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Review Article

Recapitulation of Biological and Clinical Implication of Lung Cancer

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Abstract

Lung cancers are broadly classified as small-cell carcinomas and non-small-cell carcinomas. Non-small-cell lung cancer is more common and it accounts for up to 75% of lung cancers. Determination of the development of cancer to lungs is solely dependent on mutation of cells leading to the expression of tumor specific proteins. Hence a clear understanding of the vital structural design and physiology of the lungs assists in determination of the stages of this disease. The anatomical architecture of the lungs and their organization with adjacent organs throws light on the site of origin of malignancy, its spreading pattern and clinical presentation etc. This article has summarized the types of lung cancer, pathophysiology along with the microenvironment. The article includes the discussion on the treatment interventions such as surgery, chemotherapy, radiation therapy, the promising potential of immunotherapies and target-oriented therapies in NSCLC. Even though, the lung cancer is escapable however, it is usually diagnosed at an incurable stage.

Keywords: lung cancer; Non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC); Target Therapies; Immuno checkpoints; Tumor Microenvironment; Oncogene.

HIGHLIGHTS:

Objective: In this review article, our main focus was on the pathophysiology and the various treatments of lung cancer.

- Lung cancer is one of the most fatal chronic respiratory diseases, accounting for more than one million cases were diagnosed annually.
- Treatment of lung cancer severs as a big challenge for an oncologist. SCLC (small cell lung cancer) and NSCLC (non- small cell lung cancer) are two types of lung cancer.
- There are various conventional strategies to treat lung cancer at specific stages of lung cancer. These are either used as along or in combination with other chemotherapeutic agents.
- Chemotherapy is still an effective solution for the treatment, especially in NSCLC. Development of molecular targeted therapy; immunotherapy and immune-checkpoints inhibitors are one of the promising therapies options in both NSCLC and SCLC.

INTRODUCTION

Carcinomas that originate from respiratory epithelium dominantly in bronchi, bronchioles and alveoli are referred to as lung cancer. This type of cancer is mostly diagnosed at later stages hence leading to high mortality rate. Based on the sizes and appearance of cancerous cells cancer has been classified into two type's i.e. non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). According to WHO, lung cancer is the leading cause of mortality across world approximately 18.4 million deaths cases were reported in International agency for research on cancer (IARC global agency observatory) in September, 2018. Lung cancer is also known as bronchogenic carcinoma which affects both females and males. The primary function of the lungs is the exchange of gases between air and blood. It exactly occurs in epithelial cells [1]. There are two main factors which are responsible for causing lung cancer such as external agents including exposure to asbestos, arsenic, chromic, nickel, smoking (over 60 known carcinogens, including radioisotopes, nitrosamine, benzopyrene, etc.), tobacco, air pollution (particulate matter 2.5) {diesel funnels particle with PAH (polycyclic aromatic hydrocarbons)}, radon gas (breakdown of radium and decay product of uranium, cause genetic mutation) whereas gene mutation, genetic and epigenetic mutations come under internal factors. These agents are responsible for initiation, progression and malignancy of cancer [2-3]. Different stages of NSCLC and SCLC shown in figure 1. Table 1 summarizes the types of lung cancer according to WHO, 2015.

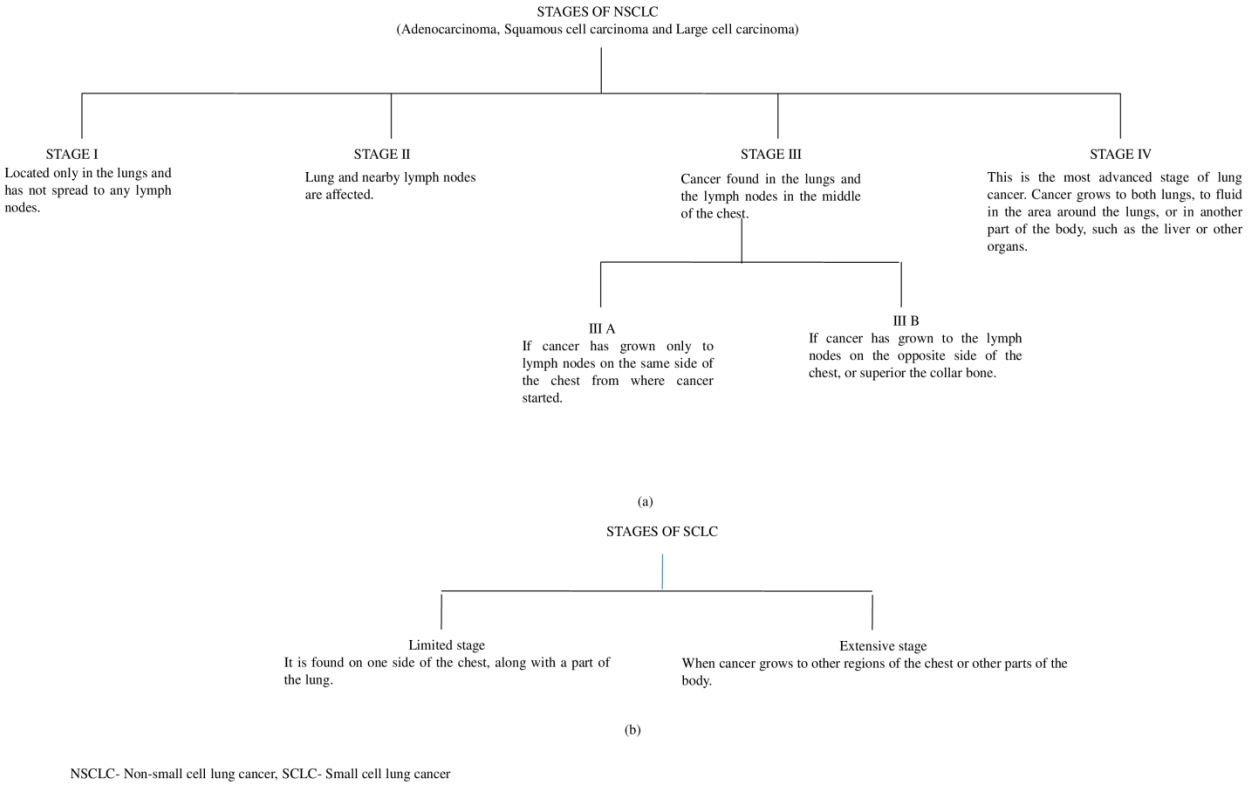

Fig-1: Stages of lung cancer is depicted in figure (a) NSCLC and (b) SCLC

Table-1: Latest classification of lung cancer proposed by World Health Organization 2015

