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RESEARCH

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Patients outcomes in lung adenocarcinoma transforming to small-cell lung cancer after tyrosine kinase inhibitor therapy

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Abstract

Background Non-small cell lung cancer (NSCLC) transforming to small cell lung cancer (SCLC) is one of the mechanisms of resistance to tyrosine kinase inhibitors (TKIs). Cases of NSCLC transforming into SCLC have been discovered. However, we lack concentrated data on the characteristics of this population and the transformed SCLC to aid our insight of the biology and clinical value of NSCLC transforming with positive.

Methods We systematically reviewed the published literatures and summarized the pathological and clinical characteristics, and the prognosis, of published cases.

Results 140 patients with lung adenocarcinoma (LUAD) were included in this study, with a median age of 56.8 years. The median time from the first diagnosis of LUAD transforming to SCLC (ttSCLC) was 20.0 months. The median overall survival (mOS) after the diagnosis of SCLC was 11.0 months (95% CI, 7.41 to 14.59 months). In the univariate analysis, ever smoking (either former or current) was a promising predictor of a shorter ttSCLC (HR, 1.73; 95% CI, 1.14 to 2.62; $P=0.010$). TKIs therapy administered as a second line and beyond treatment was related to a significant delay in SCLC onset compared to first-line therapy (HR, 0.62; 95% CI, 0.40 to 0.96; $P=0.031$). The median progression-free survival (mPFS) on first-line platinum plus etoposide after the conversion to SCLC was 3.0 months. Female appeared to be related to worse outcomes after transformation of SCLC.

Conclusion Transformed SCLC exhibited poor response to primary SCLC classic chemotherapy and immunotherapy. It carries a worse prognosis. Exploring novel therapeutic strategies for transformed SCLC is imperative.

Keywords Non-small cell lung cancer, Transformation, Small cell lung cancer, TKIs, Resistance

Introduction

Lung cancer ranks among the most prevalent malignancies globally and stands as the primary contributor to cancer-related fatalities [1]. It can be categorized into two primary pathological subtypes: non-small cell lung cancer (NSCLC) (85%), with approximately 50% being lung adenocarcinoma (LUAD), and small cell lung cancer (SCLC) (15%) [2]. Generally, SCLC is characterized by high aggressiveness, malignancy, and poor outcomes. The 5-year survival rate is only 5% to 10% [1]. Transformed SCLC is a phenotype of typical SCLC.

Epidermal growth factor receptor (EGFR) mutations are identified in about 50% of advanced NSCLC in Asian

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patients [3]. Anaplastic lymphoma kinase (ALK)-positive tumors constitute approximately 3–7% of NSCLC [4, 5]. Tumors carrying targetable driver oncogenes such as EGFR, ALK, rearranged during transfection (RET) and c-ros oncogene 1 (ROS1) inevitably face treatment resistance and disease progression. Histological transformation into SCLC is among the mechanisms of resistance to TKIs in NSCLC. Lineage plasticity in cancer can result in the transformation of tumor cells into different histological subtypes, leading to treatment resistance [6]. Studies on the mechanism of EGFR-TKIs resistance have revealed that SCLC transformation occurs in 3–14% of TKIs-resistant tumors [7, 8]. A less common and poorly understood resistance mechanism observed in around 1.2% of TKI-resistant ALK-positive NSCLC is lineage conversion, typically manifesting as a histological transformation from adenocarcinoma to neuroendocrine or squamous histology [9]. Neuroendocrine carcinomas are often sensitive, albeit transiently, to platinum-etoposide but are resistant to immune checkpoint inhibitors(ICIs) [10, 11] and have a poorer prognosis [12].In 2006, the first case of SCLC transformed from NSCLC after treatment with EGFR-TKIs was reported [13]. Consequently, numerous reports on the transformation of NSCLC to SCLC and related research have emerged. However, the literature on the patient characteristics, treatment, and prognosis of SCLC transformed from TKI resistance is still limited, and there is a lack of studies with large sample sizes. Transformed SCLC is more aggressive and has a worse prognosis [14], and there are currently no unified treatment guidelines for transformed SCLC.

Therefore, we systematically reviewed the literatures on SCLC patients who transformed from LUAD carrying targeted mutations after receiving TKIs treatment, and aimed to obtain exploratory information on the clinicopathological characteristics of patients with phenotypic transformation of SCLC, and to provide clinical reference for clinicians with the efficacy and prognosis.

Patients and methods

Search strategy

We carried out an extensive review of the literature using the PubMed/Medline database from 2006 to the present. Our search strategy included keywords like "transition from NSCLC to SCLC," "NSCLC conversion to SCLC," "TKI resistance," and "TKI therapy." The search was specifically limited to the human studies in English. Additionally, we manually reviewed reference lists in relevant publications to identify any additional articles. It is worth noting that we excluded scientific conference abstracts from our systematic literature search, considering that the general data and treatment information of the cases available in scientific conference abstracts are limited. In cases of duplicated publications, we opted for the most recent version. The PRISMA flow diagram for this systematic review was shown in Fig. 1.

