Genomic profiling of relapsed small cell lung cancer reveals potential pathways of therapeutic targets

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Contributions: (I) Conception and design: W Ouyang, C Xie; (II) Administrative support: None; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: Z Zeng, W Ouyang; (V) Data analysis and interpretation: W Ouyang, J Yu, Z Zeng, J Gong, J Zhang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Background: Almost all patients with small cell lung cancer (SCLC) relapse. The therapeutic options of relapsed SCLC are limited, and the clinical outcomes are poor. Thus, genomic profiling of relapsed SCLC patients may help to develop more effective therapeutic options.

Methods: We collected blood specimens and follow-up information from a consecutive cohort of 31 patients diagnosed with relapsed SCLC in Zhongnan Hospital, Wuhan University, between 2018 and 2019, to analyze the comprehensive genomic profiling, and to investigate the impact of genomic alterations on therapeutic options and survival.

Results: In our cohort of relapsed SCLC, the median number of genomic alterations was 5 (range, 1–11) per sample. The majority of patients were defined as low tumor mutation burden (TMB; 83.9%) and microsatellite stability (MSS; 87.1%). Immune checkpoint inhibitors (ICIs)-based treatment still brought considerable progression-free survival (PFS; 4.93–20.27 months) for patients with low TMB and MSS. Additionally, the most frequent genetic alterations observed in relapsed SCLC were *TP53* (77%) and *RB1* (52%). Other genomic alterations of high frequency were breast cancer 2 (*BRCA2*) (32%), ataxia telangiectasia mutated (*ATM*) (13%), epidermal growth factor receptor (*EGFR*) (10%), Notch receptor 1 (*NOTCH1*) (10%), and Fanconi anemia complementation group A (*FANCA*) (10%), in turn. Finally, based on the survival of therapeutic strategies targeting potential mutation genes, the role of genotyping in relapsed SCLC was confirmed.

Conclusions: Our studies first exhibited comprehensive genomic profiling of relapsed SCLC, identifying several candidate genes, and briefly analyzed the association of survival and genomic alterations. Our data from a small cohort of relapsed SCLC will benefit further exploration the potential targets or biomarkers.

Keywords: Small cell lung cancer (SCLC); relapse; genomic profiling; immune checkpoint inhibitor (ICI); breast cancer 2 (*BRCA2*)

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Introduction

Small cell lung cancer (SCLC), which accounts for approximately 15% of lung cancer cases, is characterized by high growth fraction, rapid doubling time, and poor clinical outcomes (1). Despite the past 30 years of clinical trials aimed at improving the outcomes for SCLC, the majority of SCLC remains incurable (2). Currently, chemotherapy remains the cornerstone of therapy for both extensive disease (ED) and limited disease (LD)-SCLC, with high response rates to first-line cytotoxic chemotherapy; the response rates of first-line platinum plus etoposide (EP) chemotherapy are 50–70% (2,3). However, in most cases, the duration of the clinical response is extremely limited, with nearly all patients relapsing, usually within a few months (1,4-6). Unfortunately, therapeutic options available for relapsed SCLC patients are limited: the response rates to second-line chemotherapy are as low as 5–30% (7-11); and there are currently no United States Food and Drug Administration (FDA)-approved targeted agents for the treatment of SCLC; immune checkpoint inhibitors (ICIs), as the first non-chemotherapy

alternative for patients with metastatic and relapsed SCLC (2,11-14), are of benefit to only a minority of patients, who cannot be well identified by existing biomarkers. Therefore, there is an urgent need to explore more effective therapies and specific biomarkers in relapsed SCLC.

Genetic testing could be used to better understand the pathogenesis of SCLC and to explore the potential pathways or targets for therapeutic strategies. Previous study has revealed a few recurrently mutated genes in untreated SCLC (15), whereas the genomic profiling of relapsed SCLC remains unclear, and there is a lack of data on the impact of genomic alterations on therapeutic options and survival among patients with relapsed SCLC. To develop more effective therapeutic strategies and optimal biomarkers of SCLC, it is necessary to improve our understanding of genomic profiling of relapsed SCLC.

