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ORIGINAL ARTICLE

Genetic Investigation of Polymorphic OGG1 and MUTYH Genes Towards Increased Susceptibility in Lung Adenocarcinoma and its Impact on Overall Survival of Lung Cancer Patients Treated with Platinum Based Chemotherapy

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Abstract
Genes OGG1 and MUTYH are the two primary genes in Base excision repair pathway. OGG1 hydrolyzes the sugar phosphate backbone and remove the damaged base creating abasic site. MUTYH complements OGG1 as it particularly remove adenine mispaired with 8-oxo-G. Both OGG1 and MUTYH act as a check for the mis-incorporation of bases may be due to damages incurred on DNA. DNA isolation for 326 lung cancer cases and 330 controls was followed by genotyping making use of PCR-RFLP. Logistic regression was done to analyze the risk towards lung cancer. Patients were followed through telephonic conversation. Kaplan meier and Cox-regression were used for survival analysis. OGG1 presented a high risk towards lung cancer (CG: OR = 2.44, $p = 0.0003$; CG + GG: OR = 1.88, $p = 0.0093$). On the same lines adenocarcinoma for OGG1 were potent risk factors towards lung cancer (CG: OR = 4.72, $p = 0.0002$; CG + GG: OR = 3.63, $p = 0.0018$). Single allelic carriers for MUTYH gene imposed a high risk towards overall lung susceptibility and for all the three histology. Stratified analysis for chemotherapeutic drugs revealed administration of Cisplatin/Carboplatin + Pemtrexed for OGG1Ser ^{326} Cys showed a better survival (MST CG vs. CC: 9.1 vs. 0.56, p = <0.0001; HR =0.051, $p = 0.0025$). Whereas, MUTYH Gln^{324}His showed a smaller survival for mutant genotype (CC) (MST CC vs. GG: 4.0 vs. 9.4, $p = 0.05$; HR = 1.75, $p = 0.26$). Single allelic carriers for both OGG1 and MUTYH were risk factors towards lung cancer. The risk was amplified on combining both OGG1 and MUTYH.

Keywords Polymorphism · Lung cancer · Overall survival · Chemotherapy · OGG1 · MUTHY

Introduction

Worldwide there is an increase in the incidence and mortality of lung cancer and it represents one of malignancies that has the largest number of patients all over the world (https://www.iaslc.org/lung-cancer-fact-sheet-2016-asia). The rates of mortality and morbidity associated with lung cancer in India has also paralleled to the world data [1]. Mostly lung cancer is diagnosed at later stages of the disease when the option of curative surgery is ruled out. Platinum based chemotherapy is the major remedial option for these advanced stages. It has been observed that the survival rate of patients undergoing platinum based chemotherapy is a dismal 15% only and the reason for such low efficiency could be the resistance offered to the drugs by DNA repair system. Moreover, there are many side effects of chemotherapy such as toxicity which are more detrimental to human health compared to the chemotherapy [2]. Presently standard pathological TNM staging and histological diagnosis are used for predicting the clinical treatment and survival [3]. However recent advances in the area of molecular genomics studies have provided a way to define individualized chemotherapy regimens and dosages based on molecular profiles of individual's tumor.

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At genetic level lung cancer is a result of deregulated expression of cell-cycle genes, DNA repair genes and apoptotic genes. There are many factors responsible for these molecular alterations which may be endogenous or exogenous. Reactive oxygen species (ROS) produced inside the cell arises due to oxidation, methylation and deamination and constitute important endogenous risk factors. On the other hand factors like smoking, ultraviolet rays, chemical mutagens, air pollution are important exogenous risk factors responsible for the generation of ROS. ROS start acting as a risk factor when an imbalance occurs between biochemical antioxidants and ROS. Oxidative stress has been observed in cancerous cells compared to normal cells therefore it may be related to oncogenic stimulus. ROS developed in the process are responsible for oxidative damage and development of cytotoxic DNA lesions such as 8-hydroxoguanine (8-oxo-G) and 7, 8-dihydro-8oxo-2′-deoxyguanosine. These lesions are studied to be cytotoxic, mutagenic and contribute towards neuro-degeneration, ageing and cancer. The lesion 8-oxo-G can base pair with adenine as well as cytosine thereby responsible for G:C-T:A transversions.

Human glycosylases, responsible for removal of 8-oxo-G is encoded by *hOGG1* gene. Glycosylases are the first group of enzymes that work on the base damage caused. They hydrolyzes the N-glycosyl bond between oxidized base and sugar moiety thereby releasing free damaged base and develop abasic site followed by repair of damage by polymerases and ligation [4]. *MUTYH* gene (mutY homolog) is another glycosylases which is responsible for the removal of adenine paired with 8-oxo-G or 1,2-dihydro-2-oxo-adenine(2-OH-A) [5]. *hOGG1* gene is mapped on chromosome 3 at 3p26.2, and encodes a 345 amino acid product. *hOGG1* gene is highly polymorphic and it has been reported that it has 231 single nucleotide polymorphisms (SNPs) and out of these, twenty five SNPs have reported an amino acid change [6] where out of them $Ser^{326}Cys$ has been immensely explored an it is located on exon 7. On the same lines *MUTYH* $Gln^{324}His$ is extensively analyzed for its effects on cancer. The gene *MUTYH* is located on chromosome 1at 1p34.1. It spans a region of 11.2 kb. Initial studies revealed that recessive familial form of colorectal cancer (CRC) known as MUTYH associated polyposis (MAP) was linked to *MUTYH* gene of base excision repair pathway. It has been also speculated that biallelic germline mutations in *MUTYH* gene were associated with increased colorectal risk [7].

To this end this study is focused on susceptibility and prognosis of lung cancer patients treated with platinum based doublet chemotherapy in relation to SNPs *hOGG1* $Ser^{326}Cys$ (rs1052133) and *MUTYH* $Gln^{324}His$ (rs3219489). These SNPs of the two genes have been explored in many cancers such as colorectal [8], head and neck [5], pancreas [9], lung [4]. Prognosis of lung cancer has also been altered by the two above discussed SNPs in cancers like lung [2], colorectal cancer [10]. However, till the literature is surveyed our study is first of its type in Indian population. We intend to use candidate pathway based approach to analyze the concomitance of the two SNPs towards lung cancer.

