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Perspective

Biological Context for the Use of Key Therapies in Advanced Non-Small Cell Lung Cancer

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Abstract

Genotype-directed treatments and immunotherapies are changing the way healthcare professionals manage the most common cause of cancer-related death - lung cancer. A better understanding of the genetic makeup and immune milieu of the predominant histological subtype, non-small cell lung cancer (NSCLC), has led to the inclusion of signal-transduction inhibitors, gene-expression modulators, immunotherapies, and other agents in the treatment of advanced disease. Unlocking a landscape of driver mutations and targetable immune checkpoints has also led to a paradigm shift in the treatment of advanced NSCLC, with profound tumor responses in select patients; however relative 5-year survival rates for metastatic NSCLC remain dismal for the broader patient population.

There remains an important role for combination chemotherapy in multimodal care, but inevitable resistance propels a search for newer agents. This article is a brief overview of the biological context and some of the agents currently being assessed as complementary treatments for advanced disease.

Keywords: *Non-Small Cell Lung Cancer; Metastasis; Targeted Therapies; Immunotherapies; Checkpoint Inhibitors*

Abbreviations

ALK: Anaplastic Lymphoma Kinase; *BRAF*: B-Raf Proto-Oncogene; CSC: Cancer Stem Cell; CTL: Cytotoxic T Lymphocytes; CTLA4: Cytotoxic T-Lymphocyte Associated Protein 4; *EGFR*: Epidermal Growth Factor Receptor; *KRAS*: Kirsten Rat Sarcoma Viral Oncogene Homolog; M: Presence of Metastasis; *MET*: MET Proto-Oncogene, Receptor Tyrosine Kinase; N: Nodal Involvement; NGS: Next-Generation Sequencing; NK: Natural Killer Cells; NKT: Natural Killer T-Cells; NSCLC: Non-Small Cell Lung Cancer; PD-1(also known as CD279): Programmed Cell Death Protein 1; PD-L1: Programmed Death-Ligand 1; *ROS1*: ROS Proto-Oncogene 1, Receptor Tyrosine Kinase; SCLC: Small-Cell Lung Cancer; T: Characteristics of the Primary Tumor; *V600E*: An Amino Acid Substitution at Position 600 in BRAF, from a Valine (V) to a Glutamic Acid (E); VEGF: Vascular Endothelial Growth Factor

Introduction

Lung cancer – a heterogeneous disease originating at various sites in the bronchial tree or at the pulmonary apex [1]– remains the biggest global cancer killer of men and women. Major known carcinogens triggering lung cancer are chemicals inhaled voluntarily or involuntarily from cigarette smoke. Past studies have linked patterns of smoking behavior to the higher incidence rates of lung cancer among men than women; however, this trend has been reversed among non-Hispanic whites and Hispanic Americans born since the 1960s in a manner that cannot be fully explained by sex differences in smoking behaviors [2]. Moreover, more and more people who have never smoked are now being diagnosed with the disease [3].

Traditionally, the neoplasm has been categorized based on cellular appearance as small cell lung cancer (SCLC; 10% - 15%) [1] or non-small cell lung cancer (NSCLC). The second group is more common and is the focus of this perspective.

NSCLC can be further subdivided into adenocarcinoma, squamous cell carcinoma, adenosquamous cell carcinoma, large cell carcinoma, and sarcomatoid carcinoma [4]. Overall, the estimated proportion of US patients with lung and bronchus cancer surviving at 5 years is only 18.6% [5]. Anatomic burden of the disease is one factor that impacts prognosis. This means, that for approximately 40% of patients presenting with advanced disease [1], curative-intent treatment may not be possible and the relative 5-year survival rate could drop to as low as 5% [5]. Other factors impacting NSCLC progression include tumor-, environmental-, and treatment-related influences (age, characteristics [clinical/demographic], tumor histology, treatment access and/or care quality, geographic region where treatment is received, and response to treatment. Additionally, pulmonary reserve in patients with early-stage disease, comorbidities, and mutations in advanced-stage tumors are among the important considerations in guiding therapy in specific settings [6].

It is an open question as to how closely any given patient with NSCLC resembles the more than 100,000 patient-dataset that forms the basis of the American Joint Committee on Cancer (AJCC) eighth edition T (characteristics of the primary tumor), N (nodal involvement), M (presence of metastasis) stage classification for lung cancer. Nevertheless, the recently updated staging system, along with surgery, chemotherapy, and radiation, form the backbone of the current standard of care. The updated TNM staging system also enables nuances of management of patients with specific characteristics [6].

