Polymerase η mRNA Expression Predicts Survival of Non–Small Cell Lung Cancer Patients Treated with Platinum-Based Chemotherapy

Paolo Ceppi,[1,2] Silvia Novello,[1] Alberto Cambieri,[1] Marina Longo,[1] Valentina Monica,[1] Marco Lo Iacono,[3] Matteo Giaj-Levra,[1] Silvia Saviozzi,[3] Marco Volante,[2] Mauro Papotti,[2] and Giorgio Scagliotti[1]

Abstract

Purpose: The effect of translesion DNA synthesis system in conferring cellular tolerance to DNA-damaging agents has been recently described. DNA polymerase η (Pol η) is part of this machinery and *in vitro* models showed that it can overcome DNA damages caused by cisplatin and UV rays. The aim of the present study was to investigate the role of Pol η mRNA expression levels in non–small cell lung cancer (NSCLC).

Experimental Design: Pol η mRNA expression levels were evaluated by real-time PCR in (*a*) formalin-fixed paraffin-embedded biopsies of 72 NSCLC patients treated with platinum-based chemotherapy, (*b*) fresh snap-frozen surgical specimens of tumor and corresponding normal lung tissue from 50 consecutive patients not treated with perioperative or postoperative chemotherapy, and (*c*) five NSCLC cell lines.

Results: High Pol η expression levels were strongly associated with shorter survival at both univariate (6.9 versus 21.1 months; $P = 0.003$) and multivariate (hazard ratio, 3.18; 95% confidence interval, 1.73-5.84; $P = 0.008$) analysis in the group of platinum-treated patients. By contrast, Pol η expression was not significantly correlated with the prognosis in surgically resected patients ($P = 0.54$) and mRNA levels did not significantly differ in tumor versus normal lung ($P = 0.82$). Moreover, endogenous Pol η mRNA expression was found to be inducible by cisplatin in three of five cell lines and significantly associated with *in vitro* sensitivity ($P = 0.01$).

Conclusions: Taken together, these data indicate Pol η as a predictive rather than prognostic marker worth of further investigation in NSCLC patients candidate to platinum-based chemotherapy.

Non–small cell lung cancer (NSCLC) accounts for up to 85% of all lung cancer diagnoses (1), and at diagnosis, the disease is already unresectable in many patients due to locoregional or metastatic spread (2). Although platinum-based chemotherapy has been definitely proven to be active in this setting, its efficacy is still limited (3). Cisplatin and carboplatin share the same mechanism of action (4) and cause monoadducts and intrastrand or interstrand cross-links in the double DNA helix that severely block synthesis and induce miscoding events in human cells (5). These adducts are mainly repaired by nucleotide excision repair system, and this process is currently accepted as the leading mechanism responsible for cisplatin resistance (6). However, the effect of an alternative mechanism, the translesion DNA synthesis, has been more recently clearly linked to the cisplatin tolerance (7). In the last few years, many DNA polymerases having the function of bypassing DNA damages have been discovered; among them, polymerase η (Pol η; xeroderma pigmentosum variant gene product) has been reported to modulate the cellular sensitivity to chemotherapeutic agents (8). Primarily detected in yeast, it was found to be mutated in patients with xeroderma pigmentosum variant (9). It is a low-fidelity polymerase capable of doing translesion synthesis error-free in general (10) and error-prone on 8-oxoguanine (11). When compared with the classic polymerases (α, β, γ, δ, and ε), it has a higher fidelity in replicating over damaged DNA (12, 13). Pol η incorporates the correct nucleotide over lesions secondary to DNA-damaging agents, including alkylating and alkylating-like agents, such as platinum compounds and UV rays (14–16). In *in vitro* studies, Pol η showed a higher efficiency in catalyzing translesion synthesis through cisplatin-DNA adducts than any other eukaryotic polymerases (17). In lung cancer, a significant down-regulation of Pol η compared with the adjacent normal lung tissue has been reported (18); however, thus far, in NSCLC, no data are available on Pol η expression compared with platinum-based drug sensitivity. The aim of the present study is to investigate the significance

Authors' Affiliations: [1]Thoracic Oncology Unit, [2]Pathology Division, and [3]Genomics and Informatics Unit, Department of Clinical and Biological Sciences, University of Turin, San Luigi Hospital, Orbassano (Torino), Italy

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Requests for reprints: Paolo Ceppi, Department of Clinical and Biological Sciences, University of Turin, San Luigi Hospital, Regione Gonzole 10, 10043 Orbassano, Torino, Italy. Phone: 39-011-9026719; Fax: 39-011-9026753; E-mail: paolo.ceppi@unito.it.

