Molecular mechanisms and therapeutic strategies for small-cell lung cancer transformation after TKI therapy in EGFR-mutated lung adenocarcinoma (Review)

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Abstract. Lung adenocarcinoma with epidermal growth factor receptor (EGFR) mutations is a common subtype of non-small cell lung cancer (NSCLC). Although it responds well to EGFR-tyrosine kinase inhibitors (EGFR-TKIs), acquired resistance to EGFR-TKIs inevitably occurs, which limits the use of the EGFR-TKIs. One resistance mechanism is small-cell transformation, which refers to the histological switch of EGFR-mutant lung adenocarcinoma to a small-cell lung cancer phenotype following TKI exposure. Small cell transformation is associated with a poor prognosis and requires different treatment modalities compared with NSCLC. The molecular mechanisms underlying small cell transformation are not fully elucidated, but may involve the loss of tumor suppressor genes, such as RB1 and TP53, and the activation of neuroendocrine pathways. In the present review, the current advances in the molecular characteristics and therapeutic regimens for small-cell transformation in patients with EGFR-mutated lung adenocarcinoma who are resistant to EGFR-TKIs, are summarized.

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Contents

1. Introduction

Lung cancer is a highly malignant tumor, and non-small-cell lung cancer (NSCLC) accounts for ~85% of all lung cancers (1). A subset of patients with NSCLC harbors mutations in the epidermal growth factor receptor (EGFR) gene that confer sensitivity to targeted therapy with EGFR tyrosine kinase inhibitors (TKIs). However, resistance to EGFR-TKIs inevitably develops, resulting in disease progression. The mechanisms associated with resistance to TKIs include EGFR secondary mutations, activation of alternative signaling pathways, and histological or phenotypic transformation, which refers to the conversion of NSCLC into small-cell lung cancer (SCLC) or other lung cancer types (2-4).

SCLC transformation is a rare mechanism of resistance to EGFR-TKIs, accounting for 3-10% of patients exhibiting EGFR-TKI resistance (2,5). The specific molecular mechanisms of SCLC transformation are unclear, but they may involve gene mutations or aberrant gene expression in tumor cells. For example, the co-inactivation of the retinoblastoma 1 (RB1) and tumor protein 53 (TP53) genes, amplification or overexpression of the MYC protooncogene (MYC) gene, and the upregulation of the Achaete-Scute family BHLH transcription factor 1 (ASCL1) gene may contribute to the conversion of NSCLC to SCLC (5,6). SCLC transformation shares similarities with primary SCLC in pathological morphology, molecular profiles, clinical manifestations and drug sensitivity, but it is not considered classical SCLC (4,7). Thus, it may represent a new subtype of SCLC. The diagnosis of SCLC transformation requires tumor re-biopsy and a pathological diagnosis remains the gold standard. Currently, there are no unified standards or guidelines for the molecular mechanism,

prognosis, or treatment strategy for SCLC-transformed tumors. Further basic and clinical studies are needed to identify and verify these aspects. In the present review, recent progress on the molecular mechanisms and treatment options for SCLC transformation is summarized.

2. Molecular mechanism

The molecular mechanism of small cell transformation after targeted therapy for lung cancer involves the interaction of multiple factors. The following is a summary of these putative mechanisms (Table I).

RB and TP53 mutations. RB and TP53 are two important tumor suppressor genes, whose mutation results in the dysregulation of the cell cycle and apoptosis, thereby promoting lung cancer etiology and progression. The RB1 gene encodes the RB protein, which inhibits the transition from the G1 phase to the S phase of the cell cycle by binding to the E2F transcription factor (8). The TP53 gene encodes the p53 protein, which activates downstream target genes, such as p21, to induce cell cycle arrest, apoptosis, or senescence. Under normal conditions, the RB and TP53 proteins coordinate with one another to maintain cellular homeostasis (9).

