Pulmonary Embolism And Bradycardia in a NSCLC Patient Treated With Crizotinib For a Rare Mutation: A Case Report

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Research Article

Keywords: pulmonary embolism, bradycardia, non-small-cell lung cancer, MET Y1003S mutation, crizotinib

Posted Date: November 18th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-1031981/v1

Abstract

Lung cancer is a major global health problem because of its high incidence and mortality. Targeted therapies have transformed treatment of driver-mutated metastatic non-small cell lung cancer (NSCLC). Nevertheless, recent studies demonstrated that cardiovascular disease (CVD) was the second leading cause of mortality in cancer survivors now, management of patients' cardiovascular health during the course of anticancer therapy has become a great challenge faced by the oncologists. Anticancer related CV complications are not limited to traditional chemotherapy, but are also increasingly recognized in targeted therapy. We present a case of pulmonary embolism and bradycardia in a 91-year-old NSCLC patient treated with crizotinib for a rare MET Y1003S mutation. To our knowledge, this is the second report to show antitumor response of crizotinib in lung cancer patients with such a rare mutation. However, the patient complained chest tightness and shortness of breath after a month of standard dose crizotinib therapy. Non-invasive examination revealed new onset bradycardia and pulmonary embolism (PE). Such clinical manifestations were associated with targeted therapy-related cardiovascular（CV） toxicity, on which the emerging discipline cardio-oncology focused, and a multidisciplinary investigation and treatment was conducted. The case highlights the CV adverse events of novel therapies and the current challenges to be tackled in cardio-oncology.

Introduction

There has been a major paradigm shift in the understanding, diagnosis and management of NSCLC with molecular translational research advances over the last decade. Targeted agents, are now preferred first-line therapy for those with actionable genetic aberrations such as EGFR, ALK, ROS1, BRAF and MET in NSCLC. Albeit being generally well-tolerated in NSCLC patients, targeted therapy related CV adverse events including arrhythmias and heart failure have been reported. Considerable number of anti-neoplastic agents was approved without matched knowledge in underlying CV toxicity, for which long term post-approved surveillence should be emphasized,especially in those patients complicated with cardiovascular diseases.

Crizotinib, an ATP-competitive tyrosine kinase inhibitor, approved for ALK or ROS1 positive advanced NSCLC patients, shows clinical efficacy in NSCLC with abnormal ALK, ROS and MET/ HGFR kinase activity(1). Studies have shown that the HGFR/c-MET pathway plays an important role in cardiovascular remodeling after tissue injury by promoting angiogenesis, anti-inflammation and anti-fibrosis, suggesting MET inhibitors have potential cardiotoxicity related to the HGFR/cMET pathway (2).According to a recent study that comprehensively compared CV adverse events for commonly used TKIs in NSCLC, crizotinib ranked first in related conduction disease among ALK/ROS1 inhibitors(3). Previous studies in crizotinib mainly focused on its impact on cardiac electrophysiology, namely causing bradycardia and QT interval prolongation, but it may also trigger other cardiovascular adverse events. In this study,we described a case of pulmonary embolism and bradycardia in a NSCLC patient treated with crizotinib for a rare mutation.We present the following case in accordance with the CARE Reporting checklist.

Patient Information

A 91-year-old male presented to the cardiology clinic for 1 week of fatigue, chest tightness and shortness of breath. His self-measured oxygen saturation was around 90% and pulse rate was around 50 bpm using a finger pulse oximetric device. The patient denied chest pain, hemoptysis, productive cough, abdominal bloating, edema or oliguria. He had no swelling or palpable cords in the legs. Heart auscultation found no *abnormal* heart rhythm or pathological murmurs except for reduced heart rate. He had a history of hypertension for more than 10 years with the highest systolic blood pressure over 160mmHg and took candesartan 8mg in the morning and 4mg at night, which had his blood pressure well controlled around 120-130/60-80mmHg. Besides, he was diagnosed with lung adenocarcinoma (stage T3N3M1, MET Y1003S mutation) 2 months ago (2020-11-18) and accepted targeted therapy alone because of intolerance of surgery and chemotherapy. He had taken crizotinib orally 250mg twice a day for more than 1 month till then and non-specific discomfort emerged since the therapy initiation.

