ERCC1 Expression Can Predict Response to Platinum-Based Induction Chemotherapy in Head and Neck Cancer Cases

Ahmad Ameri1, Nafiseh Mortazavi2, Helaleh Khoshbakht Ahmadi1, Kambiz Novin1*

Abstract

To investigate whether excision repair cross complementing-group1 (ERCC1) expression status could serve as a bio-predictor of response to platinum-based induction chemotherapy for head and neck cancers (HNCs) patients with a diagnosis of epithelial HNC were studied retrospectively. Paraffin embedded tumor samples of the patients were analyzed by reverse transcription-polymerase chain reaction (RT-PCR) to determine ERCC1 expression status and its correlation with response to platinum-based induction chemotherapy was investigated. Of 44 included patients, 33 were male (75%) and 11 were female (25%) with a mean age of 53 years. Some 36% of patients whose tumor samples had high ERCC1 expression showed no response to induction chemotherapy. The value for patients with low ERCC1 expression was 9% and the difference was statistically significant (p=0.03). The ERCC1 expression state did not significantly vary between patient groups according to sex, age, primary tumor site, and tumor and node stage. Our study indicates that ERCC1 expression status detected by RT-PCR might serve as a bio-predictor of response to platinum-based induction chemotherapy for epithelial HNCs.

Keywords: ERCC1 - induction chemotherapy – response - head and neck cancer

Asian Pac J Cancer Prev, 17, Cancer Control in Western Asia Special Issue, 87-91

Introduction

Worldwide, head and neck cancer is the seventh most common malignancy and also a major cause of morbidity and mortality (Ferlay et al., 2010; Alvarenga et al., 2008). Squamous cell carcinoma (SCC) represents the most common histologic subtype of cancers originating from this anatomic region (Ragin et al., 2007; Carey et al., 2015). Unfortunately, most head and neck cancer patients present with loco-regionally advanced disease (Jun et al., 2008) and despite improvements in treatment techniques, the five-year overall survival of such patients is still poor (Jemal et al., 2010). Currently, the standard non-surgical approach for loco-regionally advanced head and neck squamous cell carcinoma (HNSCC) is cisplatin-based concurrent chemoradiation (Bauman et al., 2013). Another approach used by many oncologists in this setting is adding induction chemotherapy to definitive local treatment. Induction cisplatin-based chemotherapy induces response rates of 80% to 90% and can potentially reduce distant metastasis rate in loco-regionally advanced HNSCC (Brockstein et al., 2004; Argiris, 2005). Cisplatin (cis-diamminedichloroplatinum(II)) performs its cytotoxic effect by formation of either intra-strand or inter-strand DNA adducts (Gossage and Madhusudan, 2007). In normal cells, these cisplatin–induced DNA damages are repaired by the nucleotide excision repair (NER) pathway. Excision repair cross complementing-group1 (ERCC1) enzyme is a key protein in NER pathway and its increased expression correlates with resistance to cisplatin-based chemotherapy (Jun et al., 2008; Zamble et al., 1996). There is some clinical evidence suggesting that ERCC1 status (ERCC1 mRNA expression, ERCC1 protein expression, and ERCC1polymorphisms) is associated with platinum-based therapy efficacy in some kinds of cancers (Vilmar and Sorensen, 2009; Bohanes et al., 2011; Langer, 2012). In a recent meta-analysis, ERCC1 protein expression status detected by immunohistochemical methods significantly correlated with response to platinum-based chemotherapy in ovarian cancers (Li et al., 2013). Another meta-analysis evaluated non-small cell lung cancer patients treated with platinum-based chemoradiation showed that both low tumoral mRNA and protein levels were associated with a better response rate and overall patient survival (Chen et al., 2010). In head and neck cancers, the available studies have mixed results. Of six studies evaluating the relation between ERCC1 status and outcomes of head and neck cancer patients, three showed positive (Jun et al., 2008; Fountzilas et al., 2009; Handra-Luca et al., 2007) and another three were with negative results (Fountzilas et al., 2009; Koh et al., 2009; Hayes et al., 2011).

We conducted the present study to investigate whether ERCC1 mRNA expression status in tumor cells could serve as a bio-predictor of response to induction platinum-based chemotherapy for head and neck cancer.

1Department of Clinical Oncology, 2Department of Pathology, Shahid Beheshti University of Medical Sciences, Tehran, Iran *For Correspondence: kamnar2005@yahoo.com
Materials and Methods

We performed a retrospective analysis of 44 non-metastatic epithelial head and neck cancer patients treated with induction platinum-based chemotherapy at our clinical oncology center (Jorjani Cancer Center, Emam Hossein Hospital, Tehran, Iran) from 2010 to 2014. The study inclusion criteria were as follows: (a) patients of any age with the biopsy proven diagnosis of primary epithelial head and neck cancer, (b) the primary disease was measurable by physical examination or imaging studies, and (c) the patient had not undergone definitive surgical treatment. Each patient received one of the following induction chemotherapy regimens: TPF (docetaxel plus cisplatin plus 5-fluorouracil for two cycles with three-week intervals); PF (cisplatin plus 5-fluorouracil for two cycles with three-week intervals) and TC (weekly paclitaxel plus carboplatin for six cycles).

