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Review Article

Non-small Cell Lung Carcinoma: Current Treatment Strategies and Emerging Challenges

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ABSTRACT

The most prevalent cause of death linked to cancer in the lungs is still lung cancer. Lung cancer, specifically non-small cell lung cancer (NSCLC) is a form of lung cancer that is widely common. Around 85% of all lung cancer patients are diagnosed with NSCLC. NSCLC also is further classified into multi histological subtypes which are adenocarcinomas, squamous cell carcinoma, large cell carcinoma, and mixed. The treatment of NSCLC relies heavily on systemic chemotherapy using platinum-based drugs. AN When treating NSCLC, a number of techniques and challenges are involved. These methodologies include targeted therapy, immunotherapy, or a combination of both, with the goal of targeting and inhibiting certain molecular pathways or expanding the extent of the patient's defense response. In treating NSCLC, this is one of the biggest issues. Targeted therapies were designed to improve NSCLC therapeutics. However, it has proven difficult due to the early emergence of resistance. Resistance mechanisms include targeted drug resistance development and trait variations, including gene mutations and anomalies specific to each NSCLC subtype. Relative differences in the amount of NSCLC there is also explain the reasons why treatment targeting each NSCLC subtype is difficult. In addition to this, the age and sex of the patient will play a significant role in making treatment decisions as well as the outcomes of the NSCLC treatment in this study. To conclude, a synopsis of the various approaches being used in tackling NSCLC and the corresponding difficulties, including that of each type of therapy, has been presented.

Introduction

The cancer of the lungs is the most prevalent and deadliest form of malignancy affecting both sexes all around the world. It has a high mortality rate, with half of patients succumbing within one year of diagnosis.[1] The most recent Globocan 2022 report states lung cancer is the prime cause of cancer across the world.[2] Lung cancer is also significant in terms of the lowest 5-year survival rate among all major cancer types, which is less than 20% across all stages.[3] The environmental risk factors, genetics, occupational hazards and tobacco consumption heavily influence the incidence and death rate of lung cancer. In contrast to other diseases, lung cancer is more prevalent in economically developed and developing countries.[4] In this review, we've tried to summarize the currently available treatment strategies, focusing on novel approaches, feasibility and challenges associated with them.

Pathophysiology

Depending on the kind of cell impacted, lung malignancy can either be non-small cell lung carcinoma (NSCLC) type or small cell lung carcinoma (SCLC). Fig. 1 gives a summarized image describing the different types of lung cancer categorized as per the cells that they affect.

NSCLC comes from the cells of the epithelium that lines the airway's surface. These cancers are slow spreaders. They were initially differentiated from SCLC by morphology as seen through microscopy. Most of the cases of lung cancer are specifically NSCLC (80–85%). Tripartite classification

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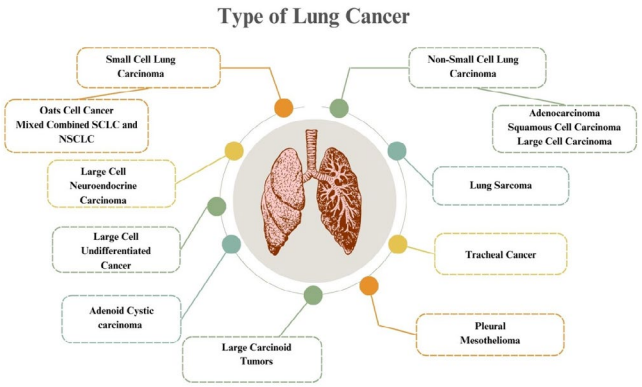

Fig. 1: The different types of lung cancers based on the kind of cells affected

of NSCLC can be achieved by considering the cellular structure of the cells involved. These are described below. Adenocarcinoma, the most prevalent type of NSCLC (40% cases), begins in the outer layer of the lung, affecting small airway epithelial cells of type II alveolar origin.[5] It is common among both smokers and non-smokers and develops slowly without a specific cause or target, making it an early detection. Squamous-cell carcinoma, a 2nd type, is characterized by 25 to 30% of cases and targets the epithelium of the bronchial tube located near the center of your lungs tube. Cigarette smoking is responsible for this condition.[6] The large cell carcinoma that occurs in 5 to 10% of cases is characterized by large, abnormal-looking cells. It can originate in the lungs, but is typically located in one part of the body and spreads rapidly to the chest wall, making diagnosis challenging.[7]

Current Treatment Strategies for Lung Cancer

Treatment strategies for lung cancer are complex and dependent on tumor histology, tumor stage or location, tumor size, and patient-specific factors such as pulmonary function co-morbidity. However, they can vary from one individual to another. The following are the key approaches implemented.

Surgery

Different stages can be attributed to cancer, depending on how it is treated and the extent of its impact. In stage I and II cancers, as well as stage IIIa cancer where lymph nodes are involved, surgery is the most potent treatment. The size and location of the tumor determine whether a full or partial lobectomy is performed. A projected mortality rate of 5 to 8%[8] is correlated with an operative mortality risk of 1.4%. The chances of survival after surgical resection are between 60 to 80% and 30 to 50% for stage I and stage II NSCLC, respectively.[9] Tumor removal is often challenging due to mediastinal involvement, obstruction, atelectasis, and pleural involvement.[9]

Radiotherapy

In those with a localized tumor that does not require or are not fit for surgery, radiotherapy may be the recommended course of action. The DNA of malignant cells is disrupted by high-energy radiation beams in radiotherapy, which then destroys them. Despite being an adjunctive therapy, radiotherapy is frequently used as well.[10] Radiotherapy has comparable 5-year survival rates to those seen with surgery, but its effectiveness may be affected by locoregional recurrences.[11] A sophisticated, coordinated system in SBRT precisely identifies the tumor. The placement of highly targeted and precise radiation therapy is facilitated by the tracking device in SBRT. In 2010, Timmerman *et al.* conducted a study that revealed the benefits of SBRT, including higher survival rates, lower costs, and improved patient convenience. Among the 59 patients with inoperable NSCLC, only three showed signs of it recurrence within their lobe, and the patients had a good local tumor control mild treatment-related morbidity but remarkably little to no symptoms.[12] *Fakiris AJ* and co-authors conducted another prospective phase II study that examined 70 patients who were medically inoperable for SBRT. A 50-month study revealed that patients receiving SBRT in stage I and medically inoperable cases have higher rates of local control.[13] SBRT has been found to be effective in reducing local control morbidity with treatment. These studies have shown significant benefits. However, chest radiation therapy can cause respiratory problems, coughing, breathing difficulties, and breathing disruptions, as well as radiation pneumonitis.

