Lung Cancer: Targets and Therapy

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ORIGINAL RESEARCH

Impact of Subsequent Treatment on Clinical Outcomes in Patients with EGFR-Mutant Non-Small Cell Lung Cancer Transformed to Small-Cell Lung Cancer

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Purpose: In epidermal growth factor receptor (EGFR)-mutant non-small cell lung cancer (NSCLC) patients treated with EGFR-tyrosine kinase inhibitors (TKIs), transformation to small-cell lung cancer (SCLC) is associated with poor outcomes, and the optimal treatment strategy is unclear. This study aimed to investigate the clinical factors and treatments associated with outcomes in this group.

Patients and Methods: This retrospective multicenter study enrolled patients with SCLC transformed from advanced NSCLC after progression on EGFR-TKI treatment. We analyzed clinical and demographic characteristics, first-line EGFR-TKI treatments, and subsequent regimens to identify factors associated with clinical outcomes.

Results: Twenty-seven patients diagnosed with SCLC transformation after EGFR-TKI therapy between 2018 and 2023 were enrolled, most of whom had an EGFR exon 19 deletion (67%). The subsequent treatment regimens included traditional chemotherapy (CT) in 12 patients (44%), combined CT/EGFR-TKI in 10 patients (37%), and combined CT/immunotherapy in 5 patients (19%). The median progression-free survival (PFS) with first-line EGFR-TKI treatment, subsequent SCLC treatment, and overall survival (OS) were 16.1 months, 6.4 months, and 39.5 months, respectively. The overall response rate (ORR), disease control rate (DCR), and median PFS for subsequent treatments were 38.5%, 69.2%, and 6.4 months, respectively. The DCRs for subsequent CT, CT/TKI, and CT/immunotherapy were 41.7%, 88.9%, and 100%, respectively. ORR and PFS were higher in the CT/TKI (44.4% and 7.2 months) and CT/immunotherapy (80.0% and 11.3 months) groups compared to CT (16.7% and 3.7 months), but these differences were not statistically significant. Univariate and multivariate analyses showed no significant differences in PFS and OS among treatments.

Conclusion: In patients with SCLC transformed from advanced NSCLC after EGFR-TKI treatment, adding immunotherapy and EGFR-TKI to CT improved DCR and showed trends in ORR and PFS, but did not provide an OS benefit. More prospective studies with varied therapeutic approaches are needed to confirm these findings.

Keywords: EGFR-mutant NSCLC, SCLC transformation, EGFR-TKI, chemotherapy, immunotherapy, clinical outcomes

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Introduction

Non-small cell lung cancer (NSCLC) is the most common type of lung cancer associated with cancer-related mortality. Comprehensive genomic profiling to identify potential target therapy is highly recommended in patients with early and advanced NSCLC to achieve better survival.[1] Epidermal growth factor receptor (*EGFR*) mutations account for 50–60% of all cases of advanced NSCLC in Asian patients,[2] and patients with sensitizing *EGFR* mutations receiving first-line EGFR-tyrosine kinase inhibitor (TKI) treatment have a median progression-free survival (PFS) of 9–18 months.[3] Previous studies have discussed the possible mechanisms for acquired resistance after EGFR-TKI therapy, including T790M mutation, *MET* amplification, and *HER2* amplification, and that they may respond to specific TKIs and provide better outcomes.[3–6] Nevertheless, some patients may develop histologic transformation from NSCLC to small cell lung cancer (SCLC), which is associated with a relatively poor prognosis due to ineffective subsequent therapy.[7–12] It has been estimated that around 3–14% of NSCLCs will transform to SCLCs after EGFR-TKI treatment.[7,13] Regarding treatment outcomes, a multicenter retrospective study reported comparable response and survival rates between patients in whom NSCLC transformed to SCLC and those with classical SCLC.[10] Another retrospective study also indicated that patients with *EGFR*-mutant lung cancer who transformed to SCLC had a high response rate to platinum-etoposide (EP) or taxane chemotherapy (CT) but did not respond well to immunotherapy (IO), which is a standard first-line additional treatment to EP CT for SCLC.[11] Nevertheless, the role of immunotherapy in this setting is unclear based on limited data. If ECGR-TKI is continued, immunotherapy should be avoided due to known toxicity according to NCCN recommendation.[1] Recently, novel therapeutic agents such as tarlatamab, a bispecific T-cell engager immunotherapy targeting delta-like ligand 3, have been approved for the later-line treatment of patients with SCLC.[14] However, few studies have focused on the clinical factors or treatment strategies associated with survival outcomes in these patients. Therefore, the aim of this study was to investigate the clinical factors and different treatment strategies associated with outcomes in patients with EGFR-mutated NSCLC that transformed to SCLC after first-line EGFR-TKI treatment.

Materials and Methods

Patient Population

This retrospective study was conducted at two medical centers and four regional hospitals in Taiwan between January 2018 and December 2023. The inclusion criteria were patients: 1) previously diagnosed with locally advanced or metastatic (stage IIIb/IIIc/IV) NSCLC with an EGFR mutation; 2) received EGFR-TKI as the first-line treatment; and 3) with pathologically confirmed SCLC transformation after disease progression on initial EGFR-TKI treatment. Patients were excluded from the study if they did not receive further anti-cancer treatment or if they were involved in clinical trials. The flowchart of this study is demonstrated in Figure 1. The study followed the Declaration of Helsinki and was approved by the Institutional Review Boards of all participating hospitals.

