Case Report

Coexistence of Epidermal Growth Factor Receptor 19 Deletion and 21 Point Mutation in Nonsmall Cell Lung Cancer: A Report of 3 Cases

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Abstract

The coexistence of an epidermal growth factor receptor (EGFR) 19 deletion and 21 point mutation represents a rare event in patients with nonsmall cell lung cancer. We present three cases of female patients with lung adenocarcinoma who had the double genetic mutations. The patients were all treated with EGFR tyrosine kinase inhibitors (TKIs) because the tumors were judged inoperable. In all cases, tumor progression occurred after a few months. Further studies are needed to determine whether the EGFR-TKI resistance time in patients with double genetic mutations is longer than that in patients with a single mutation.

Keywords: Epidermal growth factor receptor mutation, epidermal growth factor receptor tyrosine kinase inhibitor, nonsmall cell lung cancer, resistance

Received: 06th July, 2017; ***Revised:*** 10th August, 2017; ***Accepted:*** 27th August, 2017

Introduction

Lung cancer continues to be the most prevalent cancer type and the leading cause of cancer-related death worldwide. Nonsmall cell lung cancer (NSCLC) accounts for 80%–90% of all lung cancer cases, and adenocarcinoma is the most common histological type of NSCLC.[1] The majority of cancer patients are diagnosed at an advanced stage, precluding the possibility of surgical resection. Thus, the main treatment option for patients with NSCLC is chemotherapy. Standard first-line therapy for advanced NSCLC consists of systemic platinum-based doublet chemotherapy, but the prognosis remains poor, with a 2-year survival rate of only 11%.[1]

Considerable evidence indicates that the epidermal growth factor receptor (EGFR) pathway plays an important role in both the pathogenesis and the progression of lung cancer. Recently, EGFR-tyrosine kinase inhibitor (TKIs) have been shown to play a significant role in the treatment of NSCLC. Patients harboring EGFR activating mutations show greater clinical benefit from EGFR-TKIs than from traditional cytotoxic chemotherapy given as first-line, second-line, or even maintenance treatment.[2] Most of the EGFR mutations occur in exons 18–21, and about 85% of the EGFR mutations are either a deletion in exon 19 or L858R in exon 21, which all flank the ATP-binding pocket that is important for TKI activity.[3] The EGFR exon 19 deletion, or exon 21 L858R point mutation, is predictive of a treatment advantage with EGFR-TKIs therapy.[4]

However, only a few reports have described concomitant EGFR exon 19 deletion and exon 21 L858R point mutation. Thus, how these patients will respond to EGFR-TKIs treatment remains unclear. Here, we report three cases of NSCLC with concomitant EGFR exon 19 deletion and exon 21 L858R point mutation and evaluate the effectiveness of EGFT-TKIs treatment in these patients.

Methods for epidermal growth factor receptor mutation detection

In patients with local advanced or metastatic NSCLC, it is often difficult to obtain large tumor samples. The direct sequencing method has poor sensitivity for the detection of EGFR mutations in a mixed tissue of normal and tumor cells.

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Access this article online

Quick Response Code:

Website: www.ijcep.org

DOI: 10.4103/ijcep.ijcep_32_17

How to cite this article: Yunyun L. Coexistence of epidermal growth factor receptor 19 deletion and 21 point mutation in nonsmall cell lung cancer: A report of 3 cases. Int J Clin Exp Physiol 2017;4:157-9.

Therefore, we used the scorpion amplification refractory mutation system (ARMS), which is a polymerase chain reaction (PCR)-based method[5] with a sensitivity ranging from 90% to 99%. The ARMS is a fluorescence-based method for specific detection of PCR production with an enhanced sensitivity of about 1% and is more commonly used for EGFR mutation detection in small tumor samples.[6] We prepared tumor tissue samples from the patients in our cases for EGFR mutation testing.

Case Report

The three cases were diagnosed as lung adenocarcinoma with concomitant EGFR exon 19 deletion and exon 21 L858R point mutation. The patients were treated with EGFR-TKIs. On RECIST response evaluation after 1 month, all three patients showed a partial response. The patients' information and the treatment process are summarized in Table 1. No obvious adverse reactions occurred with oral administration of EGFR-TKIs, and patients' symptoms were improved during treatment as is shown in Figures 1a, b and 2a, b.

