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Review Article

Small cell lung cancer transformations from non-small cell lung cancer: Biological mechanism and clinical relevance

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ABSTRACT

Lung cancer is a leading cause of cancer deaths worldwide, consisting of two major histological subtypes: small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC). In some cases, NSCLC patients may undergo a histological transformation to SCLC during clinical treatments, which is associated with resistance to targeted therapy, immunotherapy, or chemotherapy. The review provides a comprehensive analysis of SCLC transformation from NSCLC, including biological mechanism, clinical relevance, and potential treatment options after transformation, which may give a better understanding of SCLC transformation and provide support for further research to define better therapy options.

Introduction

Lung cancer has been one of the most frequent malignant cancers, and the leading cause of cancer deaths worldwide.[1] It is primarily classified into two histological subtypes: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC).[2] NSCLC accounts for 80% of patients and includes subtypes such as lung adenocarcinoma (LUAD), lung squamouscell carcinoma (LUSC), and other variants.[3] LUAD typically arises from type II alveolar cells in the lung periphery, while SCLC originates from neuroendocrine (NE) cells in the airways, exhibiting distinctive NE markers.[4] NSCLC patients commonly harbor gene mutations such as epidermal growth factor receptor (*EGFR*), Kirsten rats sarcoma viral oncogene homolog (*KRAS*), and anaplastic lymphoma kinase (*ALK*), whereas SCLC patients frequently exhibit retinoblastoma protein 1 (*RB1*) deletion and tumor protein p53 (*TP53*) mutation.[5] Due to its aggressive nature and early metastasis, SCLC has a poorer prognosis compared to NSCLC.

Early stage NSCLC patients usually undergo surgical resection, while advanced NSCLC patients may benefit from chemotherapy, targeted therapy, and immunotherapy.[6] However, the emergence of transformed SCLC (T-SCLC) from NSCLC poses a new clinical challenge. T-SCLC refers to the histological transformation (HT) of NSCLC into SCLC during the course of treatment. The first reported case involved a 45-year-old non-smoking female after erlotinib treatment. The second lung biopsy revealed metastatic SCLC, and an exon 19 deletion (ex19del) of *EGFR*.[7] Since then, multiple studies have identified the transformation as a distinct phenotype of SCLC, characterized by limited treatment options and poor prognosis.[8] While it predominantly occurs in NSCLC patients who have developed resistance to EGFR tyrosine kinase inhibitors (TKIs), cases have also been observed in non-*EGFR*-mutated patients and those not receiving EGFR-TKIs.[9,10]

The clinical implications of T-SCLC from NSCLC are significant, as it represents a distinct clinical entity requiring different treatment approaches compared to primary SCLC (devo-SCLC) and NSCLC. Therefore, a comprehensive understanding of the histological, molecular, and clinical characteristics of T-SCLC from NSCLC is crucial for accurate diagnosis and effective management. In particular, elucidating the molecular mechanisms underlying the transformation from NSCLC to SCLC is an important area of research, which may provide insights into the development of new therapeutic strategies. This review aims to comprehensively discuss the prevalence and molecular mechanisms of transformed SCLC from NSCLC, and to identify challenges and opportunities for improving the diagnosis, treatment, and prognosis of T-SCLC patients.

The mechanism of T-SCLC from NSCLC

The molecular characteristics underlying the transformation of NSCLC to SCLC are complex and heterogeneous, reflecting the diversity and plasticity of lung cancer cells at the level of the genome, transcriptome, and cell communication.[8,11] Several hypotheses have been proposed to explain the possible mechanisms of SCLC transformation

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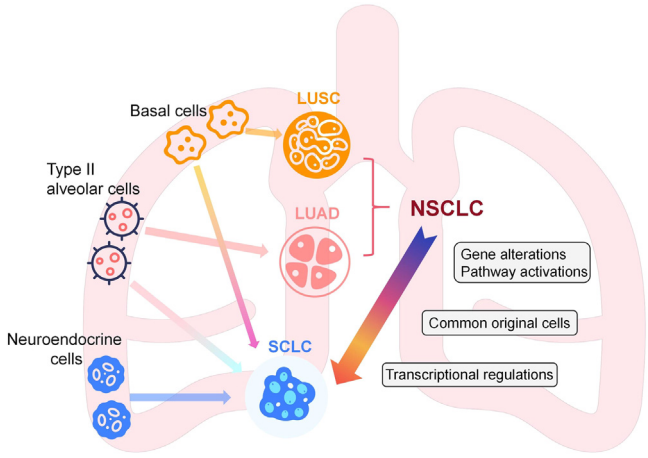