EGFR-positive lung adenocarcinoma patients with concurrent RB and TP53 mutations are more likely to undergo SCLC transformation following targeted therapy. These patients have a poor prognosis and a shorter response time to EGFR-TKIs. A previous study reported that among 863 patients with EGFR-mutant lung cancer, 43 had concurrent RB1 and TP53 mutations, whereas 18% experienced SCLC transformation (10). No SCLC transformation was observed in patients with EGFR-positive lung cancer without TP53 and RB1 mutations. Regardless of transformation, however, patients with EGFR/TP53/RB1-mutant lung cancer have a shorter treatment discontinuation time than patients with EGFR/TP53 and EGFR-only mutant (9.5 months vs. 12.3 months vs. 36.6 months, respectively). The most common mutations occurring in samples representing transformed SCLC are TP53 (17/25, 68.0%) and RB1 (9/25, 36.0%). The incidence of RB1 and TP53 mutations are similar in patients treated with first-/second-generation and third-generation TKIs (11). Another study showed that the inactivation of RB1 and TP53 was significantly higher in the transformation group compared with that in the non-transformation group (82 vs. 3%). In addition, EGFR-mutant lung adenocarcinoma patients with RB1 and TP53 mutations had a 43-fold increased relative risk of SCLC transformation. Co-mutation of RB1 and TP53 is an important genetic predictor of SCLC transformation, and compared with RB1 or TP53 mutation alone, it represents a 3.38-fold increased risk (6).

The mechanisms of RB1 and TP53 in the SCLC transformation process are unclear. A previous study found that RB1 mutation caused the release of E2F, leading to excessive cell proliferation and TP53 inactivation, which caused dysregulation of the G1/S checkpoint and uncontrolled cell cycle progression. Co-mutation of RB1 and TP53 accelerated cell proliferation and promoted the phenotypic conversion of cells. In lung cancer, RB1 mutations are associated with acquiring the neuroendocrine phenotype, whereas TP53 mutation promotes cancer cell progression and metastasis. RB1 and TP53 can synergistically drive cells to acquire a neuroendocrine phenotype, thus promoting the transformation of NSCLC into SCLC (12).

Whole genome doubling (WGD) is a phenomenon in which the number of chromosomes increases by 2-fold, resulting in the transition of cells from diploid to tetraploid; however, WGD may cause chromosomal instability, an increased mutation rate and heterogeneity. Activation-induced cytidine deaminase/apolipoprotein B mRNA editing catalytic subunit (AID/APOBEC) hypermutation is a typical mutation signature associated with DNA damage repair, which can lead to C-to-T or C-to-G transitions. This hypermutation increases the genetic diversity and adaptability of lung cancer cells. EGFR/RB1/TP53 triple-mutant lung cancer is enriched with WGD and AID/APOBEC hypermutation, which may occur before transformation and facilitate the transformation process (6,10,13).

NOTCH signaling pathway. The Notch signaling pathway is an important signal transduction system involved in cell proliferation, differentiation and apoptosis (14). Its abnormal activation or inhibition is associated with the occurrence and development of various tumors. The Notch signaling pathway plays an important role in SCLC. Based on a classical genomic analysis of SCLC (15), the occurrence rate of Notch family gene alterations was 25%, among which most (77%) of SCLC cells expressed low Notch signaling activity, while expressing high levels of ASCL1 and neuroendocrine markers.

The Notch signaling pathway is a key regulator of SCLC neuroendocrine differentiation (16,17). Another study found that in the early stage of SCLC transformation, Notch-related signaling pathway molecules, including Notch receptors, Notch homolog1/2/3 (NOTCH1/2/3), ligands jagged canonical notch ligand 2 (JAG2) and delta-like ligand 4 (DLL4), were decreased (18). Moreover, a previous study showed that NOTCH2 was negative in transformed SCLC but positive in adenocarcinoma, whereas ASCL1 was positive in transformed SCLC, but negative in adenocarcinoma (15). The inactivation of NOTCH promotes ASCL1 expression and ASCL1 overexpression induces cell cycle-dependent kinase 5. This results in RB phosphorylation and inactivation, thereby inducing TP53 mutant cell proliferation and promoting neuroendocrine phenotype transformation (17). These findings suggest that the NOTCH-ASCL1 axis plays an important role in the process of SCLC transformation.

