The Role of Precision Medicine in Lung Cancer: Case Study and Review of Literature

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Background: Lung cancer is a complex group of disorders resulting from multiple molecular aberrations. The growth of many subtypes of lung cancer is driven by complex molecular changes known as driver mutations and different abnormal molecular cell signaling pathways. Given these complex molecular subtypes, assessing, treating, and understanding lung cancer necessitates the rapid evolution of clinical trials, targeted therapy development, and application of precision medicine (also known as personalized medicine).

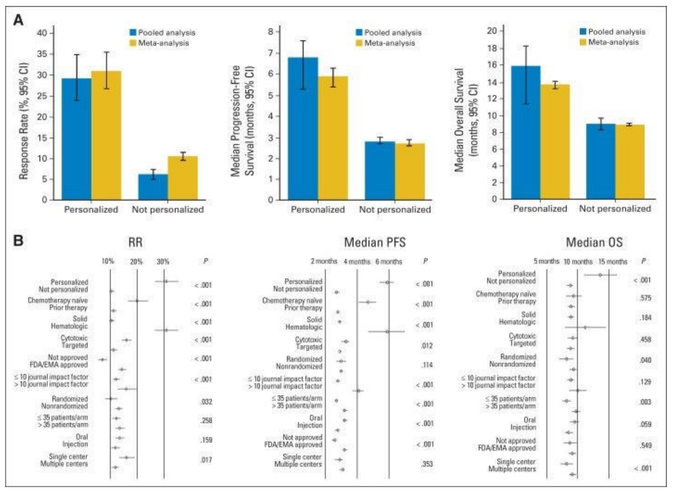

Fig.1: Benefit of personalized therapy (A) Pooled and meta-analysis results comparing response rate (RR), progression-free survival (PFS), and over- all survival (OS) between subjects receiving personalized versus non-personalized treatment. P values are < .001 for all subject arms comparing RR, PFS, and OS for subjects receiving personalized versus non-personalized therapy. RR Analysis: 638 arms had values available for the RR analysis (pooled analysis and meta-analysis; 112 arms were personalized, and 526 were not). PFS Analysis: 530 arms had values for the PFS pooled analysis (personalized, n = 86; not personalized, n = 444), and 342 arms had median PFS values and their corresponding 95% CIs available for the meta-analysis (personalized, n = 59; not personalized, n = 283). OS analysis: 441 arms had values for the pooled analysis (personalized, n = 49; not personalized, n = 392), and 247 arms had median OS values and their corresponding 95% C-Is available for the meta-analysis (personalized, n = 21; not personalized, n = 226). (B) Forest plots for RR, PFS, and OS (left to right). EMA, European Medicines Agency; FDA, US Food and Drug Administration.[5]

Precision medicine (PM) is "an approach to disease prevention and treatment to maximize effectiveness by taking into account individual variability in genes, environment, and lifestyle" according to the Precision Medicine Initiative (PMI) Work Group[1]. The goal of PM is to advance medical and scientific discoveries to offer more tailored, precise, and accurate health interventions to maximize health benefits for patients [2,3].

Essential components of PM range from bioinformatics, such as data from genetic, germline, and molecular profiling as well as pharmacogenomics, to biometric data derived from wearable health-tracking devices and lifestyle choices, to radiological data. With the use of advanced computing and technological expertise, this information can then be translated from PM into personalized healthcare.

Advances in PM in lung cancer have led to targeted cancer therapies, which work by interfering with specific cellular processes involved in the growth, spread, and progression of cancer. In cases where patients can be treated with targeted therapies, studies have shown improved patient outcomes across cancer types (Figure 1)[4,5]. PM also includes the use of bioinformatics procured from next-generation sequencing (NGS) to prevent, diagnose, and treat disease[6].

The cost-efficiency of sequencing has improved due to technological, scientific, and operational advances. The cost of deciphering the entire human genome has dropped from $10,000 in 2011 to about $1,000 today[7,8]. Other drivers of PM include more accurate sequencing, a growing number of available targeted therapies, and the recognition (especially in oncology and rheumatic illnesses) of the biodiversity of the human genome. Next generation sequencing, which is rapidly replacing Sanger sequencing, has matured enough as a technology to find its place in both clinical practice and research. In addition, whole exome sequencing (WES) and/or whole genome sequencing (WGS) are quickly becoming part of the daily operation for oncologists and hematologists for exploring clinical trials and drug development for malignancies.