Data on clinical and demographic characteristics were collected from electronic medical records, including age, sex, smoking status, cancer stage at diagnosis, metastatic sites, EGFR mutation subtype, Eastern Cooperative Oncology Group (ECOG) performance status (PS) score, and comorbid diseases at baseline. First-line EGFR-TKI, sites of progression, sites and histology of re-biopsy, and subsequent regimens (including CT, EGFR-TKI, and IO) after SCLC transformation were also recorded. Outcome analysis included objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), and overall survival (OS).

Statistical Analysis

Continuous variables with non-normal distribution were expressed as median (range), while categorical variables were expressed as frequency (percentage). The Kruskal–Wallis test was used to compare continuous variables among different groups. The chi-square test and Fisher's exact test were used to compare response rates across treatment subgroups. Median PFS and OS were calculated using the Kaplan–Meier method. Subgroup analyses of PFS and OS were conducted based on age, sex, mutation type, number of metastatic sites, TKI generation, site of progression, re-biopsy histology results, and subsequent treatment regimens. Univariate and multivariate Cox regression analyses were performed to assess the impact of clinical factors on patient outcomes across different treatment regimens. All statistical analyses were

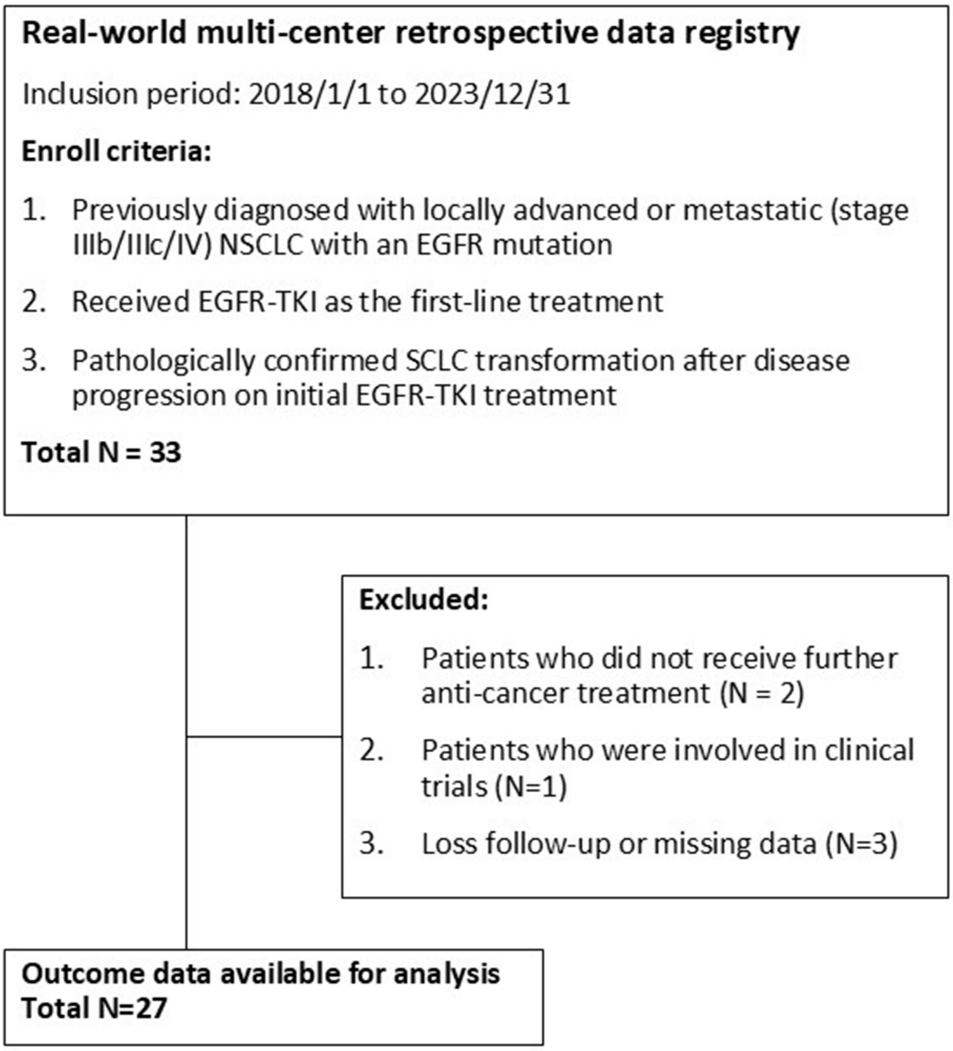

Figure 1 The flowchart of enrolled patients in this study.

carried out using SPSS version 25.0 (IBM Inc., Armonk, NY) and R version 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was defined as $p < 0.05$.