Phosphoinositide 3-Kinase (PI3K)/AKT signaling pathway. PI3K is an important signaling molecule that regulates cell proliferation, survival and metabolism. It plays an important role in various cancers. PI3K catalyzes the formation of PIP3, whereas phosphatase and tensin homolog (PTEN) dephosphorylates phosphatidylinositol (3,4,5)-trisphosphate (PIP3). PIP3 is a membrane-bound signaling molecule that activates downstream effectors, such as AKT, and the mechanistic target of rapamycin (mTOR), thereby promoting cell proliferation, migration and anti-apoptosis. When the balance between PI3K and PTEN is disrupted, excessive accumulation of PIP3 and aberrant activation of the PI3K/AKT/mTOR pathway occurs, which in turn, promotes tumor etiology and progression (19,20).

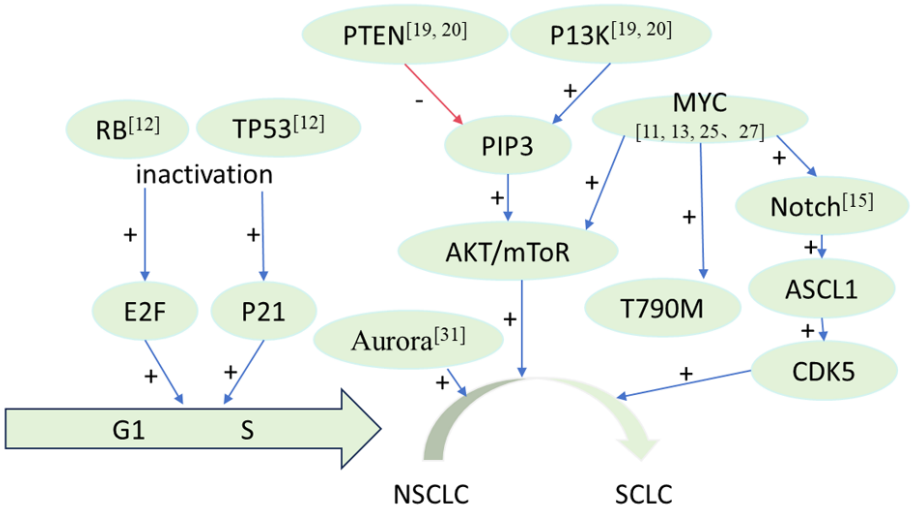

Figure 1. Horizontal diagram of potential molecular mechanisms of small cell transformation after targeted therapy in lung cancer, red arrows indicate an inhibitory effect, and blue arrows indicate a facilitating effect.

The PI3K/AKT/mTOR pathway is activated during the transformation of NSCLC into SCLC (19,20). Furthermore, PTEN mRNA and protein are downregulated during this process (20,21), which results in the activation of the PI3K/AKT/mTOR pathway and promotes transformation (18,22). A mouse model revealed that PTEN inactivation accelerates RB1/TP53 double knockout-induced SCLC transformation. In human tumor specimens, a role for the PI3K pathway in SCLC transformation has also been observed (7). For example, Suda *et al* (21) reported a case of gefitinib-resistant lung adenocarcinoma that transformed into large-cell neuroendocrine carcinoma with phosphoinositide 3-kinase catalytic subunit alpha (PI3KCA) mutation and PTEN loss.

MYC signaling pathway. MYC is an oncogene that encodes a transcription factor that regulates various biological processes such as the cell cycle, metabolism, differentiation and apoptosis (23,24). The role of MYC in lung cancer has been extensively studied, especially in SCLC, where MYC amplification or overexpression is a common genetic event associated with tumor aggressiveness, metastatic potential and poor prognosis (23,24). Comparative analysis of the genomic and clinical features of patients with SCLC or NSCLC-to-SCLC also confirmed that MYC pathway activation was related to SCLC transformation and poor prognosis. MYC plays an important role in the formation and evolution of the SCLC subtypes. Using mouse and human models and single-cell transcriptome analysis, studies have found that MYC can activate the Notch signaling pathway, driving the transformation between different SCLC subtypes (11,13,25). Therefore, targeting MYC may be a promising therapeutic approach for treating SCLC.

