Correlation of E-cadherin gene polymorphisms and epidermal growth factor receptor mutation in lung adenocarcinoma

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Abstract

Epithelial-mesenchymal transition (EMT) was recently discovered related to the efficacy of epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) in NSCLC patients and cell lines. In this study, we aimed to explore the association among the E-cadherin gene (CDH1) genetic variants, TK-domain mutations of EGFR, and clinicopathologic characteristics in patients with lung adenocarcinoma. A total of 280 patients with lung adenocarcinoma were recruited between years 2012 and 2015. All subjects underwent the analysis of CDH1 genetic variants (rs16260 and rs9929218) by real-time polymerase chain reaction (PCR) genotyping. The results showed that CA and CA + AA genotypes of CDH1 single nucleotide polymorphism (SNP) rs16260 were significantly reverse associated with EGFR mutation type (Adjusted odds ratio (AOR) = 0.43, 95% CI = 0.20-0.92 and AOR = 0.46, 95% CI = 0.22-0.96, respectively) in female lung adenocarcinoma patients. Moreover, the significantly reverse associations between CA and CA + AA genotypes of CDH1 rs16260 and EGFR hotspot mutations, namely L858R mutation and exon 19 in-frame deletion, were also demonstrated among female patients. Besides, CA + AA genotype of CDH1 rs16260 was noted significantly reverse associated with the tumor sizes (OR = 0.31, 95% CI = 0.12-0.80; p = 0.012). In conclusion, our results suggested that CDH1 variants are significantly reverse associated with mutation of EGFR tyrosine kinase, especially among the female patients with lung adenocarcinoma. The CDH1 variants might contribute to pathological development in lung adenocarcinoma.

Key words: Adenocarcinoma; E-cadherin; CDH1 gene; Polymorphism; Genetic variants; Epidermal growth factor receptor

Introduction

Lung cancer is the most common cancer worldwide and also represented the most common death in Taiwan. Based on the National Health Insurance Research Database published in Taiwan, the 5-year survival rate of lung cancer patients was 15.9% [1]. The 2015 WHO classification relies on a greater extent of immunohistochemical characterization, which allows for precise subtyping, conduction of appropriate treatment strategy, and predicting clinical course. Moreover, the molecular characterization of patients with non-small cell lung cell (NSCLC) is resulting in the use of agents with high levels of...
antitumor activity, particularly for those with driver mutations [2]. The most notorious ones are the mutations in the epidermal growth factor receptor (EGFR) and rearrangement of the anaplastic lymphoma kinase (ALK) gene or ROS1 gene, and mutation in BRAF V600E. Mutations in the EGFR tyrosine kinase are noticed in lung adenocarcinoma and occur more frequently in females and non-smokers [3]. In Asia, the incidence of EGFR mutation goes even up to 62% [4].

E-cadherin (CDH1 gene) is a Ca^{2+} dependent homotypic cell adhesion molecule (CAM) that is important in the formation of adherens junctions to bind cells altogether and functions as a binding partner for β-catenin [5]. The E-cadherin plays a key role in cellular adhesion, and its down-regulation is potentially important and highly associated with greater tumor metastasis [6-10]. E-cadherin is regarded as an important factor for Epithelial-mesenchymal transition (EMT), which is the critical step for cancer metastasis [11, 12].

Of recent knowledge, EMT is associated with the mutant status of EGFR and the efficacy of EGFR-tyrosine kinase inhibitors (TKIs) in lung cancer cell lines as well as NSCLC patients. Also, the reduction of E-cadherin expression predicts worse overall survival (OS) and disease-free survival/progression-free survival (DFS/PFS) in patients with NSCLC [13, 14]. Furthermore, decreased expression of E-cadherin was associated with decreased sensitivity to EGFR-TKIs, whereas high E-cadherin expression improved tumor cells’ sensitivity to EGFR-TKIs [15]. However, the correlation between CDH1 gene polymorphisms and EGFR mutations of lung adenocarcinoma has not been well-studied. In this study, we hypothesized that the genetic polymorphisms of CDH1 (rs16260 and rs9929218) may have an effect on the TK-domain mutations of EGFR in patients with lung adenocarcinoma.

Material and Methods

Study Population

Between years 2012 and 2015, a total of 280 patients with lung adenocarcinoma at Cheng-Ching General Hospital in Taichung, Taiwan were recruited. The study was approved by the Institutional Review Board of Cheng-Ching General Hospital (No. HP120009; 22 September 2012). All enrolled patients provided signed informed consent to participate in this study.

