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RESEARCH

Decreased ERCC1 Expression After Platinum-Based Neoadjuvant Chemotherapy in non-Small Cell Lung Cancer

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Abstract We have already demonstrated in a small cohort of 17 non-small cell lung cancer patients that ERCC1 (excision repair cross-complementation group 1) protein expression decreased after platinum-based treatment, however, certain clinicopathological parameters, such as histologic subtypes, ERCC1 expression scores, chemotherapeutic combinations, response rate, gender and smoking history were not analyzed. The aim of our present study was to extend the studied cohort and analyze those parameters. ERCC1 protein expression was examined in 46 patients treated with neoadjuvant chemotherapy. 46 bronchoscopic biopsy samples (27 squamous cell carcinomas /SCC/ and 19 adenocarcinomas /ADC/) together with their corresponding surgical biopsies were studied. ERCC1 immunohistochemistry was performed on formalin-fixed, paraffin-embedded tissues. Staining scores were calculated by multiplying the percentage of positive tumor cells (0–100) by the staining intensity (0–3). 24/27 bronchoscopic SCC tissues expressed ERCC1. Thirteen of these cases became negative after neoadjuvant therapy and the expression differences between pre- and postchemotherapy samples were highly significant ($p<0.001$). 11/19 bronchoscopic ADC tissues expressed ERCC1. Six of these cases became negative after neoadjuvant therapy and the expression differences were significant ($p<0.010$). There was no newly expressed ERCC1 postoperatively. Comparison of staining score changes revealed more pronounced decrease in SCC ($p=0.032$). We observed no correlation between initial ERCC1 level or ERCC1 decrease and overall survival, but we demonstrated correlations between decrease in ERCC1 expression and histologic subtypes of tumors and gender. We could confirm our previous data in a larger cohort that platinum-based chemotherapy affects the ERCC1 expression probably referring to an induction of tumor cell selection.

Keywords ERCC1 · Lung cancer · Platinum based chemotherapy · Immunohistochemistry · Gender differences

Abbreviations

ERCC1	excision repair cross-complementation group 1
NSCLC	non-small cell lung cancer
ADC	adenocarcinoma
SCC	squamous cell carcinoma

Introduction

First-line platinum based chemotherapy is the most commonly used therapeutic modality in the treatment of non-small cell lung cancer (NSCLC), as in about 80 % the disease is diagnosed in a late stage when surgery is not possible to perform.

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Worldwide there are 1.6 million new lung cancer cases, of which more than 80 % are NSCLCs, therefore this drug combination is applied in more than 1.2 million new patients [1]. Platinum based chemotherapy is also used in adjuvant and neoadjuvant settings. In stage II or III disease adjuvant chemotherapy improves survival by 5 % at 5 years, and the combination of vinorelbine and cisplatin is more effective than older regimens [2, 3]. An updated meta-analysis of 13 randomized control trials showed survival benefit of neoadjuvant chemotherapy in non-small cell lung cancer [4]. Recently, pathologic complete response to preoperative chemotherapy was found to predict cure in early-stage non-small cell lung cancer [5].

In the clinical practice the therapeutic effect of chemotherapies is mainly determined by the extent of tumor shrinkage visualized by chest X-ray or CT scan. However, their effects on the expression of tissue biomarkers within the tumor are far less known.

ERCC1 (excision repair cross-complementation group 1) is a nucleotid excision repair enzyme playing an important role in DNA repair mechanism that removes the therapeutic platinum-DNA adducts from the tumor DNA. NSCLC patients with surgically removed early stage tumors, who received no further therapy, had a better survival if their tumors were ERCC1-positive, thus ERCC1 positivity is a favorable prognostic marker [6, 7]. ERCC1-positive NSCLC tumors do not benefit from adjuvant platinum chemotherapy. However, ERCC1-negative NSCLC tumors, prognostically worse without treatment, derive substantial benefit from adjuvant cisplatin-based chemotherapy [8].

We have already studied the effect of platinum based chemotherapy on the expression of certain tissue biomarkers, such as Ki-67, p53, Bcl-2, Bax, Fas-ligand and ERCC1, and found that ERCC1 expression decreased after neoadjuvant chemotherapy [9]. That study, however, contained only 17 paired cases, and only ERCC1 positive and negative tumors were distinguished without scoring the level of expression. Moreover, correlations between the expression of ERCC1 and histologic subtypes of tumors, components of chemotherapeutic combinations, gender and smoking history were not analyzed, either.