Multi-omics analysis revealed that the MYC pathway was activated during NSCLC transformation into SCLC. MYC overexpression can reprogram tumor cells, leading to phenotypic changes and enhanced proliferation and metastasis (18,21). During NSCLC transformation into SCLC, MYC may contribute to various resistance mechanisms, such as genomic instability, epigenetic alterations, and threonine to methionine at position 790 (T790M) mutation (26). Genomic analysis indicated that in addition to MYC amplification or overexpression, mutations or copy number variations of other genes, such as SRY (sex determining region Y)-box 2 (SOX2), PTEN and PIK3CA, were observed in NSCLC-to-SCLC samples (21). The T790M mutation is the most common acquired resistance mechanism after EGFR-TKI treatment, which causes structural changes in the EGFR kinase and reduces TKI affinity (27). Studies have shown that MYC promotes the occurrence of the T790M mutation (21,26). Moreover, MYC can promote cell proliferation, growth, and transformation by activating AKT and other signaling pathways (21,22,26).

Aurora kinase A (AURKA). AURKA is a serine/threonine kinase that belongs to the Aurora kinase family. It has an important role in mitosis and meiosis and is involved in tumor initiation and progression (28). Studies have shown that AURKA promotes prostate neuroendocrine differentiation by interacting with N-MYC (29,30). Moreover, third-generation TKIs can activate AURKA, leading to resistance (31). Therefore, AURKA may represent a potential driver factor for SCLC transformation.

3. Treatment

No standard therapies are available to prevent or treat the transformation of NSCLC into SCLC. Although third-generation EGFR-TKIs, chemotherapy, immunotherapy and combination therapies may delay disease progression, their efficacy remains suboptimal. The development of novel AURKA inhibitors is a promising approach and may improve the outcomes of patients experiencing NSCLC-SCLC transformation when combined with current therapies; however, this will require further clinical trials to identify the optimal combination therapies (Table II).

Chemotherapy. Chemotherapy with platinum and etoposide (EP) is the cornerstone treatment for SCLC. EP is also the only

Table I. Research results.

First authors/year	Result	Potential mechanism	(Refs.)
Knudsen *et al*, 2019	The mutations of RB and TP53 can promote the	RB and TP53	(8)
Muller *et al*, 2013	occurrence and development of lung cancer.	mutations	(9)
Lee *et al*, 2017	The relative risk of SCLC transformation is		(6)
Muller *et al*, 2013	increased in EGFR-mutated lung adenocarcinoma		(9)
Wang *et al*, 2021	patients with B1 and TP53 mutations.		(11)
Peifer *et al*, 2012	RB1 and TP53 synergistically drove cells to acquire neuroendocrine phenotype, promoting the transformation of NSCLC into SCLC.		(12)
Lie *et al*, 2017	EGFR/RB1/TP53 triple-mutant lung cancer is enriched		(6)
Offin *et al*, 2019	with whole genome doubling and AID/APOBEC		(10)
Xie *et al*, 2020	hypermutation may facilitate the transformation process.		(13)
Koba *et al*, 2021	SCLC highly expresses ASCL1 and also highly expresses neuroendocrine markers.	NOTCH signaling pathway	(15)
Koba *et al*, 2021	NOTCH-ASCL1 axis may play a potential important		(15)
Sriuranpong *et al*, 2001			(16)
Meder *et al*, 2016			(17)
Quintanal-Villalonga *et al*, 2021			(18)
Tan *et al*, 2020	Excessive accumulation of PIP3 and abnormal	PI3K/ AKT signaling	(19)
Park *et al*, 2018	activation of PI3K/AKT/mTOR pathway can	pathway	(20)
DWY *et al*, 2018	promote the transformation.		(22)
Wang *et al*, 2021	MYC can activate the Notch signaling pathway,	MYC signaling	(11)
Xie *et al*, 2020	driving the transformation between different	pathway	(13)
Lin *et al*, 2018	SCLC subtypes.		(25)
Suda *et al*, 2015	MYC can promote the occurrence of T790M mutation.		(21)
Quintanal-Villalonga *et al*, 2021			(18)
Suda *et al*, 2015	MYC can promote cell proliferation, growth and		(21)
DWY *et al*, 2018	transformation by activating AKT.		(22)
Quintanal-Villalonga *et al*, 2021			(18)
Beltran *et al*, 2021	AURKA promotes prostate neuroendocrine	AURKA	(29)
Mosquera *et al*, 2013	differentiation by interacting with N-MYC.		(30)