Results

Baseline Characteristics

Thirty-three patients were diagnosed with SCLC transformation after first-line EGFR-TKI therapy, and outcome analysis was available in 27 of these patients. Baseline demographics of the included patients are shown in Table 1. Most patients (18, 67%) had an EGFR exon 19 deletion at the initial diagnosis, and 19 (70%) received afatinib as first-line treatment. At the time of disease progression, 18 (67%), 5 (19%), and 4 (15%) patients had local, distal, and both progressions, respectively. Biopsy of the primary tumor site and new lesion (metastatic) site was performed in 18 (67%) and 9 (33%) patients, respectively. Biopsy histology revealed SCLC combined with adenocarcinoma in 10 (37%) patients and pure SCLC in 17 (63%) patients. The subsequent treatment regimens were traditional CT alone in 12 (44%) patients, CT combined with EGFR-TKI in 10 (37%) patients, and combined CT/IO in 5 (19%) patients. Table 2 shows the baseline characteristics according to different subsequent treatment regimens. There were no significant differences among these three groups except that the proportion of females was highest (75%) in the CT alone group, followed by the CT/TKI group (50%), and there were no females in the CT/IO group.

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Table 1 Baseline Characteristics of the Included Patients

Characteristic	N = 27
Age at diagnosis (years)	60 (51, 67)
Age group	
< 65 years	17 (63%)
≥ 65 years	10 (37%)
Gender	
Female	14 (52%)
Male	13 (48%)
Smoking status	
Non-smoker	17 (63%)
Former smoker	6 (22%)
Current smoker	4 (15%)
ECOG PS	
0–1	27 (100%)
Initial stage	
IV	27 (100%)
Mutation type	
Exon 19 deletion	18 (67%)
Exon 21 L858R	7 (26%)
Exon 18 G719X; Exon 20 S768I	1 (3.7%)
Exon 21 L861Q	1 (3.7%)
No. of metastasis sites	
1	15 (58%)
2	8 (31%)
≥3	3 (12%)
Unknown	1
Initial brain metastasis	8 (31%)
Initial liver metastasis	2 (7.7%)
First line EGFR-TKI	
Afatinib	19 (70%)
Erlotinib	4 (15%)
Gefitinib	2 (7.4%)
Osimertinib	2 (7.4%)

(*Continued*)

Table 1 (Continued).

Characteristic	N = 27
PFS of 1st-line EGFR treatment (months, 95% CI)	16.1 (15.6, 22.4)
Newly developed or progressed brain metastasis	8 (30%)
Site of progression	
Local progression	18 (67%)
Distal progression	5 (19%)
Local and distal progression	4 (15%)
Site of re-biopsy	
Primary tumor	18 (67%)
New lesion	9 (33%)
Re-biopsy histology	
SCLC only	17 (63%)
SCLC combine adenocarcinoma	10 (37%)
Subsequent treatment after SCLC transformation	
Chemotherapy	12 (44%)
Chemotherapy + TKI	10 (37%)
Chemotherapy + Immunotherapy	5 (19%)
Response after transformation treatment	
Partial response	10 (38%)
Progressive disease	8 (31%)
Stable disease	8 (31%)
Unknown	1
PFS of subsequent treatment (months, 95% CI)	6.4 (4.0, 10.8)
OS (months; median, 95% CI)	39.5 (34.3, 48.2)
ORR of subsequent treatment (%, 95% CI)	38.5 (20.2,59.4)
DCR of subsequent treatment (%, 95% CI)	69.2 (48.2, 85.7)

Notes: Chemotherapy included etoposide plus cisplatin/carboplatin; TKI included gefitinib, afatinib, osimertinib, and erlotinib; immunotherapy included durvalumab, pembrolizumab, and atezolizumab.

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status; EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitors; DCR, disease control rate; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; SCLC, small-cell lung cancer.

Clinical Outcome Analysis

As shown in Table 1, demonstrates the median PFS for the first-line EGFR-TKI treatment and subsequent treatment for SCLC transformation were 16.1 (95% CI 15.6–22.4) months (Figure S1) and 6.4 (95% CI 4.0–10.8) months (Figure S2), respectively. Although second-generation TKIs were associated with the longest median OS, there were no significant differences in PFS and OS stratified by different first-line TKIs (Figures S3 and S4). The ORR and DCR of subsequent

treatments for all patients were 38.5% and 69.2%, respectively. Table 2 demonstrates the DCR for subsequent CT, CT/TKI, and CT/IO were 41.7%, 88.9%, and 100% (p = 0.024), respectively. The ORR was also higher in the CT/TKI (44.4%) and CT/IO (80.0%) groups compared to the CT group (16.7%), but did not reach a statistical difference (p = 0.083). Similarly, the PFS rates for subsequent CT, CT/TKI, and CT/IO were 3.7 (95% CI 3.0-NR), 7.2 (95% CI 4.4-NR), and 11.3 months (95% CI 4.1-NR), respectively, but the difference was not significant (p = 0.31) (Figure 2).