Material and Methods

Patient Recruitment

The present study is a hospital based study consisting of 326 lung cancer cases and 330 cancer-free control subjects registered at the Department of Pulmonary Medicine, PGIMER Chandigarh. Each study subject was informed about the study and a written consent was obtained from them. Ethical clearance was obtained from the Ethical committee of Post Graduate Institute of Medical Education & Research (PGIMER). We followed the same patients' recruitment method as discussed in our former study [11].The clinical details were obtained from medical records of the patients, whereas smoking history and family details were collected through individual questionnaire.

Chemotherapy Treatment

Study subjects enrolled in the study were inoperable and were treated with the following chemotherapy; Cisplatin or Carboplatin in combination with either Docetaxel, Irinotecan or Pemetrexed. Dosages were as follow Docetaxel 75 mg/m^2, 500 mg/m^2Pemetrexed or 100 mg/m^2Irinotecan (administered as a 1-h infusion, followed by cisplatin 65 mg/m2 administered over 3-h as an intravenous infusion). A total of (172) patients were administered the chemotherapeutic treatment. Seventy patients were given Docetaxel + Cisplatin/ Docetaxel + Carboplatin, forty seven were administered Pemtrexed + Cisplatin/Pemtrexed + Carboplatin, and remaining fifty five were given Irinotecan + Cisplatin/Irinotecan + Carboplatin. Patients were administered all chemotherapeutic drugs intravenously, and treatment cycles were repeated every 3–4 weeks.

Follow Up and Response Assessment

One of the important assessment of our study is overall survival and to evaluate relationship between genetic polymorphism and treatment response. For overall survival patients were followed through telephonic conversation, every two months till death or the end of the study period. They were inquired about their health and survival. Tumor response assessment was done using Response Evaluation Criteria in Solid Tumors (RECIST) criteria. By using RECIST criteria responses were broadly classified into four categories: complete response (CR), partial response (PR), stable disease (SD), and progression disease (PD). For analysis, we grouped CR and PR as "responders" and SD and PD as "non-responders".

DNA Extraction and Genotyping

We followed phenol chloroform extraction protocol for isolation of DNA from blood collected from the patients as, discussed in our other study [12]. The primer sequence for *hOGG1* Ser^{326}Cys was F-5'ctgttcagtgccgacctgcgccga3', and R-5'atcttgttgtgcaaactgac3'. The product size was 247 bp and MBOI was used for digestion [13]. Genotyping for *MUTYH* Gln*324*His was carried out by PCR-CTTP (Polymerase Chain Reaction with Confronting two pair primers). Two pair of primers were used for the procedure. The primer sequence for genotyping of *MUTYH* Gln*324*His were F1: 5′-CCTG TCGGGCAGTCCTGACG-3′ and R2: 5′-GAGGCAGGC ACAGGTGGCAC-3′ which gave a product of 241 bp. The other set of primer was F2 5′-CCCAGC TCCCAACA CTGGACAC-3'and 5′-CGCTGAAGCTGCTCTGAGGGC-3′ which gave product of 362 bp. [14].

Statistical Analysis

Statistical analysis was performed using Medcalc version 15.11.4 (Medcalc Software, Ostend, Belgium) and SPSS Version 20.0. Descriptive data for the major characteristics of the study was expressed as mean and percent. Pearsons$\chi 2$ test (gender) and independent sample t-test (age) were used to assess the differences of qualitative and quantitative data respectively. Logistic regression analysis was performed to analyze the relation between polymorphisms and lung cancer risk using age, sex and smoking as confounding factors. Association was expressed as Odds ratio (OR) with 95% confidence interval (95% C.I.) and $p < 0.005$ statistical significance. Overall survival for the two polymorphisms was assessed using Kaplan Meier and Log rank test. Cox proportional hazard model was used to calculate the hazard rate and assess the effect of genetic polymorphism on overall survival after adjusting for other covariates. Relation between response and genetic polymorphisms, adjusted for age, gender, smoking, stage, histology, and performance status and chemotherapy regimen was calculated using Logistic regression.

Results

Distribution of *OGG1* and *MUxTYH* and Clinical Features

Table 1 depicts the demographic and clinical characteristics of 330 healthy controls and 326 lung cancer cases for the two genes *OGG1 Ser^{326}Cys* and *MUTYH Gln^{324}His*. The mean age for cases and control was 57.72 ± 10.57 and 53.60 ± 10.17 respectively. There was no difference in gender distribution ($p = 0.305$) between cases (males: 282, 79.4%; females: 44, 13.4%) and controls (males: 275, 83.3%; females: 55, 16.6%). When smoking was taken as a factor it was observed that lung cancer patients had more representation as compared to control subjects (79.4% vs 72.1), however the frequency of non-smokers was higher in control subjects as compared to cases (27.8% vs 20.5%). When total cumulative smoking dose was evaluated it was observed that cases had higher mean pack years 27.9 ± 34.8 as compared to controls 17.9 ± 19.8 ($p < 0.0001$). Furthermore, when lung cancer patients were stratified on the basis of histological stratification, it revealed that there were 111(34.0%) adenocarcinomas, 138 (42.3%) squamous cell carcinomas, 75(23.0%) small cell lung carcinomas patients. The study classified 4(1.2%) stage I patients, 14(4.2) stage II patients, 151(46.3) stage III patients, 138(42.3%) stage IV patients and 19(5.8%) were unclassified.

We also carried out the survival analysis in our study where we did a follow up study for of 251patients was recorded with 220 (87.6%) events. Lung cancer subjects were distributed according to Eastern cooperative oncology group (ECOG) performance status (PS). There were 114(45.4%) patients with ECOG PS of 0–1, 96(38.2%) with ECOG PS 2 and 41(16.3%) with ECOG PS 3–4. The Karnofsky's performance scores (KPS) distribution revealed that there were 161(64.1%) subjects with KPS of 100–80, 81(32.2%) subjects with KPS of 70–60 and only 9(3.5%) cases with KPS of 50–40. Patients diagnosed with lung cancer were administered platinum based doublet chemotherapy. There were in total 172 patients who were administered the three chemotherapy regimens intravenously as described in methods section. In our study, 70(40.6%) patients were administered cisplatin/carboplatin along with docetaxel, followed by 47(27.3%) patients who were given cisplatin/carboplatin in combination with irrinotecan and 55(31.9%) were given cisplatin/carboplatin along with pemetrexed.

