FOLIA HISTOCHEMICA ET CYTOBIOLOGICA
Vol. 50, No. 1, 2012
pp. 80–86

ORIGINAL STUDY

VIA MEDICA

Predictive value of *ERCC1* single-nucleotide polymorphism in patients receiving platinum-based chemotherapy for locally-advanced and advanced non-small cell lung cancer — a pilot study

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Abstract: Platinum-based chemotherapy is the main type of I-line treatment of advanced and non-operative NSCLC patients without *EGFR* gene mutation. The excision repair cross-complementation group 1 (ERCC1) is an enzyme that executes the incision of the damaged DNA strand and removes platinum-induced DNA adducts. We investigated whether *ERCC1* gene polymorphism has an effect on the response to chemotherapy and survival in 43 patients with NSCLC treated with platinum-based chemotherapy. *ERCC1* 19007 T>C SNPs were assessed using a PCR-RFLP methods in DNA isolated from peripheral blood lymphocytes. Disease control occurred significantly (p = 0.045) more frequently in patients with CC or CT genotype compared to patients with TT genotype. Median PFS and OS for CC homozygous were 4 and 10.5 months, 4 and 12.5 months for CT heterozygous, but only 0.3 and 1.5 months for TT homozygous patients, respectively. The probability of PFS was significantly higher (HR = 0.438, 95% CI: 0.084–0.881, p = 0.03) and probability of OS was insignificantly higher (HR = 0.503, 95% CI: 0.129–1.137, p = 0.084) in patients with CC or CT genotype than in patients with TT genotype. Uncommon TT genotype of *ERCC1* 19007 T>C polymorphism could predict poor response and shortening of progression free survival in NSCLC patients treated with platinum-based I-line chemotherapy. The analysis of this polymorphism may serve as a promising tool in the qualification of advanced NSCLC patients for appropriate chemotherapy. *(Folia Histochemica et Cytobiologica 2012, Vol. 50, No. 1, 80–86)*

Key words: *ERCC1*, single-nucleotide polymorphism, non-small cell lung cancer, platinum-based chemotherapy

Introduction

Lung cancer is the commonest malignancy in the world. 20,000 people die each year in Poland because of this cancer. Non-small cell lung cancer (NSCLC) represents over 85% of lung cancer cases. Surgical resection is possible in the early stages of NSCLC. In Poland, only about 15–20% of newly diagnosed NSCLC cases could be qualified for operation. Therefore, chemotherapy and radiotherapy play the dominant roles in the multidisciplinary treatment of patients with advanced NSCLC [1].

Chemotherapy based on platinum compounds and third generation drugs is currently the main type of I-line treatment of advanced, non-operative non-small cell lung cancer (NSCLC) in patients without *EGFR* gene mutation. Unfortunately, objective response to chemotherapy is achieved in less than 40% of patients

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and median overall survival of treated patients does not exceed eight months [2].

The mechanism of action of many cytotoxic drugs (platinum compounds, gemcitabine) is based on the disruption of genetic material integrity. The destruction of cells by platinum compounds requires binding of the drug to DNA and the creation of platinum-DNA adducts, thereby inhibiting DNA replication. Therefore, one of the basic mechanisms of resistance to therapy is increased or deregulated DNA reparation. Nucleotide excision repair (NER) complex has a central role in DNA repair. The excision repair cross-complementation group 1 (*ERCC1*) with xeroderma pigmentosum-F (XPF), enzymes that belong to NER complex, execute the incision of the damaged DNA strand and remove cisplatin-induced DNA adducts [3].

