Predictive Value of Ercc1 and Xpd Polymorphisms for Clinical Outcomes of Patients Receiving Neoadjuvant Therapy

A Prisma-Compliant Meta-Analysis

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Abstract: Excision repair cross complementing 1 (ERCC1) and xerodermia pigmentosum group D (XPD) play important roles in the nucleotide excision repair (NER) pathway. The correlation between ERCC1 polymorphisms (rs11615 and rs3212986) and XPD polymorphisms (rs13181 and rs1799793) with the response rate and overall survival of cancer patients who accept neoadjuvant therapy has been extensively investigated. However, the results are inconclusive.

In this study, we performed a meta-analysis to determine the strength of this correlation. A comprehensive literature search was conducted in Medline, PubMed, and Embase up to February 2015. A review of all titles and abstracts was performed by 2 of the authors to screen the articles based on the eligibility criteria. Clinical trials, observational studies, and epidemiological studies describing ERCC polymorphisms and neoadjuvant treatment were considered for review.

The response rate was analyzed using pooled odds ratios (ORs) with corresponding 95% confidence intervals (CIs). Overall survival was assessed using the hazard ratio (HR) with corresponding 95% confidence intervals.

In the present meta-analysis, we demonstrated that the ERCC1 rs3212986 polymorphism was significantly correlated with the response rate of esophageal cancer patients to neoadjuvant therapy (OR = 0.49, 95% CI = 0.31–0.76, heterogeneity $P = 0.480$). Furthermore, a considerable correlation was observed between ERCC1 rs11615 and the response rate of esophageal cancer patients to neoadjuvant therapy (OR = 0.228, 95% CI = 0.125–0.418, heterogeneity $P = 0.291$). No correlation was observed in the meta-analysis of overall survival. The individual studies included in our study differed in their patient selection and therapeutic protocols, which might lead to some bias in the results.

These findings indicate that the ERCC1 rs11615 and ERCC1 rs312986 polymorphisms may be candidate pharmacogenomic factors capable of predicting the response rate of esophageal cancer patients who accept neoadjuvant therapy. Further studies are warranted.

INTRODUCTION

Neoadjuvant treatment plays a role in a tumor down-staging and has become a promising approach for the treatment of operable advanced stage tumor in the past decades. Neoadjuvant treatment is a component of preoperative chemotherapy and preoperative radiotherapy. A routine neoadjuvant regimen consists of cisplatin-based or 5-fluorouracil (5-FU)-based combinative chemotherapy or the graded radiotherapy schedule. Previous studies demonstrated that partial cancer patients obtained an improved response rate and overall survival after receiving neoadjuvant treatment coupled with standard surgery.

However, neoadjuvant therapy is a double-edged sword for advanced cancer patients who are not suitable for this treatment. The decision concerning the best treatment choice for these patients is still based upon the traditional evaluation of the tumor characteristics, and there is a lack of molecular biomarkers to guide therapy. Thus, the identification of these predictive biomarkers remains a promising approach to obtain the best clinical outcome with minimum side effects.

The ERCC1 and XPD genes (also named ERCC2) play important roles in the nucleotide excision repair (NER) pathway. Nucleotide excision repair pathways detect and repair DNA damages caused by radiation or chemotherapeutic drugs. ERCC1 and XPD polymorphisms can reduce the DNA repair capacity. Recently, a large number of studies suggested that ERCC1 and XPD polymorphisms predicted the therapeutic response to neoadjuvant treatment and the prognosis in human cancer. These molecular biomarkers will have vast clinical significance due to the easily clinical applications.
Using previous studies, we analyzed ERCC1 and XPD polymorphisms and the clinical outcome of neoadjuvant therapy in cancer patients by a meta-analysis.

METHODS

Information Sources and Search Strategy
To identify relevant studies, a comprehensive literature search was conducted in Medline, PubMed, and Embase up to February 2015. The following terms were used to search for relevant investigations in the above-mentioned databases: “ERCC” or “excision repair cross-complementing” or “polymorphism,” “variation,” or “nucleotide excision repair (NER) pathway genes” in combination with “neoadjuvant,” “neoadjuvant chemoradiotherapy,” or “cancer treatment.” To prevent the loss of any important and useful data, we also identified additional investigations by screening the reference lists of key studies and reviews. Only articles written in English were included. This meta-analysis was conducted and reported in accordance with the PRISMA guidelines for systematic reviews and meta-analyses (Table S1, http://links.lww.com/MD/A437. PRISMA-checklist). The literature retrieval was completed in duplicate by 2 authors (QM and WX).

