Pre-operative cardiac workup after anthracycline-based neoadjuvant chemotherapy. Is it really necessary?

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ABSTRACT

INTRODUCTION In patients receiving pre-operative anthracyclines for locally advanced breast cancer, early cardiotoxicity is a well-recognised complication that may interfere with surgery. The aim of this study was to assess the safety of breast surgery after neoadjuvant treatment with Doxorubicin.

PATIENTS AND METHODS A retrospective study of breast cancer patients treated with Doxorubicin as part of their neoadjuvant protocol. All patients were subsequently operated in our institution. Intra-operative and postoperative haemodynamic, cardiac or respiratory events were collected.

RESULTS A total of 83 patients were included. All patients had a normal left ventricular ejection fraction before starting on chemotherapy. Doxorubicin was given in conjunction with Cyclophosphamide and Paclitaxel. The cumulative dose of Doxorubicin was 240 mg/m². All patients completed their chemotherapy less than a year before surgery and were clinically asymptomatic. Of the patients, 2.3% displayed a significant reduction in cardiac function to meet cardiotoxicity criteria, although not clinically apparent. No complications occurred intra-operatively or postoperatively.

CONCLUSIONS Breast surgery can be safely performed after breast neoadjuvant chemotherapy with Doxorubicin. The risk of early cardiotoxicity does not mandate a cardiac function assessment after completion of treatment. Work-up should be individualised according to the anthracycline regimen, patient's cardiac risk factors and functional status before surgery.

KEYWORDS

Cardiotoxicity– Neoadjuvant chemotherapy – Breast surgery

Accepted 22 October 2010; published online 18 November 2010

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Cardiotoxicity is a well-recognised complication of anthracycline-based chemotherapy with a severity ranging from mild asymptomatic abnormalities¹ to severe congestive heart failure (CHF).² Myocardial pathogenesis is related to the type of anthracycline drug, the cumulative dose, and dosing schedule.³

Anthracycline-based chemotherapy represents a standard of care in patients with locally advanced breast cancer. Anthracycline-based chemotherapy improves disease-free and overall survival.^{4,5} Pre-operative chemotherapy with anthracycline has been proven to increase the rate of breast conservation.⁶

Since cardiac function can be influenced by the administration of general anaesthetics and the peri-operative stress response, it is the routine in many institutions to assess car-

diac function in patients scheduled for breast surgery after neoadjuvant chemotherapy with an anthracycline. Cardiac work-up includes left ventricular ejection fraction (LVEF) assessment, either by echocardiography or radionuclide angiography (Multi Gated Acquisition Scan or MUGA scan). Tests are performed even if cardiac function before chemotherapy was normal and no clinical deterioration in cardiac function was apparent after chemotherapy.

The aim of the present study was to assess the safety of breast surgery performed under general anaesthesia in patients previously treated with the anthracycline Doxorubicin. The data can help the process of evaluating the need for repeated cardiac imaging at the end of chemotherapy treatment, before surgery is performed under general anaesthesia.

Patients and Methods

All patients who received pre-operative Doxorubicin-based chemotherapy as part of their neoadjuvant protocol, for locally advanced breast cancer, followed by breast surgery under general anaesthesia, in the Chaim Sheba Medical Center between April 2003 and March 2007 were retrospectively studied.

Patients with active cardiac disease, including angina pectoris or cardiac arrhythmia requiring medication, severe conduction abnormalities, clinically significant heart disease, or poorly controlled hypertension, were not eligible to receive Doxorubicin. After exclusion, all patients had cardiac echocardiography or MUGA cardiac assessment performed to evaluate left ventricular function before starting on chemotherapy and patients with poor function or without documentation of cardiac function were excluded as well. Criteria for cardiotoxicity at the end of chemotherapy were as follows: more than 20% absolute decrease from baseline in LVEF, more than 10% decrease below the lower limit of normal (50%), or clinical signs and symptoms of CHF associated with a decrease in LVEF.

All patients received four cycles of Doxorubicin 60 mg/m² and Cyclophosphamide 600 mg/m² followed by four cycles of Paclitaxel 175 mg/m² as part of their chemotherapeutic regimen. The cumulative dose of Doxorubicin was 240 mg/m². Forty patients received the regimen on a 21-day schedule and 43 patients received a dose dense regimen – Doxorubicin, Cyclophosphamide and Paclitaxel every 14 days with G-CSF support. Patients who did not complete their chemotherapeutic regimen were excluded.

All patients had their breast procedure done under general anaesthesia as is our long-standing policy.⁷ All patients were anaesthetized according to the protocol used in our institution. Patients were premedicated with 5 mg oral Diazepam. Anaesthesia was induced using Midazolam (1–2 mg), Propofol (3–4 mg/kg) and Fentanyl (1–2 µg/kg), followed by tracheal intubation. Anaesthesia was maintained with Propofol infusion and inhalation of N₂O/O₂ (70/30). Patients were mechanically ventilated using a pressure controlled mode with peak inspiratory pressure of 15 cmH₂O, respiratory rate of 10 per minute, I:E ratio of 1:2 and end expiratory pressure of 2 cmH₂O throughout the procedure. The ventilator parameters were adjusted to achieve end expiratory CO₂ concentration of 30–34 mmHg. Intra-operatively, monitors included non-invasive arterial blood pressure, heart rate by ECG as well as 5-lead ECG and ST segment monitoring, peripheral oxygen saturation, end-expiratory CO₂ concentration, and oesophageal temperature. All anaesthesia and physiological data were recorded using a patient data management system (Datex-Engstrom, Helsinki, Finland).

