Targeted Therapies For Treatment of Lung Cancer – Recent Advances

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Abstract

In both men and women, Lung cancer is the number one cause of cancer-related death. The disorder is especially difficult to detect, and often develops for elderly patients at an advanced stage. Within a year of treatment, more than half of those diagnosed with lung cancer die and 5- year survival is less than 18%. Majority of all lung cancer cases are attributed to Non Small Cell Lung Cancer. Significant advancements in research and diagnosis over the past 10 years have though, culminated in the first improvements made in lung cancer survival. New developments in lung cancer's cellular pathogenesis and biological activity have culminated in the advancement of rationally developed approaches for early detection, prevention, and treatment of this illness. There are currently several novel treatments in clinical practice, including those that target actionable mutations and more recently immunotherapy. This review will outline developments and emerging debates in lung cancer treatment.

1 Introduction

Lung cancer is the world's second-largest cause of death, with an estimated 9.6 million deaths in 2018. It can be broadly classified into two groups: Small Cell Lung Cancer (SCLC), which accounts for roughly 20-25% of bronchiogenic carcinomas and Non Small Cell Lung Cancer (NSCLC), almost all of the remainder (75-80%)¹. NSCLC is further categorized into three types: squamous cell carcinoma, adenocarcinoma, and large cell carcinoma²

Adenocarcinoma is the most prevalent subtype which accounts for about 40% of all lung cancer, which develops gradually and typically arises in the outer peripheral areas of the lungs³. Squamous-cell carcinoma accounts for 25–30% of all cases of lung cancer. It is a very slow-growing type of NSCLC that often occurs in one of the bronchi (lung airways)⁴. Large cell (undifferentiated) carcinoma accounts for 5–10% of lung cancers. It is the rarest subtype of NSCLC, which is growing rapidly and more likely to spread⁵.

2 Risk Assessment, Early Detection and Prevention

The most important source of carcinogens and tumor promoters is cigarette smoking which accounts for about 90% of the cases in men and 70% of the cases in women⁶. Epidemiological studies find a nearly 2-fold increased risk due to a family history of lung cancer following the management of the sensitivity to tobacco smoke⁷. A substantial chance of developing passive smoking lung cancer was measured to be 1.14 to 5.20 in people who had never smoked but lived with a smoker based on meta-analysis and thorough study⁸. Radon, a naturally occurring poison, is one of the contributing factors associated with lung cancer, and around 21,000 lung cancer deaths in the United States have been linked with Radon toxicity⁹.

Lung cancer is hard to detect and is often detected late, only when signs become clinically evident¹⁰. Signs and symptoms of lung cancer include dyspnea (shortness of breath), hemoptysis (coughing up blood), chronic coughing or change in regular coughing pattern, wheezing, chest pain or pain in the abdomen, cachexia (weight loss), fatigue, and loss of appetite, dysphonia (hoarse voice), clubbing of the fingernails (uncommon), dysphasia (difficulty swallowing).

Identifying molecular biomarkers for lung cancer in sputum and blood is an area of active research that offers potentially useful tests to complement radiological imaging and bronchoscopy for screening and early diagnosis¹¹.

Big molecular variations in the pathogenesis of lung cancer include growth factors, receptors and activation of GRP/BN proto-oncogenes and their receptors, IGF, HGF, and their receptor MET, EGFR, HER2/neu¹², RAS mutations, MYC amplification and deregulated expression, abnormal expression of BCL-2, cyclin D1 expression, lack of tumor suppressor genes, aberrant methylation leading to loss of gene expression, tumor development due to stimulation of tumor-induced angiogenesis, expression of telomerase function, cell immortality and likely failure of DNA repair mechanism¹¹. Emerging genomic and proteomic innovations have led to the discovery of observable biomarkers in blood with possible clinical applications¹³.

Future studies strongly require assessing the therapeutic utility of molecular biomarkers in sputum and blood for monitoring and early diagnosis.

