ORIGINAL ARTICLE

Dual Phase Qualitative and Quantitative ^{99m}Tc-MIBI Scintimammography for Predicting Response to Neoadjuvant Chemotherapy in Breast Cancer

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ABSTRACT

Objective: To determine the role of dual phase ^{99m}Tc-MIBI scintimammography in predicting chemotherapeutic response in breast cancer.

Study Design: Cross-sectional study.

Place and Duration of Study: Karachi Institute of Radiology and Nuclear Medicine (KIRAN), from September 2004 to March 2005.

Methodology: Female patients with locally advanced breast cancer being planned for the anthracycline-based neoadjuvant chemotherapy were included in this study. All subjects received a 740 MBq bolus intravenous injection of ^{99m}Tc-MIBI. Ten minutes and 3 hours post-injection planar images were obtained in prone, lateral and supine positions using double head gamma camera. MIBI washout was scored as follows: >30% as a positive prognostic test (predicting a poor response to chemotherapy) and <30% as negative prognostic test (predicting a good response to chemotherapy). Qualitative analysis of MIBI scans was also performed and categorized as visual wash-out or no visual washout as apparent on the early and delayed images. The criterion for the good and bad response was the reduction of >50% and <50% in the tumour burden respectively. Accuracy analysis, Chi-square test and Wilcoxan sign rank test were applied.

Results: There were 32 females (mean age: 46.3 years; median age 46 years; age range 33-65 years). Quantitative dual phase ^{99m}Tc-MIBI scintimammography was found to be a good predictor of chemotherapeutic response in breast cancer. These were true positive in 8 patients and true negative in 19 patients with sensitivity (Sens.) 72%, specificity (Spec.) 90%, Positive Predictive Value (PPV) 80%, Negative Predictive Value (NPV) 86.5%, p <0.03. Receiver Operating Characteristics (ROC) curve analysis demonstrates 30% as a cut-off value for the wash-out in quantitative dual phase MIBI for the prediction of the chemotherapeutic response. In comparison, qualitative scintimammography had Sens. 82%, Spec. 53%, PPV 29%, NPV 93% and p <0.38. Statistical difference was found between early and delayed uptake ratios in the responders and non-responders.

Conclusion: Quantitative dual phase ^{99m}Tc-MIBI scintimammography is a simple, reliable, non-invasive and effective tool for predicting the response to neoadjuvant chemotherapy. Furthermore, quantitative assessment is more precise than qualitative (visual wash-out) approach.

Key words: *^{99m}Tc-sestaMIBI. Multidrug resistance. Neoadjuvant chemotherapy. Breast cancer.*

INTRODUCTION

In most western countries, breast cancer is the most common malignancy among women.

England and Wales have the highest mortality rates in the Europe and this cancer accounts for 27 deaths per 100,000 women per year.[1] Pakistan has been reported to have the highest rate of breast cancer of any Asian population.[2] Biochemical resistance to chemotherapy is the major cause of treatment failure in patients with breast cancer. Infact, an intrinsic chemo-resistance is present in 18-51% of untreated cancer, whereas resistance is acquired later during the treatment in upto 75% of patients.[3-4]

The term Multidrug Resistance (MDR) is commonly used to indicate an overexpression of transmembrane glycoproteins, the P-glycoprotein (Pgp), and the MDR-associated glycoprotein.[3,5] These proteins allow outward transport of the most important anti neoplastic chemotherapeutic drugs, such as anthracyclines, and are responsible for the clinical manifestation of the MDR phenotype in breast cancer.[6,7]

Knowledge of the MDR pattern before and during the treatment can improve therapy planning, including selection of drug-resistant patients for chemorevertant drugs.

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^{99m}Tc-Sesta MIBI [hexakis (2-methoxy-isobutylisonitrile) technetium (1)], a radiopharmaceutical widely used as a tumour-seeking agent for diagnostic imaging,[8,9] has been recently used as a general probe for functional imaging of these 2 MDR pumps.[10,11] Several clinical studies have, therefore, been designed to study Pgp functionality with ^{99m}Tc-sesta MIBI in cancer patients,[12,13] and a correlation between the efflux rate of ^{99m}Tc-sesta MIBI and quantitative Pgp expression in breast carcinoma patients was clearly evident in a pilot study.[14] Furthermore, this is a simple and cost-effective modality with safe radiation dosimetry.

