Molecular tumor board: Case 1-Interplay of EGFR, MET and PD-L1 in non-small cell lung carcinoma

HISTORY

A 62-year-old woman with hypertension controlled on amlodipine and olmesartan presented with a 2-month history of progressive cough, weight loss, and dizziness.

DIAGNOSIS

The patient consulted a chest physician for her complaints. Contrast-enhanced computed tomography scan showed a 3.4 cm × 3.2 cm mass in the lingular segment of the left lung [Figure 1] with consolidation along with left hilar and mediastinal lymphadenopathy and left pleural, renal, and multiple skeletal lesions. Besides, there was a hyperdense focus in the right cerebellum with minimal perilesional edema. Biopsy from the lung mass revealed poorly differentiated adenocarcinoma, which was thyroid transcription factor 1 positive.

MOLECULAR TESTING

Real-time polymerase chain reaction (PCR) was positive for epidermal growth factor receptor (EGFR) exon 19 deletion, and tumor proportion score (TPS) for programmed death-ligand 1 (PD-L1) by immunohistochemistry (IHC) using SP263 clone was 85%–90% positive. Next-generation sequencing (NGS) testing was done on the lung biopsy using 52 solid tumor gene panel, including 35 hotspots, 19 copy number variants, and 23 fusion drivers. NGS revealed EGFR exon 19 746 deletion (allele fraction [AF]: 26.7%) and mesenchymal–epithelial transition (MET) N375S (AF: 48.87%), along with amplification of MYCN (chr2: 16080663), FGFR3 (chr4: 1797211), EGFR (chr7: 55198956), MYC (chr8: 128748885), and AR (chrX: 66776186). Variants of unknown significance were detected in ALK, FGFR4, and BRCA1.

TREATMENT

The patient was discussed in the molecular tumor board, and she was started on EGFR-directed therapy with afatinib and zoledronate from July 2019. The patient had symptomatic improvement in cough; however, she developed an episode of Grade 3 diarrhea requiring supportive care and interruption of afatinib. Post resolution of diarrhea, afatinib was restarted (at the same dose), which she then tolerated well. Response scan done post 3 months of afatinib in October 2019 suggested stable left lingular segment mass with few new-onset, subcentimeter pleural-based nodules in the left lower lobe and an irregular nodule in the right upper lobe. The nodules were small and indeterminate; afatinib was continued with close follow-up.

EXCERPTS FROM THE DISCUSSION IN MOLECULAR TUMOR BOARD

In this patient with non-small cell lung cancer (NSCLC) with EGFR (Ex 19Del), NGS revealed four amplifications of MYCN, FGFR3, EGFR, and MYC, along with AR positivity and variants of unknown significance in ALK, FGFR4, MET, and BRCA1. EGFR mutation is a well-known activating mutation in NSCLC. The presence of multiple mutations and amplifications in the patient’s tumor indicated high intratumor heterogeneity, likely to show early resistance to targeted agents. There was also a possibility of early resistance to EGFR-directed oral tyrosine kinase inhibitor (TKI), possibly mediated by MET.

As the patient had a classical EGFR-activating mutation, EGFR-directed therapy was recommended. The allele frequency of MET amplification was not very high (48.9%); therefore, the need for confirmation of MET amplification by fluorescence in situ hybridization (FISH) assay was also discussed. However, this was deferred in view of the nonavailability of a clinical trial and no MET inhibitor being approved in combination with an EGFR TKI in this setting. Thus, despite finding multiple mutations which can help in the prognostication and prediction of the chance of early progression, the treatment decision in the first line was based on the gold standard PCR testing for EGFR in this patient. However, if combination EGFR and MET therapy becomes approved in this setting in future, the treatment choice will also change.

INTERPLAY OF EPIDERMAL GROWTH FACTOR RECEPTOR AND PROGRAMMED DEATH-LIGAND 1 IN LUNG CANCER

EGFR activation has been reported to upregulate the expression of PD-L1 in lung cancer cells, and this may lead to immune escape.[1] There is a definite correlation between
PD-L1 expression and modifications in tumor suppressor genes and oncogenes. For example, deletion of PTEN can upregulate PD-L1 expression in squamous cell carcinoma of lung.\(^{[2]}\) EGFR-mutant NSCLC patients are also amenable to PD-1-directed immunotherapy.\(^{[3]}\)

