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Predictive Value of ERCC1 Expression on Treatment Response to Cisplatin-Based Regimens in Small Cell Lung Cancer: A Retrospective Analysis

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Abstract

We aimed to determine whether the excision repair cross-complementation group 1 (ERCC1) expression predicts response to cisplatin-based chemotherapy in patients with small cell lung cancer (SCLC). This was a retrospective study, in which hospital files of 31 patients (29 males, 2 females; mean age, 62.26±7.71 years) were reviewed. All patients were treated with etoposide+cisplatin. The lung biopsy and mediastinal lymph node samples were applied anti-human monoclonal antibodies against ERCC1: immunohistochemical staining was considered positive if 25-100% of the cells showed nuclear staining, and negative if less than 25% of the cells showed negative or slight staining. Response to treatment was evaluated as regression (complete or partial response), progressive disease, or stable disease. Of the patients, 18 (58.1%) had limited-stage, and 13 (41.9%) had extensive-stage SCLC. Median follow-up duration was 15 months (range: 1-60 months). ERCC1 staining was positive in 9 of 31 patients (29.0%). In 12 patients (38.7%), tumor regression (complete or partial response) was obtained after chemotherapy. Tumor regression rate was higher in ERCC1 positive patients than those with negative ERCC1 expression (66.7% vs. 27.3%, p=0.036). In conclusion, high expression of ERCC1 was associated with higher response rate to cisplatin-based regimens in patients with SCLC.

Keywords: Small Cell Lung Carcinoma; Cisplatin; Human ERCC1 Protein; Remission Induction; Immunohistochemistry

Introduction

Lung cancer is the most commonly diagnosed cancer and the leading cause of cancer death around the world [1,2]. It is divided into two broad categories: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). SCLC is derived from cells exhibiting neuroendocrine characteristics and accounts for 15-20% of new lung cancer cases. SCLC is highly malignant and an aggressive type of lung cancer [3,4]. Despite improvements in treatment, five-year survival for patients with SCLC is only 5-10% [5]. At the time of diagnosis, approximately 30% of patients with SCLC have limited-stage disease, which confined to the hemithorax of origin, the mediastinum or the supraclavicular lymph nodes; while 70% of patients have extensive-stage disease, which presents outside of the hemithorax [6]. While five-year survival up to 14% has been reported for patients with limited-stage disease, <1% of patients with extensive-stage disease can survive beyond 12 months [7].

Cisplatin-based regimens form the basis of chemotherapy in the management of SCLC. Combination of chemotherapy and radiotherapy results in complete response rate of 50-80% in limited-stage disease. In case of extensive-stage disease, the main treatment is a combination of cisplatin with either etoposide or irinotecan, which provides response rate of 60-80% and median survival of 7-12 months [8,9].

Cisplatin, a platinum agent, exerts its anti-tumor activity by binding to DNA and creating platinum-DNA adducts that can lead to cell destruction [10]. Nucleotide excision repair, which has a central role among DNA repair pathways, has been associated with resistance to cisplatin-based chemotherapy by recognizing and removing cisplatin-induced DNA adducts. The excision repair

cross complementation group 1 (ERCC1) enzyme plays a rate-limiting role in the nucleotide excision repair pathway [11,12]. Current data suggest that ERCC1 is a potentially useful marker for predicting clinical resistance to cisplatin in NSCLC [10,13]. In NSCLC patients treated with platinum-based chemotherapy, response and survival rates have been reported to be lower in patients with high expression of ERCC1 than those with low expression of ERCC1 [10]. Prognostic value of ERCC1 has also been reported in cancers other than lung cancer, such as ovarian cancer, gastric adenocarcinoma, colorectal cancer, or esophageal cancer [14-17]. However, the role of ERCC1 in predicting response to cisplatin-based chemotherapy and prognosis of disease in patients with SCLC has not been studied extensively, and few previous studies on this subject have conflicting results [18-20]. In this retrospective pilot study, we aimed at evaluating the predictive value of ERCC1 expression for response to cisplatin-based chemotherapy in patients with SCLC and provide the basis for future studies on the clinical use of ERCC1 immunohistochemistry to predict resistance to chemotherapy.