Inclusion and Exclusion Criteria
Clinical trials, observational studies, and epidemiological studies describing ERCC polymorphisms and neoadjuvant treatment were considered for review. Eligibility criteria were as follows: human-based studies; pathologically confirmed cancer receiving neoadjuvant regimens; full text written in English; evaluation of the association between ERCC polymorphisms and clinical outcomes (ie, therapeutic response rate, overall survival (OS) or progression-free survival (PFS)); and the largest study from all studies with overlapping data published by the same investigators was chosen. Studies that did not include the data necessary to extract the therapeutic response rate, OS, or PFS were excluded. Studies that addressed the association of ERCC expression and neoadjuvant treatment were also removed from this review.

Study Selection
Based on the eligibility criteria, a preliminary review of all titles and abstracts was necessary to screen the articles. Full text publications of all studies that were not eliminated during the previous screening were retrieved for comprehensive review. Two individuals (GD and WX) independently screened all of the search results. Differences were resolved by discussion with another author (JF).

Outcome Definition and Data Extraction
In this meta-analysis, we focused on the 2 major clinical outcomes: response to neoadjuvant therapy and overall survival. Response to the regimen was evaluated using the RECIST or TRG criteria. Data concerning overall survival (HR and 95% CIs) were directly gained from the studies which displayed in text. Data extraction was performed independently by the 2 reviewers (QM and WX) in terms of tumor type, tumor node metastasis (TNM) stage, author, publishing year, ethnicity, treatments, numbers of cases and controls, and 2 major clinical outcomes.

Methodological Quality Assessment
The quality of the methodology of the included studies was assessed with the Newcastle–Ottawa scale (NOS). Studies scored 5 or more stars were defined as high-quality studies. Quality assessment was performed by 2 authors (QM and GD).

Statistical Analysis
The correlation strength of ERCC polymorphisms and response of cancer patients to neoadjuvant treatment was assessed by pooled odds ratios with corresponding 95% CIs. The hazard ratio (HR) was utilized to estimate the relationship between ERCC variations and the prognosis of cancer patients. A χ²-based Q test was used to measure heterogeneity; P < 0.10 indicated the existence of significant heterogeneity. Both fixed-effects and random-effects models were utilized to test the effect of ERCC polymorphisms in influencing the response to neoadjuvant therapy. The random-effects model was applied in the existence of significant heterogeneity, while the fixed-effects model was used in the absence of heterogeneity. Hardy–Weinberg equilibrium (HWE) was calculated to evaluate the quality of the data in the control population. Publication bias was assessed by Begg’s funnel plot and Egger’s linear regression test; P < 0.05 was considered significant. STATA version 12 was used in all statistical analyses (Stata-Corp, College Station, Texas).

RESULTS

Eligible Studies
A total of 120 studies were identified by a comprehensive search using the aforementioned key words. After screening the titles and abstracts, we found 23 studies that reported ERCC polymorphisms and neoadjuvant treatment. The full text of the remainder of the studies was reviewed based on the inclusion criteria. Four studies were excluded: 1 publication was a literature review, 2 articles did not present sufficient genotype or allelic data, and 1 article did not include HR (hazard ratios) and 95% CI. Finally, 19 studies were included in this meta-analysis. Figure 1 portrays the screening process.

Clinical Characteristics of Studies
The main clinical characteristics of the 19 studies included in the meta-analysis are summarized in Table 1. Fourteen studies were conducted in Caucasian populations, while the remainders were performed in Asian and African populations. All studies enrolled patients treated with neoadjuvant regimens. Neoadjuvant regimens consisting of chemotherapy and radiotherapy were reported in all studies. ERCC1 polymorphisms were investigated in 15 studies, while XPD polymorphisms were explored in 11 studies. The results of quality assessment are presented in Table 2S, http://links.lww.com/MD/A437.