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Translational Relevance

The retrospective study here reported investigated the role of DNA polymerase η (*Pol η*), a gene belonging to the translesion DNA synthesis system, as assessed by real-time PCR in non–small cell lung cancer (NSCLC). Pol η showed to be a predictive factor for survival in a case series of patients with advanced NSCLC treated with platinum-based chemotherapy, to lack any prognostic effect on survival of patients with radically resected early-stage NSCLC not treated with adjuvant chemotherapy, and to be correlated with *in vitro* cisplatin sensitivity in a panel of NSCLC cell lines. Although these results should be confirmed in a prospective setting, the present study highlights the potential role of low levels of tumoral Pol η as a reliable marker of cisplatin sensitivity. If these data will be further confirmed, Pol η could be considered among stratification factors in clinical trials assessing the efficacy of platinum-based chemotherapies in advanced NSCLC; alternatively, patients with high Pol η levels should be treated with nonplatinum combinations.

of Pol η mRNA expression levels in chemotherapy-naive and platinum-treated NSCLC cases.

Materials and Methods

Patients and samples. Eighty-six formalin-fixed paraffin-embedded samples, corresponding to pretreatment bronchoscopic or fine-needle aspiration biopsies, were retrospectively collected from patients with unresectable NSCLC. Patients received platinum-based chemotherapy at the Thoracic Oncology Unit of San Luigi Hospital between December 2004 and June 2007. A control group of fresh snap-frozen surgical specimens of both tumor and corresponding normal lung tissue of 50 consecutive NSCLC patients completely resected between 2003 and 2004 not treated perioperatively or postoperatively with chemotherapy and/or radiotherapy was also analyzed. The selection criteria included a minimum follow-up time of 8 mo and 4 y for the patients with advanced and early-stage tumors, respectively. The study was approved by the institutional review board of the hospital. All samples were anonymized by a pathology staff member not taking part in the study, and none of the researchers conducting the gene expression analyses had access to disclosed clinicopathologic data.

Cell lines, cultures, and drugs. Five human NSCLC cell lines (H596, Calu-1, H520, H522, and H1299) were purchased from the American Type Culture Collection. Cell lines were maintained in RPMI 1640 supplemented with 10% FCS, 2 mM L glutamine, penicillin (25 units/mL), and streptomycin (25 μg/mL; all from Sigma-Aldrich) in a humidified atmosphere containing 5% CO_2 at 37°C. Original stock solutions of cisplatin (*cis*-diamminedichloroplatinum, Pfizer) at a concentration of 0.5 mg/mL were stored at 4°C and freshly dissolved in culture medium before use.

Cytotoxicity assay. To determine the IC_{50} values of cisplatin in cell lines, a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay (Sigma-Aldrich) was used according to the instructions of the manufacturer. Briefly, 2×10^3 cells were plated onto each well of a 96-well plate for 24 h and then treated with indicated concentrations of cisplatin for 48 h. Absorbance was measured at 590 nm with a microplate reader (Bio-Rad). Each point represents the mean of eight replicates with SD and IC_{50} values calculated using a curve-fitting software (GraphPad Prism).

RNA isolation and cDNA synthesis from formalin-fixed paraffin-embedded specimens. Microdissection from formalin-fixed paraffin-embedded specimens was done as previously described (19). After microdissection, tissue samples were heated at 92°C for 30 min in 4 mol/L DTT-guanidine isothiocyanate/sarcosine [4 mol/L guanidinium isothiocyanate, 50 mmol/L Tris-HCl (pH 7.5), 25 mmol/L EDTA; Invitrogen]. Fifty microliters of 2 mol/L sodium acetate (pH 4.0) followed by 600 μL of freshly prepared phenol/chloroform/isoamyl alcohol (250:50:1) were added to the tissue suspensions. The suspension was centrifuged at 13,000 rpm for 8 min in a chilled (8°C) centrifuge. The upper aqueous phase was removed and combined with glycogen (10 μL) and 300 to 400 μL of isopropanol. The tubes were placed at -20°C for 30 to 45 min to precipitate the RNA. After centrifugation at 16,000 × *g* for 7 min in a chilled (8°C) centrifuge, the supernatant was carefully poured off and the pellet was resuspended in 50 μL of 5 mmol/L Tris and cDNA synthesis was carried out as previously described (20).

RNA isolation and cDNA synthesis from cells and fresh snap-frozen specimens. Total RNA was isolated from lung specimens using the RNeasy 96 kit (Qiagen) implemented on Biorobot 8000 (Qiagen) according to the manufacturer's instructions. RNA was extracted and retrotranscribed to cDNA as previously described (21). Total RNA was isolated from cell lines with Qiazol lysis reagent (Qiagen) according to the manufacturer's instructions.