Furthermore, the introduction of screening tests into clinical practice will classify patients at high risk for developing lung cancer (based on irregular results from CT imaging, bronchoscopy, and/or biomarker profiling), and appropriate approaches for selective treatment and surveillance of these individuals will need to be formulated and enforced.

3 Novel Targeted Or Personalised Targeted Therapies

Treatment for non small cell lung cancer (NSCLC) has advanced in the last decade. Although early diagnosis and surgical treatment contribute to better patient outcomes, most patients are diagnosed with lung cancer at later stages, which are essentially incurable and often need multimodal therapy. Over the past decade, significant improvements in the treatment of advanced stages have been identified largely due to increased knowledge of the molecular complexity and mechanisms of the onset and development of lung cancer, as well as advances in radio and surgical therapies. Different roles for selective therapies arise as standard first- or second-line treatments in patients with identified mutations from clinical trials. Some experimental medicines have been developed specifically for these key components (Figure 1 and Table 1), and clinical trials have shown promising results so far.

3.1 EGFR pathway inhibitors

EGFR is a cell-surface tyrosine kinase receptor that can activate cell growth and proliferation pathways when activated. For cancers, EGFR mutations generate unregulated cell division through continuous activation. EGFR mutations occur for up to 10-15% of all NSCLC patients¹⁴. The EGFR receptor family consists of receptors for a transmembrane tyrosine kinase

(TK) which comprises EGFR (also known as HER1 or ERBB1), HER2 (EGFR2 or ERBB2/NEU), HER3 (EGFR3 or ERBB3), and HER4 (EGFR4 and ERBB4)¹⁵. EGFR tyrosine kinase inhibitors (gefitinib, erlotinib, and afatinib) are first-line medicines currently available for patients with EGFR-positive mutations with a median initial response rate of 70–80%^{16, 17}.

Many clinicopathological characteristics were observed to associate with the occurrence of EGFR mutations and EGFR gene amplification, including histology of adenocarcinoma, never-smoking background, female sex, and East Asian ethnicity¹⁸. However, most people undergo secondary development of the condition to the developed resistance. T790M pushes up to 60% of the acquired resistance mutations¹⁹. Drugs which inhibit EGFR with the mutation T790 M were established and tested in clinical trials²⁰. The EGFR TKIs Gefitinib and Erlotinib have tested extensively for NSCLC either independently or in combination with cytotoxic chemotherapy. The results showed that erlotinib extended life relative to best supportive care while gefitinib failed to show a survival benefit^{21, 22}. Cetuximab, a humanized monoclonal antibody to EGFR extracellular domain, was also studied in NSCLC. the activity was close to that of other line cytotoxics when given to patients with previously diagnosed NSCLC²³. Cetuximab is also being used in patients with resectable level IB–IIIA NSCLC in conjunction with chemoradiation for stage III NSCLC²⁴ and with neoadjuvant chemotherapy²⁵.

Certain EGFR pathway inhibitors in clinical trials include panitumumab (EGFR targeting), lapatinib (targeting EGFR and HER2), and HK-272 (targeting EGFR and HER2).

3.2 Anti-angiogenic agents

Angiogenesis is one of the hallmarks of cancer, and blocking of receptor-2 (VEGFR-2) vascular endothelin growth factor which blocks the development, propagation and movement of new blood vessels²⁶. Several agents are currently under investigation for breaching the VEGF/VEGFR. Among the most tested are monoclonal antibodies against VEGF and the VEGFR TKIs.

According to first-line chemotherapy with carboplatin-paclitaxel, Bevacizumab, a recombinant humanized monoclonal antibody against VEGF, resulted in a significant increase in OS in qualifying patients with non-squamous NSCLC²⁷. A phase III trial of erlotinib with or without bevacizumab in NSCLC was conducted on the basis of supporting phase I/II research²⁸. ZD6474 (Zactima) is an oral, dual kinase inhibitor targeting VEGFR-2 and, to a lesser degree, EGFR. In a randomized phase II clinical trial, the application of ZD6474 with docetaxel as a second-line treatment for patients with advanced NSCLC increased progression-free survival compared with docetaxel alone²⁹ and a confirmatory phase

III study has been initiated. Several other VEGFR TKIs and outcomes from phase II lung cancer studies are have shown appropriate safety profiles in phase I studies, predicted.