Materials and Methods

Study Design and Patients

This was a retrospective study, which included 93 patients diagnosed with SCLC and followed up at our clinic between 2007 and 2011. Clinico-pathological and immunohistochemical data were complete in hospital files of 31 patients, thus data of these 31 patients were analyzed. Demographic, clinical, pathological, and immunohistochemical data were recorded. The study was approved by the Institutional Ethics Committee and performed in accordance with the latest version of Helsinki Declaration. The requirement for informed consent was waived due to the retrospective design of the study.

Pathology and ERCC1 Immunohistochemistry

Four-micrometer-thick sections were cut from the bronchoscopic lung biopsy and mediastinal lymph node samples that were fixed in 4% formaldehyde and embedded in paraffin, and stained with hematoxylin and eosin for pathological evaluation with light microscopy (Olympus Bx51, Olympus Corporation, Tokyo, Japan). Tissue sections were also applied anti-human monoclonal antibodies against ERCC1 (Excision Repair Cross Complementing antibody, mAb anti-ERCC1 antibody, 1/100 dilution, ERCC1 (8F1): sc-56673, U.S.) immunohistochemically. The positive controls for immunohistochemical ERCC1 expression were made by nuclear staining of tonsillar epithelium.

We used a standard protocol for the immunostaining of the samples. The specimens were exposed to 10 mM citrate buffer (pH 6.0) and heated for 30 minutes in a water bath. Tumor samples were incubated for 60 minutes with a monoclonal antibody specific against the ERCC1 protein at a 1:100 dilution. Antibody binding was detected by means of an ABC kit and Mayers hematoxylin as the counterstain. Sections of normal tonsil tissues were included as external control.

Immunohistochemical staining was quantified using a grading system based on the percentage of tumor cells stained with ERCC1 according to Sereno *et al.* with slight modifications. It was considered positive if 25-100% of the cells showed nuclear staining, and negative if less than 25% of the cells showed negative or slight staining [18]. Four investigators evaluated ERCC1 staining under a light microscope at a magnification of 400x. They recorded the tumor cells that expressed ERCC1. The staining intensity was graded on a scale of 0 to 3 (with a higher number indicating a higher intensity and with epithelial cells in tonsil control tissue used as a reference). Five foci of representative areas were acquired at a magnification of 400x for each specimen. A total of 100 positive or negative tumor nuclei per specimen were counted with magnification of 400x on a Olympus BX51 microscope. The percentage of positive tumor nuclei was calculated for each specimen, and a proportion score was assigned as negative for staining less than 25% of tumor cells and positive for 25%-100%. This proportion score was evaluated by the staining intensity of nuclei to obtain a final semiquantitative score.

Management of Patients and Evaluation of Treatment Response

The stage and the extent of the disease were determined on the basis of available staging procedures: physical examination, laboratory evaluation, pathology, and imaging tests (computed tomography, magnetic resonance imaging, X-ray, positron emission tomography, radionuclide bone scan, etc.) Two-stage system is used for staging of SCLC: limited-stage disease and extensive-stage disease. Limited-stage is disease confined to the hemithorax of origin, the mediastinum or the supraclavicular lymph nodes. Extensive-stage is disease present beyond one hemithorax [21]. Treatment regimen was determined based on the stage and extent of the disease, patient's performance status, co-morbidities, clinical experience of our center, and consent of the patients. All of the patients included in the analysis were treated with etoposide+cisplatin chemotherapy regimen (etoposide 100 mg/m2, cisplatin 25 mg/m2) on days 1-3.

After treatment, patients were followed up with every 3 months, with radiological and clinical evaluation. Response to treatment was evaluated according to WHO response criteria and documented as regression (complete or partial response: >30% decrease in the longest axis), progressive disease (>20% increase in the longest axis), or stable disease (neither partial response nor progressive disease) [22].