Real-time PCR. Relative cDNA quantitation for Pol η, using *β-actin* as internal reference gene, was done by a fluorescence-based real-time detection method [ABI PRISM 7900 Sequence Detection System (Taqman); Applied Biosystems]. The sequences of the primers and probes used for β-actin have been previously published (19). Pol η (gene name POL H) primers were designed according to the RefSeq NM_006502 and sequences were as follows: forward, 5′-AGTCCCGT GGGAAAGCTAAC-3′; reverse, 5′-CGAGACATTATCTCCATCACTTCA-3′; probe, (FAM)-5′-TCACCAAGTACCGGGAAGCCAGTG-3′-(TAMRA). Primers and probes were designed to be intron spanning to avoid genomic DNA contamination. The PCR product size generated for Pol η (70 bp) was validated through gel electrophoresis, whereas the efficiency of primers and probe was tested to be comparable with that of β-actin (the difference is <2%) by means of serial cDNA dilution as previously described (22). PCR mixture and cycling conditions were as previously described (19).

Statistical analyses. Relative Pol η levels were estimated with the $\Delta\Delta C_t$ method normalizing with cDNA obtained from commercial RNA (Total RNA, Stratagene). To test significant associations between Pol η expression with clinicopathologic variables, the Mann-Whitney *U* and the Kruskal-Wallis tests were used, setting the significance threshold according to Bonferroni's correction. Univariate analysis of survival was done by Kaplan-Meier method and validated with log-rank test. Multivariate analysis was carried out with Cox's proportional hazard model adjusting for major clinicopathologic variables. To test differential Pol η expression between tumor and corresponding normal lung, the $\Delta\Delta C_t$ method was used and Pol η was considered differentially expressed when $2^{-\Delta\Delta Ct}$ values were >2 or <0.5 (i.e., 2-fold changes). To test differential Pol η expression in the overall population of tumor versus normal lung, the Mann-Whitney *U* test was done. In cell line experiments, Pol η transcriptional regulation following cisplatin treatment was analyzed by means of the *t* test. Correlation of endogenous Pol η mRNA levels with cisplatin sensitivity and with patient outcome was tested with the nonparametric Spearman rank order correlation (Spearman *R*). Statistical significance was set at $P = 0.05$.

Results

Pol η predicts the outcome of platinum-treated NSCLC patients. In paraffin-embedded tumor samples from platinum-treated patients, 14 of the 86 extracted mRNA (16%) were not

successfully amplified by real-time PCR because of minimal amounts of preserved tumor cells or the presence of necrotic areas in the specimens; therefore, these samples were excluded from further analyses. Clinicopathologic characteristics of the remaining 72 patients are shown in Table 1. Among these, 51 (71%) received carboplatin (associated with gemcitabine or paclitaxel in 20 and 31, respectively) and 21 (29%) patients were treated with cisplatin (combined with gemcitabine or pemetrexed in 19 and 2, respectively) as first-line treatment. In addition, 16 patients (10 stage III and 6 stage IV) received sequential radiotherapy. Type of response to first-line chemotherapy was available in 66 patients: 1 had complete and 18 partial response for an overall response rate of 29%; 22 had stable and 25 had progressive disease and for the purpose of this study were collectively grouped as nonresponders (71%). Twenty-four patients (33%) received second-line therapy. Overall median survival was 14.57 months and 41 patients of 72 (57%) had died at the time of the data analysis. Median Pol η expression was 1.07 (range, 0.12-10.98, all unitless ratios) and no significant association between Pol η levels and clinicopathologic variables was found (Table 1). No difference between bronchoscopic (n = 52) and fine-needle aspiration (n = 20) biopsies in terms of Pol η expression was found (data not shown). Kaplan-Meier univariate analysis (Table 1) indicated Pol η (P = 0.003; Fig. 1A) as well as response to therapy (P = 0.01; Fig. 1B) and grade 3 to 4 hematologic toxicity (P = 0.04) as significant predictors of survival. Distribution of second-line therapies in the two Pol η expression groups was comparable. When data were disaggregated by extent of disease, the predictive role of Pol η was maintained in stage III and IV (P = 0.03 and 0.02, respectively), as shown in Fig. 1C and D. Multivariate analysis by Cox, adjusting for major clinicopathologic variables, indicated both Pol η expression [hazard ratio (HR), 3.18; 95% confidence interval (95% CI), 1.73-5.84; P = 0.008] and response to therapy (HR, 2.24; 95% CI, 1.10-2.51; P = 0.02) as independent factors for overall survival. To analyze the variability of Pol η expression among groups of patients with different prognosis, the 72 patients were divided into two groups by median Pol η levels and each group into short- and long-term survivors adopting the median survival as a cutoff (>14.57 months). The results showed no difference between short and long survivors for both groups in terms of Pol η expression (Fig. 2A and B), but a significant reduction in the percentage of long-term survivors among patients with low compared with high polymerase-expressing tumors was found (44% and 14%, respectively; $P < 0.01$, χ^2 test). Similarly, a significant inverse correlation was found between Pol η levels and patient survival time (P = 0.04) as shown in Fig. 2C.

