High ERCC1 expression is associated with platinum-resistance, but not survival in patients with epithelial ovarian cancer

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Abstract. The present study aimed to investigate the association between excision repair cross-complementation group 1 (ERCC1) expression and clinical resistance to platinum-based chemotherapy or clinical characteristics, including survival time, in patients with epithelial ovarian cancer (EOC). ERCC1 expression was determined by immunohistochemical staining in 92 tumor specimens from patients with EOC. The effect of ERCC1 expression on progression-free survival time (PFS) or overall survival time (OS), and its association with clinical resistance to platinum-based chemotherapy was investigated by Kaplan-Meier survival analysis, Cox regression analysis and the χ^2 test. Of 92 patients with EOC, 89.13% (82/92) had ERCC1-positive tumors. The positive rate was significantly higher in platinum-resistant patients compared with those who were platinum-responding (P<0.05). The PFS and median OS were 12 and 30 months, respectively, in ERCC1 high expression patients, and 17 and 39 months, respectively, in ERCC1 low expression patients. However, there was no statistically significant difference in PFS (P=0.099) or OS (P=0.103) between the high and low expression groups. Furthermore, it was identified that ERCC1 was not an independent factor affecting the prognosis of patients with EOC based on Cox proportional hazards regression analysis. These results demonstrate that high ERCC1 expression is associated with resistance to platinum-based chemotherapy, but not with survival time, and ERCC1 protein expression is not an independent factor or the only factor affecting the prognosis of patients with EOC.

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Introduction

Ovarian cancer is the second most prevalent cancer and the leading cause of mortality in women amongst all gynecological malignancies, with epithelial ovarian cancer (EOC) accounting for >95% of all ovarian cancer cases (1,2). As it is difficult to detect the disease at early stages, the majority of patients with EOC have advanced-stage disease at the time of diagnosis. EOC metastasizes and transfers easily, is recurrent and is also resistant to chemotherapy, thus resulting in high mortality rates (3,4). Currently, the 5-year survival rate of patients with EOC remains at <50% despite recent advances in chemotherapeutic agents and cytoreductive surgery (5). Platinum-based therapy is the first-line chemotherapy regimen for EOC; however, platinum-resistance is a major factor affecting patient prognosis (6,7). If the potential sensitivity of platinum chemotherapy and prognosis is able to be predicted prior to treatment, it may guide individualized treatment, protect patients from inappropriate chemotherapy and reduce the occurrence of secondary resistance.

Nucleotide excision repair (NER) is a versatile DNA repair system that identifies platinum-based therapy-induced DNA damage (8). The excision repair cross-complementation group 1 (ERCC1) gene is critical within NER and serves a leading role in this pathway (9,10). Cisplatin-resistant ovarian cancer exhibits increased expression of ERCC1 (11-13). Stefensen *et al* (13) reported that patients with ERCC1-negative tumors had a significantly greater response to platinum-based therapy compared with patients with ERCC1-positive tumors, while other studies demonstrated that examination of ERCC1 expression fails to identify therapy-responsive or resistant patients (14,15). Although the overexpression of ERCC1 may function as a prognostic indicator of poor survival in patients with advanced ovarian cancer, the differences in response rates cannot be translated into survival rates (16,17). Muallem *et al* (18) recently reported that there were no significant differences in the progression-free survival time (PFS) of patients with low, intermediate and high H-scores for ERCC1 expression. The variation in results of previous studies demonstrates that there is no conclusive evidence indicating that ERCC1 expression is associated with platinum-resistance and survival of patients with EOC.