Histological type	Subtype	Immunohistochemical changes	Sub-classification of subtype	Reference
Epithelial tumors	Adenocarcinoma (malignant epithelial neoplasm with glandular differentiation)	Mostly occurring in 60% of NSCLC. **Features**: Originates in peripheral lung tissue with central fibrosis and pleural puckering. **Pneumocyte marker:** TTF-1 and/or Napsin A **Main cause**; Nonsmokers, ex-smokers, smokers, and modest smoking history.	Lepidic adenocarcinoma Acinar adenocarcinoma Papillary adenocarcinoma Micropapillary adenocarcinoma Solid adenocarcinoma Invasive mucinous adenocarcinoma a) Mixed invasive mucinous adenocarcinoma b) Non mucinous adenocarcinoma Colloid adenocarcinoma Fetal adenocarcinoma Enteric adenocarcinoma Minimally invasive adenocarcinoma a) Mucinous adenocarcinoma Non mucinous adenocarcinoma	[4-5]
	Squamous cell carcinoma	Mostly occurring in 30% of NSCLC **Features**: Originate in centeral lung tissue and shows keratinization and intercellular bridges (hollow cavity and related cell death). **Selective squamous cell markers:** p40, CK5/6, CK5, and p63 **Main cause:** Associated with smoking.	Keratinizing squamous cell carcinomae Nonkeratinizing squamous cell carcinomae Basaloid/squamous cell carcinomae Preinvasive lesion Squamous cell carcinoma *in situ*	[4-5]
	Neuroendocrine tumors	Mostly occurring in 20-30% of lung cancer. **Features**: Epitomized by tumor proliferation rate, tumor aggressiveness and prognosis and cells having organoid growth pattern, finely granular or "salt-and-pepper" chromatin pattern, and several hallmark neuroendocrine markers. **Neuroendocrine markers**: Chromogranin A, synaptophysin, and CD56	Small cell carcinoma (Combined small cell carcinoma) Large cell neuroendocrine carcinoma (Combined large cell neuroendocrine carcinoma) Carcinoid tumors a) Typical carcinoid tumor b) Atypical carcinoid tumor Preinvasive lesion Diffuse idiopathic pulmonary Neuroendocrine cell hyperplasia	[4-5]

	Large cell carcinoma	Mostly occurring in 15% of NSCLC **Effective area**- originates in peripheral region with bulky and necrotic in appearance have heterogeneous group of tumors with adenocarcinoma. Squamous cell differentiation, or a null immunophenotype and genotype.	*	[4-5]
	Adenosquamous carcinoma	Rare type of NSCLC, less than 5% of lung cancer. Hybrid type of carcinoma of adenocarcinoma and squamous cell carcinoma	*	[4-5]
	Sarcomatoid carcinomas	Rare type of NSCLC, less than 3% of lung cancer. **Features**: Spindle and/or giant cell differentiation **Epithelial markers** : Pancytokeratin, cytokeratin AE1/AE3, CK7, and EMA	Pleomorphic carcinoma Spindle cell carcinoma Giant cell carcinoma Carcinosarcoma 8980/3 Pulmonary blastoma	[4-5]
	Other and Unclassified carcinomas	Rare type of NSCLC, less than 10% of lung cancer. **Features:** Rarely arise from bronchial glands	Lymphoepithelioma-like carcinoma NUT carcinoma	[4-5]
	Salivary gland-type tumors	Less than 1% of lung cancer. **Feature**: Arise from submucosal glands of the tracheo-bronchial tree, rare intrathoracic malignant neoplasm	Mucoepidermoid carcinoma Adenoid cystic carcinoma Epithelial-myoepithelial carcinoma Pleomorphic adenoma	[4-6]
	Papillomas	Mostly occurring in less than 1% of lung cancer. **Features:** Proximal or peripheral (fibrovascular core covered by an epithelium), polypoid, tan-white and friable lesions are protrude into airways lumens **Cause**: Smoking	Squamous cell papilloma (Exophytic and Inverted) Glandular papilloma Mixed squamous and glandular papilloma	[4-7]
	Adenomas	Less than 1% of lung cancer. **Features**: Originate in the mucous glands and ducts of the lung airways (bronchi) or windpipe (trachea), and in the salivary glands	Sclerosing pneumocytomae Alveolar adenoma Papillary adenoma Mucinous cystadenoma Mucous gland adenoma	[4-6]
Mesenchymal tumors	Vascular tumors and vessel-associated tumors	Rarely occurring tumor. **Features:** Multiple nodules with an intra-alveolar architecture and central region of hyalinization Originate from arterial intima of elastic type arteries Subungal regions Localized mass composed of perivascular epithelioid cells with clear-to-pale eosinophilic cytoplasm Proliferation of lymphatic vessels Proliferation of capillaries **Markers**- 1. Positive stain for endothelial markers CD31, CD34 and factor VIII. 2. No specific biomarkers 3. Smooth muscle cell markers α-SMA, h-Caldesmon, calponin, desmin. 4. Melanocyte markers HMB45, Melan A and S100. 5. Lymphatic endothelial marker D2-40, CD31 and factor VIII 6. Both endothelial and smooth muscle cell markers.	Epithelioid hemangioendothelioma Pulmonary artery intimal sarcoma Glomus tumor PEComatous tumor Diffuse pulmonary capillary hemangioma Solitary pulmonary capillary hemangioma	[4,8]
	Nonvascular spindle cell tumors	Rarely develop in the lung (fibroblastic tumors) **Features**: Develop in pleura, extra-pleuropulmonary organs and soft tissues **Markers:** 1.CD34,BCL2,CD99,STAT6 2.α SMA, ALK 3. CD99, BC12 epithelial markers and TLE1	Intrapulmonary solitary fibrous tumor Inflammatory myofibroblastic tumor Synovial sarcoma Pulmonary myxoid sarcoma with EWSR1-CREB1 translocation.	
	Other mesenchymal tumors and tumor–like lesions	Rarely occurring tumor **Features:** Similar genomic features with sarcomas and proliferation of cells **Markers:** Cytokeratin, α-SMA, calponin, p63, and S100.	Myoepithelial tumor/myoepithelial carcinoma Pulmonary hamartoma Chondroma Granular cell tumor	

			Nodular pulmonary amyloidosis IgG-4 related disease	
	Metastatic mesenchymal tumors (pediatric tumors)	**Features**: Solid masses, various types of metastatic tumors (e.g., leiomyosarcoma, synovial sarcoma, low-grade endometrial stromal sarcoma, and undifferentiated uterine sarcoma) occasionally appear as cystic lesions	Congential peribronchial myofibroblastic tumor Pleuropulmonary blastoma	
Lymphohistiocytic tumors	Lymphohistiocytic tumors Extranodal marginal zone lymphomas of mucosa-associated	Less than 1% of all lymphomas. **Features**- arises from peripheral small bronchi or alveolar epithelial cells **Markers-** B cell markers (CD19, CD20, CD22, CD79a) complement receptors (CD21 and CD35), and are usually negative for CD5, CD10, and CD23	Lymphohistiocytic tumors Extranodal marginal zone lymphomas of mucosa-associated Lymphoid tissue (MALT lymphoma)	[4-5,9]
	Diffuse large cell lymphoma	11–19% of primary pulmonary lymphomas. **Feature**: Lymphomas chronic inflammation of the marginal zone B cells of the "bronchial-associated lymphoid tissue" **Markers:** CD20, CD43, Bcl-2, Bcl-6, and MUM-1 (focally) and negative for CD10 and Cyclin D1	*	[4-5,10]
	Lymphomatoid granulomatosis	0.5-1% of primary pulmonary lymphomas. **Feature**: B-lymphoproliferative disorder (B cells and T cells) **Markers:** CD20, CD3, CD68, ALK1, CD30, CD15, EBV	*	[4-5,11]
	Intravascular large B cell lymphoma	Rarely occurring tumors. **Features:** Occlusive proliferation in vessels (capillaries, small arteries and veins) **Markers:** C-reactive protein (CRP), LDH, β_2-MG, interleukin-2R (IL-2R) or serum albumin	*	[4-5,12]
	Pulmonary Langerhans cell histiocytosis	Rarely occurring tumors. **Features:** Damaging of distal bronchioles and infiltrating of Langerhans' cell within the lung parenchyma **Markers-** specific marker langerin (CD207)	*	[4-5,13]
	Erdheim–Chester disease	Less than !% of lung cancer **Features:** Infiltration of lipid-laden histiocytes with foamy or eosinophillic cytoplasm **Markers:** Positive and negative stain for CD68 and CD1a respectively	*	[4-5,14]
Tumors of ectopic origin	Germ cell tumors Intrapulmonary thymoma Melanoma Meningioma, NOS	4.5% of patients with SCLC **(**Uncommon type of tumors). **Features:** Proliferation of spindle cells, pseudoglands, cystic lesion **Markers:** Epithelial cells AE1/AE3 or EMA, T cell phenotypes , CD20-positive B cells	*	[4-5,15]
NSCLC: non-small cell lung cancer; SCLC : small cell lung cancer; TTF-1: thyroid transcription factor; CK5 :cytokeratin; Factor VIII: anti-hemophilic factor(AHF); ALK: Anaplastic lymphoma kinase; SMA: Smooth muscle actin; TLE1: transducin-like enhancer of split -1; β2- MG: microglobulin, *not found				