Pol η transcript is not regulated in NSCLC compared with normal lung tissue. In the series of 50 consecutive resected NSCLC patients, 37 were males, the median age was 69 years, 31 had stage I, 10 had stage II, and 9 had stage III of disease, 25 tumors were adenocarcinomas, and 18 were squamous carcinomas. Pol η mRNA expression was evaluated in tumoral versus corresponding normal lung tissues, and although in the whole series Pol η expression did not significantly differ (median tumor/normal ratio = 0.90 from 0.32 to 2.94; P = 0.82, Mann-Whitney U test; Fig. 3A), the analysis of individual patients showed that Pol η mRNA

Table 1. Clinicopathologic characteristics of platinum-treated NSCLC patients (n = 72) compared with median Pol η expression levels

		n	Pol η median (range)	*P*	MS	HR (95% CI)	*P*
Sex	M	51	1.03 (0.12-10.98)	0.39	11	1.44 (0.73-2.75)	0.3
	F	21	1.3 (0.3-4.55)		17.4		
Age	<63 (median)	34	1.3 (0.21-6.02)	0.48	15.3	0.87 (0.47-1.61)	0.65
	≥63	38	1.01 (0.12-10.98)		13.6		
Histology	Adenocarcinoma	44	1.26 (0.31-6.02)	0.11	15	0.91 (0.48-1.71)	0.76
	Other	28	0.79 (0.12-10.98)		14.57		
Extent of the disease	III	27	0.95 (0.3-10.98)	0.22	15.9	0.66 (0.35-1.23)	0.18
	IV	45	1.21 (0.12-6.02)		10.1		
Serum LDH	<216	29	0.92 (0.12-6.02)	0.28	14.57	0.8 (0.4-1.6)	0.52
	≥216	29	1.14 (0.21-2.95)		11		
Smoking status	No	17	1.3 (0.35-6.02)	0.76	21.6	0.46 (0.26-1.01)	0.05
	Current/former	55	1.07 (0.12-10.98)		10.1		
ECOG performance status	0	54	1.03 (0.21-10.98)	0.92	14.57	0.9 (0.43-1.83)	0.7
	1	18	1.3 (0.12-2.72)		7.98		
Hematologic toxicity	Grade 0-2	44	1.05 (0.12-10.98)	0.15	15.3	0.52 (0.21-0.95)	0.04
	Grade 3 and 4	20	1.30 (0.66-6.02)		6.9		
Objective response	No	47	1.29 (0.12-10.98)	0.98	6.9	2.04 (1.15-4.13)	0.01
	Yes	19	1.03 (0.4-5.32)		15.9		
Radiotherapy	No	56			11	1.14 (0.53-2.47)	0.74
	Yes	16			13.6		
Pol η	Low	36			21.1	0.41 (0.19-0.73)	0.003
	High	36			6.93		

NOTE: Significant associations were determined by Mann-Whitney U and Kruskal-Wallis tests. The unadjusted hazard ratios for each variable were estimated by Cox regression (P values are log-rank tests). Objective responders are partial and complete responders, nonresponders are patients with stable or progressive disease.
Abbreviations: MS, median survival (months); LDH, lactate dehydrogenase; ECOG, Eastern Cooperative Oncology Group.

levels were significantly up-regulated in tumor compared with normal tissue in 5 of 50 (10%; tumor/normal fold change ≥2) and down-regulated in 11 patients (22%; fold change ≤0.5). Median Pol η levels in tumors were 0.46 (from 0.23 to 2.22) and no significant association with any clinicopathologic variable was found. Pol η expression was not significantly correlated neither with histologic grade nor with Ki67 proliferation index (data not shown). In this group of resected patients, mainly with pathologic stage I disease (62%), overall median survival time was 56 months and 21 patients (42%) had died at the time of the data analysis. When patients were separated into two groups according to median Pol η expression (low versus high), no significant correlation with survival was found at univariate analysis (HR, 0.86; 95% CI, 0.36-2.09; P = 0.54; Fig. 3B). Pol η up-regulation or down-regulation in tumors compared with normal tissues was not associated with outcome. Conversely, as expected, significant prognostic factors were tumor stage (I and II versus III; HR, 0.18; 95% CI, 0.05-0.63; P = 0.008) and tumor grade (1 and 2 versus 3; HR, 0.26; 95% CI, 0.1-0.67; P = 0.004).