The aim of our present work was, therefore, to study the expression of ERCC1 in a larger cohort of NSCLC patients before and after cisplatin-containing chemotherapy using immunohistochemistry on diagnostic bronchoscopic biopsy materials together with the corresponding surgical tumor tissue samples obtained. Moreover, we aimed to examine the correlation between the histopathologic effect of platinum based neoadjuvant chemotherapy on ERCC1 expression scores and different clinicopathological parameters, such as age, gender, tumor histology, disease stage, composition of neoadjuvant chemotherapy, and response rate.

Patients and Methods

Case Series

We have investigated 92 non-small cell lung cancer tissue samples from 46 patients (29 males, 17 females, mean age: 57.1±7.3 years). They included 46 bronchoscopic biopsies (27 squamous cell carcinomas /SCC/ and 19 adenocarcinomas /ADC/) together with their corresponding surgical biopsies after platinum based neoadjuvant chemotherapy. Out of these 46 cases 16 had already been examined for ERCC1 expression, but were not analyzed in details regarding clinical and histopathological data. The tumors were classified histologically according to the criteria of the World Health Organization and the TNM stage was determined using the revised TNM staging system for lung cancer [10]. One stage I patient received chemotherapy before operation as he initially refused surgical intervention. Most of the patients with stage II disease suffered from Pancoast tumor. All patients with initial stage IIIB had clinical T4N2 disease. Three patients had stage IV disease. Two of them had solitary brain metastasis and were treated by metastasectomy and one patients had solitary adrenal metastasis that was later surgically resected. Permission for using the archived tissue blocks was obtained from the Regional Ethical Committee (TUKEB N^{o} 7/2006). The clinical and histopathological data for all cases are summarized in Table 1 (Table 1.).

ERCC1 Immunohistochemistry

ERCC1 immunohistochemistry was performed on formalin-fixed and paraffin-embedded tissues. 4 μm thick tissue sections were deparaffinized in xylene and rehydrated. Staining for ERCC1 was performed automatically using the Leica Bond Max immunostainer with Bond Polymer Refine Detection Kits and heat-induced epitope retrieval pH 8.0 (Bond max ER2 (EDTA) solution, Australia) for 15 min. The ERCC1 expression was analyzed using a mouse monoclonal antibody (clone 8 F11, Neomarkers, Fremont, CA, USA; dilution 1:200, incubation for 20 min at room temperature). After counterstaining with hematoxylin, the sections were coverslip-mounted using glycerol-gelatin. Immunostained sections were examined independently by two pathologists, and only nuclear staining was regarded as positive. Staining scores (Hirsch score) (0–300) were calculated by multiplying the percentage of positive tumor cells (0–100) by the staining intensity (0–3).

Statistical Analysis

Statistical analysis was performed using Mann–Whitney *U* test for correlation between age, ERCC1 score differences and clinicopathological features, such as gender, tumor histology,

Table 1 Patients' characteristics

Characteristics	SCC	ADC
Number of patients	27	19
Males / females	21/6	8/11
Mean age	57.8 years (43–73 years)	56.1 years (46–72 years)
Stage (at time of diagnosis)	IB: 1	IIA: 1
	IIA: 1	IIB: 1
	IIB: 2	IIIA: 9
	IIIA: 19	IIIB: 5
	IIIB: 4	IV: 3
Postoperative stage (available in 40 cases)	IA: 2	IA: 1
	IB: 4	IB: 4
	IIA: 6	IIA: 2
	IIIA: 10	IIB: 1
	IIIB: 2	IIIA: 4
		IV: 4
Components of neoadjuvant chemotherapy (≥2 cycles)	Cisplatin-Gemcitabine: 15	Cisplatin-Gemcitabine: 11
	Carboplatin-Paclitaxel: 3	Carboplatin-Paclitaxel: 3
	Cisplatin-Etoposide: 4	Cisplatin-Etoposide: 2
	Other combination: 5	Other combination: 3
Response rate (available in 40 cases)	CR: 1	CR: 0
	PR: 23	PR: 11
	SD: 0	SD: 4
	PD: 0	PD: 1
Overall survival (available in 28 cases)	51.0±46.8 months	43.1±31.5 months
Smoking history (available in 36 cases)	non-smoker: 1	non-smoker: 5
	current smoker: 19	current smoker: 11

type of chemotherapy. Wilcoxon signed rank test was used for comparison preoperative and postoperative ERCC1 scores. Kruskal-Wallis test was used to compare ERCC1 score differences and age with disease stage and smoking history. Spearman's rho test was used to calculate correlations. Overall survival was estimated from the date of primary tumor surgery until the date of death using the Kaplan–Meier survival analysis method. The impact on survival of variables were assessed by univariate cox regression for continuous and log-rank test when necessary for discrete variables. Significance was assumed for p value less than 0.05. The analysis was carried out using the SPSS 16.0 statistic program.