Consequently, a consecutive cohort of 31 patients, diagnosed with relapsed SCLC in Zhongnan Hospital, Wuhan University between October 2018 and November 2019, was recruited and followed up. Blood samples were collected at enrollment for next-generation sequencing (NGS), to analyze the comprehensive genomic profiling of relapsed SCLC, and to explore the impact of mutated genes on therapeutic options and survival among patients with relapsed SCLC. We aimed to yield instructive results for the development of innovative clinical management strategies and specific biomarkers for patients with SCLC. We present this article in accordance with the REMARK reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1657/rc).

Methods

Patients

Between October 2018 and November 2019, there were a total of 68 consecutive patients with SCLC at the Department of Pulmonary Oncology, Zhongnan Hospital, Wuhan University. Among the 68 patients, a total of 31 eligible patients with relapsed SCLC were enrolled in this study. Thirty-seven patients of those were excluded due to non-relapsed SCLC. Our inclusion criteria were as follows: (I) SCLC confirmed by cytology (2 patients), or histology (29 patients) [World Health Organization (WHO)]; (II)

Highlight box

Key findings
- It was identified several genomic alterations with potential therapeutic implications for small cell lung cancer (SCLC).
- DNA damage response pathways represented attractive targets in relapsed SCLC.
- Genotyping of relapsed SCLC may reveal patient who has benefit from targeted therapy.

What is known and what is new?
- SCLC is characterized by high growth fraction, rapid doubling time, limited treatment options, and poor clinical outcomes. Previous studies have revealed a few recurrently mutated genes in untreated SCLC, whereas the genomic profiling of relapsed SCLC remains unclear.
- Our study first exhibited comprehensive genomic profiling of relapsed SCLC, identifying several candidate genes for exploring potential targets or biomarkers.

What is the implication, and what should change now?
- Next-generation sequencing for monitoring relapsed SCLC evolution is essential to develop more effective therapeutic options and potential biomarkers.

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the patients diagnosed with relapsed SCLC, who had undergone at least the first-line chemotherapy. The whole blood specimens from 31 patients were collected for NGS assessment (Euler Genomics Technology Co., Ltd., Beijing, China) at enrollment, circulating tumor DNA (ctDNA) extracted from the plasma separated from whole blood specimen was sequenced to high, uniform coverage (Illumina HiSeq 2500; Illumina, San Diego, CA, USA) and analyzed for all classes of genomic alterations. Genomic alterations of these patient samples, including base substitutions, small indels, rearrangements, copy number alterations, and so on, were determined and then reported. Additionally, the clinical characteristics and follow-up information of included patients were collected and analyzed.

The study was approved by the Ethical Committee of Zhongnan Hospital, Wuhan University (No. 2021017). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Written informed consent was provided by all included patients. Additionally, blood samples from participants with relapsed SCLC were collected for free NGS assessment, the results of which might help physicians to make decisions for subsequent treatment. We collected participant information by reviewing their electronic medical records, for which we preserved patient anonymity. We ensured that the data collection, analysis, and publication would not jeopardize participants' health, safety, or privacy.

Treatment and follow-up

All 31 patients with relapsed SCLC had received EP as the first-line chemotherapy. Blood samples were collected for NGS assessment in 16 patients who exhibited disease progression following the first-line treatment, in 13 patients with disease progression following the second-line treatment, and in 2 patients with disease progression following the third-line treatment.

Follow-up examinations were performed every 2 months, including thoracic and abdominal computed tomography (CT) scan, and brain magnetic resonance imaging (MRI) scan. Progression-free survival (PFS) was defined as the duration from the onset of illness to the failure of the first-line treatment. Overall survival (OS) was defined as the duration from the onset of illness to death from any cause.

Statistics

All statistical analyses were performed by using SPSS 22.0

(IBM Corp., Armonk, NY, USA). Descriptive statistics are used for categorical variables (frequency and percentage) and continuous variables (median and range). The cumulative survival rate was calculated by the Kaplan-Meier method with 95% confidence intervals (CIs). Univariable Cox regression analyses was used to investigate the factors associated with PFS and OS. All tests were two-sided and P<0.05 was considered statistically significant.