Key laboratory test results were demonstrated as follows: CK-MB 7 ng/mL↑ (reference range, 0.3 to 4), troponin I 0.01ng/mL (reference range, ≤0.20), D-dimer 3.09mg/L↑ (reference range,≤0.55), NT-proBNP 53.0pg/mL (reference range, 5 to 263). Electrocardiogram (ECG) on presentation showed sinus bradycardia (HR 57bpm) and first degree atrioventricular block (PR interval 280ms). Out of caution, the patient was admitted into our department for further evaluation. Vital signs were measured as follows: T 36.3℃, HR 51 bpm, R 18 breaths/min, BP 138/65 mmHg. No dynamic change was found after repeat myocardial enzyme and D-dimer tests (CK-MB 5.8↑ng/mL, troponin I 0.01ng /mL, D-dimer 2.58↑mg/L). The ECG showed persistent bradycardia (HR 51bpm) and first degree atrioventricular block (PR interval 288ms) (figure 1A). The arterial blood gas analysis indicated hypoxemia with partial pressure of oxygen at 8.67↓kPa, partial pressure of carbon dioxide at 6.07↑kPa, oxygen saturation at 91.4↓% when breathing ambient air. Other routine laboratory test results were normal. Accordingly, supportive therapies including oxygen inhalation, ECG telemetry monitoring, and 24-hour urine volume recording were initiated in the first place and diagnostic examinations were performed to clarify the patient's etiology.

Diagnostic assessment

Given the history, clinical manifestations and current examinations of the patient, a comprehensive evaluation for circulatory and respiratory disorders was conducted to identify the causes of his bradycardia and hypoxemia.

A computed tomography (CT) scan of the chest was notable for a rounded mass in the right upper lobe with the largest cross-section at 26*11 mm and multiple enlarged lymph nodes in the mediastinum and both hilum (figure 2B), which regressed remarkably in comparison with previous CT images acquired at diagnosis. And no sign of pneumonia, atelectasis or emphysema was observed. Thus, common etiology of hypoxemia such as pneumonia, neoplasm progression or chronic obstructive pulmonary disease was ruled out.

A transthoracic echocardiography showed normal systolic function with left ventricular ejection fraction of 64%.There were no ventricular hypertrophy or dialation other than an enlarged left atrial with diameter of 41 mm.The diastolic function was evaluated by the Doppler echocardiography and tissue Doppler imaging (TDI), which revealed that the ratio of peak Doppler velocities of early (E) to late diastolic flow (A) was 0.5, the ratio of mitral velocity to early diastolic velocity of the mitral annulus E/E' on the side of the ventricular septum and left ventricular lateral wall were 15.2 and 7.8, respectively, both indicating diastolic dysfunction.

The ECG telemetry displayed persistent bradycardia, so an ambulatory ECG monitoring was ordered to rule out severe arrhythmia. The result confirmed the diagnosis of bradycardia with an average heart rate at 54bpm, ranging from 41bpm to 78bpm (total heart beats 68040 in 21 hours) and persistent first degree atrioventricular block (average PR interval 292ms). The arrhythmia was recently formed based on an ECG obtained 2 months earlier when he was hospitalized in the respiratory department for lung cancer (figure 1B).

In absense of chest pain, myocardial enzyme elevation and ST variation in ECG, there was no indication for urgent coronary angiography. Howerver, the patient had high risks for coronary heart disease. His fasting blood glucose and glycosylated hemoglobin was 6.17↑mmol/L and 6.9↑% respectively. Besides, arterial plaques in carotid and femoral arteries were detected by vascular ultrasound regardless of normal lipidemia. Accordingly, a coronary computed tomography angiography was performed, which showed mild multivessel stenosis and a local myocardial bridge in the middle-to-distal segement of the left anterior descending branch. The patient was then diagnosed with chronic coronary syndrome for atherosclerosis and myocardial bridge.

