Efficacy of osimertinib in a metastatic lung adenocarcinoma patient harboring somatic EGFR delL747_S752 and germline BIM deletion polymorphism: a case report and literature review

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Background: Epidermal growth factor receptor (EGFR) exon 19 deletion (19del) and the exon 21 L858R point mutation are the most established predictive factors for the efficacy of EGFR-tyrosine kinase inhibitor (TKI) in patients with non-small cell lung cancer (NSCLC). To date, more than 50 subtypes of EGFR 19dels have been documented in NSCLC. Evidence suggests that different subtypes of 19dels exhibit different survival outcomes to EGFR-TKI treatment. Whether patients harboring EGFR Leu747_Ser752 deletion (delL747_S752) as an uncommon subtype of 19dels benefit from EGFR-TKIs has not been investigated. BIM (B-cell chronic lymphocytic leukemia/lymphoma-like 1) deletion polymorphism is common in East Asian with EGFR-mutant NSCLC. Currently, the predictive role of BIM deletion polymorphism in patients with EGFR-mutant NSCLC treated with osimertinib remains debatable.

Case Description: A 34-year-old female patient was diagnosed with stage IV lung adenocarcinoma (LUAD) harboring somatic EGFR del L747_S752 and germline BIM deletion polymorphism in August 2018. She obtained benefit from the front-line treatment of osimertinib lasting for 8 months. After progression from osimertinib, the patient received bevacizumab combined with platinum-doublet chemotherapy, stereotactic radiosurgery plus osimertinib and crizotinib, anlotinib, and a programmed cell death-1 inhibitor sintilimab plus bevacizumab and docetaxel. She succumbed to her disease in June 2020 with an overall survival of 23 months.

Conclusions: Our work suggests that osimertinib might be a compromised treatment option for NSCLC patients with somatic EGFR delL747_S752 and germline BIM deletion polymorphism. Development of more effective regimens are needed for this small subset of NSCLCs.

Keywords: Lung adenocarcinoma (LUAD); osimertinib; EGFR delL747_S752; BIM deletion polymorphism; case report

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Introduction

Exon 19 deletion (19del) and the exon 21 L858R point mutation are the most established predictive factor for the efficacy of epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI) in patients with non-small cell lung cancer (NSCLC). EGFR 19dels comprise a heterogeneous group of genetic aberrations, including deletions, substitutions, and insertions. Different subtypes of 19dels exhibit heterogeneous response to EGFR-TKIs treatment. More than 50 subtypes of EGFR 19dels have been identified in NSCLC (1-7). delE746_A750 (65.9–72.3%), delL747_P753insS (6.1–8.1%) and delL747_
T751 (5.8–7.7%) are the most frequent subtypes (2,4,5,7). Published literature have reported the associations between common subtypes of EGFR 19dels and survival outcomes in NSCLC patients who received EGFR-TKI therapy (1,2,4,5,7). However, the efficacy of EGFR-TKI in NSCLC patients harboring EGFR L747_S752 deletions (delL747_S752) as an uncommon subtype of 19dels remains elusive.

BIM, also known as B-cell chronic lymphocytic leukemia/lymphoma (Bcl-2)-like 11, encodes BCL2L11, which is a member of Bcl-2 protein family. BIM deletion polymorphism, resulting from the 2903-bp genomic deletion occurring in intron 2 of BIM gene, is commonly seen in East Asian and Hispanic patients with EGFR-mutant lung cancer with an incidence rate of 11.3–18.6% (8,9). Some studies reported that BIM deletion polymorphism predicted an unfavorable prognosis in EGFR-mutant NSCLC patients when treated with EGFR-TKIs (8,10-12), but other studies failed to find an association between the presence of BIM deletion polymorphism and the clinical outcome in these patients (13,14). Moreover, an array of studies have demonstrated that increased BIM at the RNA level enhances killing of NSCLC cells by the EGFR-TKIs, which contributes to the molecular mechanisms leading to tumor regression (15-18).

Here, we present a metastatic lung adenocarcinoma (LUAD) patient harboring EGFR delL747_S752 and BIM deletion polymorphism who benefited from third-generation EGFR-TKI osimertinib with a progression-free survival (PFS) of 8 months. We present the following case in accordance with the CARE reporting checklist (available at https://tcrr.americanjournal.com/article/view/10.21037/tcr-22-1050/rc).