Results

Patient characteristics and treatment

Between October 2018 and November 2019, a total of 31 eligible patients with relapsed SCLC were analyzed in the current study. The baseline characteristics of these patients are shown in *Table 1*. In detail, there were 27 male and 4 female relapsed SCLC patients with a median age of 62 (range, 43–75) years. The majority of patients (20 patients, 64.5%) were heavy smokers, and 96.8% of patients (30 patients) presented a Karnofsky performance status (KPS) score ≥80. There were 15 patients of LD stage and 16 patients of ED stage. Of the 15 LD stage patients, 3 cases received surgery initially. All patients had received prior chemotherapy and had disease progression at enrollment. The number of prior lines of cancer treatment ranged from 1 to 3 (median 2) before NGS assessment, and 64.5% (20 patients) were platinum sensitive, defined here as having a chemotherapy-free interval of at least 90 days from completion of the first-line treatment to initiation of the second-line treatment. Additionally, all of 31 patients received radiotherapy during the whole course of treatment, whereas before NGS sequencing, a total of 3 patients did not receive radiotherapy.

The comprehensive genomic profiling of relapsed SCLC

Among the 31 blood samples used for DNA extraction, no differences were observed in the quality of sequencing results. All 31 relapsed SCLC specimens (100%) harbored at least 1 genomic alteration, with 162 total alterations identified for a median of 5 alterations per sample (range, 1–11). Additionally, patients with relapsed SCLC exhibited relatively low blood tumor mutation burden (TMB), among whom most patients (26 patients, 83.9%) were defined as low TMB (TMB value <20) according to the cut-off value of TMB in this current NGS sequencing package. Likewise, the majority of patients (27 patients, 87.1%) were defined

Table 1 Clinical characteristics of patients

Characteristics	Value (n=31)
Age (years)	62 [43–75]
≥60	19 (61.3)
<60	12 (38.7)
Gender	
Male	27 (87.1)
Female	4 (12.9)
KPS score	
≥80	30 (96.8)
<80	1 (3.2)
Smoking history	
Yes	20 (64.5)
No	11 (35.5)
Clinical stages	
LD	15 (48.4)
ED	16 (51.6)
Pattern of relapse after the first-line chemotherapy	
Platinum-sensitive disease (progression ≥90 days)	20 (64.5)
Platinum-refractory disease (progression <90 days)	11 (35.5)
Whether patients received radiotherapy before NGS sequencing?	
Yes	28 (90.3)
No	3 (9.7)
Prior lines of therapy before NGS sequencing	2 [1–3]
1	16 (51.6)
2	13 (41.9)
3	2 (6.5)
Time from diagnosis to DNA sequencing (months)	10.9 [2.1–47.6]
TMB	6 [1–66]
Low, TMB <20	26 (83.9)
Medium, 20≤ TMB <40	3 (9.7)
High, 40≤ TMB <60	1 (3.2)
Very high, TMB ≥60	1 (3.2)

Table 1 (*continued*)

Table 1 (*continued*)

| Characteristics	Value (n=31)
MSI/MSS	12 [4.1–32.0]
Stable (MSS), MSI <20	27 (87.1)
Moderate instable (MSI), 20≤ MSI <40	4 (12.9)
High instable (MSI-H), 40≤ MSI <60	0 (0.0)
Very high instable (MSI-VH), MSI ≥60	0 (0.0)
Genomic alterations per sample	5 [1–11]

Values are presented as median [range] or n (%). KPS, Karnofsky performance status; LD, limited disease; ED, extensive disease; NGS, next-generation sequencing; TMB, tumor mutation burden; MSI, microsatellite instability; MSS, microsatellite stability; MSI-H, MSI-high; MSI-VH, MSI-very high.

as microsatellite stability (MSS) [microsatellite instability (MSI) value <20] (*Table 1*).