Inclusion and exclusion criteria

We included case reports that recorded a histopathological shift to SCLC after previous treatment with TKIs for LUAD. The TKIs encompassed in this study included Gefitinib, Icotinib, Erlotinib, Afatinib, Osimertinib, Aumolertinib, Crizotinib, Alectinib, Ceritinib, or Pralsetinib. The diagnosis of SCLC had to be confirmed through high-quality tumor biopsies or well-preserved cytological samples in accordance with the 2015 WHO classification [15].

Statistical analysis

Demographic details, tumor histology, clinical treatments, molecular pathology, and outcomes for all reported cases were meticulously extracted from the included literatures by Shuai Wang and Yongsen Wang. This information was then compiled into a dedicated database and subjected to detailed analysis as a case series.

In our study, we defined ttSCLC as the duration between the initial pathological diagnosis of LUAD and the subsequent biopsy confirming the presence of metachronous SCLC phenotype. The T-ttSCLC interval referred to the time elapsed from the initiation of TKIs treatment to the additional biopsy that revealed the metachronous SCLC phenotype. The t-patients referred to the patients from the initial pathological diagnosis of LUAD to the additional biopsy revealing the metachronous SCLC phenotype. The T-patients referred to the patients from the initial TKIs usage to the additional biopsy revealing the metachronous SCLC phenotype. Survival curves were generated using the Kaplan–Meier method and compared using the log-rank test. Exploratory analyses were conducted using Cox proportional hazards regression models to evaluate the predictive value of patient and tumor characteristics (reported as hazard ratios and 95% confidence intervals) for ttSCLC. Statistical significance was set at P values < 0.05 (two-sided). We performed all statistical analyses using SPSS version 25.0 (SPSS, Armonk, USA) and R package version 4.3.2 (R Foundation for Statistical Computing, Vienna, Austria). For graphical representation, we utilized GraphPad Prism version 8.0.0 (GraphPad Software, San Diego, USA).

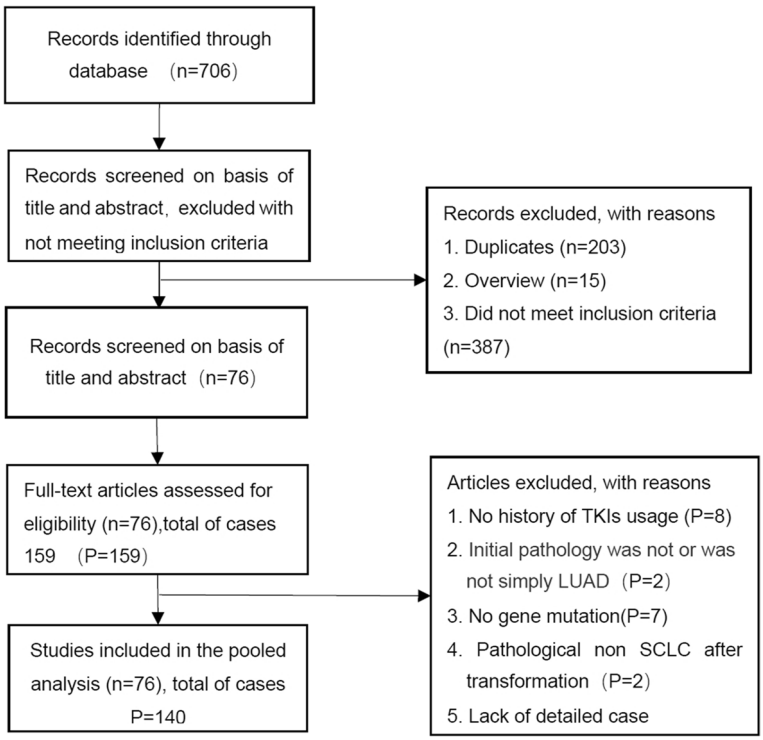

Fig. 1 PRISMA flow-chart of this study

Results

Case characteristics of the incorporated studies

Our search approach yielded a total of 706 articles (Fig. 1). Within this pool,76 articles constituted pertinent accounts of cases undergoing histopathological transformation from LUAD to SCLC after TKIs treatment. Out of the 76 literatures, 61 were individual case reports [10, 16–75], while 15 presented findings small patient series [76–90]. In aggregate, we identified 140 patients who experienced the transformation to SCLC from a previous diagnosis of adenocarcinoma.

Pre-transformation characteristics

Patients characteristics

The baseline characteristics of the 140 identified cases were encapsulated in Table 1.

