Case Report

Novel *ALK* mutation with durable response to brigatinib—a case report

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Abstract: Anaplastic lymphoma kinase (*ALK*) tyrosine kinase inhibitors are the preferred initial treatment for *ALK* rearranged non-small cell lung cancer (NSCLC). While initial responses to next-generation inhibitors are robust, acquired resistance is expected for nearly all patients. Resistance is often mediated by point mutations along the solvent front. Use of the acquired mutational profile to guide therapy is still investigational and largely based on preclinical data demonstrating sensitivity of resistant cell lines to available kinase inhibitors. Here, we describe outcomes after development of an *ALK* L1196Q mutation. We present a patient with stage IV *ALK* rearranged lung cancer received who received first line crizotinib at 250 mg twice daily, then at progression, second line alectinib at 600 mg twice daily. When radiographic evidence of progression was noted, a biopsy was performed. Next generation sequencing (NGS) identified an acquired *ALK* L1196Q mutation. The patient was treated with third line brigatinib, at 90 mg daily and escalating to 180 mg daily, and achieved a partial response that is still ongoing, one year later. We highlight false-negative *ALK* mutation results when only plasma is used, particularly in early metastatic disease. We also discuss how the use of specific *ALK* resistance mutations to guide therapy is clinically relevant is being investigated.

Keywords: Anaplastic lymphoma kinase (*ALK*); L1196Q; brigatinib; acquired resistance; case report

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Introduction

Rearrangements in the anaplastic lymphoma kinase (*ALK*) gene occur in about 6–13% of non-small cell lung cancer (NSCLC) (1). When present, ALK tyrosine kinase inhibitors are the clear standard of care for these tumors, based on improvements in response rate, progression-free survival and tolerability compared to cytotoxic chemotherapy (2). While responses with newer, next-generation ALK TKIs are increasingly durable, most patients eventually develop acquired resistance, often mediated by point mutations within the ALK kinase solvent front (3). Investigation into how specific acquired mutations predict sensitivity to ALK kinase inhibitors is ongoing, but much of the available evidence is preclinical. We present the following case in accordance with the CARE Guideline. Here, we discuss an *ALK* L1196Q mutation emerging during treatment with alectinib for a NSCLC harboring an *EML4-ALK* fusion that then responded to third-line brigatinib therapy. We present the following case in accordance with the CARE reporting checklist (available at http://dx.doi.org/10.21037/tlcr-20-145).

Patient information

A 60-year-old female presented in November 2016 with cough and right sided flank pain. She was a never smoker. Diagnostic CT imaging revealed a primary left lower lobe lung mass, pathologically enlarged mediastinal and hilar lymphadenopathy and multiple liver metastases. A CT guided liver biopsy confirmed stage IV lung adenocarcinoma and molecular testing identified an *EML4-*

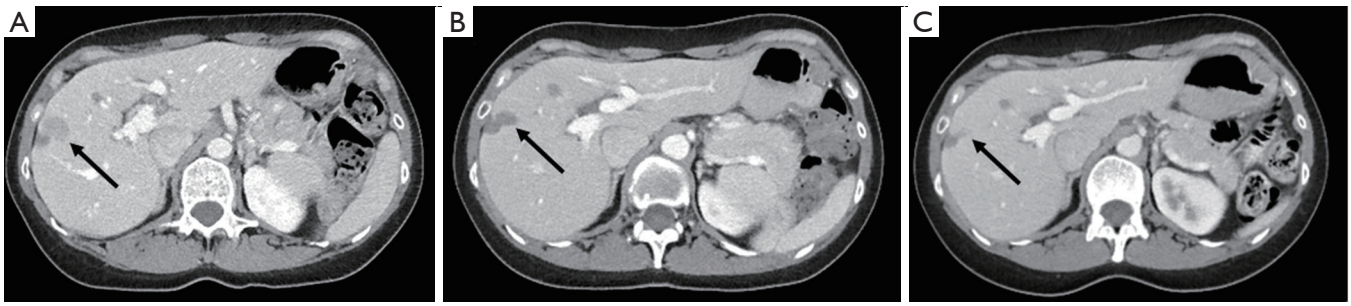

Figure 1 Contrast enhanced CT scan images completed in (A) October 2018, (B) December 2018, and (C) October 2019 demonstrating progressive decrease in the size of a peripheral liver metastasis (arrow) that was found to harbor an *ALK* L1196Q mutation.