Pathophysiology of Lung Cancer

All cells in the body consist of genetic material called deoxyribonucleic acid (DNA). At the time of maturity cell divides into two new cells and its DNA is exactly duplicated. The normal aging process or environmental factors sometimes lead to DNA mutation (somatic cells mutation) [4-5]. It further leads to activation of promoting oncogenes due to imbalance in hormones or chronic inflammation and inactivation of tumor suppressor genes. These two factors are responsible for alteration in genes and produce abnormal structural proteins which cause tumor. Pathophysiology of lung cancer with their some diagnostic tests and treatment are described in figure 2 whereas, its clinical symptoms are depicted in figure 3.

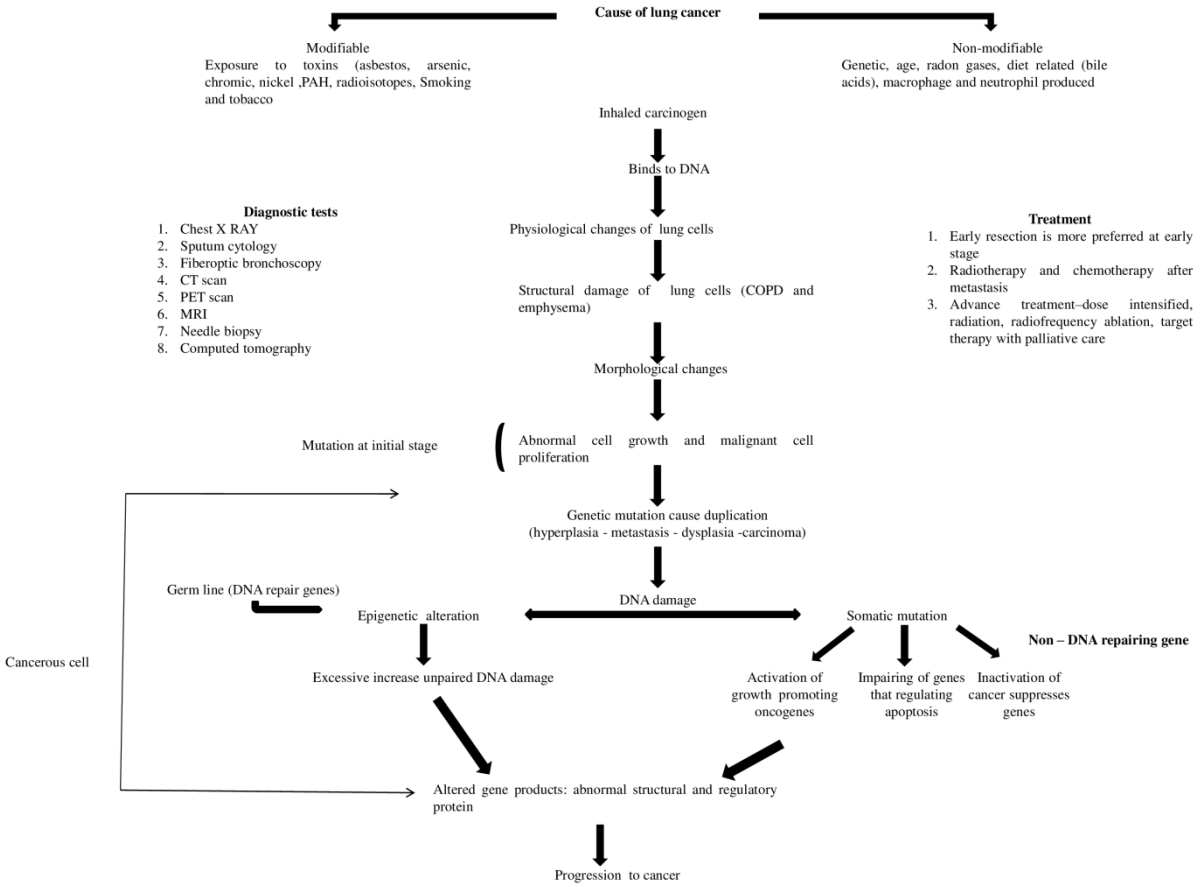

Fig-2: Pathophysiology of lung cancer along with diagnosis tests and suggested treatment