Chemotherapy

The cancer in NSCLC is usually stage IV and most patients (40%) do not show any symptoms. Patients who are in unresectable stages IIIA and IIIB may receive chemotherapy along with radiation therapy (chemoradiation) either individually or at a time. Often, chemotherapy consists of combining two types of cytotoxic drugs for patients with stage IV non-small cell lung cancer. First line of treatment is platinum-based chemotherapy, such as carboplatin or cisplatin. Cisplatin or carboplatin with adjuvant combination, such as vinca alkaloids (vinblastine), antimetabolites (gemcitabine or pemetrexed), or taxanes (paclitaxel, docetaxell, vinorelbine) are used in the chemotherapeutic process.[14] Other approved drugs include ifosfamide[15], mitomycin C,[15] vindesine,[15] vinblastine,[15] gemcitabine,[15] Paclitaxel,[15] Vinorelbine[15] and Etoposide.[15] From the many clinical studies conducted, it has been found that there is no single regimen with significant superiority over other combinations.[16–19] Chemotherapy is either a singlet or doublet regimen and is changed if associated with serious adverse events or if the cancer grows or the tumor doesn't shrink even after four treatment cycles.[20,21] Clinical studies have revealed that there is no single regimen that is superior to other combinations of drugs,

as evidenced by clinical trials. In cases where cancer or tumors persist after four treatment cycles, chemotherapy can be modified to include either a singlet or doublet regimen, as indicated by serious adverse events.

Recent Advances in Treatment of NSCLC

Targeted therapy

The genetic makeup of cancerous cells is different than that of normal cells and also differs in comparing the different types of tumor cells. Alteration in protein or enzyme activity leads to uncontrolled proliferation with a false positive message, which is characteristic of some cancers.[22] The objective of targeted therapy is to identify faulty proteins or enzymes and inhibit or inactivate signals that promote cancer cells for proliferation or suicide. NSCLC research has characterized the potential targets for safe drug delivery. Tumoral molecular targets are first identified through biomarker testing. The most potent targets to date are associated with EGFR mutations and the abnormal fusion of ALK are most potent. These are in the approval stages. Research has been carried out on gene rearrangement and fusion mutations in ROS1 and RE as well as activation of BRAF V600E, HER2, and KRAS genes to determine potential treatments for future treatments. It may be possible to allow the development of efficient targeted[23] by identifying and inhibiting the aberrant cross-talk pathways. Identification of overexpressed or under-expressed pathways is the key to successful targeted therapy. These pathways can be blocked by small molecules or receptor monoclonal antibodies (mAb) through one of the most studied methods. Table 1 reports drugs that are meant to counteract a specific mutation. A large majority of NSCLC arises through alterations in the pathway related to the tyrosine kinase receptor, particularly EGFR. Amongst the others, there are cases of EGFR/ERBB1, HER2/ERBP2/NEU, HERR3/ERBM3, and HAPER/ERABB4. As can be seen, EGFR mutation among non-smokers is quite prevalent.

Immunotherapy

By utilizing the body's natural immune system, cancer immunotherapy seeks to eliminate tumor cells. Immunotherapy enhances the body's ability to fight disease and helps distinguish between healthy and malignant cells. The growth of cancer cells is further prevented by this step, which inhibits its growth. Passive immunotherapy and active immunotherapies both involve targeting the immune system for therapy.[24] In immunotherapy, immune checkpoint pathways are halted. Specifically, it is done through the inhibition of CTLA-4 receptors.[25] It can be further used in the blocking of PD-1 followed by the usage of the latter two methods to regulate PCD-L1.[26] The specific checkpoints in the normal human body help in the regulation of the immune response to prevent tissue injury caused by pathogens. Nivolumab, a human immunoglobulin G4 antibody, is the first immunotherapeutic agent used in NSCLC that has metastasized. PD-1 immune-checkpoint-inhibitor. The antibody attaches to the PD-1 receptor. This means that the PD-L1 no longer binds with the T-cell DP-1 receptor, which is necessary for immunity against tumors. Patients with stage IIIB/IV NSCLC (CheckMate 017 and CheckMet057) have been given nivolumab as a single-agent therapy in clinical trials. It was learned that nivolumab in comparison to docetaxel, had a better survival rate.[27] KEYNOTE-010 brought the results regarding this study. Phase II/III studies related to advanced and metastasized NSCLC

