Original Article

Response Prediction to Neoadjuvnat Chemotherapy in Locally Advanced Breast Cancer with Scintimammography

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ABSTRACT

Objectives: To measure Retention index (RI) at 120 minutes through scintimammography technique and to determine its relationship with mammographic results and Multi Drug Resistant-1 Messenger Ribonucleic Acid (MDR-1 mRNA) expression.

Place and Duration: Data collected at Nuclear Medicine Department of Nuclear Medicine, Oncology and Radiotherapy Institute (NORI), Islamabad for 6 months (February to August 2012)

Study Design: Prospective cross-sectional study.

Material and Methods: 20 patients with locally advanced breast cancer, candidates for NACT with no previous history of mastectomy or chemotherapy were included. All underwent mammograms of the diseased breast before and after NACT to measure the size of the lesion according to the response evaluation criteria in solid tumors (RECIST). All the patients then underwent scintimammography with 740 MBq Technetium 99m Sestamibi (Tc-99m-MIBI). Two sets of images acquired at 15 and 120 minutes after the injection of Tc-99m-MIBI. RI as a fraction of initial uptake (15 min) at 120 min was calculated. MDR-1 mRNA levels of all patients were measured with Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) method. The patients then underwent three cycles of anthracycline based NACT. The patients with > 30% reduction in tumor size on final mammographic image were labeled as responders (R) and rest as non-responders (NR) to NACT.

Results: The results showed 11 (55%) responders and 9 (45%) non responders. RI at 120 min showed significant association with mammographic results and MDR-1 mRNA expression ($P<0.05$).

Conclusions: Response to neo-adjuvant chemotherapy for LABC can be predicted by scintimammography as it is linked with high retention index ($P=0.017$) and weak MDR-1 mRNA expression ($P=0.018$).

Key words: Locally advanced breast cancer, Neoadjuvant chemotherapy, Technetium 99m Sestamibi, Scintimammography, MDR-1 mRNA

Introduction

Breast cancer is the most common cancer amongst females in Pakistan.[1,2] It has been seen that more than half of the patients present with locally advanced stages (stages III and IV).[3] Neoadjuvant chemotherapy is now standard for patients with locally advanced breast cancer. This treatment approach converts many patients with initially unresectable disease to reasonable surgical candidates, with acceptable rates of locoregional disease control. Human P-glycoprotein (Pgp) is a 170-kDa transmembrane protein that is encoded by the MDR-1 gene, and acts as an energy-dependent drug efflux pump of broad specificity.[4,5] Over expression of this protein confers resistance to a large number of chemotherapeutic agents including anthracyclines, vinca

alkaloids, epipodophyllotoxins, actinomycin D and Taxanes.[6] A number of studies document that Tc-99m methoxy isobutyl isonitrile (Tc-99m MIBI) is a transport substrate of Pgp in a variety of tumor cells.[7] Scintimammography (SM) with Tc-99m-MIBI is an accurate technique in predicting tumor presence or absence after treatment, and useful for the in vivo detection of intrinsic and acquired chemotherapy resistant breast cancers, which is a very important factor for planning the best therapeutic options.[8] There is evidence that the measurement of sestamibi uptake as fractional retention obtained by dynamic imaging is a reliable parameter for predicting the response to NACT.[9] Rationale of the study was to assess whether scintimammography could predict resistance to NACT at an early stage so that change of regimen may be incorporated. Chemotherapy is an expensive affair and consumes lots of resources of patients and needs highly monitored clinical environment. Moreover, its therapeutic index is much narrower than other drugs in clinical use and high rates of adverse effects have significant impact on quality of life of the patient. Early detection of resistance to chemotherapeutic drugs may result in saving resources and early change in regimen may result in better clinical outcomes. Our objective was to measure Retention Index (RI|) at 120 minutes through scintimammography technique and to determine its relationship with mammographic results and MDR-1 mRNA expression.

Materials and Methods

It was a prospective cross-sectional study and was carried out at nuclear medicine department, NORI, Islamabad after approval from scientific and ethical review committee of the institute. Duration of study was six months (February to August 2012) and twenty (n=20) patients with locally advanced breast cancer were included in the study after taking informed and written consent. LABC was clinically defined as any tumor that is greater than 5 cm or that involves the skin or chest wall including fixed axillary lymph nodes or ipsilateral supraclavicular, infraclavicular, or internal mammary nodal involvement. Patients underwent mammography before and after three cycles of neoadjuvant chemotherapy. The lesion size was measured before and after the NACT on mammographic images measuring the largest dimension of the tumor as seen on mammogram by applying the RECIST criteria[10]. Scintimammography of the lesion was done before neoadjuvant chemotherapy after injecting 740 MBq of Tc-99m sestamibi. The patients were imaged in anterior supine and prone lateral positions at 15 and 120 minutes after the injection. Planar images were reviewed on the screen, region of interest (ROI) were drawn on the lesion and the number of counts and number of pixels were noted. The same region of interest was drawn on the normal tissue with the same number of pixels and the counts from both ROI were noted. Tumor to background ratio (TBR) at 15 and 120 min was calculated by dividing the mean counts per pixel in tumor with those in the background keeping the pixel number same. RI at 120 min post injection was calculated by taking delayed (120 min) to early (15 min) TBR. RI at 120 < 1.0 was taken as cut off value for non responding tumors. MDR-1 mRNA levels as molecules per reaction of all patients measured with standard RT-PCR method. High expression was arbitrarily defined as greater than 1000 and low as less than 1000 molecules/reaction. SPSS-17 was used for descriptive and analytical statistics. Chi-square test was used to see the association of RI with mammographic results and MDR-1 mRNA expression. *P* value of < 0.5 was taken as significant.