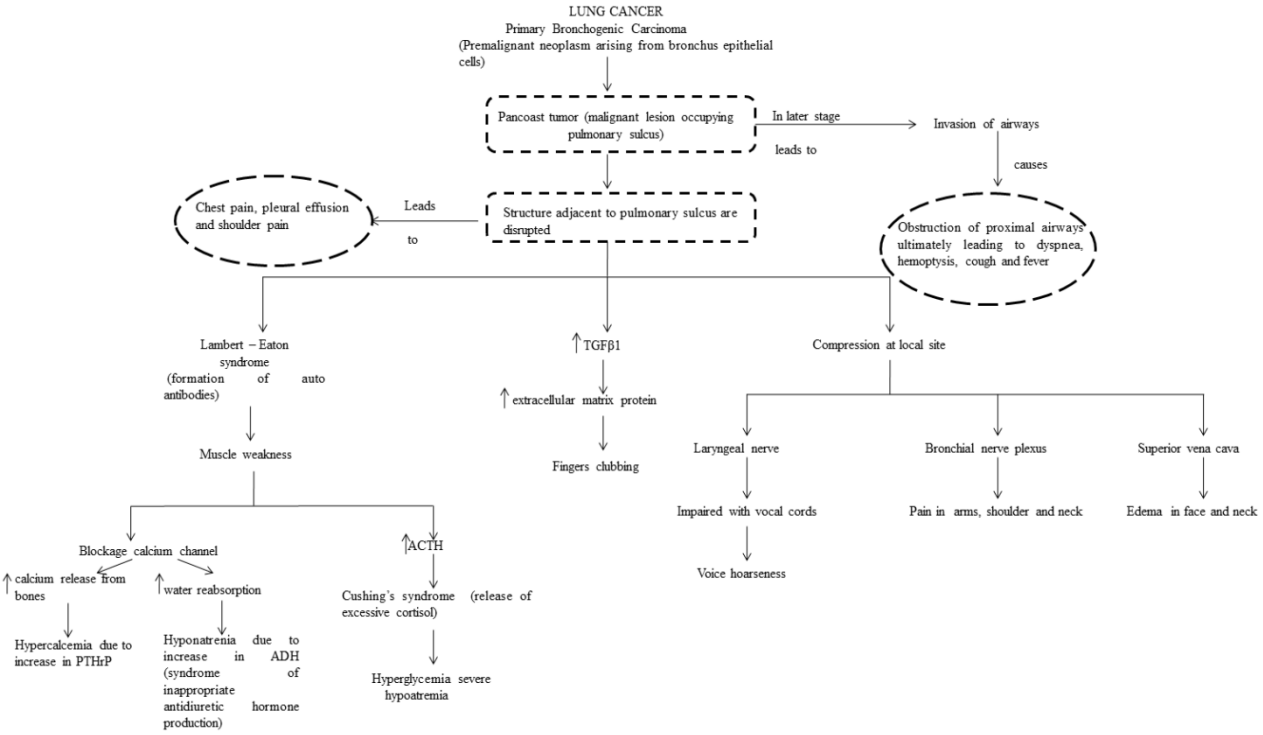

Fig-3: Clinical symptoms of lung cancer

Microenvironment of Lung Tumor

The concept of lung immune microenvironment is in existence since the "seed-soil" theory of Stephen Paget's tumor-specific tumor metastasis in 1889. The understanding of microenvironment of lung cancer is very important to further understand how the affected cells can overcome the check point blockade. The tumor microenvironment (TME) is heterogeneous in composition and comprises of cellular components like endothelial cells, as well as its precursor cells, pericytes, myeloid-derived suppressor cells (MDSC), tumor-associated fibroblast (CAF), tumor-associated macrophages (TAM), T cells and B Cells, NK (natural killer) cells, DC_s (dendritic cells), growth factors, proteases, and extracellular matrix [16]. The interactions between genetically altered tumor cells and genetically stable intratumoral stromal cells lead to either activated or reprogrammed stroma that may further promote carcinogenesis by contributing to inflammation, immune suppression, therapeutic resistance, or generating premetastatic niches that support the initiation and establishment of distant metastasis. It also affects the activation and metabolism of T cells through various mechanisms. Tumor-infiltrating T lymphocytes have an immune surveillance effect that inhibits the binding to PD-1 and PD-L1, which is positively correlated with resistance, and this resistance develop tumor. Tumor infiltrating T cells can be activated by co-stimulatory receptors (e.g. tumor necrosis factor receptor superfamily members OX40, CD40, 41BB and B7-CD28, and immunoglobulin superfamily member ICOS etc.) and a co-stimulatory receptor in combination with its ligand by enhancing the function of Th1 (T helper type 1) cells or inhibiting the function of Treg (regulatory T cells) cells, killing tumor cells. Its combination with ICB (immune check point blockers) can enhance its anti-tumor efficiency. Treg cells can promote the production of vascular endothelial growth factor (VEGF) in tumor cells and CAF (cancer associated fibroblasts), and reduce IFN-γ and granzyme produced by T cells to reduce immune killing. In tumor patients, Treg cells inhibit specific T cell responses and express greater level of glucocorticoid-induced tumor necrosis factor receptor-associated proteins (GITR) and CTLA-4 [17].

Treatment of Lung Cancer

The basic choice of treatment of a patient depends upon the type of cancer and whether the disease has metastasized to distant organs. Lung cancer can be treated with various methods such as surgery, radiofrequency ablation, immunotherapy, stereotactic ablative, radiation therapy, photodynamic therapy, Radiofrequency ablation (RFA), tyrosine kinase inhibitors (TKI) and targeted specific therapy [3, 18, 19].

Surgery

The surgery is the primary treatment for restricted patients with early-stage cancer and is performed basically for the stage- I NSCLC, stage-II NSCLC and limited-stage SCLC and lymph node tumors may not be benefited from surgery, after which ancillary chemotherapy is given [20]. The surgery involves the removal of the entire lobe in which the tumor is located and a margin of healthy tissue. Agenda for removal of lung cancer includes wedge resection to remove cancerous tissue, segmental resection to remove a major portion of the lung, but not an entire lobe, lobectomy (removal of entire lung lobe), pneumonectomy (removal of entire lung). The objective of surgery is to totally eradicate all the tumor cells and thereby provide a cure [3, 18-19]. Prior surgical techniques such as video-assisted thoracic surgery (VATS) minimal involved invasion and were used to perform a lobectomy or wedge resection, the procedure involves inserting a long thin tube with an attached camera (thoracoscope) connected to a video monitor so that the surgeon can see inside the chest and remove cancerous tissue from the lung [18]. Robotic-assisted thoracic surgery (RATS) is another minimally invasive way of treating lung cancer [19].

Chemotherapy

Chemotherapy is the most powerful tool to treat lung cancer, new or existing drugs are used to treat/kill cancerous cells [20]. These drugs, may be targeted to cancerous cells (less damage to normal cells) and involve immunotherapy (use the own body's immune system to destroy cancer cells). It is used in all stages of cancer [21]. Chemotherapy works in three different ways such as neoadjuvant or primary systemic lung cancer chemotherapy (before surgery to destroy or remove cancerous cells) [18, 22], adjuvant chemotherapy (to prevent cancer spreading throughout) [18, 23] and lastly large circulation of chemotherapeutic drugs [18, 24].Cisplatin was approved by the FDA in 1978 and is the most successful drug discovery against cancer still and is widely used in combination with other chemotherapeutic agents. To overcome various side effects like nephrotoxicity, neurotoxicity, retinotoxicity, and ototoxicity, cisplatin derivatives are used [19, 25]. Chemotherapeutic agents which are commonly used to treat lung cancer are carboplatin (Paraplat or Paraplatin), cisplatin (Platinol-AQ or Platinol), docetaxel (Taxotere), etoposide (Toposar or VePesid), gemcitabine hydrochloride (Gemzar) with cisplatin (Platinol-AQ or Platinol), paclitaxel (Taxol) in combination with cisplatin (Platinol-AQ or Platinol), paclitaxel albumin-stabilized nanoparticle formulation (Abraxaned also called albumin-bound paclitaxel or nabpaclitaxel) in combination with carboplatin pemetrexed disodium (Alimta), topotecan hydrochloride (Hycamtin), and vinorelbine tartrate (Navelbine) [26]. US- FDA approved

chemotherapeutic drugs for lung cancers are summarized in table 2.