Results

In normal bronchial mucosa ERCC1 positivity was observed in the apical layer of bronchial cells (Fig. 1). Overall 35/46 preoperative tumor samples showed ERCC1 nuclear immunopositivity with a mean score of 129.4 (Fig. 2). Regarding the mean ERCC1 scores of the preoperative biopsies the difference between SCC and ADC groups was not significant, however, a trend with higher scores in the SCC group could be observed (151.7 and 97.6, respectively, $p=0.065$) (Table 2). In SCC all but three bronchoscopic tissues (24/27) expressed ERCC1 usually with high score. Thirteen of these cases (13/25) became negative after neoadjuvant therapy, in another 10 cases the level of expression decreased, and the expression differences were highly significant ($p<0.001$). In

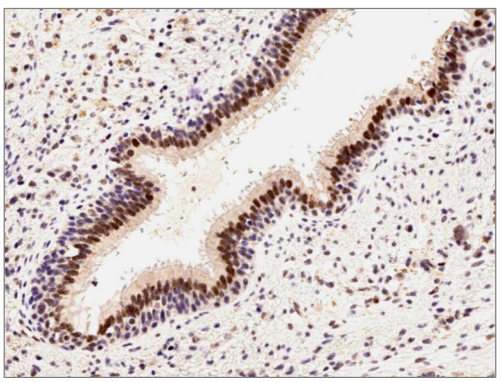

Fig. 1 ERCC1 positivity in apical layer of normal bronchial cells HE x200

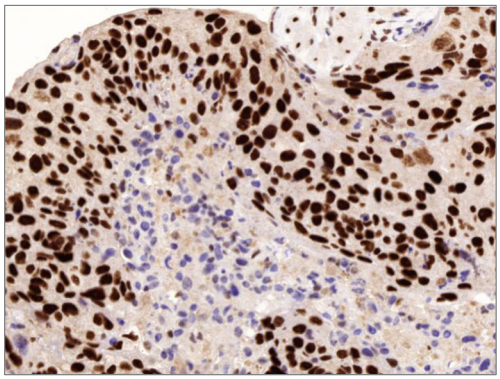

Fig. 2 ERCC1 positive SCC (score 285) HE x400

the ADC group 11/19 bronchoscopic tissues expressed ERCC1. Seven of these cases (6/11) became negative after neoadjuvant therapy, in 3 cases the level of expression decreased, and the expression differences were significant (p= 0.010). There was no newly expressed ERCC1 positive case in the surgical biopsy group. Upregulation of ERCC1 protein expression was observed exclusively in the ADC group in 2 cases, but was only moderate with a mean score increase of 42.5. Comparison of staining scores before and after chemotherapy revealed more pronounced decrease in squamous cell carcinomas (p<0.001) versus adenocarcinomas (p=0.010), and in male patients (p<0.001) versus female patients (p= 0.007) (Fig. 3). When compared ERCC1 score changes measured individually in each patients, more pronounced decrease could be demonstrated in squamous cell carcinomas (p= 0.032). When examined separately 16 NSCLC patients from our previously studied cohort studied by Papay et al. [9], but using ERCC1 scores for the first time and the presently analyzed 30 patients, similar tendency in the decrease of ERCC1 expression after chemotherapy could be observed. When comparing the ERCC1 immunohistochemical scores in these two groups, however, lower levels were found in the previously studied samples (Fig. 4). It could be partly explained by the fact that reevaluation of ERCC1 immunostaining took place after a 5 years period that might influenced the staining intensity.

