Clinical characteristics and gene mutation analysis of patients with transformed small-cell lung cancer

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Research Article

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Abstract

Background

Transformed small-cell lung cancer (T-SCLC) is one of the mechanisms by which lung adenocarcinoma (LADC) becomes resistant to treatment with epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs). However, this phenomenon remains poorly understood. The study aims to analyze the clinical features and gene mutation characteristics of T-SCLC patients in our hospital.

Methods

Clinical data were collected from 2013–2022 on patients with the initial diagnosis of LADC treated with EGFR-TKIs followed by re-biopsy case type transform into SCLC in our hospital, and their clinical features, tumor pathology, gene mutation characteristics, clinical treatment, and prognosis were analyzed.

Results

A total of 6 (6/362, 1.7%) patients with T-SCLC who were all initially diagnosed with LADC and all had EGFR 19 or 21 mutation, the same mutation status as after transformation, as well as combined RB1, TP53, PIK3CA, PTEN, FGFR, YES1 mutation. The mean progression-free survival after EGFR-TKIs treatment was 33.3 months (IQR, 28.8–37.5 months), compared to 3.6 months (IQR, 2.6-5.0 months) after T-SCLC. 4 cases transformed to SCLC and 2 cases to compound SCLC after TKIs treatment; the mean increase in Neuron-specific enolase (NSE) after conversion was 11.6-fold. The follow-up first-line treatment regimen was etoposide-platinum in all cases. There are currently 3 cases of survival and 3 deaths, with a mean overall survival of 51.7 months (IQR, 42.8–60.5 months).

Conclusions

LADC may transform into SCLC after the failure of EGFR-TKIs. Dynamic NSE changes should be monitored and aggressive re-biopsy should be performed to clarify the mechanism of drug resistance. Multidisciplinary treatment should be provided for T-SCLC, and an integrated treatment strategy based on chemotherapy, Anlotinib and radiotherapy should be considered to improve the prognosis.

Introduction

Lung cancer, a malignancy originating from bronchial or alveolar cells, is the leading cause of cancer-related deaths worldwide and imposes a heavy disease burden worldwide. Non-small-cell lung cancer (NSCLC) accounts for 85% of lung cancers and small cell lung cancer (SCLC) for 15%. Epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs), such as Gefitinib, Afatinib, and Osimertinib, play a powerful therapeutic role for NSCLC carrying EGFR gene mutation While progression-free survival (PFS) has even reached 18.9 months, the progression of tumor resistance is still unavoidable. One important mechanism of resistance is the transformation of NSCLC to SCLC, known as Transformed small-cell lung cancer (T-SCLC). This rare mechanism was first reported in 2006 in the New England Journal of Medicine in a non-smoking, female patient treated with Erlotinib for an EGFR19 mutation. As research continues and re-biopsy cases increase, this histologic transformation (HT) resistance mechanism has been identified in an increasing number of patients, accounting for approximately 2.8%-13.5% of drug resistance mechanisms.

Furthermore, because NSCLC and SCLC originate from different cells, they were once considered to be two distinct diseases requiring different treatment strategies. However, SCLC transformation has turned the traditional perception of lung cancer on its head. T-SCLC has now been found to have similar clinical features to primary SCLC, with short-term effectiveness to chemotherapy and a median survival of only about 1 year. Several studies have identified potential mechanisms by which both can originate from a common precursor cell, the alveolar type II cell. While T-SCLC retains its original EGFR mutation, Studies have found that Retinoblastoma1 (RB1) deletion and tumor protein p53 (TP53) mutation and somatic copy number variation (CNV) are closely associated with T-SCLC. The exact molecular mechanism of T-SCLC is still unclear. As a special phenomenon of lung cancer, T-SCLC lacks timely diagnosis and effective therapeutic strategies. The poor prognosis and short survival of these patients pose a great challenge to the prevention and treatment of lung cancer, and an in-depth understanding of the disease characteristics of these patients is of great clinical significance. Therefore, this study aims to better understand T-SCLC by analyzing the clinical features, tumor pathology, gene mutation characteristics, clinical treatment, and prognosis of all T-SCLC patients, and thus improve the awareness and ability of diagnosis and treatment.
Materials And Methods