Table-2: USFDA approved chemotherapeutic drugs for lung cancer

Drug Name/ Brand	Stages	Formulation	Dose	FDA Approval	Patent expiry(US)	Reference
ANGIOGENESIS INHIBITOR/VEGF RECEPTOR INHIBITOR						
Bevacizumab (Avastin)	Non-squamous NSCLC at stage IV	Solution for IV infusion after dilution	100 mg, 400 mg	February, 2004	July, 2019	[27]
Ramucirumab (Cyramza)	2nd line of treatment metastatic NSCLC at stage IV and hepatocellular carcinoma with elevated alpha-fetoprotein	Solution for IV infusion after dilution	10 mg/ml	December, 2014	November, 2031	[28]
ANTIMETABOLITES						
Gemcitabine (Gemzar)	NSCLC at stage IIIA, IIIB, IV and SCLC (adenocar-cinoma & squamous cell carcinoma)	Powder for IV infusion after reconstitution,	200 mg or 1mg,	August, 1998	May, 2013	[29]
Infugem		solution for IV infusion	1200 mg/ 120 ml to 2200 mg/220 ml			
Methotrexate	Squamous cell and small cell lung cancer	Solution for IV, IM, intra-arterial, or Intrathecal administration after dilution	25 mg/ml	April, 2005	January, 2026	[24]
		powder for IV, IM, Intra-arterial, or Intrathecal administration after dilution				
(Trexall)		scored tablets	1g 5mg, 7.5mg, 10mg, 15mg	March, 2001		
Pemetrexed (Alimta)	first-line treatment of non-squamous-cell lung cancer, second-line treatment of NSCLC at stage IV	Powder for IV infusion after reconstitution and dilution,	100mg, 500mg	August, 2004	May, 2022	[30]
ANTIMICROTUBULE AGENTS						
Docetaxel (Taxotere)	Advance and metastatic NSCLC at stage IIIA, IIIB, IV	Solution for IV infusion after dilution	40 mg/ml	December, 1999	May, 2014	[31-32]
Paclitaxel (Taxol)	Squamous NSCLC at stage IV	Solution for IV infusion after dilution	6 mg/ml	October, 2012	February, 2026	[32-33]
Paclitaxel (Abraxane)-bound to albumin	NSCLC	Powder for IV infusion after reconstituti-on, first-line treatment of locally advanced or metastatic non-small cell lung cancer, in combination with carboplatin	100 mg/ vial	October, 2012	December, 2023	[34]
Vinorelbine (Navelbine)	NSCLC at stage III,	Solution for IV injection after dilution	10 mg/ml	December, 1994	February, 2003	[35]
HUMAN EGFR INHIBITOR						
Necitumumab (Portrazza)	Metastatic squamous NSCLC	solution for IV infusion after dilution	800 mg/ 50 ml	November, 2015	2025	[36]
Kinase inhibitors						
Afatinib (Gilotrif)	Metastatic squamous NSCLC with EGFR mutation at stage IV	Tablets	20 mg, 30 mg, 40 mg	July, 2013	October, 2029	[37]
Alectinib (Alecensa)	ALK+ and Metastatic squamous NSCLC	Capsules	150 mg	December,2015	May, 2031	[38]

Brigatinib (Alunbrig)	Metastatic squamous NSCLC	Tablets	30 mg, 90 mg, 180 mg	April, 2017	May, 2029	[39-40]
Ceritinib (Zykadia)	Metastatic squamous NSCLC at stage IV	Hard gel capsules	150 mg	April, 2014	November,2027	[41]
Crizotinib (Xalkori)	ALK^+ NSCLC at stage IV	Capsules	200 mg, 250 mg	August, 2011	November, 2026	[42-43]
Dacomitinib (Vizimpro)	Metastatic squamous NSCLC	Tablets	15 mg, 30 mg, 45 mg	September, 2018	*	[44]
Erlotinib (Tarcev)	Treatment of locally advanced or metastatic NSCLC Stage III and IV after failure of at least one prior chemotherapy regimen	Tablets	25 mg, 100 mg, 150 mg	November, 2004	November, 2020	[45-46]
Gefitinib (Iressa)	2^{nd} line treatment of NSCLC	Tablets	250 mg	May, 2003	May, 2017	[47-48]
Lorlatinib (Lorbrena)	Metastatic squamous NSCLC	Tablets	25 mg, 100 mg	2 November 2018	*	[49]
Osimertinib (tagrisso)	EGFR T790M mutation positive NSCLC	Tablets	40 mg, 80 mg	November, 2015	July, 2032	[50-51]
Trametinib (Mekinist)	metastatic NSCLC with BRAF V600E mutation	Tablets	0.5 mg, 2 mg	May 2013	September, 2025	[52]
PD-1/ PD-L1 BLOCKING ANTIBIODIES						
Atezolizumab (Tecentriq)	Extensive SCLC and adenocarcinoma	Solution for IV infusion after dilution	60 mg/ml	March, 2019	May, 2026	[53]
	Metastatic squamous NSCLC			May, 2016		
Durvalumab (Imfinzi)	Stage III NSCLC	Solution for IV infusion after dilution	50 mg/ml	May, 2017		[54]
Nivolumab (Opdivo)	Metastatic squamous NSCLC	Solution for IV infusion after dilution	10 mg/ml	March, 2015 December, 2014	June, 2028	[55]
	SCLC and at stage III or IV of NSCLC			August, 2018	May, 2026	
Pembrolizumab (Keytruda)	Cell carcinoma	Solution for IV infusion after dilution,	50 mg/ vial	December, 2018	March, 2032	[56-57]
	Stage III NSCLC			April 2019		
	Metastatic SCLC			June, 2019		
	Adenocar-cinoma	powder for IV infusion after reconstitution	25 mg/ml	October, 2015		
	Advance NSCLC			September, 2018		
PHOTOSENSITIZING AGENT						
Profimer (photofrin)	Microinvasive endobronchial NSCLC	Powder for IV injection after reconstitution	75 mg	January 1998	*	[55]

NSCLC: non-small cell lung cancer; SCLC : small cell lung cancer; ALK: Anaplastic lymphoma kinase; EGFR: epidermal growth factor receptor; BRAF: proto-oncogene B-raf, *not found

Radiotherapy

Radiotherapy is used to deliver high energy X-rays/ionizing radiation i.e. Radium (228Ra), Iridium (192Ir), Phosphorous (32p), and Cobalt (60Co) that destroys DNA of cancer cells or shrink the tumor cells. It is especially used as primary treatment for NSCLC; before surgery it is used to shrink the tumor, after surgery it is used to remove remaining cancer cells in the treated area. It is also in used different cancer treatments that have spreaded to the brain and other parts of the body [58]. A delivery technique in radiotherapy includes external beam technique (EBT), conformal radiation therapy or Intensity-modulated radiation therapy (MRT), and branchytherapy or localized therapy (BLT). EBT is an intervention technique used for lung cancer treatment in which a beam of very few highly focused doses or fractionated radiation therapy is used directly at the site of the tumor [59]. MRT is comparatively new technique that uses 3D image of tumor cell CT scanner; it serves as the target for a high dose radiation beam. BLT is an after surgery procedure in which radiation is directly delivered at the site of obstruction through the plastic tube which is temporarily inserted into the airway [60].

Radiotherapy and Microwave Ablation (MWA) of Lung Tumor

Radiofrequency ablation (RFA) for lung tumors was first introduced in 2000 by Dupuy *et al.* [61]. It is an invasive treatment that uses image guidance technique to insert a needle containing multiple electrodes through the skin into the specific site of the tumor. Due to high frequency sinusoidal

(electrical) currents are passed through the electrode to ground pads (placed on the body) which create focal heat that destroys the cancer cells surrounding the electrode (thermal destruction of cells and coagulation necrosis). MWA is the minimally invasive treatment that uses microwaves heat which destroys the tumor and also used for the guidance of needle placement in the tumor. MWA is used for the treatment of lung cancer whereas radiofrequency ablation may be limited by the accelerated lung's low electrical conductivity and poor thermal conduction [19].

Stereotactic Ablative Body Radiotherapy (SABRT)

SABRT is an advancement of an external beam of radiation therapy; high dose radiation is directly delivered to extracranial target within the body either as single dose or as a small fraction [62].This technique of treatment is widely used for inoperable stage I NSCLC and it improves local control or prolongs overall survival without an increase in major toxicity as compared to standard radiotherapy. Radiotherapy represents a safer and potentially curative option for stage I NSCLC in many patients who have smoking-related cardiac or respiratory comorbidities that make them unfit for operation [63].