Table 2 Baseline Characteristics of the Patients According to Line of Treatment After SCLC Transformation

Characteristic	Chemotherapy N = 12	Chemotherapy+TKI N = 10	Chemotherapy+Immunotherapy N = 5	p-value
Age at diagnosis (years)	59 (51, 68)	62 (58, 66)	57 (50, 70)	>0.9
Age group				0.9
< 65 years	7 (58%)	7 (70%)	3 (60%)	
≥ 65 years	5 (42%)	3 (30%)	2 (40%)	
Gender				**0.019**
Female	9 (75%)	5 (50%)	0 (0%)	
Male	3 (25%)	5 (50%)	5 (100%)	
Smoking status				0.3
Non-smoker	9 (75%)	6 (60%)	2 (40%)	
Former smoker	1 (8.3%)	2 (20%)	3 (60%)	
Current smoker	2 (17%)	2 (20%)	0 (0%)	
ECOG PS				
0–1	12 (100%)	10 (100%)	5 (100%)	
Initial stage				
IV	12 (100%)	10 (100%)	5 (100%)	
Mutation type				>0.9
Exon 19 deletion	8 (67%)	6 (60%)	4 (80%)	
Exon 21 L858R	3 (25%)	3 (30%)	1 (20%)	
Exon 18 G719X; Exon 20 S768I	0 (0%)	1 (10%)	0 (0%)	
Exon 21 L861Q	1 (8.3%)	0 (0%)	0 (0%)	
No. of metastasis sites				>0.9
1	6 (55%)	6 (60%)	3 (60%)	
2	3 (27%)	3 (30%)	2 (40%)	
≥3	2 (18%)	1 (10%)	0 (0%)	
Unknown	1	0	0	
Initial brain metastasis	5 (45%)	1 (10%)	2 (40%)	0.2
Initial liver metastasis	2 (18%)	0 (0%)	0 (0%)	0.7

(*Continued*)

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Table 2 (Continued).

Characteristic	Chemotherapy N = 12	Chemotherapy+TKI N = 10	Chemotherapy+Immunotherapy N = 5	p-value
First line EGFR_TKI				0.3
Afatinib	6 (50%)	9 (90%)	4 (80%)	
Erlotinib	3 (25%)	0 (0%)	1 (20%)	
Gefitinib	2 (17%)	0 (0%)	0 (0%)	
Osimertinib	1 (8.3%)	1 (10%)	0 (0%)	
PFS of 1st-line EGFR-TKI (months; median, 95% CI)	16.0 (15.7, NA)	16.0 (13.7, NA)	18.1 (12.9, NA)	0.94
Newly developed or progressed brain metastasis	3 (25%)	3 (30%)	2 (40%)	0.9
Site of progression				0.3
Local progression	8 (73%)	8 (80%)	2 (40%)	
Distal progression	1 (9.1%)	2 (20%)	2 (40%)	
Local and distal progression	2 (18%)	0 (0%)	1 (20%)	
Unknown	1	0	0	
Site of re-biopsy				0.4
Primary tumor	9 (75%)	7 (70%)	2 (40%)	
New lesion	3 (25%)	3 (30%)	3 (60%)	
Re-biopsy Histology				0.15
SCLC only	10 (83%)	5 (50%)	2 (40%)	
SCLC combine adenocarcinoma	2 (17%)	5 (50%)	3 (60%)	
Response after transformation treatment				**0.045**
Partial response	2 (17%)	4 (44%)	4 (80%)	
Progressive disease	7 (58%)	1 (11%)	0 (0%)	
Stable disease	3 (25%)	4 (44%)	1 (20%)	
Unknown	0	1	0	
PFS of subsequent treatment (months; median survival, 95% CI)	3.7 (3.0, NA)	7.2 (4.4, NA)	11.3 (4.1, NA)	0.31
ORR of subsequent treatment (%; 95% CI)	16.7% (2.1%, 48.4%)	44.4% (13.7%, 78.8%)	80% (28.4%, 99.5%)	0.083
DCR of subsequent treatment (%; 95% CI)	41.7% (15.2%, 72.3%)	88.9% (51.8%, 99.7%)	100% (47.8%, 100%)	**0.024**
OS (months; median survival, 95% CI)	34.4 (29.8, NA)	38.9 (31.4, NA)	42.1 (39.5, NA)	0.92

Notes: Chemotherapy included etoposide plus cisplatin/carboplatin; TKI included gefitinib, afatinib, osimertinib, and erlotinib; immunotherapy included durvalumab, pembrolizumab, and atezolizumab. Bold values indicated statistically significant (p-value < 0.05).

Abbreviations: CI, Confidence Interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitors; DCR, disease control rate; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; SCLC, small-cell lung cancer.