Elevation of D-dimer arouse concern about pulmonary embolism. The hypoxemia and history of malignancy were both highly suggestive of pulmonary embolism. Albeit lacking evidence of venous thrombosis in lower extremity ,the patient was confirmed of thrombus in the lower lobe of the left lung by the computed tomography pulmonary angiography (CTPA) . Furthermore, the simplified Pulmonary Embolism Severity Index (sPESI) was 2 points in the patient, which evaluates blood pressure, heart rate, oxygen saturation, age, and a history of cancer,lung disease or heart disease. A score of sPESI≥0 is associated with notable elevation of in-hospital or 30-day mortality as ESC guidlines illustrated(4).

Taken together, the patient was now notable for partial remission of the lung adenocarcinoma, chronic coronary syndrome, new onset bradycardia and subsegmental pulmonary embolism. Given the close association between crizotinib application and aforementioned manifestations on the timeline, the potential impact of crizotinib,a widely used tyrosine kinase inhibitor (TKI) targeting ALK, ROS1 and MET/HGFR, raised our concern. In light of this, a multidisciplinary team including respirologists, oncologists, radiologists and cardiologists was brought together.

Targeted therapy was a more appropriate option for an elderly advanced lung cancer patient than surgery, chemotherapy or radiotherapy from an oncologist perspective. Although, common driver mutation genes such as EGFR, ALK, ROS1 and MET Exon14 was failed to be detected via the conventional PCR method

and the next generation gene sequencing technology, a very rare MET Y1003S mutation was eventually identified by the high-throughput sequencing. The patient was thus endowed with a treatment opportunity and opted targeted therapy of crizotinib.

As radiologists point of view, CT scan of tumor at baseline and after less than 2 months of crizotinib treatment demonstrated rapid reduction in tumor volume, meeting RECIST partial response criteria (-30%), which indicated remarkable anticancer efficacy of crizotinib (figure 2A, B).

From respirologists interpretations, it's difficult to determenate whether the PE was a new onset due to absence of a previous CTPA image for the patient. While no complain of chest tightness or breath shortness at the first place may suggest for a new onset. Once thrombosis in the pulmonary artery is identified, risk stratification is necessary to determine the appropriate treatment strategy. The patient was classified into the intermediate risk category of PE with a positive sPESI score and stable hemodynamics. So anticoagulation alone with no need for mechanical intervention was recommended.

From the perspective of cardiologists, the patient posessed multiple risk factors, including age, hypertension, diabetes and chronic coronary artery syndrome, which increased his susceptibility to antitumor-related CV complications and undesired CV complications hampered his targeted therapy course, leaving him at the crossroads of oncology and cardiology. Optimization of CV risk factors is imperative during whole course of cancer treatment to achieve best possible outcomes.

Therapeutic intervention

The paradox is that the most beneficial oncological therapy for the adenoma caused grave cardiological complications. A consensus was reached in a multidisciplinary approach. First of all, anticoagulation is an important strategy in patients with submassive subsegmental pulmonary embolism. Thus, subcutaneous, weight-adjusted low molecular weight heparin once a day in hospital under the monitoring of coagulation indices and conversion to the oral anticoagulant agent rivaroxaban at discharge was recommended. Secondly, given the non-severity of his CV complications and symptom alleviation after oxygen inhalation, there was no indication for drug withdrawal then. A preservation of standard dose of 250 mg each time twice a day was recommended. Taking a step back, the dose could be reduced to 250 mg once a day or 250 mg twice every other day till the maximum tolerable dose, if the negative dromotropic and thrombogenesis effect persisted. Thirdly, it was imperative to stick on cardiovascular protective medications and have regular cardiovascular examinations. Statins and candesartan were prescribed for the patient to modify risk factors. What's more, other selective MET inhibitor such as capmatinib or savolitinib could be a cardiac-safe alternatives, though no evidence for their antitumor efficacy in NSCLC patients with MET Y1003S mutation.

Follow up

The patient was regularly followed up in the outpatient clinic after discharge. No significant change was observed in terms of tumor progress between the chest CT image in March 2021 and January 2021, with

the largest cross-section of the mass in right upper lobe at 26*11 mm (figure 2B,2C). Considering his high CVD risks and stable progress of tumor, the dosage of crizotinib was halved to 250 mg twice every other day to optimize the balance between oncological benefit and CV hazards. The sustained remission of tumor was confirmed by another chest CT image two months after the dose reduction (figure 2D). And the patient had an amelioration of subjective symptoms, characterized by a relief of chest tightness and an elevation of pulse rates around 65 bpm. Therefore, it came to the conclusion that the dose adjustment alleviated adverse CV reactions and maintained the antitumor efficacy simultaneously. It was the joint efforts of oncologists and cardiologists that brought optimal clinical outcome for the patient, setting the way forward for the cardio-oncology towards multidisciplinary consultation and individualized medicine.