Fig. 1. Mechanism hypotheses of T-SCLC from NSCLC. NSCLC and SCLC may share a common stem cell type, and some gene alterations, pathway activations, and translation relations are frequently reported in transformation to SCLC. LUAD: lung adenocarcinoma; LUSC: lung squamous-cell carcinoma; NSCLC: non-small-cell lung cancer; SCLC: small-cell lung cancer; T-SCLC: transformed SCLC.

(Fig. 1). The first hypothesis suggests that SCLC transformation occurs through a phenotypic switch originating from a common cell type rather than tumor heterogeneity.[12,13] According to the common progenitor cell hypothesis, NSCLC and SCLC originate from a multipotent stem cell that can differentiate into either type depending on the microenvironment and signaling pathways.[14] Ferrer et al[15] found that most tumors with *EGFR* mutations retained the same mutation after transforming from NSCLC to SCLC, indicating a common lineage. A next-generation sequencing (NGS) analysis of consecutive repeat biopsies from a T-SCLC patient transformed from LUAD with *EGFR* ex19del revealed the presence of *TP53* C176S and *EGFR* ex19del with consistent changes in both T-SCLC tissues and blood.[13] Transitional form cells found at the border of SCLC and LUAD components also support that these tumors may share a common stem cell type.[16,17] A study with the whole genome sequencing of transformation samples collected found that transformed LUAD (T-LUAD) and T-SCLC had the same cloning origin and went through the same branch evolution track.[18] Furthermore, studies have shown that the loss of *TP53* and *Rb1* in NE and surfactant protein C (SPC) expressing cells (alveolar type II cells) could efficiently initiate SCLC transformation, while Clara cells were largely resistant to transformation.[18] And the *Rb1* deletion was found in all cases of the T-SCLC and only in those T-SCLC patients after resistance to EGFR-TKIs, but not in those patients who remained NSCLC with resistance to EGFR-TKIs.[19] This hypothesis challenges traditional views on the origins of lung cancer and has important implications for the diagnosis and treatment of patients.

The second hypothesis proposes that NSCLC cells undergo genetic and epigenetic changes that result in SCLC transformation under therapy-induced stress.[20] These changes involve alterations in DNA methylation, histone modifications, and gene expression.[21] Therapy-induced stress or environmental factors can activate oncogenic pathways or suppress tumor suppressor genes, leading to the acquisition of SCLC features by NSCLC cells.[22] Niederst et al[19] suggested that T-SCLC had many of the characteristics of classical SCLC, including *RB* loss, increased NE marker expression, decreased *EGFR* expression, and higher sensitivity to B cell lymphoma 2 (BCL-2) family inhibition. The mutation of activation-induced cytidine deaminase (*AID*) was more enriched in T-SCLC patients without *EGFR/Rb1/TP53* mutation compared to patients without HT.[23] In a mouse model of normal human bronchial epithelial cells, the alterations of all five genes (*TP53*, *AKT*, *Rb1*, *c-MYC*, and *Bcl2*) were needed for the occurrence of SCLC.[24] Additionally, whole exome sequencing (WES) analysis of T-SCLC from LUAD has demonstrated that the T-SCLC subgroup branches off from the early stage of LUAD rather than evolving from the initial LUAD, and the copy number variation (CNV) is related to the timing of SCLC transformation and survival of T-SCLC patients.[25]