In a study by D’Incecco et al., the patients who had PD-L1 expression were mostly males and/or smokers, harboring KRAS-mutated lung adenocarcinoma, whereas patients with PD-L1 expression had more probability of being females and/or former/never smokers with molecular-positive (EGFR/ALK) adenocarcinoma.\(^{[4]}\) Another important observation was better survival in PD-L1-positive patients who received EGFR TKIs (in the presence of EGFR mutation). PD-L1-positive \((n = 38, 70.4\% )\) patients had a statistically significant longer time to progression (TTP) of 13.1 months as against PD-L1-negative patients \((n = 16, 29.6\% )\) with a TTP of 8.5 months \((P = 0.01)\). There was also a trend toward longer overall survival (OS) (29.5 months vs. 21.1 months, \(P = 0.75\)).\(^{[4]}\) These findings can be explained by PD-L1 downregulation caused by EGFR inhibition. As PD-L1 expression has been correlated with poorer outcomes in multiple cancers, this further supports the improvement in TTP to be related to EGFR TKI-mediated downregulation of PD-L1 expression.\(^{[5]}\)

In a Phase II study by Lisberg et al., patients with both EGFR mutation and PD-L1 positivity (with TPS of at least 1\%) were given 3-weekly pembrolizumab 200 mg.\(^{[6]}\) The trial was closed early, after 11 of the target 25 patients were enrolled, owing to a lack of efficacy despite the majority of the patients having high PD-L1 expression \((TPS \geq 50\% ).\) Only one patient had response, which was also found to be EGFR negative at reanalysis. Two patients died in the first 6 months after enrollment: one death was due to immune-mediated pneumonitis, and the trial was prematurely stopped.\(^{[6]}\)

In a recent study by Hastings et al., patients with EGFR exon 19 deletion receiving PD-L1 inhibitors had worse outcomes as against patients with EGFR non-mutated lung cancers, whereas patients with EGFR/L858R lung tumors had similar outcomes.\(^{[7]}\) The presence of T790 mutation or expression of PD-L1 did not lead to difference when treated with immunotherapy. PD-L1 expression was similar across various EGFR alleles. Furthermore, tumor mutation burden was lower in del19 mutation patients as compared to L858R-mutated lung tumors, even if they had similar smoking history.\(^{[7]}\)

The combination of EGFR-TKIs and checkpoint inhibitors has been tried, but it has not yet been established to be a safe and effective option. Osimertinib and durvalumab combination was tried; however, it was associated with significant pneumonitis, with poor overall response rate (ORR).\(^{[8]}\) Results from a Phase Ib safety trial of erlotinib and atezolizumab combination were presented at the World Congress on Lung Cancer 2018; 28 patients were enrolled and no Grade 5 adverse events (AEs) were reported.\(^{[9]}\) The ORR was 75\%, with a median duration of response of 19 months. Interestingly, increased PD-L1 expression and infiltration of the tumor by CD8+ T cells was found in biomarker analysis after EGFR-TKI therapy. The authors concluded that further investigation of this combination is warranted.

With rapid evolution of the treatment of advanced lung cancer, first-line options now include PD-L1 inhibitors, as well EGFR-TKIs. A recent study revealed that anti PD-L1 immunotherapy followed by osimertinib was complicated by severe immune-related AE (irAE) in 15\% patients, with the highest risk in those who received immunotherapy within the preceding 3 months.\(^{[10]}\) The severe irAEs included Grade 3/4 pneumonitis, colitis, and hepatitis. No excess of irAEs was reported when osimertinib was given prior to PD-L1-directed therapy. The association seems to be specific to osimertinib, as no excess of irAEs was observed with the use of other EGFR-TKIs.\(^{[10]}\) This particular situation may arise in clinical practice when PDL1 report comes first (as it did in our patient), patient gets started on immunotherapy, and is later found to be EGFR positive. Thus, it is prudent to wait for EGFR and ALK reports before starting immunotherapy in patients with advanced lung cancer. Furthermore, if such a situation arises, it would be best to start a first-generation oral TKI after waiting for a duration of about 3 months from the last immunotherapy dose.