Discussion

Among NSCLC patients, 5% carry a mutation at the MET site, in which 47% develop a MET14 exon skipping mutation, 46% develop MET amplifications, only 3% carry a rare point mutation as we present here(5, 6). Current MET inhibitors including crizotinib, cabotinib, terbotinib and carmartinib mainly target MET14 exon skipping mutations or MET amplifications while no standard treatment for NSCLC patients with Y1003S point mutation is available(7–9). The MET Y1003S mutation was predicted to share similar biological characteristics with the MET14 exon skip mutation. According to a case reported in 2019, MET inhibitor crizotinib showed antitumor response to a NSCLC patient with MET Y1003S mutation for the first time(10). As this case presented, the efficacy of crizotinib to such a rare mutation was verified for the second time. But the occurence of PE and bradycardia raised our concerns over adverse CV complications in patients receiving MET-targeted therapy.

Impact of crizotinib on cardiac electrophysiology was demonstrated by previous clinical trials, characterized by bradycardia and QT interval prolongation. Grade 3 or 4 QT interval prolongation was reported in 27 of 1722 patients (1.6%) in a clinical trial(11), and the causality between crizotinib and QT interval prolongation was confirmed in a subsequent study by collecting a series of electrocardiograms following a. single dose of crizotinib(11). The underlying mechanism may be the inhibition of the delayed rectifier potassium current (I_{kr}) ion channel in the heart(12). Therefore, prudent application of crizptinib in patients who are prone to QT prolongation or receive other QT interval-prolonging drugs contemporaneously is recommeded. In addition, about 5% of patients treated with crizotinib would develop bradycardia, usually at grade 1or 2(13). The extent of heart rate decline is reported to be dose-dependent so that the heart rate drops by an average of 2.5 bpm per 100 ng/mL increase in serum crizotinib concentration.The inherent manchanism might be a chronotropic effect on sinoatrial node, an antimesenchymal-epithelial transition effect, and the blockade of L-type calcium channels and α-1 adrenergic receptors(14).

An increased risk of pulmonary embolism in patients receiving crizotinib treatment was also reported in clinical trials, but was easily neglected due to relatively low incidence(15–17).In the A8081007 study of 343 ALK-positive metastatic NSCLC patients, adverse event analysis showed that compared with the control group, the incidence of PE in the critzotinib group was higher in which 9 patients developed PE

and 1 death reported(15). Permanent discontinuation of crozotinib due to serious PE events was reported by another A8081029 study restricted to East Asian population which enrolled 205 patients with ALK-positive metastatic NSCLC patient(17). Albeit the PE was non-severe in this case, it impacted the patient's quality of life and was at risk of deterioration into a life-theratening event without proper management.

Evolution of targeted therapy over last two decades has transformed cancer treatment, especially in lung cancer. The advancement altered the natural course of malignant tumors, but these favorable antitumor efficacy sometimes come at the expense of an increased risk for CV complications. Lessons could be taken from EGFR-TKIs, the development of which is an important milestone in the targeted therapy of NSCLC. Osimertinib, an oral third-generation EGFR-TKI, showed superior efficacy compared to previous EGFR-TKIs in prolonging the progression-free survival time of NSCLC patients,but its cardiotoxicity remained a hotly debated issue.A significant LVEF decline was displayed in 3%-5% patients treated with osimertinib out of expectation in the clinical trials(3). A retrospective analysis of the Federal Drug Administration Adverse Events Reporting System demonstrated that osimertinib had about 2.2 times risk of heart failure compared with first-and-second generation EGFR-TKIs(18).