Pol η expression correlates with cisplatin sensitivity of NSCLC cell lines. Cisplatin sensitivity of five NSCLC cell lines (H596, Calu-1, H520, H522, and H1299) was determined by treating cells with increasing micromolar concentrations of cisplatin for 48 hours. Figure 4A shows the ratio of living cells following treatments at indicated doses compared with untreated controls; H596 and H1299 were the most sensitive and the most resistant, respectively. Endogenous Pol η mRNA levels in cells were quantified by real-time PCR (Fig. 4B) and Pol η transcript levels were significantly directly correlated with cisplatin resistance (expressed as IC_{50} values), as shown in Fig. 4C (R_S = 0.93; P = 0.01). Moreover, cisplatin exposure for 40 hours at IC_{50} dose significantly up-regulated Pol η mRNA levels in the three relatively more sensitive cell lines, H596, Calu-1, and H520, whereas Pol η increase failed to reach the

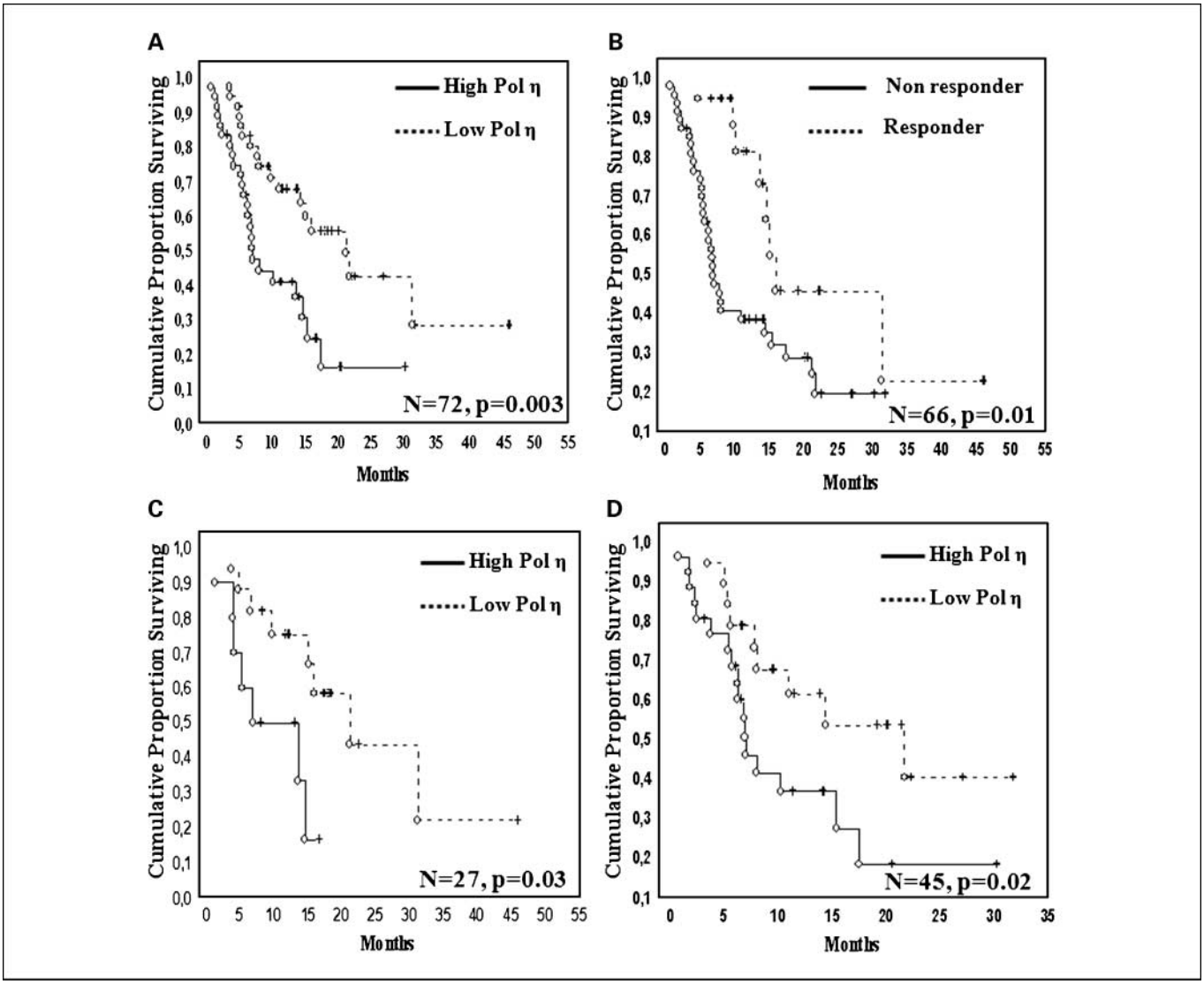

Fig. 1. Pol η expression in platinum-treated NSCLC. *A, C,* and *D,* Kaplan-Meier survival analysis of platinum-treated NSCLC patients divided by Pol η expression in overall population, disease stage III, and disease stage IV, respectively. *B,* Kaplan-Meier survival curves of patients divided for response to chemotherapeutic treatment. All *P* values are log-rank tests.