Study Variables

The main endpoint of the present study was the prevalence of EGFR mutation among these lung adenocarcinoma patients, and its association with E-cadherin (CDH1) genotypes. We selected two CDH1 SNPs, including rs16260 (-160, C/A) in the promoter region and the intron 2 variant rs9929218 based on their potential involvement in the various cancer types [16-20]. Different associating factors relating to the mutations in EGFR were considered and analyzed as previously described [21, 22]. Data obtained from medical record of each patient included demographics (age, gender), tobacco smoking status, and tumor staging and differentiation.

Patients Specimens for Genomic DNA

Extraction and E-cadherin (CDH1) Genotyping

Venipuncture was performed and withdrawn blood from each participant into Vacutainer blood collection tubes containing EDTA and stored at 4°C. Genomic DNA was extracted from QIAamp DNA blood mini kits according to the manufacturer’s instructions as previously described [23]. Allelic discrimination of CDH1 rs16260 (C_11934298_10) and rs9929218 (C_11509221_10) gene polymorphisms was assessed with the ABI StepOne™ Real-Time PCR System (Applied Biosystems, Foster City, CA, USA) and analyzed using SDS version 3.0 software (Applied Biosystems) with the TaqMan assay.

Statistical Analysis

Categorical variables, including demographics, smoking status, tumor characteristics, and genotypes polymorphisms, were summarized as number and percentage by EGFR mutation status; continuous variables were expressed as mean and standard deviation. The distributions of demographics, clinical characteristics and genotype frequencies among lung adenocarcinoma patients, as well as clinicopathological features in different genotypes, were analyzed with a χ2-test. A p-value of <0.05 indicated statistically significant.

Results

Characteristics of Study Population

This study included a total of 280 patients, 127 males and 153 females with a mean age of 65 years, for analysis. The baseline demographics and clinical characteristic of enrolled patients were shown in Table 1. There were 111 (39.6%) and 169 (60.4%) patients in the EGFR wild-type and mutation type groups, respectively. These two groups differed with respect to gender, tobacco smoking status, and tumor differentiation (p<0.001). The EGFR mutation type group, compared with subjects in the EGFR wild-type group, were predominantly female (64.5% vs. 39.6%, respectively), non-smoker status (77.5% vs. 45.0%), and mostly well-differentiated (12.4% vs. 7.2%) and moderately-differentiated tumor (81.7% vs. 72.1%).
Abbreviations: SNP, single nucleotide polymorphism; AOR, adjusted odds ratio; CI, confidence interval.

Table 1. Baseline demographic and clinical characteristics of patients with lung adenocarcinoma by EGFR mutation status (N=280)

| Variable                        | Wild-type  | EGFR mutation | p-value |
|---------------------------------|------------|---------------|---------|
|                                 | (N=111)    | (N=169)       |         |
| **Age, n (%)**                  |            |               |         |
| <30                             | 1 (0.9%)   | 1 (0.6%)      | p=0.657 |
| 30-39                           | 3 (2.7%)   | 2 (1.2%)      |         |
| 40-49                           | 11 (9.9%)  | 16 (9.5%)     |         |
| 50-59                           | 21 (18.9%) | 44 (26.0%)    |         |
| 60-69                           | 26 (23.4%) | 31 (18.3%)    |         |
| ≥70                             | 49 (44.1%) | 75 (44.4%)    |         |
| **Mean ± SD**                   | 65.36 ± 13.42 | 65.76 ± 13.57 | p=0.810 |
| **Gender, n (%)**               |            |               |         |
| Male                            | 67 (60.4%) | 60 (35.5%)    | p<0.001 |
| Female                          | 44 (39.6%) | 109 (64.5%)   |         |
| **Tobacco smoking, n (%)**      |            |               |         |
| Non-smoker                      | 50 (45.0%) | 131 (77.5%)   | p<0.001 |
| Smoker                          | 61 (55.0%) | 38 (22.5%)    |         |
| **Pack-years ± SD**             | 46.32 ± 28.21 | 19.94 ± 23.83 | p<0.001 |
| **Tumor AJ/CC staging, n (%)**  |            |               |         |
| IA                              | 11 (9.9%)  | 17 (10.1%)    | p=0.570 |
| IB                              | 9 (8.1%)   | 23 (13.6%)    |         |
| IIA                             | 5 (4.5%)   | 7 (4.1%)      |         |
| IIB                             | 1 (0.9%)   | 0 (0%)        |         |
| IIIA                            | 10 (9.0%)  | 11 (6.5%)     |         |
| IIIB                            | 17 (15.3%) | 19 (11.2%)    |         |
| IV                              | 58 (52.3%) | 92 (54.4%)    |         |
| **Tumor differentiation, n (%)**|            |               |         |
| Well                            | 8 (7.2%)   | 21 (12.4%)    | p=0.001 |
| Moderate                        | 80 (72.1%) | 138 (81.7%)   |         |
| Poor                            | 23 (20.7%) | 10 (5.9%)     |         |