Table 1: Targeted therapy used in the treatment of NSCLC

Target	*% cases*	*Drug*
EGFR	15–35%	Tyrosine kinase inhibitors such as erlotinib, afatinib, gefitinib, osimertinib, amivantamab, mobocertinib, dacomitinib.
ALK gene	2–7%	Crizotinib, ceritinib, alectinib, brigatinib, lorlatinib
Cancerous cells with ROS1 gene alterations	1–2%	Crizotinib, ceritinib, lorlatinib, entrectinib
Cancerous cells with NTRK gene alterations	1%	Larotrectinib and entrectinib
Cancerous cells with MET gene alterations	3%	MET inhibitors: Capmatinib and tepotinib
Cancerous cells with RET gene alterations	1–2%	RET inhibitors: Selpercatinib and pralsetinib
Cancerous cells with BRAF gene alterations	1–3%	Dabrafenib, trametinib
KRAS mutation	14% (adenocarcinoma)	KRAS mutation inhibitors: Sotorasib
Cancerous cells with HER2 gene alterations	3% cases 10% of all EGFR-mutated NSCLC	Trastuzumab, deruxtecan
Inhibition of Angiogenesis (Target: Vascular endothelial growth factor (VEGF))	<1%	Bevacizumab, ramucirumab

showed that pembrolizumab results in higher survival rates than those associated with docetaxel.[28] A study that goes by the name KEYNOTE-024 was an open-label phase III trial that made a comparison of the first-line pembrolizumab monotherapy and platinum-based chemotherapy. The KEYNOTE-042 phase III trial of pembrolizumab had demonstrated a tumor proportion score greater than 1%, and it was established that compared to chemotherapy, it provided pembrolizumab at the cost of an improvement in progression-free survival and median overall survival.[29] Other than pembrolizumab, cemiplimab and spartalizumab have also shown to be effect against different subtypes of NSCLC as an anti-PD-1 drug.[30,31] The human-made conjugate antibody type atezolizumab targets PD-L1 specifically. Atezolizumab, bevacizumab, small molecules like paclitaxel, and carboplatin have been used as an initial treatment in adult patients diagnosed with metastatic non-small cell lung cancer, though there is little evidence to suggest this type of approach. Fully humanized IgG1 antibody atezolizumab has been engineered to target PD-L1. A combination therapy that includes atezolizumab, bevacizumab and small molecules such as paclitaxel as well as carboplatin has been approved for the invasive treatment of adult patients with metastatic NSCLC but there is no supporting evidence against EGFR or ALK mutation.[32] The inclusion of camrelizumab, monoclonal antibody targeting PD-L1 in the treatment of advanced NSCLC after its approval for treatment of Hodgkin's lymphoma.[33] In NSCLC, immunotherapy using other checkpoint inhibitors is also being investigated. Some of them are mentioned below.

A novel immunological checkpoint, Siglec15 gene, has been found in various cancers. An association has also been found between the stage of the tumor, the lymph node involvement, the metastasis in bone by NSCLC, and the expression of the siglec 15 gene.[34] Adenosine receptor A2AR is also under investigation. Accrual and the enhanced activity of A2AR receptors are a result of the tumor microenvironment and hypoxia conditions. Generally, the adenosine/A2aR pathway suppresses overall immunology and regulate[35] inflammation and harmful injury in normal physiological conditions. NSCLC activates the pathway, resulting in the proliferation of tumors. Research has indicated that the hypoxia adenosine axis more play a significant role in affecting the tumor microenvironment.

Recent research focuses on discovering compounds that have a higher safety profile than immunotherapeutic approaches by targeting A2AR. Two molecules, NIR178 and AB928, are included in the clinical trials of NSCLC therapy.[36] Some other immunotherapy agents are under investigation with certain adverse events. Table 2 describes the results of a comparison between the said therapies.[37] Immunotherapy also targets cluster of differentiation (CD) as a form of treatment for non-small cell lung cancer. The CD molecules serve as markers in NSCLC. The CD40 and CD122 agonists are the drugs being tested in trials for NSCLC.[38,39]

Challenges in Treatment of NSCLC

In the case of NSCLC, studies have been going on with ongoing high-throughput screening, but many hurdles need to be crossed for the effective therapy of patients. The hurdling factors involve the inability to screen for lung carcinoma at a later age, late stage of detection, small molecule chemotherapy failing, and the development of resistance.

Late stage detection and unavailability of screening programmes for lung carcinoma

It is often diagnosed in the advanced stages because the contagion illness lung cancer is one of those diseases, though a common causative factor for coughing, congestion, and shortness of breath. There are some other causes of diseases that may also manifest in similar symptoms like smoking, infection, allergies, among others. Furthermore, overlapping causative agents and manifestations of diseases provide relatively little basis for early detection, as misdiagnosis will account for a lot. Most countries still lack screening programs and awareness, thus being the biggest barrier to therapy. Stage IIIb and stage IV of the disease cause more than 80% of all diagnosed patients.[40] Early lung cancer detection remains a crucial factor for effective treatment and improved outcomes.

Failure of small molecule chemotherapy

Small molecule chemotherapeutic failure is often due to the decreased intracellular drug accumulation by cisplatin. In resistance cases, cisplatin has also been demonstrated to have reduced uptake by NSCLC cells.[41] Studies have established a connection between copper protein transport 1 (CTR1) and the growth of platinum resistance.[42] CTR1 mainly regulates platinum uptake and its storage in the cytoplasm. The mutation of this gene is the cause of failure in platinum based chemotherapy since it reduces the uptake and drug accumulation. The taxanes (Paclitaxel and docetexal) are the second type of small molecules. The mechanism of these drugs is to stabilize the microtubules, hence preventing their disabling and leading to cell death. Some tumor cells exhibit the over expression of class III ß-tubulin, thus evading treatments.[43] In addition, the existence of histone deacetylase 6 in their microtubular structure promoted its increase in instability. Additional studies have indicated that a mutation either in exon 1 or 4 of ß-tubulin can result in an erratic response to chemotherapy that leads to a decrease in the median survival from 10 to 3 months. Almost 33% of NSCLC patients have these mutations.[44] Resistance is a crucial factor for failure of chemotherapy. Both acquired and innate resistance can lead to the failure of therapy. A major characteristic of lung cancer treatment is that

Table 2: Immunotherapy under clinical trials.