AURKA, Aurora kinase A; NSCLC, non-small-cell lung cancer; SCLC, small-cell lung cancer; RB1, retinoblastoma 1; ASCL1, Achaete-Scute family BHLH transcription factor 1; AID/APOBEC, activation-induced cytidine deaminase/apolipoprotein B mRNA editing catalytic subunit; EGFR, epidermal growth factor receptor.

viable and clinically validated option for SCLC-transformed tumors after EGFR-TKI failure and is considered first-line treatment. A retrospective study reported an objective response rate (ORR) of 54% for EP in transformed SCLC and an ORR of 80% (8 out of 10 patients achieved remission) in those who had prior exposure to platinum chemotherapy, with a median progression-free survival (PFS) of 3.4 months (32). Another study showed an ORR of 44.4% (12/27) for the EP regimen in transformed SCLC and a median PFS of 3.5 months (11). A total of three patients in the aforementioned study received platinum and irinotecan, with an ORR of 66.7%, a disease control rate (DCR) of 100%, and a median PFS of 7.6 months.

Taxanes are effective for the treatment of transformed SCLC. A retrospective study reported an ORR of 50% and a median PFS of 2.7 months for 21 patients who received taxane therapy (14 as monotherapy). The type of taxane also influenced the response rate as paclitaxel and nab-paclitaxel achieved an ORR of 71% (5/7), whereas docetaxel showed no clinical benefit (32).

A phase I trial (NCT03567642) of osimertinib plus platinum-etoposide chemotherapy in patients with advanced EGFR/TP53/RB1 co-mutated lung cancer demonstrated promising efficacy. Further follow-up and analysis will be required to evaluate the clinical outcomes and prognostic factors. This trial offers a novel therapeutic approach for patients harboring EGFR/TP53/RB1 co-mutation.

Radiotherapy. The incidence of central nervous system (CNS) involvement in transformed SCLC is relatively high and similar to the clinical characteristics of classic SCLC. One study showed that 38 of 59 patients (64%) with SCLC transformation had CNS progression after SCLC diagnosis, but no treatment methods were mentioned (4). Currently, radiotherapy for transformed SCLC is often combined with

Table II. Current treatment.

First authors/year	Treatment	Objective response rate, %	PFS, months	Disease control rate, %)	(Refs.)
Chemotherapy					
Marcoux *et al*, 2019	EP	54	3.4		(32)
Wang *et al*, 2021	EP	44.4	3.5		(11)
Wang *et al*, 2021	Platinum and irinotecan	66.7	7.6	100	(11)
Marcoux *et al*, 2019	Taxanes	50	2.7		(32)
Radiotherapy					
Xu *et al*, 2021	chemotherapy + radiotherapy	33	6.5 (mPFS)		(7)
	chemotherapy + radiotherapy + targeted therapy	50	11.5 (mPFS)		
Targeted therapy					
Lai *et al*, 2021	EP + erlotinib		8		(36)
Immunotherapy					
Fujimoto *et al*, 2022	PD-1/PD-L1		5.6 (mPFS)		(38)
Zhang *et al*, 2023	ABCP/ECT	73	5.1 (mPFS)		(44)
Anti-angiogenic therapy					
Wang *et al*, 2021	anlotinib	66.7	6.2 (mPFS)	80.0	(11)