In the perspective of cardio-oncology, strengthened awareness and management of CV adverse events following targeted therapy, despite its relative lower incidence, is warranted. Firstly, plenty molecular anticancer agents are now available in oral preparation, which provides opportunity for patients to be treated at home. But it increased difficulty in identification and management of adverse events in ambulatory setting, compared with patients receiving intravenous chemotherapy under professional care(19). The neglection of targeted therapy related CV adverse events by the academe also accounts for unfavorable outcome, partly. Secondly, progress in targeted therapy improved survivorship of cancer patients, yet along with prolonged drug exposure and manifestation of potential CV toxicity. The co-existance of cancer and CVD becomes a common phenomenon in contemporary clinic context, which brings new clinical challenge in terms of treatment. Finally, a close interdisciplinary collaboration between oncologists and cardiologists in both clinical practice and trial design could further benefit cancer patients. Cardiologists participation in the whole course of antitumor therapy by close CV monitoring and early medical intervention could prevent unwished hasty cessation of oncologic therapy due to CV side effects that might hazard long-term prognosis.

Conclusions

A rare MET Y1003S mutation was detected via molecular profiling and was proved sensitive to crizotinib for a second time, while the antitumor efficacy came along with the CV hazard,namely crizotinib-related pulmonary embolism and bradycardia. Fortunately, through joint efforts of oncologists and cardiologists, the patient achieved an optimal clinical outcome. The case is of value to enlighten clinicians on the CV adverse events of targeted therapies, especially when applied in high CV risk population. Considerable number of anti-neoplastic agents were approved without matched knowledge in potentialCV toxicity, for which long-term post-approved surveillence should be emphasized. The nature of cardio-oncology is to achieve a better balance between anticancer benefits and cardiovascular risks after weighing the pros

and cons.We expect the concept of patient-oriented, individualized, evidence-based, and multidisciplinary consultation to be fulfilled in the field of cardio-oncology in the future.

Declarations

Author Declarations

Ethics approval and consent to participate: The patient declared to consent to participate in this study

Consent for publication: The patient declared to consent to the publication of the current paper

Availability of data and materials: Not applicable

Competing interests: All authors have declared no conflicts of interests

Funding: National Natural Science Foundation of China (81970337)

Authors' contributions: Conceptualization: W.J. and Y.D. Writing – original draft: Y.S.

Writing – editing: Z.Q. Material preparation, data collection, and analysis: Y.S., Z.Q.,

Y.C., A.Z. Supervision: W.J.All authors contributed to the article and approved the submitted version

Acknowledgements: We thank the patient for giving his written informed consent for the publication of this case report.

Compliance with Ethical Standards

Disclosure of potential conflicts of interest: No potential conflicts of interest

Research involving Human Participants and/or Animals Not applicable

Informed consent Written informed consent was obtained from the individual for the publication of any potentially identifiable images or data included in this article.

References

1. Shaw AT, Solomon B, Kenudson MM (2011) Crizotinib and testing for ALK. J Natl Compr Canc Netw 9:1335–1341
2. Camidge DR, Ou S, Shapiro G et al (2013) Efficacy and safety of crizotinib in patients with advanced c-MET-amplified non-small cell lung cancer (NSCLC).Journal of Clinical Oncology; 32
3. Soria JC, Ohe Y, Vansteenkiste J et al (2018) Osimertinib in Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer. N Engl J Med 378:113–125

