TCR TRANSLATIONAL CANCER RESEARCH
ADVANCES CLINICAL MEDICINE TOWARD THE GOAL OF IMPROVING PATIENTS' QUALITY OF LIFE
IMPACT FACTOR 0.986

Peer Review File

Article information: https://dx.doi.org/10.21037/tcr-21-653

Reviewer A

This study aimed to analyze the clinicopathological features of the patients with the transformation from lung adenocarcinoma into SCLC. It is interesting topic and has relatively low incidence.

But there have been several well-designed published studies in this field, such as reference #10 - J Clin Oncol 2019;37:278-285. We can obtain treatment response as well as clinicopathological characteristics of SCLC transformation case.

The submitted paper seemed to be necessary of novelty for publication.

Reply: The EGFR mutant incidence of lung adenocarcinoma in Asian population is different from that in Europe and America, however, it is uncertain whether the clinicopathological features of the patients with the transformation from lung adenocarcinoma into SCLC are different in different races. The incidence of ADC with SCLC transformation is low and there are not many articles about case series. Some of our results are similar to those of the above literatures, so we quoted them in the part of discussion, however, the contents of these studies are not exactly the same as our study. 10 cases in our study are Asian population. The focus of our study is to summarize the clinical characteristics and provide reference for the prediction of transformation in advance, our study also observed the contents that have not been analyzed in other studies, such as: staging at initial diagnosis, different treatment methods and different treatment sequence before transformation may affect the time interval of transformation, NSE level before transformation, biopsy site at the time of transformation, treatment methods after transformation, etc, These are of great significance in guiding clinical practice. (see Page 7, line 140-154 and Table 1, 4, 5)

Reviewer B

The authors presented 10 cases of lung ADC with SCLC transformation after TKI treatment. This is an interesting paper as there are not many articles about case series of ADC with SCLC transformation.

There are several points needing revision:

Comment 1: Please do not use abbreviations in the abstract such as Syn (page 1 line 27), E19 (page 2, line 36).

Reply 1: "Lung adenocarcinoma patients harboring EGFR exon 19 del mutation and receiving targeted therapy are more prone to SCLC transformation" has been deleted from the conclusion. The abbreviations in the abstract such as Syn have been modified in our text as advised
Changes in the text: see Page 2, line 34-36.

Comment 2: English editing is needed. Many errors like

Page 3 line: 71: The average age was 55 (ranged from 30 to 68) years "old". The word "old" should be deleted.
Page 3 line 75: "on" Figure 1 not "in" Figure 1

Reply 2: we have modified our text as advised.
Changes in the text: see Page 4, line80, 84; Page 6, line 126.

Comment 3: Page 3 line 75: "three patients underwent left low pneumonectomy" is not correct. What is left low pneumonectomy?

Reply 3: This sentence is not correct; the correct expression is "three patients underwent resection of lower lobe of left lung".
Changes in the text: see Page4, line 84-85; and the footnotes of Table1.

Comment 4: Page 4 line 119: "Eight patients maintained the original EGFR gene mutation type (80%) after transformation, but the mutation type of two patients changed to EGFR T790M mutation." According to your Table 1, there is only one patient with T790M?

Reply 4: This is a clerical error, it is correct in Table 1, and we have modified our text.
Changes in the text: see Page 6, line 131-132.

Comment 5: In this manuscript I believe there is no evidence to say "Lung adenocarcinoma patients harboring EGFR E19 mutation and receiving targeted therapy are more prone to SCLC transformation." You definitely cannot get this conclusion just because there are 9 EGFR exon 19 del patients in this case series.

Reply 5: The evidence is indeed inadequate; this sentence has been deleted from the conclusion.

Changes in the text: see Page2, line 45.

Comment 6: The pathological figures need to be adjusted. The white balance is terrible.

Reply 6: we have adjusted our pathological figures as advised.
Changes in the text: see Figure 1-3.