The primary objective of this study was to evaluate the utility of quantitative and qualitative dual phase ^{99m}Tc-MIBI scintimammography in predicting the response to neoadjuvant chemotherapy in locally advanced breast cancer.

METHODOLOGY

This was a cross-sectional study conducted at Karachi Institute of Radiotherapy and Nuclear Medicine (KIRAN) from September 2004 to March 2005. The outcome variable was considered the residual tumour size evaluated on ultrasound and clinical examination as assessed before and after 3 cycles of neoadjuvant chemotherapy. Patients were enrolled for the study prospectively after consideration of inclusion and exclusion criteria on referral by the outdoor patients department of the Karachi Institute of Radiotherapy and Nuclear Medicine (KIRAN). The tests and the outcome results were read in a standardized and masked fashion. The local ethics committee approved the study, and all patients gave verbal consent before entering the study.

Inclusion criteria were women of all ages with locally advanced disease intended for FAC neoadjuvant chemotherapy, having a palpable lesion and a baseline total white blood cell count >4x10^9/L, neutrophil count >2x10^9/L, and total platelet count >100x10^9/L. Furthermore, biochemical parameters like Liver Function Tests (LFTs), serum creatinine, blood urea and serum electrolytes were also within normal limits in all patients. Male patients, nursing mothers or patients with previous history of surgery/neoadjuvant chemotherapy/ hormonal therapy or inadequate TLC or platelets counts were excluded from the study.

All patients underwent a baseline evaluation that included a clinical history (age, parity, gravidity, age at menarche, menopausal status, and family history), clinical examination, ultrasonographic evaluation, fine-needle aspiration cytology or tissue biopsy of the lesion, bone scintigraphy, standard chest X-ray, liver sonography and a dual phase scintimammography using ^{99m}Tc-MIBI. The clinical and ultrasonographic tumour size was determined by measuring the two largest perpendicular diameters and single dimension as evidenced on ultrasound and clinical examination respectively.

Single chemotherapy regimen was used. The regimen was FAC (cyclophosphamide 400 mg/m^2; fluorouracil 500 mg/m^2 and adriamycin 50 mg/m^2, every 3 weeks). At the end of 3 cycles of chemotherapy, patients were re-evaluated both clinically and ultrasonographically.

^{99m}Tc-sestaMIBI (PINSCAN-MIBI by RIPG, PINSTECH, Nilore, Islamabad, Pakistan) about 740-925 MBq (20 mCi-25 mCi) according to the body weight was injected intravenously in the contralateral arm. Ten minutes and 3 hours after injection planar images were acquired with the patient in prone (right and left lateral views) and supine (anterior view), with 128 x 128 matrix size and zoom of 1.5. Each of the images was acquired for 1200 kilo counts (Figure 1). Decay factor for ^{99m}Tc- was applied by the computer software. A large-field-of-view gamma camera (Toshiba GCA 7200A/PI double head) equipped with high-energy, low-energy parallel holes collimators and a dedicated foam rubber mattress was used.

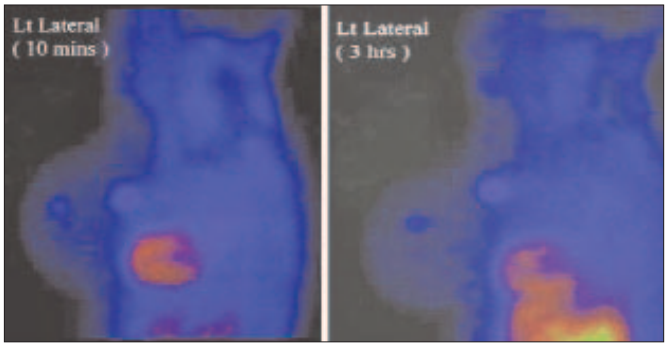

Figure 1: 10 minutes and 3 hours left lateral images showing a quantitative washout of 23% but NO visual (qualitative) washout.