Overall and Histological Distribution and Risk Associated

The genotypic and allelic distribution and risk associated with *OGG1 Ser^{326}Cys* and *MUTYH Gln^{324}His* polymorphisms are summarized in Table 2. The genotypic frequencies for controls of *MUTYH Gln^{324}His* followed the Hardy Weinberg Equilibrium (HWE) ($\chi 2 = 1.13$, $p = 0.286$), however the *OGG1 Ser^{326}Cys* showed deviation from the HWE. Analysis revealed that in case of *OGG1 Ser^{326}Cys* both the wild type (Ser/Ser*)* and mutant type (Cys/Cys) genotype were found to be over-represented in controls as compared to cases (18.1 vs. 9.5 and 24.5 vs. 7.6). Risk analysis revealed that single allelic variant (*Ser/Cys*) carriers had a two-fold increased risk towards lung cancer (OR = 2.44, 95%C.*I* = 1.50–3.9, $p = 0.0003$) as compared to control group carrying the same genotype. On the contrary carriers of double allelic variants (Ser/Ser) or mutants exhibited a protective effect towards lung cancer (OR = 0.4, 95%C.I. = 0.22–0.87, $p = 0.0185$). Combining both the

Table 1 Demographic characteristics among cases and controls

Variable	Cases, n (%) $N = 326$	Controls, n (%) $N = 330$	p – value
Age (years) Mean ± SD	57.72 ± 10.57	53.60 ± 10.17	
Range			
Gender			
Male	282 (86.5)	275 (83.3)	0..305
Female	44 (13.4)	55 (16.6)	
Smoking status			
Smokers	259 (79.4)	238 (72.1)	0.03
Non–smokers	67 (20.5)	92 (27.8)	
Pack years Mean±SD	27.9 ± 34.8	17.9 ± 19.8	<0.0001
Histology			
ADCC	111 (34.0)		
SQCC	138 (42.3)		
SCLC	75 (23.0)		
Others	2 (0.6)		
TNM staging			
I	4 (1.2)		
II	14 (4.2)		
III	151 (46.3)		
IV	138 (42.3)		
Unclassified	19 (5.8)		
Overall survival		$N = 251$	
ECOG performance status			
0–1		114 (45.4)	
2		96 (38.2)	
3–4		41 (16.3)	
KPS performance status			
100–80		161 (64.1)	
70–60		81 (32.2)	
50–40		9 (3.5)	
Events, Deaths		220 (87.6%)	
Chemotherapy regimen		$N = 172$	
Docetaxel+Cisplatin /Docetaxel +Carboplatin		70 (40.6)	
Irinotecan+cisplatin/ Irinotecan +Carboplatin		47 (27.3)	
Pemetrexed+Cisplatin/Pemetrexed +Carboplatin		55 (31.9)	

Abbreviations: *SD* Standard Deviation, *n* total number of case patients or control subjects

[a] p-values were derived from Pearson Chi – square test except age; Student t-test was used for age. All p-values are two – sided. $p < 0.05$ was considered statistically significant

single (Ser/Cys) and double allelic variants (Cys/Cys) a 2 fold risk was observed towards lung cancer (OR = 1.8, 95%C.I. = 1.17–3.05, $p = 0.009$) which was found to be significant. Furthermore, histological stratification analysis showed that subjects who were heterozygous (Ser/Cys) for *OGG1* $Ser^{326}Cys$ genotype possessed a four-fold high risk towards adenocarcinomas (OR = 4.72, 95%C.I. = 2.0–10.65, $p = 0.0002$). Further SQCC subtype did not show any prominent relation with lung cancer. Study subjects who were carrying single allele of variant genotype (Ser/Cys) exhibited a high propensity towards SCLC (OR = 2.55, 95%C.I. =0.98–6.61, $p = 0.052$).

In case of *MUTYH* $Gln^{324}His$ polymorphism and lung cancer risk, it was observed that controls had a higher frequency of wild (Gln/Gln) and mutant type (His/His) type as compared to cases (68.7 vs. 48.7 and 3.9 vs. 1.5). Overall risk analysis revealed that subjects carrying the heterozygous (Gln/His) genotype had a two-fold risk towards ADCC (OR = 2.6, 95%C.I. =1.8–3.7, $p < 0.0001$). When the polymorphic variant of MUTHY was analyzed on basis of histological

Table 2 Genotypic distribution of the OGG1 and MUTYH genetic variants and their association with risk of Lung cancer along with the stratified association analysis based on histology

	Controls n (%) N = 330	OVERALL			ADCC			SQCC			SCLC		
		Cases n (%) N = 326	AOR (95% CI)[a]	p^b	Cases n (%) *N* = 111	AOR (95% CI)[a]	p^b	Cases n (%) *N* = 138	AOR (95% CI)[a]	p^b	Cases n (%) *N* = 75	AOR (95% CI)[a]	p^b
OGG1 $Ser^{326}Cys$ (C/G)													
CC	60 (18.1)	31 (9.5)	1		61 (54.9)	1		62 (44.9)	1		35 (46.6)	1	
CG	189 (57.2)	270 (82.8)	2.44 (1.50–3.9)	0.0003	48 (43.2)	4.72 (2.0–10.65)	0.0002	75 (54.3)	1.32 (0.70–2.49)	0.38	38 (50.6)	2.55 (0.98–6.61)	0.052
CC	81 (24.5)	25 (7.6)	0.4 (0.22–0.87)	0.0185	2 (1.8)	0.67 (0.19–2.27)	0.52	1 (0.7)	0.26 (0.10–0.65)	0.004	2 (2.6)	0.43 (0.11–1.62)	0.21
CG + GG	270 (81.8)	295 (90.4)	1.88 (1.17–3.05)	0.0093	50 (45.0)	3.63 (1.61–8.16)	0.0018	76 (55.0)	1.0 (0.54–1.89)	0.97	40 (53.3)	1.98 (0.76–15.1)	0.158
C	309	332											
G	351	320											
MAF	0.48	0.49											
MUTYH Gln^{324} His (G/C)													
GG	227 (68.7)	159 (48.7)	1		61 (54.9)	1		62 (44.9)	1		35 (46.6)	1	
GC	90 (27.2)	162 (49.6)	2.6 (1.8–3.70)	<0.0001	48 (43.2)	2.08 (1.30–3.3)	0.0022	75 (54.3)	2.88 (1.86–4.44)	<0.0001	38 (50.6)	2.3 (1.34–4.14)	0.0027
CC	13 (3.9)	5 (1.5)	0.59 (0.200–1.75)	0.34	2 (1.8)	0.59 (0.12–2.85)	0.51	1 (0.7)	0.26 (0.03–2.24)	0.22	2 (2.6)	1.18 (0.24–5.71)	0.83
GC + CC	103 (31.2)	167 (51.2)	2.64 (1.88–3.70)	<0.0001	50 (45.0)	1.88 (1.19–2.98)	0.0065	76 (55.0)	2.5 (1.67–3.91)	<0.0001	40 (53.3)	2.26 (1.3–3.89)	0.0032
G	544	480											
C	116	172											
MAF	0.17	0.26											

