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A Case Report: The Potential Clinical Benefits of Comprehensive Molecular Profiling in an Aggressive NSCL Grade IV

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Abstract

We present a Non-Small Cell Lung Cancer Grade IV patient, diagnosed at 46 years of age, with multiple relapse from the diagnosis and demonstrating a poor prognosis after 3 cycles of treatments. A clinical comprehensive genomic profile was performed with the goal of finding potential actionable molecular alterations. The patient showed significant symptomatic and laboratory improvement with a combination chemotherapy determined by the molecular profiling, which would otherwise not have been considered. The mentioned approach was conducted since no other targeted therapies seemed actionable for him.

INTRODUCTION

Worldwide, lung cancer caused an estimated 1.8 million deaths in 2020 [1]. In the United States, there are over 230,000 new cases of lung cancer and 130,000 deaths annually [2]. However, survival after diagnosis has been improving, likely due to treatment advances (eg, targeted therapy and immunotherapy) (3).

In 1953, lung cancer was the leading cause of cancer deaths in men, in 1985 in women, and now causes approximately twice as many deaths as breast cancer. Overall, lung cancer causes more deaths than breast, prostate, colorectal, and brain cancers combined [2]. There is good news that lung cancer deaths are declining in men and women, largely due to decreases in smoking.

The term lung cancer, or bronchogenic carcinoma, refers to malignancies that originate from the airways or pulmonary parenchyma. Approximately 95 percent of all lung cancers are classified as either small cell lung cancer (SCLC) or non-small cell lung cancer (NSCLC). This distinction is required for proper staging, treatment, and prognosis. Other cell types comprise about 5 percent of malignancies arising in the lung.

SCLC is distinguished clinically from most types of non-small cell lung cancer (NSCLC) by its rapid doubling time, high growth fraction, and the early development of metastases. Large cell neuroendocrine carcinoma, a rare form of lung cancer, and extra pulmonary small cell carcinomas are generally treated with the same chemotherapy regimens used for SCLC.

Rapid advances in understanding the molecular pathogenesis of NSCLC have demonstrated that NSCLC is a heterogeneous group of diseases. Although the initial treatment of localized disease is the same, the molecular characterization of tumor tissue in patients with NSCLC serves as a guide to treatment both in those who present with metastatic disease and in those who relapse after primary therapy.

Currently defined NSCLC subsets for which specific targeted therapies have been standard therapy include those with mutations in the epidermal growth factor receptor (EGFR) as well as B-Raf proto-oncogene (BRAF), those with the echinoderm microtubule-associated protein-like 4 (EML4)-anaplastic lymphoma kinase (ALK) fusion oncogene, and c-ROS oncogene 1 (ROS1) fusions. Other driver mutations have also been identified and specific treatments are being developed.

Genotype subtype analysis in NSCLC and the development of targeted therapy for specific gene mutations has resulted in individually tailored therapy. Targeted treatment results in responses better than

that with standard chemotherapy for subtypes of NSCLC including epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), and c-ROS oncogene 1 (ROS1) mutations, and others [3]. Using multiplexed assays, one group identified driver mutations in over 60 percent of more than 700 patients with adenocarcinomas.

CASE REPORT

In November 2011, a 46-years-old male patient, with no history of smoking, referred with chronic cough.

A CT scan of the chest revealed a large nodule about 28*20 mm with speculation and air bronchogram at left Lobe with adjacent pleural thickening which was doubted to be BAC.

Also multiple small adenopathy in mediastinal compartment with short axis about 13mm size and T12 bone lesion were detected.

Patient underwent Lung mass, CT guided biopsy and aspiration and pathology confirmed Non-Small Cell Lung Cancer (NSLC) of the left lower lobe. Molecular and Histopathology evaluation was positive for CK7, TTF-1 and negative for CK20 and TG. A mutation in the tyrosine kinase domain of the EGFR and deletion of exon 19 (EGFR del19) was detected and EML4-ALK fusion was not detected. Initial TNM stage was considered as cT2a cN2 cMb(PUL OSS), stage IV. According to the result patient was treated with standard therapy Erlotinib 150 mg/ day until July 2016 when patient presented with dyspnea and pleural effusion.

Serum liquid biopsy and evaluation of plural effusion cells revealed a Mutation in T790M (substitution of a methionine for a threonine at position 790 in exon 20) in result of exposure to EGFR tyrosine kinase inhibitor. As a result of this findings patient`s treatment started with Osimertinib 80 mg/day until February 2021 which patient presented with dyspnea and plural effusion and supraclavicular lymphadenopathy was detected. PET/CT scan from VERTEX to MID-THIGH results were:

-BRAIN: No findings

-NECK: Small sized right lower cervical FDG-avid adenopathies

-CHEST: Small sized subcarinal (SUV max=3) and bilateral hilar (left SUV max up to 2.7, right SUV max up to 3.4) FDG- avid adenopathies were detected. Bilateral pleural effusion with metabolic activity were noted (SUV max=0.6). Hypermetabolic focal parenchymal infiltration in right upper lobe was seen (SUV max=1.7). Multiple pulmonary parenchymal and pleural based nodules were seen in both lungs.

-ABDOMEN & PELVIS: Small sized retroperitoneal FDG-avid adenopathies were seen (SUV max=1.5). Prostate was enlarged with focal metabolic activity in left lateral peripheral zone (SUV max=2.4).