Statistical Analysis

Study data are presented using descriptive statistics (mean, median, range, standard deviation, freqeuncy and percentage). Distributions of study variables (age, gender, stage, ERCC1 expresion, response to therapy) were compared using students't test for continuous variables and the chi-square test or Fisher's exact test for categorical variables. Results were considered significant at $p<0.05$.

Results

Patient Characteristics

Thirty-one patients (29 males, 2 females; mean age, 62.26±7.71 years) were included in the study. Median follow-up duration was 15 months (range: 1-60 months). Of the patients, 18 (58.1%) had limited-stage, and 13 (41.9%) had extensive-stage SCLC (Table 1). The age of the patients did not have a significant correlation with the stage of disease, ERCC1 expression, and response to therapy (Table 2). The sample images of pathology specimens from bronchoscopic lung biopsy and mediastinal lymph node samples are shown in Figure 1.

Parameters		Results
Age (years)		62.26±7.71 (47.00-79.00)
Gender	Male	*29 (93.5%)*
	Female	2 (6.5%)
Stage	Limited-stage	18 (58.1%)
	Extensive-stage	13 (41.9%)
Response to therapy	Regression	12 (38.7%)
	Stable disease	6 (19.4%)
	Progressive disease	13 (41.9%)
ERCC1	Negative (0-25%)	22 (71.0%)
	Positive (25-100%)	9 (29.0%)

Regression corresponds to complete or partial response (>30% decrease in the longest axis), stable disease is neither regression nor progressive disease, and progressive disease is >20% increase in the longest axis. Age data are given as mean ± standard deviation (min-max), other data are given as n (%).

Table 1: Demographic and clinical characteristics of 31 patients with small cell lung cancer

		Age (years) (mean±standard deviation)	p
Stage	Limited-stage (n=18)	62.72±8.62	0.7
	Extensive-stage (n=13)	61.62±6.52	
ERCC1	Negative (n=22)	60.68±7.17	0.075
	Positive (n=9)	66.11±8.04	
Response to therapy	Regression (n=12)	61.92±8.67	0.772
	Stable disease (n=6)	64.33±8.21	
	Progressive disease (n=13)	61.62±6.99	

Table 2: The mean age of study patients (n=31) with respect to stage of small cell lung cancer, ERCC1 expression, and response to therapy

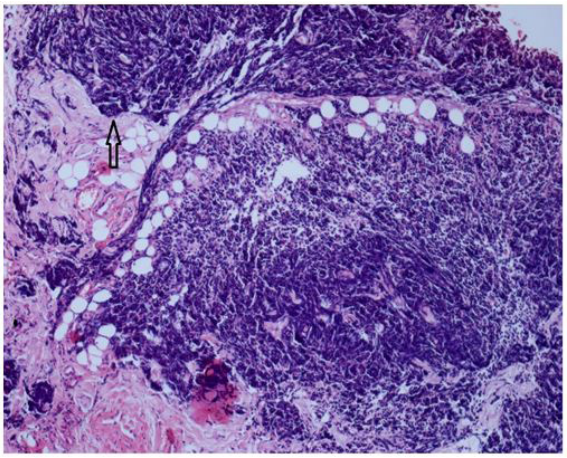

Figure 1a: Small cell lung cancer with atypical cells showing crush artefact in mediastinal lymph node biopsy specimen **(a)**