Data on chemotherapy treatment, time interval between the end of chemotherapy and time of surgery, type of surgery,

intra-operative and postoperative haemodynamic, cardiac or respiratory events were collected. Intra-operative events were defined as a decrease in systolic blood pressure (SBP) to a value lower than 80 mmHg, increase in SBP to a value higher than 20% from baseline, increase in heart rate to a value higher than 100 per minute for longer than 2 min, decrease in heart rate to a value lower than 50 per minute for longer than 2 min, significant ST segment depression, cardiac arrhythmias, decrease in oxygen saturation to a level lower than 95% when the patient was ventilated with 100% oxygen.

Postoperative events were defined as elevated cardiac enzymes following a patient's complaint of chest pain or shortness of breathing, ECG evidence of significant ST segment changes or cardiac arrhythmias.

Results

The study group included 83 women with a mean age of 49 years (range, 29–73 years). Mean LVEF value before treatment was 63% (range, 55–77%). Mean LVEF after chemotherapy was 60% (range, 52–70%). The mean decrease in LVEF value was 5.5%. Echocardiographic cardiotoxicity rate was 2.4%, all asymptomatic.

A total of 94 procedures under general anaesthesia were done. Sixty-seven patients underwent a breast conservation procedure and 20 patients underwent mastectomy. Nine of the patients underwent more than one procedure (either relumpectomy for positive margins or completion to mastectomy). All patients had completed their chemotherapy less than a year before any of their operations. All patients were clinically asymptomatic (*i.e.* no dyspnoea on exertion) and had a haemoglobin level above 10.5 mg/dl. Throughout the anaesthesia, there were no intra-operative events as defined earlier. No anaesthesia-related complications occurred intra-operatively or postoperatively other than mild complaints usually associated with general anaesthesia and tracheal intubation. Postoperative mean hospital stay was 3 days.

Discussion

A commonly used anthracycline in breast cancer patients is Doxorubicin; however, as with other anthracyclines, its use raises concerns regarding the risk for cardiotoxicity. Anthracycline cardiotoxicity is well recognised, although the exact mechanism has not been definitely established. Anthracyclines cause a cumulative loss of cardiac myocytes, probably mediated by toxic free radicals.⁴ Independent risk factors for anthracycline cardiotoxicity include higher rates of anthracycline administration and previous cardiac irradiation.⁸ Anthracycline cardiotoxicity comprises both an early toxicity, generally light and reversible, and a late toxicity,

dose-dependent and irreversible.⁹ Cardiotoxicity severity is also variable and ranges from abnormalities that become apparent only during exercise² to severe congestive heart failure (CHF).⁴ Swain *et al.*¹⁰ estimated the incidence of Doxorubicin-induced CHF at 5.1%. Doxorubicin toxicity is dose-dependent and increases dramatically after exceeding 500 mg/m². Dose dense regimens given weekly or every 2 weeks were not associated with a higher rate of cardiotoxicity.¹¹ Taxanes interfere with anthracycline metabolism and may potentiate anthracycline-induced cardiotoxicity.¹² Gianni *et al.*¹⁵ reported the incidence of cardiac toxicity for a regimen of Doxorubicin (50–60 mg/m²) and the taxane Paclitaxel (175–220 mg/m²). Cardiac toxicity rate was 25% when the total amount of Doxorubicin was greater than 440 mg/m², whereas it was lower than 5% when the amount was less than 380 mg/m².

In our cohort, patients received Doxorubicin-based chemotherapy, either dose dense (every 2 weeks) or every 3 weeks. Doxorubicin was given in conjunction with Cyclophosphamide and Paclitaxel. The cumulative Doxorubicin dose was 240 mg/m². All patients had normal cardiac function at rest before chemotherapy and had their surgery done in less than a year from completion of chemotherapy.

This study's conclusion is limited by the overall small number of the cohort. We have only 83 patients in our breast surgery database who are within our inclusion criteria. In this respect, this study may be statistically underpowered to measure the true incidence of cardiac events significantly. However, even considering this short-coming, we found it striking that 94 general anaesthesia procedures were done safely without any untoward events, and no patients evidenced clinically significant change in cardiac function, in spite of anthracycline therapy. Our study indicates that, although there is a small measurable degree of cardiotoxicity related to Doxorubicin-based pre-operative chemotherapy, general anaesthesia can be safely given thereafter for breast cancer patients. This is true for patients with baseline normal LVEF and no clinical change during therapy and up to the time of surgery. This may be explained by the relatively low dose of Doxorubicin given pre-operatively for breast cancer patients and by the short time course from treatment to surgery.

Considering this, it may be beneficial to evaluate more seriously the need for cardiac function work-up prior to surgery in breast cancer patients. Although costs can vary between countries and locales, based on our pricing in Israel, we estimate that the average cost for a cardiac echogram to be approximately US\$250 (£157) and the cost of MUGA scan to be US\$1000 (£630). Considering that there are approximately 45,000 new cases of breast cancer a year in the UK, of which up to a third may be candidates for pre-operative therapy, the drain on health resources by possibly unnecessary testing may be considerable. Nonetheless, in

order to determine the real benefit of cardiac function work-up for detecting and preventing intra-operative complications, much larger series should be examined, maybe on a national level.

Conclusions

This study has shown that, for patients receiving Doxorubicin in a cumulative dose not exceeding 240 mg/m², a further cardiac work-up may not be necessary before surgery. This could save considerable time and valuable resources, as time consuming and expensive cardiac work-ups can be safely avoided.

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