Response Assessment

Tumor response was based on the first computed tomography (CT) scan or magnetic resonance imaging (MRI) performed following completion of induction chemotherapy and was assessed using Response Evaluation Criteria in Solid Tumors (RECIST 1.1 Published in January 2009) with four categories of complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). The patients were categorized into response (CR plus PR) and no-response (SD plus PD) groups.

RNA Extraction, Reverse Transcription and Quantitative Real Time RT-PCR (QRT-PCR) Assays

RNA was extracted from the cancerous tissues using the RNeasy FFPE kit (Qiagen, Germany) according to manufacturer’s instructions. Concentration of total RNA was estimated by a nanodrop spectrophotometer (A and E, England), complementary DNA (cDNA) was synthesized using Super Script III Reverse Transcriptase (Invitrogen, Carlsbad, CA, USA) and stored at -20°C until use. The mRNA expression levels of ERCC1 and beta-actin were measured by quantitative RT-PCR using SLAN Real-Time PCR Detection System (HONGSHI, Shanghai, China). The cycling conditions were as follows: 15 min of an
ERCC1 and Response to Chemotherapy in Head and Neck Cancer

Results

Patient and Tumor Characteristics

Of 44 included patients, 33 were male (75%) and 11 were female (25%) with mean age of 53 years (23 to 79 years). For 13 patients (29.5%) the primary tumor site was nasopharynx and for 31 non-nasopharyngeal cases, larynx was the most common primary tumor site (57% of all patients). According to primary tumor and lymph node stage, most cases were T3/T4 (59%) and N2/N3 (61%) respectively. The patient, tumor and treatment characteristics are detailed in Table 1.

Treatment’s Efficacy

25 patients (57%) received PF and 13 patients (29%) received TPF induction chemotherapy regimen and for remaining 6 patients (14%) weekly paclitaxel plus carboplatin (wTC) was administered. The overall response rate (CR plus PR) was 77% in our patient population and in ten patients (23%) no objective responses were observed (SD plus PD group).

ERCC1 analysis

For all 44 patients, the median value of 2-ΔΔCT was 2.0 (0.0 to 396.2). The specimens with 2-ΔΔCT values lower and higher than 2.0 were categorized as low expressed and high expressed ERCC1 respectively. As shown in Table 2, 4% of patients whose tumor samples had high ERCC1 expression showed no-response to induction chemotherapy. This value for patients with low ERCC1 expression was 9% and this difference was statistically significant (p=0.03). The ERCC1 expression states were not significantly different between patient groups according to sex, age, primary tumor site, tumor and node stage. The correlation between ERCC1 expression status and patient, tumor and response characteristics are detailed in Table 2.

We analyzed the distribution of some variables other than ERCC1 expression status that could probably interfere with response to induction chemotherapy.
revealed a range of 64% to 81% for response to induction chemotherapy (Hitt et al., 2013; Cohen et al., 2014; Zhong et al., 2012).

In our patients, ERCC1 expression status was demonstrated to be associated with response to platinum-based induction chemotherapy. Patients in poor response group compared with good response one had more often high ERCC1 expression states and this difference was statistically significant (P=0.03). In a cohort study of 107 patients who were treated by a cisplatin-based induction chemotherapy regimen for locally advanced head and neck squamous cell carcinoma, Handra-Luca et al showed that patients with tumors expressing ERCC1at lower levels had a 4-fold greater odds of benefiting from an objective response to chemotherapy (P = 0.01) compared with the group of patients with high ERCC1expression. Unlike our study, they assessed ERCC1 expression status by immunohistochemical methods (Handra-Luca et al., 2007). In the only available study using RT-PCR to determine ERCC1 expression in patients with locally advanced head and neck cancer, Fountzilas et al (2009) identified no association between high ERCC1 mRNA expression and complete response to treatment Small sample size of their study and different treatment modalities (radiation concurrent with cisplatin plus cetuximab in Fountzilas et al study versus induction chemotherapy in the present study) are two possible explanations for the discordance between their result and one observed in our patients. In the present study no association between ERCC1 expression status and different demographic and clinicopathologic characteristics like sex, age, primary tumor site and stage were detected (Table2). Primary tumor site (nasopharynx versus non-nasopharynx) could be a possible confounding variable interfering with response to treatment as all nasopharyngeal primary tumors showed objective response to induction chemotherapy (Table3).