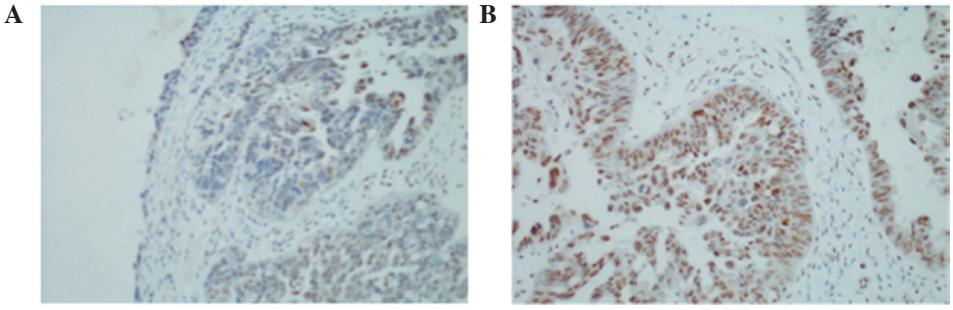

Figure 1. Immunohistochemistry of ERCC1 expression in epithelial ovarian cancer tissues. (A) Weakly positive (+) and (B) strongly positive (+++) ERCC1 expression. Magnification, x200. ERCC1, excision repair cross-complementation group 1.

The present study aimed to investigate the association between ERCC1 expression and the platinum-resistance and survival of patients with EOC using immunohistochemical analysis. The results demonstrated that high ERCC1 expression is associated with clinical resistance to platinum-based chemotherapy, but not with survival or other clinical characteristics. The current study also determined that ERCC1 expression is not an independent or lone factor affecting the prognosis of patients with EOC.

Materials and methods

Patients. A total of 92 patients diagnosed with EOC were recruited between January 2008 and December 2008 in The First Affiliated Hospital of Guangzhou Medical University (Guangzhou, China). The age of the patients ranged between 21-79 years. The tumors were classified according to the International Federation of Gynecology and Obstetrics classification system, with 29 samples classified as stage I, 9 as stage II, 35 as stage III and 19 as stage IV. The pathological types of the tumor samples were as follows: 52 Serous carcinoma samples, 25 mucinous carcinoma, 8 endometrium cancer and 7 clear cell carcinoma, and the pathological classifications were as follows: 18 High-differentiation, 32 medium-differentiation and 42 low-differentiation. All 92 patients underwent a comprehensive staging laparotomy and comprehensive or satisfactory cytoreductive surgery (clean removal/basic removal/majority removal), and received chemotherapy following surgery. Chemotherapy regimens consisted of 175 mg/m^2 taxol plus 75 mg/m^2 cisplatin (or carboplatin calculated at AUC 5-7). Each treatment cycle lasted 3 weeks and 6-8 cycles were required. This study was approved by the ethical committee of The First Affiliated Hospital of Guangzhou Medical University and written informed consent was obtained from all patients.

Immunohistochemical analysis of ERCC1 expression. Tumor specimens were harvested from 92 patients prior to receiving cisplatin-based treatment. Formalin-fixed and paraffin-embedded specimens were cut into 5 μm sections for immunohistochemical analysis. Antigen retrieval was performed using target retrieval solution (Dako, Carpinteria, CA, USA) at 95˚C for 20 min. Specimens were then blocked with 3% H_2O_2 for 10 min, rinsed with dH_2O and Tris-buffered saline and incubated with CAS Block™ solution (Invitrogen; Thermo Fisher Scientific Corporation, Waltham, MA, USA) for 5 min. Slides were then incubated with monoclonal mouse anti-human ERCC1 antibody (cat. no. MOB336-05; 1:300; Diagnostic Biosystems, Pleasanton, CA, USA) for 60 min at room temperature, followed by incubation with biotinylated goat anti-mouse secondary antibody (cat. no. M001; 1:500; Diagnostic Biosystems) for 30 min and DAB for 5 min at room temperature (Vectastain ABC kit; Vector Laboratories, Burlingame, CA, USA). Identification of brown-yellow granules in the nuclei and/or plasma of the tumor cells corresponded with positive ERCC1 expression. A total of 500-1,500 tumor cells were randomly selected from each specimen at a magnification of x400 . The intensity of positive cell staining was examined and the percentage of positive cells was calculated. The cell staining intensity was categorized as follows: 0, No color; 1, canary yellow; 2, brown-yellow; and 3, brown or dark brown. Additionally, the composition ratio of positive cell percentage was scored as follows: 0, <10%; 1, 10-25%; 2, 26-50%; and 3, >50%. These two scores were added to calculate the total score, which corresponded with expression as follows: 0-1, negative (-); 2-3, weakly positive (+); 4-5, positive (++); and 6, strongly positive (+++). The +/- groups were defined as low expression and the ++/+++ groups as high expression.

