Precision Therapy for Lung Cancer: Tyrosine Kinase Inhibitors and Beyond

Arun Rajan, MD, and David S. Schrump, MD, MBA, FACS

For patients with advanced cancers there has been a concerted effort to transition from a generic treatment paradigm to one based on tumor-specific biologic, and patient-specific clinical characteristics. This approach, known as precision therapy has been made possible owing to widespread availability and a reduction in the cost of cutting-edge technologies that are used to study the genomic, proteomic, and metabolic attributes of individual tumors. This review traces the evolution of precision therapy for lung cancer from the identification of molecular subsets of the disease to the development and approval of tyrosine kinase, as well as immune checkpoint inhibitors for lung cancer therapy. Challenges of the precision therapy era including the emergence of acquired resistance, identification of untargetable mutations, and the effect on clinical trial design are discussed. We conclude by highlighting newer applications for the concept of precision therapy.

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INTRODUCTION

With an estimated 224,000 cases diagnosed in 2014, lung cancer continues to account for a large share of the cancer burden in the United States. Additionally, the estimated 159,000 deaths related to this disease account for 27% of all cancer deaths, and the overall 5-year survival for patients with lung cancer remains distressingly low (17%).[1] Non–small cell lung cancer (NSCLC) is the most common type of lung cancer, and adenocarcinoma is the most common histologic subtype of this disease.[2] Unfortunately most of patients with lung cancer are diagnosed with locally advanced or metastatic disease which is unamenable to surgical resection or definite radiation therapy; the 5-year survival of these patients is 4%.[1]

Advanced NSCLC has traditionally been treated with platinum-doublet chemotherapy with the addition of the vascular endothelial growth factor inhibitor, bevacizumab when clinically indicated. Response rates (RRs) of 12%-37% have been observed in the frontline setting with median overall survival (OS) ranging from 10-14 months.[3] The identification of molecular subsets of NSCLC in the genomic era, and the development of drugs targeting specific oncogenic mutations have resulted in significant alterations in the management of advanced lung cancer. These changes provide a vivid illustration of the evolution of the therapeutic paradigm from a "one-size-fits-all" approach to that of "precision therapy" with the biology of the disease forming the bedrock of treatment choice. In this article we focus on the identification of molecular subsets of NSCLC and describe the effect of these discoveries on clinical management of advanced NSCLC, as well as its effects on clinical trial design.

CLASSIFICATION OF NSCLC: EFFECT OF THE GENOMIC ERA

The classification of NSCLC has traditionally been based on the histologic appearance of the tumor supplemented by information provided by immunohistochemistry.[4] With the advent of genomic testing, it has been recognized that NSCLC is composed of multiple molecular subsets with distinct phenotypes, natural histories, and sensitivities

Thoracic and Gastrointestinal Oncology Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, Maryland

Address reprint requests to David S. Schrump, MD, MBA, FACS, Thoracic and GI Oncology Branch, CCR, NCI, NIH, Building 10; Room 4-3942, 10 Center Dr, MSC 1201, Bethesda, MD 20892-1201. E-mail: david.schrump@nih.gov

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to targeted therapies. The discovery of oncogenic drivers, which has been facilitated by large multi-institutional studies using cutting-edge genomic technologies forms the bedrock of precision therapy for lung cancer.[5-8]