Table 2 ERCC1 expression scores before and after chemotherapy

	SCC		ADC	
No	Before chemotherapy	After chemotherapy	Before chemotherapy	After chemotherapy
1	**285** ♀	**0**	**285** ♀	**0**
2	**285** ♀	**0**	**285**	**160**
3	**285** ♀	**20**	**270**	**20**
4	**285**	**30**	**270**	**60**
5	**270**	**10**	**240** ♀	**0**
6	**270**	**10**	**150** ♀	**0**
7	**270**	**100**	**140** ♀	**0**
8	**270**	**140**	**120**	**0**
9	**240**	**0**	80 ♀	160
10	**240**	**0**	**10** ♀	**0**
11	**240**	**210**	5	10
12	**210**	**60**	0 ♀	0
13	**160**	**0**	0 ♀	0
14	**160**	**0**	0 ♀	0
15	**140**	**0**	0 ♀	0
16	**140** ♀	**0**	0 ♀	0
17	120	120	0	0
18	**100**	**60**	0	0
19	**40**	**0**	0	0
20	**40**	**20**		
21	**20**	**0**		
22	**10** ♀	**0**		
23	**10**	**0**		
24	**5**	**0**		
25	0	0		
26	0	0		
27	0 ♀	0		

♀: female

Bold: when ERCC1 expression decreased after chemotherapy

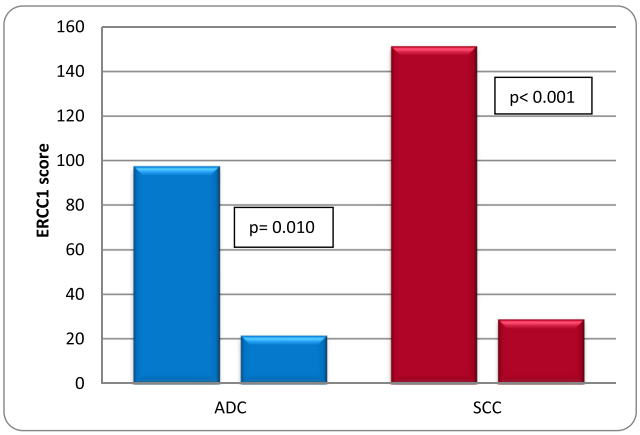

Fig. 3 Differences in ERCC1 expression scores before and after chemotherapy in ADC and in SCC (n=46)

In both genders the age correlated positively with the preoperative ERCC1 score (r=0.295, p=0.046). This correlation was almost significant in ADC patients (r=0.429, p=0.067), and highly significant in females (r=0.654, p=0.004). In women the age showed positive correlation also with the ERCC1 score changes (r=0.504, p=0.039) (Fig. 5).

When examined the correlation between cigarette smoking and ERCC1 score changes, pack-year index inversely correlated with the ERCC1 score changes, but only in males (r=−0.627, p=0.009).

The number of neoadjuvant chemotherapy cycles was higher in women than in men (2.48 versus 3.41, p=0.013). It was also higher in ADC when compared to SCC (3.26 versus 2.52, p=0.060). In males the number of cycles depended on the combination drug (paclitaxel: 3.33, gemcitabine: 2.37, etoposide: 1.75, p=0.031). In SCC the number of cycles depended on the combination drug (paclitaxel: 3.5, gemcitabine: 2.33, etoposide: 2.0, p=0.028).

Regarding the platinum compounds of preoperative chemotherapies we observed no significant differences between the cisplatin and carboplatin subgroups, however, the low number of cases within each group made no possible to draw firm conclusion. Nevertheless, it is of note, that in SCC the rate of ERCC1 score decrease was higher in case of carboplatin versus cisplatin (231.7 versus 109.2, p=0.070). Similarly, the ERCC1 score decrease was more pronounced when paclitaxel (224.2 versus gemcitabine: 109.0 versus etoposide: 48.6) was used as a combination drug (p=0.041).

When examined the correlation between response rate after neoadjuvant chemotherapy and clinical parameters, such as age and smoking history, no significant correlation was observed (p=0.205 and p=0.313, respectively).

Similarly, there was no correlation between response rate and number of chemotherapy cycles (p=0.518), response rate and preoperative ERCC1 score (p=0.757), response rate and postoperative ERCC1 score (p=0.711), and response rate and decrease in ERCC1 score (p=0.640).

When examined the correlation between the initial ERCC1 score and overall survival as well as between the change in ERCC1 score and overall survival, no significant correlation was observed either in ADC (p=0.142 and p=0.140, respectively) or in SCC (p=0.739 and p=0.892, respectively).