Case presentation

In August 2018, a 34-year-old female presented with fever at night and lower back pain. Ultrasound-guided biopsy of right supraclavicular lymph nodes revealed a metastatic carcinoma. She was diagnosed with stage IV LUAD with metastases to brain, bone, liver, right kidney gland, bilateral hilar lymph nodes, left and right supraclavicular lymph nodes, retroperitoneal lymph node and left external iliac lymph nodes. Plasma-based genotype was performed and revealed the presence of EGFR 19del (delL747_S752) with an allele frequency (AF) of 38.8% and BIM deletion polymorphism. The patient’s treatment history is shown in Figure 1. She was initially given with icotinib combined with zoledronic acid. Her symptoms of lower back pain and fever were subsequently relieved. On October 20, 2018, the patient was switched to oral osimertinib based on the findings from FLAURA trial reported in January 2018 (19) that osimertinib demonstrates a longer progression-free survival than gefitinib/erlotinib in Asian patients with EGFR-mutant advanced NSCLC. In March 2019, the chest and abdominal computed tomography (CT) scans showed partial response (PR) (>50% reduction) in the primary lung tumor and metastatic liver tumor, and the magnetic resonance imaging (MRI) showed complete remission of the brain metastases (Figure 2). In June 2019, the chest and abdominal CT scans showed the presence of nodular mass in bilateral lungs, the enlarged primary lung tumor and a metastatic liver tumor (Figure 2A, 2B). The brain MRI

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showed a newly developed lesion in the right frontal lobe with a diameter of 2 mm (Figure 2C). The assessment of tumor response was progressive disease (PD) with a PFS of 8 months (Figure 1). We also reviewed the previously reported clinical outcomes to EGFR-TKIs in NSCLC patients harboring different 19del, which are summarized in Table 1.

The patient was treated with bevacizumab plus pemetrexed and carboplatin as second-line therapy on July 24, 2019. Meanwhile, next-generation sequencing (NGS) analysis using a panel covering 520 cancer-related genes (20) was performed on the plasma sample after failure of osimertinib treatment. The results revealed a blood tumor mutation burden (bTMB) of 9.5 mutations/Mb and the presence of new alterations, including \textit{EGFR} G724S, \textit{MET} amplification with a copy number of 4.0, \textit{EML4-ALK} fusion and \textit{CCDC6-RET} fusion. After three courses of the treatment, the brain MRI showed PD with newly developed metastases to the brain and enlarged tumor in right frontal lobe with a diameter of 4 mm (Figure 2C). The treatment response assessment was stable disease (SD). She had loss of appetite during treatment of osimertinib plus crizotinib. In January 2020, the chest CT scans demonstrated PD with enlarged bilateral lung metastatic lesions and newly developed lesions in the lower lobe of the left lung (Figure 2A,2C). At PD, NGS analysis was performed on plasma sample. NGS results showed the presence of new alterations, \textit{EGFR} C797S and loss of \textit{MET} amplification. She was administered with anlotinib as a single agent in February 2020. After one month of the treatment, the chest CT and brain MRI revealed newly developed metastatic lesions in bilateral lungs and brain metastatic tumors (Figure 2A,2C). The assessment of the response to fourth-line treatment was PD. In April, 2020, she was treated with sintilimab plus bevacizumab and docetaxel. The patient underwent nausea, vomiting, and muscle pain. After two months of the treatment, she succumbed to her disease in June 2020.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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| Publication       | Year of publication | Clinical setting of EGFR-TKI treatment                                                                 | EGFR 19dels | No. of patients | Median PFS or PFS in mo | P value |
|-------------------|---------------------|-------------------------------------------------------------------------------------------------------|-------------|-----------------|--------------------------|---------|
| Chung et al. (5)  | 2012                | First-line, second-line, third-line, or subsequent line gefitinib/erlotinib                          | Delta E746  | 219             | 9.8                      | 0.665   |
|                   |                     |                                                                                                       | Delta E747  | 79              | 10.5                     |         |
|                   |                     | Non-LRE deletions                                                                                   |             |                 |                          |         |
|                   |                     | Delta751-759insn                                                                                     | 1           | NA              |                          |         |
|                   |                     | Delta751-e758                                                                                       | 1           | NA              |                          |         |
|                   |                     | S752-i759                                                                                           | 1           | NA              |                          |         |
|                   |                     | Delr748-P753                                                                                         | 1           | 6.6             |                          |         |
|                   |                     | Delr748-S752                                                                                         | 1           | 20.8            |                          |         |
|                   |                     | Dels752-i759                                                                                         | 1           | 3.3             |                          |         |
|                   |                     | Dels752-i759                                                                                         | 1           | 2.7             |                          |         |
|                   |                     | Delt751-i759insd                                                                                    | 1           | 5.9             |                          |         |
|                   |                     | Delt751-i759insd                                                                                    | 1           | 4.9             |                          |         |
|                   |                     | Delt751-i759insn                                                                                    | 1           | 4.8             |                          |         |
| Lee et al. (1)    | 2013                | First-line gefitinib/erlotinib                                                                       | Delta E746  | 46              | 14.2                     | 0.021   |
|                   |                     |                                                                                                       | Delta L747  | 16              | 6.5                      |         |
|                   |                     | Dell747_p753insss                                                                                  | 10          | 6.5 (2.1–15.3)  |                          | 0.021   |
|                   |                     | Dele746_A750                                                                                         | 42          | 12.4            |                          |         |
|                   |                     | Mix insertions/substitution                                                                          | 12          | 22.3 (0.7–63)   |                          |         |
|                   |                     | Dell747_k754insank                                                                                   | 1           | 0.7             |                          |         |
|                   |                     | Dell747_a750insp                                                                                    | 1           | 1.5             |                          |         |
|                   |                     | Delt751_i759insn                                                                                    | 1           | 2.4             |                          |         |
|                   |                     | Dell747_a750insp                                                                                    | 1           | 5.7             |                          |         |
|                   |                     | Dele746_t751insv                                                                                    | 1           | 7.6             |                          |         |
|                   |                     | Delt751_i759insss                                                                                  | 1           | 13.3            |                          |         |
|                   |                     | Dele746_t751insl                                                                                    | 1           | 16.1            |                          |         |
|                   |                     | Dell747_a755inssk                                                                                   | 1           | 18.3            |                          |         |
|                   |                     | Dele746_t751insva                                                                                   | 1           | 22.3            |                          |         |
|                   |                     | Dell747_t751insp                                                                                    | 1           | 40.6            |                          |         |
|                   |                     | Dele746_s752insv                                                                                    | 1           | 43.1            |                          |         |
|                   |                     | Dele746_a750insap                                                                                   | 1           | 63              |                          |         |
|                   |                     | Non-LRE deletions                                                                                    |             |                 |                          |         |
|                   |                     | Delta T751                                                                                          | 1           | 13.3            |                          |         |
|                   |                     | Delta T751                                                                                          | 1           | NR              |                          |         |
Table 1 (continued)