Patients

Patients with an initial diagnosis of LADC treated with EGFR-TKIs and re-biopsy after treatment with T-SCLC from January 1, 2013 to December 31, 2022 in our hospital were consecutively included as study subjects. Inclusion criteria: 1. Initial histopathological confirmation of LADC with stage IIIb-IV; 2. Genetic testing for EGFR gene-sensitive mutation (including exon 18 G719X mutation, exon 19 deletion mutation, exon 21 L858R mutation, etc.); 3. Treatment with EGFR-TKIs and after progression of drug resistance, the patient underwent a repeat histopathological biopsy with pathological type confirmed as SCLC; 4. Detailed information on clinical treatment and survival follow-up is available. Exclusion criteria: 1. Patients with stage IIIb-IV lung adenocarcinoma resistant to EGFR-TKIs who have not been re-biopsied or whose histopathological type has not converted to SCLC; 2. Patients with incomplete clinical data or who have been missed during follow-up.

Data Collection And Follow-up

Their clinical data (including gender, age, smoking history, family history of tumor, clinical stage, etc.), tumor pathology, gene mutation characteristics, tumor markers, clinical treatment and prognosis were collected, and their clinical characteristics were analyzed. All patients were followed up regularly, with the last follow-up visit on 2023.02.01. The histopathological findings of the patients included were reviewed again by two experienced pathologists. Informed consent for genetic testing and re-biopsy was obtained from patients and families at the time of consultation for all patients.

Objective tumor efficacy was evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST 1.1), with Progression-Free-Survival (PFS) defined as the time from the start of treatment with EGFR-TKIs until disease progression or death from any cause. Overall survival (OS) is defined as the time from the time a patient receives EGFR-TKIs therapy until the patient dies.

The study was approved by the hospital ethics committee. The study was conducted in accordance with the Declaration of Helsinki.

Statistical analysis

The categorical variables were presented as n (%) and the continuous variables as mean and interquartile range (IQR, Q1-Q3). Descriptive statistics were performed using SPSS 23.0 software (IBM Inc, Chicago, IL, USA). The bioinformatic analyses for EGFR mutation test, Hematoxylin and eosin (H&E) staining, and Immunohistochemistry were performed by our hospital and commercial vendors.

Results

Patients and clinical characteristics

A total of 362 patients with IIIb-IV LADC carrying EGFR-TKIs-sensitive mutation were screened in this study. 6 patients finally met the inclusion criteria and the incidence of T-SCLC was 1.7%. Four of them were male and two were female; the mean age was 53 years. 2 patients had a history of smoking. All patients had no family history of tumor; the first symptom was cough in 2 patients, chest tightness in 2, chest and back pain in 1 and no obvious symptoms in 1 (lung mass found on physical examination); the clinical stage of all patients was stage IV; as for the type of tissue specimen, 4 were lung tissue, 1 was pleural biopsy and 1 was pleural fluid. The basic characteristics of the patients are shown in Table 1. 6 patients were treated with EGFR-TKIs including Gefitinib, Osimertinib, Crizotinib and Erlotinib, and the mean PFS of EGFR-TKIs treatment was 33.3 months (IQR, 28.8–37.5 months). 4 cases were transformed to SCLC after EGFR-TKIs treatment, 1 case of compound SCLC (SCLC-adenocarcinoma) and 1 case of compound SCLC (SCLC-adenosquamous carcinoma). All T-SCLC patients with TKIs-resistant subsequent first-line treatment regimens were etoposide-platinum (EP), with a mean PFS of 3.6 months (IQR, 2.6-5.0 months). Other subsequent treatments: case 1, Anlotinib, Almonertinib - Gefitinib, EP-sintilimab, radiotherapy and integrated treatment; case 2, see next paragraph; case 3, radiotherapy and integrated treatment; case 4, Erlotinib, Anlotinib, irinotecan-cisplatin; case 5, radiotherapy, integrated treatment and palliative care; case 6, irinotecan-cisplatin, Temozolomide, palliative care. Three cases are currently alive, cases 1, 2 and 4 died due to disease progression. The remaining patients survived the follow-up period with a mean overall survival of 51.7 months (IQR, 42.8–60.5 months). Characteristics of patients before and after transformation are shown in Table 2.
Table 1
Patients’ basic characteristics