The initial clinical stage and the pathologic stage after neoadjuvant treatment differed significantly (p<0.001), however, there were no correlations between the changes in stages and either initial ERCC1 scores or ERCC1 score changes.

Discussion

Platinum based chemotherapy remains the first choice of treatment in most of the inoperable NSCLC cases. It is also used in neoadjuvant and adjuvant settings. The therapeutic effect is usually determined by the radiological tumor shrinkage, while the pathologic changes within the tumor tissue are not widely analyzed. In human lung cancer the histopathologic comparison before and after chemotherapy is often limited by the fact that of NSCLC patients receiving chemotherapy for advanced disease, 80 % will have only a small biopsy specimen or cytology samples available for diagnosis [11].

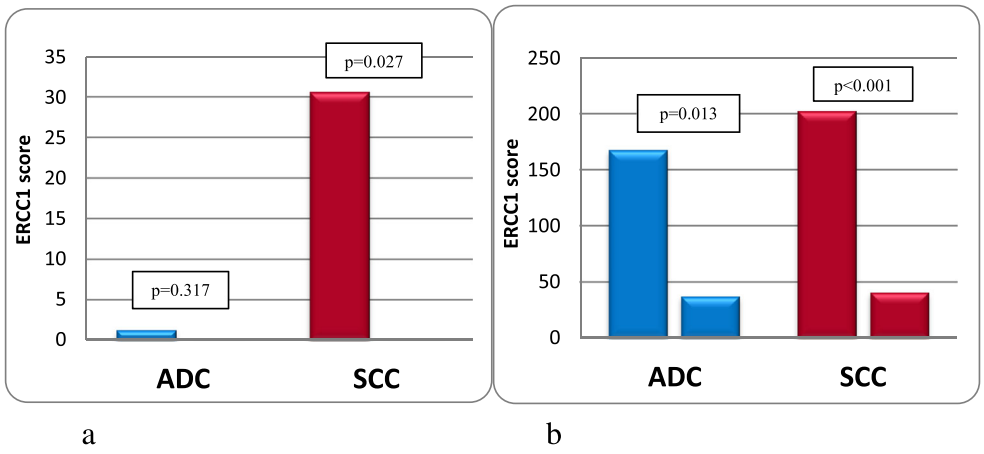

Fig. 4 Differences in ERCC1 expression scores before and after chemotherapy in ADC and in SCC. **a**. in the previously studied cohort of 16 NSCLC patients (8 ADC, 8 SCC) and **b**. in the newly examined 30 patients (11 ADC, 19 SCC)