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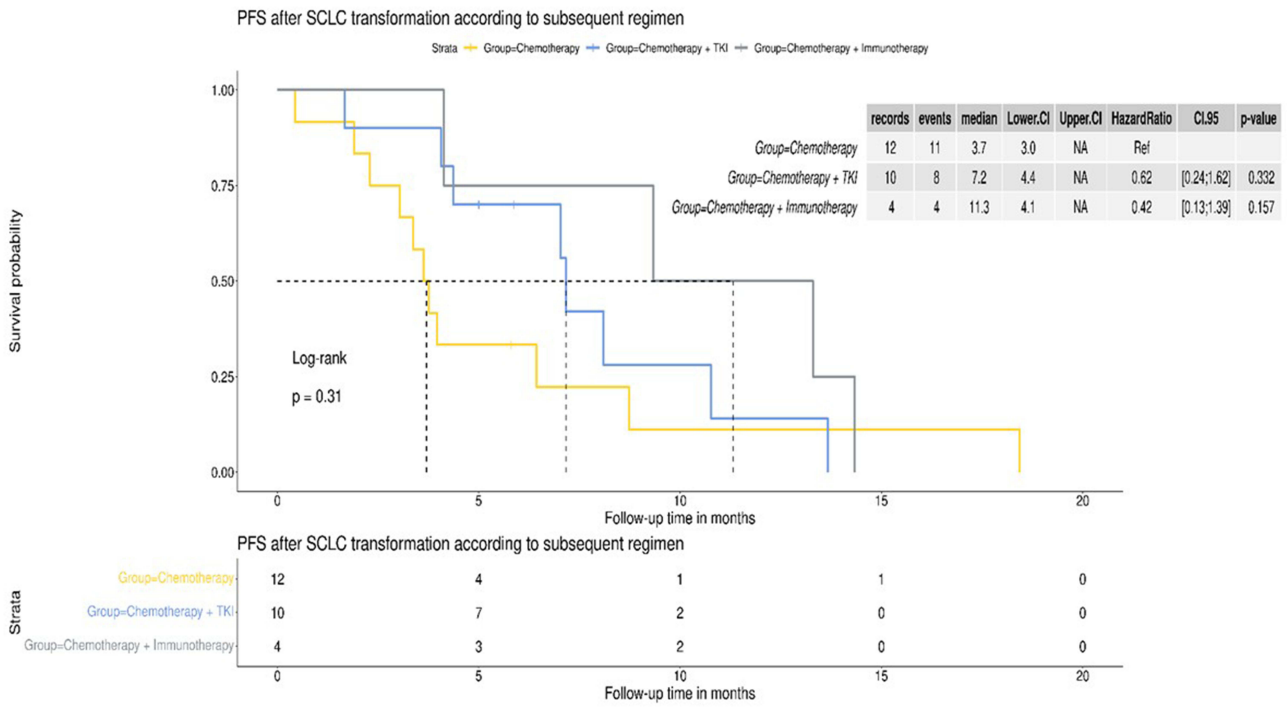

Figure 2 PFS of different subsequent treatments after SCLC transformation.

The median OS for all patients was 39.5 (95% CI 34.3–48.2) months (Figure S5). Stratified analysis by different first-line TKIs did not impact the median OS (Figure S6). The OS rates for subsequent CT, CT/TKI, and CT/IO were 34.4 (95% CI 29.8-NR), 38.9 (95% CI 31.4-NR), and 42.1 (95% CI 39.5-NR) months, respectively (Figure 3). However, univariate and multivariate analyses showed that age, sex, EGFR mutation type, numbers of metastatic sites, TKI generation, and re-biopsy histology were not associated with OS, PFS or SCLC transformation (Tables 3 and 4).

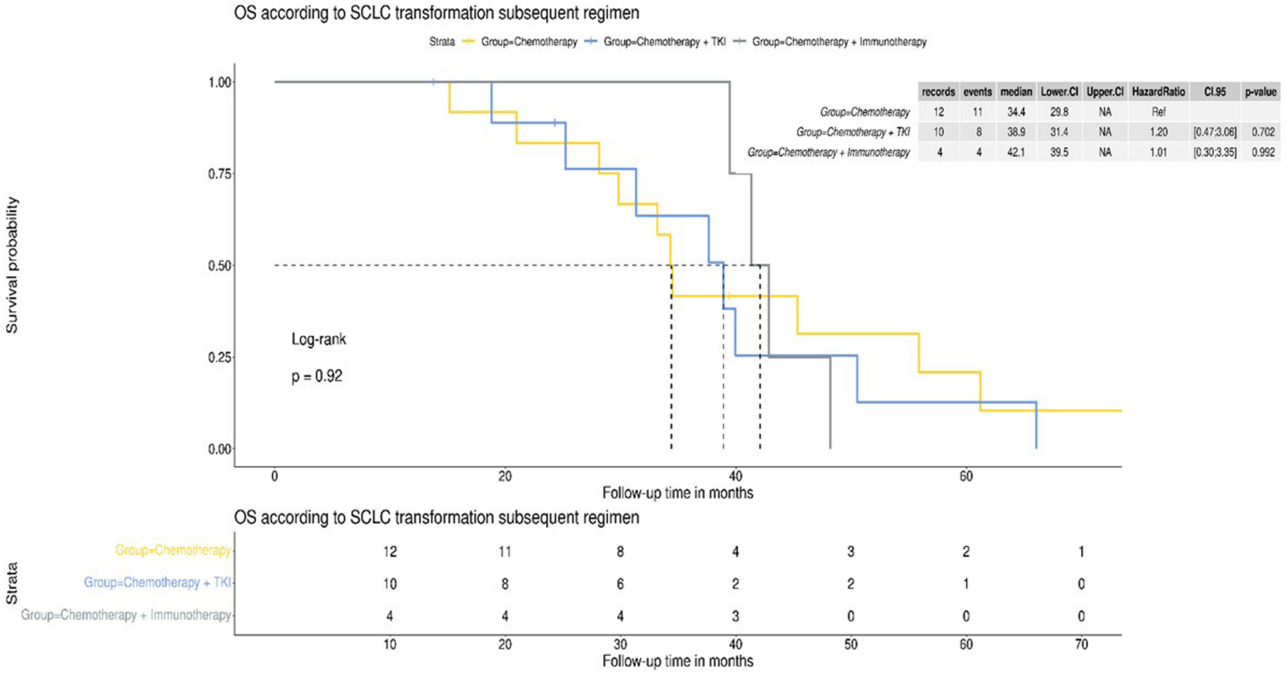

Figure 3 Overall survival stratified by different subsequent treatments.