Chemotherapy outcome. Clinical curative effect was assessed by routine gynecological examination, imaging analysis (color ultrasound, magnetic resonance imaging or positron emission tomography-computed tomography for abdominal or pelvic regions) and detection of serum carbohydrate antigen (CA)-125 levels per month. No recurrence at 6 months post-chemotherapy was referred to as 'clinically sensitive' and included normal serum CA-125 levels, no new lesions, or the original residual lesions had decreased in size or disappeared as identified by pelvic and imaging examination. By contrast, disease progression during chemotherapy, a continual increase in serum CA-125 levels or the appearance of new lesions identified by imaging at 6 months post-chemotherapy was recognized as 'clinical resistance'.

Follow-up. The final follow-up (range, 5-62 months) occurred on June 6, 2014. Out of 92 patients, 1 was lost to suicide and 5 were lost to follow-up without reason. Disease PFS was described as the time from ovarian cancer surgery to disease recurrence or mortality, whichever came first. The time between surgery and mortality or the end of follow-up was described as the overall survival time (OS).

Table I. Association between ERCC1 expression and clinicopathological features.

Clinical feature	n	Low expression	High expression	χ^2	P-value
Age, years					
>50	53	19	34	1.731	0.188
≤50	39	9	30		
Pathological type					
Serous	52	14	38	1.506	0.681
Mucinous	25	10	15		
Endometrium	7	2	5		
Clear cell	8	2	6		
Pathological differentiation					
Good	16	3	13	1.320	0.517
Medium	32	10	22		
Poor	44	15	29		
Clinical stage					
I	29	12	17	2.835	0.418
II	9	3	6		
III	35	9	26		
IV	19	4	15		

ERCC1, excision repair cross-complementation group 1.

Table II. Association between ERCC1 expression and chemoresistance.

Group	n	High ERCC1 expression, n (%)	χ^2	P-value
Total	92	64 (69.57)		
Sensitive	61	37 (60.77)	6.787	0.009
Resistant	31	27 (87.10)		

ERCC1, excision repair cross-complementation group 1.

Statistical analysis. SPSS 13.0 software (SPSS, Inc., Chicago, IL, USA) was used for statistical analysis. The χ^2 test was performed to analyze the association between ERCC1 expression and clinical pathological features or the platinum-resistance of EOC. Kaplan-Meier survival curve comparison analysis was used for survival data, and the log-rank test was used for comparing survival analysis data. Cox proportional hazards regression analysis of multiple factors was employed to assess the association between ERCC1 and PFS or OS. P<0.05 was considered to indicate a statistically significant difference.

Results

ERCC1 immunohistochemistry. Brown-yellow granules were observed in the majority of tumor cell cytoplasm and nuclei, and corresponded with positive ERCC1 expression (Fig. 1). Immunohistochemistry identified that 82/92 specimens (89.13%) were ERCC1 positive, with high expression observed in 64 cases (69.57%). A total of 10 cases (10.87%) were classified as ERCC1(-), 18 cases (19.57%) as (+), 28 cases (30.43%) as (++) and 36 cases (39.13%) as (+++).

Association between ERCC1 expression and clinical pathological features. As presented in Table I, no significant association was identified between ERCC1 expression and age (P=0.188), pathological type (P=0.681), cell differentiation (P=0.517) or clinical stage (P=0.418).