**INTERPLAY OF EPIDERMAL GROWTH FACTOR RECEPTOR AND MESENCHYMAL–EPITHELIAL TRANSITION FACTOR GENE**

MET proto-oncogene encodes the hepatocyte growth factor receptor protein. MET is altered in 2.7\% of all cancers,
They reported tolerable adverse effects with presented the Phase I study of JNJ-372, an MET amplification. These include monoclonal antibodies emibetuzumab, rilotuzumab, and ficlatuzumab and TKIs such as crizotinib, cabozantinib, tepotinib, and capmatinib. Furthermore, combined MET and EGFR-TKI is one of the strategies under evaluation to overcome resistance. IHC testing for MET can miss patients with MET amplification, and thus is considered an inefficient tool for screening for these genomic changes. FISH and multiplex NGS panel are considered to be better options for the same.

Despite encouraging Phase II study results, the Phase III METLung trial of onartuzumab plus erlotinib versus placebo plus erlotinib failed to achieve the primary endpoint in patients with MET-positive (by IHC) NSCLC along with EGFR mutation. Exploratory analyses were performed using FISH and NGS, but they also failed to show any benefit for onartuzumab; in fact, patients with EGFR mutations tended to have a poorer OS when treated with onartuzumab.

In TATTON trial, EGFR-mutated, T790M-negative NSCLC patients who acquired MET amplification (based on IHC, FISH, or NGS) following one or more first/second-generation EGFR-TKIs were offered a combination of osimertinib 80 mg and 600 mg daily of savolitinib, which is a highly selective oral MET-TKI. The criteria for MET positivity specified in the study protocol included IHC (3+ in ≥50% of tumor cells), FISH (MET CNG ≥5 or MET:CEP7 ratio 2 or more), and NGS (20% or more tumor cells with ≥200 times depth of coverage). ORR with the combination was reported to be 52% (all partial responses), with a median duration of response of 7.1 months. Around 35% of the patients had to discontinue the treatment due to AEs with two (4.3%) AE-related deaths; at least one of which (acute kidney injury) was potentially related to savolitinib. Another Phase II study, SAVANNAH, is recruiting patients with EGFR-mutated NSCLC who also have MET+ disease by FISH, IHC, or NGS. The patients should have progressed on 1–3 lines of prior therapy, including osimertinib. They will receive osimertinib plus savolitinib, with the primary end point of the study being response rate in patients who are MET+ on FISH.

In yet another Phase II study of MET inhibitor in combination with EGFR-TKI, patients with EGFR mutation who have disease control following 8 weeks of erlotinib 150 mg were randomized to continue erlotinib alone versus combination with emibetuzumab (750 mg Q2W). There was no difference in median progression free survival (PFS) in emibetuzumab plus erlotinib arm (9.3 months) versus erlotinib alone (9.5 months). Encouraging results were provided by exploratory post hoc analysis, in which 24 patients with MET expression of 3+ in ≥90% of tumor cells had a median PFS for the emibetuzumab + erlotinib arm of 20.7 months versus erlotinib alone 5.4 months; hazard ratio: 0.39; 90% confidence interval: 0.17–0.91.

Haura et al. presented the Phase I study of JNJ-372, an EGFR-cMet bispecific antibody, in EGFR mutant advanced NSCLC. They reported tolerable adverse effects with responses in patients who had failed third-generation TKI harboring C797S and MET amplification and exon20ins disease; enrollment in the dose expansion cohort is ongoing.

CONCLUSIONS

The findings, in this case, illustrate the complexity of a genomic profile of NSCLC and provide a strong support for NGS as a preferred method for routine clinical testing. In patients with targetable molecular drivers, molecular-directed therapy should be the priority regardless of the PD-L1 status. However, the cost of testing and treatment accessibility and affordability can be a challenge and should be discussed with the patient and caregivers. MET immunohistochemistry has largely failed as a screening test for MET alterations and therefore the tissue should be prioritized for NGS.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.
Kapoor, et al.: Interplay of EGFR, MET and PD-L1

Akhil Kapoor1,3, Vanita Noronha1,3, Anuradha Chougule1,3, Vitez M. Patil1,3, Nandini Menon1,3, Amit Joshi1,3, Pratik Chandrani1,3, Rajiv Kumar2,3, Vikas Talreja1,3, Hollis D’Souza1,3, Kumar Prabhash1,3

1Departments of Medical Oncology and 2Pathology, Tata Memorial Hospital, 3Homi Bhabha National Institute (HBNI), Mumbai, Maharashtra, India.

Address for correspondence: Dr. Anuradha Chougule, Department of Molecular Pathology, Tata Memorial Hospital, Mumbai, Maharashtra, India. E-mail: anu_c1112@hotmail.com

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