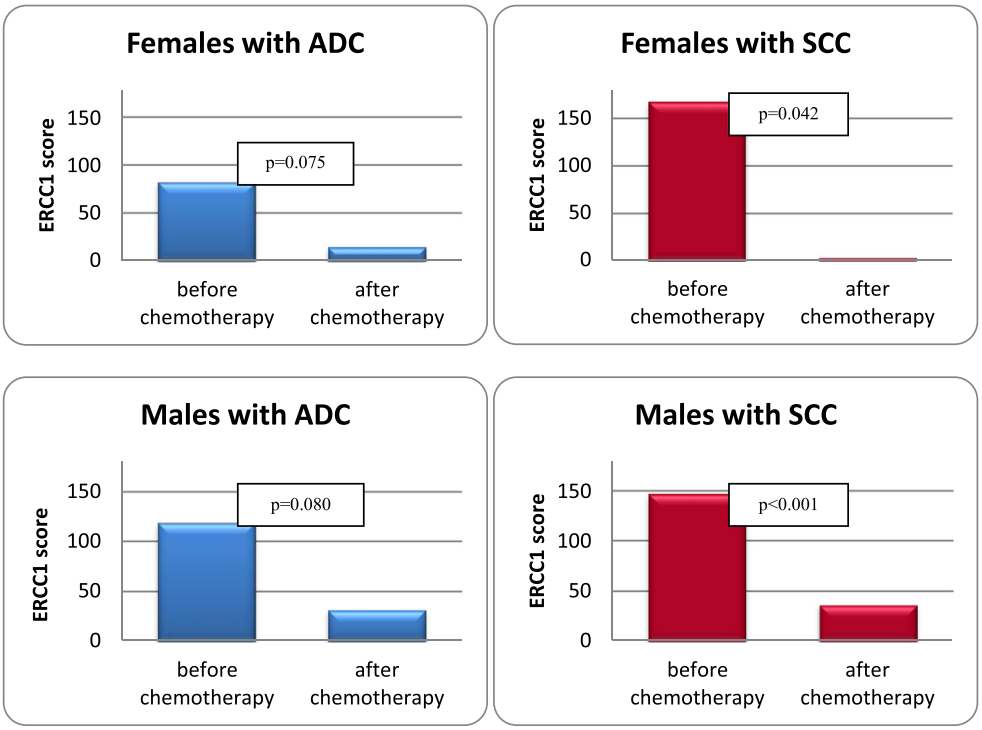

Fig. 5 Gender differences in ERCC1 expression scores before and after chemotherapy

In our present work we found correlation neither between response rate and certain clinical parameters like age and smoking habits, nor between response rate and ERCC1 scores. It is, however, due to the fact that the vast majority of patients included in this study was current smoker and had partial response after neoadjuvant chemotherapy, therefore the data for statistical analysis were imbalanced.

In a recent study Pomerri et al. compared volume measurements on computed tomography (CT) images with histopathological assessments of chemoradiotherapy-induced tumor regression in 25 patients with locally advanced rectal cancer [12]. They concluded that measuring tumor size on CT images is of limited value in predicting the histopathological response to preoperative chemoradiotherapy in rectal cancer patients, so it may be unwise to select surgical treatment strategies based on CT volumetry. In lung cancer management the evaluation of therapeutic response after cytotoxic treatment is based on the revised RECIST guideline (version 1.1) [13]. It is also used in case of molecular targeted treatment and in a study of Nishino et al. RECIST 1.1 provided almost perfect agreement in response assessment after erlotinib therapy compared with RECIST 1.0. A major factor that influenced the difference in best response assessment between RECIST 1.1 and RECIST 1.0 was assessment with PET/CT [14]. Lee et al. however, proposed new response criteria with additional morphological characteristics of target lesions for NSCLC patients treated with EGFR-TKI [15]. They found that their new response criteria are reproducible and have statistically significant association with overall survival. Using PET-CT the correlation between change in FDG uptake before and after chemotherapy in hepatic metastases of colorectal carcinoma and a histopathologic tumor regression grade in 31 lesions detected in 23 patients was evaluated by Burger et al. [16]. Their results demonstrated that a relative change in FDG activity (dSUV) of more than 41 % decrease correlated significantly with histopathological tumor regression.

Pataer et al. evaluated the ability of histopathologic response criteria to predict overall survival and disease-free survival in patients with 358 surgically resected NSCLCs treated with or without neoadjuvant chemotherapy [17]. They found that long-term overall survival and disease-free survival were significantly prolonged in patients who had ≤10 % viable tumor compared with patients with >10 % viable tumor cells. In a recent study of Sun et al., cytotoxic treatment-induced damage to the tumor microenvironment was found to promote prostate cancer therapy resistance [18]. In our previous work we observed increased Ki-67 expression after platinum based chemotherapy in one third of our studied NSCLC cases [9]. Moreover, from 10, initially p53 negative tumors, 4 became immunohistochemically p53 positive after treatment. This observation might be in accordance with the findings of Xiang et al., when the induction of drug resistance protein expression, such as P-gp, LRP, MRP and GST-π was found after neoadjuvant chemotherapy in NSCLC [19]. They concluded that neoadjuvant chemotherapy may lead to the enhancement of acquired drug resistance in stage I and II NSCLC, and this may decrease the therapeutic effect of chemotherapy after surgery. These results might be in accordance

with a study of Liu et al., who found both in cell lines and in tumor specimens that cisplatin selected for multidrug-resistant CD133+ cells in lung adenocarcinoma [20].

