Targeted Therapies in Lung Cancer: Management Strategies for Nurses and Practitioners

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Introduction

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Beth Eaby-Sandy

Lung cancer is the second most common type of cancer diagnosed in men after prostate cancer, and the second most common type of cancer diagnosed in women after breast cancer. There are an estimated 228,150 new cases of lung cancer to be diagnosed in 2019 [1]. While lung cancer is prevalent, it is also deadly, resulting in an estimated 142,670 deaths in 2019, which is more than breast, colon, and prostate cancers combined and accounts for approximately 25% of all cancer deaths in the United States (US) [1].

There are two main categories of lung cancer, non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). NSCLC is the most common type of lung cancer, resulting in 83% of cases in the US, and is the most common type of lung cancer diagnosed in patients who are never or light smokers. SCLC accounts for the other 17% of cases and is strongly associated with heavy cigarette smoking. As smoking rates decline in the US, there has been a slow decline in the incidence of SCLC as well [2].

Within the realm of NSCLC, there are two predominant histologic subtypes: adenocarcinoma and squamous cell carcinoma. See Fig. 1.1 for the breakdown of histologic subtypes of lung cancer. Adenocarcinoma is the most common histologic subtype and the most common type in patients with light or no smoking history. Over the past 15 years, researchers have found that within the adenocarcinoma histology, several molecular biomarkers have emerged such as epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), and many others, which will be further discussed in this book.

The diagnosis and detection of these biomarkers in NSCLC lead to the development of several targeted therapies to treat NSCLC which harbor one of these mutations or gene alterations. Given their different mechanisms of action and side effect

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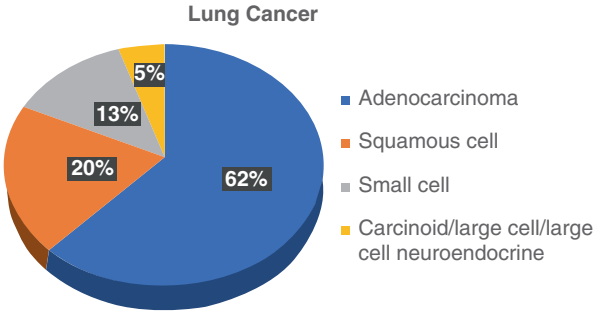

Fig. 1.1 Histologic subtypes of lung cancer (www.onclive.com)

profiles, it has been a challenge for oncology nurses to effectively educate patients about the drugs and their toxicities.

This book will focus on providing a thorough understanding of the different techniques used to detect these biomarkers and populations of lung cancer patients who may be more likely to display certain biomarkers. The National Comprehensive Cancer Network (NCCN) guidelines recommend testing for EGFR, ALK, ROS1, BRAF, and PD-L1 in all patients with a non-squamous histology and consideration in patients with squamous cell carcinoma who exhibit certain clinical characteristics such as never smoking [3].

Following detection and diagnosis, the book aims to educate nurses and healthcare providers with the rationale for use of these targeted therapies as well as an in-depth look at potential toxicities and management strategies. Nurses, whether in the clinic, infusion room, or triaging phone calls, are often charged with identifying these toxicities.

Nurses remain a constant first point of contact for most oncology patients who are experiencing toxicities due to their cancer treatments. In this ever-changing landscape of oncology, specifically lung cancer, there is a huge need for oncology nurses and other oncology healthcare providers to stay up to date and educated on the indications, mechanisms of action, and the toxicity profiles. Management strategies differ depending on the drug and the toxicity. While some toxicities may be minimal, others are life threatening at times. This book will review each of these targeted therapies, their toxicities, and strategies for nursing management.

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Introduction to Mutation Testing

