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ERCC1 plays an important role in predicting survival outcomes and treatment response for patients with HNSCC: A meta-analysis

Ma Xuelei [a,c,1], Huang Jingwen [b,1], Du Wei [a], Zhuo Hongyu [c], Zhang Jing [b], Shi Changle [b], Liu Lei [a,c,*]

[a] State Key Laboratory of Biotherapy and Cancer Center, West China Hospital, West China Medical School Sichuan University, China
[b] West China Medical School, West China Hospital, Sichuan University, China
[c] Cancer Center, West China Hospital, Sichuan University, China

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SUMMARY

Background: Excision repair crosscomplementing-1 (ERCC1) has been reported to play a prognostic role and may indicate the treatment response in patients with head and neck squamous carcinoma (HNSCC). Nevertheless, the strength of evidence of ERCC1 predicting these two clinical outcomes are still controversial.

Methods: Potentially eligible studies were retrieved using PubMed, Embase and Medline. Basic clinical characteristics of patients and statistical data with the survival data were collected. Then a meta-analysis model was established to investigate the correlation between over-expression of ERCC1 and survival outcome in HNSCC patients as well as to determine whether the treatment response is dependent on expression stature of ERCC1 or not.

Results: 17 eligible studies and 1263 patients were yielded in our meta-analysis. The pooled HRs with 95% confidence intervals (CIs) for OS and PFS were 2.14 [1.51, 3.05] and 2.60 [1.98, 3.42], respectively. In terms of subgroup analysis, race was found to be a significant factor divided for these analyses, and the pooled HRs for the Asian subgroup are 2.97 [2.05, 4.32] and 2.75 [1.82, 4.13] respectively. In non-Asian subgroup, Pooled HRs indicate the predict role for PFS 2.42 [1.60, 3.66], but no value for OS ($P < 0.05$). With regard to treatment response, the pooled ORs were 3.04 [1.99, 4.62]. Results from subgroup analysis that divided by race further showed that pooled ORs in Asian group were 3.95 [2.30, 6.78] and 1.93 [0.97, 3.84] in non-Asian group.

Conclusion: ERCC1 could be a fine prognostic factor of HNSCC and can also prompt the treatment response, which might be proven by further multicenter clinical trials.

Introduction

Squamous cell carcinoma of the head and neck (HNSCC) is one of the most frequent cancer worldwide, with a global yearly incidence exceeding half a million cases, causing more than 350,000 deaths every year [1]. Moreover, fewer than 50% of cases presenting with locally advanced disease could be cured, while patients with recurrent or metastatic disease have a median survival rate of no more than 6 months [2,3]. Recent trials reported improved locoregional control and overall and/or progression-free survival of HNSCC by adding chemotherapy to radiotherapy concurrently [4,5]. Cisplatin-based combination chemotherapy is one of the most commonly used treatments for palliation in recurrent metastatic HNSCC [6,7]. ERCC1 is an endonuclease and the main factor, along with its partner XPF, forming the ERCC1/XPF complex, utilized by nucleotide excision repair (NER) pathway in Single-Strand DNA-damage repair. They excise damaged ssDNA, encompassing the ionizing radiation lesion pressure and cisplatin damage, which cause inter-/intra-strand bulky DNA lesion [8,9]. Moreover, ERCC1 has been suggested to play a role in Double-Strand Break Repair, which is found mainly caused by radiation [10], and can be a target to overcome the pressure of resistance of chemotherapy, especially cisplatin [11].

High levels of ERCC1 are associated with an increased rate of NER and reduced sensitivity to cisplatin and radiotherapy, both of whom may damage the cell by causing DNA damage, whereas cancer cells with low levels of ERCC1 are more sensitive to platinum [12,13]. In addition, a low expression of ERCC1 per se may at the same time be associated with the accumulation of DNA

* Corresponding author at: Medical Oncology, West China Hospital, 37 Guoxuexiang Street, Chengdu 610000, China. Tel.: +86 18980768879.
E-mail address: liuleihx@gmail.com (L. Lei).
[1] These authors contributed equally to the study.

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mutations and results in a more aggressive tumor phenotype [14,15]. In conclusion, the dysfunction and abnormal expression of ERCC1, both the over-/hypo-expression, can cause aggressive and metastatic phonotype.

What is particularly noteworthy, some pre-clinical data suggest that increased ERCC1 mRNA expression levels or ERCC1 protein expression levels correlate with cisplatin resistance in human cancer with cervical carcinoma, melanoma, HNSCC, NSCLC, bladder cancer [16–20]. We can also infer the radiation resistance from the DNA-damage rapier role of ERCC1. Although it has been established pre-clinically, and experiment in vitro, whether the ERCC1 can be really applied in predicting the survival and treatment response based on radiation plus mainly cisplatin for clinical use, is still obscure. Some reports' results showed positive effect of ERCC1, and some others display no correlation between ERCC1 level and the outcome events (survival and treatment response), while others even show the completely opposite outcome. The role of ERCC1 to predetermine treatment response to radiation plus cisplatin is indistinct as well.