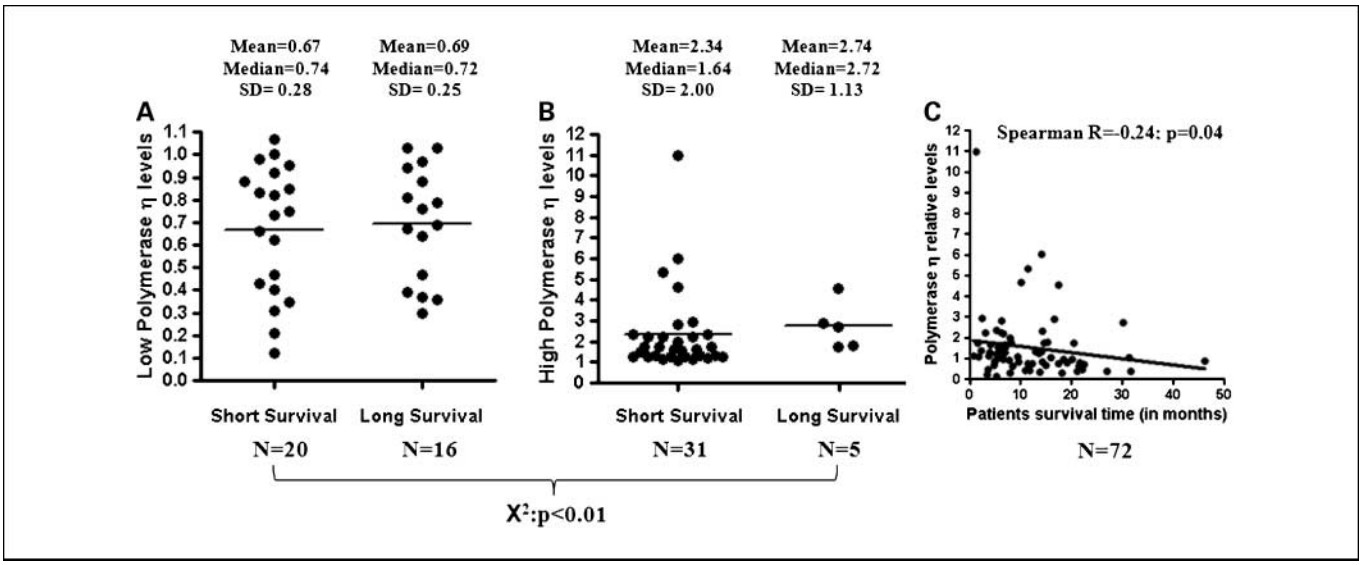

Fig. 2. Pol η transcript expression correlates with the outcome of platinum-treated NSCLC patients. Scatter plots of Pol η relative expression levels of patients with low (*A*) and high (*B*) Pol η – expressing tumors divided into short and long survivors. Horizontal lines represent the mean values. The *P* value is calculated by the χ^2 test. *C,* inverse correlation between Pol η relative expression levels and patient survival time.

statistical significance in H522 and in the most cisplatin-resistant H1299, as shown in Fig. 4D.

Discussion

Chemotherapy improves survival of NSCLC patients at any stage, with the exclusion of stage I, and front-line treatment for stage IV patients with good performance status should include a platinum-based doublet, including third-generation agents such gemcitabine, taxanes, or vinorelbine (American Society of Clinical Oncology guidelines 2003, *Journal of Clinical Oncology*; ref. 3). NSCLC is frequently resistant to chemotherapy, and this resistance has been associated with elevated nucleotide excision repair in tumor tissue. In a case-control study, 375 patients with newly diagnosed NSCLC were accrued and nucleotide excision repair activity was estimated as the DNA repair capacity (DRC) measured in the patient's peripheral lymphocytes by the host cell reactivation assay. For every unit of increase in DRC, a progressive increase in the relative risk of death was observed. Of those 86 patients treated with chemotherapy, patients in the top quartile of the DRC distribution were at twice the relative risk of death as those in the lowest quartile (relative risk, 2.72; 95% CI, 1.24-5.95; *P* = 0.01), whereas effective DRC was not a risk factor for death in patients who were not treated with