| Publication       | Year of publication | Clinical setting of EGFR-TKI treatment | EGFR 19dels         | No. of patients | Median PFS or PFS in mo | P value |
|-------------------|---------------------|---------------------------------------|---------------------|-----------------|-------------------------|---------|
| Kaneda et al. (4) | 2014                | First-line, second-line or subsequent line gefitinib/erlotinib | Delta E746         | 11.7            | 0.022                   |
|                   |                     |                                       | Delta E747         | 10.0            |                         |
|                   |                     |                                       | With ins/sub       | 10.0            | 0.024                   |
|                   |                     |                                       | Without ins/sub    | 11.7            |                         |
| Zhao et al. (2)   | 2020                | First-line gefitinib/erlotinib        | Delta E746         | 78              | 12.1                    | 0.816   |
|                   |                     |                                       | Delta L747         | 15              | 10.6                    |
|                   |                     |                                       | Delta L747 with insertions | 8 | 8.3 | 0.017 |
|                   |                     |                                       | Delta L747 without insertions | 7 | 15.0 |
|                   |                     |                                       | Dele746_A750       | 72              | 12.1                    | 0.795   |
|                   |                     |                                       | Dele746_a750ins    | 6               | 10.0                    |
|                   |                     |                                       | Deletions with insertion | 14 | 9.5 | 0.102 |
|                   |                     |                                       | Deletions without insertion | 76 | 12.6 |
| Peng et al. (3)   | 2020                | First-line gefitinib/erlotinib        | Uncommon 19delins  | 93              | 19                      | 0.0016  |
|                   |                     |                                       | Common19del (E746_A750) | 93 | 13 |
|                   |                     |                                       | Dell747_p753ins    | 23              | 18                      | 0.58    |
|                   |                     |                                       | Dell747_a750insp   | 24              | 20                      |
| Xu et al. (6)     | 2020                | First-line gefitinib/erlotinib/icotinib | Delta E746         | 126             | 11.4                    | <0.001  |
|                   |                     |                                       | Delta L747         | 62              | 17.2                    |
|                   |                     |                                       | Delta T51 or S752  | 6               | 2.9                     |
| Wang et al. (7)   | 2021                | First-line gefitinib/erlotinib/icotinib | Del L747_T751delinsP | 6 | 18.7 | 0.035 |
|                   |                     |                                       | Others              | 35              | 13.1                    |
| Our work          | 2022                | First-line osimertinib                | DellL747_S752      | 1               | 8                       |

