

Immunotherapy and small cell lung cancer (SCLC)

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Abstract

Lung cancer is the leading cause of cancer death worldwide. Lung cancers are mainly of two types: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). Small cell lung cancer accounts for about 15% of all the types of lung cancers. The SCLC is also known as small cell undifferentiated carcinoma, oat cell carcinoma and oat cell cancer. Neuroendocrine tumors are another group of tumors that are found in lungs and show a spectrum of tumors, ranging from slow growing non metastatic carcinoid tumors to highly malignant small cell resembling cancers. SCLC has a unique biology with specific molecular and cellular changes. Chromosomal alterations, tumor suppressor genes, oncogenes, aberrant signaling pathways, receptor tyrosine kinases and growth factors are known to occur in SCLC. Immunotherapy might be beneficial for small cell lung cancer (SCLC). There is no immunotherapeutic, which is approved by FDA approved for SCLC. However, a wide variety of immunotherapeutics are under clinical trials for the treatment of SCLC.

Abbreviations

CPI: Check point inhibitors; CGH: Comparative genomic hybridization analyses; CIK: Cytokine-induced killer; HPV: Human papilloma virus; HCV: Hepatitis C virus; LAK: Lymphokine-activated killer; MHC: Major histocompatibility complex; mTOR: Mammalian target of rapamycin; MRD: Minimal residual disease; MAB: Monoclonal Antibody Drugs; NSCLC: Non-small cell lung cancer; RTK: Receptor tyrosine kinases; SCLC: Small Cell lung cancer; TSG: Tumor Suppressor Genes; 4EBP1: 4E-binding protein 1; S6K1: Ribosomal protein S6 kinase 1

Introduction/Epidemiology

Lung cancer is the leading cause of cancer death worldwide. Lung cancers are mainly of two types: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). In 2014, American Cancer Society estimated that there were 224,210 (116,000 in men and 108,210 in women) new cases and in the same year, 159,260 (86,930 in men and 72,330 among women) cases of death were estimated in the United States for both (NSCLC) and (SCLC) [1]. SCLC accounts for 10-15% of all the lung cancers.

The SCLC is also known as small cell undifferentiated carcinoma, oat cell carcinoma and oat cell cancer [2].

Etiology/Predisposing factors

Small cell lung cancer accounts for about 15% of all the types of lung cancers. Neuroendocrine tumors are another group of tumors that are found in lungs and show a spectrum of tumors, ranging from slow growing non metastatic carcinoid tumors to highly malignant small cell resembling cancers. The various common signs and symptoms of SCLC are voice change, recurrent bronchitis or pneumonia, chest pain, hemoptysis, and persistent cough. The most common risk factors of SCLC are smoking cigarettes, cigars, or pipes, radiation therapy to the chest or breast, air pollution, family history of lung cancer, exposure to chromium, asbestos, arsenic, radon, and nickel in the workplace, and HIV [3]. About 87% cases of lung cancer occur due to smoking in the United States [4].

Pathophysiology/Molecular basis

SCLC has a unique biology with specific molecular and cellular changes. Chromosomal alterations, tumor suppressor genes, oncogenes, aberrant signaling pathways, receptor tyrosine kinases and growth factors are known to occur in SCLC.

Chromosomal alterations

The majority of SCLCs have deletions, affecting multiple chromosomal sites, with recurrent losses at 3p, 5q, 13q and 17p, which are the loci for tumor suppressor genes, including p53. Comparative genomic hybridization analyses (CGH) have revealed that a large number of SCLCs harbor gains of 1p, 2p, 3q, 5p, 8q and 19p. These regions encode well-known oncogenes, such as MYC and KRAS. SCLC cell lines are found to have amplifications of 1p, 2p and 3q, with the deletions of 18q, displaying a more aggressive phenotype of the disease [5]. Allelic loss on chromosome 3p occurs with a frequency greater than 90% in SCLC, and is believed to be an early event in lung cancer [6]. Distinct areas of loss that have been identified, include 3p21.3, 3p12, 3p14.2 and 3p24 [7].