Expression of ERCC1 protein by the tumor cells could predict response and survival benefit from platinum-based adjuvant and I-line chemotherapy in non-small cell lung cancer [4, 5]. 19007 T>C (N118N, rs11615) and 8092 C>A (Q504K, rs3212986) polymorphisms of *ERCC1* gene could change ERCC1 mRNA expression, ERCC1 protein expression or ERCC1 enzyme function [6, 7]. However, other authors have suggested that these polymorphisms are not related to phenotypic differences in the ERCC1 protein, but rather may be linked to other causative variants or haplotypes [8]. Nevertheless, this data lets us hypothesize that differences in response to chemotherapy could be related to single nucleotide polymorphisms (SNPs) in genes encoding proteins which play a key role in DNA repair. Therefore, in this report, we analyzed the significance of the *ERCC1* gene 19007 T>C polymorphism as a predictive and prognostic marker in NSCLC patients treated with platinum-based I-line chemotherapy.

Material and methods

Study population. The study population consisted of 43 pathologically verified non-small cell lung cancer patients. Patients were staged as locally advanced (stage IIIB) or advanced (metastatic, stage IV) disease using computed tomography and other available methods. Detailed medical history about each patient was collected. The clinical characteristics of lung cancer patients are presented in Table 1. Patients received platinum-based first-line chemotherapy. All cases were treated in the Department of Pneumonology, Oncology and Allergology of the Medical University of Lublin. Response to chemotherapy was evaluated according to the RECIST criteria. The results of *ERCC1* genotyping were correlated with response to treatment, progression free survival and overall survival of examined patients.

Before the investigation, the agreement of the Ethical Committee of the Medical University of Lublin was obtained.

From each patient, venous blood was collected and genomic DNA was extracted using Qiagen Blood Mini Kit (Qiagen, Germany).

***ERCC1* genotyping.** The *ERCC1* 19007 T>C genotypes were detected using the PCR-based restriction fragment length polymorphism (PCR-RFLP) method as previously described. The primers were: forward primer: 5'-AGGACCACAGGACACGCAGA-3' and reverse primer: 5'-CATAGAACAGTCCAGAACAC-3', which produced a 525 bp fragment. PCR reaction was performed in a total volume of 25 μl containing 100 ng of template DNA, 1 μM of each primer, 0.2 mM of each dNTP, 2.4 mM $MgCl_2$ and 1.0 U Taq polymerase with 1 × reaction buffer (Fermentas, Canada). PCR amplification was carried out in a T Personal (Biometra, Germany) thermocycler in the following conditions: initial denaturation at 96°C for 5 min, followed by 35 cycles of 30 sec. at 94°C, 30 sec. at 61°C and 1.0 min. at 72°C and a final elongation step of 10 min. at 72°C. PCR products were digested overnight with 5 U of *Bsr*DI enzyme (Fermentas, Canada). The three possible genotypes were defined by three distinct banding patterns: homozygous of TT genotype corresponded to 368- and 157-bp fragments, heterozygous of CT genotype corresponded to 525-, 368- and 157-bp fragments, and finally homozygous of CC genotype corresponded to an undigested band of 525bp (Figure 1). The restricted products were analyzed by electrophoresis in 2% agarose gel containing ethidium bromide.

Statistical analysis. Chi-square test was used to compare the characteristics of the patient groups divided according to *ERCC1* 19007 T>C polymorphism. The U-Mann–Whitney test and Kruskal–Wallis ANOVA median test were used for testing equality of population medians among groups. Kaplan–Meier method was used for the comparison of survival probability between the groups of different *ERCC1* genotypes. Finally, the Cox regression model with stepwise selection procedures by minimum AIC was used to establish factors affecting patient survival.

Figure 1. Representative analysis of *ERCC1* 1907 T>C polymorphism (lanes: 7, 13, 15 — CC homozygotes, lanes: 4, 6, 9, 10, 12, 14 — CT heterozygotes, lanes: 1, 2, 3, 5, 8 11 — TT homozygotes, M — DNA ladder)

Results

Patient characteristics and frequencies of ERCC1 genotypes

Baseline characteristics and frequencies of *ERCC1* genotypes in the group of 43 NSCLC patients (median age 63 years) are shown in Table 1. 76.7% of the patients were male. The pack-years value was calculated as the number of cigarette packs smoked per day multiplied by the number of years. Median pack-years value was 48. Very good performance status (ECOG PS = 0) accounted for 58.1% of patients. Squamous-cell carcinoma was diagnosed in 58.1% of patients, adenocarcinoma in 25.6% and other histological types in 16.3% of patients. 53.5% of patients had locally advanced NSCLC (stage IIIB). The median number of platinum-based chemotherapy cycles was four (range: 1–6). Platinum (cisplatin or carboplatin) was combined with vinorelbine in 30 patients (69.8%), gemcitabine in seven patients (16.3%), paclitaxel in three patients (6.95%), and with etoposid in three patients (6.95%). Sequential radiation therapy was administered in nine patients (20.9%).

