Expression of Multidrug Resistance (MDR) genes in Lung Cancer

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Abstract :

In lung cancer, despite the considerable progress made with treatment protocol, Multidrug Resistance (MDR) is a major obstacle to cancer treatment and leads to poor prognosis. Multidrug resistance genes like MDR1, ABCG2, MRP1, LRP play a significant role in drug resistance in NSCLC. **Methods :** Blood samples were collected from pre-therapeutic NSCLC patients (N=34). Gene expression of MDR genes was done by qRT-PCR. Immunohistochemistry (IHC) was performed to correlate the MDR1gene expression with its protein expression (P-gp) in pre-therapeutic patients. **Results :** In this study, a significant direct intermediate correlation was found in between MDR1 and MRP1 (r= 0.355, p= 0.043). MDR1 expression was significantly associated with clinical stages (p=0.000) while a trend of ABCG2 expression was shown with clinical stages (p=0.091). MRP1 expression was significantly correlated with gender (p=0.023), habit (p=0.023), histology (p=0.001) and trend was observed with age (p=0.07). LRP expression was significantly correlated with age (p=0.023), clinical stage (p=0.019) and a trend of significance in patients with tobacco habit. (p=0.089) was also observed. **Conclusion :** These findings suggested that the assessment of MDR genes' expression plays a significant role to predict treatment response in lung cancer.

Keywords : ABCG2, Drug resistance, Gene expression, BCRP, LRP, MDR1, MRP1

Introduction :

Lung cancer is currently the leading cause of cancer deaths worldwide. According to GLOBOCAN, 1.8 million new cases (12.9% of the total) of lung cancer estimated in 2012. It is the most common cause of death from cancer worldwide, estimated to be responsible for nearly one in five (1.59 million deaths, 19.4% of the total). [1] In India, according to ICMR report, lung cancer constituted 6.9% of all new cancer cases and 9.3% of all cancer related deaths in both sexes in 2015. According to the Hospital based cancer registry of The Gujarat Cancer and Research Institute (GCRI), Ahmedabad, yearly incidence rate of lung cancer patients is ~5.8%. Lung cancer consists of major two types, Non-Small Cell Lung Cancer (NSCLC) comprises approximately 85% of all lung cancers and Small Cell Lung Cancer (SCLC) contains around 15%. Over the past decades, the prognosis of lung cancer is very poor even with foremost approach of chemotherapy and radiotherapy. For metastatic tumors, chemotherapeutics are the most effective treatment but the major problem is the expression of inherent and acquired drug resistance of cancer cells. [2-4] The emergence of resistance to anticancer drugs is thought to be the most vital problem for achieving effective cancer therapy. "Multidrug Resistance" or MDR is a significant obstruction to successful chemotherapy. MDR is defined as the ability of the cancer cells to be concomitantly resistant to different anticancer and chemotherapy drugs. In another way, it is insensitivity of cancer cells to cytostatic and cytotoxic response to structurally and functionally related drugs. [4, 5]

It is observed that drug resistance genes such as Multi-Drug Resistance gene-1 (MDR1), ATP-binding cassette sub-family G member-2(ABCG2),Multidrug Resistance-associated Protein-1(MRP1), Lung resistance protein (LRP) developed drug resistance due to chemotherapeutic drugs in NSCLC. [2-11] P-gp of MDR1 or ABCB1 gene is 170-kDa protein present on chromosome 7q21.12 belongs to ABC transporter protein superfamily. It acts as a drug efflux pump and is up-regulated in numerous drug-resistant cancer cell

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Table 1: Primers used in qRT-PCR analysis

Name of Primer	5' to 3' Primer Sequence
β- Actin	F: TCACCCACACTGTGCCCATCTACGA R: CAGCGGAACCGCTCATTGCCAATGG
MDR1	F:GTGGTGGGAACTTTGGCTG R:TACCTGGTCATGTCTTCCTCC
ABCG2	F:GCGACCTGCCAATTTCAAATG R:GACCCTGTTAATCCGTTCGTTT
MRP1	F: GAGCTGGAACCTGACAGCATC R: GATCCGCGTCTTGATAGCCAC
LRP	F:TTCTGGATTTGGTGGACGC R: ACTTCTCTCCCTTGACCAC