A multi-omic analysis of lung cancer proposed a new hypothesis that the transformation could occur *via* the methylation-induced transcriptional reprogramming of cells with *TP53* and *Rb1* loss.[26] The T-SCLC derivatives constructed a new subtype of SCLC and proposed to arise from transformation of tuft cells.[27] The authors found the increasing expression level of genes involved in the polycomb repressive complex 2 (PRC2), phosphoinositide 3-kinases (PI3K)/protein kinase B (AKT), and neurogenic locus notch homolog protein (NOTCH) pathways. It was also found that pre-transformed LUAD had an intermediate pattern between never-transformed LUAD and post-transformed SCLC in the methylation profiling. These different hypotheses have important implications for the diagnosis and treatment of T-SCLC. The first hypothesis enables sensitive detection of SCLC in its early stages, while the second hypothesis emphasizes the need for early intervention to prevent T-SCLC transformation. Therefore, further research is essential to fully understand the underlying mechanisms and develop effective strategies for the prevention and treatment of T-SCLC.

T-SCLC from NSCLC with *EGFR* mutation

Sequist et al[10] firstly reported that 14% of patients with lung cancers had HT in a comprehensive genetic assessment study, and 2–15% of patients upon the acquisition of resistance. A cohort study of 2624 cases reported a prevalence of HT to SCLC with 2.2%, and the time from diagnosis of T-SCLC ranged from 13 months to 22 months.[28]

EGFR mutation has been the most common gene alternation type in NSCLC, particularly among Asian patients, accounting for almost 50% of cases, and includes ex19del, exon 21 point mutations (L858R), and exon 20 mutation (T790M).[29] EGFR-TKIs, such as gefitinib, afatinib, and osimertinib, have become the first-line treatment for NSCLC patients with *EGFR*-activating mutations, significantly improving patient survival and quality of life.[30] However, the inevitable development of acquired drug resistance after EGFR-TKIs treatment has been a great challenge for the clinical management of NSCLC. There are two main categories of mechanisms underlying acquired drug resistance to EGFR-TKIs: on-target (*EGFR*-dependent, such as T790M) and off-target (*EGFR*-independent).[31] The HT is one of the off-target mechanisms of acquired drug resistance to EGFR-TKIs which occurs in 5–14% of NSCLC patients with resistance to EGFR-TKIs.[32] Marcoux et al[33] found that the transformation from about 3–10% of *EGFR*-mutant NSCLC occurred on an average of 17.8 months after diagnosis of NSCLC, and the prognosis of T-SCLC patients was poorer than that of primary NSCLC patients with the overall survival (OS) of 10.9 months. About 80% of T-SCLC patients retained the same *EGFR* mutation in a study of 48 NSCLC patients with *EGFR* mutation.[15] A pooled analysis of NSCLC patients taking TKIs reported the median time from the beginning of treatment to the diagnosis of T-SCLC was 19 months, and the median survival after HT was 6 months.[34] Another study of 58 cases of *EGFR* mutant NSCLC showed the median time to HT and median OS after HT were 17.8 months and 10.9 months.[20] Additionally, most T-SCLC patients had no history of smoking, which was different from the patients with devo-SCLC. The early detection and precision treatment for T-SCLC are vital based on the high incidence and poor prognosis of T-SCLC patients with *EGFR*-mutant patients. Thus, it is important to investigate the underlying mechanism deriving T-SCLC from *EGFR*-mutant NSCLC to develop the new therapeutic strategies.

The gene alterations and signaling pathway activations involved in the transformation from *EGFR*-mutant NSCLC to SCLC are summarized in Table 1. The first reported and most common gene alterations are *RB1* and *TP53* in the process of T-SCLC transformation, which occurs in the initiation stage after treatments for NSCLC patients with *EGFR*

Table 1
Related genes in T-SCLC from *EGFR*-mutant NSCLC.