Table 1: Selected active agents for managing lung cancer in clinical development

Target	Generic Name	Brand Name	Stage of development in cancer
EGFR pathway inhibitors			
EGFR	Gefitinib	Iressa	Approved for advanced NSCLC
EGFR	Erlotinib	Tarceva	Approved for advanced NSCLC
EGFR	Cetuximab	Erbitux	Phase II/III
EGFR	Matuzumab	-	Phase I
EGFR	Panitumumab	Vectibix	Phase II
EGFR, HER2	Lapatinib	Tykerb	Phase II
EGFR, HER2	HKI-272	-	Phase II
EGFR, HER2,ERB4	CI-1033	-	Phase II
VEGF/VEGFR pathway inhibitors			
VEGF-A	Bevacizumab	Avastin	Approved for advanced NSCLC
VEGFR-2, EGFR	ZD6474	Zactima	Phase II/III
VEGFR-1-3	Vandetanib	Recentin	Phase II/III
VEGFR-1-3, PDGFR, c-KIT, FLT-3	AZD2171	Sutent	Phase II/III
c-KIT, FLT-3	SU11248; Sunitinib	-	Phase II
VEGFR-1-3, PDGFR-b, c-KIT, c-fms	PTK787; Vatalanib	Champix	Phase II
VEGFR-1-3, PDGFR, c-KIT	AG-013736; Axitinib	-	Phase I
VEGFR-1-3, PDGFR, c-KIT	AMG 706	-	Phase I
Ras/Raf/MEK pathway inhibitors			
Ras	-	Zarnestra	Phase III
Ras	Tipifarnib (FTI)	Sarasar	Phase III
Raf-1, VEGFR-2 and -3, PDGFR, c-KIT	Lonafarnib (FTI)	Nexavar	Phase II
MEK	BAY 43-9006; Sorafenib	-	Phase II
MEK	CI-1040	-	Phase I/II
MEK	PD-0325901, AZD6244	-	Phase I
PI3K/Akt/PTEN pathway inhibitors			
mTOR	LY294002	Rapamune	Phase I
mTOR	Rapamycin; Sirolimus	-	Phase I/II
mTOR	CCI-779; Temsirolimus	-	Phase I/II

mTOR	RAD001; Everolimus AP23573	-	Phase I
Tumor suppressor gene therapies			
p53	-	-	Phase I
p53	p53 retrovirus, p53 adenovirus (Ad5CMV- p53)	Advexin	Phase I
FUS1	FUS1 nanoparticle	-	Phase I
Proteasome inhibitors			
Proteasomes	Bortezomib	Velcade	Phase II
HDAC inhibitors			
HDAC	SAHA; Vorinostat	Zolinza	Phase II
HDAC	Depsipeptide	-	Phase I
Telomerase inhibitors			
Telomerase	GRN163L	-	Phase I

Fig 1: New treatments aimed at main oncogenic pathways in lung cancer

3.3 RAS and MEK Pathway Inhibitors

The protooncogenic RAS family (HRAS, KRAS, and NRAS) codes G- proteins associated with 21-kDa plasma membrane that regulate signal transduction pathways affecting the normal differentiation, proliferation and cell survival³⁰. Activating RAS mutations are observed in 10%–15% of all NSCLCs (15%–35% of adenocarcinomas) but seldom in SCLCs³¹. KRAS mutations are the most prominent motor modifications, observed in up to 25% of all adenocarcinoma cases. A number of agents have been developed which target different components of the RAS pathway and are being clinically investigated³⁰. Among these, farnesyl transferase inhibitors (FTIs) are the most studied, and in lung cancer clinical trials, two orally bioavailable FTIs (tipifarnib and lonafarnib) were tested in combination with cytotoxic therapy³².

