RESEARCH ARTICLE

Meta-analysis of Excision Repair Cross-complementation Group 1 (ERCC1) Association with Response to Platinum-based Chemotherapy in Ovarian Cancer

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Abstract

    Recent studies suggested that the ovarian cancers with negative excision repair cross-complementation group 1 enzyme (ERCC1) expression have a better response to platinum-based chemotherapy than those with positive ERCC1 expression. The objective of this study was to evaluate whether ERCC1 expression is associated with response to platinum-based chemotherapy in ovarian cancers. MEDLINE, PubMed, Web of Science and CNKI databases were used for searching studies relating to ERCC1 protein expression and response to platinum-based chemotherapy in ovarian cancers. Statistical analysis was based on the method for a fixed effects meta-analysis. Pooled odds ratios (ORs) with 95% confidence intervals for ERCC1 protein expression and response to platinum-based chemotherapy were generated. Publication bias was investigated with Begg's test. Five studies involving 306 patients with ovarian cancer were included. Compared to patients with positive ERCC1 expression, those with negative ERCC1 expression had a better response to platinum-based chemotherapy. The pooled OR was 5.264 (95% CI: 2.928 – 9.464, $P < 0.001$) and publication bias was not found ($P = 0.904$). The result was similar in both in Asians and Caucasians ($P < 0.001$ and $P = 0.028$, respectively). ERCC1 protein expression status is significantly associated with response to platinum-based chemotherapy in ovarian cancers.

Keywords: ERCC1 - platinum-based chemotherapy - ovarian cancer - meta-analysis

Introduction

    Ovarian cancer is the major cause of death among the gynecological malignancies (Siegel et al., 2012). One of the standards of care for the optimal treatments of ovarian cancer is a systemic chemotherapy regimen that bases on a platinum-based drug (Lebwohl & Canetta, 1998). However, a large proportion of patients treated with platinum-based chemotherapy fail to benefit from it. Predictive biomarkers are needed for personalized medicine which identify subpopulations of patients who most likely respond to a given therapy and those who not.

    The nucleotide excision repair (NER) system plays a key role in mediating resistance or sensitivity to platinum chemotherapeutic agents (Rabik & Dolan, 2007). It repairs platinum-induced DNA damage by altering the helical structure of the DNA molecule and interfering with DNA replication and transcription. ERCC1 is a key gene involved in NER, and ERCC1 status (ERCC1 RNA expression, ERCC1 protein expression, and ERCC1 polymorphisms) are associated with platinum-based therapy efficacy in some kinds of cancers (Vilmar & Sorensen, 2009; Bohanes et al., 2011; Langer, 2012). Recent studies indicated ERCC1 protein expression could be predictive of sensitivity to platinum-based

chemotherapy in ovarian cancers. However, these studies were of small sample size and have shown inconsistent results. In this study, we performed a meta-analysis of the published literature to assess an association between ERCC1 protein expression and response to platinum-based chemotherapy in patients with ovarian cancer.

Materials and Methods

Study selection

    We carried out a search in MEDLINE, PubMed, Web of Science and CNKI databases covering all papers published till July 2012. No language restrictions were applied. The following keywords were used: "Ovarian Cancer", "Ovarian Neoplasms" and "ERCC1".

    Studies included in the meta-analysis had to meet the following criteria: (1) patients had to have pathologically confirmed ovarian cancer under platinum-based chemotherapy regimens; (2) ERCC1 expression were measured using immunohistochemistry (IHC), or western blot (WB); (3) the study should provided data for objective response rate according to ERCC1 expression.
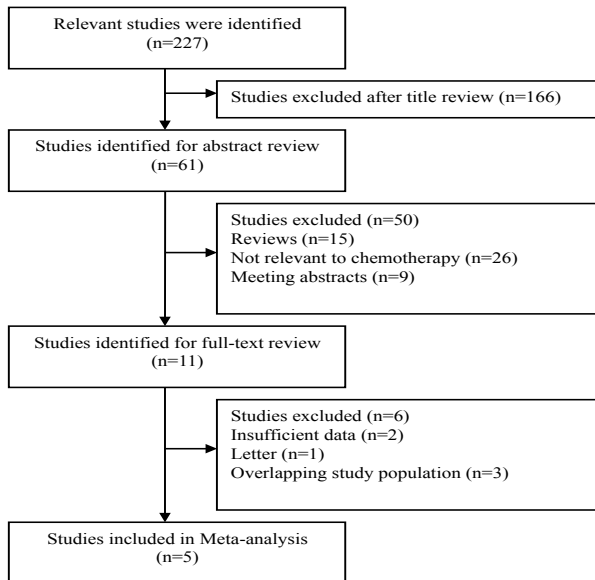
    Reviews, abstracts, letters and papers reported only at academic meetings were excluded for this meta-analysis. When overlapping data of the same patient population