However, postoperative recurrence can be troublesome in many patients with NSCLC [7]. Most of these cases are treated with platinum-based regimens [7], but chemotherapy provides only a modest benefit in terms of overall survival [8]. Moreover, as stated by Chang, chemoresistance to approved chemotherapeutics represents "one of the most significant barriers to improving long-term outcomes" [9] for patients with advanced NSCLC. Taken to its extreme, prolonged exposure to a single chemotherapy may cause cross-resistance/multidrug resistance in some patients i.e., resistance develops to many other structurally unrelated agents [10].

Indeed, resistance, whether to chemotherapeutics or targeted agents, represents a serious impediment to the management of all cancers. At the cellular level, drug resistance and persistence/tolerance may partly be driven by mutations and epigenetic programs. A growing body of evidence points to the need for combination/intermittent therapies, rather than sustained monotherapies, to attenuate tumor refractoriness to drug treatment.

These strategies may entail addition of one or multiple lines of tailored therapies to compensate for cancer stem cell (CSC)-induced NSCLC metastasis/resistance to first-line therapy [11] or the development of modalities that modulate or interact with cell surface receptors (monoclonal antibodies), intracellular cascade pathways and signaling (small molecule tyrosine kinase inhibitors) or micro-environmental effects related to tumor vasculature or hypoxia [12]. Reclassification of tumors have also led to the development of therapies harnessing the patient's own immune system to treat NSCLC.

Here, I provide a brief overview of some of the biological context for the use of key genotype-directed treatments and immune checkpoint inhibitors in the management of advanced NSCLC.

Genotype-Directed Therapies and Angiogenesis Inhibitors

Managing advanced NSCLC with homogeneous treatments may be one reason for no substantial improvement in overall survival in many years. Of the NSCLC subtypes, squamous cell cancer and adenocarcinoma account for about 70% of all lung tumors. Like their rarer counterparts, these cancers can be regarded as distinct diseases, based on histology and subtype-specific prognostic signatures [13]. Therefore, broad molecular profiling is an important aspect of the improvement of care for patients with NSCLC. According to the National Comprehensive Cancer Network (NCCN), the goal is to identify rare driver mutations that can be treated with available, approved drugs or to counsel the patient regarding the availability of clinical trials [4].

Clinically relevant biomarkers have been identified based on molecular profiling of tissue biopsies i.e. epidermal growth factor receptor (*EGFR*) gene mutations, anaplastic lymphoma kinase (*ALK*) gene rearrangements, a proto-oncogene that encodes for the heterodimeric transmembrane *MET* tyrosine receptor kinase (*MET*), orphan receptor tyrosine kinases that are phylogenetically related to *ALK* i.e. *ROS1* gene rearrangements, and B-Raf proto-oncogene (*BRAF*) point mutations [14]. About 50% of *BRAF*-mutated NSCLC tumors harbor the *V600E* mutation. This mutation is more common in never-smokers versus smokers and is also more likely to occur in adenocarcinomas compared to non-adenocarcinoma NSCLC [15]. Patients with advanced *EGFR*-mutated adenocarcinoma of the lung account for 15% of tumors, while translocations involving the *ALK* gene are present in ~5% of lung adenocarcinomas. Additionally, driver mutations and gene rearrangements, which should at a minimum include *EGFR*, *ALK*, *ROS1*, *MET* and *BRAF* are mainly relevant in non-squamous tumors [16].

Most of the above-mentioned mutations are observed in a non-overlapping fashion, although up to 3% of NSCLCs may harbor concurrent changes. First-line therapies in the presence of a sensitizing *EGFR* mutation may include afatinib, erlotinib, gefitinib, or osimertinib. *ALK*+NSCLC tumors may be responsive to alectinib, ceritinib, or crizotinib as a first-line treatment in an appropriate setting. Mutations that arise due to primary or secondary resistance to *EGFR* and *ALK* tyrosine kinase inhibitors can now successfully be inhibited by third-generation tyrosine kinase inhibitors (osimertinib, rociletinib) and second-generation *ALK* tyrosine kinase inhibitors (ceritinib, alectinib), respectively. Therefore, molecular testing for *EGFR* mutations and *ALK* rearrangements is now the evidence-based standard of care in the initial diagnostic evaluation of select patients with advanced/metastatic disease [17].