The Cancer Genome Atlas Project

The Cancer Genome Atlas (TCGA) analysis of lung cancer was conducted to identify molecular alterations in NSCLC and uncover potential targets for biologic therapy. Tumor samples and matched normal controls from patients with previously untreated NSCLC (230 adenocarcinomas and 178 squamous cell carcinomas) were analyzed using multiple platforms including whole genome, messenger RNA, and microRNA sequencing, as well as DNA copy number, methylation, and proteomic analyses.[5,7] These studies confirmed the presence of a large number of somatic mutations in NSCLC (mean mutation rate per megabase, adenocarcinoma: 8.9, squamous cell carcinoma: 8.1) including statistically significant mutations in 18 genes in adenocarcinoma and 11 genes in squamous cell carcinomas. Adenocarcinomas without known oncogenic mutations (*EGFR*, *KRAS*, and *BRAF*) were found to harbor aberrations in *NF1*, *RIT1*, *KEAP1*, *TP53*, *MET*, and *ERBB2*. Biologic pathways with recurrent alterations included the RTK/RAS/RAF, PI3K/mTOR, p53, and oxidative stress response pathways, cell cycle regulators, and chromatin and RNA splicing factors. Squamous cell carcinomas nearly always harbored mutations in *TP53*. Other important findings in squamous cell carcinomas included newly discovered loss-of-function mutations in the human leukocyte antigen-A class 1 major histocompatibility gene, and recurrent alterations affecting the PI3K/AKT, CDKN2A/RB1, NFE2L2/KEAP1/CUL3, and SOX2/TP63/NOTCH1 pathways.

Lung Cancer Mutation Consortium Trial

The Lung Cancer Mutation Consortium (LCMC) conducted a study designed to determine the frequency of 10 oncogenic drivers in lung adenocarcinoma, select treatment based on the identified target, and determine survival.[8] Unlike the TCGA project, tumors analyzed in the LCMC study were derived from patients with advanced or recurrent adenocarcinoma of the lung. More than 50% of the patients had received prior chemotherapy, and analyzed tumor specimens were not exclusively obtained by surgical resection. Among 1102 eligible patients, analysis of at least 1 gene was possible in 1007 patients including 341 (34%) never-smokers. Tumor samples were screened for *EGFR*, *KRAS*, *ERBB2*, *AKT1*, *BRAF*, *MEK1*, *NRAS*, and *PIK3CA* mutations, as well as *ALK* rearrangements and *MET* amplification. Full genotyping was feasible in 733 (67%) cancers, and an oncogenic driver was detected in 466 (64%) cases (Fig. 1). Based on these results, 260 (26%) patients received appropriate targeted

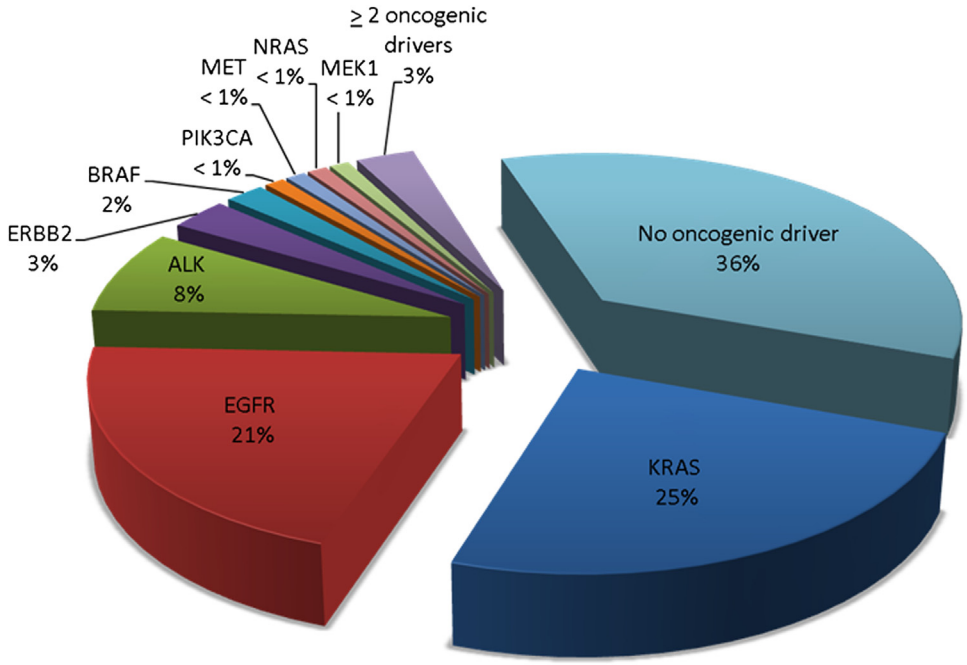

Figure 1. Frequency of oncogenic drivers in adenocarcinoma of the lung detected by the Lung Cancer Mutation Consortium.[8]