Category	Name	Ref.
Gene alterations		
Common	*EGFR, TP53, Rb1, PIK3CA*	23,25
NE-related	*SYP, SYN1, SALL3, NEURL1, DLX1*	26,80
Others	*MYC* family	80
	SOX family	20
	APOBEC	23,26
	MUC17, PUM1, NSD3, FGFR1	25,43,80
Signaling pathways		
PI3K/AKT	*PIK3CA, PIK3R1, AKT3, TSC2*	29,43
NOTCH	*NOTCH1/4, ASCL1, DLL3, HSE6*	26
MAPK	*DUSP6, ERBB2, MAPK13*	26
WNT	*BCL9, SMO, AXIN2*	26
Epigenetic regulation	*FOXA1, KMT2B/C/D*	26
Cell cycle/DNA repair	*ATR, BRCA1/2*	26

AKT: Protein kinase B; MAPK: Mitogen-activated protein kinase; NE: Neuroendocrine; NOTCH: Neurogenic locus notch homolog protein; NSCLC: Non-small-cell lung cancer; PI3K: Phosphoinositide 3- kinase; T-SCLC: Transformed small cell lung cancer; WNT: Wingless and int-1.

mutation.[35] Several studies found that the loss of *RB1* and *TP53* would drive the tumorigenesis, cell proliferation, and metastasis of most tumors, including devo-SCLC.[36-38] Niederst et al[19] detected the loss of *RB1* in almost all cells or tissues of T-SCLC patients who were *EGFR*-mutant NSCLC resistant to EGFR-TKIs, but rarely in those without T-SCLC. Another research found that T-SCLC rarely occurred in NSCLC patients without baseline loss of *RB1* and *TP53* and with *EGFR* mutation.[20] The concurrent alterations of *RB1* and *TP53* define a new subgroup of patients with NSCLC with high risk of transformation and poorer prognosis, especially co-mutations of *EGFR/RB1/TP53*.[20] The *RB1* loss induces the lineage plasticity and then drives the NE transformation from prostate cancers by promoting the expression of sex determining region Y-box 2 (*SOX2*) and enhancer of zeste homolog 2 (*EZH2*), which possibly also facilitates T-SCLC transformation of *EGFR*-mutant NSCLC in a similar way.[39] And the research also supported the hypothesis that loss of *RB1* and *TP53* could induce the transformation from NE and alveolar type II cells to SCLC cells.[18] In summary, the loss of *RB1* and *TP53* is essential for the T-SCLC transformation.

However, only the loss of *RB1* and *TP53* could not sufficiently induce the HT in *EGFR*-mutant NSCLC. As the *RB1* and *TP53* deletion in NE cells of mice models with NSCLC did not result in the transformation to SCLC, and the *RB1* and *TP53* loss were also found in the patients without T-SCLC.[40] Studies found higher enrichment of apolipoprotein B messenger RNA-editing enzyme (APOBEC) signature in patients with T-SCLC from *EGFR/RB1/TP53*-mutant NSCLC compared to those without T-SCLC,[20,23] indicating that other molecular alterations may have also participated in the progress of the transformation. For example, cellular myelocytomatosis oncogene (*c-MYC*) was detected in the tissues of T-SCLC patients with *EGFR*-mutant NSCLC.[20,23] And transcription factors like one cut domain family member 2 (ONECUT2) and POU class 3 homeobox 2 (POU3F2) were also detected in prostate NE cancers and T-SCLC, and related to the resistance to osimertinib treatment.[26,41,42]

Furthermore, the activation of PI3K/AKT pathway has been detected in T-SCLC patients, which plays an important role in lineage plasticity and HT.[33,43] And the suppression of the PI3K/AKT pathway could delay the progression of transformation and tumor growth.[26] The deletion of *PTEN* was also detected in T-SCLC from LUAD with *EGFR* mutant but rare in NSCLC.[44] And AKT has been found to drive the switch to NE phenotype in normal lung cells.[24] The downregulation of NOTCH pathways has been found in the early stage of transformation.[26] The overexpression of achaete-scute homolog 1 (*ASCL1*) could interact with the RB–P53 axis and promote NE transformation.[26,45] Besides, the aberrant expression of genes involved in the pathways of cell cycle progression, DNA repair, and wingless and int-1 (WNT) signaling were found in T-SCLC samples.[26] Several other changes such as tumor microenvironment and hypoxia could facilitate the progress of SCLC transformation.[24,31] However, the detailed mechanisms of SCLC transformation remain to be investigated.