Consistent with prior reports of untreated SCLC (15,16), the most frequent genomic alterations observed in relapsed SCLC were also *TP53* (24 patients, 77%) and *RB1* (16 patients, 52%) mutations. Other genomic alterations of high frequency were breast cancer 2 (*BRCA2*) (10 patients, 32%), ataxia telangiectasia mutated (*ATM*) (4 patients, 13%), epidermal growth factor receptor (*EGFR*) (3 patients, 10%), Notch receptor 1 (*NOTCH1*) (3 patients, 10%), Fanconi anemia complementation group A (*FANCA*) (3 patients, 10%) in turn (*Figure 1*). It was worth highlighting that untreated SCLC was not characterized by frequent mutations in *BRCA1/2* (15-17), which was not consistent with relapsed SCLC in our current study.

The survival of relapsed SCLC cohort

For the cohort of relapsed SCLC patients, the median duration of follow-up was 36.5 months (95% CI: 10.4–62.6). The median OS of these patients was 17.8 months (95% CI: 16.1–19.5) (*Figure 2*). The 1- and 2-year OS rates were 67.7% and 32.0%, respectively. For PFS, all patients had disease progression and had received a least the first line of chemotherapy at enrollment. Thus, the PFS of first-line treatment was defined as the duration from the onset of illness to the failure of the first-line treatment. The median PFS was 7.9 months (95% CI: 6.2–9.7) (*Figure 2*). The 1- and 2-year PFS rates were 25.8% and 12.9% respectively.

