Case Report

Clinical Response and Safety of Alternating Daily Dosage of Crizotinib due to Side Effects in Advanced NSCLC patient harboring ROS1-rearrangement: A Case Report

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Abstract

Background: Advanced lung cancer has the lowest overall survival than other stage and tyrosine kinase inhibitor (TKI) are promising to prolong life and prevent disease progression. ROS1 rearrangement was very rare and constitute around 1.4 % of all NSCLC. Previous preclinical and clinical trial have reported the efficacy and safety of crizotinib against advanced NSCLC with ROS1 rearrangement, but little is known about its efficacy with nonstandard dosage.

Case: A female, 58 years old, with no history of cancer nor smoking, came with persistent chest pain and cough for three months. The patient was then diagnosed with advanced lung cancer by FDG-PET CT Scan. The biopsy confirmed adenocarcinoma with genotyped ROS1-rearrangement. After receive standar dose of 200 mg bid, the patient intolerated and treatment plan was adjusted with 200 mg of alternated daily dosage (one-day on-off drug administration). Fortunately, the intolerance symptoms were alleviated and showed positive response during 3-years therapy.

Discussion: Pulmonary tuberculosis has been linked to pneumothorax in HIV-associated TB patients. This study is done to better our understanding of the link between the two. The patient had active pulmonary tuberculosis as well as HIV and a rare case of bilateral pneumothorax in the ER.

Conclusion: This case showed that advanced NSCLC with ROS1 rearrangement has positive response to crizotinib despite using alternating daily dose, with good response during 3 years and on.

Keywords: Crizotinib, NSCLC, ROS1 rearrangement

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INTRODUCTION

Advanced lung cancer has the lowest overall survival than other stage, thus pose great challenge to the physician.[1] By far, current available treatment could not optimize the survival rate. However, immunotherapy and targeted therapy, i.e. tyrosine kinase inhibitors are promising to prolong life and prevent disease progression, especially for non-small cell lung cancer (NSCLC).[2] The decision of prescribing small molecules kinase inhibitor is based on the present of molecular profile of lung cancer, for example, C-ros oncogene 1 (ROS1) and anaplastic lymphomakinase (ALK).[3]

Lung cancer detected positive for both markers are proven to be sensitive to multiple receptor protein kinases inhibitors, for instance crizotinib (first generation), ceritinib (second generation), and lorlatinib (third generation).[4–6] Previous preclinical and clinical trial have reported the efficacy and safety of crizotinib against NSCLC, especially in late stage.[4,7–13] However, since the cost for the treatment was high, small molecule kinase inhibitor is not the first line treatment in lung cancer with ROS1-positive especially in developing countries. Here, we report our case of naïve-advanced NSCLC with ROS1-positive treated with the first generation of small molecule inhibitor of multiple receptor tyrosine kinases, crizotinib, as first-line therapy. The patient showed both clinical and radiological remission and long-term progression free-survival (PFS).

CASE

A 58 years old housewife with no history of cancer and smoking, came with persistent chest pain

and cough for three months. The patient later diagnosed advanced lung cancer with liver nodule (metastasis) through CT Scan and FDG-PET Scan (figure 1A). Biopsy confirmed adenocarcinoma with genotyped ROS1-rearrangement, EGFR wild type, ALK-negative, and PD-L1 0% through next-generation sequencing (NGS).

As the diagnosis confirmed with ROS-1 positive, the patient was then initiated with crizotinib 250 mg bid per day without starting other therapy regimens. The patient experienced diarrhea 8–10 times/days, nausea and vomiting with mild dehydration with limited daily activities after 1 week administration. Common terminology criteria for adverse events (CTCAE) grade 3–4. Patient was hospitalized and treated with loperamide, proton pump inhibitor and rehydration while crizotinib was stopped. No evidence of gastrointestinal infection based on stool evaluation. The treatment was started again after 1 week recovery with lowering dose 200 mg ones a day. But after 1 week therapy, the patient remain intolerant.

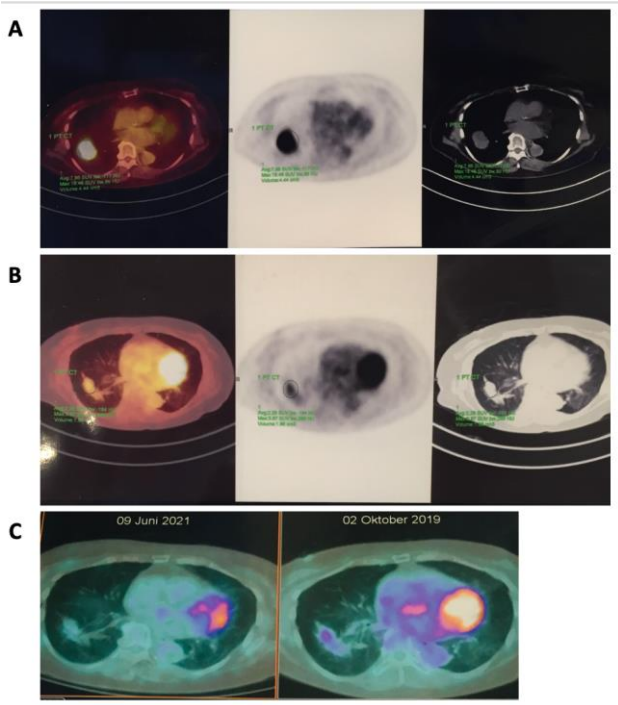

Figure 1. A) ^{FDG}-PET-CT scan in 2018 showed pulmonary mass with enhanced uptake; B) PET-CT scan taken 1 year later show stable disease; and C) PET-CT scan after 3-years therapy showed decreased mass with fibrotic loci and no metabolic activity.