Targeting KRAS itself was challenging, primarily because KRAS activates multiple downstream effectors, among many others, including MEK. MEK1 inhibitors are currently being tested while defining RAS mutants^{33–35}. Sorafenib is an oral, dual-action, an antiproliferative and antiangiogenic multikinase inhibitor that serves as a powerful inhibitor of RAF kinase and several other receptor TKs including VEGFR-2, VEGFR-3, PDGFR- β , Flt-3, and c-KIT³⁶.

MEK inhibitors that aim further downstream along the RAS/RAF pathways have been recently published (CI-1040, PD-0325901, and AZD6244). Preclinical and early clinical trials with these agents demonstrated positive antitumor activity in the treatment of NSCLC, with extended stabilization of the disease recorded in phase I trials in patients with NSCLC³⁷.

3.4 PI3K/Akt/PEN pathway inhibitors

Among human cancers, the PI3K signaling system is often triggered through a sequence of events including activation of upstream receptor TKs (including EGFR and PDGFR) and/or PIK3CA mutations, encoding the PI3K catalytic subunit³⁸. Preclinical studies of LY294002, a PI3K inhibitor, revealed that the drug improves the responsiveness of NSCLC cells to chemotherapy and radiation, and phase I trials of this agent are in progress³⁹. Additionally, several inhibitors of the mammalian target of rapamycin (mTOR), a downstream target of PI3K signaling, were developed. These are rapamycin and its analogs temsirolimus (CCI-779), everolimus (RAD001), and AP23573. During early clinical trials, these compounds have shown positive antitumor activity.

3.5 Tumor suppressor gene therapy

The tumor suppressor p53 is a crucial cellular gatekeeper that is triggered by numerous stress signals such as DNA disruption, oncogenes, and hypoxia, culminating in the expression of downstream genes involving cell-cycle arrest,

allowing DNA repair or apoptosis initiation. For lung cancer, the most often mutated gene is p53⁴⁰. p53 is often inactivated by mutation in lung cancer (50% of NSCLCs and 90% of SCLCs)⁴¹.

Clinical trials of p53 gene therapy with a retroviral expression vector p53 in NSCLC patients have shown that gene therapy is safe and feasible, with some proof of antitumor activity⁴². FUS1 is a novel gene for tumor suppression located on chromosome 3p21.3, a site usually deleted in lung cancer. Frequent loss of FUS1 protein expression or post-translation protein alteration deficiency has been documented in most of NSCLCs and SCLCs^{43,44}. Further trials are awaited to determine the clinical benefit of these gene therapies in lung cancer.

3.6 Enhancing apoptosis

A central attribute of cancer cells is their capacity to resist apoptosis⁴⁵. Bcl-2 is a crucial anti-apoptotic protein that is over-expressed in 10%–35% of NSCLCs and 75%–95% of SCLCs³². Randomized step II trials with oblimersen in conjunction with chemotherapy are ongoing for SCLC and NSCLC⁴⁶. Also, a potent small-molecule inhibitor of the antiapoptotic proteins Bcl-2, Bcl-XL, and Bcl-w was developed (ABT-737) and showed preclinical action against both NSCLC and SCLC⁴⁷.

3.7 Role of immunotherapy

Immunotherapy is a cutting-edge oncology technique that utilizes the body's own natural defense mechanism to fight cancer. Some cancer cells share characteristics with healthy cells and therefore the immune system cannot differentiate between normal and abnormal (cancer) cells in the body⁴⁸. New immunotherapy strategies are directed at immune-modulating mechanisms that help tumor cells protect themselves against the immune system. Treatments for inhibitory checkpoint molecules like cytotoxic T-lymphocyte-associated protein 4 (CTLA4), programmed death 1 (PD-1) and programmed death-ligand 1 (PD-L1) have all shown therapeutic effectiveness⁴⁹. The immune system utilizes these immune checkpoints to preserve self-tolerance and control the immune response in the body to protect tissues from injury as the immune system launches a pathogen response⁵⁰.