Figure1: Expression of MDR1 genes in pre-therapeutic NSCLC patients

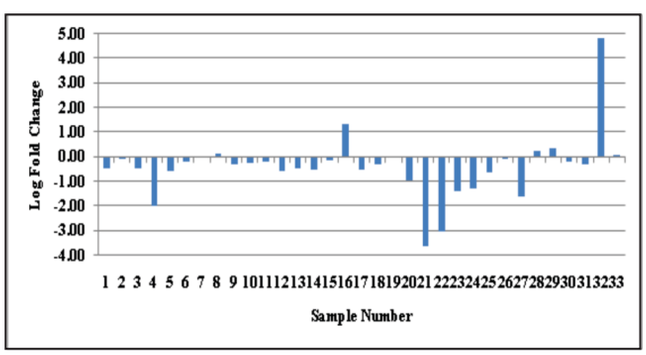


Figure 2 : Expression of ABCG2 genes in pre-therapeutic NSCLC patients

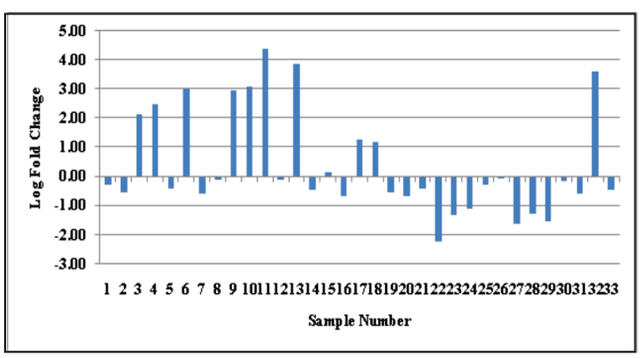


Figure 3 : Expression of MRP1 genes in pre-therapeutic NSCLC patients

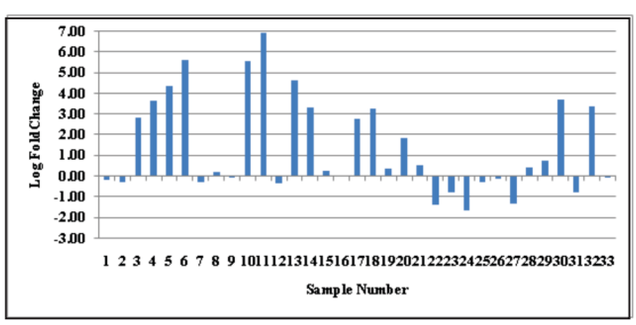
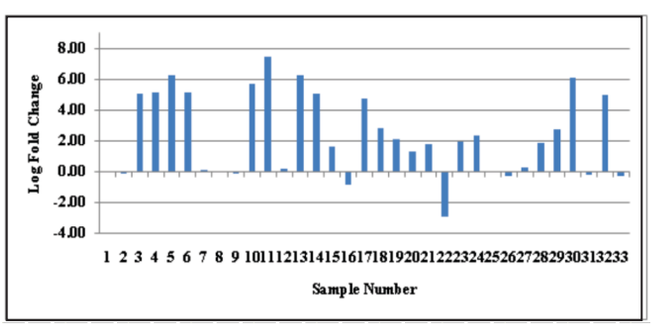


Figure 4 : Expression of LRP genes in pre-therapeutic NSCLC patients



lines. Thus, it plays an important role as a detoxifying agent by pumping toxins or xenobiotics, including anticancer agents out of the cells. [2, 12] MRP1 of ABCC1 gene which is located on chromosome 16p13.11 with 190-kDa molecular weight, member of the ABC transporter protein superfamily which has been associated with drug resistance via a mechanism similar to P-gp. [13] BCRP of ABCG2 gene of 72.31-kDa on chromosome 4q22.1 also belongs to ABC transporter protein superfamily. ABCG2 is an ABC half

Table 2: Clinico-pathological characteristics of NSCLC patients.