Tumoral and background region of interests were drawn on the lateral images. Margins of the lesion were drawn carefully. Same Region of Interest (ROI) as that of the lesion was copied and drawn in the opposite breast at the same site for the background and count statistics calculated using the computer software.

Two independent, experienced nuclear medicine physicians, who were blind to the clinical information of the patient, analyzed the scintimammograms. A focal area of increased uptake in the breast, axilla, supraclavicular region and chest wall compared to the surrounding normal tissue was defined as a positive result for tumour. Wash-out was also assessed visually comparing delayed and early images.

The uptake ratio was calculated both for early and delayed images by the ratio of tumour to background mean count, with decay correction for delayed images. The Wash-out Rate (WOR) was computed by the ratio

of delayed to early uptake index, with decay and background corrections as follows:

WOR= [(T-B) 10 min-(T-B) 3 hrs] / (T-B) 10 min]

Where, T=tumoral region of interest, B=Background region of interest.

Film reading and processing were performed in clinically masked fashion. Intra- and interobserver agreements for WOR estimation were evaluated.

Prediction of tumour response to neoadjuvant chemotherapy was based on the results of the pretherapy ^{99m}Tc-MIBI WOR. Accordingly, the test was defined as a positive prognostic test when it predicted high WOR (high expression of intrinsic chemo-resistance) and, consequently, a high risk of no tumour response to the therapy. The test was conversely defined as a negative prognostic test when it predicted low expression of intrinsic chemoresistance and, consequently, a low risk of no tumour response to the therapy. The criteria for defining a test as positive or negative were based on the WOR cutoff point identified by the likelihood ratio method.

The Gold standard of the study was the response of the tumour to neoadjuvant chemotherapy, as evaluated on ultrasound after 3 cycles of chemotherapy according to WHO criteria (i.e. reduction of the product of the two largest perpendicular diameter of the residual tumour size vs. the baseline tumour size). Tumour response was also measured clinically. The ultrasound response criteria were based on the WHO criteria according to which Complete Response (CR) was the complete resolution of the tumour, Partial Response (PR) as the reduction in size of >50%, No Change (NC) or Non Responder (NR) as the reduction in size of <50% or an increase in size of <25%, and as Progressive Disease (PD) if the tumour size increased to >25%. In this study, CR and PR were considered as responders and NR and PD as non-responders.

The results of ^{99m}Tc-sestaMIBI prognostic tests were expressed in terms of sensitivity, specificity, positive and negative predictive values, and likelihood ratio. Pearson Chi-square test was applied to test the null Hypothesis (Ho) i.e. there is no predictive value of ^{99m}Tc- dual phase scintimammography in predicting the response to neoadjuvant chemotherapy. The level of probability significance (p-value) was set at a value of 0.05. The repeatability of the test was assessed by evaluating intra-reader and inter-reader agreement among the institutional reader (a dedicated senior resident) and 2 other masked readers using statistics. Kappa test was applied and K-value > 0.75 was considered an index of strong agreement beyond chance, whereas a K-value of 0.40–0.75 was considered an index of intermediate to good agreement.[15] Kappa agreement test was also applied between the quantitative and qualitative prognostic test for the prediction of chemotherapeutic response.

RESULTS

A total of 32 females (mean age 46.3±9.6 years ranging from 33-65 years) were included in this study.

The mean pre-therapy tumour size noted was 64±30 mm for the first dimension and 54±27 mm for the second perpendicular dimension. The mean post-therapy size noted was 37±21 mm for the first dimension and 27±16 mm for the second perpendicular dimension. The mean percentage reduction in size was 63±28%.