2

Vanna Dest and Kathryn Medow

2.1 Introduction/Lung Cancer Statistics/Histology

Lung cancer remains the leading cause of cancer related mortality in the United States, with 142,670 deaths anticipated in 2019 [1]. Lung cancer incidence continues to decline with 228,150 estimated new cases in 2019. The decline in lung cancer in males is twice the number compared to females, which may be related to tobacco consumption and smoking cessation [2]. Mortality rates from lung cancer remain substantial despite significant advances in the field of cancer treatment in recent years. Historically, chemotherapy has been the cornerstone of treatment for NSCLC, with treatment decisions based empirically on tumor histology. The World Health Organization (WHO) identified two classifications of lung cancer, small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) [3–5]. SCLC accounts for approximately 10–15% of all lung cancers and is directly related to tobacco smoking [1]. NSCLC accounts for approximately 85% of lung cancer cases with associated histologies that include adenocarcinoma, squamous cell, and large cell carcinoma [4]. Over 50% of NSCLC are adenocarcinoma in histology [6]. In 2015, the World Health Organization (WHO) updated the lung cancer classification based upon molecular profiles and genetic alterations. It is recommended that pathologists categorize lung cancer into adenocarcinoma and squamous cell carcinoma secondary to targetable driver genetic alterations. Adenocarcinoma markers include TTF-1 and Napsin 1. Squamous cell carcinoma markers include p40, CK5/6, and p63. Adenocarcinoma is classified by the extent of invasiveness. There are also variants of invasive carcinoma including invasive mucinous adenocarcinoma (IMA), which replaced mucinous bronchi alveolar carcinoma (BAC). Squamous cell carcinomas are classified into keratinizing, non-keratinizing, and basaloid [3–5].

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The treatment of lung cancer with cytotoxic chemotherapeutic agents has led to improved overall survival, however survival rates remain low and patients often incur significant treatment related toxicity, thus driving the need for novel therapies and treatment strategies. The role of molecular testing for NSCLC has grown rapidly, leading to the discovery of a number of molecular markers that are now being used to determine treatment plan, and often to predict potential response to treatment. Recent evidence suggests that lung cancer is a histologically and molecularly heterogeneous disease [3–5]. The result has been a clear shift toward targeted and histologically directed therapies.

The distinction between squamous and non-squamous histology remains the first step in delivering personalized therapeutic options to patients with NSCLC. More recent molecular studies have demonstrated that subsets of NSCLC can be further defined at the molecular level, with a significant proportion of adenocarcinomas harboring distinct genomic alterations. These alterations are commonly referred to as "driver mutations," as their role is implicated in driving the development and proliferation of lung cancer through the activation of mutant signaling proteins that induce and sustain tumorigenesis. Driver mutations are somatic genome alterations that can help to promote cancer through a number of different mechanisms. They are often transformative, initiating the change from a noncancerous cell to a malignant one, or preventing normal cellular mechanisms such as regular cell growth, differentiation, and cell death [7]. The Lung Cancer Mutation Consortium has identified one or more of such mutations in approximately two-thirds of patients diagnosed with Stage IV NSCLC [8]. Driver mutations can be found in all NSCLC histologies, though are far more commonly seen in adenocarcinoma. Similarly, they are found in current, former and never smokers [9]. There are currently a number of targeted small molecule inhibitors available or being developed to treat these specific, molecularly defined subsets of patients. These agents show improved efficacy with superior survival rates as compared to chemotherapy when given to the appropriate patient with the corresponding driver mutation [10, 11].

Several biomarkers have been identified as predictive and/or prognostic markers for NSCLC; predictive markers indicate therapeutic efficacy when there is a direct interaction between the mutation and the therapy on the patient's outcome. Prognostic markers indicate innate tumor behavior (i.e., aggressiveness), independent of the treatment that the patient receives. Testing for these mutations continues to become more efficient and affordable, resulting in a rapid rise in the use of genomic sequencing which will undoubtedly continue to affect routine clinical practice. In turn, this will further expand our knowledge of these markers and thus influence potential treatment recommendations in routine clinical practice, allowing providers to identify patients who are most likely to benefit from a specific drug. It is paramount that molecular profiling is obtained at the time of diagnosis for all patients with advanced stage NSCLC so that the full armament of treatment options can be tailored to their particular cancer with the goal of providing efficacious targeted therapies, as well as avoiding therapies unlikely to provide clinical benefit. Increased utilization of personalized therapies has shown clear promise for the future of lung cancer treatment, with a necessary shift from the "one size fits all"

treatment paradigm of chemotherapy, to allowing for specific recommendations for individual patients based on the presence of specific genetic alterations. In the past decade, the United States FDA has approved numerous new medications to treat patients with these mutations [3]. This, along with the increasing use of immunotherapy in NSCLC, has greatly expanded the catalog of treatment options.

2.2 Types of Lung Cancer Mutations

The most common driver mutations found in lung cancer are EGFR mutations, ALK gene rearrangements, and KRAS mutations [3], though several others have been identified (HER2, MET, BRAF, FGFR4, PIK3CA, ROS1, and RET). Figure 2.1 depicts the incidence rate of these mutations.

Actionable mutations are classified as those that are potentially targetable with an FDA-approved anti-cancer drug. They are found in roughly 20–25% of the non-squamous population [7].