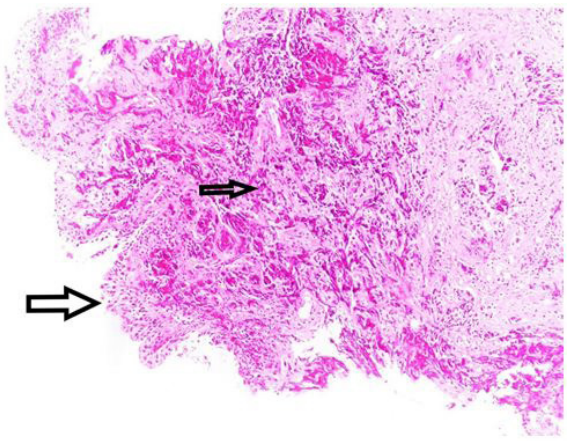

Figure 1b: In bronchial mucosa subepithelial infiltrates **(b)** (H&E, ×100)

ERCC1 Expression

ERCC1 immunohistochemical staining was positive in 9 of 31 patients (29.0%). Samples of positive and negative immunohistochemical stainings are shown in Figure 2.

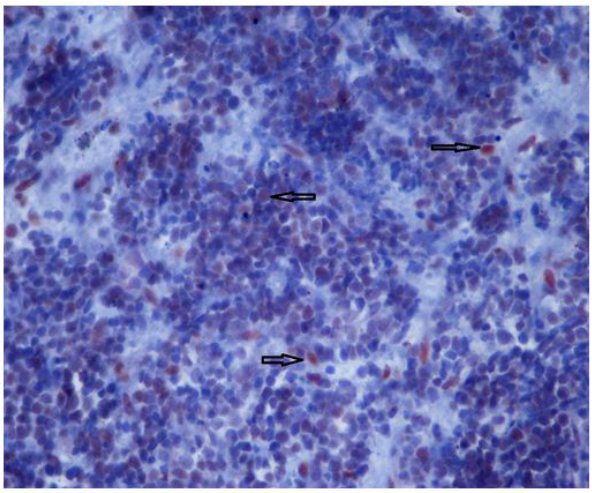

Figure 2: Positive ERCC1 immunohistochemical staining in 60% of atypical cells of infiltrating small cell lung cancer (ERCC1 positive) in mediastinal lymph node biopsy specimen **(a)**

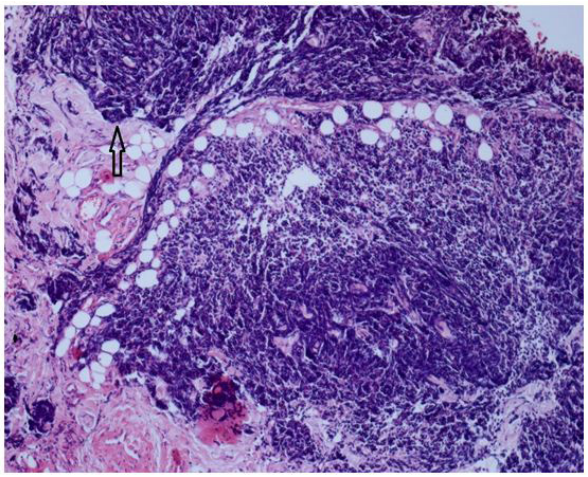

Figure 2b: Negative ERCC1 immunohistochemical staining (ERCC1 negative) in atypical small cell lung cancer cells showing subepithelial infiltration and crush artefact in bronchial mucosa biopsy specimen **(b)** (ERCC1, ×400)

ERCC1 Expression and Response to Treatment

In 12 patients (38.7%), tumor regression (complete or partial response) was obtained after chemotherapy. Tumor regression rate was higher in ERCC1 positive patients than those with negative ERCC1 expression (66.7% vs. 27.3%, p=0.036) (Table 3, Figure 3).