Results

Twenty female patients diagnosed with LABC with mean age of 43.8 years ± 6.11 SD were enrolled in this study. Our results showed 11/20 (55%) of the patients represented as responders and rest 9/20 (45%) were non-responders according to the cut off described in RECIST criteria (>30% decrease in pre-chemotherapy tumor size). 12/20 (60%) of the patients showed high and 8/20 (40%) showed low expressions of MDR1-mRNA. RI at 120 min with cut off value of < 1 showed significant association with mammographic results and MDR1-mRNA expressions (*P* < 0.05). Results are presented in table I and II.

Table I: Association of RI with mammographic results

RI	Mammography Results		*P*-Value
	Non-responders	Responders	
<1	8	4	.017
>1	1	7	

Table II: Association of RI with MDR-1 m-RNA expressions

RI	MDR-1 m-RNA		*P*-Value
	High Expression	Low Expression	
<1	11	1	**.018**
>1	1	7	

Discussion

Tc-99m sestamibi has emerged as a powerful tool to explore the functions of tumor tissue at the cellular levels. This radiopharmaceutical freely diffuses across the cell membranes by a passive phenomenon based on its electric charge and partition co-efficient. Quantitative in vivo imaging with this agent is an easy and non-invasive technique to evaluate the functional status of multidrug resistance proteins in predicting the response of tumor to neoadjuvant chemotherapy. Moretti et al[11] first addressed the issue through clinical studies in breast cancer whether Tc-99m-MIBI uptake was reduced in Pgp over expressing tumors. There are several reports in the literature correlating a single early uptake ratio of Tc-99m-MIBI with response to treatment[12]. Although the absent or reduced uptake of Tc-99m-MIBI in breast carcinoma is indeed correlated with a poor response to therapy, it is not clear, in the absence of a direct evidence of Pgp expression in individual tumors, whether resistance is either due to the over expression of Pgp or because of other Pgp-independent mechanism of resistance altering MIBI uptake.

There were 04 out of 11 responders (36%) who showed RI value was < 1.0 which means that on scintigraphy the tumor showed washout of tracer when compared with early images, but on response evaluation by mammography imaging patient turned out to be a responder. Two of these patients presented with strongly positive inflammatory disease that showed very diffuse uptake. This finding probably interfered with the mechanisms of Tc-99m-sestamibi kinetics. In the third patient, the tumor was found to be located at the inner quadrant and showed low uptake due to soft tissue attenuation and increased distance from the detector. In the fourth patient the cause could not be ascertained.

01 out of 09 non-responders (11%) showed RI value was ≥ 1.0, means that on scintigraphy tumor showed further accumulation when compared with early images, but on response evaluation by mammography imaging the patient turned out to be a non-responder. A repeat scintimammographic image after three cycles of chemotherapy was obtained which showed a low RI (< 1) on the post therapy study. This patient could have acquired chemoresistence during neoadjuvant chemotherapy. Acquired resistance develops mostly through mutation of gene induction but can also arise when a resistant fraction survives from a tumor that initially responded to the chemotherapy. Rosa Sciuto et al[13] had observed the same phenomenon in their study. The change in RI pattern from high to low during neoadjuvant chemotherapy can represent survival of a resistant tumor fraction or any other mechanism implied in induction of chemoresistence. However, data on long-term follow-up are clearly needed to confirm this hypothesis. These parameters were also previously employed in multiple studies regarding breast, lung and oral cancers in response prediction[14,15]. Their other synonyms are fractional retention and washout rate[16]. These parameters give the detailed information about the tracer accumulation in the lesion relative to the initial tracer uptake.

Del Vecchio et al[17] studied 30 patients with untreated breast carcinomas and correlated the sestamibi efflux rates calculated from decay-corrected time–activity curves over the tumor with Pgp levels measured in the tumors. In the group with strong Pgp expression, the sestamibi efflux from tumors was almost 3 times as high as that in the group with low Pgp expression. Mezi at al[4] in his study had concluded that scintimammography with Tc-99m-MIBI was accurate in predicting tumor presence or absence after treatment, and useful for the in vivo detection of intrinsic and acquired chemo-resistant breast cancers.

Conclusion

Response to neo-adjuvant chemotherapy for LABC can be predicted by scintimammography as it is linked with high retention index (*P*=0.017) and weak MDR-1 mRNA expression (*P*=0.018).

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