Here we conducted a meta-analysis, the aim of which was to evaluate the hypothesis that over-expression of ERCC1 could predict survival outcome, including OS and PFS, and to evaluate the treatment response mainly for CCRT or IC, which can now be regarded as the effective treatment regimen in patients diagnosed with HNSCC.

Materials and methods

Search strategy

PubMed, Embase and Medline were searched on Mar 7th, 2014. The following keywords were used to retrieve articles and abstracts: head and neck squamous carcinoma (HNSCC), nasopharyngeal carcinoma (NPC), cancers of larynx, cancers of oral tongue, cancers of oropharynx, cancers of maxillary sinus, cancers of laryngopharynx and ERCC1.

Study selection and inclusion/exclusion criteria

Titles and abstracts were reviewed for all searched papers, and full texts were perused for potentially eligible studies according to our inclusion criteria. To avoid duplication data, if more than one trial was completed in one particular center, only the biggest one was included and the updated ones were used.

In our meta-analysis, we used the following inclusion criteria: (1) studies containing patient cases of head and neck squamous carcinoma (HNSCC) including: nasopharyngeal carcinoma (NPC), cancers of larynx, cancers of oral tongue, cancers of oropharynx, cancers of maxillary sinus, cancers of laryngopharynx; (2) studies measuring expression of the biomarker ERCC1; and (3) studies with data available regarding the prognostic value of ERCC1 in HNSCC patients with survival rates (OS, PFS) and/or treatment response. In the meanwhile, studies were excluded based on any of the following criteria, (1) were review articles or letters (2) with duplicated data, (3) lacked key information to calculate the log hazard ratio (logHR), SE (logHR) (SE) and odd ratio (OR) for analysis.

Data extraction

Articles were independently reviewed by two investigators (Ma XL and Huang JW) for data extraction. Any discrepancy was discussed further to reach a consensus. The data were independently extracted from eligible studies by two investigators (Ma XL and Huang JW). The primary data were HR with 95% confidence interval (CI) of survival outcomes, including OS and/or PFS and the response number of patients of over-expression cohort and normal/lower expression cohort respectively. The additional data obtained from the studies included, first author, publication year, patient source(region), percentage of the female, ERCC1 cut-off value, TNM stage, chemotherapy regimens, high/low expression, methods to determine ERCC1 over-expression, ERCC1 high/positive (OR (patients), total patients), ERCC1 low/negative (OR (patients), total patients), tumor site (N), survival. The statistical data for acquiring logHR and the SE were also obtained, such as HR with 95% CI, the Kaplan–Meier survival curves with p value, and response rate of over-expression cohort and normal/lower expression cohort respectively [21].

Statistical methods

The logHR and SE were required in our analysis. A part of the original papers provided the logHR and SE directly; whereas in other studies, logHR and SE were not available directly. As mentioned above, we utilized other data to calculate them using methods developed by Parmar et al. [22], Williamson et al. [23], and Tierney et al. [24]. Those logHRs and SEs were calculated with the methods described earlier when there was HR with 95% CI, or the p value for the log-rank test with the Kaplan–Meier survival curve.

As the result of the analysis of survival in patients, the significant outcome was defined as a P value <0.05. A pooled HR > 1 frequently indicated a poor prognosis in the ERCC1 over-expression cohort. Therefore, we use the term "positive" while referring to the over-expression of ERCC1 predicting a worse outcome, and "negative" for no correlation between a high level of ERCC1 and prognosis or the reverse prognostic significance of ERCC1 in contrast to "positive."

If $P < 0.10$ or $I^2 > 50\%$ represents the significant heterogeneity existing in pooled HRs (Higgins et al., 2003) [25]. When homogeneity was fine ($p \geqslant 0.10$, $I^2 \leqslant 50\%$), a fixed-effects model was applied to secondary analysis; otherwise, a random-effects model was used. All the earlier calculations, and publication bias that was measured using the Begg's funnel plot, were performed by STATA 11.0 (STATA Corporation, College Station, TX). Odds ratio (OR) was calculated as the measure index to describe the correlation between ERCC1 expression level and treatment response. Similar with HR, $P < 0.05$ indicates the predictive value, and the pooled ORs > 2 suggest the solid fundament position when applied to test the correlation between ERCC1 over-expression and treatment response. This calculation for the current meta-analysis was performed using REVIEW MANAGER (version 5.0 for Windows; the Cochrane collaboration, Oxford, UK).

The sensitive analysis, which aims to test whether the heterogeneity of these included studies group is from one single study, is performed by STATA 11.0 (STATA Corporation, College Station, TX). In analytic figure, if no study run out of the constricted interval, defined between lower confidence interval (CI) limit and Upper CI limit, indicate no obvious heterogeneity, or if one single study exist far away outside the confidence interval, indicate the heterogeneity is due to this one.

Results

Eligible studies

The initial search yielded 193 studies in PubMed. After reviewing these abstracts, 28 potentially relevant studies were identified as candidate for a full-text review. We excluded 11 studies for the following reasons: Two were reviews, and seven were clinical trials