Several genes on these regions have tumor suppressor activity and often lose their expression by epigenetic mechanisms. The 3p21 tumor

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Key words: non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), undifferentiated carcinoma, oat cell carcinoma, oat cell cancer, chromosomal alterations, oncogenes, aberrant signaling pathways, tumor suppressor genes (TSGs), comparative genomic hybridization analyses (CGH), xenograft models, phosphoinositide 3-kinase signaling pathway, receptor tyrosine kinases, check point inhibitors, cytokine-induced killer (CIK), major histocompatibility complex, minimal residual disease (MRD), lymphokine-activated killer (LAK), tumor microenvironment

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suppressor genes include RASSF1A, FUS1, SEMA3B and SEMA3F. RASSF1A gene is inactivated by tumor acquired promoter hypermethylation. It encodes a protein similar to RAS effectors proteins and is inactivated in greater than 90% of SCLC [8]. The 3p24 region contains the RAR β gene, which is methylated in 72% of SCLC, leading to the loss of its expression. RAR β plays an important role in the growth regulation of epithelial cells and suppression of tumorigenesis [9].

Tumor suppressor genes (TSGs)

The tumor suppressor gene p53, located on chromosome 17p13, is the gatekeeper of the cell and protects the cell against genetic instability by regulating cell survival and damage response pathways. It acts as a negative regulator of cellular proliferation by targeting downstream genes, involved in cell cycle arrest (G1 and G2) [p21], DNA repair (GADD45) and apoptosis (BAX) [10]. Inactivating mutations of p53 are seen in approximately 90% of SCLC, of which most of the mutations are missed mutations in the DNA binding domain, while some of them being, homozygous deletions [6].

Non-receptor oncogenes

Bcl-2 genes

The up regulation of Bcl-2 is present in 75–95% of SCLC [11]. Inhibition of bcl-2 shows antitumor activity in SCLC cell lines and in xenograft models [12-14].

MYC-genes

Amplification of the chromosomal bands, 1p32, 2p23 and 8q24.1 regions, encoding for C-MYC, N-MYC and L-MYC, respectively, has been detected through CGH. The use of genespecific probes has confirmed that C-MYC, N-MYC and L-MYC genes are amplified in small cell lung cancer. The MYC gene encodes for a transcription factor, which aids cell proliferation. This proliferation is induced by the activation of growth-promoting genes and occasionally by repression of growth suppressing sequences [15]. MYC activation has been reported in 18–31% of SCLC and correlates with decreased survival [7].

Phosphoinositide 3-kinase (PI3K)/AKT/mTOR signaling pathway

The mTOR is a major downstream mediator of PI3K/AKT that targets eukaryotic translation establishment factor 4E-binding protein 1 (4EBP1) and ribosomal protein S6 kinase 1 (S6K1) [16], which controls the protein synthesis [17,18]. The PI3K/AKT/mTOR signaling pathway is an imperfect pathway in small cell lung cancer (SCLC). The SCLC cells keeps an essentially active PI3K [19] and port PTEN and PI3K mutations [20]. The phosphorylated AKT exists in 70% of

the tumors in SCLC patients [21]. The protein expression of 4EBP1, S6K1 and mTOR are raised in the SCLC cells as compared to the type-2 epithelial cells [22].

Receptor tyrosine kinases and growth factors

There are various tyrosine kinase receptors, which are overexpressed in the SCLC. They are also associated with the activation of downstream signaltransduction molecules, migration and survival, cell proliferation, and modification of reactive oxygen group. The numerous defective tyrosine kinase receptors and their particular growth factors comprise FGFR/FGF, c-Kit/SCF, IGF-1R/IGF, c-MET/HGF, and VEGFR/VEGF in SCLC. Throughout the activation of several pathways, as well as the activation of the PI3K/AKT/mTOR, these signaling pathways are recognized to be dys-regulated in SCLC. These are also concerned in the translation, apoptosis, survival, and cell cycle regulation [7]. The inhibitors of tyrosine kinase receptors have developed into probable anti-tumor agents in the SCLC.