T-SCLC from NSCLC with alternation of other genes

ALK rearrangement counts for 3–5% of NSCLC patients, and the application of ALK-TKIs has significantly benefited patients nowadays.[46] The transformation from NSCLC to SCLC not only occurs in the *EGFR*-mutant NSCLC patients but also in patients with *ALK* rearrangement or *ALK*-positive expression after taking ALK-TKIs (crizotinib, ceritinib, and alectinib).[46–49] Hobeika et al[50] reported 8 T-SCLC patients from *ALK*-rearranged LUAD that developed HT after receiving ALK-TKIs, and the progress of HT to SCLC often appeared 2–44 months after diagnosis. And the *ALK* rearrangement was detected in post-HT tissues of most T-SCLC patients with *ALK* rearrangement.[51,52] Similar to the mechanism of resistance to EGFR-TKIs, the mechanism of resistance to ALK-TKIs includes *ALK* amplification, *ALK* secondary mutation (G1202R), the upregulation of bypass signaling pathways, epithelial-to-mesenchymal transition (EMT), and transformation from NSCLC to SCLC.[53,54] Among these, the alternation of *RB1* and *TP53* could cause the resistance to ALK-TKIs and then lead to the HT.[50] Several studies found that the *ALK*-rearranged patients with inactivation of *RB1, TP53, PTEN,* and *NOTCH1* may have a high risk of the HT from NSCLC to SCLC.[51,55] However, *ALK*-rearranged cases without alterations of *RB1* or *TP53* were also found to have the transformation from NSCLC to SCLC, and some T-SCLC patients with *ALK*-rearrangement only took chemotherapy rather than any ALK-TKIs.[56] Because of the lower frequency of NSCLC patients with *ALK* rearrangement than those with *EGFR* mutation, the specific mechanism of T-SCLC from *ALK*-rearranged NSCLC remains unclear, which needs further studies.

In addition to T-SCLC from NSCLC patients with *EGFR* mutation and *ALK* rearrangement, patients with the alternation of other genes like ROS proto-oncogene 1 (*ROS1*) and *KRAS* could also experience HT. *ROS1*-rearranged NSCLC patients have benefited from the targeted treatment with ROS1-TKIs such as crizotinib and entrectinib, but will inevitably develop acquired resistance to ROS1-TKIs.[57,58] A study of a T-SCLC patient with *ROS1* fusion receiving ROS1-TKIs indicated that the HT from NSCLC to SCLC led to the resistance to ROS1-TKIs.[59] The NGS analysis detected the gene alternations of *RB1* and *TP53* from the tissues of autopsy samples, while the resistance mutation of *ROS1* G2032R lost after transformation.

KRAS mutation was identified as one of the mechanisms of acquired resistance to EGFR-TKIs in NSCLC.[60] A study of T-SCLC patients under erlotinib treatment detected *KRAS* p.G12C mutation from the peripheral blood samples after HT, which provided a new insight into the mechanism of resistance to EGFR-TKIs erlotinib.[61]

T-SCLC from NSCLC with immunotherapy

In addition to molecular targeted treatment, immunotherapy has emerged as a significant treatment option for advanced NSCLC patients.[62] Immune checkpoint inhibitors (ICIs), including programmed cell death 1 (PD-1) inhibitors (such as sintilimab, nivolumab, and pembrolizumab) and programmed cell death ligand 1 (PD-L1) inhibitors (such as atezolizumab, avelumab, and durvalumab), are the most common form of immunotherapy used.[63] Consistent with EGFR-TKIs, the HTs from NSCLC to SCLC after treatment with ICIs have also been considered as one of the mechanisms of the resistance to immunotherapy.[64–66] The specific frequency and the mechanism of T-SCLC from NSCLC treated with ICIs remain largely unknown, as repeated biopsies are not commonly performed in advanced NSCLC patients undergoing ICI treatment.