ERCC Polymorphisms and Response Rates
ERCC1 rs11615 polymorphism Nine studies were performed to assess the correlation of the ERCC1 rs11615 polymorphism and neoadjuvant therapy. The genotype data for ERCC1 rs11615 were separated for CC, CT, and TT. Subjects carrying the CC genotype maintained a weak trend toward a better response rate to neoadjuvant therapy compared with subjects with the CT-TT genotype (OR = 1.11, 95% CI = 0.83–1.48, heterogeneity P = 0.836) (Fig. 2). In contrast, no significant associations were observed in the comparisons of CC-CT versus TT and CC-TT versus CT. However, subgroup analysis based on the tumor type identified a significant correlation in esophageal cancer patients receiving neoadjuvant therapy. There was a significantly increased chance of treatment...
response in the subjects carrying the CC-CT genotype compared with subjects carrying the TT genotype (OR = 4.002, 95% CI = 2.078–7.707, heterogeneity P = 0.253) (Fig. 3). Furthermore, we demonstrated that patients carrying the homozygous CC-TT genotype presented a worse response rate compared with subjects with the heterogeneous CT genotype (OR = 0.228, 95% CI = 0.125–0.418, heterogeneity P = 0.291). By testing the impact of the CT and TT genotypes, we found that the probability of response was also decreased in subjects with the TT genotype compared with subjects carrying the CT genotype (OR = 0.199, 95% CI = 0.098–0.403, heterogeneity P = 0.247). No evidence of publication bias was detected. All of the results are listed in Table 2.

**ERCC1 rs3212986 polymorphism** In this group of genes, subjects with the mutation genotype presented a higher rate of response to neoadjuvant chemotherapy in 4 studies (OR = 1.93, 95% CI = 0.82–4.56, heterogeneity P = 0.847) compared with subjects with the wild-type genotype. However, no significant association was found in patients with the CC genotype compared with subjects with the CA-AA genotype in 6 studies. Additionally, none of the patients carrying the homozygous genotypes CC and AA showed a better response rate to neoadjuvant therapy than the subjects with the heterozygous genotype CA. The results of subgroup analysis by tumor type indicated that a significant correlation was observed between the ERCC1 rs3212986 polymorphism and the response rate of esophageal cancer patients to neoadjuvant therapy (OR = 0.49, 95% CI = 0.31–0.76, heterogeneity P = 0.480) (Fig. 4). The finding demonstrated that subjects carrying ERCC1 rs3212986 with at least one A allele (CA-AA genotype) presented a better response rate than subjects with the CC genotype. In the rectal subgroup, patients carrying the CC-AA genotype had a higher probability of obtaining a better response rate than subjects with the CA genotype (OR = 2.55, 95% CI = 1.551–4.192, heterogeneity P = 0.666). No evidence of publication bias was detected. These results are presented in Table 2.

**XPD rs1799793 polymorphism** A total of 5 studies with 547 subjects were included in this analysis. No correlation with the XPD polymorphism (GG vs. GA-AA) was confirmed for the response rate to neoadjuvant therapy (OR = 0.86, 95% CI = 0.56–1.31, heterogeneity P = 0.516) (Table 3S, http://links.lww.com/MD/A437). Owing to the scarcity of literature regarding the other 2 comparison models (GG-AA vs. GA and GG-GA vs. AA), we did not find any significant differences. Subgroup analysis was not performed due to the insufficient number of studies in each subgroup.