Abbreviations: *ADCC* Adenocarcinoma, *SQCC* Squamous cell carcinoma, *SCLC* Small cell lung carcinoma

[a] Two- sided $\chi 2$ test for either genotype distribution or allelic frequencies between the cases and controls

[b] Adjusted Odds ratios, 95% confidence intervals and their corresponding p-values were calculated by unconditional logistic analysis after adjusting for age, gender, smoking status

stratification, our data showed that patients with the heterozygous genotype (Gln/His) had an increased risk for the development of all the three subtypes of lung cancer. ADCC showed a 2 fold risk (OR = 2.08, 95% C.I. = 1.30–3.3, $p = 0.002$), SQCC exhibited almost 3 fold risk (OR = 2.88, 95%C.I. = 1.86–4.44, $p < 0.0001$) and SCLC depicted a 2-fold risk (OR = 2.3, C.I. =1.34–4.14, $p = 0.002$).

OGG1/MUTHY Polymorphisms and Smoking Interaction

Association analysis was extended further to investigate the effect of smoking on lung cancer. In case of *OGG1 Ser^{326}Cys* it was observed that smokers who were carriers of double allelic variant genotype (Cys/Cys) had a protective effect towards lung cancer (OR = 0.3, 95%C.*I* = 0.13–0.6, $p = 0.002$). On the contrary our study reports that, carriers of single allelic variants (Ser/Cys) had a higher propensity towards lung cancer especially for non-smokers (OR = 7.9, 95C.I. =2.94–21.2, $p < 0.0001$). Since the frequency of the mutant genotype was very small we combined the two genotypes together as a single genotype (Ser/Cys + Cys/Cys). Our data suggests that a high risk of lung cancer was found to be implicated for non-smokers (OR = 5.7, 95%C.I. =2.2–15.1, $p = 0.0004$). In case of *MUTHY* it was observed that smoker subjects who were heterozygous for *MUTHY Gln^{324}His* of single allelic variants (*GC*) in case of MUTYH Gln^{324}His exhibited a 2-fold risk for lung cancer (OR = 2.35, C.I. = 1.59–3.4, $p = <0.0001$). Similarly, heterozygotes (Gln/His) were at high risk in non-smokers (OR = 3.37, C.I. =1.62–7.02, $p = 0.001$) (Table 3).

Combination of OGG1 Ser^{326}Cys and MUTYH Gln^{324}His and Risk Associated

Table 4 shows the combinatorial assessment of the SNPs of the two genes and its synergistic role towards development for lung cancer. Our data reveals that the subjects who were carrying a single variant copy of both the SNP's i.e. (Ser/Cys + Gln/His) had a very high propensity towards lung cancer (OR = 7.26, 95%C.I. =3.5–14.97, $p < 0.0001$). Furthermore, when the combined genotypes of both SNPs' were stratified towards histology, it was observed that individuals who were heterozygotes (Ser/Cys/ Gln/His) for both the SNPs had a 14-fold risk towards ADCC development (OR = 14.1, 95% CI =4.00–50.30, $p = <0.001$). Both SQCC (OR = 5.0, 95%CI = 1.92–13.10, $p = 0.001$) and SCLC (OR = 5.7, 95%CI = 1.39–23.4, $p = 0.015$) were also found to be associated towards lung cancer risk.

Overall and Histological Prognostic Role of OGG1 Ser^{326}Cys and MUTYH Gln^{324}His

Overall survival did not show much modification due to the two SNPs. In case of *OGG1 Ser^{326}Cys* the median survival time was higher for carriers of homozygous wild type (Ser/Ser) and homozygous variant genotype (Cys/Cys) (MST = 12.0 vs. 16.1, Log Rank $p = 0.54$) though statistically insignificant as compared to subjects who were heterozygotes (Ser/Cys). Further, multivariate analysis by Cox-regression revealed almost no effect on hazard rate. In case of *MUTYH Gln^{324}His* median survival time for mutant (His/His) genotype was almost double in comparison to wild type (Gln/Gln) (MST = 15.3 vs.7.6 Log

Table 3 Genotypic distribution of genetic variants based on smoking status and its association with risk of Lung Cancer

	SMOKERS				NON SMOKERS			
	Controls n (%) $N = 238$	Cases n (%) $N = 259$	AOR (95% CI)[a]	p[b]	Controls n (%) $N = 92$	Cases n (%) $N = 67$	AOR (95% CI)[a]	p[b]
OGG1 Ser^{326}Cys (C/G)								
CC	27 (11.3)	25 (9.6)	1.00 (Reference)		33 (35.8)	6 (8.9)	1.00 (Reference)	
CG	148 (62.1)	213 (82.2)	1.41 (0.79–2.58)	0.25	41 (44.5)	57 (85.0)	7.9 (2.94–21.2)	<0.0001
GG	63 (26.4)	21(8.1)	0.3 (0.13–0.6)	0.002	18(19.5)	4 (5.9)	0.77(0.16–3.78)	0.75
CG + GG	211 (88.6)	234 (90.3)	1.04 (0.57–1.90)	0.87	59 (64.1)	61 (91.0)	5.7 (2.2–15.1)	0.0004
MUTYH Gln^{324} His (G/C)								
GG	157 (65.9)	125 (48.2)	1.00 (Reference)		70 (76.0)	34 (50.7)	1.00 (Reference)	
GC	72 (30.2)	131(50.5)	2.35 (1.59–3.4)	<0.0001	18 (19.5)	31 (46.2)	3.37 (1.62–7.02)	0.001
CC	9 (3.7)	3 (1.15)	0.48 (0.12–1.93)	0.30	4(4.3)	2 (2.9)	0.95(0.16–5.58)	0.95
GC + CC	81 (34.0)	134 (51.7)	2.14 (1.47–3.12)	0.0001	22 (23.9)	33 (49.2)	2.91 (1.45–5.80)	0.0025