4. Konstantinides SV, Meyer G, Becattini C et al (2019) 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS): The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC).Eur Respir J;54
5. Drilon A, Clark JW, Weiss J et al (2020) Antitumor activity of crizotinib in lung cancers harboring a MET exon 14 alteration. Nat Med 26:47–51
6. Drilon A, Cappuzzo F, Ou SI et al (2017) Targeting MET in Lung Cancer: Will Expectations Finally Be MET? J Thorac Oncol 12:15–26
7. Paik PK, Felip E, Veillon R et al (2020) Tepotinib in Non-Small-Cell Lung Cancer with MET Exon 14 Skipping Mutations. N Engl J Med 383:931–943
8. Wolf J, Seto T, Han JY et al (2020) Capmatinib in MET Exon 14-Mutated or MET-Amplified Non-Small-Cell Lung Cancer. N Engl J Med 383:944–957
9. Guo R, Luo J, Chang J et al (2020) MET-dependent solid tumours - molecular diagnosis and targeted therapy. Nat Rev Clin Oncol 17:569–587
10. Miao YL, Xu QQ (2019) MET Y1003S point mutation shows sensitivity to crizotinib in a patient with lung adenocarcinoma. Lung Cancer 130:84–86
11. Tartarone A, Gallucci G, Lazzari C et al (2015) Crizotinib-induced cardiotoxicity: the importance of a proactive monitoring and management. Future Oncol 11:2043–8
12. Shopp GM, Helson L, Bouchard A et al (2014) Liposomes ameliorate Crizotinib- and Nilotinib-induced inhibition of the cardiac IKr channel and QTc prolongation. Anticancer Res 34:4733–4740
13. Ou SH, Tang Y, Polli A et al (2016) Factors associated with sinus bradycardia during crizotinib treatment: a retrospective analysis of two large-scale multinational trials (PROFILE 1005 and 1007). Cancer Med 5:617–622
14. Ou SH, Tong WP, Azada M et al (2013) Heart rate decrease during crizotinib treatment and potential correlation to clinical response. Cancer 119:1969–1975
15. Solomon BJ, Mok T, Kim DW et al (2014) First-line crizotinib versus chemotherapy in ALK-positive lung cancer. N Engl J Med 371:2167–2177
16. Shaw AT, Kim DW, Nakagawa K et al (2013) Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. N Engl J Med 368:2385–2394
17. Wu YL, Lu S, Lu Y et al (2018) Results of PROFILE 1029, a Phase III Comparison of First-Line Crizotinib versus Chemotherapy in East Asian Patients with ALK-Positive Advanced Non-Small Cell Lung Cancer. J Thorac Oncol 13:1539–1548
18. Kunimasa K Is Osimertinib-Induced Cardiotoxicity Really Harmless?J Clin Oncol2021:JCO2100266
19. Rao VU, Reeves DJ, Chugh AR et al (2021) Clinical Approach to Cardiovascular Toxicity of Oral Antineoplastic Agents: JACC State-of-the-Art Review. J Am Coll Cardiol 77:2693–2716