<table>
<thead>
<tr>
<th>ID#</th>
<th>Sex</th>
<th>Age</th>
<th>Past history</th>
<th>Smoking history</th>
<th>Family history of tumor</th>
<th>Primary symptom</th>
<th>Clinical stage</th>
<th>Baseline histology</th>
<th>Sample type</th>
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<tr>
<td>1</td>
<td>M</td>
<td>57</td>
<td>Gallstone</td>
<td>Yes</td>
<td>No</td>
<td>Cough</td>
<td>T3N0M1a</td>
<td>ADC</td>
<td>Lung biopsy</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>68</td>
<td>Uterine fibroids, Allergic rhinitis</td>
<td>No</td>
<td>No</td>
<td>Chest and back pain</td>
<td>T3N2M1a</td>
<td>ADC</td>
<td>Pleura biopsy</td>
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<tr>
<td>3</td>
<td>M</td>
<td>44</td>
<td>Hypertension</td>
<td>Yes</td>
<td>No</td>
<td>Chest tightness</td>
<td>T4N0M1a</td>
<td>ADC</td>
<td>Hydrothorax</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>48</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Cough</td>
<td>T4N2M1a</td>
<td>ADC</td>
<td>Lung biopsy</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>50</td>
<td>Arthrolithiasis</td>
<td>No</td>
<td>No</td>
<td>Chest tightness</td>
<td>T4NxM1c</td>
<td>ADC</td>
<td>Lung biopsy</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>52</td>
<td>Hypertension</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>T4N0M1a</td>
<td>ADC</td>
<td>Lung biopsy</td>
</tr>
</tbody>
</table>

ADC, adenocarcinoma.

Table 2
Characteristics of patients before and after transformation

<table>
<thead>
<tr>
<th>ID#</th>
<th>Gene mutation</th>
<th>Primary TKI</th>
<th>PFS</th>
<th>Re-histology</th>
<th>Re-gene detection</th>
<th>First-line treatment</th>
<th>PFS</th>
<th>CEA before</th>
<th>CEA after</th>
<th>NSE before</th>
<th>NSE after</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>EGFR21 L858R</td>
<td>Gifitinib, Osimertinib</td>
<td>30m</td>
<td>SCLC</td>
<td>L858R, T790M</td>
<td>EP</td>
<td>4m</td>
<td>8.65</td>
<td>2.03</td>
<td>28.97</td>
<td>ND</td>
<td>52m alive</td>
</tr>
<tr>
<td>2</td>
<td>EGFR19</td>
<td>Gifitinib, Osimertinib</td>
<td>36m</td>
<td>SCLC</td>
<td>EGFR19, TP53, Rb1, FGFR1, YES1</td>
<td>EP + Osimertinib</td>
<td>5m</td>
<td>169.5</td>
<td>15.08</td>
<td>10.99</td>
<td>112.6</td>
<td>45m</td>
</tr>
<tr>
<td>3</td>
<td>EGFR19, PTEN, TP53</td>
<td>Gifitinib, Osimertinib</td>
<td>42m</td>
<td>SCLC</td>
<td>EGFR19, PTEN, TP53</td>
<td>EP</td>
<td>5m</td>
<td>8.42</td>
<td>4.41</td>
<td>12.19</td>
<td>30.69</td>
<td>53m alive</td>
</tr>
<tr>
<td>4</td>
<td>EGFR19, c-met</td>
<td>Erlotinib, Erlotinib + Crizotinib</td>
<td>31m</td>
<td>SCLC</td>
<td>EGFR19</td>
<td>EP</td>
<td>3m</td>
<td>6.15</td>
<td>8.81</td>
<td>2.5</td>
<td>51.48</td>
<td>36m</td>
</tr>
<tr>
<td>5</td>
<td>EGFR19, PTEN, TP53</td>
<td>Gifitinib, Osimertinib</td>
<td>36m</td>
<td>Complex SCLC</td>
<td>EGFR19, PTEN, TP53, PIK3CA</td>
<td>EP</td>
<td>1.5m</td>
<td>233.2</td>
<td>30.39</td>
<td>ND</td>
<td>370</td>
<td>59m</td>
</tr>
<tr>
<td>6</td>
<td>EGFR19</td>
<td>Icotinib</td>
<td>25m</td>
<td>Complex SCLC</td>
<td>EGFR19, PIK3CA</td>
<td>EP</td>
<td>3m</td>
<td>13.32</td>
<td>60</td>
<td>3.42</td>
<td>107.42</td>
<td>65m alive</td>
</tr>
</tbody>
</table>