Among the available data for 131 patients, 64 were male (48.9%), and 67 were female (51.1%). Available in 122 patients, the median age stood at 56.8 years (with a range of 31–84 years). Among 126 patients where smoking status data were available, 43 patients (34.1%), including former smokers, tested positive, while the majority, 83 patients (65.9%), had never smoked. The majority, 83 patients (65.9%), were never smokers. Nearly all cases (99%) were diagnosed of advanced-stage LUAD (TNM stage III or IV), with positivity noted for EGFR mutation (122/140), ALK rearrangement (16/140), ROS1 fusion (1/140) or CCDC6: RET rearrangement (1/140).EGFR mutation profiles were distributed as follows: 93 patients (66.4%) had exon 19-deletion, 24 patients (17.1%) exhibited exon 21-L858R mutation, one patient (0.7%) showed co-mutations of exon 21-L858R and exon 18-G719X, another patient (0.7%) presented with exon 20-S768I mutation, and one patient (0.7%) had exon 18-G719X mutation. Two patients were reported with an EGFR mutation without specifying the involved exon. The remaining 18 patients (12.9%) presented with ALK rearrangement in 16 patients (11.4%), ROS1 fusion in one patient (0.7%) and CCDC6: RET rearrangement in one patient (0.7%).

Among 140 patients, information on TKIs medication was available for 124 patients. Out of the 106 patients harboring EGFR mutations, 88 (83.0%) received first-line therapy, while 18(17.0%) received second-line therapy. 79 patients (74.5%) received first-generation TKIs (Gefitinib, Icotinib, Erlotinib), nine patients (8.5%) received second-generation TKI (Afatinib), and 18 patients (17.0%) received third-generation TKIs (Osimertinib, Aumolertinib). Among the 16 patients with ALK rearrangement, (25.0%) were treated as first-line therapy, 10 (62.5%) as second-line therapy, one (6.25%) as third-line therapy, and one (6.25%) as fifth-line therapy. Out of these, 11 patients (68.75%) used first-generation TKIs (Crizotinib),

Table 1 Clinical characteristics of patients with mutated lung adenocarcinoma transforming to SCLC

Characteristics	t-patients		T-patients	
	Total (n, %)	ttSCLC (95% CI, m)	Total (n, %)	T-ttSCLC (95% CI, m)
Gender	114		103	
Male	53(46.5%)	15.0 m(8.48–21.52 m)	50(48.5%)	15.0 m(10.05–19.95 m)
Female	61(53.5%)	24.0 m(19.33–28.67 m)	53(51.5%)	20.0 m(17.34–22.66 m)
Age(y)	105		103	
≤ 56	49(46.7%)	21.0 m(16.43–25.57 m)	49(47.6%)	20.0 m(14.52–25.48 m)
> 56	56(53.3%)	20.0 m(15.11–24.89 m)	54(52.4%)	16.0 m(10.86–21.14 m)
Smoking	109		98	
Never smoking	75(68.8%)	22.7 m(18.46–26.94 m)	65(66.3%)	18.0 m (14.05–21.95 m)
Ever smoking	34(31.2%)	16.0 m(9.14–22.86 m)	33(33.7%)	18.0 m (11.36–24.64 m)
TNM stage	123		112	
II-III	9(39.1%)	37.0 m(34.08–39.92 m)	10(8.9%)	20.0 m (16.90–23.10 m)
IV	114(60.9%)	19.8 m(16.31–23.29 m)	102(91.2%)	16.0 m (12.19–19.81 m)
Initial mutation	123		112	
EGFR	105(85.4%)	20.0 m(18.07–21.93)	95(84.8%)	18.0 m(15.36–20.64)
ALK	16(13.0%)	13.0 m(2.55–23.45 m)	15(13.4%)	12.0 m (8.21–15.79 m)
ROS1 fusion	1(0.8%)	36.0 m	1(0.9%)	8.0 m
CCDC6: RET fusion	1(0.8%)	14.0 m	1(0.9%)	14.0 m
TKI line	108		111	
1st line	77(71.3%)	18.0 m(13.31–22.69 m)	85(76.6%)	17.0 m(13.66–20.34 m)
Subsequent	31(28.7%)	28.0 m(11.64–44.36 m)	26(23.4%)	18.0 m(5.51–30.49 m)

Abbreviations: *m* months, *t-patients* the patients from the initial pathological diagnosis of LUAD to the additional biopsy revealing the metachronous SCLC phenotype, *T-patients* The patients from the initial TKIs usage to the additional biopsy revealing the metachronous SCLC phenotype, *ttSCLC* the time from the initial pathological diagnosis of LUAD to the additional biopsy revealing the metachronous SCLC phenotype, *T-ttSCLC* The time from the initial TKIs usage to the additional biopsy revealing the metachronous SCLC phenotype, *EGFR* Epidermal growth factor receptor, *SCLC* Small cell lung cancer, *TKI* Tyrosine kinase inhibitor, *ALK* Anaplastic lymphoma kinase, *ROS1* c-ros oncogene 1, *CCDC6*: RET fusion, coiled-coil domain-containing protein 6 (CCDC6)-rearranged during transfection (RET) gene fusion mutation

while five patients (31.25%) opted for second-generation TKIs (Alectinib, Ceritinib). Additionally, one patient with ROS1 fusion received Crizotinib as second-line treatment, and another patient with CCDC6: RET fusion underwent first-line treatment with Pralsetinib, a tyrosine protein kinase receptor RET inhibitor.