Figures

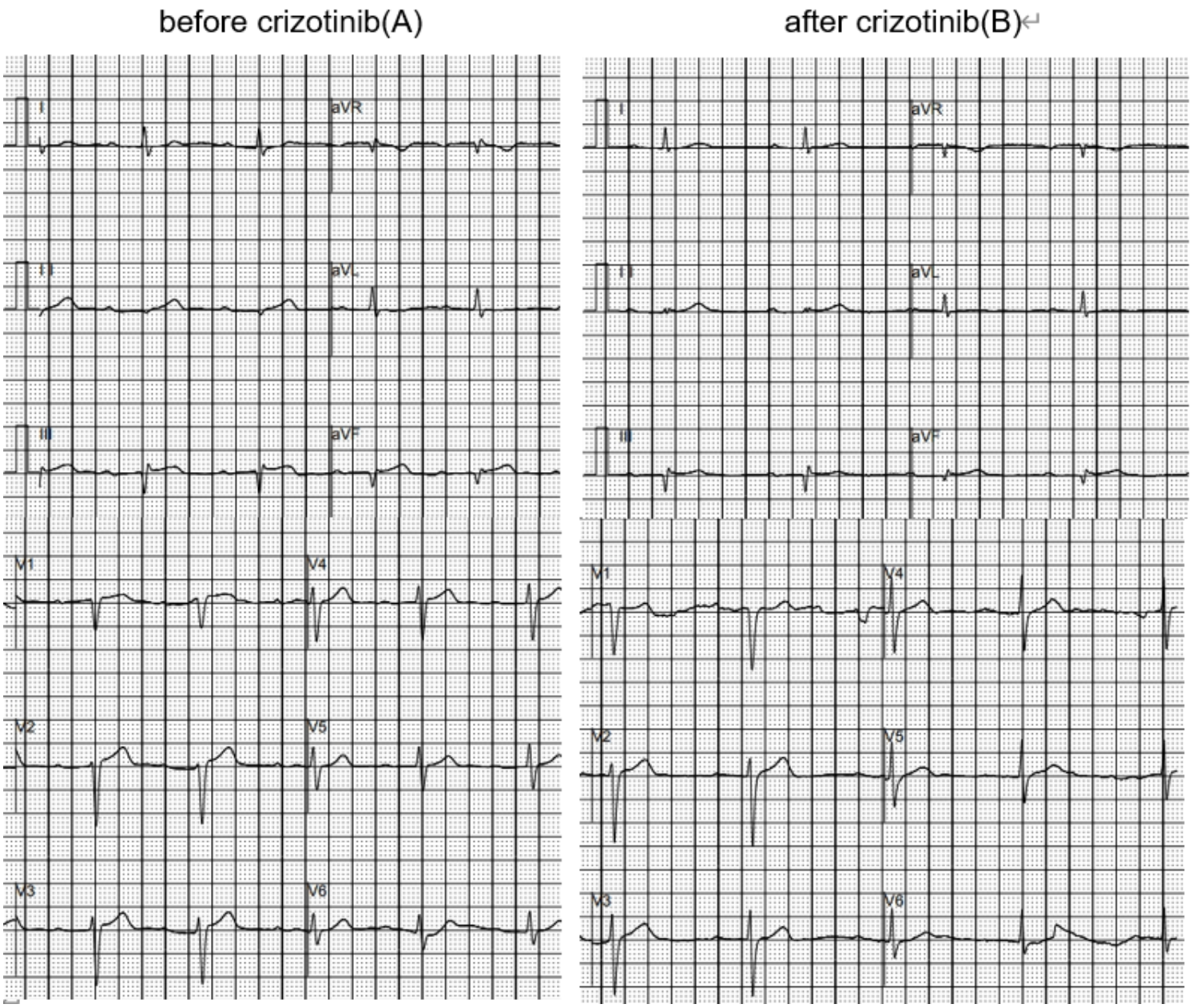

Figure 1

(A)ECG on addmission（2021-01-13） showing sinus bradycardia (heart rate 51bpm) and I degree atrioventricular block (PR interval 288ms). (B)ECG at the diagnosis of lung cancer（2020-11-05） showing normal heart rate (64bpm) and I degree atrioventricular block (PR interval 294ms).

