PCM PRECISION CANCER MEDICINE
A JOURNAL AIMING TO DELIVER A LASTING BLOW TO CANCER
复旦大学附属肿瘤医院 Fudan University Shanghai Cancer Center
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Peer Review File

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Review Comments

Reviewer A

The case report by Ordóñez-Reyes et al. describes an NSCLC patient with a 15 bp deletion in exon 19 of EGFR, who received 10 lines of treatment, including chemotherapy, EGFR-TKIs (erlotinib, afatinib, and osimertinib), plus anti-VEGF or EGFR antibody over a period of 10 years. The authors mentioned that it should be the responsibility of oncologists to identify optimal strategies to treat individual patients, with the aim of maximizing the overall survival and avoiding drug resistance.
Although the manuscript included some interesting results, some further clarifications are required.

Comment 1:
The authors should describe the novel points of this case report.

Reply 1:

Novel points of case report

- After years of standard care prescribed to cancer patients without any selection except the primary site and histology of the tumor, the era of precision medicine has revolutionized lung cancer care.
- Targeted therapy inhibiting specific actionable driver genes has resulting in a significant improvement in response rate and disease control.
- Evaluating the molecular profile using NGS completely changed the diagnosis, prognosis, and management of this case considering the use of information to dynamically adapt treatment according to resistance patterns.

Comment 2:
Institutional ethical committee approval is required and should be mentioned in the

manuscript.

Relply 2:

Disclosure: case presentation was consented to AFC by the patient's family after her death and authorized by the Institutional Ethics Committee of the Clínica del Country, Bogotá, Colombia (Cayre 2020-17E21).

Comment 3:
Please describe the reasons for the failure of carboplatin/etoposide/osimertinib therapy in this patient.

Reply 3:
As described in the case, the therapeutic failure to carboplatin/etoposide /osimertinib was due to transdifferentiation to SCLC with greater meningeal involvement. The clinical deterioration was rapid and irreversible at this time of the disease, the moment in which cranial nerve involvement, severe swallowing limitation, and evolutionary respiratory compromise were found.

Comment 4:
Please clarify the performance status of each therapy in this patient.

Reply 4:
Included

Comment 5:
The authors performed multiple gene analyses in this patient. Was the activating EGFR mutation comprising the 15 bp deletion in exon 19 detected at all times or did he lose it?

Reply 5:
The exon 19 deletion was maintained until the end of the disease as included in the case report.

Reviewer B

Comment 1:
The present study reported long term survival in a patient with lung cancer. Overall the study is well performed, however, there is one thing that I want to confirm in this study. .Do the authors analyze germ line mutations in the study? Are there any

mutations in Rb and TP53 in the genomic DNA from a whole blood sample or from the normal tissue of the lung?

Reply 1:
Throughout the 12 years of evolution of the case, no evaluation was carried out for germ disorders (absence of family history or basal germ T790M). Although the NGS tests performed can detect some germ alterations as background, these were never documented or reported. In all evaluations, the mutations always had a FAM less than 50%.

Reviewer C
Authors presented a patient with EGFR mutant non-small cell lung cancer treated with EGFR-TKI and cytotoxic agents showing a survival duration of over 10 years. The patient also showed histological transforming to small cell lung cancer. It has been reported that TP53 and RB1 gene mutation are involved in the development of small cell lung cancer from type 2 alveolar cells. It is considered worthwhile that the association between these gene mutation and histological transforming was demonstrated in clinical practice.
On the other hand, it may be scarce in terms of new findings or hypothesis presentation in treatment for EGFR mutant non-small cell lung cancer.

I have following three questions.

Comment 1:

Why did the authors administer RAM?

Reply 1:
The patient did not receive ramucirumab, the use of the erlotinib/bevacizumab combination stopped between 2012 and 2013, six years before the presentation and publication of the RELAY study. The results using erlotinib/bevacizumab were optimal, reaching a PFS close to one year.

Comment 2:
Why did not administer combined platinum with PEM?

Reply 2:
Before learning about the presence of the EGFR mutation in 2007, the patient received six cycles of CBP/Paclitaxel, one of the standard treatments for the time. Pemetrexed was then used as a second line (without success) based on the phase III clinical trial published in 2004 by Nasser Hanna (J Clin Oncol. 2004; 22 (9): 1589-1597.).

Comment 3:
Do the authors administer TKI combined therapy as routine?

Reply 3:
Before the appearance of Osimertinib in regular clinical practice, the authors used the following combinations in multiple patients:
1. Erlotinib / Bevacizumab
2. Afatinib / Paclitaxel
3. Afatinib / Cetuximab
4. Afatinib / Pemetrexed

At present we use in selected cases Erlotinib / Ramucirumab, Gefitinib / CBP / Pem, Osimertinib / Bevacizumab, platinum based chemotherapy plus Osimertinib, and Osimertinib / Cetuximab or Necitumumab.