Distribution of CDH1 Genotypes of Study Population and Its Association with EGFR Mutation by Gender Difference

The distribution frequency of CDH1 genotypes (rs16260 and rs9929218) of patients with lung adenocarcinoma was shown in Table 2. The alleles with the highest distribution frequency for rs16260 and rs9929218 in the enrolled patients were homozygous C/C and homozygous G/G for both EGFR wild-type and mutation type groups, respectively. After adjusting for variance, there was no significant difference between the wild-type and mutation type of EGFR and polymorphisms of the CDH1 genotypes in rs16260 and rs9929218, when compared with wild-type individuals.

To elucidate the association between the polymorphism of CDH1 gene and EGFR mutations in different gender, the distribution frequency of CDH1 single nucleotide polymorphism (SNP) (rs16260 and rs9929218) of EGFR wild-type and mutation type in lung adenocarcinoma patients was estimated in Table 2. In females, CA and CA + AA genotypes of CDH1 rs16260 were significantly reverse associated with EGFR mutation type (AOR = 0.43, 95% CI = 0.20-0.92 and AOR = 0.46, 95% CI = 0.22-0.96, respectively). Hence, further analyses were focused on the association between the polymorphism of CDH1 gene and EGFR hotspot mutations in female patients with lung adenocarcinoma.

Association between Polymorphisms of CDH1 genotypes and EGFR Hotspot Mutations among the Female Lung Adenocarcinoma Patients

Table 3 showed the association between the polymorphisms of CDH1 and the EGFR hotspot mutation in the female patients. Also, the significantly reverse associations between CA and CA + AA genotypes of CDH1 rs16260 and EGFR hotspot mutations, namely L858R mutation (OR = 0.40, 95% CI = 0.18-0.90 and OR = 0.44, 95% CI = 0.20-0.97, respectively) and exon 19 in-frame deletion (OR = 0.39, 95% CI = 0.16-0.95 and OR = 0.41, 95% CI = 0.17-0.97, respectively), were demonstrated.

Table 2. Distribution frequency of CDH1 genotypes of patients with lung adenocarcinoma and multiple logistic regression analysis of EGFR mutation association

| Genotypes SNP | All cases (N=280) | Male (N=127) | Female (N=153) |
|---------------|-------------------|--------------|----------------|
| CDH1 rs16260  | Wild type (N=111) | Mutation type (N=169) | AOR (95% CI) | Wild type (N=67) | Mutation type (N=60) | AOR (95% CI) | Wild type (N=44) | Mutation type (N=109) | AOR (95% CI) |
| CC            | 55 (49.5%)        | 90 (53.3%)  | 1.00           | 38 (56.7%)    | 26 (43.3%)    | 1.00           | 64 (58.7%)    | 1.00           | 64 (58.7%)    | 1.00           |
| CA            | 49 (44.1%)        | 70 (41.4%)  | 0.90 (0.53-1.53) | 24 (35.8%)    | 31 (51.7%)    | 1.95 (0.92-1.44) | 25 (56.8%)    | 39 (53.8%)    | 0.43 (0.20-0.92) |
| AA            | 7 (6.3%)          | 9 (5.3%)    | 0.81 (0.27-2.45) | 5 (7.5%)      | 3 (5.0%)      | 0.90 (0.19-4.31) | 2 (4.6%)      | 6 (5.5%)      | 0.72 (0.13-3.90) |
| CA+AA         | 56 (50.5%)        | 79 (46.7%)  | 0.89 (0.54-1.48) | 29 (43.3%)    | 34 (56.7%)    | 1.77 (0.85-3.65) | 27 (61.4%)    | 45 (41.3%)    | 0.46 (0.22-0.96) |
| CDH1 rs9929218 | GG            | 68 (61.3%)  | 108 (63.9%)    | 1.00           | 43 (64.2%)    | 34 (56.7%)    | 1.00           | 25 (56.8%)    | 74 (67.9%)    | 1.00           |
| CA            | 41 (36.9%)        | 51 (33.1%)  | 0.87 (0.51-1.49) | 23 (34.3%)    | 25 (41.7%)    | 1.37 (0.65-2.89) | 18 (40.9%)    | 31 (28.4%)    | 0.54 (0.25-1.15) |
| AA            | 4 (3.6%)          | 5 (3.0%)    | 1.17 (0.21-1.29) | 1 (1.5%)      | 1 (1.6%)      | 0.99 (0.05-18.34) | 1 (2.3%)      | 4 (5.7%)      | 1.14 (0.12-10.79) |
| GA+AA         | 43 (38.7%)        | 61 (36.1%)  | 0.89 (0.52-1.50) | 24 (35.8%)    | 26 (43.3%)    | 1.36 (0.65-2.83) | 19 (56.8%)    | 35 (32.1%)    | 0.57 (0.27-2.10) |