PFS, progression-free survival; mPFS, median PFS; EP, platinum and etoposide; ABCP, atezolizumab-bevacizumab-carboplatin-paclitaxel; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; ECT, atezolizumab-etoposide-carboplatin.

chemotherapy or targeted therapy and the number of cases is small. A review summarized the relevant studies and found that in four patients receiving chemotherapy combined with radiotherapy, the ORR was 33% and the mPFS was 6.5 months. In cases including chemotherapy combined with radiotherapy and targeted therapy, the ORR was 50% and mPFS was 11.5 months (7). Guidelines of the Chinese Society of Clinical Oncology (CSCO) recommend feasible standard SCLC chemotherapy regimens or continuing the original EGFR-TKI treatment combined with local therapy in cases of local progression (33).

Targeted therapy. Continued EGFR-targeted therapy may benefit patients with transformed SCLC following treatment. Several studies have shown that in most patients (84-88%), the original gene mutation in the lung adenocarcinoma is retained after SCLC transformation (32-35). One case report found that after EGFR treatment of resistant transformed SCLC, EP chemotherapy combined with erlotinib was administered and yielded a PFS of 8 months (36). The CSCO guidelines recommend standard SCLC chemotherapy regimens or continuing the original EGFR-TKI plus local treatment in patients with local slow progression (33). In patients with systemic slow progression, standard SCLC chemotherapy regimens ± continued original EGFR-TKI treatment are recommended (33).

Immunotherapy. Immune checkpoint inhibitors have been approved for first-line SCLC and chemotherapy combined with programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) significantly improves the survival of SCLC patients (37). Therefore, immunotherapy may also be applied to transformed SCLC; however, a retrospective study found that no clinical benefit was observed in 17 patients with transformed SCLC who received either PD-1 or PDL-1 monotherapy (8/17) or ipilimumab plus nivolumab (9/17) (32). The same result was obtained in another study of 15 patients (38). In another two patients exhibiting SCLC transformation, immunotherapy was also ineffective and no PD-L1 expression was detected (39,40). These studies suggest that immunotherapy monotherapy is ineffective for SCLC. Moreover, patients with EGFR mutation are immunosuppressive and insensitive to immunotherapy (41). Most transformed SCLCs retain the original EGFR mutation characteristics of lung adenocarcinoma, which may also contribute to the poor response to immunotherapy (33,35,42). A previous study analyzed the tumor tissues of 45 patients with NSCLC who progressed after immunotherapy and found 9 showing SCLC transformation (43). The researchers proposed that SCLC transformation is a mechanism of resistance to immunotherapy. This also suggests that patients with SCLC transformation after EGFR-targeted therapy may have poor outcomes with immunotherapy.

In a study of six patients treated with chemotherapy plus PD-1/PD-L1 therapy, clinical activity was observed in three cases, with a median PFS (mPFS) of 5.6 months (38). A retrospective study was conducted on the efficacy and safety of combined PD-L1 inhibitors and chemotherapy for the treatment of SCLC transformation of lung cancer and yielded similar results (44). The analysis included 47 patients who had EGFR-mutated lung adenocarcinoma and developed SCLC transformation after receiving EGFR-TKI treatment. Of these, 11 received immunotherapy and were defined as the I/O group, whereas 36 patients did not receive immunotherapy

and were designated the Non-I/O group. Despite most patients in the I/O group not expressing PD-L1 (7/11), 9 received the atezolizumab-bevacizumab-carboplatin-paclitaxel albumin-bound regimen and 2 were administered the atezolizumab-etoposide-carboplatin regimen, resulting in an ORR of 73% (8/11). The mPFS after SCLC transformation was 5.1 months in the I/O group and 4.1 months in the Non-I/O group. In addition, the mOS after SCLC transformation was significantly longer in the I/O group compared with that in the Non-I/O group (20.2 months vs. 7.9 months, P<0.01). Patients with SCLC transformation and harboring the EGFR L858R mutation were more likely to have a longer mPFS compared with those containing the EGFR 19del mutation (not reached vs. 3.7 months, P=0.11). A positive PD-L1 status was also associated with a favorable PFS (mPFS: 6.0 months vs. 3.7 months, P=0.2). The study demonstrated that combining PD-L1 inhibitors with chemotherapy ± bevacizumab represents a treatment option for patients who have undergone SCLC transformation.