Association between ERCC1 expression and chemoresistance and survival time. As presented in Table II, the number of resistant cases with high ERCC1 expression (27/31; 87.10%) was significantly greater than the number of sensitive cases with high ERCC1 expression (37/61; 60.77%) (P<0.05). For the 92 EOC cases, the median OS was 33.0 months and the median PFS was 14.0 months. The PFS of cases with high ERCC1 expression was 12.0 months and the median OS was 30.0 months. The PFS of cases with low ERCC1 expression was 17.0 months and the median OS was 39.0 months. There was no significant difference in PFS and median OS between patients with high ERCC1 expression and patients with low expression (OS, P=0.103; PFS, P=0.099) (Fig. 2).

Independent risk factors for patient survival time. Cox proportional hazards regression was used to analyze five possible risk factors, including age, histopathological type, degree of cancer cell differentiation, clinical stage and ERCC1 expression. As presented in Table III, pathological differentiation and clinical stage were identified as independent factors significantly affecting the prognosis of patients (P=0.005 and P<0.001, respectively), whilst ERCC1 expression (P=0.056), age (P=0.223) and pathological type (P=0.276) did not significantly affect prognosis.

Table III. Cox proportional hazard regression analysis for independent risk factors affecting patient survival time.

							95% CI for Exp (B)	
	B	SE	Wald	df	P-value	Exp (B)	Lower	Upper
Age	0.467	0.391	1.483	1	0.223	1.609	0.748	3.460
Pathological type	0.255	0.234	1.187	1	0.276	1.290	0.816	2.040
Pathological classification	-1.230	0.441	7.773	1	0.005	0.292	0.123	0.694
Clinical stage	0.985	0.265	13.782	1	<0.001	2.677	1.592	4.501
Expression of ERCC1	-0.782	0.409	3.662	1	0.056	0.458	0.205	1.019

ERCC1, excision repair cross-complementation group 1; CI, confidence interval; SE, standard error; df, degrees of freedom.

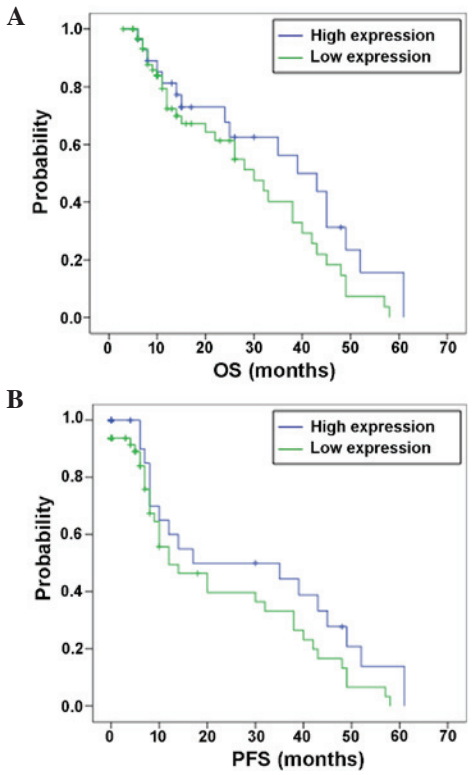

Figure 2. Kaplan-Meier estimates of (A) OS and (B) PFS between patients with strongly positive expression vs. those with negative or weakly positive expression of excision repair cross-complementation group 1. OS, overall survival; PFS, progression-free survival.

Discussion

Over 200,000 women are affected by EOC, with 125,000 mortalities each year worldwide (19). Chemotherapy drug resistance is a major factor restricting the improvement of patient survival rates, with 20-30% of patients with EOC undergoing primary platinum-resistance; however, 80% of patients are likely to eventually encounter resistance (20,21). The majority of patients experience relapse, and may eventually succumb to the disease as a result of drug resistance.

A key factor impacting the survival of patients with EOC is the response to initial or subsequent platinum-based chemotherapy, which is subjected to the development of platinum resistance. With the rapid development of pharmacogenomics and molecular biology, the mechanism of cisplatin resistance is closely associated with NER (22). In DNA repair, ERCC1 is a key gene of the NER pathway due to its binding with DNA repair endonuclease ERCC1-xeroderma pigmentosum group F (XPF) (23,24). In addition, the ERCC1-XPF complex is required for the removal of DNA interstrand crosslinks (ICLs), which are highly cytotoxic lesions induced by bifunctional genotoxins, including cisplatin (25). ERCC1-XPF is the only enzyme that is essential for ICL repair and NER, and therefore, removal of all platinum-induced DNA damage.