**XPD rs13181 polymorphism (Lys751Gln)** The correlation of the XPD polymorphism and response rate of neoadjuvant
| Author               | Year | Country | Ethnicity | Treatment                                      | Cases | Age  | Tumor type       |
|---------------------|------|---------|-----------|------------------------------------------------|-------|------|------------------|
| Rumig              | 2013 | Italy   | Italian   | Neoadjuvant cisplatin/5-FU-based chemotherapy   | 63    | 62/68| esophageal cancer|
| Metzger             | 2012 | Germany | German    | Cisplatin/5-fluorouracil (5-FU)                 | 153   | 63   | esophageal cancer|
| Biaison             | 2011 | Italy   | Caucasian | IOR OS-N4/IOR OS-N5                            | 130   | 16   | osteosarcoma     |
| Cecchin             | 2011 | Italy   | Caucasian | Fluoropyrimidine-based chemotherapy/ Raltitrexed | 238   | 61   | rectal cancer    |
| Chung               | 2006 | Korea   | Asian     | 5-FU-based combination/etoposide chemotherapy  | 36    | –    | bulky cervical cancer |
| Lamas               | 2012 | Spain   | Caucasian | Radiotherapy 50.4 Gy and with 5-FU 225 mg/m²/d.| 93    | 67   | rectal cancer    |
| Okuda               | 2011 | Japan   | Asian     | Platinum-based chemotherapy                    | 90    | 66   | NSCLC           |
| Ryu                 | 2004 | Korea   | Asian     | Cisplatin combination chemotherapy             | 109   | 60   | NSCLC           |
| Stocker             | 2009 | Germany | Caucasian | Platinum/5FU-based chemotherapy                | 178   | 56   | gastric carcinoma|
| Wang                | 2011 | China   | Asian     | 5-fluouracil and cisplatin chemotherapy         | 241   | 58   | esophageal cancer|
| Warneck-Eberz       | 2009 | Germany | Caucasian | Cisplatin, 5-fluorouracil, radiation 36 Gy      | 52    | 59   | esophageal cancer|
| Yoon                | 2011 | USA     | Mixed     | Radiotherapy 45 Gy, cisplatin                   | 81    | –    | esophageal cancer|
| Sebio               | 2015 | Spain   | Spanish   | Radiotherapy 45 Gy, capcitabine/ FOLFOSX       | 84    | 67.6 | rectal cancer    |
| Ott                 | 2011 | Germany | German    | Cisplatin (50 mg/m² + fluorouracil) (2000 mg/m² over 24 h) | 258   | 58   | Esophageus or Stomach cancer |
| Wu                  | 2006 | USA     | American  | Platinum analogs, 5-FU+radiotherapy            | 210   | 65   | Esophageus cancer|
| Li-Min Yang         | 2012 | China   | Chinese   | Methotrexate, cisplatin                        | 187   | 61   | Bone tumor       |
| TENGSTR Ö M         | 2014 | Finland | Caucasian | Adjuvant tamoxifen/TAM and radiation           | 65    | –    | Breast cancer    |
| Castro              | 2014 | Spain   | Spanish   | Anthracyclines/Tamoxifen                       | 84    | 62.5 | Breast cancer    |
| Pedro               | 2012 | Spain   | Spanish   | Paclitaxel/gemcitabine                        | 46    | 49.5 | Breast cancer    |

NSCLC = non-small-cell lung cancer.



**TABLE 1. Baseline of Eligible Studies**

therapy was explored in 7 studies containing 1687 patients. We detected no significant difference in the response rate between patients carrying the variant 751Lys allele and patients with the 751Gln allele after pooling all eligible studies (LysGln vs. GlnGln; OR = 0.98, 95% CI = 0.66–1.46, heterogeneity $P = 0.406$). Similarly, the XPD polymorphism had no effect on the response rate to neoadjuvant therapy in the other 2 genotype model comparisons. No correlation was identified in the subgroup analysis.

**ERCC Polymorphisms and Overall Survival (OS)**

**ERCC1 rs11615 polymorphism** The ERCC1 rs11615 polymorphism and OS were reported in 5 studies. A greater than 1.5-fold higher risk of poor prognosis was observed for genotype CC compared with genotype CT-TT. The analysis indicated that genotype CC was potentially relevant to the poor prognosis of esophageal cancer (heterogeneity $P = 0.574$). Subjects carrying genotype GG did not gain any advantage from neoadjuvant treatment compared with subjects carrying genotype GA-AA. The HR of the comparison (GG vs. GA-AA) was 0.87, with a 95% CI ranging from 0.6 to 1.26 (heterogeneity $P = 0.574$). Subjects carrying genotype GG did not gain any advantage from neoadjuvant treatment compared with subjects carrying genotype GA-AA. The XPD rs179973 polymorphism was not of prognostic relevance for neoadjuvant regimens.