Patients' Characteristics	n= 33 (100%)
Age (in Completed Yrs.)	
<59	17 (51.5%)
>59	16 (48.5%)
Gender	
Male	23 (69.7%)
Female	10 (30.3%)
Habits	
None	10 (30.3%)
Smoking	18 (54.5%)
Tobacco Chewing	3 (9.1%)
Alcohol Drinking	1 (3%)
Tobacco + Alcohol	1 (3%)
Histology	
Adenocarcinoma	25 (75.8%)
Squamous cell carcinoma	4 (12.1%)
Undetermined	4 (12.1%)
Clinical stages	
Stage – II	1 (3%)
Stage – III	6 (18.2%)
Stage – IV	26 (78.8%)

transporter, and putatively forms a homo-dimer of two half-transporters. ABCG2 can transport large, hydrophobic, both positively and negatively charged molecules out of the cells including anticancer drugs. Thus, similar to MDR1and MRP1, ABCG2 overexpression is sufficient to confer resistance to a broad profile of anticancer agents. [14] The transporter proteins such as LRP of MVP gene also known as LRP gene of110-kDa present on chromosome 16p11.2 have been implicated as drug resistance marker in lung cancer by decreasing the concentration of chemical drugs in the nucleus and the drugs that are transported to the cytoplasm can then be extruded from the cancer cell by exocytosis. [2, 12]

Looking to the importance of these MDR genes in lung cancer the aim of the study is to find the expressions of MDR genes in NSCLC patients.

Methods :

Patient's selection and Gene Expression Analysis:

Total of 33 pre-therapeutic patients diagnosed at GCRI with NSCLC were enrolled in the study. Informed consent was obtained from all the subjects. Peripheral EDTA blood was collected, plasma was separated and then remaining blood was used for RNA isolation by TRIzol method. The quantity of RNA was determined by Qubit 2.0 Fluorometer (Invitrogen, USA). The RNA

Table 3 : Inter-correlation of MDR markers

(N=33)	MDR1	ABCG2	MRP1	LRP
MDR1 Pearson Correlation	1	-0.029	0.355*	-0.197
P-Value		0.871	0.043	0.272
ABCG2 Pearson Correlation	-0.029	1	0.238	0.197
P-Value	0.871		0.182	0.272
MRP1 Pearson Correlation	0.355*	0.238	1	0.034
P-Value	0.043	0.182		0.849
LRP Pearson Correlation	-0.197	0.197	0.034	1
P-Value	0.272	0.272	0.849	

Table 4: Correlation of MDR1,ABCG2, MRP1 and LRP expressions with clinico-pathological characteristics.

Patients' characteristics	MDR1 Mean ± SE	ABCG2 Mean ± SE	MRP1 Mean ± SE	LRP Mean ± SE
Age (in Completed Yrs.)				
<59	0.529 ± 0.12	0.588 ± 0.12	0.882 ± 0.08$^{\#}$	0.941 ± 0.05^{+}
>59	0.437 ± 0.128	0.437 ± 0.12	0.687 ± 0.12	0.81 ± 0.1
Gender				
Male	0.39 ± 0.10	0.56 ± 0.10	0.739 ± 0.094	0.86 ± 0.07
Female	0.7 ± 0.15	0.40 ± 0.16	0.9 ± 0.1$^{\#\#}$	0.9 ± 0.1
Habits				
None	0.6 ± 0.16	0.3 ± 0.15	0.90 ± 0.1$^{\#\#\#}$	0.8 ± 0.13
Habituated	0.434 ± 0.11	0.609 ± 0.10	0.739 ± 0.09	0.913 ± 0.6^{++}
Histology				
Adenocarcinoma	0.44 ± 0.10	0.48 ± 0.10	0.72 ± 0.91	0.88 ± 0.66
Squamous cell carcinoma	0.50 ± 0.288	0.50 ± 0.288	1.0 ± 0.0$^{\#\#\#\#}$	1.0 ± 0.0
Clinical stages				
Stage-III	0.166 ± 0.16	0.166 ± 0.21	0.66 ± 0.21	1.0 ± 0.0
Stage-IV	0.53 ± 0.99*	0.5 ± 0.10$^{\vee}$	0.8 ± 0.07	0.85 ± 0.72^{+++}