Immunotherapy

Current immunotherapy option for SCLC are discussed in following categories: kinase inhibitors, monoclonal antibodies, mTOR inhibitors, Proteasome inhibitors and vaccine therapy.

Kinase inhibitors

Non-FDA approved Kinase Inhibitors: (Table 1)

Mammalian target of rapamycin (mTOR) Immunotherapy

Non-FDA approved Mtor Inhibitors: (Table 2)

Monoclonal antibody drugs (MABs) and check point inhibitors (CPIs)

Non-FDA Approved drugs: (Table 3)

Proteasome inhibitors

Non-FDA Approved proteasome inhibitors: (Table 4)

Vaccines

Non-FDA Approved vaccines: (Table 5)

Miscellaneous

Cytokine-induced killer (CIK) cells: A preparation of autologous lymphocytes with potential immunopotentiating and antineoplastic activities. Cytokine-induced killer (CIK) cells are CD3- and CD56-positive, non-major histocompatibility complex (MHC) -restricted, natural killer (NK) -like T lymphocytes, generated ex-vivo by

Table 1. Non-FDA approved tyrosine kinase drugs [23-28].

Drug	Clinical trial identifier number	Phase	Study design	Target
Sunitinib malate	NCT00453154	Phase 2	Randomized, Double blind, Safety/Efficacy Study	VEGF
Sorafenib	NCT00182689	Phase 2	Open label, Efficacy Study	RAF/VEGF
Trametinib	NCT02079740	Phase 2	Open label, Safety/Efficacy Study	MEK 1 and 2
BIBF 1120	NCT01441297	Phase 2	Open label, Efficacy Study	VEGFR, PDGFR, FGFR
Pazopanib	NCT01713296	Phase 2	Open label, Efficacy Study	VEGFR, PD-GFR
Ponatinib	NCT01935336	Phase 2	Open Label, Efficacy Study	Bcr-Abl

Table 2. Non-FDA approved mTOR drugs [29,30].

Drug	Clinical trial identifier number	Phase	Study design	Target
Everolimus	NCT00374140	Phase 2	Open label, Treatment	mTOR
ME-344	NCT02100007	Phase 1, 2	Open Label, Safety Study	mTOR

Table 3. Non-FDA approved MAB drugs [31-40].

MABs	Clinical trial identifier number	Phase	Study design	Target
Ipilimumab	NCT01450761	Phase 3	Efficacy Study, Double blind	CTLA4
Bevacizumab	NCT00118235	Phase 2	Open label, Efficacy Study	VEGF
Dalotuzumab	NCT00869752	Phase 1, 2	Non-Randomized, Open label, Safety/Efficacy Study	IGF1R
BIW-8962	NCT01898156	Phase 1, 2	Open label, Safety/Efficacy Study	GM2-expressing tumor cells
Nivolumab	NCT01928394	Phase 1, 2	Open label, Efficacy Study	PD-L1
Pembrolizumab	NCT02331251	Phase 1, 2	No-Randomized, Open label, Safety/Efficacy Study	PD-1
Mogamulizumab	NCT01929486	Phase 1	No-Randomized, Open label, Safety/Efficacy Study	CCR4
Tremelimumab	NCT02261220	Phase 1	Non-Randomized, Open Label	B7-1 and B7-2
Monoclonal antibody Hu3S193	NCT00084799	Phase 1	Treatment	Lewis Y antigen
SC16LD6.5	NCT01901653	Phase 1, 2	Open Label, Safety/Efficacy Study	Fyn3

Table 4. Non-FDA approved proteasome inhibitor drugs [41,42].

Proteasomeinhibitors	Clinical trial identifier number	Phase	Study design	Target
Carfilzomib	NCT01941316	Phase 1	Open label, Safety/Efficacy Study	20S proteasome
Bortezomib	NCT00720785	Phase 1	Non-Randomized, Open label, Safety/Efficacy Study	(NF)-kappaB

Table 5. Non-FDA approved vaccines [43,44].