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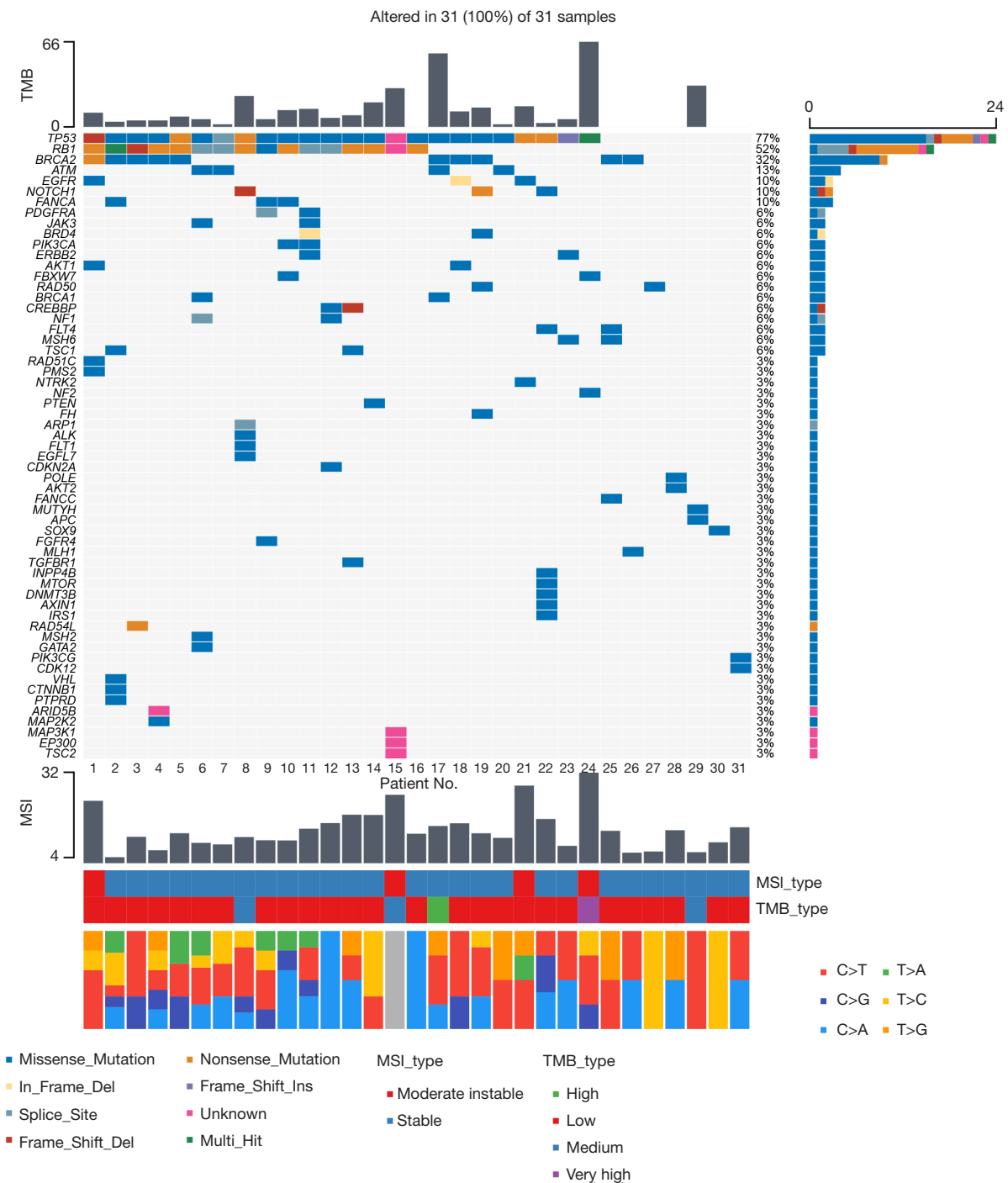
Figure 1 Genomic alterations in relapsed SCLC. Tumor samples are arranged from left to right. Alterations of SCLC candidate genes are annotated for each sample according to the color panel below the image. Each column from left to right corresponds to the genomic alterations of No. 1 patient to No. 31 patient in turn. The mutation frequencies for each candidate gene are plotted on the right panel. TMB value and type, MSI value and type, and types of base-pair substitution are displayed in the top and bottom panel, respectively. TMB, tumor mutation burden; MSI, microsatellite instability; SCLC, small cell lung cancer.
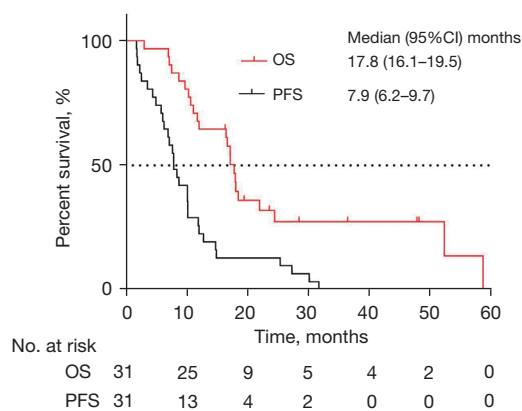
Figure 2 The survival of patients with relapsed SCLC. The Kaplan-Meier plot of OS and PFS in patients with relapsed SCLC. CI, confidence interval; OS, overall survival; PFS, progression-free survival; SCLC, small cell lung cancer.

At last, the median duration from the onset of illness to enrollment/NGS assessment was 10.9 months. As expected, the clinical stages and pattern of relapse were confirmed significantly associated with OS and PFS by univariable Cox regression analyses (P<0.05).

### The individualized approach and survival of relapsed SCLC cohort

Moreover, we analyzed the impact of genomic alterations on therapeutic options and survival among patients with relapsed SCLC. The individualized approach and survival of 31 relapsed SCLC patients are shown in *Figure 3*. A total of 3 patients (No. 11, 13, and 27) eventually received ICIs-based treatment as the third-line therapy, and their PFS of ICIs-based treatment was 20.3, 4.9, and 7.0 months, respectively. Interestingly, all of these 3 cases exhibited low TMB and MSS. For patients with mutations of potential therapeutic targets, cases No. 18 and 19 had mutation in *BRCA2*, were treated with poly-ADP-ribose polymerase inhibitor (PARPi, olaparib) monotherapy in the subsequent-line therapy, whereas the PFS was 2.53 and 3.1 months, respectively. In addition, there was 1 male (No. 18) and 2 females (No. 1 and 21) harbored common *EGFR* mutation. In detail, 19-del mutation in case No. 18, and L858R mutation in cases No. 1 and 21. After EGFR tyrosine kinase inhibitor (TKI) treatment, the male patient exhibited a PFS of only 1.87 months, and the PFS of the 2 females were 5.1 and 7.7 months, respectively. At last, we observed that a total of 3 patients with absence of driver mutations (No. 9, 11,

and 14) receiving anti-angiogenic TKI treatment showed the PFS of 3.2, 12.53, and 3.7 months, respectively.