$^{*}p < 0.001$, $^{\vee}p = 0.091$, $^{\#}p = 0.07$, $^{\#\#}p = 0.023$, $^{\#\#\#}p = 0.023$, $^{\#\#\#\#}p = 0.001$, $^{+}p = 0.023$, $^{++}p = 0.089$, $^{+++}p = 0.019$

was stored at -80°C till further use. RNA was reverse transcribed to complementary DNA (cDNA) using reverse transcriptase (Applied Biosystems™) which was further used for the mRNA expression analysis of MDR1, ABCG2, MRP1 and LRP by SYBR green qRT-PCR (QuantiNova™SYBR Green PCR®). Primer sequences for the mentioned genes are provided in Table 1.

Immunohistochemistry :

Monoclonal antibodies against P-gp (p170 / p-Glycoprotein / MDR Ab-2; Clone F4;#MS-660-0.5ml, Thermo Fisher Scientific, UK) was used as primary antibody. Biotin-Streptavidin-peroxidase staining with 3, 3'-diaminobenzidine-tetrahydrochloride detection was used to stain the cell membrane of tumor cells which considered being positive.

Statistical Analysis :

Statistical analysis was carried out using SPSS statistics version 20.0. The results were presented as mean ± Standard Error (SE) of MDR1, ABCG2, MRP1 and LRP fold change gene expressions. The independent t-test was performed to determine whether there is a statistically significant difference between the means in two unrelated groups. Pearson's correlation was performed for combination expressions of drug resistance markers. P=<0.05 was considered to indicate a statistically significant difference.

Results :

Clinico-pathological Characteristics of NSCLC patients :

Table 2 shows the clinico-pathological details of the total 33 pre-therapeutic NSCLC patients. The median age of the patients was 59 years. Majority of the patients had age less than 59 years. Among all NSCLC patients, 23 (69.7%) were males and 10 (30.3%) were females. Adenocarcinoma was the major (25,75.8%) histological type. Majority of the patients were with stage IV disease. The cohort includes according to habit of patients involved, patients who habituated to smoking bidi 18 (54%) and others with different habits like tobacco chewing, alcohol drinking, etc, while 10 (30.3%) patients didn't have any habits.

Expression of MDR1,ABCG2, MRP1 and LRP genes in pre-therapeutic NSCLC patients :

Figure-1, 2, 3 and 4 showed expression pattern of MDR1, ABCG2, MRP1 and LRP genes in pre-therapeutic NSCLC patients respectively. The pre-therapeutic expression of MDR1, ABCG2, MRP1 and LRP genes varied in different NSCLC patients. MDR1 up-regulation was found in 16 (48.5%) patients and down-regulation was seen in other 17 (51.5%) out of 33 patients. The gene expression of ABCG2 was up-regulated in 17 (51.5%) patients while down-regulation was found in other 16 (48.5%) out of 33 NSCLC patients. The gene expression of MRP1 was up-regulated in 26 (78.8%), while down-regulated in other 7 (21.2%) pre-therapeutic NSCLC patients out of 33 patients. The gene expression of LRP was up-regulation was observed in 29 (87.9%) patients while down-regulated in other 4 (12.1%) out of 33 patients.

Inter-correlation of MDR1, ABCG2, MRP1 and LRP genes :

Inter-correlation of various drug resistance genes is shown in Table-3. A significant direct intermediate correlation was found in between MDR1 and MRP1 (r= 0.355, p= 0.043) while ABCG2 and LRP gene expression is independent of each other in NSCLC.

Association of MDR1, ABCG2, MRP1 and LRP gene expression with clinico-pathological characteristics of NSCLC patients:

Table 4 showed association of MDR1,ABCG2, MRP1 and LRP gene expression with different clinico-pathological parameters in NSCLC patients. MDR1 expression was significantly associated with clinical stages (p=0.000) while, no significant correlation was found between any other parameters. A trend of ABCG2 expression was shown with clinical stages (p=0.091) while, no significant correlation was found between any other parameters. MRP1 expression was significantly correlated with gender (p=0.023), habit (p=0.023), histology (p=0.001) and trend was observed with age (p=0.07) and LRP expression was significantly correlated with age (p=0.023), clinical stage (p=0.019) and trend was found with habit (p=0.089).