Ipilimumab was the first immunotherapeutic to show survival benefits in metastatic melanoma and was approved by the FDA for advanced melanoma care in 2010⁵¹. The monoclonal antibody nivolumab guided to the PD-1 receptor has demonstrated efficacy through NSCLCs with various histological features⁵². In March 2015, the FDA approved nivolumab for the management of squamous NSCLC. This was accompanied by FDA approval of nivolumab for the non-squamous NSCLC diagnosis⁵³. The monoclonal antibody, guided by a PD-1 receptor, pembrolizumab, was approved by the FDA as a second-line treatment in NSCLC in October 2015. The therapeutic efficacies of nivolumab and pembrolizumab have

been shown to be histologically independent. Smokers and patients with PD-L1-positive expression experience greater benefit⁶³.

Atezolizumab is a humanized IgG1 monoclonal anti-PD-L1 antibody that prevents association between PD-L1-PD-1 and PD-L1-B7-1, restoring anti-tumor T-cell activity and enhancing T-cell priming. In October 2016 the FDA approved atezolizumab for the treatment of patients with metastatic NSCLC whose cancer worsened during or after platinum-containing chemotherapy. Several trials are ongoing to compare anti-PD-1 and anti-PD-L1 agents, individually and in combination with a cytotoxic T-lymphocyte-associated protein 4 inhibitor (ipilimumab), with platinum-based combination regimens as first-line therapy⁵⁴⁻⁵⁶.

3.8 Telomerase inhibitors

There is increasing evidence that the enzyme telomerase is upregulated in stem cells of cancer and those telomerase inhibitors can potentially target both stem cells of cancer and more mature cancer cells⁵⁷. Chromosomal ends (telomerase) contain hexameric nucleotide repeat tandem tracks of the TTAGGG. During normal cell division, The loss of telomerase activity is associated with incremental shortening of the telomere, contributing to cell senescence and normal cell death⁵⁸. Telomerase is expressed almost universally in human tumors, whereas in normal tissue telomerase activity is reduced or absent. Detectable amounts of telomerase are present in approximately 80% of NSCLCs and 100% of SCLCs⁵⁸. GRN163L is a novel telomerase antagonist designed to target the hTR RNA template region. Preclinical studies have shown that GRN163L inhibits anchorage-independent growth and the development of lung cancer cells in vivo xenograft tumors⁵⁹, and phase I trials with this agent are underway. Several other drugs are currently under development that targets telomerase, including immunotherapy (vaccines), gene therapy (telomerase oncolytic virus therapy), and inhibitors of reverse transcriptase.

4 Radiotherapy

Stereotactic ablative radiotherapy (SABR) has become a treatment option for patients with early-stage node-negative NSCLC patients who are not surgical candidates or who reject surgical options⁶⁰. In addition to the importance of radiotherapy in stage I NSCLC, new studies have investigated its role in the treatment of stage IV NSCLC in conjunction with chemotherapy, and have shown increased survival when primary tumor radiotherapy was implemented.

Radiotherapy has also shown interest in improving contact with CNS. Depending on the volume and amount of brain metastases, stereotactic radiation is often compared to whole-brain radiation therapy (WBRT), when possible, mostly due to fewer neurological side effects. With WBRT a higher response rate is noted in patients with EGFR- mutant NSCLC with brain

metastasis. Despite these results, many practitioners and patients avoid WBRT to prevent hair loss, tiredness and WBRT neurocognitive sequelae⁶¹. In patients with oligoprogressive disorder with EGFR tyrosine kinase inhibitor monotherapy, local radiotherapy or surgical resection is advised on a case-by-case basis with continuity of the EGFR tyrosine kinase inhibitor⁶².

5 Surgical therapy

Surgery is the main therapy for patients with non-small-cell lung cancer, especially early disease patients. Surgery may include resection (pneumonectomy or lobectomy) and regeneration of the mediastinal node. Total dissection of the lymph-node should be performed when the tumor becomes resectable and mediastinal nodes are concerned⁶³.