Discussion

SCLC remains one of the most aggressive and lethal malignancies, with a minimal role of curative surgery and no targetable agents approved. Almost all patients with SCLC relapse ultimately. Over the past two decades, there has been no significant improvement in clinical outcomes for patients with SCLC. Although ICIs were demonstrated as the first and only non-chemotherapy option with survival benefit to SCLC, only a minority of SCLC patients could benefit from immunotherapy, and there was a lack of the specific biomarker for identification optimal sub-population that could benefit from immunotherapy (2,11-14). Consequently, exploring the genomic profiling of relapsed SCLC could help to develop more effective therapeutic options and to explore optimal biomarkers. A recent consensus proposal suggested grouping SCLC into four subtypes defined by expression of *ASCL1*, *NEUROD1*, *POU2F3*, and *YAP1*, referring to these respectively as SCLC-A, SCLC-N, SCLC-P, and SCLC-Y. Whereas the clinical implications of this molecular categorization remain to be explained (18). Recently, the liquid biopsy in genetic sequencing could potentially allow physicians to identify patients whose tumors harbor specific mutations in the least invasive way. Considering that repeated biopsies after initial treatment are typically outside of standard of care in SCLC, genomic profiling of relapsed SCLC in the current study was detected by blood sample.

The median OS and the first-line treatment PFS of our relapsed SCLC cohort was 17.8 and 7.9 months (*Figure 2*), respectively. As expected, the clinical stages and pattern of relapse (platinum-sensitive or -refractory) were confirmed as significantly associated with PFS and OS (P<0.05), whereas it was more concerned with the significance of genomic alterations on therapeutic options and survival among relapsed SCLC. As in previous reports, the absolute number of genomic alterations in most SCLC patients is much higher than in other tumors (15,16,19). In our cohort of relapsed SCLC, the median number of genomic alterations per sample was 5 (range, 1–11). Whereas in contrast to untreated SCLC previously reported (15,16,20), patients with relapsed SCLC exhibited relatively low TMB. The majority of patients (26 patients, 83.9%) were defined as low TMB (TMB value <20) according to the cut-off value of TMB in the current NGS sequencing package. Likewise,
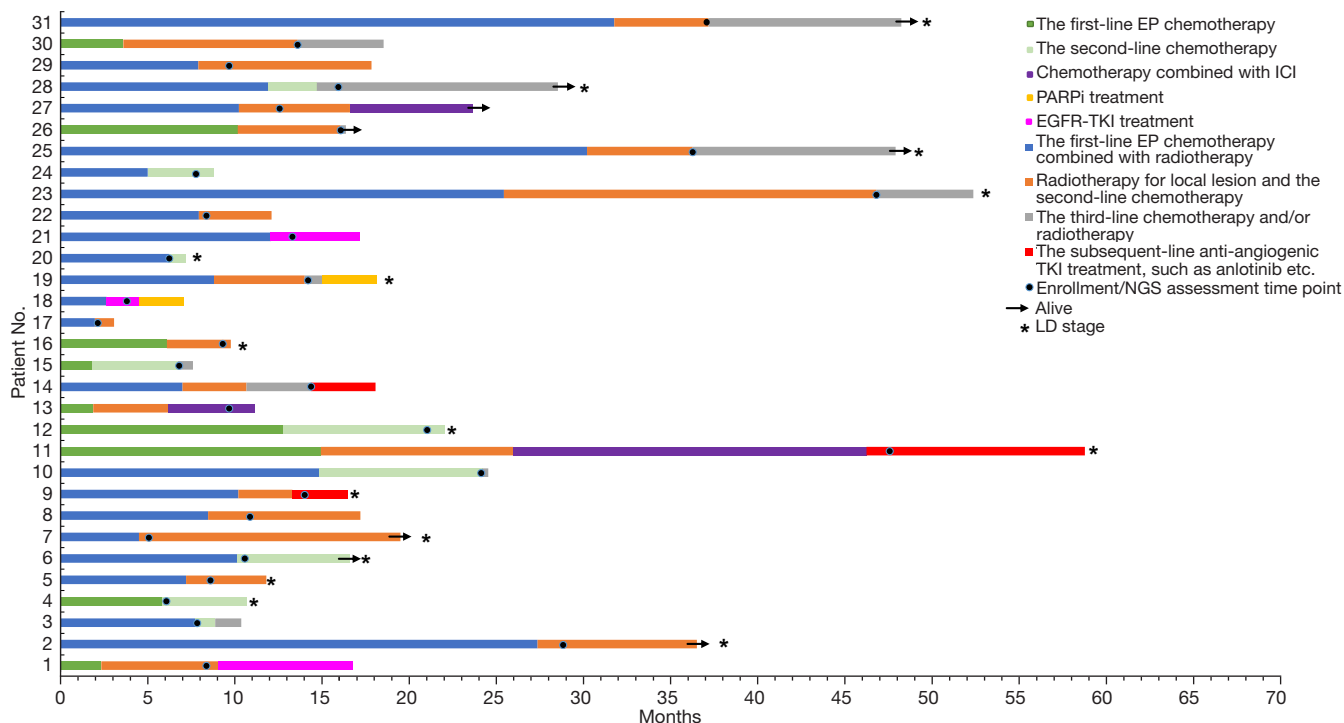