Supportive and Palliative Care (SPC)

SPC also plays a vital role in the management of lung cancer that improves the quality of lung cancer patients. Temel and co researchers studied and analyzed the effect of early specialised palliative care support as compared to standard care in ambulatory patients with metastatic NSCLC referred to the medical oncology outpatient department [64] and found a significant difference in patient survival [65]. SPC includes medication to manage dyspnoea in patients with lung cancer, which includes use of systemic opioids (dose 10 to 30 mg/ml) [66, 67], sustained release morphine [68], frusemide nebulised (dose of 40 mg/4 ml) to support chronic refractory breathlessness [69, 70]. It further includes non-pharmacological management of dyspnoea in lung cancer to reduce anxiety and distress [71, 72], and interventions to control psychological distress and unmet needs in lung cancer patients nurse-led care in gradually increasing muscle relaxation combined with education on self-management of symptoms at the beginning and middle of radiotherapy [73], coping skills training for care givers also showed improvements in patient- and care giver-reported outcomes, including depression and self-efficacy over time [74]. An overarching specialist approach to palliative care delivery (by Quill and Abernathy and supported within the 2017 ASCO guidelines) introduced different types of potential models which are; concurrent care model that involves interdisciplinary palliative care team and triggered integration model which involves the oncology care team backed by the palliative care team. Concurrent and triggered integration models are hybrid of the models [75].

Immunotherapy

Immunotherapy is one of the most preferred treatments for lung cancer especially in the advanced metastatic stage of NSCLC because it can change or even enhance the survival rate of cancer patients. The significance of immune system lies in its potential to protect from attacking normal cells in body. For this purpose the proteins i.e. checkpoints on normal cells are required to be turned on/off to trigger/start the immune response. Two immune checkpoint inhibitor pathways are programmed cell death protein 1 (PD-1)/Programmed death-ligand 1 (PD-L1) and cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4). Immunotherapy of cancer works against tumor cells by repairing and enhancing the immune system which controls the killing of the tumor cells. The very first-time immune phenomenon was discovered by Coley *et al.*, 1893 [76-77]. An immunological checkpoint inhibitor severs as an immune blocker that prevents the release of tumors, and also induces the re-activation of T cells for the immune response to the tumor effect, thereby achieving an anti-tumor role as a new weapon against tumors. The prevalent mechanism by which lung cancer cells get away from the host's immunological response is through the expression of PD-L1, also called B7-H1 or CD274 [78]. PD-1 is an immune-regulatory receptor present on the surface of activated T cells. The PD-1 and PD-L1 interaction inhibits T cell responses leading to apoptosis of tumor-specific T cells and thus promotes differentiation of CD4+ T cells into regulatory T cells, and further avoids tumor cell resistance [79]. Immunotherapy can have a major role in cancer management either as a monotherapy or in the combination of standard treatment. However, the biggest threat is to ensure the maximum durable response with the minimum toxicity. There are three stages of cancer immune editing theory which involves elimination/ immune surveillance, equilibrium, and escape. Tumor cells (less immunogenic) are successfully destroyed by the host's immunity; this is called the elimination stage and reaches to equilibrium stage. In this stage, the immune system fails to completely abolish all cancer cells, but it can effectively manage further tumor growth. In the escape stage, the tumor outgrowth is out of immune control, as the cancer cells that have escaped continue to reproduce [80]. The cancer cells co-opt specific pathways of the immune system, especially against T cells targeting specific tumor antigens, leading to tumor resistance. However, as numbers of checkpoints are developed by ligand-receptor interactions, they can be easily blocked by antibodies or regulated by engineered ligands or receptors [81]. Two of the most encouraging approaches for blockade of immune checkpoints are through checkpoint inhibitor that includes cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) and PD1 inhibitors as well as vaccine

therapy [82]. Vaccines involved in immunotherapy are summarized in Table 3.

Table 3- Summary of immunotherapy vaccines

Vaccines	Immunological responses	Stages	Reference
ANTIGEN- SPECIFIC VACCINES			
Mucin 1: A Cell Surface-Associated Antigen (type 1 transmemberane proteins) L-BLP25 (BLP25) Stimuvax, Biomira, Alberta, CA	Extracellular core peptide of MUC1	Stage III NSCLC after treatment	[60,83-85]
GD3 (cell surface ganglioside antigen) Anti-idiotype Antibody Bec2Plus, BCG Vaccine	Surface of cell	Phase 3 SCLC after chemotherapy and radiotherapy	[83,86-87]
Neu-Glycosylated Gangliosides 1E10 Antiidiotype	Cell surface	Phase 1 SCLC and stage IIIB/IV NSCLC	[83,88-89]
Toll-like Receptor 9 Vaccine PF-3512676	TLR9 is expressed on B and T lymphocytes, plasmacytoid cells, and dendritic cells	Stage IIIB/IV NSCLC	[83,90-91]
Melanoma-Associated Antigen A3 Immunotherapeutic	Tumor-specific antigen that is not expressed on normal cells.	stage 1B to II NSCLC	[83,92-93]
Nine class I peptides (from CEA, p53, HER-2/neu, MAGE-2 and -3) with PADRE	CTL responses	IIIB–IV or recurrent	[94]
Modified Ankara virus containing MUC-1 and IL-2	CTL responses	IIIB–IV	[95]
Optimized class I hTERT peptide p572Y and native peptide p572	CTL responses	III–IV	[96]
Immature DCs pulsed with apoptotic bodies from NSCLC cell line	CTL responses	I–IIIB	[97]
Seven ras peptides encompassing predicted mutations of codon 12	DTH responses	I or IV	[98]
hTERT class I peptide p611 and class II peptide p540 with GM-CSF	T-cell proliferation	IIB–IV	[99]
L523S gene immunized in a plasmid followed by a viral vector	Humoral responses	IB–IIB	[100]
Autologous tumor cells with K562 cells transfected with GM-CSF	DTH/humoral responses	III–IV	[101]
Dexosomes pulsed with MAGE-A3, -A4, -A10 and -3DPO4 peptides	DTH responses	IIIB–IV	[102]
Class I WT1 peptide p235	CTL/DTH responses	IV	[103]
SART-1, -2 and -3, CypB, Lck, and ART-1 and -4 peptides	CTL/DTH responses	IV or recurrent	[104]
B7.1 and HLA A1- or A2-transfected allogenic NSCLC cell line	CTL responses	IIIB–IV	[105]
TUMOR CELL VACCINES			
Granulocyte-Macrophage Colony-Stimulating Factor-Transduced Allogeneic Cancer Cellular Immunotherapy	APCs to the site of vaccination	Stage I/II NSCLC	[83,106-107]
Transforming Growth Factor _2 Antisense Gene-Modified Allogeneic Tumor Cell Vaccine:	Antisense oligonucleotide to transforming growth factor-2 (TGF-2).	Stage II –IV NSCLC	[83,108]
NSCLC: non small cell lung cancer; SCLC: small cell lung cancer; CTL: cytotoxin T-lymphocytes; DTH: delayed type hypersensitivity; APC: antigen presenting cell.			