No., number; NSCLC, non-small cell lung cancer; EGFR, epidermal growth factor receptor; PFS, progression-free survival; mo, month; delta E746, deletions starting from E746; delta L747, deletions starting from L747; ins/sub, insertions/substitutions; NR, the patient was still free from progression after taking EGFR-TKI for 2.4 months; TKI, tyrosine kinase inhibitor; NA, the PFS data of those patients was unavailable; delta T751, deletions starting at T751; Non-LRE, deletions not encompassing the entire amino acid string from L747 through E749; 19delins, exon 19 insertion-deletion variants; others, delL747_P753delinsS, L747_A750delinsP, and E746_S752delinsV.

Discussion

To the best of our knowledge, we reported for the first time that a metastatic LUAD patient with EGFR delL747_S752 and BIM deletion polymorphism received osimertinib treatment. A prior study reported by Chung et al. (5) is the first to subcategorize EGFR 19dels into three groups, deletions starting on codon E746 (delta E746), deletions starting on codon L747 (delta L747), deletions not involving the entire amino acid string from L747 through E749 (Non-LRE deletions). Chung et al. (5) and Zhao et al. (2) found that subgroup of 19dels was not associated with PFS in NSCLC patients, but have obtained conflicting results.
NSCLC patients treated with first-generation EGFR-TKIs. However, some studies demonstrated the presence of association between subgroup of 19dels and clinical outcome to EGFR-TKI in NSCLC patients. Lee et al. (1) revealed that delta L747 predicted a significantly shorter PFS compared to delta E746 (6.5 vs. 14.2 months) in NSCLC patients treated with first-generation EGFR-TKIs as first-line treatment. The similar results (10.0 vs. 11.7 months) were observed in a cohort of NSCLC patients treated with EGFR-TKIs as any line of first-generation EGFR-TKIs (4). In contrast, Xu et al (6) reported that delta L747 predicted a longer PFS than delta E746 (17.2 vs. 11.4 months). The controversial results may be attributed to several factors. Some studies (1-3,6) only included patients who were treated with EGFR-TKIs as first-line setting, in contrast, others included patients using EGFR-TKIs as first-, second- or later-line treatment (4,5).

EGFR delL747_S752 is an uncommon subtype of 19dels, accounting for 0.6–3.6% of cases with EGFR 19dels (2,4,5). Due to its rarity, patients with this rare subtype are commonly pooled for investigating the clinical outcomes to EGFR-TKIs in NSCLCs. There are very few reports in the efficacy of EGFR-TKI against delL747_S752. The previous study (2) has demonstrated delta L747 with insertions (n=22) predicted a significantly shorter PFS than delta L747 without insertions (n=16) (8.3 vs. 15.0 months) in a cohort of 208 NSCLC patients treated with first-line EGFR-TKIs. Only one patient (6.25%, 1/16) harboring EGFR delL747_S752 was observed in delta L747 without insertions group (2). The true efficacy of EGFR-TKI in EGFR delL747_S752 patients could be masked by other patients. Evidence suggested that patients carrying EGFR delL747_S752 showed a good response (an objective response rate of 88.9%) to gefitinib or erlotinib in first-, second- or later-line treatment (4,5).

In conclusion, our work revealed that an EGFR delL747_S752/BIM deletion polymorphism double-positive LUAD patient obtained a PFS of 8 months with osimertinib treatment. Our work suggests that osimertinib might be a compromised treatment option for NSCLC patients with EGFR delL747_S752 and BIM deletion polymorphism. Further studies are needed to develop the more effective regimen for this small subset of NSCLCs, such as afatinib followed by osimertinib.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-1050/coif). SJ declares that this study was supported by the project from the Shenzhen Science and Technology Program (Grant No. RCJC20200714114436049) and Cancer Hospital, Chinese Academy of Medical Sciences, Shenzhen Center/Shenzhen Cancer Hospital Research Project (No. SZ2020ZD006). The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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