The hypotheses for potential mechanism of T-SCLC transformation from NSCLC with ICIs are similar to those observed in EGFR-TKIs treat-

ment. These include the hypothesis of HTs with genetic and epigenetic changes, as well as the common progenitor cell hypothesis.[66–68] A study focusing on T-SCLCs arising from LUSC during ICI therapy suggested that the HTs from NSCLC to SCLC may serve as a mechanism of resistance to ICIs from the loss of mutations associated with the immune response.[69] Several studies have identified the mutation of *TP53* in the pre-HT tissues of T-SCLC from NSCLC with PD-1 inhibitors therapy.[64,67] Additionally, a case report by Iams et al[68] described T-SCLC transformation from LUAD with *KRAS* mutation after treatment with nivolumab, where post-HT tissue analysis using NGS revealed the loss of *KRAS* G12C driver mutation. These findings resemble those observed in T-SCLCs resulting from targeted agents, indicating that HT of patients with ICIs treatment could potentially be a resistance mechanism in NSCLC that requires further validation through larger studies.

Detection and treatment of T-SCLC

Methods and biomarkers to detect T-SCLC

T-SCLC patients typically exhibit more aggressive disease progression and poorer prognosis compared to those without T-SCLC, with an OS ranging from 9 months to 15 months from the initial diagnosis of T-SCLC.[70] While re-biopsy has been the most accurate method for diagnosing T-SCLC, it is not recommended for patients without *EGFR* mutations or undergoing targeted therapy. In such cases, molecular techniques such as NGS, liquid biopsy, and droplet digital polymerase chain reaction (ddPCR) could enhance the early detection efficiency at the molecular level, for example, gene mutation status of *RB1*, *TP53*, and *PIK3A* could serve as prediction biomarkers for HT to SCLC.[20] Additionally, the burden of CNVs in T-SCLC patients has been found to be higher compared to those without T-SCLC, and increased CNV burden was associated with a worse prognosis, particularly in T-SCLC patients with *EGFR* mutation.[33] Therefore, assessing the CNV burden could aid in predicting the occurrence of transformation and prognosis in T-SCLC patients.

Moreover, the blood levels of neuron-specific enolase (NSE) and pro-gastrin-releasing peptide (pro-GRP) could also be associated with the HT progression.[71,72] Several studies reported the elevation of the serum levels of NSE and pro-GRP in T-SCLC after treatment with EGFR-TKIs, ALK-TKIs, and ICIs, indicating the importance of repeated examination of serum NSE and pro-GRP levels for early detection and risk stratification of T-SCLC patients.[72–75] In addition, the blood levels of carcinoembryonic (CEA) and sialyl-Lewis X-i (SLX) antigens were also increased in T-SCLC patients after taking cytotoxic treatment.[46]

Possible treatment strategies for T-SCLC

Currently, there is no established clinical consensus regarding the treatment strategy for T-SCLC. Based on the poor prognosis and fast disease progression of T-SCLC, it is crucial to explore effective strategies for treating and preventing the transformation to SCLC. The most commonly used approach in T-SCLC patients is SCLC-based cytotoxic chemotherapy, typically platinum plus etoposide(EP) or irinotecan. In a clinical study using platinum plus EP, this regimen showed a high response rate (54% in 46 patients) and a median progression-free survival (PFS) time of 3.4 months.[76] Clinical trials, such as NCT03567642, are investigating the use of EP following osimertinib therapy in T-SCLC patients with mutations of *EGFR/RB1/TP53*. It has been observed that T-SCLC patients treated with EP chemotherapy had a higher response rate than patients with devo-SCLC, although their prognosis was poorer than that of devo-SCLC patients.[76] ABT-263, an oral inhibitor of the BCL-2 family, has shown a remarkable curative effect on T-SCLC patients which significantly enhances the apoptotic response in *EGFR* mutant T-SCLC.[19] And T-SCLC cell lines had a higher response rate to ABT-263 compared to EGFR-TKI-resistant NSCLC cell lines with the T790M resistance mutation.[19]