6 Chemotherapy

Around 40% of newly diagnosed patients with lung cancer are in stage IV. The aim of treating these patients is to improve their survival and reduce the adverse effects associated with the disease. Many chemotherapeutic agents are effective against both small-cell and non-small-cell lung cancer (Table 2). Among the most active are those of the platinum family: cisplatin, which cross-links DNA, and carboplatin, a cisplatin analog^{64, 65}.

Chemotherapy adverse effects can be severe but are usually manageable and reversible. Major effects include nausea, vomiting, alopecia, myelosuppression, nephrotoxicity, neuropathy, loss of hearing at high tones, and depletion of electrolytes. Etoposide, docetaxel, paclitaxel, gemcitabine, vinorelbine, and irinotecan are often used in conjunction with a platinum agent.

7 Conclusion

Significant progress has been made in reducing the occupational health risks correlated with lung cancer, in particular smoking, and to avoid numerous disorders. Intense research in translational oncology over the last decade has provided important insights into the molecular basis of carcinogenesis and human cancer biological behavior. Based on this information, new strategies have been created for screening, early diagnosis, prevention, staging, and therapy which show promise to enhance the management of lung cancer. Targeted therapy and immunotherapy have made important contributions in recent decades, to better lung cancer management. Progress in lung cancer therapy has been sluggish yet gradual, and has improved thanks to changes in the disease's medical base and testing and care technical advancements. Continued interdisciplinary research efforts will accomplish the ambitious target of reducing mortality rates in the next 50 years.

8 Conflict of interest

The author's declares that there is no conflict of interest.

9 Author's contribution

FK carried out literature review and draft the manuscript. SSS participated in Clinical correlation, scientific output and guided to

write manuscript. All authors read and approved the final manuscript.

Table 2: Chemotherapy for Lung Cancer

Drug	Type of Agent	Major adverse effect
Platinum agents		
Cisplatin (Platinol)	Atypical alkylator	Nausea and vomiting (common), nephrotoxicity, ototoxicity, neuropathy, myelosuppression (mild), electrolyte wasting (potassium and magnesium)
Carboplatin (Paraplatin)	Atypical alkylator	Myelosuppression, nausea, and vomiting (mild), neurotoxicity (rare), nephrotoxicity (rare)
Nonplatinum agents		
Etoposide (VePesid)	Topoisomerase II Inhibitor	Myelosuppression, nausea, vomiting, stomatitis, diarrhea
Topotecan (Hycamptin)	Topoisomerase I inhibitor	Myelosuppression, nausea, vomiting, diarrhea, headache
Irinotecan (Camptosar)	Topoisomerase I inhibitor	Myelosuppression, diarrhea, nausea, Vomiting
Gemcitabine (Gemzar)	Antimetabolite	Myelosuppression, nausea, vomiting, diarrhea, edema, influenza-like syndrome
Paclitaxel (Taxol)	Microtubule Inhibitor	Myelosuppression, mucositis, peripheral neuropathy, hypersensitivity reaction, nausea and vomiting
Docetaxel (Taxotere)	Microtubule inhibitor	Myelosuppression, edema & fluid retention, mucositis, diarrhea, nausea, vomiting
Vinorelbine (Navelbine)	Microtubule Inhibitor	Myelosuppression, nausea, vomiting
Vincristine (Oncovin)	Microtubule inhibitor	Neuropathy, constipation
Doxorubicin (Adriamycin)	Anthracycline antibiotic	Myelosuppression, cardiomyopathy, nausea, vomiting, diarrhea, stomatitis
Cyclophosphamide (Cytoxan)	Alkylating agent	Myelosuppression, nausea, vomiting, hemorrhagic cystitis
Ifosfamide (Ifex)	Alkylating agent	Myelosuppression, nausea, vomiting, hemorrhagic cystitis, nephrotoxicity, neurotoxicity

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