On the other hand, crizotinib or ceritinib may be first-line therapeutic options for NSCLC tumors with *ROS1* rearrangements [4]. With the approval of dabrafenib and trametinib, additional tools are now available for the treatment of patients with tumors that harbor a *BRAF V600E* mutation [4,15]. However, inhibition of the most commonly mutated oncogene in lung adenocarcinoma, the Kirsten Rat Sarcoma Viral oncogene homolog (*KRAS*), remains a challenge [18]. Nevertheless, the list of "actionable targets" continues to grow. Additionally, new *EGFR* and *ALK* inhibitors (osimertinib and alectinib, respectively) are now first-line preferences, according to the 2018 update to the NCCN guidelines for NSCLC [19].

What does the future hold in terms of improving the use of genotype-directed therapies? A recent report stated that "next-generation sequencing (NGS) was found to be more effective and faster than single-gene testing methods among patients with newly diagnosed metastatic NSCLC" [20]. Continued molecular profiling using NGS, in the setting of NSCLC progression while on targeted therapies, may thus rapidly shed light on next therapeutic steps [4]. In addition, the mutational burden and level of microsatellite instability characteristic of each tumor, can also help guide immunotherapy treatment decisions [21,22].

Small biopsies or cytology specimens are usually taken for histological analysis from most of the patients who present with advanced, unresectable disease [23]. This means that, for some patients, not enough tissue may be left over for molecular profiling. In addition, solid tumors are typically heterogeneous, with a mutational landscape that changes over time following treatment [24].

These challenges may partially be overcome by simple non-surgical methods such as liquid biopsies i.e., fluids, usually blood, that can be analyzed for different kinds of tumor material (e.g. circulating tumor DNA, RNA, proteins, exosomes, and whole cells). To date, only the *cobas*® *EGFR* Mutation Test v2 companion diagnostic (Roche Molecular Diagnostics) has been approved by the US Food and Drug Administration (FDA) as having clinical utility in terms of liquid biopsy analysis. According to a 2018 news release from the American Society of Clinical Oncology, more evidence is needed to establish effective and appropriate use in the clinic [25].

Another targeted strategy involves thwarting the growth of blood vessels to tumors (this process is called angiogenesis). The vascular endothelial growth factor (VEGF) has been identified as an important regulator in angiogenesis and in subsequent tumor growth and metastasis. Of the available angiogenesis inhibitors, bevacizumab holds promise, but ramucirumab and nintedanib have also demon-

strated clinical efficacy in the second-line setting [26]. However, resistance to anti-VEGF agents, likely through a compensatory angiogenic pathway, is an omnipresent issue [1]. Moreover, Doroshow., *et al.* suggests not using bevacizumab in patients older than 75 years of age, because no benefit is seen and they report significantly more adverse effects [16].

Other patient subgroups may benefit from different treatment strategies. These patient subgroups are those with squamous cell lung cancers, patients who have progressed through genotype-directed therapy, and patients with non-squamous cancers without targetable mutations. These patients are potential candidates for immunotherapies such as immune checkpoint inhibitors and standard platinum doublet chemotherapy [16].

Immune Responses and Immune Checkpoint Inhibitors

Boosting the body's immune system to fight cancer can be achieved with different types of immunotherapies e.g. monoclonal antibodies, non-specific immunotherapies, oncolytic virus therapy, chimeric antigen receptor (CAR) T-cell therapy, and cancer vaccines. Immunotherapies may help recruit more immune cells to attack the tumor, change the way cancer cells grow (perhaps by coaxing cancer cells to behave more like normal cells) or make cancer cells more vulnerable to attack by the immune system [27]. The main anti-tumor immune response is conducted by the cytotoxic T lymphocyte (CTL) population, e.g. CD8+ and CD4+ lymphocytes, natural killer (NK) cells, and natural killer T (NKT) cells. To effectively induce programmed death (PD, apoptosis) of cancer cells, this anti-tumor defense system requires the presentation of tumor antigens via antigen-presenting cells (chiefly dendritic cells and macrophages).

Our current understanding is that lung cancer hides from this immune attack by low antigen expression and low costimulatory molecule expression. Other elements such as the tumor cell expression of PD-1 ligands (PD-L1s) that interact with the PD-1 receptor present on T-helper, T-cytotoxic, T-regulatory, NK cells and B lymphocytes, contribute to a strong immunosuppressive effect. Another protein receptor that functions as an immune checkpoint and that can contribute to the downregulation of immune responses is Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA4) [28].