The AORs with 95% CIs were estimated by multiple logistic regression models after controlling for age and smoking.

Note: Bold text indicated a significant association with p value <0.05.

Abbreviations: SNP, single nucleotide polymorphism; AOR, adjusted odds ratio; CI, confidence interval.
Table 3. The associations between the polymorphisms of CDH1 and the EGFR hotspot mutations in female patients with lung adenocarcinoma.

| Genotypes | Wild-type (N=64) | L858R (N=61) | Exon 19 in-frame deletion (N=13) |
|-----------|-----------------|-------------|---------------------------------|
|            | n (%)           | n (%)       | OR (95% CI)                     | OR (95% CI)               |
| CDH1 rs16260 |                 |             |                                 |                           |
| CC         | 17 (38.6%)      | 36 (59.0%)  | 1.00 (0.25-1.32)                | 1.00 (0.26-1.52)          |
| CA         | 25 (56.8%)      | 21 (34.4%)  | 0.40 (0.18-0.90)                | 0.41 (0.17-0.97)          |
| AA         | 2 (4.6%)        | 6 (9.6%)    | 0.94 (0.36-2.47)                | 0.08 (0.01-0.99)          |
| CA+AA      | 27 (61.4%)      | 25 (41.0%)  | 0.44 (0.20-0.97)                | 0.41 (0.27-0.97)          |

Note: bold text indicated a significant association with p value <0.05. Abbreviations: SNP, single nucleotide polymorphism; OR, odds ratio; CI, confidence interval.

Association between CDH1 SNP rs16260 and Tumor Classification among Male Lung Adenocarcinoma Patients

The AJCC Tumor, Node, Metastasis (TNM) staging system for lung cancer (NSCLC) is an internationally accepted system to describe the extent of disease [24]. It combines features of the tumor into disease stage groups that correlate with survival and are linked to recommendations for treatment, as well as an indicator of prognosis. In this study, we further investigated the association between polymorphisms of CDH1 gene and clinicopathologic characteristics among male patients with lung adenocarcinoma. As shown in Table 4, CA + AA genotype of CDH1 rs16260 was noted significantly reverse associated with the “T” classification (primary tumor size and extension) based on eighth edition of AJCC TNM staging system (OR = 0.31, 95% CI = 0.12-0.80; p = 0.012). Furthermore, while stratified male patients based on EGFR mutation status, consistent reverse association was seen in the mutation type male patients (OR = 0.20, 95% CI = 0.04-0.99; p = 0.037). These findings indicated that the polymorphisms of CDH1 rs16260 may be associated with the tumor size and extension of lung cancer.

Discussion

Our study investigated 280 patients with lung adenocarcinoma, and the role of E-cadherin (CDH1) gene polymorphism in regards to the EGFR mutation status, as well as a possible prognostic marker for tumor invasiveness and metastasis and predictive marker for the resistance of EGFR-TKI therapy. The significance of E-cadherin (CDH1) polymorphism, as an important epithelial marker/factor of EMT, have been well-studied and established in several human cancers, such as breast cancer [25, 26], gastric cancer [27], pancreatic cancer, ovarian cancer [28, 29], prostate cancer [26], esophageal squamous cell carcinoma [30], head and neck cancer [31] and skin cancer [32-34]. Regard to lung cancers, though E-cadherin is highly associated with risk of NSCLC carcinogenesis [14, 35, 36], particular adenocarcinoma, the mutant status of EGFR, the efficacy of EGFR-TKIs therapy [37], and survival prognosis, no study exploring the relationship between CDH1 gene polymorphisms and the mutations of EGFR of lung cancers was conducted. To our best knowledge, this is the first time discovering the statistically significant association between CDH1 SNP rs16260 variant types (CA and CA + AA genotypes) and hotspot mutations (in-frame deletion mutation in exon 19 and L858R mutation) of EGFR, especially in the female lung adenocarcinoma patients.