[a] Adjusted Odds ratios, 95% confidence intervals and their corresponding p-values were calculated by unconditional logistic analysis after adjusting for age, gender, smoking status

[b] Two-sided χ^2 test for either genotype distribution or allelic frequencies between the cases and controls

Table 4 Genotypic distribution of the OGG1 and MUTYH genetic variants and their association with risk of Lung cancer along with the stratified association analysis based on histology

OGG1Ser^{326}Cys & MUTYH Gln^{324} His	Controls n (%) $N = 94$	OVERALL			ADCC			SQCC			SCLC		
		Cases n (%) $N = 144$	AOR (95% CI)[a]	p[b]	Cases n (%) $N = 42$	AOR (95% CI)[a]	p[b]	Cases n (%) $N = 68$	AOR (95% CI)[a]	p[b]	Cases n (%) $N = 34$	AOR (95% CI)[a]	p[b]
0	41 (43.6)	14 (9.7)	1		4 (54.9)	1		7 (10.2)	1		3 (8.8)	1	
1	50 (53.1)	129 (89.5)	7.26(3.5–14.97)	<0.0001	38 (43.2)	14.1(4.00–50.30)	<0.001	60 (88.2)	5.0(1.92–13.00)	0.001	31 (91.1)	5.7(1.39–23.4)	0.015
2	3 (3.1)	1 (0.6)	0.8(0.06–10.78)	0.8	–		–	1 (1.4)	2.0(0.13–29.30)	0.61	–		
3	53 (56.3)	130 (90.2)	6.8(3.24–14.70)	<0.0001	38 (43.2)	12.6 (3.60–43.50)	0.0001	61 (89.7)	4.75(1.84–12.26)	0.0013	31 (91.1)	5.3(1.31–21.48)	0.0192

Abbreviations: *ADCC* Adenocarcinoma, *SQCC* Squamous cell carcinoma, *SCLC* Small cell lung carcinoma

[a] Two- sided $\chi 2$ test for either genotype distribution or allelic frequencies between the cases and controls

[b] Adjusted Odds ratios, 95% confidence intervals and their corresponding p-values were calculated by unconditional logistic analysis after adjusting for age, gender, smoking status

Rank $p = 0.61$). Similar to the above gene, hazard rate was unaffected with the SNPs as given in Table 5.

Stratified analysis suggested that in case of *OGG1 Ser^{326}Cys* mutant genotype (Cys/Cys) had almost double the survival time than heterozygotes (Cys/Ser) (MST = 13.0 vs.7.6) for ADCC subtype. Similarly the survival time was higher for mutant genotype for SQCC (MST = 14.2, $p = 0.78$) and SCLC (MST = 20.3, $p = 0.85$) subtype when compared to wild type as shown in Table 6.

Chemotherapeutic Regimen and Overall Survival

The chemotherapeutic drugs were administered to the study subjects in a cyclic manner. Patients were analyzed for independent effect of drugs on survival of lung cancer patients. The three chemotherapeutic regimens administered along with Cisplatin/Carboplatin were docetaxel, pemetrexed, irinotecan. In case of *OGG1 Ser^{326}Cys* patients who were administered docetaxel and carrying the wild type genotype (Ser/Ser) had a higher MST as compared to subjects carrying heterozygous genotype (Ser/Cys) (MST = 12.1 vs 7.5). Further, subjects with double allelic variants (Cys/Cys) showed a better survival with 15.7 months. However, cox-regression analysis did not show any effect on survival. Further, patients given pemtrexed along with cisplatin/carboplatin showedthat carriers of single allelic variants (Ser/Cys) showed a significant survival of 20.3 months. However, a high death rate was observed for heterozygous (Ser/Cys) genotype (OR = 3.97, 95C.I. = 1.04–15.08, $p = 0.04$). Irrinotecan was given majorly to SCLC subtype where it was observed that study subjects treated with irinotecan showed an improved survival compared to the other two regimens. Subjects with wild type genotype (Ser/Ser) showed a poor MST of 0.56 months as compared to 9.1 months in case of heterozygotes (Ser/Cys) which was significant ($p < 0.0001$). The hazards rate was very small for the same genotype (HR = 0.051, 95%C.I. = 0.0076–0.349, $p = 0.0025$). MST improved further for the double allelic variant carriers (Cys/Cys) (MST =16.5, $p = 0.038$). As the sample size was very small for double allelic carriers the Cox regression could not solve the equation.

Furthermore, for MUTYH Gln^{324}His the survival analysis for the chemotherapeutic drugs independently did not show any significant alteration. Subjects given Docetaxel along with platinum with mutant genotype (His/His) showed a smaller MST of 3 fold as compared to10.1 months for wild type genotype (Gln/Gln) ($p = 0.0096$). Univariate analysis showed a high death rate for the same genotype.Whereas, multivariate analysis did not show much modification in the death rate as shown in the Table 7.

Table 5 OGG1 and MUTYH polymorphic variants and their association with overall survival

GENES	CASES n (%) $N=251$	DEATH n (%) $N=219$	ALIVE n (%) $N=32$	Univariate analysis			Multivariate analysis	
				MST (months)	Log rank p-value	Unadjusted HR[a]	Adjusted HR[b] (95% CI)	p-value
OGG1 $Ser^{326}Cys$								
CC	24(9.5)	20(9.1)	4(12.5)	12.0		1	1	
CG	210(83.6)	185(84.4)	25(78.1)	7.2	0.42	1.20	1.0(0.66–1.71)	0.79
GG	17(6.7)	14(6.3)	3(9.3)	16.1	0.54	0.81	0.70(0.46–1.06)	0.10
CG + GG	227(90.4)	199(90.8)	28(87.5)	7.3	0.50	1.16	0.98(0.72–1.3)	0.92
MUTYH Gln^{324} His								
GG	116(46.2)	98(44.7)	18(56.2)	7.6		1	1	
GC	125(49.8)	112(51.1)	13(40.6)	7.5	0.50	1.09	1.08(0.81–1.44)	0.58
CC	10(3.9)	9(4.1)	1(3.1)	15.3	0.75	0.89	0.9(0.64–1.29)	0.61
GC + CC	135(53.7)	121(55.2)	14(43.7)	7.5	0.56	1.08	1.05(0.79–1.39)	0.72