		Stage		Response to therapy			ERCC1	
		Limited-stage (n=18)	Extensive-stage (n=13)	Regression (n=12)	Stable disease (n=6)	Progressive disease (n=13)	Negative (n=22)	Positive (n=9)
Gender	Male (n=29)	18 (62.1%)	11 (37.9%)	11 (37.9%)	6 (20.7%)	12 (41.4%)	20 (69%)	9 (31%)
	Female (n=2)	0 (0%)	2 (100%)	1 (50%)	0 (0%)	1 (50%)	2 (100%)	0 (0%)
	p	0.055		0.639			0.232	
Stage	Limited-stage (n=18)	-	-	6 (33.3%)	3 (16.7%)	9 (50%)	12 (66.7%)	6 (33.3%)
	Extensive-stage (n=13)	-	-	6 (46.2%)	3 (23.1%)	4 (30.8%)	10 (76.9%)	3 (23.1%)
	p	-		0.559			0.532	
ERCC1	Negative (n=22)	12 (54.5%)	10 (45.5%)	6 (27.3%)	6 (27.3%)	10 (45.5%)	-	-
	Positive (n=9)	6 (66.7%)	3 (33.3%)	6 (66.7%)	0 (0%)	3 (33.3%)	-	-
	p	0.532		**0.036**			-	

Data are given as n (%).

Table 3: The relations between the stage of SCLC, response to therapy, ERCC1 expression, and gender of the patients

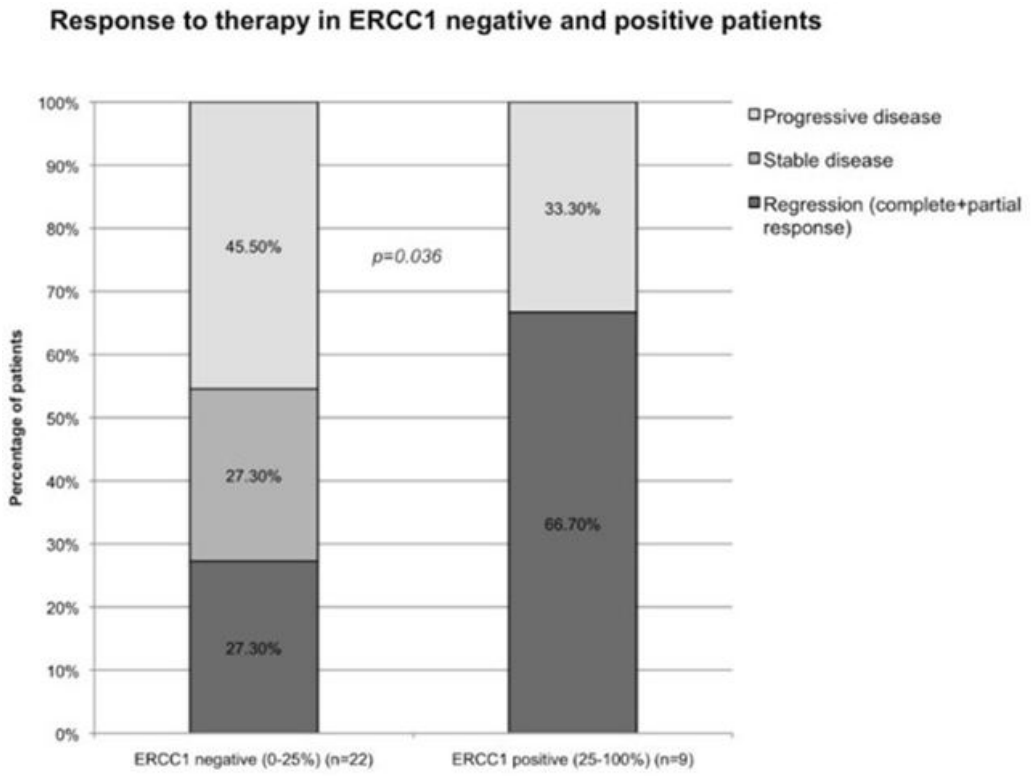

Figure 3: Response rates to chemotherapy in ERCC1 negative (0-25%) and ERCC1 positive (25-100%) patients

Gender and stage of SCLC had also no effect on response rates (p=0.639 and p=0.559). There was no relation between ERCC1 expression and gender (p=0.232) or stage of the disease (p=0.532) (Table 3).