**XPD rs179973 polymorphism** Only 3 investigations were available to assess the XPD rs179973 polymorphism. The HR of the comparison (GG vs. GA-AA) was 0.87, with a 95% CI ranging from 0.6 to 1.26 (heterogeneity $P = 0.574$). Subjects carrying genotype GG did not gain any advantage from neoadjuvant treatment compared with subjects carrying genotype GA-AA. The XPD rs179973 polymorphism was not of prognostic relevance for neoadjuvant regimens.

**DISCUSSION**

Neoadjuvant chemotherapy and radiotherapy have been adopted as a routine therapy for operable advanced stage cancer. However, severe toxicity and side effects from the
neoadjuvant therapy contribute to patient morbidity and may limit the promotion and efficacy of treatment.1 Moreover, a significant proportion of patients receive only minor benefits from therapy, and delaying surgery may negatively influence their clinical outcome.4,8,35,36 No appropriate predictive methods have been applied to evaluate the clinical outcome of the neoadjuvant approach in locally advanced cancer to date.

Established predicted methods are insufficient to predict and guide individualized treatment.6,12,37,38 Therefore, mature predictive methods are urgently needed in order to select more efficient treatment strategies with minimal toxicity and side effects.

FIGURE 2. Forest plot for the ERCC1 rs11615 polymorphism and response rate in cancer patients receiving neoadjuvant therapy.

FIGURE 3. Forest plot for the ERCC1 rs11615 polymorphism and response rate in esophageal cancer patients receiving neoadjuvant therapy.
Nucleotide excision repair plays an important role in DNA repair pathways. ERCC1 is part of the nucleotide excision repair (NER) complex and can repair chemical drug-induced DNA injuries. The XPD gene encodes an ATP-dependent 5'-3' helicase. The helicase is a subunit of the basal transcription factor IIH (TFIIH) complex that functions to separate the double helix structure of DNA during NER. Studies have indicated that XPD polymorphisms are also involved in chemical drug resistance.

A number of studies have investigated the detection and validation of predictive and prognostic markers of neoadjuvant therapy. Both ERCC1 and XPD have been extensively studied among all of the molecular markers. However, the findings of previous studies concerning the predictive impact of ERCC1 and XPD polymorphisms toward neoadjuvant therapy are discordant with one another. Rumiato, Metzger, Biason, and Cecchin reported in 4 independent studies that ERCC1 and XPD played a vital role in the response rate and predicted the outcome of patients who received the neoadjuvant regimens. However, no association between the ERCC gene and the response to neoadjuvant therapy was reported by Ott, Castro, and Pedro Sánchez-Rovira et al, which brought new impetus to the debate concerning neoadjuvant efficiency.

In the present meta-analysis, we demonstrated that the ERCC1 rs11615 and rs3212986 polymorphisms were significantly correlated with the response rate to neoadjuvant therapy in esophageal cancer patients. However, no significant correlation was identified between the ERCC gene and the response to neoadjuvant therapy was reported by Ott, Castro, and Pedro Sánchez-Rovira et al, which brought new impetus to the debate concerning neoadjuvant efficiency.

In this study, a total of 4 SNPs in ERCC1 and XPD were studied in an attempt to predict the clinical outcome of cancer patients who received neoadjuvant treatments. We found that ERCC1 rs3212986 was significantly correlated with the response rate of esophageal cancer patients who received the neoadjuvant regimens. Esophageal cancer patients carrying the CC genotype presented a poorer response rate to neoadjuvant therapy.