EGFR, epidermal growth factor receptor; c-met, hepatocyte growth factor receptor; PTEN, phosphatase and tension homolog; PIK3CA, phosphatidylinositol-3-kinase catalytic subunit alpha; TP53, tumor protein p53; Rb1, retinoblastoma1; FGFR1, fibroblast growth factor receptor 1; YES1, YES proto-oncogene 1; SCLC, small cell lung cancer; EP, platinum-etoposide; PFS, progression-free-survival; OS, oversurvival; CEA, carcinoembryonicantigen, Reference range: 0-4.30 ng/mL; NSE, neuron specific enolase, Reference range: 0-16.30 ng/mL; ND, not-detected.

Mutation Characteristics Before And After Transformation

Among the 6 patients with EGFR mutation, 5 had 19 mutation and 1 had 21 mutation; 2 had TP53 and phosphatase and tension homolog (PTEN) mutation and 1 had hepatocyte growth factor receptor (c-met) mutation before transformation; 6 patients were biopsied and genetically tested again after transformation, and the original EGFR mutation were unchanged, but 3 of them had P53 mutation, 2 PTEN mutation, 2 PIK3CA mutation, 2 PTEN mutation, 1 Rb1 mutation, and rare fibroblast growth factor receptor 1 (FGFR1) and YES proto-oncogene 1 (YES1) mutation. See Table 2.
Changes In Tumor Biomarkers

Carcinoembryonic antigen (CEA) decreased in 4 cases and increased in 2 cases post-transformation; except for 2 cases with missing data, neuron-specific enolase (NSE) was significantly increased in all 4 cases, with an average increase of 11.6-fold. See Table 2.

Typical Case Description

Case 2 is a typical case of T-SCLC, divided into 4 stages according to the patient's disease progression characteristics, 4 biopsies and treatment.

Stage 1-Initial diagnosis: The patient presented to our hospital in August 2018 with pain in the right side of the chest and back, and underwent chest computerized tomography (CT): right pleural effusion and right lung infection. Positron emission tomography-computed tomography (PET-CT) suggested the presence of pleural metastases and bone metastases, and genetic testing (common 8 genes) suggested EGFR 19 mutation; programmed cell death ligand 1 (PD-L1) 0%. A definitive diagnosis of stage IVa LADC (T3N2M1a) with EGFR 19 mutation was made and oral Gefitinib was administered.