Anti-angiogenic therapy. In a retrospective study, 5 patients received erlotinib treatment, of which 2 experienced transformation to SCLC after first/second generation TKI treatment and 3 cases transformed to SCLC after third-generation TKI treatment. The ORR was 66.7%, the DCR was 80%, and the mPFS was 6.2 months (11). In another study, 18 patients were administered anti-angiogenic therapy, of which erlotinib was the most used drug (83.3%) and primarily combined with chemotherapy, EGFR, or both, whereas only 6 patients received single-drug erlotinib treatment. Compared with patients who did not receive anti-angiogenic therapy, patients who received anti-angiogenic therapy had a significantly longer OS after transformation (15.1 months vs. 4.3 months) (45). Another study comparing chemotherapy and combined therapy found that EGFR-TKI treatment of SCLC transformation after EP/IP combined with bevacizumab or TKI treatment was significantly superior compared with EP/IP-based chemotherapy (46).

Palliative care. World Health Organization definition of palliative care is 'an approach that improves the quality of life of patients and their families who are facing problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification, correct assessment and treatment of pain and other problems, whether physical, psychosocial or spiritual'. Palliative care should provide comprehensive physical, psychological, social and religious support and care for patients and their families through physical pain control, family affection service, psychological counseling and religious belief (47).

Other treatments. SCLC transformation involves the dysregulation of various molecular pathways, which provide potential therapeutic targets. For example, ABT-263 is an oral agent that inhibits B-cell lymphoma 2 (BCL-2) family proteins, which exhibit anti-apoptotic activity (48). It has been previously indicated that ABT-263 induces apoptosis in transformed SCLC (35). In addition, cell cycle dysregulation following the loss of RB protein expression is another target of interest. Checkpoint kinase (CHK) and polo-like kinase (PLK) are key regulators of cell cycle progression that can be blocked by specific inhibitors with antitumor activity in transformed SCLC (35). Moreover, AURKA inhibition may be effective against transformed SCLC (31). Enhanced expression of the histone methyltransferase enhancer of zeste homolog 2 (EZH2) was observed during prostate cancer small cell transformation (49) and in SCLC (50), suggesting that EZH2 inhibitors may be effective for treating SCLC transformation; however, these drugs require clinical trials to evaluate their safety and effectiveness.

4. Conclusion

SCLC transformation is an important mechanism of resistance to EGFR-TKIs and has a significant impact on prognosis. The transformation process may involve mutations in RB1 and TP53, as well as alteration in the NOTCH signaling pathway, the MYC protein family, PI3K/AKT signaling pathway, and related molecules. Chemotherapy as first-line treatment provides clinical benefits to patients after transformation. Certain small studies have suggested that chemotherapy combined with immunotherapy, targeted therapy, or anti-angiogenic therapy has improved effects (44-46). Potential therapeutic agents for transformed SCLC include inhibitors of BCL-2, CHK, PLK, Aurora kinase and EZH2, although they require further clinical validation for safety and efficacy. Patients with advanced SCLC often require palliative and hospice care, which includes physical pain control, family affection service, psychological counseling and religious care. At present, there is no literature or case of surgical intervention., which needs further research and exploration. Overall, the current treatment options for patients with SCLC transformation after EGFR-TKIs are limited. Therefore, further studies of the molecular mechanisms, identification of new therapeutic targets, and large-scale prospective studies are needed to improve the treatment and prognosis assessment for these patients.

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Authors' contributions

HZ, HG and PG conceptualized the study, performedformal analysis, and wrote the original draft. PG conducted investigation. JC wrote, reviewed and edited the manuscript, and acquired funding. HL conducted data visualization and project administration, and supervised the study. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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