S. No.	*Molecules*	*Target*	*Clinical trial phase*	*Adverse event*
1	NC318	Singlec-15	I	Pneumonitis
2	Human T cells	MAGE-A10^{C796}	I	Pancytopenia, hyponatremia, cytokine release
3	Tumor infiltrating lymphocytes LN-144/LN-145 (Single as well as combination)	Cell transfer immunotherapy	II	No results available
4	NIR178	A2a receptor	I/II	Nausea, vomiting, fatigue, dyspnoea, chest pain, pneumonitis
5	AB928	A2a/A2b receptor	I	No results available
6	PBF-1129	A2a	I	No results available
7	BMS-986253	IL-8	I	Fatigue, hypophosphatemia, hypersomnia
8	APX005M + Nivolumab	CD40 (Agonist)	I/II	Stable disease
9	SEA-CD40	CD40 (Agonist)	I	Infusion related reactions, chills, nausea, fatigue, vomiting, dyspnoea, headache
10	NKTR-214 + Nivolumab	CD122 agonist	I/II	Flu like symptoms, fatigue, rash & pruritis
11	ALT-803	IL-13 super agonist	I/II	No results available
12	MSC-1	Anti LIF	I	No results available
13	AXL148	CD47 binding domain of SIRPα	I	Fatigue, AST increase, ALT increase, anaemia, & platelet decrease

resistance to small molecules becomes resistant to other agents from the same class. This means that drug class fails to respond elicit a response, and thereby leads to the development of MDR. MRP family of transporters are also known as ABCC or ABC P-glycoprotein familial (ABCB). MDR is usually caused by them. Small molecule accumulation of small molecules in cells is reduced when MRP is expressed. An increase in resistance to vinca alkaloids,[45,46] etoposide,[45,47] docetaxel,[48] paclitaxel,[48] gemcitabine[45,49] and cisplatin[45,50] has been correlated with an increase in MRP mRNA or protein expression. The ABC transporters in NSCLC cause chemo-drug efflux, which results in drug accumulation being either poor or none the high. Multidrug resistance is promoted by reduced intracellular drug concentrations and increased intracell ATP levels that promote a binding effect. Further, the small molecule affects normal cells that display rapid cell division and causes severe side effects. The expensive nature of the therapy makes it hard to continue with.

Failure of immunotherapy and targeted therapy

- *Failure due to KRAS mutation*

The Kirsten rat sarcoma virus (KRAS) mutation is one of the major cause for the occurrence of failure. NSCLC is affected by mutations associated to KRAS. The treatment options and therapy effectiveness are all hampered by such mutations.[51] Therapy failure is common when not screened for the KRAS mutation before the therapy starts. KRAS is the central data source for cell signals. This signalling regulates cell growth. KRAS mutation conditions are characterized by uncontrolled signals that result in abnormal and unregulated cell proliferation. Up to 25% of human tumors are characterized by KRAS mutation, which is one the most commonly activated oncogenes.[52] Further analysis of this has shown that there are many different types of KRAS mutations, most commonly a variant called the KRAS G12C mutation. The KRAS oncogene causes a "genetic cascade" starting up, hence causing the tumor to switch from benign to malignant. The most common cause of KRAS mutation found with lung cancer is smoking. KRAS mutation is the main cause of ineffective response of NSCLC to EGFR inhibitors. Erlotinib resistance is the prevalent characteristic in non-small lung cancer patients with KRAS mutations, as supported by many studies performed so far.

- *Secondary pathways development*

EGFR-tyrosine kinase inhibitors (TKIs) have proven themselves to be a reliable treatment with high launch response rates. However, research further suggests that 50% of individuals affected with first and second generation TKIs develop T790M mutation within one year and result in a resistance mechanism. Third-generation TKIs have been developed to address the problem. The third generation TKIs could provide a good response in the presence of the T790M mutation, but later they showed the emergence of another mutation called C797S.[45]

The failure of the third generation TKIs resulted from the mutation of the C797S gene. The study indicates that cancer cells have a higher ability to survive due to their mutation inducing power. Resistance can be derived from genetic changes, epithelial mesenchymal transition (EMT), or phenotypic heterogeneity. Immunotherapy and targeted therapy are the primary sources of genetic alteration. Conversely, mutations in other targetable genes (e.g., EGFR, ALK) can cause secondary mutation to provide resistance to the kinase inhibitors or activate alternative signalling pathways. Heterogeneity of the tumor cells' phenotype can lead to diminished responsiveness to treatment and consequently, relapse.

- *Epithelial-mesenchymal transition*

EMT is the main mechanism of cancer metastasis dissemination. EMTs induce resistance to therapies by stimulating cell mobility, invasion, and immune suppression.[45] The presence of immunosuppressive conditions in the tumor microenvironment may lead to innate resistance, which can delay the immune cells' activation and effectiveness of some of the immunotherapies. Tumor heterogeneity in the tumor can lead to resistant clones, which can influence the overall response to treatment. The latest immunotherapy and targeted therapy is also susceptible to drug resistance. When treated with the checkpoint inhibitor PD-1 and subsequently, a recent research study showed that tumor cells start to downregulate PD-L1 expression to evade immune surveillance.[54] Another challenge that has been presented while treating lung cancer involves the secondary proto-oncogene activation that can adapt as driver gene. Tumor cells exhibit rapid mutagenesis, and use pathways such as LAG-3 and TIM-4 that suppress and safeguard against mutations.[54,55] Treatment of lung cancer is also hindered by the rapid mutations, drug targets expression alterations, and microenvironment changes.

Impact of Economy on Treatment of NSCLC

The cost of treating NSCLC is often higher because it requires specialized care in the advanced stages of the disease. The cost of treating other types of cancer, such as prostate or breast cancers, may be lower in comparison to other conditions, but this is subject to several factors. The treatment of non-small cell lung cancer (NSCLC) may come with a high cost, which can be unavoidable.