2.2.1 EGFR

EGFR (epidermal growth factor receptor) is a trans-membrane ligand-binding receptor normally found on the surface of epithelial cells, and has a significant role in cellular proliferation and differentiation. When ligands bind to the extracellular

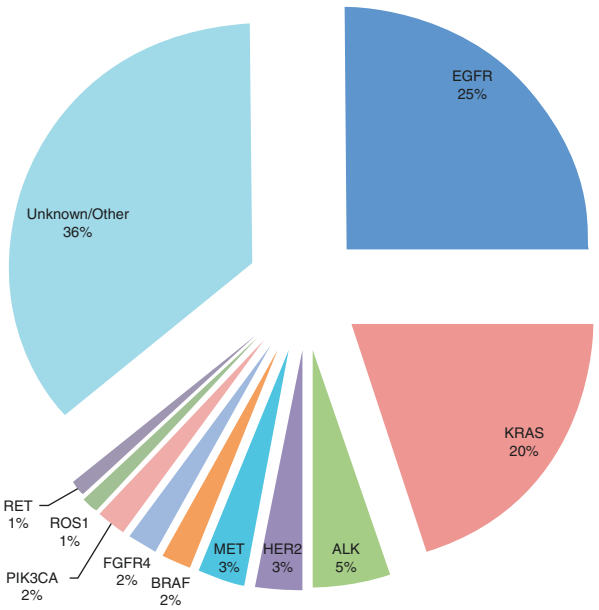

Fig. 2.1 Incidence of molecular etiologies in NSCLC in the United States. Adapted from [3]

receptor, auto-phosphorylation occurs, initiating an intracellular cascade of downstream signals that result in normal cell growth, differentiation, and cell death. In malignant cells, there is dysregulation of the intracellular activity of EGFR, caused by EGFR protein overexpression or EGFR gene mutations resulting in uncontrolled cellular proliferation, invasion, and inhibition of apoptosis [7]. EGFR mutations are the most commonly found actionable driver mutations, occurring in 15% of Caucasian and African American patients with NSCLC, and in 30–50% of those with Asian ethnicity [3, 7, 8]. They are associated with adenocarcinoma histology, female gender, and nonsmoking status [3, 7, 8]. Within the category of EGFR mutations, there are four subcategories of mutations that exist in the first four exons (exons 18 through 21) of the tyrosine kinase domain of EGFR. The most commonly described EGFR mutations are:

1. Insertions/deletions in exon 19–45% of EGFR mutations. They are sensitive to oral EGFR TKIs. These mutations include in-frame deletions L747 and E749.
2. Point mutations in exon 21–40% of EGFR mutations. They are sensitive to EGFR TKIs. The most common point mutation for exon 21 is L858R [3, 7, 8, 12].

Some, less common mutations in EGFR are associated with lack of responsiveness to EGFR TKIs, including most EGFR exon 20 mutations (4–5% of EGFR mutations). The T790M mutation is most commonly associated with cancer recurrence following initial treatment with an EGFR TKI, however if this mutation is identified prior to initial TKI exposure, genetic counseling should be considered, as a germ line T790M mutation is associated with familial lung cancer predisposition. Multiple phase 3 studies of treatment naïve EGFR mutated lung cancer have shown improved efficacy in the first line setting for patients with EGFR mutated NSCLC who receive EGFR TKIs as compared to chemotherapy (platinum doublet) with regard to progression free survival and response rate [8, 10]. Thus, these should be used as first line systemic therapy in patients with documented sensitizing EGFR mutations. EGFR TKIs approved for first line treatment of EGFR mutated NSCLC include osimertinib, afatinib, erlotinib, gefitinib, and dacomitinib [12].

2.2.2 ALK

ALK (anaplastic lymphoma kinase) is a receptor tyrosine kinase not normally expressed in the lung. However, when the ALK gene fuses with another gene (most commonly EMLA4, echinoderm microtubule-associated protein-like4) it can become rearranged, causing dysregulation and inappropriate signaling through the ALK kinase domain resulting in uncontrolled cell growth and proliferation [12, 13]. ALK gene rearrangements are the second most commonly identified actionable driver mutation in NSCLC. These activating mutations are found in approximately 3–7% of patients with NSCLC. They are associated with male patients of younger age and adenocarcinoma histology [7]. Rates are higher in patients who have never smoked (defined as less than 100 cigarettes in their lifetime) or who are "ever smokers" (less than a 15-pack year history) [7]. ALK-positive tumors are sensitive to

treatment with TKIs that inhibit ALK rearrangements (alectinib, crizotinib, ceritinib, brigatinib, and lorlatinib).