Expression of MDR1,ABCG2, MRP1 and LRP genes in post-therapeutic follow up NSCLC patients:

Out of 33 pre-therapeutic NSCLC patients, follow up of 4 patients were obtained, to whom platinum based chemotherapy was given. Out of them, age groups were divided into equal numbers of patients (Age <59; n=2; Age >59; n=2) from which all 4 (100%) were males with smoking habit while 2 (50%) were having histology of adenocarcinoma and 2 (50%) having squamous cell carcinoma of lung cancer. Out of 4 patients, 3 patients were with stage-IV disease. High variations were found in MDR genes expression with respect to before & after chemotherapy in all follow up patients, which was also found to be varied patient to patient according to treatment response of the patient. Figures-5 (a-d) show representative patterns of drug resistance gene expressions before therapy and after therapy and also pre-therapeutic P-gp expression in all follow up patients.

Figure-5 (a) showed representative pattern of a male NSCLC patient with age of 70 years having stage-IV metastatic adenocarcinoma. The patient had history of chronic smoking. Chemotherapy in combination of Carboplatin and Pemetrexed was later given to the patient and follow up blood sample was collected after two cycles of chemotherapy. In this patient, MDR1, ABCG2 and MRP1 expression was highly down-regulated before completion of two cycles of chemotherapy while LRP expression was up-regulated before completion of two cycles of chemotherapy. The correlation between MDR1 gene and its protein (P-gp) expression at pre-therapeutic level was done by Immunohistochemistry (IHC). IHC study showed very weak expression of P-gp protein in this patient who had showed significant down-regulation of MDR1 gene in same patient.

Figure-5(b) showed a representative pattern of a male NSCLC patient with age of 72 years having stage-IV metastatic adenocarcinoma and had habit of smoking bidi- 20/day. Chemotherapy in combination of Carboplatin and Pemetrexed was later given as treatment protocol. Follow up blood sample was collected after one cycle of chemotherapy. MDR1 and ABCG2 expression was found to be highly up-regulated

Figure 5 : (a-d) Representative patterns of drug resistance gene expressions before therapy and after therapy and also pre-therapeutic P-gp expressions in all follow up patients.

Figure 5 (a)

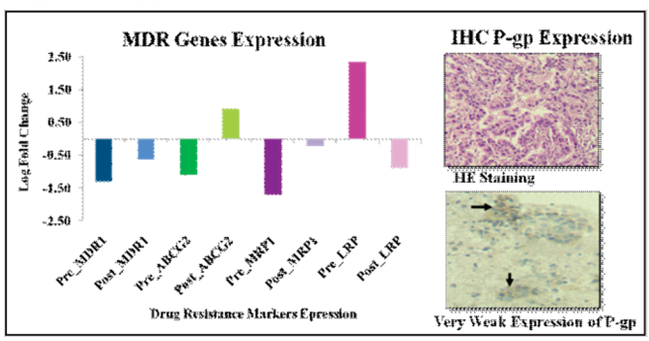


Figure 5 (b)

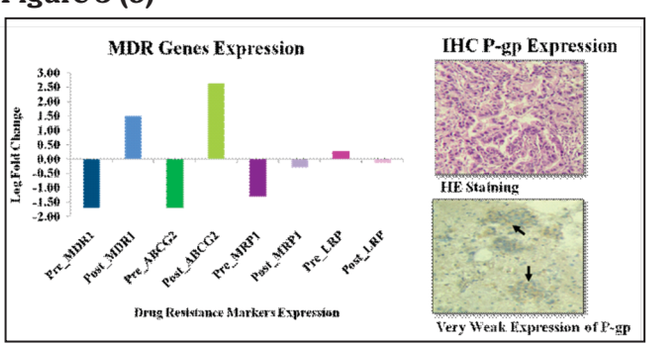


Figure 5 (c)