Predictors of SCLC transformation

The projected median duration to ttSCLC was 20.0 months (95% CI, 16.90 to 23.11 months), whereas the anticipated median timeframe to T-ttSCLC stood at 17.0 months (95% CI, 13.44 to 20.57 months) (Fig. 2A). Compared with non-smoking patients, the ttSCLC was significantly shorter in smoking patients (16.0 months vs. 22.7 months, $P=0.009$) (Fig. 2B). Assessing the number of lines of TKI application before transformation, there was a significant reduction in ttSCLC when TKI was used in the first-line treatment compared to later-line treatment (18.0 months vs. 28.0 months, $P=0.027$) (Fig. 2C). Gender, age, TNM stage, and initial gene mutation type (EGFR vs. ALK) showed no impact on ttSCLC. In the univariate analysis, ever smoking (either former or current) emerged as a predictor of shorter ttSCLC (HR,1.73; 95% CI, 1.14 to 2.62; $P=0.01$). Administering TKIs therapy as second-line treatment was related to a significant delay in the onset of SCLC compared to first-line therapy (HR, 0.62;95% CI, 0.40 to 0.96; $P=0.031$). Moreover, stage IV was related to an early occurrence of the SCLC phenotype, approaching borderline significance (HR, 1.78; 95% CI, 0.90 to 3.52; $P=0.098$). Age, gender and mutation type (EGFR vs. ALK) showed no association with ttSCLC (Fig. 3).

Post-transformed characteristics

First-line therapy and efficacy

First-line therapeutic data post-transformation were available for a total of 86 cases. (Table 2). Among these, 46 cases (53.5%) received the platinum + etoposide chemotherapy regimen, and the mPFS was 3.0 months (95% CI, 2.05 to 3.95 months)0.19 cases (22.1%) received the platinum + etoposide + TKI regimen, with a mPFS of 3.2 months (95% CI, 2.21 to 4.19 months). 21 cases (24.4%) received other therapies. After transformation to SCLC, the mOS was 5.7 months in the platinum plus etoposide