2.2.3 ROS1

ROS1 is a receptor tyrosine kinase within the insulin receptor family. A rearrangement of ROS1 causes dysregulation and inappropriate activation of other intracellular pathways through the ROS1 kinase domain, resulting in promotion of cell survival and proliferation. These mutations are found in 1–2% of patients with NSCLC, and are associated with younger age, never smokers, Asian ethnicity, and advanced stage disease [7, 13]. They are most commonly found with adenocarcinoma histology, however are also seen in both large cell and squamous cell etiologies. ROS1 rearrangements occur more frequently in those who are negative for EGFR mutations, KRAS mutations, and ALK gene rearrangements. Presence of ROS1 rearrangement is associated with responsiveness to oral ROS1 TKIs. Crizotinib is currently the only FDA-approved therapies for ROS1 positive patients, with crizotinib preferred given its substantial response rates of 70–80% [12].

2.2.4 BRAF

BRAF is a serine tyrosine kinase enzyme that links cell signaling between RAS GTPases and the enzymes of the MAPK family, which work to control cell proliferation. While these mutations are well documented in melanomas, they are also seen in 1–3% of adenocarcinomas of the lung. They are more likely to occur in former or current smokers [8]. When this mutation results in a change in amino acid position 600 (p.V600E), disease may respond to combined therapy with oral inhibitors of BRAF and MEK; the combination of dabrafenib and trametinib is recommended for patients with vBRAF 600E mutations [12].

A number of other mutations that occur in NSCLC have shown response to medications that are approved for other cancers, but have yet to be approved for lung cancer.

2.2.5 KRAS

KRAS proto-oncogene point mutations are activating mutations that result in unregulated signaling through the MAP/ERK pathway. In the United States, activating KRAS mutations are found in approximately 15–20% of all patients with NSCLC, and approximately 30–50% of patients with adenocarcinoma histology [8]. These mutations are commonly associated with a significant smoking history, as well as larger tumor size [8]. KRAS mutations are correlated with decreased survival [12]. Additionally, KRAS-positive tumors have demonstrated lack of therapeutic response to EGFR TKIs. While there are currently no available therapies to target the

KRAS-mutant variant, there is suggestion that KRAS mutations may sensitize tumors to antifolates such as pemetrexed [7], as well as immune-checkpoint inhibitors [12].

2.2.6 ERBB2 (HER2)

HER2 status is reported in about 2% of NSCLC, with increased frequency in women, never smokers, and patients of Asian origin. It is also more commonly associated with adenocarcinoma histology [8].

2.2.7 MET

The MET gene is located on chromosome 7q21-q31 and encodes for the hepatocyte growth factor receptor. MET amplifications occur in 2–4% of NSCLC, and can be found in both squamous and adenocarcinoma histologies. They are associated with poor prognosis [8]. Crizotinib is approved as treatment for patients with MET exon 14 alterations.

2.2.8 NTRK

NTRK gene fusions act as oncogenic drivers, and are linked with a diverse range of solid tumors including lung, salivary gland, thyroid, and sarcoma. They are rare in NSCLC, occurring only in 0.2% of patients, and do not generally overlap with other oncogenic drives such as EGFR, ALK, or ROS1. Larotrectinib is a TRK inhibitor that has shown efficacy across a diverse range of solid tumors in patients with TRK gene-fusion positive disease [12].

2.2.9 Other

Other non-actionable driver mutations that have been seen in lung cancer are FGFR1, MEK1, RET, PIK3CA, and PTEN. Targeted therapies for these mutations are currently in clinical development. See Table 2.1 for more details on molecular alterations in NSCLC.

While it is not traditionally considered a driver mutation, it is important to also discuss PDL1 as an actionable target for patients with NSCLC. PDL1, programmed cell death ligand 1, is a coregulatory molecule that can be expressed on tumor cells, and works to inhibit T-cell mediated cell death, thus allowing cancer cells to avoid destruction. A number of human immune-checkpoint inhibitor antibodies have been created to block the PD-1 and PD-L1 interaction, thus freeing cytotoxic t-cells to mediate the killing of cancer cells that express PDL1. Monoclonal antibodies that are currently approved and utilized include nivolumab and pembrolizumab, which inhibit PD-1 receptors, and atezolizumab and durvalumab, which