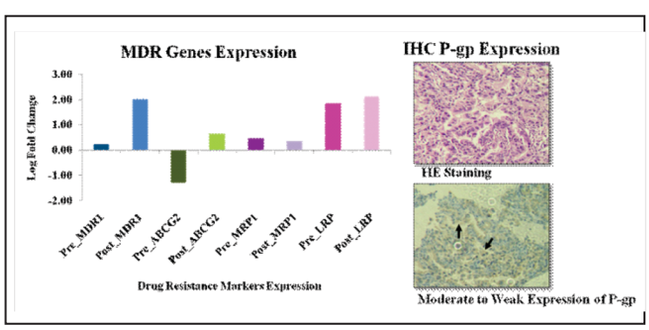
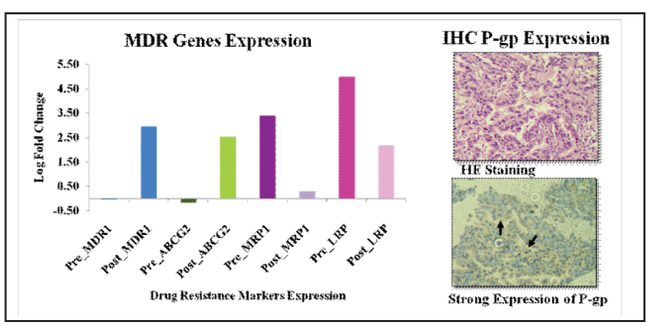


Figure 5 (d)



after completion of one cycle of chemotherapy in comparison to pre-therapeutic status. MRP1 was down-regulated while, LRP was up-regulated before treatment. The correlation between MDR1 gene and its protein (p-gp) expression showed very weak expression of P-gp protein in this patient who had showed significant down-regulation of MDR1 gene in same patient.

Figure-5(c) represents a 58 years male NSCLC patient having stage-III squamous cell carcinoma and had history of smoking bidi-25/day. Combination of Carboplatin and Paclitaxel was later given as chemotherapy and follow up blood sample was collected after two cycles of chemotherapy. MDR1, ABCG2 and LRP expressions were found to be highly up-regulated after completion of two cycles of chemotherapy than before treatment. The correlation between MDR1 gene and P-gp protein expression at pre-therapeutic level was done which showed moderate to weak IHC expression of P-gp.

Figure-5(d) represents a male NSCLC patient with age 58 years having stage-IV squamous cell carcinoma and habit of smoking bidi- 25/day. Combination of Carboplatin & Gemcitabine was later given as treatment protocol. Follow up blood sample was collected after two cycles of chemotherapy. In this patient, expression of MDR1 and ABCG2 was highly up-regulated after treatment started while, MRP1 and LRP was highly up-regulated before treatment. The correlation between MDR1 gene and its protein (p-gp) expression at pre-therapeutic level was obtained. IHC study showed strong expression of P-gp in above patient which was correlated with up-regulation of MDR1 gene.

Discussion :

The overall prognosis of lung cancer is poor with low median survival rate. Majority of patients showed locally advanced or metastatic disease and it is often due to late prognosis, high recurrence rate and lack of response to curative systemic therapy. Drug resistance is a major problem in the clinical management of lung cancer. Studies have reported that, the use of traditional chemotherapy in the treatment of NSCLC is majorly limited due to primary or acquired resistance to drugs.[12] Thus, it is important to rule out factors affecting treatment response in NSCLC patients with respect to drug resistance. Normal physiological process of ABC transporters is efflux of drug from the cell that is also a known mechanism of drug resistance in cancer cells. Three transporters- MDR1, ABCG2, MRP1 and even LRP- are implicated in many drug resistant cancers. All these transporters have broad substrate specificity and are able to efflux many xenobiotics, including vinca alkaloids, epipodophyllotoxins, anthracyclines, taxanes, and kinase inhibitors from cells.[15]

