of cardiotoxicity and 6 for noncardiac reasons, out of which...
1 patient refused therapy after 3 courses and 4 patients had metastatic disease (brain metastasis in 3 and liver metastasis in 1) (Fig. 3).

Out of 11 patients, 5 patients had symptomatic heart failure: 2 patients had NYC Class I, 2 patients had NYC Class II, 1 patient had NYC Class III, and no patients had NYC Class IV symptomatic heart failure (Fig. 4). In all patients with cardiotoxicity, trastuzumab therapy was withheld; the case was referred to a cardiologist, and appropriate treatment commenced. Patients were reviewed weekly for symptomatic improvement and had a 2-weekly echocardiogram initially for 1 month and then monthly until recovery of the EF. None of the patients required intensive care admission, and there were no cases of therapy-associated mortality.

It was observed that recovery of the EF was dependent on symptomatology as an asymptomatic drop in the EF 10–15% below baseline level recovered in 4–6 weeks, while for an EF drop below normal level (EF = 55%), recovery usually took 8–10 weeks if the patient was asymptomatic. A symptomatic NYC Class I drop in the EF took 38–40 weeks to recover, and an NYC Class II drop in the EF took 60–65 weeks to recover. An NYC Class III symptomatic drop in the EF took 80 weeks to recover in our patient; no patient had NYC Class IV, which is reported to take even more time for recovery (>90 weeks) (Fig. 5).
4. Discussion

Our study attempted to address the concept of reversibility of acute CD and underlined the importance of lesser degrees of asymptomatic left ventricular dysfunction. Cardiac systolic function decreases during trastuzumab administration. There seems to be full or partial recovery after its withdrawal, with or without heart failure medications. Although the LVEF generally recovers after trastuzumab is stopped, it often does not recover to baseline level, and these patients are often maintained on cardiac medications. It is possible therefore that the damage will be sustained and that any damage may worsen over time and/or the myocardium may be more susceptible to future damage from other cardiac events. It is therefore possible that the long-term effects will become more clinically relevant than the acute effects (Telli et al., 2007).

In our study, depending on the severity of LVEF drop at 28–95 weeks, patients took longer to recover EF, but EF did not recover to pretreatment levels in a number of patients, and a few patients continued to require heart failure medications long after that, questioning the concept of reversibility.

In our study, trastuzumab had to be discontinued in 17 patients: 11 had cardiotoxicity, 1 patient had a noncardiogenic reason for withdrawal, 4 patients had progression of disease, and 1 patient refused therapy.

5. Conclusions

In conclusion cardiotoxicity seems to be dose-dependent as most patients had a drop in EF, symptomatic or asymptomatic, after receiving more than 10 courses of treatment. It is suggested that more regular than usual monitoring of cardiac function at the end of therapy is needed.

References