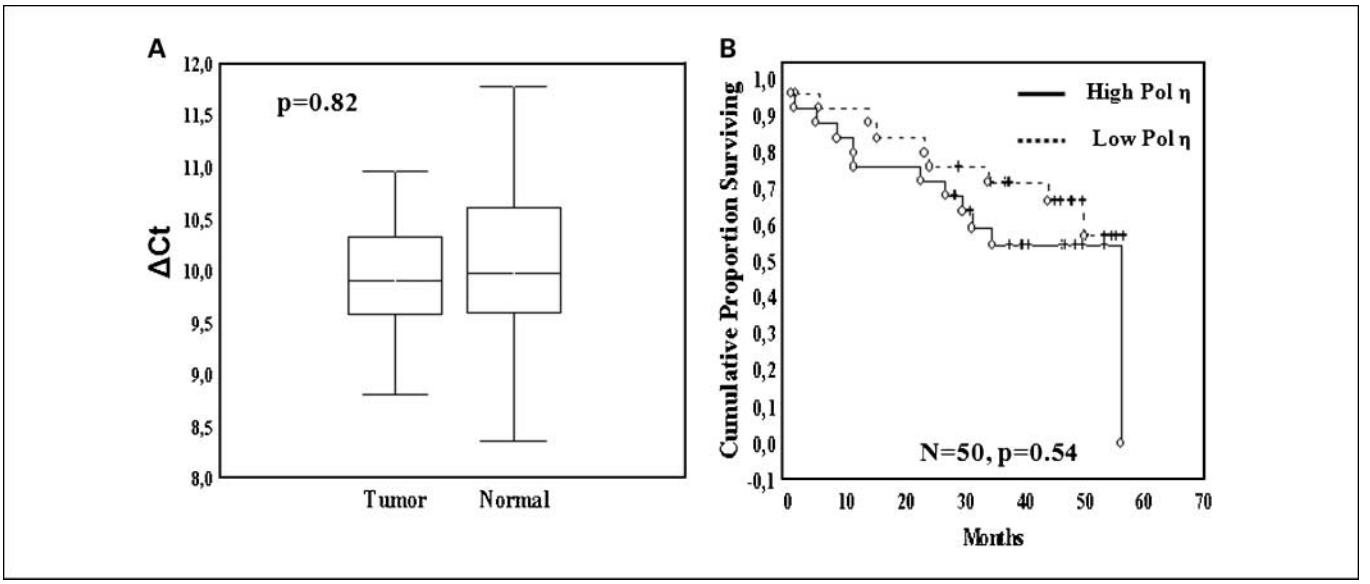

Fig. 3. Pol η expression in untreated NSCLC (n = 50). *A,* Pol η relative transcript levels in tumor versus adjacent normal lung. *P* is Mann-Whitney *U* test. *B,* Kaplan-Meier analysis of survival of untreated NSCLC patients divided by Pol η expression with median as a cutoff value. *P* is a log-rank test.

