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Literature Review

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

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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 (driver mutations) and different abnormal molecular cell signaling pathways. With these complex molecular subtypes, assessing, treating, and understanding lung cancer necessitates rapid evolution of clinical trials, targeted therapy development, and application of personalized medicine also known as precision medicine). with advanced NSCLC.

The Precision Medicine (PM) is as "an approach to disease prevention and treatment "to maximize effectiveness by considering 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 the health benefits for patients [2,3].

Essential components of PM include the integration of information from genetic and molecular profiles, imaging data, records from wearable health-tracking devices and lifestyle choices as well as germline data, pharmacogenomics and associated bioinformatics using computing power and technological expertise to translate PM into personalized healthcare.

Advances in PM in lung cancer have led to targeted cancer therapies. They 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 [4,5]. PM uses bioinformatics procured from NGS to prevent, diagnose, or treat disease [6].

The cost-efficiency of sequencing has improved a lot 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 targeted therapies, and the recognition (especially in oncology and rheumatic illnesses) biodiversity of the human genome. Next-generation sequencing (NGS), which is replacing the Sanger sequencing rapidly, has matured enough as a technology, and found it's place both in clinical practice and research. In addition, other, Whole Exome Sequencing (WES) and/or Whole Genome sequencing (WGS) are becoming part of daily operation for oncologists and hematologists for exploring clinical trials and drug development for malignancies.

The rapid strides in sequencing technics, bioinformatics and PM has not been matched with efforts of implementation in day to day practice. Factors like integration onto practice guidelines, lack of consensus and standardization between different stakeholders regarding minimum number of mutational analysis, germline studies, platforms for testing and payer coverage threaten realization of PMI.

An addition to factors mentioned above, the biggest challenge for success in personalized or Precision Medicine is lack of diver-

sity in the knowledge of genomics and bioinformatics in research and studies. 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 cites as an excuse for lack of representative data in PM and clinical trials, real life observation is somewhat different, where 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. From an analysis of Genome-Wide Association Studies (GWAS) representing 1.7 million samples conducted in 2009, it resulted 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 racial and ethnic representativeness of the samples still had a long way to go [13]. We present a case report of a patient and review of literature to identify the gaps in care due to lack of adequate testing and how NGS testing can improve 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 their outcome is adversely affected as targeted therapies are not offered despite being clinically indicated. We present the case study 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 UK as an student 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, (which included EGFR, BRAF, TP53, PTEN, PIK3CA, PDGFRA, NRAS, and KRAS). He needed 2 to 3 liters of oxygen continuously.) None of the test was indicative of actionable mutation.

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 (me) at the Carolina Blood and Cancer Care in Rock Hill, South MD, CEO of Carolina Blood and Cancer Care, Rock Hill, SC for consulted remotely, providing guidance to the patient's oncologist in India throughout the course of the patient's treatment. Pending a second opinion, his primary oncologist in India administered 1 cycle of pemetrexed, carboplatin, and bevacizumab (Avastin). I recommended additional biomarker testing and PDL 1 which revealed We recommended starting 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 metastases and adrenal metastases. His lung lesions also resolved.

In December 2018, the patient completed the thesis for his doctoral degree and got married. In March 2019, his scans confirmed no evidence of disease. He continued alectinib for another year until summer of 2020. He then developed multi organ failure and was hospitalized for several days at a local hospital in India. His restaging studies indicated progression including pericardial space, adre-

nal also brain mets and multiple progressive liver metastases. His repeat biopsy revealed same molecular profile. He received whole brain radiation. Once he completed radiation, he was placed on Brigatinib at a FDA approved dose schedule. Within three months, his follow up brain MRI revealed near complete resolution of all lesions and his liver lesions are also have responded. At the time of writing this article. He currently runs 3 to 4 kilometers every day, rides motor cycles, works full-time in India, and is enjoying married life.

Discussion and Conclusion

More than 228,000 people in the United States will be given a diagnosis of lung cancer [14] in 2019. Lung cancer accounts for 13% of all new cancer cases and almost 25% of all cancer deaths [14]. It is the leading cause of cancer death 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, for stage IIIB and IV the rate is 6% [16,17].

Lung cancer is a complex group of disorders associated with a tremendous number of possible molecular aberrations. The growth of many subtypes of lung cancer is driven by complex molecular changes and different abnormal molecular cell signaling pathways, which are often triggered by driver mutations. With these complex molecular subtypes, assessing, treating, and understanding lung cancer necessitates rapid evolution of clinical trials, targeted therapy development, and application of personalized medicine with advanced NSCLC. 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 ICI 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; hence, it is important to check for all biomarkers prior to initiating immunotherapy. 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 treatment adverse effects in patients with NSCLC. We are at the cusp of a paradigm shift, with scientific discoveries offering optimism and hope even for patients with stage IV NSCLC, who were once destined for limited survival rates and short life expectancies.

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Volume 5 Issue 11 November 2021