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Table 1. Characteristics of the Studies Included in the Meta-analysis

First author	Year	Ethnicity	Laboratory method	Stage	Therapy regimen	ERCC1 negative		ERCC1 positive	
						Res	No res	Res	No res
Liu	2008	Asian	ICH	I-IV	Cisplatin-based	28	8	11	11
Steffensen	2009	Caucasian	ICH	I-IV	Carboplatin-based	67	6	11	3
Tang	2009	Asian	ICH	I-IV	Cisplatin-based	18	7	8	23
Xie	2011	Asian	ICH	I-IV	Platinum-based	27	9	9	19
Bösmüller	2011	Caucasian	ICH	III/IV	Carboplatin-based	6	0	21	14

ICH, immunohistochemistry; Res, response

Figure 1. Flow Chart of Study Selection in the Meta-analysis

Figure 2. Forest Plot for the Association Between ERCC1 Expression and Response to Platinum-based Chemotherapy in Patients with Ovarian Cancer

out. All the statistical analyses were performed by Stata version 11 (Stata Corporation, College Station, TX, USA). *P*-value < 0.05 was considered as significant.

Results

Eligible studies

In total, 227 potentially relevant studies were identified. Of these, 167 studies were excluded after title review, leaving 60 studies for abstract review. 50 studies were excluded for review or for no relevance to chemotherapy or for meeting abstract. After full-text review, 5 studies were excluded from the remaining 10 studies (1 studies were lack of sufficient data (Lin et al., 2008) ; 1 study was letter (Stadlmann et al., 2008) ; 3 studies were found to overlap other study population (Wang & Qu, 2006; Liu et al., 2008; Steffensen et al., 2008)). Finally, 5 studies were included in our meta-analysis (Liu et al., 2008; Steffensen et al., 2009; Tang et al., 2009; Bosmuller et al., 2011; Xie et al., 2011). The flow chart of study selection was shown in Figure 1. Characteristics of the 5 eligible studies are presented in Table 1. A total of 306 participants with ovarian cancer were included in these studies. No publication bias was detected based on the Begg's test (*P* = 0.904).

Response to platinum-based chemotherapy

Data of the 5 studies including 306 patients were eligible for the analysis of response to platinum-based chemotherapy in patients with ovarian cancer. Since no heterogeneity was found across studies (I-squared < 0.1%, *P* = 0.823), the fixed-effect model was applied to perform meta-analysis. The meta-analysis showed that ovarian cancer patients with negative expression of ERCC1 had a
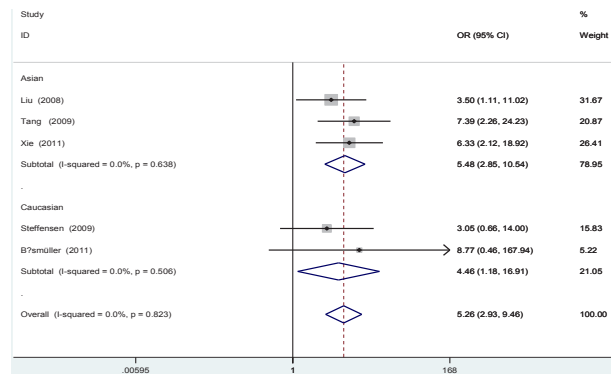
were included in more than one publication, only the most recent or complete one was included. Study eligibility was determined by Jun Zhang and Fengying Li, any disagreement were resolved by consensus.

Data extraction

All the data were independently abstracted by two investigators, using a standardized data extraction form. The information was collected including first author's name, year of publication, ethnicity, sample size, disease stage, method used to detect expression of ERCC1, treatment regimen, the numbers of the patients with or without response to chemotherapy in ERCC1 positive or negative expression group. Responders included complete response and partial response patients; non-responders included stable disease and progressive disease patients.

Statistical analysis

Pooled odds ratios (Pooled ORs) with 95 % confidence interval (95 % CI) were calculated to assess the strength of association between ERCC1 expression and response to platinum-based chemotherapy. To investigate the heterogeneity between the included studies, I-squared was performed (I-squared > 50% was considered significant heterogeneity). If heterogeneity was found, Pooled OR was calculated using a random-effects model; if not, pooled OR was calculated using a fixed-effect model. To evaluate the publication bias, the Begg's test was carried

better response to chemotherapy than those with negative expression of ERCC1, with the pooled OR of 5.264 (95% CI: 2.928 – 9.464, *P* < 0.001, Figure 2).