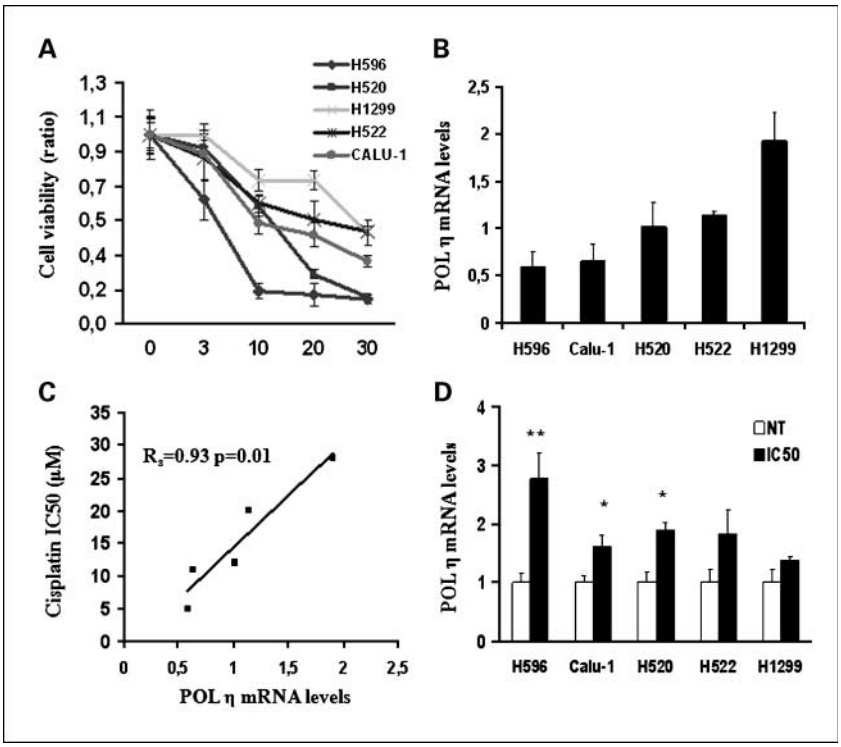

Fig. 4. Pol η expression in NSCLC cell lines. *A,* cisplatin sensitivity of five NSCLC cell lines. Cells were treated at indicated doses of cisplatin for 48 h. Each data point is the ratio of living cells compared with controls. Points, mean of eight replicates; bars, SD. *B,* endogenous Pol η levels. Cells ($1\text{-}2 \times 10^4$) were seeded in 24-well plate and left for 24 h before RNA extraction. Relative levels are expressed as ratio to control cDNA. Columns, mean of six experiments; bars, SD. *C,* correlation between Pol η transcripts and cisplatin IC_{50}. R_S is Spearman rank test. *D,* cisplatin-induced Pol η transcription. Cells (10^4) were plated in 24-well plate and treated for 40 h with their IC_{50} doses of cisplatin (*P* values are *t* tests). NT, not treated. *, $P < 0.05$; **, $P < 0.01$.

chemotherapy. In univariate analysis of the relationship between DRC and clinical and demographic variables, DRC was statistically significantly higher in men than in women (8.37 ± 2.92% versus 7.13 ± 2.37%, respectively; $P < 0.001$) but was not related to stage of disease, histology, differentiation of the tumor, or self-reported weight loss (23).

In recent years, many investigators reported the role of DNA repair molecules in modulating platinum-based drug response of NSCLC patients and identified potential biomarkers of platinum resistance. For NSCLC, there are many small retrospective studies supporting the role of high mRNA levels (generally expressed as ratio of the PCR gene product and the β-actin gene) of *excision repair cross-complementing 1* (*ERCC1*) or *breast cancer 1* (*BRCA1*) genes in cisplatin resistance (19, 24) and *ribonucleotide reductase M1* (*RRM1*) gene in gemcitabine resistance (25). Patients treated with such agents having higher gene expression generally had a shorter outcome. A recent large retrospective study indicated that the benefit of adjuvant chemotherapy was exclusively observed in the subgroup of ERCC1-negative tumors by immunohistochemistry (26). However, it should be also noticed that these genes when investigated in early-stage NSCLC treated with surgery alone were positively associated with survival (27–29).

Although future investigations should better elucidate the role of DNA repair genes, alternative repair pathways could have a profound role in the resistance of NSCLC to DNA-damaging agents. The translesion synthesis is a DNA damage tolerance process that allows the DNA replication machinery to replicate past DNA lesions and involves the switching off of regular DNA polymerases for specialized translesion polymerases (7).

According to the results of the present study, in chemotherapy-naive early-stage NSCLC patients, Pol η expression is neither drastically up-regulated nor down-regulated, being not significantly different from the corresponding peritumoral lung tissue in the majority of tumors (68%). This observation is in contrast with a previously published article that reported a significant Pol η transcript down-regulation in tumoral versus nontumoral lung tissues (18) compared with a housekeeping gene different from that used in the present study. Furthermore, no correlation was found in resected NSCLC between tumoral Pol η mRNA levels and survival. On the contrary, in advanced NSCLC treated with platinum-based chemotherapy, Pol η expression levels predicted survival and it was found to be an independent factor associated with survival. According to these results and differently from ERCC1 and BRCA1 expression in NSCLC, Pol η seems to be a predictive rather than a prognostic marker in NSCLC. In addition, with all the limitations related to a small sample of patients, no significant differences in Pol η expression according to gender have been detected.

Furthermore, to confirm the association with platinum sensitivity, the endogenous Pol η mRNA levels of five NSCLC cell lines were quantified and the results indicate a linear relationship between basal Pol η levels and cisplatin *in vitro* sensitivity (Fig. 3C). Moreover, Pol η transcript levels in NSCLC cell lines were found to be significantly induced by the treatment. The amount of increase was found higher in the most cisplatin-sensitive cell line, H596, and lower in cells with comparable degree of cisplatin resistance: Calu-1, H520, and H522 (in the latter failing to reach the statistical significance). The most resistant cell line, H1299, was also the one with the highest basal transcript level and Pol η expression was not found significantly modified after 40 hours of cisplatin administration at IC_{50} dose. In conclusion, although the evaluation of the expression levels in lung

cancer of the other DNA polymerases involved in the process of translesion synthesis as well as the relationship with other biomarkers is worth of future investigations, the findings of the present study highlight the potential relevance of the assessment of endogenous Pol η levels in tumors as a reliable marker of cisplatin efficacy. Translating into clinical practice, NSCLC patients with high Pol η levels could be excluded from the administration of platinum-based drugs and alternative nonplatinum chemotherapy regimens could be preferentially suggested. Taken together, the present findings suggest a role of translesion pathway in the determination of resistance to platinum-based therapy and indicate that the evaluation of Pol η expression levels could represent a novel tool to predict survival of NSCLC patients undergoing platinum-based therapeutic strategies.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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