Discussion

To the best of our knowledge, this is the first report in which three patients exhibited double mutations in exons 19 deletion and 21 point mutation. Some of the clinicopathological features of EGFR double mutant NSCLC were seen in our cases, such as being female, lack of a smoking history, and adenocarcinoma histology. Patients with activated EGFR mutants developed resistance eventually, with a median progression-free survival (PFS) of approximately 8–11 months when treated with EGFR-TKIs.[7] To overcome such resistance, the development of next-generation EGFR-TKIs has been actively pursued. Amazingly, the third-generation EGFR-TKIs, such as AZD9291, have demonstrated antitumor activity in both sensitizing and resistant EGFR mutation tumors preclinically, with a low rate of adverse effects. The Oral Abstract Session of 2015 American Society of Clinical Oncology reported that osimertinib treatment results in an objective response rate (ORR) of 70% and the median PFS had not yet been reached. The disease control rate was 97%. Overall, the 3- and 6-month PFS rates were 93% and 87%, respectively. In a second-line setting, after the failure of EGFR-TKI harboring exon 20 T790M, osimertinib was confirmatory improved PFS compared to the platinum-pemetrexed combination administered in the phase III trial (AURA3 trial) conducted by Mok *et al*. The median PFS as the primary endpoint was successfully completed at 10.1 months for the osimertinib arm and over 4.4 months for the chemotherapy arm (hazard ratio [HR]: 0.30; 95% confidence interval [CI]: 0.23–0.41; $P < 0.001$). The ORR was 71% versus 31% for osimertinib and chemotherapy, respectively (HR: 5.39; 95% CI: 3.47–8.4; $P < 0.001$).[8] Regrettably, our cases were not further detected after resistance.

Our three cases were particularly interesting because of the abnormality of two mutations in one potential "tumor-driving" receptor gene in a single tumor. Whether tumor progression

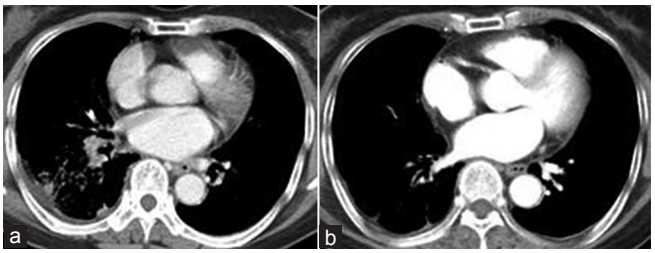

Figure 1: (a) Computed tomography of Case 1: Nonsmall cell lung cancer patient before tyrosine kinase inhibitor treatment. (b) Computed tomography of Case 1: Nonsmall cell lung cancer patient after tyrosine kinase inhibitor treatment

Table 1: The patients' information and the treatment process

	Case 1	Case 2	Case 3
Age (years)	64	43	54
Gender	Female	Female	Female
Diagnosis	Right lower lobe lung adenocarcinoma with multiple metastasis in bilateral pulmonary and lymph nodes of the mediastinum and bilateral lung hilus	Adenocarcinoma of the left lung with multiple pulmonary nodules bilaterally and enlargement of lymph nodes of the mediastinum	Right lower lung with right pleural metastasis
ECOG PS[10] score	3	1	1
Previous medical history	No	No	No
TNM stage	cTXN3M1	cT1N3M1	cT1N0M1
Previous surgical treatment/ chemotherapy treatment	No	Left lower lobectomy and lymphadenectomy followed by adjuvant chemotherapy with cisplatin and gemcitabine	First-line chemotherapy with cisplatin and pemetrexed
EGFR-TKIs treatment	Icotinib, 125 mg/day, three times a day	Icotinib, 125 mg/day, three times a day	Erlotinib (150 mg/day)
PFS	7.6 months	15.3 months	12 months
Tumor progression status	Tumor enlarge	Having new metastasis	Tumor enlarge
EGFR mutation testing again after tumor progression	No	No	No

ECOG PS: Eastern Cooperative Oncology Group performance status, EGFR: Epidermal growth factor receptor, EGFR-TKIs: EGFR-tyrosine kinase inhibitors, PFS: Progression-free survival, TNM: Tumor, node, and metastasis

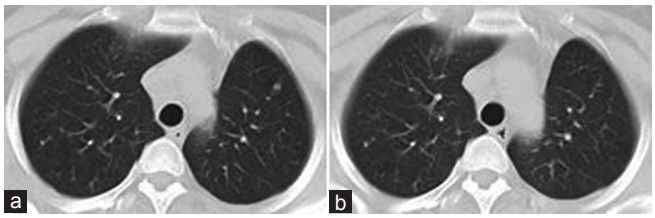

Figure 2: (a) Computed tomography of Case 2: Nonsmall cell lung cancer patient before tyrosine kinase inhibitor treatment. (b) Computed tomography of Case 2: Nonsmall cell lung cancer patient after tyrosine kinase inhibitor treatment

was dependent on both mutations or on only one of the two mutations was unclear in the three cases. Moreover, the PFS was not significantly improved in these EGFR double-positive NSCLC patients. Because the number of cases was small, these issues need to be further studied.