- *Economic disparities and access to NSCLC treatment*

The economic disparity is a significant factor in determining access to treatment for NSCLC, reflecting the wider social inequality that affects patient outcomes. The likelihood of timely and appropriate treatment is influenced by socio-economic status, as evidenced by consistent research. An analysis found that individuals from low-income families encounter significant barriers to obtaining lung cancer surgery and chemotherapy, suggesting a direct relationship between financial resources and treatment accessibility. Furthermore, dissimilarities in treatment implementation and longevity are exacerbated by factors such as location and race, with rural communities experiencing more challenges in finding treatment[56,60] compared to urban areas. Health inequalities are not only being perpetuated by the lack of equitable access, but also requiring targeted interventions to improve treatment pathways for those with limited access. By addressing the economic gaps, we can enhance patient care and increase chances of survival. Only then can we ensure that all patients receive appropriate treatment.

- *Direct costs associated with NSCLC treatment*

Healthcare systems are burdened by the high costs of treating NSCLC, which is a significant issue for patients and providers alike. A detailed study found that the mean direct costs per patient during follow-up period differed significantly across countries, with France paying €19,057, Germany paying $ 14,185, and the United Kingdom accounting for €8,377.35.[57] Costs incurred for received therapies were the most significant portion of these expenses, which highlights the financial burden of new treatments. Additionally, the impact of febrile neutropenia and leukopenia during chemotherapy adds to financial burdens, with hospitalization costs typically reaching €3,627 for NSCLC patients.[58] The financial burden of NSCLC treatment extends beyond initial therapy, affecting healthcare expenditure and resource allocation in oncology, given the significant cost of treatment and associated economic impact of complications that may necessitate hospitalization.

- *Indirect costs and societal implications of NSCLC*

Beyond the direct costs of treatment, NSCLC also incurs significant indirect costs to both patients and society. Prolonged illness can result in reduced income and economic stability for families, as patients experience a loss of productivity. In addition, a cancer diagnosis can negatively impact individuals' capacity to participate in social and economic activities, leading to damage of the local resources and support systems. Investigations indicate that the administration of immune checkpoint inhibitors (ICIs) can affect treatment expenses and outcomes, leading to additional economic consequences as health systems confront regulatory and valuation obstacles.[59] Additionally, analyses of alternatives such as pemetrexed and docetaxel demonstrate that while pemetrexed is a relatively cost-effective medication, the overall economic burden remains high due to indirect costs that are not always factor.[60] Hence, it is crucial to bear in mind these indirect expenses for a complete understanding of the actual economic burden on NSCLC.

- *Economic implications of NSCLC treatment in india*

The economic implications of NSCLC treatment in India are not solely determined by direct healthcare expenses, but rather by examining the financial factors of society and individuals. Often, patients pay significant out-of–pocket costs; resulting in catastrophic health expenditures that hit hardest on low-income families. Experiencing the logistical challenges of traveling to specialized treatment centres can lead to delayed diagnosis and inadequate treatment, which in turn contributes to financial strain.[63] This has an unmistakable impact on productivity, as long-term treatment and frequent hospitalizations can render patients unable to function properly or care for their families, thus diminishing family income. Furthermore, the emergence of modern medical technologies, such as nano-shells for drug delivery, while promising, raises questions about affordability and the variability of risks related to new treatment methods.[62] Addressing these economic challenges requires a multi-faceted approach, including policy reforms that aim to increase access to affordable healthcare.

Conclusion

Lung cancer is still one of the most fatal types of cancer, despite the many treatments available. Due to the limited treatment options for earlier stages of cancer, chemotherapy is the only option available due to surgery and radiotherapy. Advanced or metastatic disease patients may still require more effective treatment options.' Creating new treatments and personalized therapies is an ongoing challenge. The difficulty in balancing treatment benefits against the potential harm to the patient's health and quality of life is constant. It can be challenging for both parties involved. Those living in remote or underserved areas may face challenges in accessing appropriate care for lung cancer. Optimal outcomes can only be achieved through timely access to highly trained medical professionals, state-of the art diagnostic equipment, and targeted therapies. To overcome these challenges, we must rely on ongoing research and healthcare collaborations, as well as patient-centred approaches to lung cancer treatment and care.