Combination therapy with EGFR-TKIs and chemotherapy has shown promise in delaying drug resistance and improving PFS compared to chemotherapy alone.[70] In a clinical retrospective study, anlotinib, a multi-kinase inhibitor, demonstrated potential as a novel treatment option for T-SCLC, with a median PFS of 4.3 months.[77] The clinical response rate to taxanes was comparatively higher (71%) in T-SCLC from *EGFR* mutant NSCLC compared to docetaxel (0%), therefore, taxanes may be used for the combination treatment with EGFR-TKIs.[33] Furthermore, alectinib in combination with chemotherapy was also efficient to T-SCLC patients with *ALK* rearrangement after failure to chemotherapy alone.[46] These findings suggest that combination therapy with TKIs and chemotherapy could be a promising treatment strategy for T-SCLC. Immunotherapy with ICIs has been used in some T-SCLC cases but has shown limited efficacy. However, the combination of ICIs and chemotherapy has shown better responses in T-SCLC patients transformed from *EGFR*-mutated LUAD.[70] In addition, olaparib, a poly-ADP ribose polymerase (PARP) inhibitor that plays an anti-tumor role in SCLC, has been researched in combination with durvalumab in T-SCLC patients with *EGFR* mutation in a phase II trial (NCT04538378). Alisertib, a cell cycle kinase aurora kinase A (AURKA) inhibitor targeting *RB1*-deficient T-SCLC cells,[78] has been researched in combination with osimertinib in T-SCLC from *EGFR*-mutated LUAD in a clinical trial (NCT04085315).

As for T-SCLC patients after taking ALK-TKIs, some studies suggested cisplatin–irinotecan may be helpful, which could induce a continuous partial response in the primary lesion.[79] The sequential treatment of alectinib and cytotoxic chemotherapy found that ALK-TKIs could also treat T-SCLC, which was still efficient after chemotherapy failure.[46] And the combination of anti-PD1 antibody and ALK-TKIs could be a promising strategy.[50]

Conclusion

The HT from NSCLC to SCLC frequently occurs in patients undergoing treatments such as molecular targeted therapy and ICIs. T-SCLC patients often experience more aggressive disease progression and worse survival outcomes compared to patients without T-SCLC. The HT to SCLC serves as one of the mechanisms of acquired resistance in NSCLC patients, and it is most commonly observed in those with *EGFR* mutation, followed by *ALK* rearrangement, ICIs treatment, and *KRAS* mutation. However, it is important to note that the actual number of T-SCLC patients may be underestimated due to the limited use of repeated biopsies in patients without *EGFR* mutations or without receiving targeted therapy and ICIs.

Advancements in NGS and WES have led to the proposal of several molecular hypotheses for T-SCLC. However, the precise molecular mechanism of T-SCLC remains unclear and requires further research, particularly through the application of single-cell and spatial transcriptome sequencing technologies. These advanced techniques can provide a more detailed understanding of the cellular heterogeneity and spatial organization of T-SCLC, which could uncover novel therapeutic targets and help develop personalized treatment strategies. Re-biopsy remains the most accurate method for diagnosing T-SCLC, as it allows for the detection of specific molecular alterations associated with the transformation process. In addition to re-biopsy, molecular biomarkers, CNV burden, as well as serum levels of NSE and pro-GRP could serve as auxiliary tools for early detection of T-SCLC. These methods may help identify patients at high risk of T-SCLC transformation and enable timely intervention.

Currently, cytotoxic chemotherapy has been the most effective treatment for T-SCLC patients. However, emerging evidence from clinical trials suggests promising efficacy when combining chemotherapy with targeted inhibitors such as EGFR-TKIs and ICIs in the treatment of T-SCLC. These combination therapies have shown potential in overcoming drug resistance and improving patient outcomes. Nonetheless, further research at the cellular level and additional clinical experiments are

necessary to advance our understanding of the underlying mechanisms and clinical relevance of T-SCLC. These researches are crucial for the development of precise treatments and improved survival outcomes for patients with lung cancer.

In conclusion, the HT from NSCLC to SCLC is a complex and heterogeneous process that occurs in response to various treatments. T-SCLC represents a significant challenge in the management of lung cancer due to its aggressive nature and poor prognosis. Understanding the molecular mechanisms underlying T-SCLC and developing effective diagnostic methods and targeted therapies are essential for improving patient outcomes. Further research efforts, including advanced sequencing technologies and clinical trials, are needed to unravel the complexities of T-SCLC and pave the way for more precise treatments in the future.

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Declaration of competing interest

None.

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