Discussion

Although SCLC is an aggressive type of lung cancer, longer survival terms with good quality of life can be obtained with earlier and correct diagnosis, staging and appropriate multidisciplinary management of SCLC. On the other hand, resistance to chemotherapy is the main cause of poor outcome in patients with SCLC [23]. In order to manage the treatment, determining the risk group, prediction of treatment response to chemotherapy or prognosis of patients provides valuable information. On this ground, prognostic potential of polymorphisms in genes involved in DNA repair enzymes active in nucleotide excision repair, such as ERCC1, have been studied in some cancer types [4]. Although there are many clinical studies and meta-analyses showing the prognostic potential of ERCC1 protein expression and also being associated with increased resistance to platinum-based chemotherapy in NSCLC, SCLC data in literature are still inadequate to draw firm conclusions [24-29].

Sereno *et al.* found significant association between the positive immunohistochemistry expression of ERCC1 and the lack of platinum response (p=0.001) [18]. Additionally, significant association was found between better progression-free survival and negative

ERCC1 immunostaining (p=0.009) in 76 patients with SCLC. Lee *et al.* reported that high expression of ERCC1 was associated with poor overall survival, thus was an independent prognostic factor in patients with limited stage SCLC. Similarly Ceppi *et al.* showed that among 45 patients with limited disease, those with low ERCC1 expression had significantly longer survival (14.9 vs. 9.9 months, p=0.012), while no significant role was found for ERCC1 in extensive disease patients [19,20]. In a recent analysis by Karachaliou *et al.,* primary tumor samples of 184 SCLC patients treated with cisplation-etoposide were analyzed for ERCC1 mRNA expression [30]. The study found that in limited stage patients, high expression of ERCC1 was correlated with decreased median overall survival. However, Sodja *et al.* studied 77 SCLC patients and found no correlation between ERCC1 protein expression with either response rate to platinum-based chemotherapy or survival outcomes [31]. In the present study, out of 31 patients evaluated, 12 had tumor regression (complete or partial response) after standard cisplatin-etoposide chemotherapy, providing a response rate of 38.7%, which is consistent with the literature [32]. ERCC1 immunohistochemical staining was positive in 9 of 31 patients (29.0%). This rate was lower than the rate (52%) in the study by Sereno *et al.,* in which ERCC1 immunohistochemical staining was considered positive when more than 10% of the cells showed nuclear staining [18]. On the other hand, we considered positive staining if more than 25% of the cells showed nuclear staining. In contrary to the above-mentioned previous reports, the current study found that the treatment response rate was higher in ERCC1 positive patients than those with negative ERCC1 expression (66.7% vs. 27.3%, p=0.036).

It should be noted that the method of ERCC1 determination varies between studies in literature, thus it is difficult to meta-analyse or to draw a final conclusion from previous studies. Therefore, a consensus is required to provide consistent, validated ERCC1 assessment methodology.

The major limitations of our study were its retrospective design and small sample size. These limitations prevent us from reaching a definitive conclusion for the predictive value of ERCC1 expression on the cisplatin-based chemotherapy response on patients with SCLC. Furthermore, we did not evaluate prognostic criteria such as progression-free or overall survival; thus, we cannot speculate on the predictive value of ERCC1 expression on prognosis of SCLC. However, our preliminary finding on the conflicting relationship between ERCC1 expression and response to treatments will form a basis for further prospective clinical trials to obtain a definitive answer on the predictive value of ERCC1 in SCLC.

Conclusion

In conclusion, in contrast to previous reports, the findings of the present retrospective study showed that high expression of ERCC1 was associated with higher response rate to cisplatin-based regimens in patients with SCLC. In view of the previous studies and the present work, it is obvious that there is a relationship between the expression of ERCC1 and response to treatment with cisplatin-based chemotherapies in patients with SCLC, but to reach a definitive conclusion on the direction, extent, and clinical significance of this relationship, comprehensive and large-scale prospective clinical studies are needed.

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