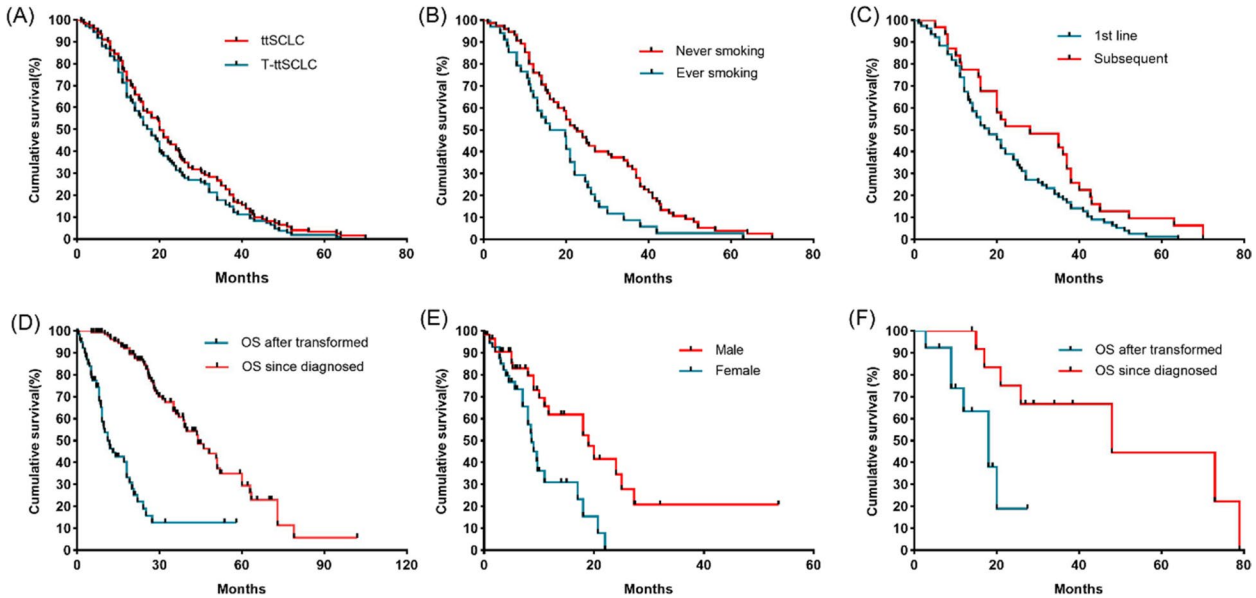

Fig. 2 Time to Small Cell Lung Cancer and Overall Survival (OS). **A** Kaplan–Meier estimates of time from initial diagnosis of LUAD to development of SCLC phenotype (ttSCLC) and time from start of TKI treatment to development of SCLC phenotype (T-ttSCLC). **B** Kaplan–Meier estimates of ttSCLC according to the smoking status (current or former smokers vs. never smokers). **C** Kaplan–Meier estimates ttSCLC according to TKI-line treatment (1st line vs. 2nd line and beyond). **D** Kaplan–Meier estimates of OS after transformed and OS since diagnosed. **E** Kaplan–Meier estimates of OS after occurrence of SCLC according to gender (Male vs. Female). **F** Kaplan–Meier estimates of OS from initial diagnosis of LUAD and OS after occurrence of SCLC in ICIs subgroups

group. The mOS since diagnosis in the platinum + etoposide group and the platinum + etoposide + TKI group were 42.7 months and 59.3 months, respectively, with no statistically significant difference ($P = 0.096$).

Thirteen patients received ICIs after transformation to SCLC (Table 3). Among them, four patients (30.8%) used ICIs for first-line treatment, while nine patients (69.2%) used ICIs for late-line treatment (3rd line and beyond). Immunotherapy efficacy information was available for 11 patients, with an objective response rate (ORR) of 33.3% and a mPFS of 3.0 months (95% CI, 1.58 to 4.42 months). Among these, six cases were treated with EP plus anti-PD-1/PD-L1, and the mPFS was 6.0 months (95% CI, 1.38 to 10.62 months). Treatment information for anti-PD-1/PD-L1 was available for 3 patients, with a mPFS of 2.0 months (95% CI, 1.20 to 2.80 months).

Survival after LUAD transformation to SCLC

Survival data post-SCLC diagnosis was accessible for all 140 patients. The calculated mOS post-SCLC diagnosis was determined to be 11.0 months (95% CI, 7.41 to 14.59 months). And, the mOS from the time of LUAD diagnosis was 44.0 months (95% CI, 35.10 to 52.90 months) (Fig. 2D). In comparison to male, female had a shorter OS after converting to SCLC (19.0 months vs. 86.0 months, $P = 0.002$) (Fig. 2E). However, smoking status, initial mutation type (EGFR vs. ALK), age, TNM stage, and the number of TKI treatment lines had no statistically significant effects on OS after conversion to SCLC. Subgroup analysis using ICIs after conversion to SCLC revealed that the mOS after conversion to SCLC was 18.0 months (95% CI, 10.34 to 25.66 months), and the mOS from the diagnosis to death was 48.0 months (95% CI, 8.40 to 87.54 months)(Fig. 2F).

Discussion

According to reports, histological transformation from NSCLC to SCLC is identified as one of the mechanisms of therapeutic resistance in patients receiving TKIs targeting EGFR, ALK, and ROS1 or immunotherapy [12, 91]. We conducted a systematic search and provided a summary of published studies concerning the transition from LUAD to SCLC, encompassing EGFR, ALK, ROS1, CCDC6: RET, and other potentially targetable driver gene mutations.

As commonly known, resistance to TKIs generally occurs in about one year. Our analysis revealed that the median time estimated for ttSCLC was 20.0 months (95% CI, 16.90 to 23.11 months), and the median time estimated for T-ttSCLC was 17.0 months (95% CI, 13.44 to 20.57 months). When comparing first-line treatment to later-line treatment, the use of TKIs in the first-line significantly shortened ttSCLC (18.0 months vs. 28.0 months, $P = 0.027$). Univariate analysis revealed a