References

1. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA: a cancer journal for clinicians. 2014;64(1):9-29. Available from: Available from doi.org/10.3322/caac.21208.
2. Smith RA, Cokkinides V, von Eschenbach AC, Levin B, Cohen C, Runowicz CD, Sener S, Saslow D, Eyre HJ. American Cancer Society guidelines for the early detection of cancer. CA: a cancer journal for clinicians. 2009;52(1):8-22. Available from doi.org/10.3322/canjclin.52.1.8
3. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, Jemal A. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians. 2024;74(3):229-63. Available from: doi.org/10.3322/caac.21834
4. Kowalczyk A, Jassem J. Multidisciplinary team care in advanced lung cancer. Translational Lung Cancer Research. 2020;9(4):1690. doi.org/ 10.21037/tlcr.2019.11.33
5. Leiter A, Veluswamy RR, Wisnivesky JP. The global burden of lung cancer: current status and future trends. Nature reviews Clinical oncology. 2023;20(9):624-39. Available from: doi.org/ 10.1038/s41571-023-00798-3
6. Couraud S, Zalcman G, Milleron B, Morin F, Souquet PJ. Lung cancer in never smokers–a review. European journal of cancer. 2012;48(9):1299-311. Available from: doi.org/10.1016/j.ejca.2012.03.007
7. Kenfield SA, Wei EK, Stampfer MJ, Rosner BA, Colditz GA. Comparison of aspects of smoking among the four histological types of lung cancer. Tobacco control. 2008;17(3):198-204. Available from: doi.org/10.1136/tc.2007.022582
8. Brambilla E, Travis WD, Colby TV, Corrin B, Shimosato Y. The new world health organization classification of lung tumours. PULMONOLOGIYA. 2004(6):11-21. Available from: doi.org/10.1183/09031936.01.00275301
9. Rossi A, Sacco PC, Santabarbara G, Sgambato A, Casaluce F, Palazzolo G, Maione P, Gridelli C. Developments in pharmacotherapy for treating metastatic non-small cell lung cancer. Expert Opinion on Pharmacotherapy. 2017;18(2):151-63. Available from: doi.org/10.1080/14656566.2017.1280460
10. Tanoue LT, Detterbeck FC. New TNM classification for non-small-cell lung cancer. Expert review of anticancer therapy. 2009;9(4):413-23. Available from: doi.org/10.1586/era.09.11
11. Amini A, Yeh N, Gaspar LE, Kavanagh B, Karam SD. Stereotactic body radiation therapy (SBRT) for lung cancer patients previously treated with conventional radiotherapy: a review. Radiation oncology. 2014;9:1-8. Available from: doi.org/10.1186/1748-717X-9-210
12. van den Berg LL, Klinkenberg TJ, Groen HJ, Widder J. Patterns of recurrence and survival after surgery or stereotactic radiotherapy for early stage NSCLC. Journal of Thoracic Oncology. 2015;10(5):826-31. Available from: doi.org/10.1097/JTO.0000000000000483.
13. Timmerman R, Paulus R, Galvin J, Michalski J, Straube W, Bradley J, Fakiris A, Bezjak A, Videtic G, Johnstone D, Fowler J. Stereotactic body radiation therapy for inoperable early stage lung cancer. Jama. 2010;303(11):1070-6. Available from: doi.org/10.1001/jama.2010.261
14. Fakiris, A.J., McGarry, R.C., Yiannoutsos, C.T., Papiez, L., Williams, M., Henderson, M.A. and Timmerman, R. Stereotactic body radiation therapy for early-stage non–small-cell lung carcinoma: four-year results of a prospective phase II study. International Journal of Radiation Oncology, Biology Physics, 2009;75(3)677-682. Available from: doi.org/10.1016/j.ijrobp.2008.11.042
15. Lynch TJ, Patel T, Dreisbach L, McCleod M, Heim WJ, Hermann RC, Paschold E, Iannotti NO, Dakhil S, Gorton S, Pautret V. Cetuximab and first-line taxane/carboplatin chemotherapy in advanced non–small-cell lung cancer: Results of the randomized multicenter phase III trial BMS099. Journal of Clinical Oncology. 2010;28(6):911-7. Available from: doi.org/10.1200/JCO.2009.21.9618
16. Sculier JP. Anticancer treatment for advanced non-small cell lung cancer. Breathe. 2011;8(2):124-33. Available from: doi.org/10.1183/20734735.005011
17. Scagliotti GV, De Marinis F, Rinaldi M, Crino L, Gridelli C, Ricci S, Matano E, Boni C, Marangolo M, Failla G, Altavilla G. Phase III randomized trial comparing three platinum-based doublets in advanced non–small-cell lung cancer. Journal of clinical oncology. 2002;20(21):4285-91.Available from: doi.org/10.1200/JCO.2002.02.068
18. Kelly K, Crowley J, Bunn Jr PA, Presant CA, Grevstad PK, Moinpour CM, Ramsey SD, Wozniak AJ, Weiss GR, Moore DF, Israel VK. Randomized phase III trial of paclitaxel plus carboplatin versus vinorelbine plus cisplatin in the treatment of patients with advanced non–small-cell lung cancer: a Southwest Oncology Group trial. Journal of Clinical Oncology. 2001;19(13):3210-8. Available from: doi.org/10.1200/JCO.2001.19.13.3210
19. Schiller JH, Harrington D, Belani CP, Langer C, Sandler A, Krook