Stage 2-Gefitinib resistance: A repeat chest CT after 16 months of Gefitinib treatment suggested stable lung condition, but a bone scan suggested new bone metastases and tumor assessment considered progressive disease (PD). CT-guided percutaneous lung puncture biopsy, pathological biopsy of LADC, genetic testing (common 8 genes) showed EGFR 19 mutation (28.73% abundance), T790M mutation, and adjustment of treatment regimen to Osimertinib therapy.

Stage 3-Osimertinib resistance: 20 months after Osimertinib treatment, a repeat chest CT revealed an enlarged mass in the dorsal segment of the right lower lobe, and the tumor was assessed for disease progression again. Bronchoscopic pathological biopsy: small-cell lung cancer. Genetic testing (next-generation sequencing, NGS) showed EGFR 19 mutation (42.4% abundance), RB1 mutation, TP53 mutation, FGFR1 gene fusion, FGFR1 gene copy number amplification, and YES1 gene copy number amplification. The treatment regimen was adjusted to EP regimen of systemic chemotherapy (7 cycles in total) and continued in combination with Osimertinib. A repeat tumor assessment revealed PD and hemoptysis. After a multidisciplinary consultation, the patient was treated with radiofrequency knife 5 times and his symptoms improved.

Stage 4-Chemotherapy and targeted drug resistance: On 24 March 2022, the patient had a repeat chest CT indicating progression of the lung mass, new metastases in the pleura and liver metastases. Ultrasound-guided liver aspiration biopsy and pathological diagnosis of small cell carcinoma of the lung. On 15 April, the patient was readmitted with pain in the left lower abdomen and was considered to have acute intestinal obstruction due to multiple metastases in the abdominal cavity. However, the patient's tumor was advanced and the disease progressively progressed, culminating in respiratory failure and heart failure, and he died in May 2022.

Interestingly, firstly, the patient had only a pleural effusion and no lung mass in the early stages, and as the disease progressed a mass appeared and gradually increased in size. Secondly, in addition to the usual EGFR, TP53 and Rb1, mutation in the FGFR1 and YES1 genes were also found. Finally, the patient underwent four pathological biopsies, the first two for adenocarcinoma, the third for SCLC and the fourth for SCLC (liver metastases). The four pathological biopsies and the corresponding chest CT presentations are shown in Fig. 1.

Discussion

HT is one of the important mechanisms of drug resistance in NSCLC and has important implications for the treatment and prognosis of lung cancer. In patients with EGFR mutation, the most common transformation is from LADC to small-cell histology. Here, we analyzed the clinical features and gene mutation characteristics of six patients with LADC transformed into SCLC after EGFR TKIs treatment and found that the incidence of T-SCLC was 1.7% in our single center, which was lower than in multiple studies (2.8%-13.5%). It is suggested that the low rate of re-biopsy in patients may be mainly related to the low awareness of clinicians and the lack of willingness of patients. Most T-SCLC occurs between 10 months and 3 years after TKIs treatment.\textsuperscript{5,6,9,14,15} The mean time to conversion for patients at our center was 33.3 months, which is at a high level. Clinicians should consider the possibility of histologic transformation to SCLC in patients with changes in clinical presentation and disease progression after TKIs treatment failure, and should actively mobilize patients for re-biopsy to clarify drug resistance mechanisms and determine the next best treatment option.

The specific mechanism of T-SCLC is unclear, and three main hypotheses have been proposed. The first hypothesis is that there may be a composite component in the original tumor tissue, and the small amount of SCLC component present remains after multiple treatments and gradually transforms into the dominant clone. Li et al.\textsuperscript{16} found that eight of the eleven initial HT samples contained a small amount of
SCLC, suggesting pseudo-small cell transformation. However, SCLC transformation was also observed in patients who underwent tumor surgery to remove large specimens. Furthermore, if SCLC remains after LADC treatment, the high malignancy, rapid progression, and short survival of SCLC are inconsistent with the biological characteristics of long-term survival, slow progression, and rapid progression of disease after HT in patients with T-SCLC. In case 2 thoracoscopy pleural biopsy, we took material from multiple parts of the pleura with a large volume of tissue, and the possibility of missing SCLC was extremely small. In contrast, the pathological results of different sites of percutaneous lung puncture in case 2 did not reveal the tissue type of SCLC. The initial biopsies of the six patients included in the study were all LADC, and no combined small-cell component was seen. So there is less support for the first hypothesis.