Subgroup analysis was conducted based on ethnicity. The patients in three studies were Asian, and those in the other two studies were Caucasian. The correlation between negative expression of ERCC1 and better response to platinum-based chemotherapy remained significant, both in Asian (OR = 5.477, 95% CI: 2.847– 10.536, *P* < 0.001, Figure 2) and in Caucasian (OR = 4.464, 95% CI: 1.178–16.910, *P* = 0.028, Figure 2) subgroups, and no heterogeneity was found for both of them (I-squared < 0.1%, *P* = 0.638 and I-squared < 0.1%, *P* = 0.823, respectively. Figure 2).

Discussion

In the current meta-analysis, we evaluated the association between ERCC1 expression and response to platinum-based chemotherapy in patients with ovarian cancer. We included 5 studies involving 306 patients treated with platinum-based chemotherapy. The results indicated that the patients with negative ERCC1 expression had a better response to platinum-based chemotherapy than those with positive ERCC1 expression. Subgroup analyses by ethnicity yielded the same results.

In 1999, Köberle et al. found that ERCC1 protein expression levels correlated with cisplatin resistance in the well-defined 833K and GCT27 human testi tumour cell lines by immunoblotting, their study indicated high ERCC1 expression were associated with an reduced sensitivity to cisplatin (Koberle et al., 1999). Five years later, another study by the same group indicated that six of thirty five human cancer cell lines were significantly lower mean levels of ERCC1 proteins compared to others and suggested low levels of ERCC1 protein may explain their extreme chemosensitivity (Welsh et al., 2004). Li et al. (2000). performed a vitro trial suggested ERCC1 protein may be a marker to monitor the repair of platinum-DNA damage in tumor cells and inhibiting ERCC1 expression may increase cellular sensitivity to cisplatin. In fact, much clinical studies also showed that negative/low expression of ERCC1 was associated with good response to chemotherapy. Among these clinical studies, a great deal of them have been conducted and focused on ERCC1 expression and response to chemotherapy in lung cancer patients (Ren et al., 2010; Wang et al., 2010; Hayes et al., 2011; Joerger et al., 2011; Kawashima et al., 2011; Su et al., 2011; Zhang et al., 2011; Sereno et al., 2012; Simon et al., 2012; Yu et al., 2012; Zhang et al., 2012). In 2011, Hubner et al. performed a meta-analysis to investigate the correlation mentioned above and concluded that high ERCC1 may adversely influence response in platinum-treated NSCLC patients (Hubner et al., 2011). The similar mete-analysis was performed by Chen and the same conclusion was gained (Chen et al., 2010). In addition, many papers evaluated the relation between ERCC1 status and response to chemotherapy have been reported in various human cancers including Colorectal Cancer, bladder cancer, cervical cancer, Head and Neck Cancer, and most of studies showed ERCC1 expression was a predictor of response to chemotherapy (Handra-Luca et al., 2007; Braun et al., 2008; Kim et al., 2009; Ishibashi et al., 2010; Kim et al., 2010; Hayes et al., 2011; Kawashima et al., 2011; Park et al., 2011; Sun et al., 2012). In 2008, Lin et al. performed a cohort study to evaluate the difference of ERCC1 protein expression levels between 36 sensitive cases and 27 resistant cases of serous ovarian cancer receiving neoadjuvant chemotherapy and demonstrated that ERCC1 protein expression levels in resistance group of serous ovarian cancer were significantly higher than those of sensitivity group, and Lin et al's study was in accordance with our meta-analysis (Lin et al., 2008).

However, our study has several limitations. First, the number of patients included in study was limited. The pooled OR was gained from 5 studies with a small size of 306 patients, only. Because of limited studies, we did not perform subgroup analysis by regimen. Second, many factors that may influence the response to chemotherapy were not analyzed in this study, including age, pathologic classification, tumor grade and surgical resection. Third, this is a meta-analysis based on the data from the published literature, and individual patient data were not available.

In conclusion, our analysis shows that negative expression of ERCC1 was significantly associated with good response to platinum-based chemotherapy in patients with ovarian cancer, and ERCC1 status could be a potential biomarker to predict response to platinum-based chemotherapy of ovarian cancers. However, large scale and well designed studies are needed to investigate the factors that may influence the response to platinum-based chemotherapy.

Acknowledgements

References

Bohanes P, Labonte MJ, Lenz HJ (2011). A review of excision repair cross-complementation group 1 in colorectal cancer. *Clin Colorectal Cancer*, **10**, 157-64.