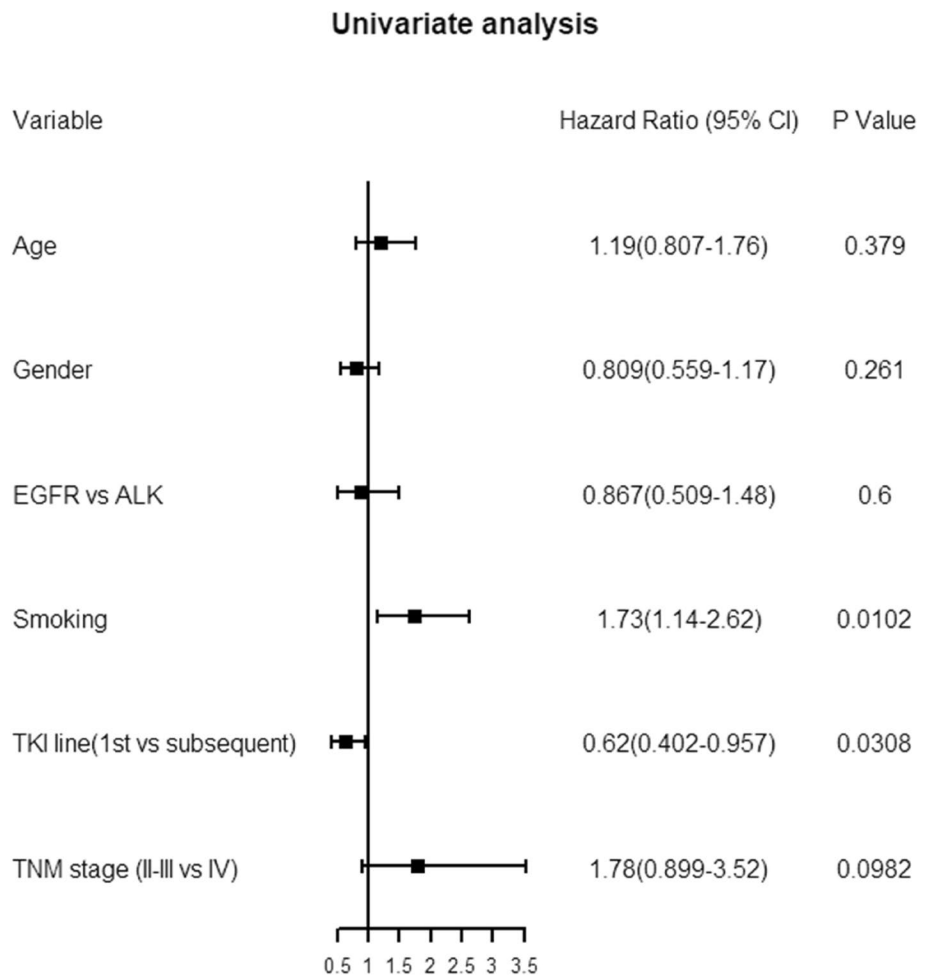

Fig. 3 Forest plots of the effect of several factors on time from initial pathological diagnosis to development of SCLC phenotype

Table 2 First-line treatment and efficacy after SCLC transformation

First line therapy after transformation	Cases (n)	Median PFS (95%CI, m)	Median OS since diagnosed (95%CI, m)
Platinum + etoposide	46	3.0 m (2.05 to 3.95 m)	42.7 m (31.61 to 53.79 m)
Platinum + etoposide + TKI	19	3.2 m (2.21 to 4.19 m)	59.3 m
Others	21	5.0 m (3.42 to 6.58 m)	37.0 m (24.45 to 49.55 m)
Total	86	4.0 m (3.43 to 4.57 m)	40.0 m (33.97 to 46.03 m)

Abbreviations: *SCLC* Small cell lung cancer, *TKI* Tyrosine kinase inhibitor, *PFS* Progression-free survival, *OS* Overall survival

significant delay in the onset of SCLC when TKIs therapy was administered as a second-line treatment compared to first-line treatment (HR, 0.62; 95% CI, 0.40 to 0.96; $P=0.031$).

Previous studies have shown that classic SCLC is closely related to exposure to tobacco carcinogens [92]. In our research, we explored factors predicting histological transformation of SCLC and found that smoking was an independent risk factor associated with shorter ttSCLC, suggesting that tobacco exposure may facilitate the histological transformation of NSCLC to SCLC. In the study results of Elisa Roca et al., female was associated with longer ttSCLC [12]. Li et al. found transformed-SCLC showed an immuno-exhausted status which was associated with the duration of EGFR-TKI before transformation [93]. Our analysis suggested that transformation of SCLC may require long-term exposure to TKIs. Moreover, in our study, female sex is associated

Table 3 Clinical characteristics of patients undergoing immunotherapy after transformation to SCLC