CC homozygous variant of the *ERCC1* 19007 T>C polymorphism was presented in 11 patients (25.6%), heterozygous variant in 25 patients (58.1%), and TT heterozygous variant in seven patients (16.3%). The distribution of polymorphic variants of *ERCC1* gene did not depend on age, gender, histological type, clinical stage of disease, chemotherapy regimen, smoking, or performance status of NSCLC patients (Table 1).

ERCC1 19007 T>C polymorphism and chemotherapeutic response

Complete remission was observed in five patients (11.6%), and partial response in 14 patients (32.6%). In the non-responders' group, stable disease was observed in five patients (11.6%) and progressive disease in 19 patients (44.2%). Disease control (CR, PR

Table 1A. Characteristics of NSCLC patients and *ERCC1* genotype distribution

Factors	All patients (n=43)	ERCC1 19007 T>C polymorphism			p and χ^2 value
		CC (n = 11, 25.6%)	CT (n = 25, 58.1%)	TT (n = 7, 16.3%)	
Age (median)	63 years	63 years	60 years	68 years	0.582 1.083
Gender					
Male	33 (76.7%)	10 (90.9%)	19 (76%)	4 (57%)	0.253
Female	10 (23.3%)	1 (9.1%)	6 (24%)	3 (43%)	2.751
Pack-years (median)	48	53	44	40	0.178 3.45
WHO performance status					
0	25 (58.1%)	7 (63.6%)	16 (64%)	2 (28.6%)	0.223
1 or 2	18 (41.0%)	4 (36.4%)	9 (36%)	5 (71.4%)	3.0
Weight loss					
Non (< 5%)	20 (46.5%)	3 (27.3%)	15 (60%)	2 (28.6%)	0.112
Yes (≥ 5%)	23 (53.5%)	8 (72.7%)	10 (40%)	5 (71.4%)	4.37
Histological type					
Squamous cell carcinoma	25 (58.1%)	8 (72.7%)	11 (44%)	6 (85.7%)	0.266
Adenocarcinoma	11 (25.6%)	3 (27.3%)	7 (28%)	1 (14.3%)	7.636
Giant cell carcinoma	5 (11.6%)	0 (0%)	5 (20%)	0 (0%)	
NOS	2 (4.7%)	0 (0%)	2 (8%)	0 (0%)	
TNM stage					
Locally advanced	23 (53.5%)	7 (63.6%)	14 (56%)	2 (28.6%)	0.322
Advanced	20 (46.5%)	4 (36.4%)	11 (44%)	5 (71.4%)	2.266
Median number of chemotherapy cycles	4	4	4	2	0.674 0.789
Median PFS (months)	4	4	4	0.3	0.116 4.31
Median OS (months)	10.5	10.5	12.5	1.5	0.203 3.188

Table 1B. Characteristics of NSCLC patients and *ERCC1* allele frequency

Factors	*ERCC1* 19007 T>C polymorphism		p and χ^2 value
	CC + CT (n = 36, 83.7%)	TT (n = 7, 16.3%)	
Gender			
Male	29 (80.6%)	4 (57%)	0.394
Female	7 (19.4%)	3 (43%)	0.727
WHO performance status			
0	23 (63.9%)	2 (28.6%)	0.189
1 or 2	13 (36.1%)	5 (71.4%)	1.728
Weight loss			
Non (< 5%)	18 (50%)	2 (28.6%)	0.531
Yes (≥ 5%)	18 (50%)	5 (71.4%)	0.392
Histological type			
Squamous cell carcinoma	19 (52.8%)	6 (85.7%)	0.412
Adenocarcinoma	10 (27.8%)	1 (14.3%)	2.872
Giant cell carcinoma	5 (13.9%)	0 (0%)	
NOS	2 (5.5%)	0 (0%)	
TNM stage			
Locally advanced	21 (58.3%)	2 (28.6%)	0.303
Advanced	15 (41.7%)	5 (71.4%)	1.062
Median PFS (months)	4	0.3	0.03 4.711
Median OS (months)	10.5	1.5	0.084 2.99