In Scintimammography, early images (10 minutes) showed marked uptake of ^{99m}Tc-sestaMIBI in all tumours. In the early images, the uptake ratio ranged from 1.22 to 3.0 with a mean of 2.30 and standard deviation of 0.70. In delayed acquisitions (3 hours), the ^{99m}Tc-MIBI uptake ratio ranged from 0.25 to 4.30 with a mean value of 1.80 and standard deviation of 0.71. All the 14 out of 14 nodes with metastases showed ^{99m}Tc-MIBI uptake. Washout rate ranged from 50-91% with a mean of 18.33 and SD of 27.45. The washout rate cutoff was set at >30% by likelihood ratio analysis for the best test results. Accordingly, the test was defined as positive (predicting a poor response to neoadjuvant chemo-therapy) for 10 of 32 patients, who had a washout rate >30%, and negative (predicting a good response to neoadjuvant chemotherapy) for 22 of 32 patients, who had a washout rate <30%. The intrareader coefficient of variation for washout rate was <3%, and the inter-reader agreement was high, ranging from 82-97% (k=0.5-0.8). Quantitative prognostic test was positive in 10 out of 32 patients. It was true positive in 8 and false positive in 2 patients. Quantitative prognostic test was negative in 22 out of 32 patients and it was true negative in 19 patients and false negative in 3 patients. The results of quantitative prognostic test were significant (p=0.03) for the prediction of tumour therapy response.

The uptake of ^{99m}Tc-MIBI by the tumour was assessed visually between the early (10 minutes) and the delayed (3 hours) image. Qualitative prognostic test was positive in 17 out of 32 patients. It was true positive in 7 and false positive in 10 patients, qualitative prognostic test was negative in 15 out of 32 patients. It was true negative in 11 and false negative in 4 patients. The results of qualitative prognostic test were non-significant (p=0.38) for the prediction of tumour therapy response.

The overall sensitivity, specificity, positive predictive value, negative predictive and likelihood ratio of quantitative and qualitative prognostic tests are given in Table I.

Kappa agreement test for no agreement between the quantitative and qualitative prediction was found (k=0.32, p=0.04).

Table I: Results of quantitative and qualitative prognostic tests.

	Sensitivity	Specificity	PPV	NPV	Likelihood	p-value
Quantitative predictive test	72%	90%	80%	86%	7.2	0.03
Qualitative predictive test	82%	53%	29%	93%	1.7	0.38

DISCUSSION

Failure of therapy due to cellular resistance to multiple chemotherapeutic agents remains a major clinical problem in the treatment of cancer including breast cancer. Resistance to chemotherapy like anthracyclines can be induced by P-glycoprotein (Pgp), a 170-kD cytoplasmic membrane protein encoded by MDR1 gene,[16] which pumps out anthracyclines, resulting in less cytotoxicity.[17,18] Development of predictors of chemotherapeutic response is very important in establishing the personalized treatment for breast carcinoma.

Piwnica-Worms *et al.* demonstration that ^{99m}Tc-MIBI is a transport substrate for Pgp indicates a possibility that expression of Pgp can be non-invasively assessed *in vivo* by ^{99m}Tc-MIBI.[19,20] Del Vecchio *et al.* made a preliminary report that a fast washout of ^{99m}Tc-MIBI was significantly associated with a high Pgp expression in primary breast carcinomas.[21]

This study evaluated the prognostic value of ^{99m}Tc-sestaMIBI washout for predicting the outcome of neoadjuvant chemotherapy in locally advanced breast cancer using variation in tumour size measured by ultrasound as the Gold standard.

In this study, a simple, reproducible and reliable method for ^{99m}Tc-MIBI WOR analysis was studied. The method, requiring only 2 sequential planar images and a quantitative measure of an index (WOR) by simple regions-of-interest design, was more practical for routine examinations. Determination of the WOR cutoff value (>30%) by likelihood ratio analysis for best test results was also a simple method and closely fulfilled the need for a clinically useful criterion. ROC curve is a good way of test accuracy because it does not depend on the prevalence of the disease. It also demonstrated that the accuracy of quantitative test is better than the qualitative prognostic test with area under curve 0.81 for quantitative vs. 0.58 for qualitative prognostic test.