[a] Unadjusted hazards ratio for Kaplan meier analysis

[b] Hazards ratio adjusted for age, sex, smoking, histology, stage, KPS, ECOG

OGG1 $Ser^{326}Cys$ and MUTYH $Gln^{324}His$ and their Response Towards Chemotherapy

The treatment outcome for the two SNPs was analyzed making use of response factors. There were in total 148 patients with treatment outcome data. Patients with complete remission (CR) and partial remission (PR) together were defined as "Good responders" and patients with stable disease (SD) and partial disease (PD) were classified as "Poor responders". OGG1 $Ser^{326}Cys$ was classified as good responders irrespective of the genotype as shown in the Table 8. Whereas in case of MUTYH $Gln^{324}His$ no clear indication was observed either towards good responders or poor responders as an adjusted odds ratio of nearly 1 was obtained as shown in Table 8.

Discussion

An increasing body of evidence suggests that oxidative stress is associated with increased initiation and progression of carcinogenesis and aging. DNA repair genes are the candidate susceptibility genes in the etiology of lung cancer, since reactive oxygen species produces a stable guanine product called 8-oxoguanine and repair of mutations involving 8-oxoguanine is a multistep process dependent on proteins of two genes MUTYH and OOG1. The polymorphic variants OGG1 Ser326Cys (rs1052133) and MUTYH Gln324His (3219489) are extensively studied for their roles in cancer susceptibility and prognosis. OGG1 Ser326Cys has been observed to have a reduced excision capacity of 8-oxoguanine from double stranded DNA [15]. Our investigative study showed that single allelic variants (*CG*) is responsible for high risk towards lung cancer (OR = 2.44, $p = 0.0003$) which is supported by other studies on lung cancer by Biuan et al. [16]. However there are studies which varied our results where no effect were observed in relation to the heterozygous genotype for OGG1 Ser326Cys [17, 18]. One of the study by Marchand et al. [19] suggested a likely protective effect of heterozygous genotype for Caucasian population and no effect in case of Japanese and Hawaiian population. One of the study in Brazilian population contradicted our study where a protective effect (OR = 0.46) was observed for the heterozygous genotype [20]. Furthermore, studies carried out in colorectal cancer [21] and head and neck [5] were in concordance with our study.

The combined variants (*CG + GG*) showed a significant increased risk towards lung cancer (OR = 1.99, $p = 0.0093$) in our study whereas a study on lung cancer showed no effect for the same genotype [22]. Whereas, study in North Indian population by Mittal et al. in bladder and prostate cancer showed similar results as our study [23] in relation to combined variant genotype. Carriers of double allelic variants (*GG*) are protective towards lung cancer (OR = 0.4, $p = 0.018$) similar to a study conducted in turkey population [24] and a study by De Ruyck et al. [25]. However certain studies in lung cancer [18, 22] and prostate cancer [23] showed varied results from our work.Whereas, some studies contradicted our study where a high risk was observed for the double allelic variants in lung [19] head and neck [5] and bladder cancer [23].

Stratified analysis according to histology revealed that single allelic carriers in case of OGG1 Ser326Cys showed a high susceptibility towards ADCC subtype of lung cancer (OR = 4.72, $p = 0.0002$). On similar lines a high susceptibility was observed towards SCLC subtype (2.55, $p = 0.052$). Population studies indicated no association of OGG1 Ser326Cys towards ADCC susceptibility [26, 27]. A study in Turkey population showed no effect towards ADCC

Table 6 Association of OGG1 and MUTYH on overall survival according to tumor histology

GENES	ADCC						SQCC						SCLC					
	Cases n (%) $N = 88$	Univariate analysis			Multivariate analysis		Cases n (%) $N = 104$	Univariate analysis			Multivariate analysis		Cases n (%) $N = 59$	Univariate analysis			Multivariate analysis	
		MST	*p*-value	HR[a]	H.R[b]	*p*-value		MST	*p*-value	HR[a]	H.R[b]	*p*-value		MST	*p*-value	HR[a]	H.R[b]	*p*-value
OGG1 $Ser^{326}Cys$ (N)																		
CC (24)	6 (28.9)	8.3		1	1		13 (12.5)	10.2		1	1		5 (8.4)	12.0		1	1	
CG (210)	76 (49.3)	7.6	0.84	1.09	0.90 (0.32–2.5)	0.85	85 (81.7)	6.4	0.78	1.09	1.24 (0.61–2.49)	0.54	49 (83.0)	7.3	0.28	1.70	1.7 (0.57–5.4)	0.31
GG (17)	6 (21.)	13.0	0.49	0.64	–	–	6 (5.7)	14.2	0.78		–	–	5 (8.4)	20.3	0.85	0.88	–	–
CG + GG (227)	81 (71.08)	8.3	0.9	1.05	0.7 (0.28–2.1)	0.64	91 (87.5)	6.8	0.8	1.07	1.19 (0.59–2.39)	0.61	54 (91.5)	8.2	0.33	1.62	1.45 (0.47–4.42)	0.51
MUTYH Gln^{324} His (N)																		
GG(116)	49 (75.)	9.2		1	1		42 (81.1)	8.0		1	1		25 (80.0)	3.5		1	1	
GC(125)	36 (22.8)	7.1	0.68	1.1	1.16 (0.68–1.95)	0.55	58 (18.8)	6.4	0.44	1.18	0.89 (0.50–1.58)	0.69	31 (20.2)	9.0	0.88	1.04	0.90 (0.47–1.70)	0.75
CC(10)	3 (1.2)	5.1	0.84	0.86	0.79 (0.36–1.76)	0.58	4 (3.8)	10.6	0.7	1.16	–		3 (5.0)	15.3	0.51	0.67	0.84 (0.41–1.69)-	0.62
GC + CC(51)	39	8.3	0.77	1.06	1.03 (0.65–1.65)	0.87	62 (59.6)	7.3	0.48		1.17 (0.76–1.80)	0.46	34 (57.6)	10.4	0.89	0.96	0.77(0.42–1.39	0.39