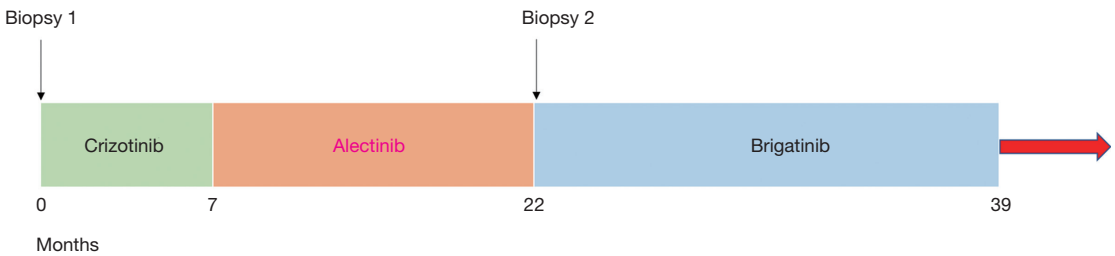

Figure 2 Timeline.

ALK fusion. She was treated with crizotinib 250 mg twice daily and achieved a partial response that lasted 7 months. Scans then showed progression in the liver and new brain metastases. She began second line alectinib 600 mg twice daily and achieved a rapid response in both the liver and brain metastases which was maintained for 15 months. A routine CT scan then revealed a new liver metastasis; all other disease remained unchanged and there were no new symptoms or findings on exam. A positron emission tomography (PET) scan revealed fluorodeoxyglucose (FDG) activity in the new liver lesion with no PET-avid disease in the other areas. Circulating tumor DNA (ctDNA) testing showed only the original *EML4-ALK* fusion with no new *ALK* mutations. Biopsy of the new liver lesion confirmed NSCLC and NGS identified the known *EML4-ALK* fusion as well as an acquired *ALK* L1196Q mutation. She began third-line brigatinib 90 mg daily, escalating to 180 mg daily in November 2018. A repeat PET/CT in December 2018 showed resolution of FDG uptake in the new liver metastasis with no change in any other sites of disease (*Figure 1*). Serial imaging of brain and body has shown ongoing disease control now 17 months after starting third line brigatinib (*Figure 2*). She has been tolerating treatment well without any untoward side effects.

All procedures performed in studies involving human participants 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). Informed consent was obtained from the subject for publication of this case report.

Discussion

ALK kinase inhibitors are the standard initial therapy for NSCLC harboring an *ALK* fusion and provide rapid, deep and durable responses. While crizotinib was the first agent approved in this setting, next-generation ALK inhibitors such as alectinib and brigatinib have further improved first-line outcomes (4,5). Resistance to next-generation ALK inhibitors such as alectinib is complex and strategies to overcome and prevent resistance are under investigation. Other ALK kinase inhibitors have shown activity, and lorlatinib is currently approved for use after progression on alectinib.

At this time, use of subsequent ALK inhibitors is empiric, but detection of specific, acquired *ALK* point mutations through NGS is increasingly feasible. Acquired *ALK* mutations are present in about 20% of patients

following first-line crizotinib but detected in more than half of patients who progress on first-line alectinib or ceritinib (6-8). Existing data predicting sensitivity to ALK inhibitors based on the acquired mutation profile could potentially guide therapeutic decisions but is largely preclinical (8-10).

The *ALK* gatekeeper mutation L1196M is one of the more commonly described resistance mutations (11). Brigatinib is expected to maintain activity in the presence of the *ALK* L1196M mutation based on preclinical models (12). The *ALK* L1196Q mutation encountered in this case has not yet been described clinically but would be expected to have similar properties to L1196M. A preclinical report has described *ALK* 1196Q-mediated resistance to both alectinib and crizotinib (13). While use of brigatinib was, in this case, successful, it is a single case which remains a major limitation in interpretation.

Conclusions

This report is the first clinical description of an *ALK* L1196Q mutation emerging on alectinib followed by successful and durable treatment with brigatinib. This case also highlights the potential for false-negative *ALK* mutation results when only plasma is used, particularly when progression is not widespread. In this case, tissue biopsy and molecular testing was required to reveal the mechanism of resistance—and care was taken that the biopsy was of the new liver lesion and not one of the responding lesions, which would not have offered useful clinical information. Use of specific *ALK* resistance mutations to guide therapy is rational but not yet clinically validated. Fortunately, this very approach is the focus of the ALK Master Protocol: an ongoing prospective, cooperative group trial (NCT 03737994) which will hopefully shed more light on the increasingly relevant field of ALK kinase inhibitor resistance.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at http://dx.doi.org/10.21037/tlcr-20-145

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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 studies involving human participants 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). Informed consent was obtained from the subject for publication of this case report.

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