To date, there is much evidence that shows prognostic and predictive role of ERCC1 expression in patients with different types of cancers undergoing platinum-based treatment. Our study proposed that ERCC1 expression status detected by RT-PCR might serve as a bio-predictor of response to platinum-based induction chemotherapy for head and neck cancers.

Acknowledgements

We are grateful to all staff members of department of pathology in Amir Alam hospital for cooperating with us in the sample collection.

References

Alvarenga LM, Ruiz MT, Pavarino-Bertelli EC, et al (2008). Epidemiologic evaluation of head and neck patients in a university hospital of Northwestern São Paulo State. Braz J Otorhinolaryngol, 74, 68-73.

Argiris A (2005). Induction chemotherapy for head and neck cancer: will history repeat itself. J Natl Compr Canc Netw, 3, 393-403.

Bauman JE, Austin MC, Schmidt R, et al (2015). ERCC1 is a prognostic biomarker in locally advanced head and neck cancer: results from a randomised, phase II trial. Br J Cancer, 109, 2096-105.

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.

Brockstein B, Haraf DJ, Rademaker AW, et al (2004). Patterns of failure, prognostic factors and survival in locoregionally advanced head and neck cancer treated with concomitant chemoradiation therapy: a 9-year, 337-patient, multi-institutional experience. Ann Oncol, 15, 1179–86.

Carey TE, Prince MEP (2015). Molecular Biology of Head and Neck Cancers. In ‘Cancer principle and practice of oncology’, Devita VT, Hellman S, Rosenberg SA. 10th ed. Wolters Kluwer, Philadelphia, 416-21.

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.

Cohen EE, Karrison TG, Kocherginsky M, et al (2014). Phase III randomized trial of induction chemotherapy in patients with N2 or N3 locally advanced head and neck cancer. Cancer Clin. Trials, 32, 2735-43.

Ferlay J, Shin HR, Bray F, et al (2010). Estimates of worldwide burden of cancer in 2008. Int J Cancer, 127, 2893-917.

Fountzilas G, Bamias A, Kalogera-Fountzila A, et al (2009). Induction chemotherapy with docetaxel and cisplatin followed by concomitant chemoradiotherapy in patients with inoperable non-nasopharyngeal carcinoma of the head and neck. Anticancer Res, 29, 529–38.

Fountzilas G, Kalogera-Fountzila A, Lambaki S, et al (2009). MMP9 but not EGFR, MET, ERCC1, P16, and P-53 is associated with response to concomitant radiotherapy, cetuximab, and weekly cisplatin in patients with locally advanced head and neck cancer. J Oncol, 2009, 305908.

Gossage L, Madhusudan S (2007). Current status of excision repair cross-complementing-group 1 (ERCC1) in cancer. Cancer Treat Rev, 33, 565-77.

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.

Hitt R, Grau JJ, Lopez-Pousa A, et al (2013). A randomized phase III trial comparing induction chemotherapy followed by chemoradiotherapy versus chemoradiotherapy alone as treatment of unresectable head and neck cancer. Ann Oncol, 25, 216-25.

Jemal A, Siegel R, Xu J, Ward E (2010). Cancer statistics, 2010. CA Cancer J Clin, 60, 277–300.

Jun HJ, Ahn MJ, Kim HS, et al (2008). ERCC1 expression as a predictive marker of squamous cell carcinoma of the head and neck treated with cisplatin-based concurrent chemoradiation. Br J Cancer, 99, 167-72.

Koh Y, Kim TM, Jeon YK, et al (2009). Class III beta-tubulin, but not ERCC1, is a strong predictive and prognostic marker in locally advanced head and neck squamous cell carcinoma. Ann Oncol, 20, 1414-9.

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

Li FY, Ren XB, Xie XY, Zhang J (2013). Meta-analysis of
excision repair cross-complementation group 1 (ERCC1) association with response to platinum-based chemotherapy in ovarian cancer. Asian Pac J Cancer Prev, 14, 7203-6.
Livak KJ, Schmittgen TD (2001). Analysis of relative gene expression data using real-time quantitative PCR and the 2− CT method. Methods, 25, 402-8.
Ragin CC, Modugno F, Gollin SM (2007). The epidemiology and risk factors of head and neck cancer: a focus on human papillomavirus. J Dent Res, 86, 104-14.
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.
Zamble DB, Mu D, Reardon JT, et al (1996). Repair of cisplatin-DNA adducts by the mammalian excision nuclease. Biochemistry, 35, 10004-13.
Zhong LP, Zhang CP, Ren GX, et al (2012). Randomized phase III trial of induction chemotherapy with docetaxel, cisplatin, and fluorouracil followed by surgery versus up-front surgery in locally advanced resectable oral squamous cell carcinoma. J Clin Oncol, 48, 1076–84.