and SD) occurred in 24 patients (55.8%). The median progression-free survival (MPFS) was four months for the whole group of patients and 16.5 months for responding patients (Tables 1, 2).

The carriers of TT genotype showed disease progression slightly (p = 0.052) more frequently than carriers of allele C (CC and CT genotype). Disease control occurred significantly (p = 0.045) more frequently in patients with CC or CT genotype compared to patients with TT genotype (Table 2).

Median progression free survival was 4 months for CC homozygous and CT heterozygous patients, but only 0.3 months for TT homozygous patients (Table 1). In Kaplan–Meier analysis, the probability of progression free survival was significantly higher (HR = 0.438, p = 0.03) in patients with CC or CT genotype than in patients with TT genotype (Figure 2).

ERCC1 19007 C>T polymorphism and overall survival

Median survival time (MST) was 10.5 months for all NSCLC patients, 10.5 months for carriers of CC genotype, 12.5 months for patients with CT genotype, but only 1.5 months for TT homozygous patients (Table 1). Patients with CC or CT genotype showed insignificantly (p = 0.084) higher probability of survival than those with TT genotype. The percentage of patients with survival longer than one year was insignificantly higher (p = 0.531) in the group of patients with CC or CT genotypes compared to the group of patients with TT genotype (Figure 3).

In Cox proportional hazard regression model, poor performance status (HR = 16.48, 95% CI: 4.48–60.65, p < 0.0001), squamous-cell carcinoma diagnosis (HR = 3.26, 95% CI: 1.38–7.74, p = 0.0075) and advanced stage of disease (HR = 3.26, 95% CI: 0.96––7.08, p = 0.05) were significantly associated with shortening of patients' survival. However, the presence of TT genotype of *ERCC1* gene did not affect survival (HR = 1.44, 95% CI: 0.44–4.74, p = 0.55).

Discussion

In NSCLC patients, significant variation in prognosis and response to treatment was observed regardless of histopathological diagnosis of cancer. Therefore, studies on predictive and prognostic molecular markers are essential in order to improve response rate as well as to prolong PFS and OS. Expression of ERCC1 is among the most promising prognostic markers for surgically treated NSCLC patients and predictive marker for patients receiving platinum-based chemotherapy [3].

Zheng et al. showed that high expression of ERCC1 enzyme in tumor cells was associated with

Table 2. Response to platinum-based chemotherapy according to *ERCC1* genotype

ERCC1 19007 T>C polymorphism	CR and PR (n = 19, 44.2%)	SD (n = 5, 11.6%)	PD (n = 19, 44.2%)	p and χ^2 value
CC (n = 11)	4 (36.4%)	2 (18.2%)	5 (45.4%)	0.127
CT (n = 25)	14 (56%)	3 (12%)	8 (32%)	7.158
TT (n = 7)	1 (14.3%)	0	6 (85.7%)	
CC and CT (n = 36)	18 (50%)	5 (13.9%)	13 (36.1%)	0.052
TT (n = 7)	1 (14.3%)	0 (0%)	6 (85.7%)	5.927
CC and CT (n = 36)	23 (63.9%)		13 (36.1%)	0.045
TT (n = 7)	1 (14.3%)		6 (85.7%	4.009
CC (n = 11)	4 (36.4%)	2 (18.2%)	5 (45.4%)	0.685
CT and TT (n = 32)	15 (46.9%)	3 (9.4%)	14 (43.7%)	0.756
CC (n = 11)	6 (54.5%)		5 (45.6%)	0.8
CT and TT (n = 32)	18 (56.25%)		14 (43.75%)	0.064