Case No	Sex	Age (y)	Smoking history	Initial mutation	TKIs type using and TKI therapy line	ICIs therapy line	ICIs therapy	PFS (m)	Best response to therapy	Survival time after SCLC diagnosis	Reference No
1	M	84	Y	exon 21 L858R	Osimertinib[1st line]	1st line	EP + durvalumab	19.0 m	CR	19.0 m	[29]
2	F	50	Y	exon 19 deletion	Osimertinib[1st line]	1st line	EP + atezolizumab	6.0 m	PR	6.0 m	[33]
3	M	70	N	exon 19 deletion	Gefitinib[1st line]	1st line	EP + anti-PD-L1	2.0 m	na	10.0 m	[81]
4	M	77	na	EML4-ALK fusion	Alectinib[1st line]	1st line	EP + atezolizumab	5.8 m	PR	9.0 m	[68]
5	F	72	Y	exon 21 L858R	Gefitinib[1st line]	3rd line	Nivolumab	2.0 m	PD	6.0 m	[18]
6	M	43	N	exon 19 deletion	Gefitinib[1st line], Osimertinib[3rd line]	3rd line	EP + durvalumab	1.0 m	PD	18.0 m	[21]
7	F	76	N	exon 21 L858R	Gefitinib[1st line]	3rd line	Nivolumab	1.5 m	PD	14.0 m	[32]
8	F	54	N	exon 19 deletion	Gefitinib[1st line], Osimertinib[2nd line]	3rd line	Anlotinib + docetaxel + carboplatin + nivolumab	1.0 m	PD	2.8 m	[54]
9	F	60	N	exon 19 deletion	Gefitinib[1st line]	4th line	Nivolumab	3.0 m	na	18.0 m	[10]
10	na	na	na	Exon 21 L861Q	Erlotinib[1st line]	4th line	Ipilimumab + nivolumab	1.0 m	PD	12.0 m	[85]
11	M	62	Y	EML4-ALK fusion	Alectinib[2nd line], ceritinib[3rd line]	4th line	Nivolumab	na	PD	20.0 m	[36]
12	M	58	N	EML4-ALK fusion	Alectinib[1st line]	5th line	EP + atezolizumab	3.0 m	na	27.5 m	[34]
13	M	56	Y	exon 19 deletion	Icotinib[1st line]	5th line	pabolizumab	na	na	9.0 m	[55]

Abbreviations: *m* months, *M* Male, *F* Female, *y* years, *Y* ever smoking, *N* Never smoking, *SCLC* Small cell lung cancer, *EP* Carboplatin and etoposide, *EML4-ALK* Echinoderm microtubule-associated protein-like 4 (EML4)-anaplastic lymphoma kinase (ALK) rearrangement, *PD-L1* Programmed death-ligand 1, *PD* Progressive disease, *SD* Stable disease, *PR* Partial response, *CR* Complete response, *PFS* Progression-free survival, *ICIs* Immune checkpoint inhibitors, *TKI* Tyrosine kinase inhibitor, *na* not applicable

with shorter post-conversion OS. This may be related to the exhaustion of the tumor immune microenvironment (TIME) caused by long-term exposure to TKIs. Therefore, Gender appears to be one variable that predicts OS after SCLC transformation. In our study, exon 19-deletion was more common in EGFR mutation profiles. The results of Nicolas et al. showed that among 63 patients with LUAD who underwent SCLC transformation and had EGFR mutations, including exon 19 deletion mutations and exon 21 L858R mutations, exon 19 deletion mutations accounted for 69% [11]. This is consistent with our research conclusions. Facchinetti et al. found no phenomenon related to the histological transformation of SCLC by studying the molecular mechanisms of BRAF V600E NSCLC resistance to BRAF/MEK inhibitors [94]. Case of NSCLC in which CCDC6:RET fusion was found in our study have been reported [63], which was inconsistent with the results of Lin et al.'s study on the resistance of RET fusion-positive NSCLC cancers to selective RET tyrosine kinase inhibitors [95]. In the future, we may discover more LUAD carrying targetable genes that transform into SCLC after the application of TKIs.

The treatment outcomes in patients with transformed SCLC have been reported in only a limited number of studies. Previous studies have shown that many patients underwent cytotoxic chemotherapy following the transformation to SCLC, with the most frequently utilized regimen being SCLC-based chemotherapy (comprising etoposide plus platinum or irinotecan and platinum) [11, 96]. The study results of MarCoux et al. showed that after conversion, the response rates of platinum plus etoposide and taxane were 54% and 50% respectively, and the PFS was 3.4 months and 2.7 months respectively, while patients receiving single or combined ICIs treatment failed to get response [11]. In another retrospective study, the results indicated that after conversion, the mPFS in the group receiving platinum plus etoposide was 3.5 months [97], similar to the findings reported by MarCoux. In our study, platinum plus etoposide chemotherapy was the most common first-line treatment option after transformation to SCLC. Our study, involving 46 patients who received platinum plus etoposide after histological transformation to SCLC, revealed a median PFS of 3.0 months, like previous findings, but shorter than the median PFS of 5.0 months in classic first-line SCLC treatment [98]. In addition, our analysis results showed that in the platinum + etoposide + TKI regimen, the mPFS was 3.2 months, which was not significantly different from the platinum + etoposide group (3.0 months vs. 3.2 months; $P = 0.35$). Research conducted by Wang et al. demonstrated that, compared with chemotherapy without EGFR-TKIs, a subgroup analysis of 16 patients treated with chemotherapy combined with EGFR-TKIs versus eight patients without chemotherapy showed that chemotherapy using EGFR-TKIs improved mPFS (5.2 months vs. 3.0 months, $P = 0.014$) [99]. Nonetheless, there was no statistically significant disparity in OS between patients who underwent chemotherapy with or without EGFR-TKIs (14.8 months vs. 13.0 months; $P = 0.474$). Similarly, in our study, we found no significant difference in OS between patients treated with first-line platinum plus etoposide chemotherapy with or without TKI after histological transformation to SCLC (42.7 months vs. 59.3 months; $P = 0.096$).