Table 3 Univariate and Multivariate Cox Regression Models for Potential Predictors of PFS After SCLC Transformation

Characteristic	Univariate Model				Multivariate Model		
	N	HR	95% CI	p-value	aHR	95% CI	p-value
Age group	26						
< 65 years		—	—		—	—	
≥ 65 years		1.67	0.67, 4.15	0.3	1.32	0.28, 6.32	0.7
Gender	26						
Female		—	—		—	—	
Male		0.87	0.37, 2.01	0.7	0.65	0.08, 5.41	0.7
Mutation type	26						
Exon 19 deletion		—	—		—	—	
Exon 21 L858R		1.14	0.41, 3.19	0.8	0.98	0.29, 3.28	>0.9
Others		0.25	0.03, 1.91	0.2	0.10	0.00, 3.10	0.2
No. of metastatic sites	25						
<2		—	—		—	—	
≥2		1.26	0.51, 3.09	0.6	2.72	0.63, 11.7	0.2
EGFR-TKI generation	26						
1st generation		—	—		—	—	
2nd/3rd generation		0.45	0.17, 1.17	0.10	1.00	0.08, 13.2	>0.9
Site of disease progression	25						
Local progression		—	—		—	—	
Distal ± local progression		0.44	0.15, 1.32	0.14	0.37	0.03, 3.92	0.4
Re-biopsy histology	26						
SCLC combine adenocarcinoma		—	—		—	—	
SCLC only		1.80	0.73, 4.46	0.2	1.68	0.19, 14.6	0.6
Subsequent treatment after SCLC transformation	26						
Chemotherapy		—	—		—	—	
Chemotherapy + TKI		0.62	0.24, 1.62	0.3	0.50	0.12, 2.11	0.3
Chemotherapy + Immunotherapy		0.42	0.13, 1.39	0.2	0.35	0.02, 7.80	0.5

Notes: Chemotherapy included etoposide plus cisplatin/carboplatin; TKI included gefitinib, afatinib, osimertinib, and erlotinib; immunotherapy included durvalumab, pembrolizumab, and atezolizumab;

Abbreviations: aHR, Adjusted HR; CI, Confidence Interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitors; DCR, disease control rate; HR, Hazard Ratio, ORR, overall response rate; OS, overall survival; PFS, progression-free survival; SCLC, small-cell lung cancer.

Discussion

In this real-world study, we found that EP-CT was the mainstay treatment for patients with SCLC transformed from advanced NSCLC after disease progression on EGFR-TKI treatment. We also found that adding IO or EGFR-TKI treatment to CT could improve DCR, but did not significantly impact clinical outcomes including PFS and OS.

Table 4 Univariate and Multivariate Cox Regression Models for Potential Predictors of Overall Survival

Characteristic	Univariate Model				Multivariate Model		
	N	HR	95% CI	p-value	aHR	95% CI	p-value
Age group	26						
< 65 years		—	—		—	—	
≥ 65 years		0.74	0.30, 1.81	0.5	0.31	0.05, 2.11	0.2
Gender	26						
Female		—	—		—	—	
Male		1.21	0.49, 2.97	0.7	0.72	0.06, 8.69	0.8
Mutation type	26						
Exon 19 deletion		—	—		—	—	
Exon 21 L858R		0.76	0.27, 2.11	0.6	0.72	0.18, 2.86	0.6
Others		0.28	0.04, 2.24	0.2	0.27	0.01, 10.1	0.5
No. of metastatic sites	25						
<2		—	—		—	—	
≥2		1.08	0.44, 2.64	0.9	1.66	0.31, 8.91	0.6
ECGR-TKI generation	26						
1st generation		—	—		—	—	
2nd/3rd generation		0.89	0.34, 2.31	0.8	0.57	0.03, 12.8	0.7
Site of disease progression	25						
Local progression		—	—		—	—	
Distal ± local progression		0.85	0.33, 2.21	0.7	0.58	0.05, 6.86	0.7
Re-biopsy histology	26						
SCLC combine adenocarcinoma		—	—		—	—	
SCLC only		2.14	0.82, 5.57	0.12	2.14	0.19, 24.3	0.5
Subsequent line of treatment after SCLC transformation	26						
Chemotherapy		—	—		—	—	
Chemotherapy + TKI		1.20	0.47, 3.06	0.7	1.49	0.36, 6.22	0.6
Chemotherapy + Immunotherapy		1.01	0.30, 3.35	>0.9	1.44	0.05, 38.1	0.8

Notes: Chemotherapy included etoposide plus cisplatin/carboplatin; TKI included gefitinib, afatinib, osimertinib, and erlotinib; immunotherapy included durvalumab, pembrolizumab, and atezolizumab;

Abbreviations: aHR, Adjusted HR; CI, Confidence Interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitors; DCR, disease control rate; HR, Hazard Ratio, ORR, overall response rate; OS, overall survival; PFS, progression-free survival; SCLC, small-cell lung cancer.