Bosmuller H, Haitchi-Petnehazy S, Webersinke G, et al. (2011). Intratumoral lymphocyte density in serous ovarian carcinoma is superior to ERCC1 expression for predicting response to platinum-based therapy. *Virchows Arch*, **459**, 183-91.

Braun MS, Richman SD, Quirke P, et al. (2008). Predictive biomarkers of chemotherapy efficacy in colorectal cancer: results from the UK MRC FOCUS trial. *J Clin Oncol*, **26**, 2690-8.

Chen S, Zhang J, Wang R, Luo X, Chen H (2010). The platinum-based treatments for advanced non-small cell lung cancer, is low/negative ERCC1 expression better than high/positive ERCC1 expression? A meta-analysis. *Lung Cancer*, **70**, 63-70.

Handra-Luca A, Hernandez J, Mountzios G, et al. (2007). Excision repair cross complementation group 1 immunohistochemical expression predicts objective response and cancer-specific survival in patients treated by Cisplatin-based induction chemotherapy for locally advanced head and neck squamous cell carcinoma. *Clin Cancer Res*, **13**, 3855-9.

Hayes M, Lan C, Yan J, et al. (2011). ERCC1 expression and

outcomes in head and neck cancer treated with concurrent cisplatin and radiation. *Anticancer Res*, **31**, 4135-9.

Hubner RA, Riley RD, Billingham LJ, Popat S (2011). Excision repair cross-complementation group 1 (ERCC1) status and lung cancer outcomes: a meta-analysis of published studies and recommendations. *PLoS One*, **6**, e25164.

Ishibashi K, Okada N, Ishiguro T, et al. (2010). The expression of thymidylate synthase (TS) and excision repair complementing-1 (ERCC-1) protein in patients with unresectable colorectal cancer treated with mFOLFOX6 therapy. *Gan To Kagaku Ryoho*, **37**, 2532-5.

Joerger M, deJong D, Burylo A, et al. (2011). Tubulin, BRCA1, ERCC1, Abraxas, RAP80 mRNA expression, p53/p21 immunohistochemistry and clinical outcome in patients with advanced non small-cell lung cancer receiving first-line platinum-gemcitabine chemotherapy. *Lung Cancer,* **74**, 310-7.

Kawashima A, Nakayama M, Kakuta Y, et al. (2011). Excision repair cross-complementing group 1 may predict the efficacy of chemoradiation therapy for muscle-invasive bladder cancer. *Clin Cancer Res*, **17**, 2561-9.

Kim KH, Do IG, Kim HS, et al. (2010). Excision repair cross-complementation group 1 (ERCC1) expression in advanced urothelial carcinoma patients receiving cisplatin-based chemotherapy. *Apmis*, **118**, 941-8.

Kim SH, Kwon HC, Oh SY, et al. (2009). Prognostic value of ERCC1, thymidylate synthase, and glutathione S-transferase pi for 5-FU/oxaliplatin chemotherapy in advanced colorectal cancer. *Am J Clin Oncol*, **32**, 38-43.

Koberle B, Masters JR, Hartley JA, Wood RD (1999). Defective repair of cisplatin-induced DNA damage caused by reduced XPA protein in testicular germ cell tumours. *Curr Biol*, **9**, 273-6.

Langer CJ (2012). Exploring biomarkers in head and neck cancer. *Cancer*, **118**, 3882-92.

Lebwohl D, Canetta R (1998). Clinical development of platinum complexes in cancer therapy: an historical perspective and an update. *Eur J Cancer*, **34**, 1522-34.

Li Q, Yu JJ, Mu C, et al. (2000). Association between the level of ERCC-1 expression and the repair of cisplatin-induced DNA damage in human ovarian cancer cells. *Anticancer Res*, **20**, 645-52.

Lin K, Ye D, Xie X (2008). Protein expression levels of excision repair cross-complementation group 1 and xeroderma pigmentosum D correlate with response to platinum-based chemotherapy in the patients with advanced epithelial ovarian cancer. *Int J Gynecol Cancer*, **18**, 1007-12.

Liu GY, Qu QX, Mi J (2008). Relationship between nucleotide repair gene ERCC1 and resistance to cisplatian in ovarian cancer. *Zhonghua Zhong Liu Za Zhi*, **30**, 184-7.

Liu GY, Qu QX, Mi RR (2008). Study on the relationships of DNA repair-assoc iated prote ins ERCC1, BRCA1, hMLH1 w ith cisplat in resistance in ovar ian epithelial carcinoma. *Zhongguo Shi Yong Fu Chan Ke Za Zhi*, **24**, 677-9.