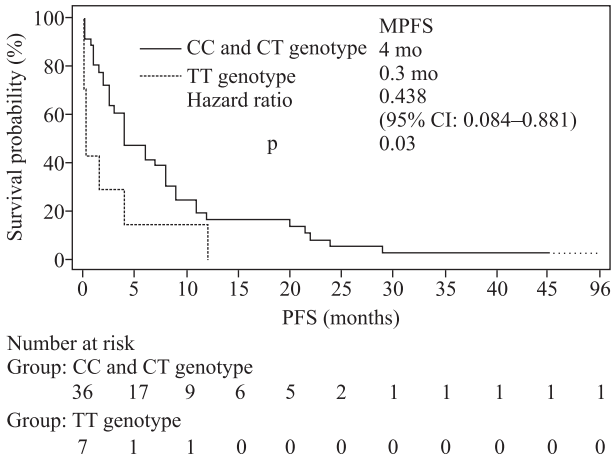

Figure 2. Kaplan–Meier curves of PFS probability according to the *ERCC1* 19007 T>C polymorphism

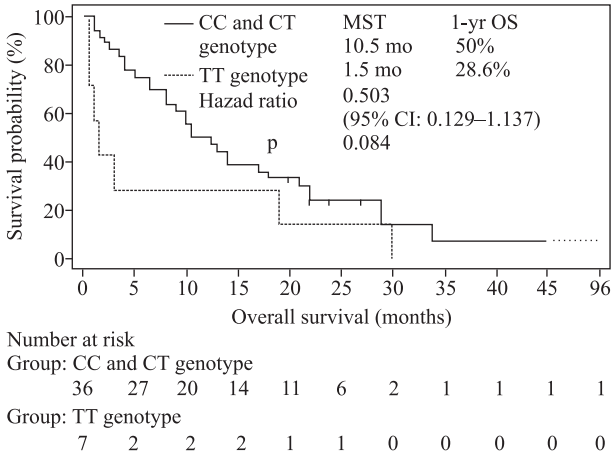

Figure 3. Kaplan–Meier curves of survival probability according to the *ERCC1* 19007 T>C polymorphism

good prognosis after surgical treatment of patients in early stage NSCLC. Co-expression of two proteins — ERCC1 and RRM1, taking part in DNA repair, characterized the group of patients with an excellent outcome after surgical resection [9]. Olaussen et al. proved that only ERCC1-negative NSCLC patients benefit significantly from adjuvant chemotherapy [4]. Ceppi et al., in a retrospective study, further validated concomitant analysis of ERCC1 and RRM1 mRNA level as reliable candidates for personalized chemotherapy, and showed a higher impact on the survival of NSCLC patients treated with cisplatin and gemcitabine [5]. In the first prospective study, Cobo et al. noted an improvement in the response rate (but not in PFS or OS) in patients qualified to cisplatin and docetaxel, or docetaxel and gemcytabine, therapy based on ERCC1 mRNA level [10].

The proposed molecular profiles are based on the analysis of protein expression measured by IHC method or gene expression (analysis of mRNA level in real-time PCR technique). Initial material for such analysis is acquired from the tumor tissue which is usually difficult to obtain. Polymorphism of DNA repair genes, which are analyzed in peripheral blood leucocytes, have greater clinical significance in terms of obtaining samples from lung cancer patients.

The literature contains only a limited number of publications that have assessed the relationship between polymorphisms of genes encoding DNA repair proteins and response to treatment based on platinum compounds in NSCLC patients.

Here, we observed that uncommon TT genotype of *ERCC1* 19007 T>C polymorphism could predict poor response and shortening of progression free survival in NSCLC patients treated with platinum-based I-line chemotherapy. 85.7% of patients with TT genotype demonstrated early progression during first or second cycle of chemotherapy, in contrast to 36.1% of C allele carriers with early progression. In consequence of these differences, the median PFS was significantly longer, and median OS insignificantly long-

er, among patients with CC or CT genotype than in patients with TT genotype.