Currently, tumor re-biopsy is recommended after disease progression on initial EGFR-TKI treatment to assess the resistance mechanism and possible phenotypes, such as SCLC transformation. Previous reports have indicated that around 3–14% will transform to SCLCs after EGFR-TKI treatment.[7,13] Although tissue biopsy remains the standard of diagnosis for SCLC transformation, a recent study indicated that SCLC transformation could also be identified by both cytologic and circulating tumor DNA (ctDNA) analysis of cerebrospinal fluid (CSF).[15] In the present study, we examined

the impact of different histologic components (SCLC combined with adenocarcinoma or pure SCLC) on the sequential treatment or clinical outcomes, however, no significant differences were found in univariate and multivariate analyses.

Most (67%) of our patients harbored an EGFR exon 19 deletion, which is consistent with previous reports by Ferrer et al (75%, 36/48) and Marcoux et al (69%, 46/63).[10,11] A retrospective analysis of genomic profiling of 34 patients with EGFR-mutant NSCLC that had transformed to SCLC revealed a relevant increase in the variant allele frequency of mutations in the TP53 and PIK3CA genes and EGFR exon 19 deletion by liquid biopsy.[16] Nevertheless, why patients with EGFR exon 19 deletions have a higher proportion of SCLC-transformed is still unclear.

In the present study, the median PFS for first-line EGFR-TKI treatment was 16.1 months, which is similar to previous studies by Wang et al (16.0 months) and Isa et al (14.0 months) after initiating EGFR-TKI therapy.[12,17] Ferrer et al analyzed 48 patients with SCLC transformation after EGFR-TKI therapy and reported a tumor response rate of 45% to EP chemotherapy regimens, with a median PFS of 9 months after SCLC transformation and median OS of 28 months.[10] In a retrospective study of 47 patients with SCLC transformation after EGFR-TKI therapy, Saalfeld et al reported ORR, PFS, and OS of 43%, 5 months, and 11 months, respectively.[18] In the present study, the ORR, PFS, and OS were 38.5%, 6.4 months, and 39.5 months. The better OS in our study is probably due to the improvement in later-line treatments after EGFR-TKI resistance in recent years, including re-challenge of EGFR-TKI, and combined therapies such as anti-angiogenesis or amivantamab after disease progression in our patients.

We further analyzed the different subsequent treatments with regard to the clinical outcomes, and found that the DCR and median PFS were better in the CT/IO (100% and 11.3 months) and CT/TKI (88.9% and 7.0 months) groups compared to the CT group (41.7% and 3.7 months), although the difference in PFS did not reach statistical significance. In addition, the median OS was similar among the CT (39.9 months), CT/TKI (37.6 months), and CT/IO (42.1 months) groups. Our results are consistent with a recent study conducted by Zhang et al, who reported 34 SCLC transformed patients do not respond to immunotherapy or continuing TKI post-transformation and no overall survival benefit was found.[16] Another study reported by Saalfeld et al found similar PFS in the CT (4 months), CT/TKI (6 months), and CT/IO (4 months) groups, and also similar median OS (CT, 10 months; CT/TKI, 10 months; and CT/IO, 13 months). Their univariate and multivariate Cox regression analyses did not show a significant association with treatment or other risk factors.[18] This is consistent with the current study, as we also did not find significant associations between clinical demographics or different treatment regimens with PFS or OS after univariate and multivariate analyses. Gay et al provide a classification for four subtypes of SCLC, each with unique molecular features and therapeutic vulnerabilities. An inflamed, mesenchymal subtype predicts the benefit of adding IO to CT.[19] Patients with SCLC transformation are perhaps more aggressive and possibly an "immune-cold" phenotype of SCLC.

In May 2024, the US Food and Drug Administration approved the bispecific delta-like ligand 3 (DLL3) T-cell engager (BiTE) tarlatamab as second and later-line treatment for SCLC patients based on the DeLLphi-301 study, which is the first BiTE therapy to be approved for the treatment of solid tumors.[20] Although the effect of tarlatamab on patients with SCLC transformed from EGFR-mutated NSCLC is still unknown, a recent retrospective study indicated that most tumors in patients with small cell transformation showed the expression of DLL3, which suggests that it may be a novel therapeutic target in these patients.[18]

There are some limitations to this study. First, this is a retrospective cohort study, which may have led to bias in data collection. Second, comprehensive genomic results at the initial diagnosis and/or SCLC transformation were not available; such results could have provided predictive or prognostic outcomes. Third, the dosage of initial EGFR-TKIs and subsequent treatment including CT and IO were inconsistent, which may have affected the treatment outcomes. Finally, the sample size was relatively small, and a larger prospective study is required to validate our findings and identify the potential factors and subsequent treatment choices for these patients.

Conclusion

The results of this study showed that EP-CT is still the mainstay treatment of choice for patients with SCLC transformed from EGFR-mutated NSCLC after disease progression on EGFR-TKI treatment. The addition of EGFR-TKIs or IO to CT did not significantly impact the clinical outcomes including PFS and OS. A large-scale, well-designed study is needed to clarify the optimal subsequent treatment to improve survival outcomes in these patients.

Ethical Approval

The research was conducted in accordance with the approval by the Institutional Review Board (IRB) of four participating hospitals (E-Da Hospital EMRP-112-128, National Taiwan University Hospital NTUH-201910103RIND, Far Eastern Memorial Hospital FEMH-113036-E, Taoyuan General Hospital, Ministry of Health and Welfare TYGH113032, Yang-Ming Chiao Tung University Hospital YMUH-2021A022, and Chang Gung Medical Foundation 202500076B0, respectively), and waived the need to obtain consent for the collection, analysis and publication of the retrospectively obtained and anonymized data for this non-interventional study with the Declaration of Helsinki.