J, Zhu J, Johnson DH. Comparison of four chemotherapy regimens for advanced non–small-cell lung cancer. New England Journal of Medicine. 2002;346(2):92-8. Available from: doi.org/10.1056/NEJMoa011954
20. Fossella F, Pereira JR, von Pawel J, Pluzanska A, Gorbounova V, Kaukel E, Mattson KV, Ramlau R, Szczesna A, Fidias P, Millward M. Randomized, multinational, phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non–small-cell lung cancer: the TAX 326 study group. Journal of Clinical Oncology. 2003;21(16):3016-24. Available from: doi.org/10.1200/JCO.2003.12.046
21. Scott WJ, Howington J, Feigenberg S, Movsas B, Pisters K. Treatment of non-small cell lung cancer stage I and stage II: ACCP evidence-based clinical practice guidelines. Chest. 2007;132(3):234S-42S. Available from: doi.org/10.1378/chest.07-1378
22. Dempke WC, Suto T, Reck M. Targeted therapies for non-small cell lung cancer. Lung cancer. 2010;67(3):257-74. Available from: doi.org/10.1016/j.lungcan.2009.10.012
23. Araghi M, Mannani R, Heidarnejad maleki A, Hamidi A, Rostami S, Safa SH, Faramarzi F, Khorasani S, Alimohammadi M, Tahmasebi S, Akhavan-Sigari R. Recent advances in non-small cell lung cancer targeted therapy; an update review. Cancer Cell International. 2023;23(1):162. Available from: doi.org/10.1186/s12935-023-02990-y
24. Zhou J. Advances and prospects in cancer immunotherapy. New Journal of Science. 2014;2014(1):745808. Available from: doi.org/10.1155/2014/745808
25. Paulsen EE, Kilvaer TK, Rakaee M, Richardsen E, Hald SM, Andersen S, Busund LT, Bremnes RM, Donnem T. CTLA-4 expression in the non-small cell lung cancer patient tumor microenvironment: diverging prognostic impact in primary tumors and lymph node metastases. Cancer Immunology, Immunotherapy. 2017;66:1449-61. Available from: doi.org/10.1007/s00262-017-2039-2
26. Dantoing E, Piton N, Salaün M, Thiberville L, Guisier F. Anti-PD1/PD-L1 immunotherapy for non-small cell lung cancer with actionable oncogenic driver mutations. International journal of molecular sciences. 2021;22(12):6288. Available from: doi.org/10.3390/ijms22126288
27. Borghaei H, Gettinger S, Vokes EE, Chow LQ, Burgio MA, de Castro Carpeno J, Pluzanski A, Arrieta O, Frontera OA, Chiari R, Butts C. Five-year outcomes from the randomized, phase III trials checkmate 017 and 057: nivolumab versus docetaxel in previously treated non–small-cell lung cancer. Journal of Clinical Oncology. 2021;39(7):723-33. Available from: doi.org/10.1200/JCO.20.01605
28. Barlesi F, Garon EB, Kim DW, Enriqueta F, Han JY, Kim JH, Ahn MJ, Fidler MJ, Gubens MA, de Castro G, Surmont V. Health-related quality of life in KEYNOTE-010: a phase II/III study of pembrolizumab versus docetaxel in patients with previously treated advanced, programmed death ligand 1-expressing NSCLC. Journal of Thoracic Oncology. 2019;14(7):1306. Available from: doi.org/10.1016/j.jtho.2019.01.016
29. Brahmer JR, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, Gottfried M, Peled N, Tafreshi A, Cuffe S, O'Brien M. KEYNOTE-024 5-year OS update: First-line pembrolizumab vs platinum-based chemotherapy in patients with metastatic non–small-cell lung cancer and PD-L1 tumor proportion score≥ 50%. Ann Oncol. 2020;31(suppl 4):S1142-215. Available from: doi.org/10.1200/JCO.21.00174
30. Mizuno T, Katsuya Y, Sato J, Koyama T, Shimizu T, Yamamoto N. Emerging PD-1/PD-L1 targeting immunotherapy in non-small cell lung cancer: Current status and future perspective in Japan, US, EU, and China. Frontiers in Oncology. 2022;12:925938. Available from: doi.org/10.3389/fonc.2022.925938
31. Suraya R, Tachihara M, Nagano T, Nishimura Y, Kobayashi K. Immunotherapy in advanced non-small cell lung cancers: Current status and updates. Cancer Management and Research. 2022:2079-90. Available from: doi.org/10.2147/CMAR.S366738
32. Ilie M, Hofman P. Atezolizumab in advanced non-small cell lung cancer. Journal of thoracic disease. 2017;9(10):3603. Available from: doi.org/10.21037/jtd.2017.09.73
33. Xie Q, Zheng H, Su N, Li Q. Camrelizumab in patients with advanced non-squamous non-small cell lung cancer: a cost-effective analysis in China. BMJ open. 2022;12(8):e061592. Available from: doi.org/10.1136/bmjopen-2022-061592
34. Liang H, Chen Q, Hu Z, Zhou L, Meng Q, Zhang T, Wang B, Ge Y, Lu S, Ding W, Zhou X. Siglec15 facilitates the progression of non-small cell lung cancer and is correlated with spinal metastasis. Annals of Translational Medicine. 2022;10(6). Available from: doi.org/10.21037/atm-22-764
35. Ye H, Zhao J, Xu X, Zhang D, Shen H, Wang S. Role of adenosine A2a receptor in cancers and autoimmune diseases. Immunity, Inflammation and Disease. 2023;11(4):e826. Available from: doi.org/10.1002/iid3.826
36. Garcia-Lorenzo E, Moreno V. Targeting the adenosine 2A receptor in non-small cell lung cancer: shooting with blank bullets?. Translational Lung Cancer Research. 2023;12(4):653. Available from: doi.org/10.21037/tlcr-23-38
37. Kareff SA, Samtani S, Burotto M, Prasad V, Kim C. Current landscape of immunotherapy trials involving the programmed cell death protein 1/programmed death-ligand 1 axis in intrathoracic tumors. JTO Clinical and Research Reports. 2021;2(4):100149. Available from: doi.org/10.1016/j.jtocrr.2021.100149
38. Zhang H, Li M, Kaboli PJ, Ji H, Du F, Wu X, Zhao Y, Shen J, Wan L, Yi T, Wen Q. Identification of cluster of differentiation molecule-associated microRNAs as potential therapeutic targets for gastrointestinal cancer immunotherapy. The International journal of biological markers. 2021;36(2):22-32. Available from:
39. doi.org/10.1177/1724600821100547
40. Djureinovic D, Wang M, Kluger HM. Agonistic CD40 antibodies in cancer treatment. Cancers. 2021;13(6):1302. Available from: doi.org/10.3390/cancers13061302
41. Nicolson M. ES05. 01 lung cancer survival: progress and challenges. Journal of Thoracic Oncology. 2019;14(10):S24. Available from: doi.org/10.1016/j.jtho.2019.08.087
42. Shen DW, Pouliot LM, Hall MD, Gottesman MM. Cisplatin resistance: a cellular self-defence mechanism resulting from multiple epigenetic and genetic changes. Pharmacological reviews. 2012;64(3):706-21. Available from: doi.org/10.1124/pr.111.005637
43. Kilari D, Guancial E, Kim ES. Role of copper transporters in platinum resistance. World journal of clinical oncology. 2016;7(1):106. Available from: doi.org/10.5306/wjco.v7.i1.106
44. Mariani M, Karki R, Spennato M, Pandya D, He S, Andreoli M, Fiedler P, Ferlini C. Class III β-tubulin in normal and cancer tissues. Gene. 2015;563(2):109-14. Available from: doi.org/10.1016/j.gene.2015.03.061
45. Orr GA, Verdier-Pinard P, McDaid H, Horwitz SB. Mechanisms of Taxol resistance related to microtubules. Oncogene. 2003;22(47):7280-95. Available from: doi.org/10.1038/sj.onc.1206934
46. Wang X, Zhang H, Chen X. Drug resistance and combating drug resistance in cancer. Cancer drug resistance. 2019;2(2):141. Available from: doi.org/10.20517/cdr.2019.10
47. Zhang Y, Yang SH, Guo XL. New insights into Vinca alkaloids resistance mechanism and circumvention in lung cancer. Biomedicine & pharmacotherapy. 2017;96:659-66. Available from: doi.org/10.1016/j.biopha.2017.10.041
48. Lagas JS, Fan L, Wagenaar E, Vlaming ML, van Tellingen O, Beijnen JH, Schinkel AH. P-glycoprotein (P-gp/Abcb1), Abcc2, and Abcc3 determine the pharmacokinetics of etoposide. Clinical cancer research. 2010;16(1):130-40. Available from: doi.org/10.1158/1078-0432.CCR-09-1321
49. Ashrafizadeh M, Mirzaei S, Hashemi F, Zarrabi A, Zabolian A, Saleki H, Sharifzadeh SO, Soleymani L, Daneshi S, Hushmandi K, Khan H. New insight towards development of paclitaxel and docetaxel resistance in cancer cells: EMT as a novel molecular mechanism and therapeutic possibilities. Biomedicine & Pharmacotherapy. 2021;141:111824. Available from: doi.org/10.1016/j.biopha.2021.111824
50. Zheng X, Carstens JL, Kim J, Scheible M, Kaye J, Sugimoto H, Wu CC, LeBleu VS, Kalluri R. Epithelial-to-mesenchymal transition