Table 4. The associations between polymorphic genotypes of CDH1 rs16260 and clinicopathologic characteristics of male patients with lung adenocarcinoma.

| Variable genotypic frequencies | Tumor AJCC “T” Classification (N=102) |
|--------------------------------|---------------------------------------|
|                                | T1 & below n (%) | T2 & above n (%) | OR (95% CI) | p value |
|--------------------------------|-----------------|-----------------|-------------|---------|
| All cases (N=127)              |                 |                 |             |         |
| CDH1 rs16260                   |                 |                 |             |         |
| CC                             | 7 (28.0%)       | 57 (55.9%)      | 1.00        |         |
| CA+AA                          | 18 (72.0%)      | 45 (44.1%)      | 0.31 (0.12-0.80) | p=0.012 |
| EGFR Wild type (N=67)          |                 |                 |             |         |
| CDH1 rs16260                   |                 |                 |             |         |
| CC                             | 5 (38.5%)       | 28 (61.1%)      | 1.00        |         |
| CA+AA                          | 8 (61.5%)       | 17 (38.9%)      | 0.40 (0.12-1.38) | p=0.139 |
| EGFR Mutation type (N=48)      |                 |                 |             |         |
| CDH1 rs16260                   |                 |                 |             |         |
| CC                             | 2 (16.7%)       | 24 (50.0%)      | 1.00        |         |
| CA+AA                          | 10 (83.3%)      | 24 (50.0%)      | 0.20 (0.04-0.99) | p=0.037 |

Note: bold text indicated a significant association with p value <0.05. Abbreviations: SNP, single nucleotide polymorphism; OR, odds ratio; CI, confidence interval.
observed in the female patients (female vs. male = 64.5% vs. 35.5%) and in non-smokers (non-smoker vs. smoker = 77.5% vs. 22.5%). These results were consistent with previous studies indicating that the mutation of EGFR was associated with gender, adenocarcinoma, and smoking status [3, 4, 38].

There were very limited studies investigating polymorphisms of different EMT-related gene expression and their relationship with carcinogenesis. Xie et al. [39] have reported lately that EMT-related gene variants, namely ADGRF1, NOTCH3, and CDH1, may be involved in susceptibility to NSCLC. Cai et al. [40] earlier revealed that genetic effect of a nonsynonymous HRH4 polymorphism (rs11662595) is a loss-of-function polymorphism that results in dysfunction of HRH4 gene and attenuates the anti-EMT function of HRH4 in NSCLC. This investigation provides a promising biomarker for prognosis and therapy of NSCLC. Kim S et al. [41] also demonstrates that EMT phenotype was related to PD-L1 overexpression in pulmonary adenocarcinoma cells and patients with EMT-phenotype pulmonary adenocarcinoma may benefit from PD-1/PD-L1-blocking immunotherapy. But to the detail of CDH1 gene polymorphisms and their association with EGFR mutation status, no specific research was found prior to ours.

Our findings relative to association between CDH1 polymorphism and EGFR mutation status suggested CA and CA + AA genotypes of CDH1 SNP rs16260 were significantly reverse associated with EGFR mutation type in female patients with lung adenocarcinoma (AOR = 0.43, 95% CI = 0.20-0.92 and AOR = 0.46, 95% CI = 0.22-0.96, respectively), as compared to the control (CC genotype). AA genotype of the same SNP also showed the same direction of association (AOR = 0.72, 95% CI = 0.13-3.90), but did not reach statistical significance. We further verified this association with the use of two EGFR hotspot mutations, namely L858R mutation and in-frame deletion mutation in exon 19, and obtained the consistent statistically significant relationship. These results may explain that CDH1 variant type is less associated with EGFR mutation type especially among the female population; in the other words, CDH1 wild type (CC genotype) is more related to mutate EGFR tyrosine kinase, which is a more favorable prognosis and strongly predicts for sensitivity to EGFR-TKIs. However, the mechanism by which this SNP (rs16260) modulates the roles of female lung adenocarcinoma patients should be further investigated.