Cancer vaccine	Clinical trial identifier number	Phase	Study design	Target
HLA-A*2402-restricted CDCA1 and KIF20A peptides	NCT01069653	Phase 1	Non-Randomized, Open label, Safety/Efficacy Study	20S proteasome
NY-ESO-1	NCT01584115	Phase 1, 2	Open label, Safety/Efficacy Study	Cancer cells

Table 6. Miscellaneous drugs [45-48].

Treatment	Clinical trial identifier number	Phase	Study design	Target
CIK cells	NCT01498055	Phase 2, 3	Randomized, Safety/Efficacy Study	Cancer cells
Ganetespi	NCT02261805	Phase 1, 2	Open Label, Safety/Efficacy Study	Hsp90
MGN1703	NCT02200081	Phase 2	Randomized, Open Label, Safety/Efficacy Study	T-helper 1 cell
Iscomatrix	NCT01258868	Phase 2	Open Label, Safety Study	Cancer cells

incubation of peripheral blood lymphocytes (PBLs) with anti-CD3 monoclonal antibody, interleukin (IL) -2, IL-1, and interferon gamma (IFN-gamma) and then expanded. When reintroduced back to patients after autologous stem cell transplantation, CIK cells may recognize and kill tumor cells associated with minimal residual disease (MRD). CIK cells may have enhanced cytotoxic activity compared to lymphokine-activated killer (LAK) cells.

Ganetespi: A synthetic small-molecule inhibitor of heat shock protein 90 (Hsp90) with potential antineoplastic activity. Ganetespi binds to and inhibits Hsp90, resulting in the proteasomal degradation of oncogenic client proteins, the inhibition of cell proliferation and the elevation of heat shock protein 72 (Hsp72); it may inhibit the activity of multiple kinases, such as c-Kit, EGFR, and Bcr-Abl, which as client proteins depend on functional Hsp90 for maintenance. Hsp90, a 90 kDa molecular chaperone upregulated in a variety of tumor cells, plays a key role in the conformational maturation, stability and function of "client" proteins within the cell, many of which are involved in signal transduction, cell cycle regulation and apoptosis, including kinases, transcription factors and hormone receptors. Hsp72 exhibits anti-apoptotic functions; its up-regulation may be used as a surrogate marker for Hsp90 inhibition.

MGN1703: A synthetic oligonucleotide based on a proprietary double stem-loop immunomodulator design with potential immunostimulating activity. TLR9 agonist MGN1703 binds to and activates intracellular Toll-like receptor 9 (TLR9) in monocytes/macrophages, plasmacytoid and myeloid dendritic cells (DCs), and natural killer (NK) cells, initiating immune signaling pathways and inducing T-helper 1 cell (Th1) production, leading to the production of memory T-cells and a Th1-mediated immune response. By activating the immune

system, MGN1703 may attack tumor associated antigens (TAAs). TLR9 is a member of the TLR family, which plays a fundamental role in pathogen recognition and activation of innate immunity.

Iscomatrix: An adjuvant comprised of saponin, derived from the bark of *Quillajasaponaria* Molina, cholesterol and phospholipid with antigen-delivery and immunostimulatory activities. This saponin-based adjuvant in combination with various antigens, including those for human papilloma virus (HPV), hepatitis C virus (HCV), and the human cancer antigen NY-ESO-1, may result in potent antibody, CD4+ T-helper-cell, and CD8+ cytotoxic T-cell responses against the targeted antigen. In addition, this agent may reduce the amount of antigen necessary to induce an efficient immune response in the host (Table 6).

Conclusion

Immunotherapy might be beneficial for small cell lung cancer (SCLC). There is no immunotherapeutic, which is approved by FDA approved for SCLC. However, a wide variety of immunotherapeutics are under clinical trials for the treatment of SCLC. The recent activities have increased our understanding of the tumor microenvironment, various immunotherapeutic modalities or combination therapy (like chemotherapy with immunotherapy). Proper preclinical and clinical designs are the important pillars in understanding the future of immunotherapy in treating patients, suffering from lung cancer.

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