Immune Resistance and Checkpoint Inhibition

CTLA4 (homologous to T cells co-stimulatory protein) is a member of the immunoglobulin family and is expressed by activated T cells, which delivers an inhibitory signal to T cells. The combination of the molecules binds to CD80 and CD86 with greater affinity, they are also known as B7-1 and B7-2, respectively, on antigen-presenting cells [17, 109]. The FDA approved CTLA-4 inhibitors are Ipilimumab (fully humanized IgG1 monoclonal antibody) and Tremelimumab. The antitumor immune response is initiated by the recognition of the tumor antigens by T lymphocytes followed by the co-stimulatory binding of T-cell receptors (TCR) to peptide-major histocompatibility complex (MHC) on antigen presenting cells (APCs). CD28, a stimulatory molecule represented on T cells that promotes T cell activation by binding to CD80 and CD86 (B7-1 and B7-2) ligands on APCs [110]. PD-1 is a member of the extended CD28/CTLA-4 family of T cell, and it is also considered as an immune checkpoint receptor, expressed on activated T cells. Its ligands consist of

PD-L1 and PD-L2, and mainly tumors are expressed by PD-L1 [111]. The combination of PD-1 and PD-L1, delivers the inhibitory signals that regulate reproduction and viability of CD4+ T and CD8+ T cells which have been shown in normal individuals in order to minimize the damage of the immune response to surrounding tissues and to prevent the development of autoimmune diseases [111-112]. In patients, it can reduce T-cell immunity killing the tumor local microenvironment leading to tumor immune escape and the progress of tumor growth [113]. A number of clinical studies [113-115] have demonstrated that PD-1/PD-L1 inhibitors have excellent efficacy in advanced NSCLC. When PD-1 binds to its ligands, PD-L1 and PD-L2 are expressed on APCs (Antigen presenting cells) on some normal and cancer cells and leads to T cell inactivation [116]. PD-L1 can interact with the B7 molecules, resulting in T cells turning off [117]. PD-1-induced inhibition is a possible mechanism for adjusting immune resistance. Thus, anti-PD-1 antibodies can be generated to bind to the PD-1 receptor and blocking its interaction with PD-L1/L2 and thus preventing T cell inactivation [118]. FDA approved drugs for PD-1/PDL-1 are Nivolumab [55] (a full human IgG4 monoclonal antibody against PD-1and first checkpoint inhibitor), Pembrolizumab [56-57] (human monoclonal antibody against PD-1 and its ligand PD-L1), Atezolizumab [53] (fully humanized, engineered monoclonal antibody of the IgG1 isotype against PD-L1), and Durvalumab [54] (human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody against PD-L1 with PD-1 and CD80). Immune cycle of lung cancer is represented in figure 4**.** Various checkpoints of lung cancer which are involved in treatment are summarized in Table 4.

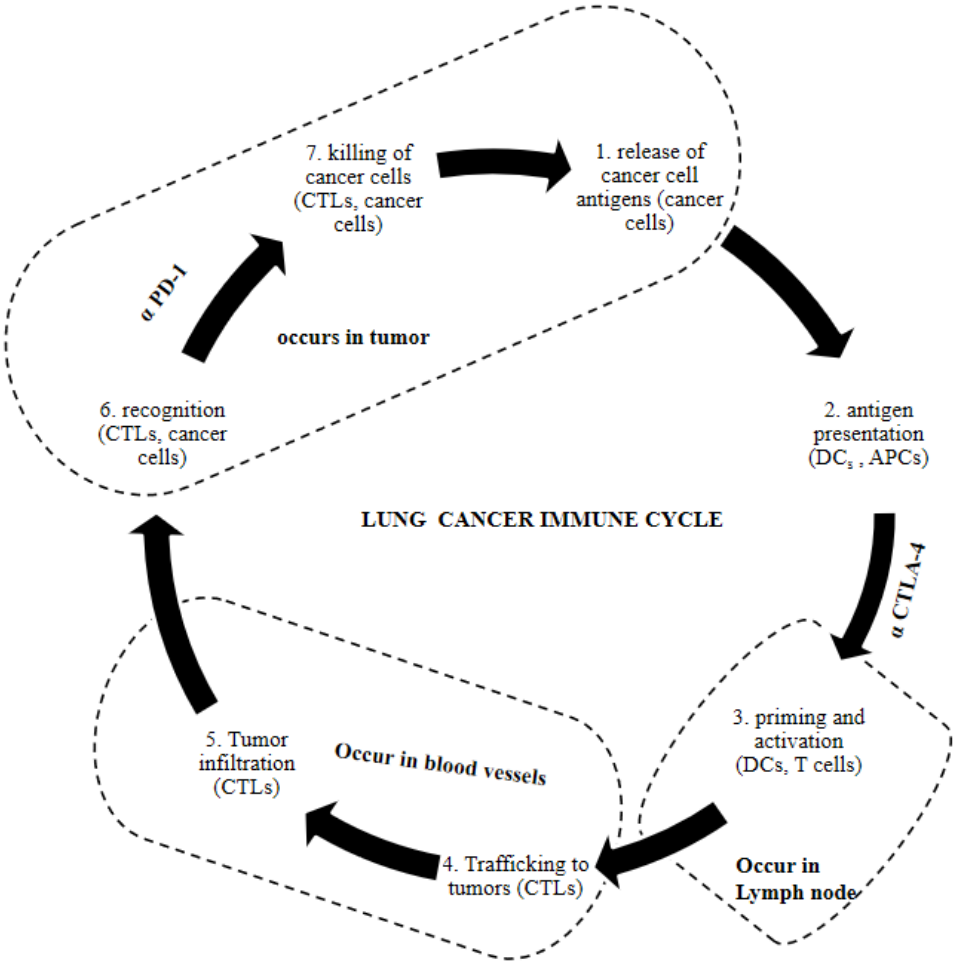

Fig-4: Lung cancer immune cycle

Table-4: Summary of Immunological checkpoints for treatment of target sites in lung cancer

Immunoglobulin Antibiotics	Targeted site	Activated by	Action /Activity	Reference
Lymphocyte activation gene-3 (LAG-3) Third Inhibitory Receptor	CTLA4	T cells NK cells B cells Plasma cells	Reduce T_{reg} activity in-vivo	[17,119]
	PD1-PDL1		Anti-tumor activity (advance lung cancer)	
T cells Ig and mucin domain-3 (TIM-3) Inhibitory Activity Of T Cells	CD4 + T helper 1 (Th1)	Galectin -9	Peripheral tolerance	[17,120]
	CD8 + T cytotoxic 1 (Tc1) and Th17 cells		Loss of T cells in tumors	
	CD4+ and CD8+		Tumor infiltrating lymphocytes in lung cancer patients	
	CD4+ T cells		Lymph node metastasis and lung cancer	
Killer cell immunoglobulin like receptor (KIR) (glycoproteins)	T CD8+ Cells	NK cells	Cytotoxic activity	[17,121]
CTLA4: cytotoxic T-lymphocyte associate protein; PD1: programmed cell death protein; PDL1: programmed death ligand 1; Treg: regulatory T cells; NK cells: natural killer cells.				

Targeted Therapies

Target Cells with Anti- Angiogenesis Inhibitor

Anti-angiogenesis therapy is a developing field in lung cancer treatment. Vascular endothelial growth factor (VEGF) is playing a significant role in blocking tumor vascularization or it interferes with the activity of the growth factor receptors and molecular pathways that are triggered by the activation of this receptor. VEGF drugs would cause a reduction in blood vessel sprouting and the formation and moderate destruction of existing tumor vasculature. However, recent studies conclude that anti-angiogenesis drugs lead to normalization of the tumor vasculature (means normal phenotype of tumor cells) and also increase the delivery of oxygen and drugs to the tumor thus lifting the local hypoxia (which leads to selection of more aggressive tumor clones) and amplification of chemotherapeutic efficiency [106].

Target Cells with Epidermal Growth Factor Receptor Inhibitors

Epidermal growth factor receptor (EGFR) is one of the proteins (transmembrane growth factor receptor) which are present on the surface of the cell and it is responsible for the growth, survival, and proliferation of the cell. The huge amount of EGFR is present on the surface of tumor cells which causes unnecessary proliferation of cells. EFGR inhibitors are used to block the signals and growth of tumor cells [77]. It may further lead to shrinkage of tumor cells due to alteration in the EGFR gene and is termed as T790M mutation [107].

