Cisplatin or Carboplatin for Advanced Non–Small-Cell Lung Cancer?

To the Editor:

We have read with great interest the article “Cisplatin versus Carboplatin-Based Regimens for the Treatment of Patients with Metastatic Lung Cancer. An Analysis of Veterans Health Administration Data” reported by Santana-Davila and colleagues in Journal of Thoracic Oncology (May 2014).1 We are impressed that the authors presented a great retrospective study with competent data and accurate statistical analysis. However, selection bias obviously existed in the study, as they stated in the discussion part. First, although the study sample is large enough, which included 4352 patients, only 291 (6.7%) patients in the cisplatin group. Second, the inhomogeneity of combined chemotherapeutic agents may affect the overall survival.2 Approximately 30% of patients treated with cisplatin were administered with etoposide, whereas only 1.7% of patients in the carboplatin group. Third, bevacizumab was used more in carboplatin group (5.9%) than in cisplatin group (0.7%). When added to paclitaxel/carboplatin, it can improve survival in previously untreated patients with advanced nonsquamous non–small-cell lung cancer (NSCLC).3 In addition, the authors did not mention the post-study treatment. During the last decade, many advances have been made in the treatment of advanced NSCLC, e.g., targeted therapy. Further treatment after first-line chemotherapy may also impact on overall survival.

As we know, good-designed randomized clinical trials provide strong evidence that may change the current treatment pattern. Rosell and colleagues conducted direct comparison of paclitaxel/carboplatin versus paclitaxel/cisplatin in advanced NSCLC.4 The baseline patient’s characteristics and follow-up therapy were well balanced between the two treatment arms. The overall response rate in the two arms of paclitaxel/carboplatin and paclitaxel/cisplatin was 28% and 25%, respectively, which was similar. However, patients received paclitaxel/cisplatin had the significantly longer median survival (9.8 months) than paclitaxel/carboplatin (8.2 months). This is confirmed by an individual patient data meta-analysis.5 In patients with non-squamous histology, cisplatin-based chemotherapy prolonged survival in comparison to carboplatin-based chemotherapy (hazard ratio = 1.12, 95% confidence interval = 1.01–1.23), but not in squamous histology. In our opinion, there are enough evidences to support use of cisplatin in advanced NSCLC, especially in non-squamous histology. In our daily clinical practice, for eligible patients with non-squamous NSCLC, we would like to recommend cisplatin preferentially.

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EGFR Mutations in Asian Patients with Advanced Lung Adenocarcinoma

To the Editor:

We congratulate Shi et al1 for their prospective multinational, epidemiological study of epidermal growth factor receptor (EGFR) mutations in patients from Asia with newly diagnosed advanced lung adenocarcinoma (PIioneer study) which showed that 51.4% of tumors from 1450 patients had a positive EGFR mutation status. Although the frequency of EGFR mutations was 50% or higher for patients of East Asian ethnicities (Vietnamese, 64.2%; Thai, 53.8%; Chinese, 51.8%, and Filipino, 50.0%), it was significantly lower for Indian patients (21.9%). Our study on Malaysian patients who were of three major ethnicities, ie, Chinese, Malay, and Indian, showed that 39.5% of tumors from 812 patients with advanced adenocarcinoma were EGFR mutation positive.2 The frequency of EGFR mutations was not significantly different between our Chinese (40.8% of 517 patients), Malay (37.2% of 239 patients), and Indian (34.6% of 37 patients) populations.

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patients), and Indian (33.3% of 39 patients) patients. Our study was the first report on the prevalence of EGFR mutation in patients of Malay ethnicity that was not covered by the PIONEER study. The Malays constitute a sizeable population in Southeast Asia including Malaysia, Indonesia, parts of the Philippines, and parts of Thailand.