In another study, the results indicated that the ORR and disease control rate (DCR) of ICIs treatment, including anti-PD-1/PD-L1 monotherapy or pemetrexed platinum combined with ant-PD-1/PD-L1 treatment, were 0% and 17%, respectively, with a mPFS of 2.0 months [96]. In our study, the survival outcomes from 13 patients who received ICIs alone or in combination after transformation to SCLC showed an ORR of 33.3% and an mPFS of 3.0 months (95%CI, 1.58 to 4.42 months). Additionally, six patients with available survival outcomes received EP plus anti-PD-1/PD-L1, showing a mPFS of 6.0 months (95% CI, 1.38 to 10.62 months). For three patients with information on anti-PD-1/PD-L1 treatment, the mPFS was 2.0 months (95%CI, 1.20 to 2.80 months). In our study, one patient received EC plus Anlotinib (multi-target TKI) plus radiotherapy as a first-line therapy after transformation to SCLC, with a PFS of 4.7 months. Previous research results suggested a mPFS of 6.5 months for the group receiving anlotinib after SCLC transformation [97]. An analysis conducted retrospectively by Zhan et al. indicated that PD-L1 inhibitors combined with chemotherapy ± bevacizumab might be a potentially safe option for patients with SCLC transformation [100].

Nicolas et al. showed that median OS since the time of SCLC was 10.9 months (95% CI, 8.0 to 13.7 months) [11]. In our study, the calculated mOS post-SCLC diagnosis was determined to be 11.0 months, which was similar to previous study. And after transformation to SCLC, the mOS was 5.7 months in the platinum-etoposide group, shorter than the median OS of 10 months in classic SCLC [98]. In addition, in our research, subgroup analysis using ICIs after conversion to SCLC revealed that the mOS after conversion to SCLC was 18.0 months (95% CI, 10.34 to 25.66 months), and the mOS from the diagnosis to death was 48.0 months (95% CI, 8.40 to 87.54 months). Considering the small sample size of the subgroup analysis, the results may be affected, and large-scale data are needed to confirm our findings. With the application of immunotherapy in primary SCLC, it is very necessary to study the characteristics of the tumor immune microenvironment of

transformed SCLC and clarify whether transformed SCLC may can benefit from immunotherapy.

A major limitation of our study is the retrospective collection of patients data from published articles. And the small sample size in subgroup analyses may have caused some results to be underpowered. Moreover, patients had varying baseline gene testing panel ranges, and the known gene testing range was limited. Each panel had different coverage of genes within the testing range, making it challenging to obtain a standardized genomic mutation map before and after transformation. Further exploration will be needed based on large-scale prospective RCT studies in the future. In summary, our comprehensive analysis indicated that NSCLC lineage transformation was a manifestation of TKIs resistance, and the prognosis of transformed SCLC patients was worse.

Conclusion

Limited data are available to recommend the optimal treatment for patients exhibiting lineage transformation to drug-resistant tumors, constituting a distinct clinical subgroup. Irrespective of the presence of oncogene-driven NSCLC, the significance of tissue biopsy and next-generation sequencing (NGS) cannot be overstated, especially as the disease advances. It is crucial to explore new therapeutic strategies for transformed SCLC with predictive biology. Platinum-etoposide is a commonly used treatment with a high response rate and should be considered as the first-line treatment for transformed SCLC. In addition, platinum-etoposide-based combination therapy may be a potential treatment strategy to replace chemotherapy alone. The exact mechanism by which TKIs treatment leads to histological transformation to SCLC remains to be elucidated. Understanding the specific molecular characteristics and signaling pathways of transformed tumors will help find new treatments strategies.

Authors' contributions

Shuai Wang: Conceptualization; Data curation; Writing – original draft; Writing – review & editing. Yongsen Wang: Data curation; Investigation; Methodology; Software. Xuan Wu: Conceptualization; Data curation; Formal analysis; Supervision; Writing – review & editing. Li Yang: Conceptualization; Data curation; Formal analysis. Xiaoju Zhang: Conceptualization; Formal analysis; Investigation; Methodology; Project administration; Supervision; Writing – original draft; Writing – review & editing.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

This retrospective study does not involve original research with human or animal subjects. Therefore, no ethical approval was required. All included studies were reviewed for ethical compliance, and approval for each primary study was obtained by the respective ethics committees.

Consent for publication

All authors provided consent to publish this study.

Competing interests

The authors declare no competing interests.

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