Tyrosine kinase inhibitors (TRI) are known to inhibit mutation of EFGR and its constitutive activation via reversible inhibition of the ATP-binding pocket in the EGFR kinase domain. The major mechanism behind this resistance is T790M mutation within the EFGR kinase domain. It also increases affinity for ATP, thus reducing inhibitor binding to the EGFR kinase domain while preserving catalytic activity [108].

Target Cells with ALK (Anaplastic Lymphoma Kinase) Genes

Translocation and functional impairment of the ALK genes is responsible for the mutation, proliferation and survival of lung cancer cells. Generally, it is a chromosomal rearrangement of genes in which EML4-ALK product is formed due to the fusion between EML4 (echinoderm microtubule-associated protein-like 4) and ALK genes. This product is responsible for the constitutive activation of the kinase [38, 40]. Approximately, 3-4% of NSCLC patients have this type of fusion gene product [90]. This rearrangement may produce abnormal ALK protein, which is also responsible for the unwanted growth of cells [122].

Target Cells with Braf (V-Raf Murine Sarcoma Viral Oncogene Homolog B1)

BRAF is a RAF serine/threonine protein kinase. Mutation of BRAF with RAF kinase activates the MAPK pathway, which causes uncontrolled growth and proliferation of the cells. Approximately 2-3% of NSCLC cases are reported to be due to a mutation in BRAF. Valine 900 Glu (V900E) mutation within exons 15 kinase domain contributes to lung cancer (lung adenocarcinoma) [108].

Anti Inflammatory Therapies

It has been observed during clinical trials that long term use of aspirin, which is primarily used to prevent cardiovascular disease, also contributes in reducing the lung cancer death rate [125]. A large randomized trial of canakinumab, an antibody targeting IL-1β in patients with atherosclerosis, showed that patients receiving canakinumab had a statistically significant reduction in new lung cancer incidence and mortality [123]. Two recent studies depicted the future therapeutic potential of the NF-κB-mediated inflammatory pathway in lung cancer. The presence of oncogenic Ras, inflammatory stimuli depicts the cox-1, cox-2 involvement of NF-κB that further augments Ras activity and enzyme IKK2 and Timp1 which activates

the inflammatory response of the body may effectively treat certain lung cancers [126].

The list of drugs used in targeted therapy along with their FDA status is discussed in Table 5.

Table-5: Summarizes drugs used in target therapy along with their FDA status

Drug	Drug type	Effect	Combine with	Clinical trials	Reference
Bevacizumab	Monoclonal antibody against VEGF	Improved PFS and RR in patients with non-squamous NSCLC	FDA approval first-line treatment along with platinum-based drugs – carboplatin and paclitaxel	Phase III	[106,123-124]
Ramucirumab (Cyramza)	Monoclonal antibody against VEGFR	Improved PFS and RR in patients with non-squamous NSCLC	FDA approval second-line treatment along with platinum-based drugs – carboplatin and paclitaxel	Phase IV	[28]
Aflibercept	Decoy receptor fusion protein, binding VEGF-A, VEGF-B, and Placental growth factor	Improved PFS and RR in patients with NSCLC	Combination with docetaxel	Phase III	[106,124]
Axitinib	MT-TKI, against VEGFR-1, 2 and 3, PDGFR and c-kit	Promising phase II results in patients with NSCLC	Combination with docetaxel	Phase II	[106]
Cediranib	MT-TKI, against VEGFR-1, 2 and 3, PDGFR and c-kit	Significant activity and toxicity in patients with NSCLC	Combination with docetaxel	Phase III advance NSCLC	[106,123-124]
Motesanib	MT-TKI, against VEGFR-1, 2 and 3, PDGFR, c-kit and RET	Improved PFS in a phase II trial in the setting of NSCLC	Combination with carboplatin and paclitaxel	Phase III	[106,123-124]
Sorafenib	MT-TKI, against VEGFR-2 and 3, PDGFR, B-Raf and C-Raf	Increased PFS in patients with NSCLC	PFS and OS negative when giving in combination with chemotherapy Pending	Phase III	[106,123-124]
Sunitinib	MT-TKI, against VEGFRs, PDGFR, c-kit, flt3, RET and CSF-1R	Increased PFS and RR	combination with erlotinib, in patients with NSCLC	Phase III	[106,124]
Endostatin	Natural inhibitor of angiogenesis Targets bFGF, VEGF	Increased PFS and RR	combination with chemotherapy and chemoradiation in NSCLC	Phase III	123
Pazopanib	Targets c-KIT, FGFR, PDGFR and VEGFR	Combination with Docetaxel	NSCLC patients who have received first- line therapy (NCT01208064) Refractory small cell lung cancer (NCT01253369)	Phase II/III Phase II	120
Vandetanib	MT-TKI, against VEGFR, EGFR and RET	Small increase in PFS in patients with NSCLC	Combination with Docetaxel	Phase III	[106,123-124]
Nintedanib	VEGFR, FGFR, PDGFR	Increased PFS and RR	Combination with Docetaxel	Phase III	123

NSCLC: non small cell lung cancer; SCLC: small cell lung cancer; VEGF: Vascular endothelial growth factor; EGFR: epidermal growth factor receptor; TRI: tyrosine kinase inhibitors; ALK: anaplastic lymphoma kinase; BRAF- V-RAF murine sarcoma viral oncogene homolog b1; PFS: Progrssive free survival; RR- respiratory rate; PDGF-R: platelet derived growth factor receptor, CSF-1R: colony simulating factor 1 receptor; FGFR: fibroblast growth receptor.

CONCLUSION

One of the culprits for lung cancer is smoking. However, many patients continue to smoke even after diagnosis which places them at higher risk of treatment toxicity and cancer recurrence. The patients who continue to smoke must be offered interventions to help them quit. Lung cancer patients and their care givers need psychological support so that they are able to cope with the consequences of diagnosis and treatment. In patients with metastatic disease, palliative radiotherapy is effective for the management of pain and coughing up of blood or blood-stained mucus from the bronchi, larynx, trachea, or lungs. Patients at advanced stage should be provided palliative care. Early palliative care improves outcomes including survival of the patient. Chemotherapy along with surgery and radiation therapy is used commonly for the management of lung cancer.

Future perspective

In the past decades, chemotherapeutic drugs are widely used either in a single form or in combination and also associated with other therapies such as surgery, radiotherapy to improve the condition of the patient. Palliative and supportive cares are given to a patient also plays an important role in the recovering of tumor patients. But, each therapy has its own limitations such as chemotherapeutic agent is non-specifically distributed throughout the body where they affect both cancerous and non-cancerous cells, which cause various side effects such as rash, alopecia, severe liver, and kidney function decline, cardio-toxicity, bone marrow suppression and also quality of patient's life. In the current scenario, enormous advancement in the development and application of bioinformatics and nanotechnology has been developed for the detection, diagnosis, and therapy of cancer. The Development of nanotechnology has revolutionized the treatment of lung cancer to a very great extent and also formulates target specific formulation with a high affinity for cancer treatment. It also helps to overcome the drawbacks and lacking specificity in conventional therapies that are not possible with other types of therapeutic drugs, and have shown a bright future as a new generation of cancer therapeutics.

Financial and competing interest's disclosure

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