ERCC1 has been the focus of numerous studies investigating the mechanisms of platinum-based resistance. A number of studies have demonstrated an association between high ERCC1 expression and resistance to cisplatin-based chemotherapy, which determined the survival rate of patients with EOC (11,13,16,17,26). During chemotherapy, platinum drugs primarily bind to and destroy tumor cells with negative ERCC1 expression, while having no effect on tumor cells with high ERCC1 expression exhibiting platinum resistance. In addition to ovarian cancer, a number of studies have evaluated the role of ERCC1 in the mechanisms of platinum resistance in other types of cancer, including head and neck cancer (27), non-small cell lung cancer (27,28) and gastrointestinal cancer (29). However, no consistent results have been obtained regarding the association between ERCC1 expression and different clinical endpoints.

A previous meta-analysis evaluated whether response to platinum-based chemotherapy was associated with ERCC1 expression in patients with ovarian cancer (30). It was observed that patients with negative ERCC1 expression had a significantly greater response to platinum-based chemotherapy compared with patients with positive ERCC1 expression (30), indicating that ERCC1 protein expression status is correlated with response to platinum-based chemotherapy in ovarian cancer. Zhao *et al* (31) identified a negative correlation between ERCC1 expression and clinical chemosensitivity in EOC. Furthermore, Steffensen *et al* (13) analyzed 100 tumor samples for ERCC1 expression and observed that 45% of ERCC1-positive samples were significantly less sensitive to chemotherapy than ERCC1-negative samples, and therefore identified a positive association between clinical resistance to platinum-based chemotherapy and ERCC1 expression in patients with EOC. Thus, it is considered to be beneficial to predict the sensitivity of clinical platinum chemotherapy by

examining ERCC1 expression in tumor tissues prior to chemotherapy. However, Muallem *et al* (18) demonstrated that there were no significant differences in the PFS between patients with low, intermediate and high H-scores for ERCC1 expression. Furthermore, Rubatt *et al* (32) reported that the tumoral expression of ERCC1 prior to chemotherapy in women with advanced stage EOC is not predictive of clinical outcomes. Additionally, Steffensen *et al* (13) observed no association between ERCC1 expression and OS in patients with EOC.

In the present study, ERCC1 expression was analyzed in the EOC tissues by immunohistochemical staining. The results demonstrated that 89.13% of the EOC tissues were ERCC1 positive, and the number of chemoresistant cases with high ERCC1 expression was significantly greater than the number of chemosensitive cases with high ERCC1 expression, suggesting that the ERCC1 expression is associated with cisplatin chemotherapy-sensitivity. As platinum chemotherapy is the first-line therapy administered for EOC, ERCC1 expression may be widely used as a predictor of clinical chemotherapy sensitivity to guide individualized treatment, avoid administration of invalid chemotherapy and eventually improve treatment for patients with cancer.

Furthermore, when compared with patients with low ERCC1 expression, PFS and OS were lower in the high ERCC1 expression group in the current study, but this was not significant (PFS, P=0.099; OS, P=0.103). Additionally, Cox regression analysis demonstrated that ERCC1 expression level was not an independent prognostic factor for the survival time of patients with EOC. Certain factors, such as the use of a comprehensive treatment as primary tumor treatment, may affect patient survival and require further analysis. In addition, genetic polymorphisms in ERCC1 genes may reverse ERCC1 mRNA level, and may also impact the curative effect and prognosis of platinum-based chemotherapy (33).

In conclusion, the present study demonstrated that high ERCC1 expression in patients with EOC was associated with resistance to platinum-based chemotherapy, but not with survival time. In addition, it was also observed that ERCC1 protein expression was not an independent or lone factor affecting the prognosis of patients. Further studies with larger sample sizes and improved study designs are required to investigate whether or not ERCC1 may function as a predictor for chemotherapy against EOC.

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