Among male lung adenocarcinoma patients, we found no statistical significance between CDH1 polymorphism and EGFR mutation status. But when we further stratified them based on tumor characteristic of AJCC “T” classification (primary tumor size and extension), CDH1 rs16260 variant type (CA + AA genotype) showed significantly reverse association as T classification progressed, as compared with the control type (CC genotype). This association was still seen in male patients with mutated EGFR gene. In the previous studies, downregulation of E-cadherin expression is highly associated with cancer progression and metastasis [13, 42-45]. The inclusion of other clinicopathologic parameters at molecular level should be further investigated.

In conclusion, our results suggested that E-cadherin gene (CDH1) variants are significantly reverse associated with mutation of EGFR tyrosine kinase, especially among the female patients with lung adenocarcinoma. This may be utilized as a prognostic factor for tumor size in Taiwanese patients with lung adenocarcinoma.

Competing Interests
The authors have declared that no competing interest exists.

References
[1] Wang BY, Huang JY, Cheng CY, Lin CH, Ko J, Liaw VP. Lung cancer and prognosis in taiwan: a population-based cancer registry. J Thorac Oncol 2013; 8: 1128-1135.
[2] Travis WD, Brambilla E, Nicholson AG, et al. The 2015 World Health Organization Classification of Lung Tumors: Impact of Genetic, Clinical and Radiologic Advances Since the 2004 Classification. J Thorac Oncol 2015; 10: 1243-1260.
[3] Kawaguchi T, Koh Y, Ando M, et al. Prospective Analysis of Oncogenic Driver Mutations and Environmental Factors: Japan Molecular Epidemiology for Lung Cancer Study. J Clin Oncol 2016; 34: 2247-2257.
[4] Shy I, Yu JS, Thongprasert S, et al. A prospective, molecular epidemiology study of EGFR mutations in Asian patients with advanced non-small-cell lung cancer of adenocarcinoma histology (PIONEER). J Thorac Oncol 2014; 9: 154-162.
[5] Alimpert S, Andreatis ST, CDH2 and CDH1 act as regulators of stem cell fate decisions. Stem Cell Research 2015; 14: 270-282.
[6] Beavon IRG. The E-cadherin–catenin complex in tumour metastasis. European Journal of Cancer 2000; 36: 167-170.
[7] Lim SC, Jang IG, Kim YC, Park KO. The role of E-cadherin expression in non-small cell lung cancer. J Korean Med Sci 2000; 15: 501-506.
[8] Kim H, Yoo SB, Sun P, et al. Alteration of the E-Cadherin/beta-Catenin Complex Is an Independent Poor Prognostic Factor in Lung Adenocarcinoma. Korean J Pathol 2013; 47: 44-51.
[9] Peclina-Šlaus N. Tumor suppressor gene E-cadherin and its role in normal and malignant cells. Cancer Cell International 2003; 3: 17.
[10] Su SC, Hsieh MJ, Yang WE, Chung WH, Reiter RJ, Yang SF. Cancer metastasis: Mechanisms of inhibition by melatonin. J Pineal Res 2017; 62: e12370.
[11] Liu X, Su L, Liu X. Loss of CDH1 up-regulates epidermal growth factor receptor via phosphorylation of YBX1 in non-small cell lung cancer cells. FEBS Lett 2013; 587: 3995-4000.
[12] Cheng HL, Lin CW, Yang JS, Hsieh MJ, Yang SF, Lu KH. Zoledronate blocks geranylgeranylation not farnesylation to suppress human osteosarcoma U2OS cells metastasis by EMT via Rho A activation and FAK-inhibited JNK and p38 pathways. Oncotarget 2016; 7: 9742-9758.
[13] Zhao C, Li X, Su C, et al. High expression of E-cadherin in pleural effusion cells predicts better prognosis in lung adenocarcinoma patients. Int J Clin Exp Pathol 2015; 8: 3104-3109.
[14] Yang YL, Chen MW, Xian L. Prognostic and clinicopathological significance of downregulated E-cadherin expression in patients with non-small cell lung cancer (NSCLC): a meta-analysis. PLoS One 2014; 9: e99763.
[15] Zhou J, Wang J, Zeng Y, et al. Implication of epithelial-mesenchymal transition in EGFR-induced resistance to EGFR-TKIs in advanced non-small cell lung cancer. Oncotarget 2015; 6: 44332-44345.
[16] Chien MH, Chou LS, Chung TT, et al. Effects of E-cadherin (CDH1) gene promoter polymorphisms on the risk and clinicopathologic development of oral cancer. Head Neck 2012; 34: 405-411.