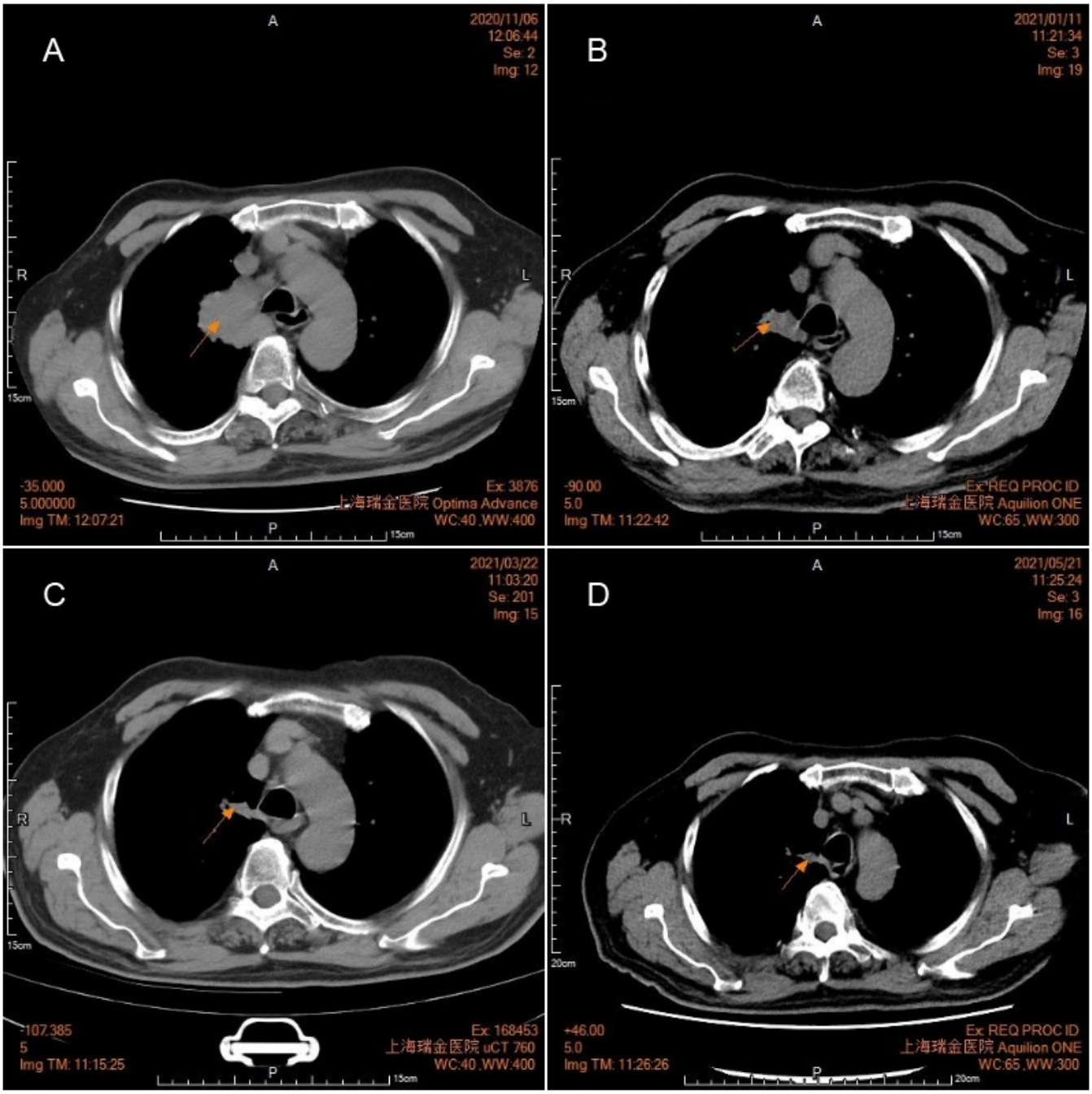

Figure 2

CT images of the mass The largest cross-section of the mass (red arrows) at the baseline (A) , after receiving crizotinib at the standard dose for over a month（B）, after receiving crizotinib at the standard dose for over three months (C)（after receiving crizotinib at the halved dose for another two months (D) on computed tomographic images of the chest respectively.

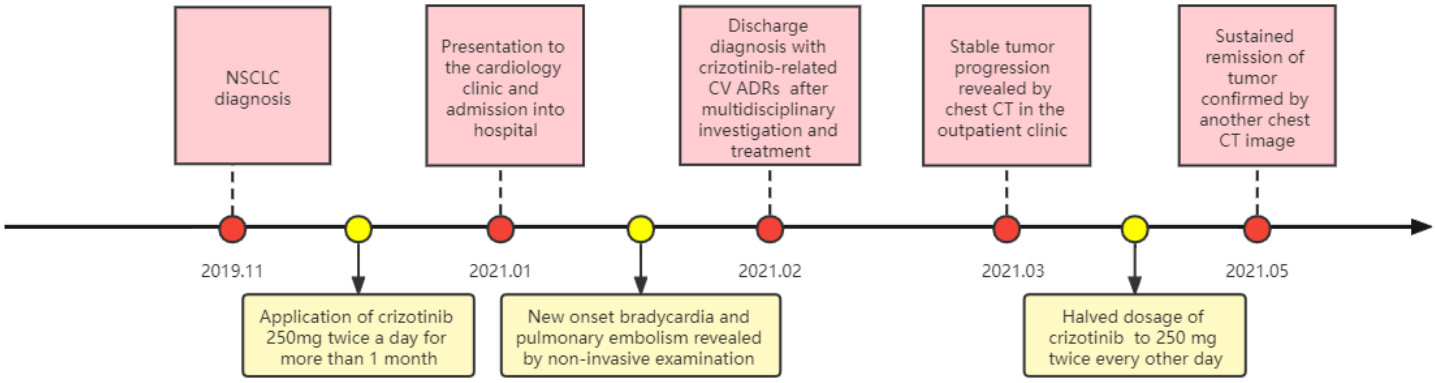

Figure 3

Time line of each treatment

Supplementary Files

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- CAREchecklist.pdf