Therapy of NSCLC is complex and challenging due to the heterogeneity of the disease. The comparison of pretreatment and post-treatment biopsies is often limited by the small sample size of preoperative bronchoscopic excisions. However, Meert et al. compared the protein expression of the two prognostic factors p53 and Ki-67, and two therapeutic targets EGFR and c-erbB-2 assessed on biopsy samples of NSCLC with that of the corresponding resected tumors in 28 patients [21]. The concordant results for these markers were 81 %, 82 %, 85 %, 81 %, respectively, therefore they concluded that biopsies may provide reliable information about p53, EGFR, c-erbB-2 and Ki-67 in lung carcinoma. In our work the fact that there were hardly any tumor pairs in which the post-treatment ERCC1 expression was higher than that of the pretreatment one renders reliable the comparison of these sample groups. We observed decrease in staining scores before and after chemotherapy that was more pronounced in squamous cell carcinomas. In a recent study Choi et al. demonstrated that in NSCLC cases low ERCC1 protein expression was a poor prognostic factor more pronouncedly in squamous cell carcinoma patients [22]. The aim of our present work was to focus merely on the tissue biomarker changes after platinum-based chemotherapy, therefore, survival differences between groups with different ERCC1 expression level or different ERCC1 level changes were not analyzed. We observed significant decrease in ERCC1 protein expression especially in patients with squamous cell lung cancer. Although low ERCC1 expression might indicate tumor sensitive to platinum treatment, we speculate that the decrease in ERCC1 after chemotherapy can be a result of tumor cell selection and indicate tumor with more aggressive biological behavior. This theory, however, is not supported by the result of Kang et al., who found that in 82 NSCLC samples ERCC1 expression was upregulated in 55 % and downregulated in 8 % of metastatic lymph nodes, when compared with primary tumors [23].

Our result is somewhat similar to the study of Schneider et al., who observed downregulation of ERCC1 together with TS, DPD, GST-Pi, EGFR, and HER2 gene expression in patients with esophageal cancer after neoadjuvant chemoradiation [24]. However, the effect of radiation on ERCC1 expression was not analyzed separately. Interestingly, the opposite was found by Xia et al., who studied the relationship between ERCC1 expression and cisplatin intervention in cell lines and found that up-regulation of ERCC1 expression could be induced by low-dose cisplatin in human lung adenocarcinoma cell line A549 [25]. Furthermore, upregulation of ERCC1 expressions after oxaliplatin-based first-line chemotherapy was recently found in metastatic colorectal cancer [26].

The predictive value of ERCC1 protein expression in NSCLC is still controversial. Olaussen and coworkers studied the ERCC1 protein expression in surgically resected 761 NSCLC specimens from the International Adjuvant Lung Cancer Trial [27]. They found that adjuvant chemotherapy, as compared with observation, significantly prolonged survival among patients with ERCC1-negative tumors but not among patients with ERCC1-positive tumors. Among patients who did not receive adjuvant chemotherapy, those with ERCC1-positive tumors survived longer than those with ERCC1-negative tumors. According to this result ERCC1 immunpositivity might be regarded as a favorable prognostic and a negative predictive factor. In our work we could not demonstrate predictive value of ERCC1, but could demonstrate powerful effect of chemotherapy on ERCC1 protein expression. In a recent study of Schneider et al., commercial laboratory testing of ERCC1 expression in NSCLC was tested and interlaboratory concordance for ERCC1 expression was evaluated in three large laboratories [28]. They found that in preselected platinum responsive and resistant specimens, none of these three commercially marketed laboratory assays achieved a specificity of greater than 50 %. They concluded that the commercial laboratory testing for ERCC1 are inconsistent and unreliable, therefore, routine clinical use of ERCC1 in decision making is probably not timely.

The finding that in our present work response to cisplatin therapy was achieved also in ERCC1 positive cases might be explained by the fact that ERCC1 is only one member of a far more complex excision repair machinery [29, 30]. Simultaneous examination of protein and mRNA expression of more excision repair markers should be carried out to answer this question.

An interesting correlation between ERCC1 expression and the effect of cisplatin was described by Yoon et al. [31]. They found that sunitinib potentiated the activity of cisplatin by down-regulating the ERCC1 expression via the modulation of PDGFRA expression in gastric cancer cells. It is a nice example of a synergistic effect when using an old cytotoxic drug and a new molecular targeted agent, however, in lung cancer treatment it is still object of studies which targeted agents could be used in combination with cytotoxic drugs.

In lung cancer treatment molecular targeted therapy became an important modality in the near past. Very recently, in breast cancer patients loss of HER2 expression was found to be significantly more common among women with residual disease after chemotherapy alone (14/35, 40 %) than among women with residual disease after chemotherapy plus anti-HER2 agents (5/34, 14.7 %) [32]. This result also support the importance of studying the effect of cytotoxic chemotherapy on different tissue biomarker expression.

In our study we observed decreased ERCC1 protein expression after platinum-based chemotherapy that might be of importance when designing treatment protocols for NSCLC patients.

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