A second hypothesis considers T-SCLC as a second primary tumor. Primary SCLC carrying EGFR mutation is rare and does not respond to TKIs therapy. The EGFR mutation status carried by LADC at baseline was found to be identical to that carried by T-SCLC in our study, consistent with the results of several studies. The current studies do not support this hypothesis.

A third hypothesis suggests that SCLC and adenocarcinoma may originate from common tumor pluripotent stem cells carrying EGFR mutation that transform to SCLC in response to TKIs treatment, and oncogene inactivation factors. Alveolar type II cells may be a common precursor of both. Genome-wide assays and clonal correlation analysis of tumor tissue before and after SCLC transformation have revealed that clonal branching of T-SCLC may occur prior to TKIs therapy, or even prior to the diagnosis of lung cancer. The absence of EGFR signaling in resistant pluripotent stem cells following EGFR-TKIs therapy accumulation of additional genetic alterations (e.g. Deletion of RB1 and TP53) and in response to different epigenetic factors, eliminates the drive to differentiate along the NSCLC lineage and drives the expansion of tumor pluripotent stem cells along the SCLC lineage. The deletion or low expression of two oncogenes, RB1 and TP53, can also promote the transformation of NSCLC to SCLC. Sutherland et al. selective targeting of Tp53 and Rb1 in type II alveolar cells led to the development of SCLC, revealing that alveolar type II cells have the potential to transform into SCLC cells. The majority of current studies support this hypothesis. Recent studies have found that activation of the Notch signaling pathway, myc proto-oncogene (MYC) amplification, PIK3CA mutation, PTEN deletion, apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like (APOBEC)-induced hypermutation, and somatic CNV are also involved in SCLC transformation. The mechanism of T-SCLC transformation is still unknown and needs to be investigated in more depth.

In EGFR-mutated advanced NSCLC, the common combined mutation are TP53, RB1 or PIK3CA, among which TP53 mutation account for approximately 50%-60%. TP53 mutation reduce patient PFS and OS and are associated with disease progression and poorer prognosis. TP53 mutation are a poorer prognosis for patients with EGFR-mutated advanced NSCLC Independent risk factors. Three of the six patients in our study combined with TP53 mutation had a mean PFS and OS of 38.0 and 52.3 months, respectively, with a long PFS and OS. Lee et al. found that EGFR mutant LADC with RB1 and TP53 inactivation had a 42.8 times higher risk of SCLC transformation than patients without RB1 and TP53 inactivation (95% CI, 5.88–311). EGFR/TP53/RB1 mutant lung cancers have a unique risk of histological transformation and a worse clinical prognosis.

Serum tumor markers are used as observational indicators for the diagnosis of lung cancer and its outcome after treatment. NSE is an ideal indicator for the assessment of SCLC, and elevated CEA contributes to the assessment of NSCLC. Several case reports have found significantly elevated NSE in T-SCLC. In our study, CEA levels decreased in 4 of 6 patients at HT and increased in 2; NSE was significantly elevated in all 4 patients at T-SCLC. Significantly elevated NSE levels may be an important marker of SCLC transformation after EGFR-TKIs resistance in NSCLC. In addition, the detection of dynamic changes in plasma NSE may help in the early detection of SCLC transformation after treatment with EGFR-TKIs.