[a] Unadjusted hazards ratio for Kaplan meier analysis

[b] Hazards ratio adjusted for age, sex, smoking, stage, KPS, ECOG

Table 7 Association of OGG1 and MUTYH SNPs with chemotherapy regimen and overall survival

GENES	Cisplatin/Carboplatin + Docetaxel						Cisplatin/Carboplatin + Irinotecan						Cisplatin/Carboplatin + Pemtrexed					
	Cases n (%) $N = 70$	Univariate analysis		Multivariate analysis			Cases n (%) $N = 47$	Univariate analysis		Multivariate analysis			Cases n (%) $N = 55$	Univariate analysis		Multivariate analysis		
		MST	*p*-value	HR[a]	H.R[b]	*p*-value		MST	*p*-value	HR[a]	H.R[b]	*p*-value		MST	*p*-value	HR[a]	H.R[b]	*p*-value
OGG1 $Ser^{326}Cys$ (C/G) N = 172																		
CC (13)	5 (7.1)	12.1		1	1		6 (12.7)	–		1	1		2 (3.6)	0.56		1	1	
CG (147)	61 (87.1)	7.5	0.9	0.94	1.27 (0.31–5.15)	0.7	36 (76.5)	7.0	0.04	2.96	3.97 (1.04–15.08)	0.04	50 (90.9)	9.1	<0.0001	0.076	0.051 (0.0076–0.349)	0.0025
GG (12)	4 (5.7)	15.7	0.24	0.46	–	–	5 (10.6)	20.3	0.53	1.59	–	–	3 (5.4)	16.5	0.038	0.194	–	–
CG + GG(159)	65 (92.8)	8.0	0.82	0.90	1.24 (0.31–4.86)	0.75	41 (87.2)	7.3	0.05	2.89	3.12 (0.81–12.0)	0.09	53 (96.3)	9.4	<0.0001	0.071	0.056 (0.0076–0.336)	0.0021
MUTYH Gln^{324} His (G/C)																		
GG(82)	30 (42.8)	10.1		1	1		17 (36.1)	6.7		1	1		35 (63.6)	9.4		1	1	
GC(84)	38 (54.2)	8.2	0.50	1.19	1.32 (0.75–2.32)	0.32	28 (59.5)	9.0	0.86	1.05	0.93 (0.40–2.14)	0.87	18 (32.7)	8.8	0.8	1.07	1.07 (0.52–2.2)	0.83
CC(6)	2 (2.8)	3.6	0.0096	5.34	–	–	2 (4.2)	–	0.3	0.36	0.74 (0.12–4.32)	0.74	2 (3.6)	4.0	0.05	1.16	1.75 (0.65–4.66)	0.26
GC + CC(90)	40 (57.1)	6.4	0.39	1.25	1.37 (0.79–2.38)	0.26	30 (63.8)	10.4	0.98	0.99	0.90 (0.39–2.08)	0.81	20 (36.3)	7.5	0.60	3.54	1.16 (0.57–2.33)	0.67

[a] Unadjusted hazards ratio for Kaplan meier analysis

[b] Hazards ratio adjusted for age, sex, smoking, stage, KPS, ECOG, histology

Table 8 Effect of OOG1 and MUTYH SNPs and treatment outcome

Genotype	Good response n (%) $N = 85$	Poor response n (%) $N = 63$	Adjusted OR (95% CI)[a]	p-value[b]
OGG1 $Ser^{326}Cys$ (C/G)				
CC	7 (8.2)	8 (12.6)	1	
CG	73 (85.8)	51 (80.9)	2.32 (0.61–8.76)	0.21
GG	5 (5.8)	4 (6.3)	1.92 (0.33–11.02)	0.46
CG+GG	82 (96.4)	55 (87.3)	1.77 (0.54–5.78)	0.39
MUTYH Gln^{324} His (G/C)				
GG	38 (44.7)	33 (52.3)	1	
GC	44 (51.7)	29 (46.0)	1.10 (0.50–2.40)	0.79
CC	3 (3.5)	1 (1.5)	0.93 (0.25–3.45)	0.91
GC+CC	47 (55.2)	30 (47.6)	1.08 (0.50–2.32)	0.82

[a] Adjusted Odds ratios, 95% confidence intervals and their corresponding p-values were calculated by unconditional logistic analysis after adjusting for age, gender, smoking status, histology, stage, regimen, KPS, ECOG

[b] Two-sided χ^2 test

whereas a protective effect was observed for double allelic variant genotype towards SCLC similar to our study [24].

MUTYH is responsible for repair of A-8oxoG. However germline mutation in MUTYH is related to heritable colorectal polyposis. However, in our attempt to look for the association of polymorphic MUTYH with lung cancer, our study suggested that carriers of single allelic variants (GC) possessed a increased risk (OR = 2.6, $p < 0.0001$) towards lung cancer similar to the study on Japanese population [28]. Cancers like colorectal cancer also had similar results where heterozygous genotype was showing an increased risk towards cancer [29]. Further study by Biyun et al. showed no effect of heterozygotes towards lung cancer. Similarly study in Glucoma did not show any association with heterozygotes [30]. The combined variant again had a high susceptibility towards lung cancer similar to the study in colorectal cancer [8]. Histological analysis of our study suggested a significant 2 fold susceptibility of single allelic variants (GC) and combined variants (GC + CC) unanimously for the three histology. Whereas, lung cancer study in Japanese population showed a borderline risk towards adenocarcinomas and squamous cell carcinoma with respect to double allelic variant genotype. The carcinogenic exposure, difference in ethnicity, sample size might be the reasons that contribute to the discrepancy between our studies and previous studies.