Meta-analysis of immune checkpoint blockade - the most thoroughly investigated immunotherapeutic strategy - confirmed a significant overall survival benefit in major NSCLC subsets [29]. More precisely, when compared to standard chemotherapy, anti-PD1 (pembrolizumab and nivolumab) and anti-PD-L1 antibodies (atezolizumab and durvalumab) have repeatedly produced greater and more durable clinical responses, with manageable treatment-related adverse events [30]. While the effects can be profound, only a small proportion of patients respond, and there is a need to understand which patients may achieve a long-lasting clinical benefit; in fact, the predictive role of PD-L1 expressed on tumor or immune cells awaits consensus, because not all PD-L1$^+$ patients respond to treatment and, there are cases where PD-L1$^-$ patients respond to treatment [29]. Preliminary studies in a mouse model have identified a transcriptionally and functionally distinct PD-1$^+$ CD8$^+$ T cell pool with predictive potential in anti-PD1-treated NSCLC, but these results need to be translated from bench to bedside [31].

Despite all these caveats, Doroshow., *et al.* have proposed measurement of PD-L1 expression at baseline for all patients with advanced lung cancer, and the initiation of platinum doublet therapy in patients with tumors expressing PD-L1 levels < 50%. The authors prefer the use of pemetrexed as part of the doublet in patients with non-squamous tumors, based on their findings of a better benefit/risk profile. Furthermore, single-agent immune checkpoint inhibitors remain an appropriate choice for second-line therapy following disease progression, given its superiority over second-line chemotherapy. In this setting, PD-1 inhibitors (pembrolizumab and nivolumab) and a PD-L1 inhibitor (atezolizumab) have improved overall survival when compared to docetaxel in patients with adenocarcinoma and squamous cell histologic findings. The authors did not note any differences among the 3 agents in terms of the incidences of immune-related adverse events [16].

However, a subset of patients who initially received this therapy may develop resistance, due to a variety of immune escape pathways or increased immunosuppression by non-T-cell immune subsets or cancer-associated stromal cells [30]. Therefore, development of fur-

ther predictors of responses to immunotherapy requires a fuller understanding of the immune landscape of NSCLC. Several interacting factors, including the epithelial-mesenchymal transition, tumor histology, molecular subtype, mutational load, tumor aneuploidy, clonal heterogeneity and tumor evolution, help shape this landscape. Facing this heterogeneity is an urgent need that will help scale the promise of immunotherapies [29].

For unselected NSCLC, the overall response rate with immune checkpoint inhibitors is currently about 20% [16]. Therefore, more combinatorial strategies targeting different facets of antitumor responses are currently under investigation to overcome resistance and to ultimately impact overall survival.

Impact on Treatment Algorithms

The NCCN recommends the use of low-dose computed tomography of the chest to screen select high-risk smokers and former smokers for lung cancer [4]. The impetus for this guidance is based on the knowledge that the dismal survival rates for patients with lung cancer can partly be attributed to most patients having advanced disease at initial diagnosis. The standard of care for patients with metastatic NSCLC used to be to treat patients with a platinum doublet for 4 - 6 cycles and to offer second-line therapy upon progression. This algorithm is now out of date, with the realization that response rates can be improved with molecular profiling and tailored treatments.

Non-squamous tumors can usually be stratified into 4 categories i.e. *EGFR+* tumors, tumors with *ALK* rearrangements, tumors with *ROS1* rearrangements, and tumors lacking any of these mutations/unknown mutational status. The complexity of tailored treatment algorithms will no doubt grow as more "actionable" targets are added to the list. Thus far, PD-L1 remains the proposed biomarker for immune checkpoint inhibitors, but whether testing will be necessary for patient selection if chemotherapy combinations are implemented will be determined in the near future [32]. Molecular profiling has also been applied to patients with squamous NSCLC, in the hopes of improving their prognosis. According to Daaboul., *et al.* the most notable advance for this patient subgroup has been immunotherapy, which has revolutionized treatment for lung cancer in patients without known driver mutations [33].

Spatial and temporal tumor heterogeneity, as well as resistance mechanisms, are ongoing challenges using the above-mentioned strategies. Validated, next-generation, comprehensive and more sensitive molecular diagnostics and dynamic monitoring technology e.g., using liquid biopsies, may overcome some of the inherent limitations to current management approaches.

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Conflicts of Interest

The author has no conflicts of interest to declare.

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