Figure 3 The swim-plot of survival among 31 patients with relapsed SCLC. Each bar from bottom to top corresponds to No. 1–31 patient in turn, which also corresponds to each column from left to right in *Figure 1*. The horizontal axis corresponds to 0–70 months. The length of each bar corresponds to the PFS duration of the first-line/second-line/subsequent-line treatment. The black dot on each bar represents the respective time point of NGS sequencing/enrollment. Patients with LD stage are asterisked at the end of the corresponding bar, and the remaining bars non-asterisked correspond to patients with ED stage. In detail, there were 15 patients of LD and 16 patients of ED. All patients received EP chemotherapy alone or combined with radiotherapy as the first-line treatment. The number of prior lines of treatments ranged from 1 to 3 at enrollment. As of 30 September 2020, a total of 23 deaths were recorded. EP, platinum plus etoposide; ICI, immune checkpoint inhibitors; PARPi, poly-ADP-ribose polymerase inhibitor; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; NGS, next-generation sequencing; LD, limited disease; SCLC, small cell lung cancer; PFS, progression-free survival; ED, extensive disease.

most patients (27 patients, 87.1%) were defined as MSS (MSI value <20). Recent studies have indicated that TMB or MSI might be a useful biomarker to predict likelihood of response to ICIs treatment among SCLC (21-23). Therefore, the above characteristics mentioned of relapsed SCLC might imply non-responsive to ICIs treatment. However, we observed that the ICIs-based treatment still brought considerable PFS (4.93–20.27 months) for 3 patients (No. 11, 13, and 27) with low TMB and MSS. Therefore, it is arguable that TMB or MSI is a useful biomarker for ICIs treatment among SCLC. Our findings also suggested the need for the development of optimal biomarker in further research.

Moreover, the most frequent genetic alterations observed in relapsed SCLC were *TP53* (77%) and *RB1*

(52%) mutations, which was consistent with previous reports of untreated SCLC (15,16). Our results further provide evidence for universal bi-allelic inactivation of *TP53* and *RB1* in SCLC, thereby reconfirming the two genes as obligatory tumor suppressors of SCLC. *TP53* and *RB1* control and influence most of the important pathways involved in detecting DNA damage, regulating cell cycle, and inducing apoptosis (24). As all control of the main tumor suppressive pathways is lost, SCLC shows the quickest and most aggressive growth among all tumor entities. Additionally, SCLC is one of tumors with the best initial response to chemotherapy and radiotherapy, probably also because SCLC induces a loss of ability to detect and repair DNA damage. Our findings reconfirmed that DNA damage response (DDR) pathways represented attractive

targets in SCLC.