This method also performed well in predicting chemoresistance. We observed a sensitivity higher than that previously reported by Ciarniello *et al.* (72% vs. 65%) and almost same specificity (90% vs. 87%).[22] The difference in test sensitivity is likely caused by the different criteria used to set the cutoff value. The sensitivity is lower than as observed by Sciuto *et al.* (72% vs. 100%) whereas, the specificity is higher (90% vs. 80%).[23] The reason for this can be the different Gold standards for response evaluation because they used pathological response as opposed to ultrasound response as Gold standard. Furthermore, the cut-off value for the washout ratio was different in the two studies (>30% vs. >45%). Also the present response criteria (>50% reduction in tumour size as responders) was different from their response criteria (>75% reduction in tumour size as responders). Another reason can be the differences in the chemotherapeutic regimens which in this case was only 3 cycles of FAC regimen as opposed to both 3 cycles of FAC and 4 cycles of high dose epirubicin in their study.

In this study, the negative predictive value of the test was 86%. This result ensured a fairly good response to neoadjuvant chemotherapy by all patients with a negative test (i.e., WOR < 30%), ruling out all patients with high expression of chemoresistance. On the contrary, a positive test was associated with a high probability of chemoresistance (positive predictive value, 80%). In these patients, the use of chemo-revertant or chemomodulator agents can be justified.

The high likelihood ratio observed (i.e. 7.2) indicated that the test result would greatly raise the prior probability of suspected disease. This analysis further confirmed that the ^{99m}Tc-MIBI WOR was clinically useful for assessing the probability of intrinsic chemo-resistance in patients with locally advanced breast cancer before neoadjuvant chemotherapy planning.

A false positive test was observed in 2 patients. One of those patients presented with strongly inflammatory disease that showed very diffuse and intense uptake. These characteristics probably interfered with the mechanisms of ^{99m}Tc-MIBI kinetics. In the second patient, the underlying cause was not clear. False negative test was observed in 3 patients. Two patients had larger sized tumour, which was firm and hard. So the lack of response can be attributed to the size and consistency of the tumour, which also influences the kinetics of ^{99m}Tc-MIBI.

As a response measure, we found that the clinical and ultrasound finding were at odds with poor agreement between the two (k=0.30, p=0.06). Clinical examination gives more false negative results and presents more favourable outcome of the chemotherapy.

As a predictive test, we found that the qualitative (visual) and quantitative prognostic tests are also at odds with poor agreement between the two (k=0.32, p=0.04). The

qualitative prognostic test gives more false positive results (predicting poor response to chemotherapy). The reason for the apparent visual washout with no quantitative washout may be due to the differential washout between the tumour and background. If the tumour and background washout are in parallel, it would visually look a washout but not quantitatively.

Other modalities are also being used for the prediction of chemotherapeutic response in breast cancer. Chintamini *et al.*[24] demonstrated a significant correlation between tumour response and immunohistochemical detection of P-glycoprotein in 50 patients with breast cancer. Immunohistochemical detection has also been shown as a predictor of breast caner recurrence. Immunohistochemical detection requires biopsy for the analysis and also is not widely available. Similarly, *in vivo* MR spectroscopy has been shown as a predictor of chemotherapeutic response. Again this technique is not widely available and is costly. MRI has been shown having a role in the prediction of tumour response in patients with locally advanced breast cancer by Martincich *et al.*[25] MRI is though widely available but is very costly for the patient. Considering the availability and cost effectiveness, scintimammography can play an established role both in predicting and assessing the tumour response to neoadjuvant chemotherapy.

This is an ongoing study and the patients will be followed for the pathological response assessment and for any recurrence after mastectomy. Long-term follow-up for the prognosis and survival of the patients is also intended which will help to validate the study further.

CONCLUSION

It is concluded that quantitative dual phase ^{99m}Tc-MIBI scintimammography is a simple, reliable, non-invasive and effective tool for predicting the response to neoadjuvant chemotherapy. Furthermore, quantitative assessment is more precise than qualitative (visual washout) approach.

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