**TABLE 2. ERCC1 Polymorphisms and Response Rate of Neoadjuvant Therapy**

| SNP           | Tumor Type | Studies | OR     | P      | Studies | OR     | P      | Studies | OR     | P      |
|---------------|------------|---------|--------|--------|---------|--------|--------|---------|--------|--------|
| ERCC rs11615  | Overall    | 9       | 1.11(0.83–1.48) | 0.836  | 8       | 1.46(0.69–3.08) | 0.000  | 8       | 0.70(0.36–1.40) | 0.000  |
|               | Esophageal | 4       | 0.969(0.634–1.48) | 0.939  | 3       | 4.002(2.078–7.707) | 0.253  | 3       | 0.228(0.125–0.418) | 0.291  |
|               | Rectal     | 3       | 1.114(0.566–2.192) | 0.290  | 3       | 0.73(0.352–1.51) | 0.147  | 3       | 1.221(0.814–1.833) | 0.776  |
| ERCC rs3212986| Overall    | 6       | 0.98(0.47–2.08) | 0.003  | 4       | 1.93(0.82–4.56) | 0.847  | 5       | 0.86(0.42–1.76) | 0.062  |
|               | Esophageal | 4       | 0.487(0.311–0.762) | 0.480  | 3       | 0.337(0.034–3.357) | 0.003  | 3       | 0.509(0.234–1.108) | 0.883  |
|               | Rectal     | 2       | 2.142(0.717–6.39) | 0.111  | 2       | 0.659(0.123–3.527) | 0.184  | 2       | 2.55(1.551–4.192) | 0.666  |

OR = odds ratios; SNP = single-nucleotide polymorphism.
therapy compared with subjects carrying the CA-AA genotype. These results were in accordance with Rumiato and Wang’s conclusions. The ERCC1 rs3212986 polymorphism is located in the 3' UTR of the gene, which contributes to ERCC1 mRNA stability. Consequently, the rs3212986 polymorphism results in a limited DNA repair capacity, thereby impacting the response to treatment and overall survival. This finding indicated that ERCC1 rs3212986 might predict the response of esophageal cancer patients to neoadjuvant therapy and offered a minimally invasive and practicable approach to detect the outcome of neoadjuvant regimens. Additionally, we observed a correlation between ERCC1 rs3212986 and the response rate to neoadjuvant therapy in rectal cancer patients. However, the weight of the study by Cecchin was 86.2%; therefore, this study may exert a dominating effect on the result of the rectal subgroup analysis. The ERCC1 rs11615 polymorphism is located at codon 118 and may reduce ERCC1 mRNA and protein expression levels, thereby reducing the DNA repair capacity. Therefore, we investigated whether ERCC1 rs11615 was correlated with the response rate to neoadjuvant therapy in esophageal cancer patients. Subjects with the CC-CT genotype showed a better response rate compared with subjects with the TT genotype, and patients carrying the CT genotype showed a better response rate than patients carrying the CC-TT genotype. These results indicated that the CT genotype might be correlated with a better response rate to neoadjuvant therapy in esophageal cancer patients. To evaluate the impact of the CT and TT genotypes, we compared CT and TT and found that subjects carrying the CT genotype presented a better response rate than subjects with the TT genotype. These results were in agreement with Metzger’s studies and suggested that ERCC1 rs11615 might predict the response rate to neoadjuvant therapy in esophageal cancer. On the other hand, our analysis indicated that XPD rs13181 and rs1799793 did not present any correlation with a better response rate in esophageal cancer patients. To the best of our knowledge, low expression of the ERCC1 protein will result in a limited DNA repair capacity, thereby impacting the response to treatment and overall survival. This finding indicated that ERCC1 rs3212986 and rs11615 polymorphisms had the potential capable of predicting the response rate in esophageal cancer patients who received neoadjuvant therapy. This approach may offer a minimally invasive and practicable method to predict the outcome of neoadjuvant therapy. More studies regarding ERCC1 and XPD polymorphisms are needed in the future to explore and identify the response rate and OS associated with neoadjuvant therapy.

CONCLUSION

In summary, in the present meta-analysis, we tested whether the ERCC1 rs3212986 and rs11615 polymorphisms had the potential capable of predicting the response rate in esophageal cancer patients who received neoadjuvant therapy. We assessed the heterogeneity of each comparison model. No significant heterogeneity was found in any of analyzes or subgroup analyzes. For the purpose of identifying publication bias, we used the funnel plot and Begg’s test. No publication bias was presented. However, several limitations should be addressed when interpreting the results of our meta-analysis. First, the data of this meta-analysis were extracted directly from the literature. Insufficient data were available to perform further stratified analyzes. Second, the numbers of studies included in the some subgroup analyzes were too small. Finally, the individual studies included in our study differed in their patient selection and therapeutic protocols, which might lead to some bias in the results.

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