Rapid strides in sequencing techniques, bioinformatics and PM have not been matched with proportional efforts to implement these technologies in day to day practice. Factors like integration into practice guidelines, lack of consensus and standardization between different stakeholders regarding minimum number of mutational analysis, germline studies, platforms for testing, and payer coverage, all threaten the realization of PM.

In addition to the factors mentioned above, the biggest challenge for success in precision medicine is the lack of genomic and bioinformatic data on diverse subject populations. Minority communities often face discrimination in healthcare and receive poor medical treatment[10]. Outreach to these communities – especially in the research field – has also been characterized by a long history of exploitation, abuse, and marginalization[11]. While hesitancy from ethnic minorities is frequently cited as an excuse for the lack of representative data in PM and clinical trials, real life observation suggests a different story. Researchers[12] observed that willingness to participate did not differ significantly between ethno-racial groups and argued that underrepresentation of minority populations is more likely due to the research design of the single study or to limited accessibility. An analysis of genome-wide association studies (GWAS) representing 1.7 million samples conducted in 2009 found that 96% of participants were of European ancestry. Seven years later, the same GWAS analysis revealed that, despite the colossal 35 million samples collected, 81% of participants were still of European ancestry. It is clear that racial and ethnic representation of minorities in research still has a long way to go[13].

Presented here is a case report and literature review to identify gaps in care due to lack of adequate testing and to demonstrate how NGS testing improves outcomes in patients with advanced cancer in the era of the targeted agents. There is a significant knowledge gap concerning the need for biomarker testing. Lack of appropriate testing affects over 50% of patients with stage IIIB or IV lung cancer, and this lack of testing adversely affects patients to whom targeted therapies are not offered despite being clinically indicated. This case study has been presented to emphasize the importance of comprehensive genomic profiling testing in patients with NSCLC. This case involved the application of clinical and practical experience as well as the use of biomarker testing and NGS, and it demonstrates how these advanced technologies have increased therapeutic options for patients with NSCLC.

Case Report: A 27-year-old student from India pursuing a doctoral degree in economics in the UK developed progressive cough, shortness of breath, and weight loss in the spring of 2017. He visited his general practitioner. He was initially treated with a course of antibiotics (azithromycin) without much relief. He continued to lose weight and began to develop cachexia.

After 2 weeks of initial symptoms, a chest radiograph revealed bilateral multiple nodular lesions and a large 3.5 × 4 cm lesion in the right lung. The patient was started on antituberculosis treatment for several weeks with an empirical diagnosis of pulmonary tuberculosis. His condition continued to worsen. After 8 weeks of treatment, he developed hemoptysis and orthopnea. He was hospitalized in early June 2017. A PET/CT scan in June 2017 revealed a fluorodeoxyglucose (FDG)-avid, 40 × 35 mm (standard uptake value 6) soft-tissue lesion in his right hilar and parahilar regions extending to the right middle lobe; multiple FDG-avid bilateral parenchymal lung nodules; bilateral mediastinal, hilar, and right supraclavicular nodes; and an FDG-avid lesion in the right adrenal gland suggestive of metastatic disease. His histopathology revealed adenocarcinoma of the lung. His initial biomarker assay for cancer panel included EGFR, BRAF, TP53, PTEN, PIK3CA, PDGFRA, NRAS, and KRAS. He needed 2 to 3 liters of oxygen continuously. None of the tests were indicative of actionable mutations.

Given his worsening condition, the patient was airlifted to India to join his parents, with a diagnosis of terminal lung cancer and possible referral for comfort and hospice care. At this juncture, his family reached out to Dr. Kashyap Patel, MD and CEO of Carolina Blood and Cancer Care Associates in Rock Hill, SC, for remote consult to provide the patient's oncologist in India guidance throughout the course of the patient's treatment.