The prognosis of T-SCLC is poor. The latest guidelines do not provide a clear definition or definitive treatment recommendations for T-SCLC. EGFR mutation in T-SCLC have lost EGFR expression and exhibit typical features of classical SCLC from a genetic, mRNA expression profile and clinical perspective, with reduced sensitivity to EGFR inhibition and sensitivity to chemotherapy regimens. Current treatment options are still dominated by chemotherapy and TKIs therapy. Studies suggest that etoposide-platinum is the first-line treatment of choice. Several studies have shown a median PFS of 3.2–3.4 months for etoposide-platinum chemotherapy with our study slightly higher than theirs (3.6 months). The response rate for T-SCLC to paclitaxel or albumin-bound paclitaxel is 71%, while the response rate to docetaxel is zero. The small molecule multi-TKI Anlotinib showed good efficacy in these patients (overall efficacy, 66.7%; mPFS, 6.2 months). TKIs combined with Enhancer of zest homolog 2 (EZH2) inhibitors may be a promising treatment strategy for T-SCLC and more clinical trials are needed. Immunotherapy has not shown satisfactory efficacy in a series of previous reports, even with a median PFS of 1.6 months, which may be related to the downregulation of PD-L1 expression after treatment. Our patient was treated in a multidisciplinary manner, and an integrated strategy of chemotherapy, Anlotinib and radiotherapy was chosen for follow-up treatment, showing a long OS. The
combination of chemotherapy, other TKIs, and anti-vascular therapy may be a better treatment direction for these patients. Novel therapies strategy must be explored in the future.

**Conclusions**

LADC may transform into SCLC after the failure of EGFR-TKIs. Dynamic NSE changes should be monitored and aggressive re-biopsy should be performed to clarify the mechanism of drug resistance. Multidisciplinary treatment should be provided for T-SCLC, and an integrated treatment strategy based on chemotherapy, Anlotinib and radiotherapy should be considered to improve the prognosis.

**Abbreviations**

T-SCLC  
Transformed small-cell lung cancer

LADC  
lung adenocarcinoma

EGFR-TKIs  
epidermal growth factor receptor-tyrosine kinase inhibitors

SCLC  
Small-cell lung cancer

NSCLC  
Non-small-cell lung cancer

HT  
Histologic transformation

NSE  
Neuron-specific enolase

CEA  
Carcinoembryonic antigen

RECIST 1.1  
Response Evaluation Criteria in Solid Tumors

PD  
Progressive disease

PFS  
Progression-free survival

OS  
Overall survival

RB1  
Retinoblastoma 1

TP53  
Tumor protein p53

CNV  
copy number variation

PTEN  
phosphatase and tension homolog

FGFR1  
Factor receptor 1

YES1  
YES proto-oncogene 1

CT  
Computerized tomography

PET-CT  
Positron emission tomography-computerized tomography

PD-L1  
Programmed cell death ligand 1

NGS
Next-generation sequencing.

Declarations

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Authors' contributions

JQ, YH, and SH drafted the manuscript, performed the research. YZ and TW collected the clinical data. YM and YY designed the study, revised the final manuscript.

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Data availability statement

The data of this article used to support the findings will be made available from the corresponding author upon request.

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of the First Affiliated Hospital of Henan University of Science and Technology. written informed consent was obtained from all subjects and/or their legal guardian(s). All methods were performed in accordance with the Declaration of Helsinki and lung cancer guidelines.

Consent for publication

Not applicable. The data of participants has been desensitized and hidden, and no any identifiable data.

Conflict of interest

The authors declare no conflict of interest.

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References


Figures

**Figure 1**

Chest CT scan and histopathologic features of case 2. (A, E) Stage 1, CT and pathologic staining for initial diagnosis of LADC, hematoxylin-eosin (H&E) staining; (B, F) Stage 2, CT and pathological staining of a second biopsy for LADC; (C, G) Stage 3, CT and pathological staining of three biopsies for SCLC with CT showing enlarged masses at other levels; (D, H) Stage 4, CT and pathological staining of four biopsies for SCLC.