The limitations of our preliminary study are the small number of analyzed patients and the high percentage of patients with poor performance status in TT genotype group. However, the genetic examination in our study was performed retrospectively, and our knowledge about patients' *ERCC1* status was obtained after therapy termination. We speculate that TT genotype is a poor prognostic factor and that patients with TT genotype, who had started chemotherapy after a delay typical for Polish hospitals, are at a worse clinical stage. Moreover, as was indicated in Tables 1A and 1B, the differences between the groups with different *ERCC1* polymorphisms according to PS status and advancement of NSCLC are not significant.

In a previous study, Ryu et al. suggested that CC genotype of *ERCC1* 19007 T>C polymorphism is a marker for predicting better survival in NSCLC patients treated with platinum-based chemotherapy. However, the authors did not find correlations between *ERCC1* genotype and response to chemotherapy [11]. Isla et al. showed similar results in advanced NSCLC patients treated with docetaxel and cisplatin. In their study, carriers of CC genotype of *ERCC1* gene demonstrated a significantly longer median PFS and median survival than carriers of CT or TT genotype without differences in response rate [6].

The study of Kalikaki et al., concerning the polymorphisms of genes encoding DNA repair proteins, had shown that the joint effect of *ERCC1* polymorphic variants (8092 C>A and 19007 T>C) as well as the *XRCC1* 1196 A>G polymorphism were independent prognostic factors for OS in advanced NSCLC patients treated with platinum-based chemotherapy. The presence of CC genotype and TT genotype of *ERCC1* gene as well as AA genotype of *XRCC1* gene was associated with shorter median survival of analyzed patients. However, only *ERCC1* 1907 T>C polymorphism significantly predicted response to therapy. CR or PR was noted in 5.5% of patients with TT genotype and in 34.7% of patients with CC or CT genotype [12].

A few studies did not find a relationship between *ERCC1* 19007 T>C polymorphism and clinical outcome in advanced NSCLC patients treated with chemotherapy and surgically resected tumor. Taron et al. conducted the largest study to date reporting the effects of *ERCC1* polymorphisms (8092 C>A and 19007 T>C) on median survival in 706 Spanish patients with advanced NSCLC treated with cisplatin and docetaxel. The uncommon AA genotype at position 8092, but not uncommon TT genotype at position 19007, predicted poor survival in examined patients [13]. In the study by Tibaldi et al., no significant associations were found between *ERCC1* 19007 T>C or *XPD* 934 G>A and 2251 A>C polymorphisms and either response or clinical outcome in advanced NSCLC patients treated with cisplatin and gemcitabine [14]. Preliminary data obtained by Zhou et al. showed that *XRCC3* but not *ERCC1* gene polymorphisms might be a strong predictor of survival in NSCLC patients treated with cisplatin-based chemotherapy [15]. Moreover, Takenaka et al. did not observe a relationship between *ERCC1* 19007 T>C polymorphism and disease free survival or overall survival in patients after tumor resection due to early stage of NSCLC [7].

In contrast to numerous researchers, we demonstrated the usefulness of analysis of *ERCC1* 19007 T>C polymorphism in the prediction of chemotherapy effect in advanced NSCLC patients. We suggest that the presence of TT genotype of *ERCC1* gene can predict a worse response for platinum-based chemotherapy. Therefore, this study could be a useful tool in the qualification of advanced NSCLC patients for appropriate chemotherapy regimen. Moreover, in patients with poor performance status (PS = 2) and TT genotype of *ERCC1* 19007 T>C polymorphisms, monotherapy with vinorelbine or gemcitabine could be considered. The analysis of this polymorphism may provide supplementary data in the routine diagnosis of NSCLC, especially as it can be easily achieved using blood samples, and may be easier to adopt in the clinical setting than tumor gene expression arrays.

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Submitted: 19 July, 2011
Accepted after reviews: 23 November, 2011