Pending a second opinion, the patient's primary oncologist in India administered 1 cycle of pemetrexed, carboplatin, and bevacizumab (Avastin). Dr. Patel recommended additional biomarker and PDL-1 testing, which revealed the *ALK* mutation. Based on this new information, Dr. Patel started the patient on alectinib in August 2017.

Within 4 weeks of initiating treatment with alectinib, his performance status improved, and he started walking with ambulatory oxygen. After 8 weeks of treatment, the patient started walking 1 mile daily and resumed his studies remotely.

His follow-up PET/CT scan in January 2018 revealed near complete resolution of all liver and adrenal metastases as well as resolution of his lung lesions. In December 2018, the patient completed his doctoral thesis and married. In March 2019, his scans confirmed no evidence of disease. He continued alectinib for another year until the summer of 2020. He then developed multi-organ failure and was hospitalized for several days at a local hospital in India. His restaging scans indicated disease progression, with metastasis into the pericardial space, adrenal glands, and brain, as well as multiple metastatic lesions in his liver. Biopsy of the patient's metastatic disease revealed the same molecular profile as his original disease. He received whole brain radiation. Once he completed radiation, he was placed on brigatinib at an FDA-approved dose schedule. Within three months, his follow up brain MRI revealed near complete resolution of all lesions, including liver lesions. At the time of writing this article, he leads a normal active life, running 3 to 4 kilometers every day, riding his motorcycle, working a full-time job, and enjoying married life.

Discussion:

An estimated 236,740 people in the United States will be diagnosed with lung cancer[14] in 2022. Lung cancer accounts for 12% of all new cancer cases and more than 20% of all cancer deaths[14]. It is the leading cause of cancer deaths regardless of gender or ethnicity. More than half of patients with lung cancer die within 1 year of receiving a diagnosis[15]. The 5-year survival rate is 19% for all stages, and for stage IIIB and IV the rate is 6% [16,17].

Due to the complex nature of lung cancer, assessing, treating, and understanding this disease necessitates rapid evolution of clinical trials, targeted therapy development, and application of personalized medicine. However, in patients with co-expression of PD-L1 and other driver mutations (in genes such as EGFR), outcomes with IO agents have been disappointing[17]. In particular, KEYNOTE-024 and KEYNOTE-021 excluded patients with sensitizing mutations in the EGFR or ALK gene[18,19]. The only study of an immune checkpoint inhibitor that included patients with EGFR mutations and PD-L1 expression was stopped prematurely because of lack of efficacy[17]. It is reasonable to conclude that there is a lack of evidence related to clinical benefit from ICIs as a first-line treatment in patients with metastatic EGFR-mutant NSCLC. Turnaround for PD-L1 testing is quick, but it may take longer to identify other driver mutations. It is prudent to check for all biomarkers prior to rushing to treatment with IO agents; it is reported that 1 of every 3 patients with EGFR mutations may also express PD-L1. National Comprehensive Cancer Network (NCCN) guidelines recommend biomarker testing of 4 genes with targetable alterations (i.e., with corresponding FDA-approved targeted therapies) EGFR and BRAF mutations as well as ALK and ROS1 rearrangements for all patients with NSCLC[20].

In a study of 1203 patients with advanced NSCLC treated in a community setting in 2017 and 2018, only 22% of patients underwent genotyping for all 4 NCCN-recommended genes, with testing rates for individual genes ranging from 29% (BRAF) to 54% (EGFR)[21]. This study also revealed that only 45% of patients who may have qualified for FDA-approved targeted therapy had evidence of receiving targeted therapy. Furthermore, 37% of patients with a mutation in EGFR or ALK and no evidence of progression on the corresponding tyrosine kinase inhibitor received an IO agent, although most of these patients were known to have the targeted alteration at the time of IO agent initiation.

In summary, the field of mutation-directed precision medicine holds the greatest promise for achieving better survival rates, while also reducing adverse effects of treatment in patients with NSCLC. Oncology is at the cusp of a paradigm shift, with scientific discoveries offering optimism and hope, even for advanced-stage NSCLC patients who were once destined for limited survival rates and short life expectancies.

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