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Disclosure

The authors report no conflicts of interest in this work.

References

1. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology (NCCN Guidelines®) in non-small cell lung cancer. 2024.
2. Shi Y, Au JS, Thongprasert S, et al. A prospective, molecular epidemiology study of EGFR mutations in Asian patients with advanced non-small-cell lung cancer of adenocarcinoma histology (PIONEER). *J Thorac Oncol*. 2014;9(2):154–162. doi:10.1097/JTO.0000000000000033
3. Ferro A, Marinato GM, Mulargiu C, et al. The study of primary and acquired resistance to first-line osimertinib to improve the outcome of EGFR-mutated advanced non-small cell lung cancer patients: the challenge is open for new therapeutic strategies. *Crit Rev Oncol Hematol* 2024;196:104295
4. Jackman D, Pao W, Riely GJ, et al. Clinical definition of acquired resistance to epidermal growth factor receptor tyrosine kinase inhibitors in non–small-cell lung cancer. *J Clin Oncol*. 2010;28:357–360
5. Yu HA, Arcila ME, Rekhtman N, et al. Analysis of tumor specimens at the time of acquired resistance to EGFR TKI therapy in 155 patients with EGFR mutant lung cancers. *Clin Cancer Res* 2013;19:2240–2247.
6. Leonetti A, Sharma S, Minari R, Perego P, Giovannetti E, Tiseo M. Resistance mechanisms to osimertinib in EGFR-mutated non-small cell lung cancer. *Br J Cancer* 2019;121:725–737.
7. Sequist LV, Waltman BA, Dias-Santagata D, et al. Genotypic and histological evolution of lung cancers acquiring resistance to EGFR inhibitors. *Sci Transl Med*. 2011;3(75):75ra26.
8. Norkowski E, Ghigna MR, Lacroix L, et al. Small-cell carcinoma in the setting of pulmonary adenocarcinoma. *J Thorac Oncol* 2013;8:1265–1271.
9. Lee JK, Lee J, Kim S, et al. Clonal history and genetic predictors of transformation into small-cell carcinomas from lung adenocarcinomas. *J Clin Oncol* 2017;35:3065–3074.
10. Ferrer L, Levra MG, Brevet M. A Brief Report of transformation from NSCLC to SCLC: molecular and therapeutic characteristics. *J Thorac Oncol* 2018;14:130–134.
11. Marcoux N, Gettinger SN, O'Kane G, et al. EGFR-mutant adenocarcinomas that transform to small-cell lung cancer and other neuroendocrine carcinomas: clinical outcomes. *J Clin Onco* 2018;37:278–285.
12. Mambetsariev I, Arvanitis L, Fricke J, et al. Small cell lung cancer transformation following treatment in EGFR-mutated non-small cell lung cancer. *J Clin Med* 2022;11:1429.
13. Yu HA, Arcila ME, Rekhtman N, et al. Analysis of tumor specimens at the time of acquired resistance to EGFR-TKI therapy in 155 patients with EGFR-mutant lung cancers. *Clin Cancer Res*. 2013;19(8):2240–2247. doi:10.1158/1078-0432.CCR-12-2246
14. Dhillon S. Tarlatamab: first approval. *Drugs*. 2024;84(8):995–1003. doi:10.1007/s40265-024-02070-z
15. Lin JX, Yin K, Yan LX, et al. Combination of cytologic findings and circulating tumor DNA from cerebrospinal fluid revealed SCLC transformation in patients with leptomeningeal metastases of lung adenocarcinoma. *JTO Clin Res Rep*. 2024;5(9):100704. doi:10.1016/j.jtocrr.2024.100704
16. Zhang B, Lewis W, Stewart CA, et al. Brief report: comprehensive clinicogenomic profiling of small cell transformation from EGFR-mutant NSCLC informs potential therapeutic targets. *JTO Clin Res Rep*. 2024;5(2):100623. doi:10.1016/j.jtocrr.2023.100623
17. Wang W, Xu C, Chen H, et al. Genomic alterations and clinical outcomes in patients with lung adenocarcinoma with transformation to small cell lung cancer after treatment with EGFR tyrosine kinase inhibitors: a multicenter retrospective study. *Lung Cancer*. 2021;155:20–27. doi:10.1016/j.lungcan.2021.03.006
18. Saalfeld FC, Moller J, Christopoulos P, et al. Small cell transformation in EGFR-mutated non-small cell lung cancer: DLL3 expression and efficacy of immune checkpoint inhibitors or tyrosine kinase inhibitors combined with chemotherapy. *Eur J Cancer*. 2024;213:115065. doi:10.1016/j.ejca.2024.115065
19. Gay CM, Stewart CA, Park EM, et al. Patterns of transcription factor programs and immune pathway activation define four major subtypes of SCLC with distinct therapeutic vulnerabilities. *Cancer Cell*. 2021;39(3):346–360e7. doi:10.1016/j.ccell.2020.12.014
20. Ahn MJ, Cho BC, Felip E, et al. Tarlatamab for patients with previously treated small-cell lung cancer. *N Engl J Med*. 2023;389(22):2063–2075. doi:10.1056/NEJMoa2307980