is dispensable for metastasis but induces chemoresistance in pancreatic cancer. Nature. 2015;527(7579):525-30. Available from: doi.org/10.1038/nature16064
51. Haslehurst AM, Koti M, Dharsee M, Nuin P, Evans K, Geraci J, Childs T, Chen J, Li J, Weberpals J, Davey S. EMT transcription factors snail and slug directly contribute to cisplatin resistance in ovarian cancer. BMC cancer. 2012;12:1-0. Available from: doi.org/10.1186/1471-2407-12-91
52. Marabese M, Ganzinelli M, Garassino MC, Shepherd FA, Piva S, Caiola E, Macerelli M, Bettini A, Lauricella C, Floriani I, Farina G. KRAS mutations affect prognosis of non-small-cell lung cancer patients treated with first-line platinum containing chemotherapy. Oncotarget. 2015;6(32):34014. Available from: doi.org/10.18632/oncotarget.5607
53. Beganoyic S. Clinical significance of the KRAS mutation. Bosnian journal of basic medical sciences. 2009;9(Suppl 1):S17. Available from: doi.org/10.17305/bjbms.2009.2749
54. Reita D, Pabst L, Pencreach E, Guérin E, Dano L, Rimelen V, Voegeli AC, Vallat L, Mascaux C, Beau-Faller M. Direct targeting KRAS mutation in non-small cell lung cancer: focus on resistance. Cancers. 2022;14(5):1321. Available from: doi.org/10.3390/cancers14051321
55. Błach J, Wojas-Krawczyk K, Nicoś M, Krawczyk P. Failure of immunotherapy—the molecular and immunological origin of immunotherapy resistance in lung cancer. International Journal of Molecular Sciences. 2021;22(16):9030. Available from: doi.org/10.3390/ijms22169030
56. Zhao LP, Hu JH, Hu D, Wang HJ, Huang CG, Luo RH, Zhou ZH, Huang XY, Xie T, Lou JS. Hyperprogression, a challenge of PD-1/PD-L1 inhibitors treatments: potential mechanisms and coping strategies. Biomedicine & Pharmacotherapy. 2022;150:112949. Available from: doi.org/10.1016/j.biopha.2022.112949
57. Lennox L, Lambe K, Hindocha CN, Coronini-Cronberg S. What health inequalities exist in access to, outcomes from and experience of treatment for lung cancer? A scoping review. BMJ open. 2023;13(11):e077610. Available from: doi.org/10.1136/bmjopen-2023-077610
58. Andreas S, Chouaid C, Danson S, Siakpere O, Benjamin L, Ehness R, Dramard-Goasdoue MH, Barth J, Hoffmann H, Potter V, Barlesi F. Economic burden of resected (stage IB-IIIA) non-small cell lung cancer in France, Germany and the United Kingdom: A retrospective observational study (LuCaBIS). Lung Cancer. 2018;124:298-309. Available from: doi.org/10.1016/j.lungcan.2018.07.042
59. Ihbe-Heffinger A, Paessens BJ, von Schilling C, Shlaen M, Gottschalk N, Berger K, Bernard R, Kiechle M, Peschel C, Jacobs VR. Management of febrile neutropenia–a German prospective hospital cost analysis in lymphoproliferative disorders, non-small cell lung cancer, and primary breast cancer. Oncology Research and Treatment. 2011;34(5):241-6. Available from: doi.org/10.1159/000327711
60. Ma LR, Li JX, Tang L, Li RZ, Yang JS, Sun A, Leung EL, Yan PY. Immune checkpoints and immunotherapy in non-small cell lung cancer: Novel study progression, challenges and solutions. Oncology Letters. 2021;22(5):787. Available from: doi.org/10.3892/ol.2021.13048.
61. Asukai Y, Valladares A, Camps C, Wood E, Taipale K, Arellano J, Cassinello A, Sacristán JA, Dilla T. Cost-effectiveness analysis of pemetrexed versus docetaxel in the second-line treatment of non-small cell lung cancer in Spain: results for the non-squamous histology population. BMC cancer. 2010;10:1-4. Available from: doi.org/10.1186/1471-2407-10-26
62. Ambroggi M, Biasini C, Del Giovane C, Fornari F, Cavanna L. Distance as a barrier to cancer diagnosis and treatment: review of the literature. The oncologist. 2015;20(12):1378-85. Available from: doi.org/10.1634/theoncologist.2015-0110
63. Haik Y, Bantekas I. Nano-drug Clinical Trials: Informed Consent and Risk Management Through Blockchain. Pitt. J. Tech. L. & Pol'y. 2020;21:35. Available from: doi.org/10.5195/tlp.2021.243

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