Comment 7: Authors should tell us the detection method of EGFR mutation. Did you use qPCR, NGS, or other methods?

Reply 7: Genotyping was performed with next-generation sequencing (NGS). we have supplemented this part in our text as advised.
Changes in the text: see Page 5, line 103-104.

Comment 8: Page 5 line 124 and 126: The abbreviation "SYN" (for synaptophysin) and "CgA" (for chromogranin A) should not be used. The information of antibodies used in this study should be mentioned in the study design part.

Reply 8: we have modified our text as advised.
Changes in the text: see Page 7, line 136-139; Page 5, line 106-108.

Reviewer C

Bai et al. describe a cohort of 10 patients with EGFR mutant lung adenocarcinoma who develop histological transformation to SCLC after EGFR TKI therapy (apart from one patient in which the EGFR status was unknown at diagnosis).

In support of previous findings where despite SCLC transformation, the EGFR mutant status is maintained (which makes sense since genomic alterations cannot be lost per se) and the clinical relevance of repeat biopsy and genomic testing in patients who develop disease progression post TKI is emphasized and worthy of consideration is standard clinical practice.

This is a small retrospective case series and although there is no mechanistic element to the work, these are still interesting clinical findings that we are yet to explain the aetiology of.

I have a few comments/suggestions:

Comment 1: I would add to the title somewhere the fact that these are EGFR mutant

adenocarcinoma that subsequently develop SCLC transformation

Reply 1: we have modified our title as advised.
Changes in the text: see Page 1, line 2

Comment 2: It was not clear if EGFR testing was only done using blood or was this also tested on tissue?

Reply 2: In clinical practice, tissue testing is the first choice, but when there is not enough tissue or the patient refuses the second biopsies, we can also choose blood testing (see Table 1). Thompson et al. compared the detection results of NGS in 50 blood and tissue paired samples, the consistency between blood and tissue was about 79%. Therefore, for the patients whose blood gene test is negative, we recommend that the patients take biopsy tissue for supplementary detection, so as to avoid missing the possible targeted treatment sites(Clin Cancer Res 2016 Dec 1;22(23):5772-5782.).

Comment 3: Given the spatial genomic heterogeneity seen in NSCLC and the potential for mixed histological subtypes, is it possible that in 7/10 cases where access to lung biopsies alone may have missed an existing SCLC that eventually led to outgrowth and overt transformation? In a way the authors do comment on this in the discussion when they present this as a limitation.

Reply 3: At present, the related mechanism of SCLC transformation is not completely clear. It is possible that in 7/10 cases where access to lung biopsies alone may have missed an existing SCLC that eventually led to outgrowth and overt transformation, but in our study, experienced oncologists have made a comprehensive evaluation according to the pathology, immunohistochemistry, tumor markers, clinical manifestations, physical examination and imaging data of the patients at the time of initial diagnosis, they think the probability of this happening is very low. The specific mechanism of occurrence needs further exploration. We do comment on this in the discussion (see Page 8-9, line 171-190).

Comment 4: Can the authors comment on whether they think EGFR TKIs might select for EGFR-resistant clones in the adenocarcinoma that then subsequently transform into SCLC, or is it possible that SCLC clones were present at diagnosis and under treatment EGFR-sensitive clones are constrained and instead SCLC clones expand and result in a majority SCLC histological subtype?

Reply 4: Seems like, as far as I can tell, it's still a possibility that although there're a lot of puzzles here. We do comment on these situations in the discussion part (see Page 8-9, line 171-182). We should pay attention to the importance of multiple biopsies and biopsies of multiple parts of the body, in hopes of earlier detection of

TCR TRANSLATIONAL CANCER RESEARCH
ADVANCES CLINICAL MEDICINE TOWARD THE GOAL OF IMPROVING PATIENTS' QUALITY OF LIFE
IMPACT FACTOR 0.986

SCLC transformation and development of a precise treatment strategy.

AME Publishing Company