In the present cases, we found that the three patients had a longer PFS, and the PS was better. This is consistent with previously reported outcomes. Yang *et al*. analyzed the quality of life (QoL) of 290 patients in the INFORM study, including 145 patients in the gefitinib arm and 145 patients in the placebo arm. They reported that patients with an improvement in QoL had longer PFS (FACT-L [Functional of Assessment of Cancer Therapy-Lung]: 9.4 m versus 2.8 m versus 2.7 m, $P < 0.001$; TOI [Trial Outcome Index]: 9.9 m versus 2.8 m versus 2.1 m, $P < 0.001$; LCS [Lung Cancer Subscale]: 9.4 m versus 2.9 m versus 2.1 m, $P < 0.001$).[9] Considering the effect of therapy from a patient perspective, the benefit in QoL is important. The improvement in QoL is likely ascribable to the lower treatment burden of oral administration in an outpatient setting and the better treatment outcome of PFS prolongation, both of which allow patients more time to spend with family and more opportunities to work in their remaining life.[10]

Conclusion

The present three cases showed some possible characteristics of concomitant EGFR exon 19 deletion and exon 21 L858R point mutation. However, patients with double genetic mutations showed better PFS after EGFR-TKI therapy. Therefore, we need more clinical cases to further characterize their features and study the EGFR-TKIs sensitivity corresponding to double genetic mutations.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Schiller JH, Harrington D, Belani CP, Langer C, Sandler A, Krook J, *et al.* Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med 2002;346:92-8.
2. Xu C, Zhou Q, Wu YL. Can EGFR-TKIs be used in first line treatment for advanced non-small cell lung cancer based on selection according to clinical factors? - A literature-based meta-analysis. J Hematol Oncol 2012;5:62.
3. Lynch TJ, Bell DW, Sordella R, Gurubhagavatula S, Okimoto RA, Brannigan BW, *et al.* Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. N Engl J Med 2004;350:2129-39.
4. Miller VA, Riely GJ, Zakowski MF, Li AR, Patel JD, Heelan RT, *et al.* Molecular characteristics of bronchioloalveolar carcinoma and adenocarcinoma, bronchioloalveolar carcinoma subtype, predict response to erlotinib. J Clin Oncol 2008;26:1472-8.
5. Ellison G, Zhu G, Moulis A, Dearden S, Speake G, McCormack R, *et al.* EGFR mutation testing in lung cancer: A review of available methods and their use for analysis of tumour tissue and cytology samples. J Clin Pathol 2013;66:79-89.
6. Young EC, Owens MM, Adebiyi I, Bedenham T, Butler R, Callaway J, *et al.* A comparison of methods for EGFR mutation testing in non-small cell lung cancer. Diagn Mol Pathol 2013;22:190-5.
7. Shepherd FA, Bunn PA, Paz-Ares L. Lung cancer in 2013: State of the art therapy for metastatic disease. Am Soc Clin Oncol Educ Book 2013;23:339-46.
8. Mok TS, Wu YL, Ahn MJ, Garassino MC, Kim HR, Ramalingam SS, *et al.* Osimertinib or platinum-pemetrexed in EGFR T790M-positive lung cancer. N Engl J Med 2017;376:629-40.
9. Yang YP, Ma YX, Huang Y, Zhao YY, Fang WF, Hong SD, *et al.* QoL analyses from INFORM study, a phase III study of gefitinib versus placebo as maintenance therapy in advanced NSCLC. Sci Rep 2015;5:11934.
10. Narita Y, Matsushima Y, Shiroiwa T, Chiba K, Nakanishi Y, Kurokawa T, *et al.* Cost-effectiveness analysis of EGFR mutation testing and gefitinib as first-line therapy for non-small cell lung cancer. Lung Cancer 2015;90:71-7.