Park JS, Jeon EK, Chun SH, et al. (2011). ERCC1 (excision repair cross-complementation group 1) expression as a predictor for response of neoadjuvant chemotherapy for FIGO stage 2B uterine cervix cancer. *Gynecol Oncol*, **120**, 275-9.

Rabik CA, Dolan ME (2007). Molecular mechanisms of resistance and toxicity associated with platinating agents. *Cancer Treat Rev*, **33**, 9-23.

Ren S, Zhou S, Zhang L, et al. (2010). High-level mRNA of excision repair cross-complementation group 1 gene is associated with poor outcome of platinum-based doublet chemotherapy of advanced nonsmall cell lung cancer patients. *Cancer Invest*, **28**, 1078-83.

Sereno M, Cejas P, Moreno V, et al. (2012). ERCC1 and topoisomerase I expression in small cell lung cancer: prognostic and predictive implications. *Int J Oncol*, **40**, 2104-10.

Siegel R, Naishadham D, Jemal A (2012). Cancer statistics, 2012. *CA Cancer J Clin*, **62**, 10-29.

Simon GR, Schell MJ, Begum M, et al. (2012). Preliminary indication of survival benefit from ERCC1 and RRM1-tailored chemotherapy in patients with advanced nonsmall cell lung cancer: evidence from an individual patient analysis. *Cancer*, **118**, 2525-31.

Stadlmann S, Dirnhofer S, Guth U, Thies S, Singer G (2008). ERCC1-immunoexpression does not predict platinum-resistance in ovarian cancer. *Gynecol Oncol*, **108**, 252-3.

Steffensen KD, Waldstrom M, Jakobsen A (2009). The relationship of platinum resistance and ERCC1 protein expression in epithelial ovarian cancer. *Int J Gynecol Cancer*, **19**, 820-5.

Steffensen KD, Waldstrom M, Jeppesen U, Brandslund I, Jakobsen A (2008). Prediction of response to chemotherapy by ERCC1 immunohistochemistry and ERCC1 polymorphism in ovarian cancer. *Int J Gynecol Cancer*, **18**, 702-10.

Su C, Zhou S, Zhang L, et al. (2011). ERCC1, RRM1 and BRCA1 mRNA expression levels and clinical outcome of advanced non-small cell lung cancer. *Med Oncol*, **28**, 1411-7.

Sun JM, Sung JY, Park SH, et al. (2012). ERCC1 as a biomarker for bladder cancer patients likely to benefit from adjuvant chemotherapy. *BMC Cancer*, **12**, 187.

Tang L, Liang J, Li YJ (2009). Relationship between the expression of ercc1 in epithelial ovarian carcinoma and cisplatin resistance. *Qi Lu Yi Xue Za Zhi*, **24**, 388-90.

Vilmar A, Sorensen JB (2009). Excision repair cross-complementation group 1 (ERCC1) in platinum-based treatment of non-small cell lung cancer with special emphasis on carboplatin: a review of current literature. *Lung Cancer*, **64**, 131-9.

Wang HY, Qu QX (2006). Study on the relation between the expression ofERCC1 and cisplatin resistance in ovarian epithelial carcinoma. *Xian Dai Fu Chan Ke Jin Zhan*, **15**, 512-4.

Wang X, Zhao J, Yang L, et al. (2010). Positive expression of ERCC1 predicts a poorer platinum-based treatment outcome in Chinese patients with advanced non-small-cell lung cancer. *Med Oncol*, **27**, 484-90.

Welsh C, Day R, McGurk C, et al. (2004). Reduced levels of XPA, ERCC1 and XPF DNA repair proteins in testis tumor cell lines. *Int J Cancer*, **110**, 352-61.

Xie C, Yin RT, Li YL, et al. (2011). The protein expression of ERCC1 and survivin in epithelial ovarian carcinoma and their clinical significance. *J Sichuan Univ*, **42**, 86-9.

Yu Y, Zhang L, Ren Z, et al. (2012). Efficacy of gemcitabine and vinorelbine in first-line treatment with advanced non-small cell lung cancer: a multicentre retrospective study. *Zhongguo Fei Ai Za Zhi*, **15**, 281-6.

Zhang GB, Chen J, Wang LR, et al. (2012). RRM1 and ERCC1 expression in peripheral blood versus tumor tissue in gemcitabine/carboplatin-treated advanced non-small cell lung cancer. *Cancer Chemother Pharmacol*, **69**, 1277-87.

Zhang L, Liu T, Zhang JQ (2011). Relationship between the protein expression of ERCC1, BRCA, beta-tubulin and K-ras and the efficacy and prognosis in advanced non-small cell lung cancer. *Zhonghua Zhong Liu Za Zhi*, **33**, 212-6.