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Targeted therapies for small cell lung cancer: Where do we stand?

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Contents

Abstract

Small cell lung cancer (SCLC) accounts for 15% of lung cancer cases and is associated with a dismal prognosis. Standard therapeutic regimens have been improved over the past decades, but without a major impact on patient survival. The development of targeted therapies based on a better understanding of the molecular basis of the disease is urgently needed. At the genetic level, SCLC appears very heterogenous, although somatic mutations targeting classical oncogenes and tumor suppressors have been reported. SCLC also possesses somatic mutations in many other cancer genes, including transcription factors, enzymes involved in chromatin modification, receptor tyrosine kinases and their downstream signaling components. Several avenues have been explored to develop targeted therapies for SCLC. So far, however, there has been limited success with these targeted approaches in clinical trials. Further progress in the optimization of targeted therapies for SCLC will require the development of more personalized approaches for the patients.

Keywords: Small cell lung cancer; Receptor tyrosine kinase; Angiogenesis; Apoptosis; Epigenetics; Immunotherapy

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1. Introduction

Lung cancer is the leading cause of cancer-related mortality in men and one of the most lethal cancers in women [1,2]. It is anticipated that the number of lung cancer cases will increase in the next decades, as has been reported in some countries, such as the United Kingdom, where projections were made [3]. Lung cancer is divided into small cell lung cancer (SCLC, 15% of all cases) and non-small cell lung cancer (NSCLC, 85% of all cases). SCLC is a very aggressive form of lung cancer, which is associated with a very poor prognosis. SCLC is typically associated with cigarette smoking and thus the incidence of SCLC has declined in the past decades, although mainly in men, due to the implementation of strategies for smoking cessation. SCLC patients are divided into limited disease and extensive disease [4–8]. Patients with limited disease are treated with combination chemotherapy (cisplatin or carboplatin with etoposide) and radiation therapy [4–7]. Their median survival is 16–24 months. Patients with extensive disease are treated with chemotherapy alone. Most SCLC patients are diagnosed with extensive disease and will relapse despite an initial response the chemotherapy. Thus, the median survival of this patient group is 7–12 months [4–7]. In view of this dismal prognosis, there is an urgent need to develop novel targeted therapies for SCLC.

2. Genetic alterations

It has been long recognized that SCLC is a cancer type presenting a very large number of genetic alterations [9,10]. Recent studies using next generation sequencing (NGS) approaches have confirmed this model [11–13]. The tumor suppressor genes *TP53* and *RB1* are frequently mutated in SCLC [12], in addition to deletions in chromosome 3p, which contains several tumor suppressor genes. Copy number gains were also found in *JAK2*, *FGFR1* and *MYC* genes [14]. In addition, somatic mutations were found in many other cancer genes, including transcription factors, enzymes involved in chromatin modification, receptor tyrosine kinases and their downstream signaling components [11,12,15].

3. Targeted therapies

Several approaches have been explored in the past decades to develop targeted therapies for SCLC [7–9,16–23]. These include targeting receptor tyrosine kinases (RTK) and their downstream signaling mediators such as Ras and phosphoinositide 3-kinase (PI3K)/v-akt murine thymoma viral oncogene homolog (Akt)/mammalian target of rapamycin (mTOR). In addition, other studies have investigated angiogenesis, the Hedgehog (Hh) pathway, the apoptotic machinery, epigenetics and immunotherapy. Below, I will summarize the different avenues that have been explored in the past decades to develop targeted therapies for SCLC.

3.1. Receptor tyrosine kinases

Targeting receptor tyrosine kinases (RTKs) and their downstream signaling mediators in SCLC has attracted considerable attention in the past decades [7,9,17,21,22]. A number of RTKs have been studied in SCLC, including v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog (c-Kit), c-Met, epidermal growth factor receptor (EGFR), fibroblast growth factor receptors (FGFRs), insulin-like growth factor-1 receptor (IGF-1R) and vascular endothelial growth factor receptors (VEGFRs).c-Kit, and its ligand stem cell factor (SCF) are expressed in SCLC [24] and imatinib, a small molecule tyrosine kinase inhibitor, was evaluated in pre-clinical studies in SCLC models [25–27]. However, subsequent clinical trials failed to show any activity of imatinib as a single agent or in combination with chemotherapeutic drugs [28–30] (Table 1). This lack of efficacy is potentially due to the absence of *KIT* mutations in SCLC, which is in contrast to the situation in gastrointestinal stromal tumors (GIST), where *KIT* is mutated and imatinib is active [31]. The activation of downstream signaling pathways, such as PI3K/Akt/mTOR (PAM), may also render SCLC cells resistant to imatinib [32]. Alternatively, multiple receptor tyrosine kinases may have redundant functions in SCLC, arguing for a need to co-target multiple receptors to achieve efficacy [33].

SCLC expresses c-Met, the receptor for hepatocyte growth factor (HGF), but in contrast to the situation with c-Kit, an autocrine loop is only rarely present [24,34]. *MET* is also mutated in a fraction of SCLC [35,36]. Phosphorylation of c-Met was correlated with poor survival in SCLC patients [37]. A small molecule inhibitor of c-Met also inhibited proliferation and invasion in SCLC cell lines with mutant *MET* [37]. The c-Met inhibitor SU11274 was reported to enhance the efficacy of SN-38, an irinotecan derivative, in SCLC cell lines [38].

The vast majority of *EGFR* mutations occur in lung adenocarcinoma [39]. However, a small proportion (4%) of SCLC tumors was reported to have *EGFR* mutations [40]. These patients may benefit from EGFR tyrosine kinase inhibitors. In a phase II clinical trial, gefitinib failed to show any activity in unselected relapsed SCLC patients [41] (Table 1). This negative result is most likely due to the rarity of *EGFR* mutations in SCLC. Intriguingly, a transformation of NSCLC into SCLC was observed in a small proportion (14%) of patients treated with EGFR tyrosine kinase inhibitors who had become resistant to these drugs [42] (Fig. 1).

The FGFR family of receptors represents attractive targets for the development of targeted therapies in SCLC. The *FGFR1* gene was reported to be amplified in a fraction (5–6%) of SCLC patients [12,43]. FGF-2 was shown to stimulate the proliferation and chemoresistance of SCLC cells, through extracellular signal-regulated kinase (Erk) and