-MUSCULOSKELETAL: DJD changes of spine were seen with hypermetabolic sclerotic bone metastasis of T12(SUV max=8.5). Additional multifocal sclerotic lesions were detected in the axial skeleton with no metabolic activity.

Analysis of serum liquid biopsy and pleural effusion cells:

-Variants which impact theranostique known (Variants class 5 with AMM in the pathology):
NM_005228.3(EGFR): c2250del p.(Glu746_Ala750del) ratio 0.4%

-Variants to be discussed RCP molecular theranostique connu (Class 5 variants outside AMM and class 4): No mutation

-Other variants with unknown predictive value to date: No mutation

According to the results metastatic tumor was resistant to any targeted therapies. Treatment courses started with Pemetrexed + Bevacizumab+ Carboplatin every 3 weeks.

At this point and due to the lack of efficacy of chemotherapy after 3 courses, as the patient's health deteriorated, comprehensive genomic profiling of the tumor was performed, using an OncoDEEP® Clinical Plus solution to obtain outcomes about its sensitivity to different types of treatment (target therapy, chemotherapy, and immunotherapy agents) and recruiting clinical trials. Paraffin-embedded tumor tissue was used to analyze 638 genes employing next-generation sequencing (NGS), in combination with immunohistochemistry (IHC) studies. The results of the NGS analysis did not identify the MET exon 14 skipping (METex14). Therefore, tyrosine kinase inhibitors targeting MET would be associated with a lack of clinical benefit for the patient. METex14 skipping is a strong predictive biomarker for response to capmatinib[4] . It was shown by IHC analysis a low expression of RRM1, a negative expression of CD8, indicating the absence of CD8+ T cells around the tumor, a negative expression of PD–L1 and a positive expression of thymidylate synthetase (TS).

REPORT RESULT SUMMARY

Drugs

36 with potential clinical benefit 15 with lack of clinical benefit 0 associated with toxicity

Variants

5 Pathogenic 2 Likely Pathogenic80 Variants of Uncertain Significance (VUS)

NGS and IHC results are summarized in Table1.

The patient was considered a candidate for a combination therapy with tyrosine kinase inhibitor and epidermal growth factor receptor (EGFR) inhibitor according to the molecular profiling outcome.

In June 2021, the patient started treatment with Crizotinib 250 mg/BID + Osimertinib 80 mg/day.

Table 1. Identified Biomarkers for Therapies Response

Biomarker	Result	VAF/CNV	Biological Impact	Therapeutical Impact
CCND1	CNV AMPL	6	Likely Pathogenic	Tier IIC
CDKN2A	CNV LOSS	0	Pathogenic	Tier IIC
CDKN2B	CNV LOSS	0	Pathogenic	Tier III
EGFR	DEL	15%	Pathogenic	Tier IA
EPHA3	LOH	1	Likely Pathogenic	Tier III
FAM175A	LOH	1	Pathogenic	Tier III
MET	CNV AMPL	1	Pathogenic	Tier IIC

Table 2. Other Biomarkers

Biomarker	Result	Scoring
CD8	Negative Expression	2%
Fusion Panel	No	-
HRD	Negative	-
METex14	No	-
MSI	Stable	-
PD-L1	Negative expression	0%
PRM1	Low Expression	2%
TS	Positive Expression	20%
TUBB3	Low Expression	1%
TMB	High	10.78 Mut/Mb

Some days after initiating treatment, the patient felt significantly better and showed further improvement over the following weeks.

Currently, 5 months after the chemotherapy started, the patient recovered from dyspnea and pleural effusion resolved.

DISCUSSION

The patient presented with a progressive cancer and rapid deterioration of his performance status after receiving standard lines of treatment. The standard of treatment of NSCL and metastatic is limited and cancer progressed.

At this point, the need for a personalized treatment was raised. Given the remarkable advances in the identification of molecular biomarkers, it was decided to perform comprehensive tumor molecular profiling.

An EGFR in frame deletion was found. EGFR E746_A750del results in the deletion of four amino acids in the protein kinase domain of the EGFR protein from amino acids 746 to 750. E746_A750del has not been characterized, however, other EGFR exon 19 deletion mutations are activating, and thus E746_A750del is predicted to result in a gain of function. EGFR exon 19 deletions are associated with responsiveness to EGFR tyrosine kinase inhibitors therapy. A genomic MET (7 copies) amplification was found . Genomic amplification of c–MET has been observed in several cancers like pleural mesothelioma, glioma, NSCLC, gastric cancer, and it might be associated with an increase of the expression of the corresponding protein. Genomic amplifications of MET have been reported in several cancers and have been associated

with poor prognosis In NSCLC, genomic amplification of MET has been associated with a mechanism of secondary resistance to EGFR–TKIs. Based on those results, several trials tested either MET inhibitors alone or in combination with EGFR–TKIs on patients with MET genomic amplification. However, the results were disappointing because of the lack of correlation between the number of copies and its associated level of expression, as well as between the number of copies and ligand–independent activation

But recently, it was reported that a CNV of 6 copies identified by FISH normalized against the centromere is associated with a resistance to EGFR–TKIs in 15 % of the cases.

Although several case reports have documented a response to the combination of EGFR–TKI and MET inhibitors, the results are too heterogeneous to make a final conclusion about the clinical benefit. A recent report mentioned that the combination MET + EGFR inhibition (Osimertinib + Crizotinib) delivered ORR 48–64% in EGFR–mutant, MET–amplified subjects who had progressed on prior EGFR–TKIs therapy but this needs to be confirmed at larger scale.

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