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Original Article

Therapeutic efficacy of gefitinib and erlotinib in patients with advanced lung adenosquamous carcinoma

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Abstract

Background: Adenosquamous carcinoma (ASC) of the lung is a rare subtype of nonsmall-cell lung cancer (NSCLC). To date, the efficacious targeted therapy for advanced ASC remains unclear and the epidermal growth factor receptor (EGFR) mutation rate is not well known.
Methods: We retrospectively reviewed clinical information of patients with ASC who were treated with gefitinib or erlotinib at Zhejiang Cancer Hospital between January 2007 and December 2011. Survival analysis was evaluated by the Kaplan-Meier method. EGFR mutations were assessed in part using direct sequencing methods.
Results: In total, 49 patients with a median age of 57 years were used in this study. Thirteen patients achieved a partial response and 19 had disease stabilization. The objective response rate was 26.5%, and the disease control rate was 65.3%. The median progression-free survival and overall survival were 4.3 and 17.6 months, respectively. In 21 patients with adequate specimens for molecular analysis, 7 (33.3%) had EGFR mutations (4 with deletions within exon 19 and 3 with L858R messenger mutation in exon 21). EGFR mutations were significantly more frequent in women (4/9, 44.4%) than men (3/12, 25%), never-smokers (6/15, 40%), and smokers (1/6, 16.7%).
Conclusion: EGFR-tyrosine kinase inhibitor (TKI) is an effective treatment for ASC. The frequency of EGFR mutation and clinical characteristics of the EGFR mutants in ASC are similar to those of Asian patients with adenocarcinoma.

Keywords: adenosquamous carcinoma; efficacy; EGFR-TKI; nonsmall-cell lung cancer

1. Introduction

Adenocarcinoma and squamous cell carcinoma (SCC) are two major subtypes of NSCLC. Adenosquamous carcinoma (ASC) is a rare subtype of NSCLC, comprising 0.4−4% of pulmonary carcinomas.[1−4] ASC is a mixed histologic tumor; according to the last WHO lung tumor classification criteria, it is defined as "a carcinoma showing components of both squamous cell carcinoma and adenocarcinoma, with each comprising to at least 10% of the tumor".[5] A clinicopathological analysis has demonstrated that ASC is more aggressive than adenocarcinoma and SCC, indicating that its biological features are different from these types of NSCLC.[6−8] The epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) including gefitinib and erlotinib are the primary drugs of choice for the treatment of NSCLC patients, especially for the patients harboring EGFR mutations.[9,10] However, no clinical study to evaluate efficacy of EGFR-TKIs and mutation frequency for ASC has been conducted thus far.

We conducted a focused analysis targeting Chinese populations in order to track the EGFR mutation status of ASC, as well as to check the feasibility of EGFR-TKIs treatment in ASC.

2. Methods

2.1. Patients

A retrospective review of patients from the Zhejiang Cancer Hospital between January 2007 and December 2011

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was conducted. The Ethics Committee at Zhejiang Cancer Hospital approved the study. NSCLC staging was performed according to the 7th TNM classification. The inclusion criteria were as follows: (1) pathologically proven primary ASC, (2) all patients were supplied with TKI during the treatment course, (3) disease recurrence was confirmed using chest computed tomography (CT), brain MRI and bone scan as well as ultrasound examination and/or CT of the abdomen, (4) without any local treatment such as radiotherapy or interventional therapy during the period of TKI therapy, and (5) at least one measurable lesion and an Eastern Cooperative Oncology Group performance status of 0 to 3.

2.2. Pathology and EGFR mutation examination method

To confirm the histology of ASC, each of the slides previously identified was examined independently by two specialists according to the World Health Organization criteria (2004 version). The molecular analysis of EGFR was performed using direct sequencing methods with formalin-fixed paraffin embedded archival tissue blocks. Additionally, EGFR mutation analysis using direct sequencing occurred as previously described.[11] Briefly, DNA was extracted from the tumors using a QIAmp DNA Mini kit (Qiagen, Hilden, Germany) following the manufacturer's protocols. The tyrosine kinase domain of the EGFR coding sequences were analyzed by Sequencer 3.1.1. software (Applied Biosystems) to compare variations. Exons 18-21 of EGFR were then examined.

2.3. Responses and toxicity

Tumor responses were assessed with computed tomography (CT) at 4−8-week intervals until the lesions were evaluated as the progressive disease. The tumor response was evaluated based on the Response Evaluation Criteria in Solid Tumor (RECIST) version 1.1. Objective tumor responses include complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). Objective response included the CR and PR. Disease control rate (DCR) was defined as the addition of objective response and stabilization rates (CR + PR + SD).

The toxicity of TKI treatment was evaluated in accordance with the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 3.0.

2.4. Follow-up

All patients that were evaluated for the TKI tumor response had a progression-free survival (PFS), and none of the patients were lost to follow-up. The median follow-up period was 20.2 months (3.9-52); the last follow-up time was January 30, 2012.

2.5. Statistical analysis

Categorical variables were compared using the χ^2 test and continuous variables by the Mann-Whitney nonparametric test. Survival was recorded from the first-line of treatment to the date of death or that of the last follow-up visit. The PFS encompassed the time from the TKI therapy to documented progression or death from any cause. The survival curves were calculated according to the method of Kaplan-Meier. The Cox proportional model was used to evaluate various prognostic factors. Values of $p < 0.05$ were considered significant. Analyses were conducted using the computer software SPSS version 16.0 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Patient characteristics

Overall, 1679 patients were diagnosed with primary NSCLC between January 2007 and December 2011. Of these, 975 had advanced disease or recurrence after surgery. TKI therapy was administered to these 975 patients (551 with adenocarcinoma, 102 with squamous cell carcinoma, 49 with ASC, 67 with other histologies).

Of the 49 ASC patients enrolled in the clinical study of TKI treatment, there were 26 males and 23 females. The performance status (PS) was 0−1 in 40 patients (81.6%) and PS 2-3 accounted for 18.4%. The median age of the patients was 56 years (range 40−76 years). Twenty-one of them were in advanced stage on presentation and 28 presented with a disease recurrence. Thirteen patients had a history of smoking. Thirty-eight patients received TKI treatment in the second-line and 11 in the third-line or further-line treatment. Thirty-one patients received gefitinib and 18 received erlotinib treatment. The patients' baseline characteristics are listed in Table 1.

3.2. EGFR mutation analysis

Twenty-one patients provided tumor samples for EGFR mutation analysis out of a total of 49 ASC patients (9 female and 12 male). EGFR mutations were identified in seven (30%) patients (4 with deletion in exon 19 and 3 with L858R in exon 21). EGFR mutations occurred significantly more frequently in women (4/9, 44.4%) than men (3/12, 25%) ($p = 0.64$). Patients who had never smoked (6/15, 40%) had EGFR mutations more commonly than smokers (1/6, 16.7%) ($p = 0.61$). One hundred and ninety-two patients provided tumor samples for EGFR mutation analysis in adenocarcinoma. EGFR mutations were identified in 58 (30.2%) patients. The EGFR mutations were identified in four patients among 74 SCC tumor samples (4/74, 5.41%). There was a significant difference among the ASC, adenocarcinoma, and SCC patients in EGFR mutation frequency ($p < 0.001$).

3.3. Efficacy and comparison among adenocarcinoma, SCC, and ASC

Among the 49 ASC patients, 13 had PR and 19 patients had SD in the gefitinib or erlotinib treatment, accounting for a disease control rate of 65.3% (32/49). The median PFS during