We could have overestimated the frequency of EGFR mutations in our patients of Indian ethnicity because of the small number of Indian patients compared with the PIONEER study\(^1\) with 73 patients of Indian ethnicity and a study in India\(^3\) where 23% of adenocarcinomas from 907 patients were EGFR mutation positive. The frequency of EGFR mutation among Indian patients with adenocarcinoma in the PIONEER study\(^1\) and the study in India\(^3\) which is intermediate between that of East Asian patients (approximately 50–64%)\(^1\) and Western patients (approximately 20%)\(^9\) is probably because of an admixture of genetic influence from Middle Eastern, Central Asian, and European ancestors on the modern-day Indian population that may confer differential susceptibility to somatic mutations in EGFR.\(^5\)

Similar to the findings by the PIONEER study,\(^1\) EGFR mutations were significantly more frequent among our female than in male patients (52.5% versus 27.8%) and in our patients who had never smoked compared with those who had smoked (54.8% versus 20.7%).\(^2\) We also observed that a never smoking status was the independent predictor of EGFR mutation positivity and female gender was not a significant predictor after adjusting for smoking status.\(^2\)

We concur with Shi et al\(^1\) that the observed high frequency of EGFR mutations in Asian patients including those of Indian ethnicity compared with Caucasian populations suggests that mutation testing should be considered for all Asian patients with advanced lung adenocarcinoma, even in males and smokers.

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**EGFR Mutation Detection by Polymerase Chain Reaction-Direct Sequencing and Allele-Specific Real-Time PCR**

To the Editor:

We read with keen interest the article by Chiu et al\(^1\) on the clinical characteristics and treatment outcomes of patients with lung adenocarcinomas with discrepant EGFR mutation testing results by polymerase chain reaction (PCR)-direct sequencing and the more sensitive mutant allele-specific real-time PCR-based Scorpion Amplification Refractory Mutation System (ARMS) which showed that 21.5% of 130 tumours which were EGFR mutation-negative by direct sequencing were found to have EGFR mutations by the latter assay.

In our study involving 812 patients with lung adenocarcinoma from 2009 to 2011,\(^2\) bidirectional sequencing\(^3,4\) was initially used to detect EGFR mutations in formalin-fixed, paraffin-embedded tumour biopsy specimens from November 2009 to August 2011 but the method was later switched to real-time PCR (EGFR RQ PCR Kit; QIAGEN, Manchester, United Kingdom). The bidirectional sequencing method used primers and PCR conditions as described by Lynch et al.\(^3\) Uncloned PCR fragments were purified and subjected to sequencing before being analyzed for the presence of mutation in both sense and antisense directions. In real-time-PCR, mutations of EGFR (exons 18, 19, 20, and 21) genes were detected by ARMS primers and Scorpion detection technology on Rotor-Gene platform (QIAGEN). The direct sequencing method was used for EGFR mutation detection in 416 (51.2%) of our tumor samples. A higher percentage of tumours were tested EGFR mutation-positive by Scorpion ARMS (170 [42.9%] of 396 tumours) than by direct sequencing (151 [36.3%) of 416 tumours) but the difference was not statistically significant (\(p = 0.053\)). However, although we did not perform a head-to-head comparison of the two methods, our results also suggested that allele-specific, real-time PCR was more sensitive than direct sequencing in detecting EGFR mutations, and this may partly explain the lower EGFR mutation frequency of 39.5% in our patients with adenocarcinoma compared with other East Asian ethnicities (Vietnamese, 64.2%; Thai, 53.8%; Chinese, 51.8%, and Filipino, 50.0%) as shown by the PIONEER study in which Scorpion ARMS was used.\(^5\) In our study, exon 19 mutations (in 23.5%) were the most common mutations followed by exon 21 mutations (in 14.9%) of 396 tumours.\(^2\) Interestingly, exon 19 mutations were significantly more frequently detected by Scorpion ARMS (108 [27.3%] of 396 tumours) but the direct sequencing (83 [20.0%] of 416 tumours; \(p = 0.018\)) in our study.\(^2\)

We agree with Chiu et al\(^1\) that direct sequencing may under-detect EGFR mutations in a significant proportion of lung adenocarcinoma patients.

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