Although genomic alterations in *TP53* and *RB1* cannot be suitable targets for treatment currently, we still found several genetic alterations in relapsed SCLC, such as mutations in *EGFR*, *BRCA1/2*, *PTEN*, *PIK3CA*, and so on (*Figure 1*), which were identified in other tumors with a potential therapeutic implication (25). To our knowledge, untreated SCLC is not characterized by homologous recombination (HR) deficiency or frequent mutations in *BRCA1/2* (15-17), which is contrast to our results of relapsed SCLC in this current study. *BRCA1* and *2* deficient cells are rendered defective in the ability to repair through HR and depend on error-prone non-homologous end joining (NHEJ) for DNA repair (23-29). PARP targeting is highly effective in the context of synthetic lethality in models with existing deficiency in DNA repair, such as deleterious mutations in *BRCA1/2* (26,27). Thus, it could be speculated that PARP targeting might be an attractive therapy option for relapsed SCLC. The PFS of *BRCA2* mutant patients (No. 18 and 19) treated with PARPi (olaparib) were 2.53 and 3.1 months, respectively. It seemed monotherapy of olaparib had limited efficacy in relapsed SCLC, even in *BRCA2* mutant patients. Therefore, the addition of other agents to PARPi treatment is probably an area worthy of further investigation among SCLC. Literatures and our previous study have proved (30,31) that DDR inhibitor can synergize with ICIs via the cGas-STING-IFN stimulation, which makes them a promising option for recurrent SCLC with DDR vulnerabilities.

Other genomic alterations such as mutations in *EGFR*, *PTEN*, *PIK3CA*, and so on, were also found in other tumors with a potential therapeutic implication. Therefore, genomic profiling of patients with relapsed SCLC may reveal individual patients who might receive potential benefit from targeted therapeutic interventions. In this current study, 3 patients (No. 18, 1, and 21) with common *EGFR* mutation all received EGFR-TKI treatment. And none of these cases is transformation of *EGFR*-mutation adeno-carcinomas. The high rate of *EGFR*-mutation in our cohort is partly explained by a small sample study, which inevitably resulted in a selection bias. However, the PFS of EGFR-TKI treatment among these relapsed SCLC patients was significantly poorer than that of lung adenocarcinoma patients with *EGFR* mutation. It was indicated that several somatic mutations do not cause genomic dependence and do not cause vulnerability to targeted therapies in SCLC. Additionally, we observed 3 patients (No. 9, 11, and 14) receiving anti-angiogenic TKI treatment who showed the PFS of 3.2, 12.53, and 3.7 months, respectively, which indicated the role of anti-angiogenic TKI in subsequent-line treatment. Consequently, our findings indicated that high-sensitivity genomic profiling could reveal potential new pathways to targeted therapies among patients with SCLC who have relapsed after primary chemotherapy.

Conclusions

Our studies first exhibited comprehensive genomic profiling of relapsed SCLC, identifying several candidate genes, and briefly analyzed the association of survival and genomic alterations. Our data from a small cohort of relapsed SCLC will benefit further exploration the potential targets or biomarkers in relapsed SCLC. Certainly, there were several limitations in our study, it was a small sample study from a single institution, which inevitably resulted in a selection bias. More well-designed, prospective, and randomized studies are needed to confirm the conclusion. We anticipate that the next 20 years, more progress will be made in the treatment of SCLC than in the past, and that prognosis for patients with this disease will be greatly improved.

Acknowledgments

Footnote

Reporting Checklist: The authors have completed the REMARK reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1657/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1657/dss

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1657/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1657/coif). The authors have no conflicts of interest to declare.

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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. This study and all experimental protocols were approved by the Ethics Committee of Zhongnan Hospital, Wuhan University (No. 2021017). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Written informed consent was provided by all patients.

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