Tobacco smokes accounts for huge generation of ROS species thereby oxidative damage. Studies have shown that patients who are smokers have huge content of 8-oxoGua in their urine. In this context smoking analysis in our study revealed that heterozygotes (CG) for OGG1 Ser326Cys in case of smokers showed a protective effect towards lung cancer (OR = 0.3, $p = 0.002$). Whereas, single allelic variants (CG) and combined variants (CG + GG) increased the risk of non-smokers towards lung cancer (OR = 7.9, $p < 0.0001$; OR =

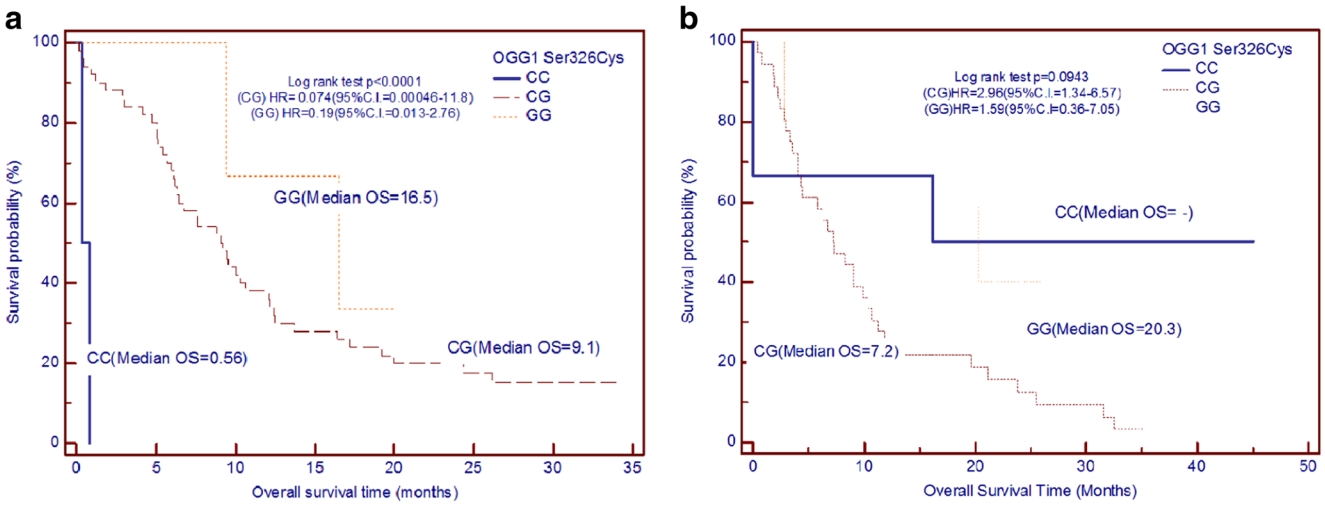

Fig. 1 Kaplan Meier overall survival curve for *OGG1 Ser326Cys*. **a** Treated with Cisplatin/Carboplatin+Irrinotecan **b** Treated with Cisplatin/Carboplatin+Pemetrexed

5.7, $p = 0.0004$ respectively). Similar to our study lung cancer study in Japanese population showed that single allelic variants (CG) possessed a high risk towards lung cancer in non-smokers whereas carriers of double allelic variants (GG) did not show any effect on lung cancer [28]. Chinese study by Li et al. revealed that polymorphic OGG1 did not show any affect on lung cancer irrespective of smoking status [31]. Further our study depicted that single allelic carriers (AG) in case of polymorphic MUTYH showed an increased risk towards lung cancer irrespective of smoking status.

Lung cancer survival is one of the most important issue being sought after. The present work has analyzed the overall survival in relation to the two SNPs. It was observed that better survival was observed in case of OGG1Ser326Cys for mutant genotype (GG) compared to wild type (CC) (16.1 VS. 12.0). However the hazard rate did not show much alteration. Chinese study reported some contradictory results to our study where patients with "G" allele were specifically associated with poor survival. The results were strengthened specifically in female, adenocarcinomas, early stage and light smokers [32].

On the same lines mutant type (CC) for MUTYH Gln324His proposed a better survival when compared to wild type (GG) genotype (15.3 VS. 7.6) whereas the death rate was not affected. Similar observations were made when stratified based on histology. For the three histology the MST was mostly higher for mutant type when compared to wild and heterozygous genotype for both SNPs as detailed in the results. Prior study on MUTYH in lung cancer showed no association with lung cancer [32]. Further in the present work chemotherapy regimens were independently analyzed for their affect on survival and it was observed that patients treated with pemtrexed showed a higher death rate when compared to wild type (Fig. 1b). Similarly, patients treated with irrinotecan showed a better survival when compared to wild type genotype (GC: HR = 0.051, $p = 0.0025$; GC + CC: HR = 0.056, $p = 0.0021$) (Fig. 1a). Further in case of MUTYH Gln324His it was observed that survival time was smaller for mutant type (CC) when compared to wild type (GG) (3.6 VS.10.1, $p = 0.0096$) where patients received docetaxel along with platinum drug. Consecutively, the univariate death rate was higher (H.R = 5.34) though multivariate analysis could not solve the equation may be due to less number of sample size.

Survival for lung cancer is not much evaluated in populations in relevance to the two BER genes i.e. OGG1 and MUTYH. However, one of the recent studies clearly indicated that OGG1Ser326Cys was not associated with overall survival however, OGG1Ser326Cys was associated with shorter PFS. Further the study detailed that OGG1Ser326Cys along with XRCC1 Arg399Gln showed an association with overall survival [2]. Further, OGG1 is studied to have a prognostic role in stratifying acute myeloid leukemia patients (AML) those who are likely not to respond to chemotherapy but to novel therapeutic approaches [33]. Study on rectal cancer has presented that OGG1Ser326Cys acts as an important factor towards tumor response in patients treated with chemotherapy as neo-adjuvant therapy [34]. However it was observed not to be associated with radiotherapy [35]. MUTYH is immensely studied in relation to colorectal cancer as alteration in both the alleles of MUTYH may lead to the development of colorectal cancer. It's been studied that patients with gastric cancer exhibiting low MUTYH expression showed a poor outcome when compared to the ones expressing high expression of MUTYH. Further reduced expression of MUTYH acted as an independent predictor of poor survival in gastric cancer patients [36].

Our study has many limitations which are needed to be addressed. Ours being a hospital based study lack heterogeneity of population. Stratified analysis records a very small sample size therefore its warranted that the study should be performed in a large population size.

In conclusion this is the first study in Indian population analyzing the two BER genes OGG1 and MUTYH. Worldwide there is very less data on lung cancer survival in relation to the above two genes, so this study provides an insight about both susceptibility and survival. This is the first study detailing the survival of patients when stratified for chemotherapy in relation to the two important BER genes.

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Compliance with Ethical Standards

Informed Consent Informed consent was obtained from all individual participants included in the study.

Conflict of Interest All of the authors of this manuscript report that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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