The diarrhea and nausea reappeared in milder symptoms (<4 times) despite loperamide and symptomatic medication. The patient decided to stop the treatment due to side effects again but started again the crizotinib with adjusted dose of 200 mg alternate-day dosing. Fortunately, increased. But when the dosage was increasing 200 mg twice daily, the symptoms reappeared and inconvenient for the patients. The alternate-day dosing was then continued since the patient has minimal side effect and significant improvement in respiratory symptoms after 2 weeks.

The patient maintains symptoms' improvement during evaluation in the first 3- and 6-months treatment with partial response based on thoracic CT scan. The tumor reduced in size from 4 cm in diameter to 1 cm. In the first year of therapy, the patient feels better subjectively. The patient also had achieved radiological partial response (Figure 1B) according to Response Evaluation Criteria in Solid Tumor Version 1.1 (RECISTv1.1). The tumor decreases in sized but still with metabolic activities and fibrotic foci. The patient continued her treatment. Thoracic CT scan were checked every 3–4 months during therapy.

After the third year of therapy, the patient continued showing partial response. FDG-PET scan (figure 1C) showed lung fibrosis without contrast enhancement, with tumor diameter <1 cm. The laboratory examination, including complete blood count, C-Reactive Protein (CRP), D-dimer, liver, and renal function, and (carcinoembryonic antigen) CEA, also remains stable, which was maintained until publication. At last, our patients showed an overall survival rate of 3 years and still on going.

DISCUSSION

ROS1 is the gene that encodes the tyrosine kinase receptor, located on chromosome 6q22 and ROS1-positive lung cancer is a type of lung cancer harboring a ROS1 gene rearrangement that is thought to be the driver mutations. The exact mechanism of mutation is translocation mutations which affect cell growth and division. ROS1-positive lung cancer is rare, approximately account 1–2% of

adenocarcinoma and 1.4% of the entire NSCLC.[14,15] Furthermore, ROS1-positive lung cancer is prevalent in middle-aged women who are never smoking.[16] Consistent with the study, our case also presents as a middle-aged female.

ROS1-positive lung cancer exhibits a phenotype of aberrant tyrosine kinase receptor and has been too active, which help the cancer cells to grow uncontrollable. Crizotinib, known as small molecule inhibitor of multiple receptor tyrosine kinases, has posed a benefit in ROS1 and ALK-positive lung cancer and developed to inhibit ligand binding and receptor oligomerization. In vitro data suggested the potent activity of crizotinib to downstream effector functions and inhibit apoptosis.[11]

Based on available clinical trials, crizotinib is administered perorally and with a daily dose of 250 mg bid and personally adjusted based on the occurrences of the side effect, such as visual disturbance, nausea, dizziness, fatigue, and decreased appetite.[4,9–13] EUCROSS clinical trial has also suggested reducing dose up to 200 mg twice daily and 250 mg of daily dosage for patients with intolerance symptoms.[11]

Rothenstein and Letarte did a review of ALK inhibitors side effects including crizotinib.[17] It is recommended to withhold crizotinib if grade 3 or grade 4 appear in the patient. In patients with diarrhea, infectious causes should be rule out. Loperamide could be used followed with dietary modification and adequate hydration are strongly recommended. If the adverse events were recovered, it is recommended to reduce the dose at 200 mg twice daily.[17]

Alternative way to introduced crizotinib after side effect is desentization procedure in cases with skin adverse events.[18] Crizotinib is given orally starting with 10 mg and increase to 25, 50 and 100 with interval of 30 minutes each. During desensitization protocol, the skin lesion will be observed carefully. This desensitization protocol could be used in skin rash or rapid onset skin hypersensitivity due to crizotinib. Unfortunately, no recommendation for crizotinib desensitization protocol other than for rapid onset skin hypersensitivity.[18]

Our patient experienced gastrointestinal intolerance symptoms with 250 mg po. For that reason, the dose was reduced to acceptable dose up to 200 mg with alternating daily dosage. To our knowledge, there is no report of efficacy and safety reducing the crizotinib with alternating dosage.

There is evidence that crizotinib is superior than chemotherapy (platinum-pemetrexed based) as the first-line and maintenance of therapy in advanced ROS1-positive lung.[19] Our case was unique in that she had prolonged PFS and OS longer with lower dose than reported in previous trial. Our finding infers the need for randomized controlled trials to confirm crizotinib alternating daily dose superiority over regular dosage in the purpose for both achieving maximum response rate and avoiding detrimental adverse effects.

LIMITATION

There are limitations in this case report. Despite the favorable response with alternating dose of crizotinib, there was no data regarding serum concentration of crizotinib in this case whether it was still within therapeutic dose and factors that affect its concentration in serum i.e., changes in crizotinib metabolism. We do not have data regarding details molecular characteristic/mutations of the tumor that might effect the treatment responses. Since this is only one case and the treatment protocol is not mention in the guideline, generalization into all NSCLC patients should be used with cautious.

CONCLUSION

Our case report showed that advanced NSCLC with ROS1 rearragement showed positive response to crizotinib alternating day as first line therapy and remain stable after 3 years, respectively, with acceptable side effects.

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CONFLICT OF INTEREST

None.

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