In this study, high alterations in the MDR1 and ABCG2 gene expression were noticed between all 33 pre-therapeutic NSCLC patients where MDR1 up-regulated in 16 (48.5%) patients and down-regulated in 17 (51.5%) patients while, ABCG2 up-regulated in 17 patients (51.5%) and down-regulated in 16 (48.5%) patients. Moreover, high variations were also found in all MDR-markers gene expressions between pretreated and post-treated follow up of patients. So, it might be interpreted that as the genetic profile varies in each patient with respect to the treatment. Further variation in the gene expression of MDR was correlated with its P-gp protein expression showing good signature pattern in pretreated patients whose follow up was also taken. Yet, majority of the pre-therapeutic NSCLC patients were up-regulated with MRP1 i.e. 26 (78.8%) patients and LRP gene expressions i.e., 29 (87.9%) patients. So, it is suggests that gene expression of MDR markers- MRP1 and LRP was found to be highly significant predictor of poor response to chemotherapy. In this study, significant direct intermediate correlation was found in between MDR1 and MRP1 gene expressions ($r=0.355, p=0.043$) which suggest the combination of MDR1 and MRP1 gene expression is a better option for prognosis evaluation for assessment of drug resistance in individual NSCLC patient. Though, the ABCG2 and LRP gene expression is independent of each other in NSCLC.

Though, the MDR mechanism remains to be interpreted, it may be probably concomitant with changes in the expression level of MDR- related proteins.[16] In the present study, we reported the correlation of these MDR markers with clinico-pathological characteristics of NSCLC patients. MDR1

is significantly associated with clinical stages (p=0.000) which means MDR1 gene expression was considerably increased in stage IV NSCLC patients compared to stage III while MDR1 is not associated with age, gender, habits or histology. Earlier many studies were carried out at protein level (p-gp) by IHC technique for understanding the correlations of clinico-pathological characteristics of lung tumor with P-gp. In which they found P-gp expression was significantly correlated with patient age, smoking history and tumor histology. [12, 16] In one prior study, no significant correlation between MDR1 gene expressions with clinico-pathological characteristics in their selected NSCLC patients for their study.[13]

A study reported a higher expression level of ABCG2 mRNA by Real-time PCR in chemo-naïve metastatic cells of NSCLC then SCLC. [17] In this study, a trend of ABCG2 gene expression was found with clinical stages (p=0.091) and no correlation of ABCG2 was observed with age, gender, habits or histology. One prior research study have also been found the correlations of clinico-pathological characteristics of lung tumor with BCRP by IHC technique in which strong correlation was reported between ABCG2 gene expressions in tumor samples from untreated stage IIIB or IV NSCLC patients and the platinum-based chemotherapy response rate.[18]

Few studies have reported that MRP gene expression also appears in normal cells thus it can be used as a control for comparison with malignant cells.MRP1 was found to be often overexpressed in a large proportion of tumors prior to treatment exposure. One study had reported the MRP1 was significantly associated with poor differentiation of tumor.[19, 20] In this study, MRP1 was significantly correlated with gender (p=0.023), habits (p=0.023) and with tumor histology (p=0.001) even trend was found with age (p=0.07). Moreover one study stated, MRP1 as an independent predictive factor by multivariate analysis. [16]

Previously studies were carried out to understand the correlations of LRP with clinico-pathological characteristics of lung tumor mostly using IHC technique which stated that the prognosis of NSCLC patients with high LRP expression was significantly poorer than those with low expression of it. Even LRP was found significantly correlated with gender, tumor histology, regional lymph node metastasis and clinical stage at protein level. [4, 16, 21] Though in this study, LRP gene expression was considerably associated with age (p=0.023), clinical stage (p=0.019) and trend was found with habits (p=0.089).

To check the post treatment effect of various genes, patients were followed up during the course of the treatment. Among 33 patients follow up from only 4 patients were obtained. Post treatment gene expression analysis showed that expression of MDR1, ABCG2 and MRP1 was up-regulated after treatment. These findings interpreted that these patients might have developed drug resistance to given chemotherapy. Thus our study further supports a central role of ABC-transporter proteins in the chemotherapy resistance of NSCLC and places emphasis on the necessity for new treatment modalities that are not limited by these drug-resistance mechanisms. However, large number of sample and longer follow-up time will be essential to confirm these results.

In conclusion, the current study suggest that the monitoring of gene expressions of MDR markers-MDR1, ABCG2, MRP1 and LRP play a significant role to provide treatment response in lung cancer.

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