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ROS1-gene Rearranged Lung Adenocarcinomas: Demographic, Clinicopathologic, and Treatment Profile in a Cohort of 409 Indian Patients

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BACKGROUND

- The *ROS1* oncogene, a receptor tyrosine kinase with no known ligand, is mutated in many different types of solid tumors and results in the deregulation of a tyrosine kinase–mediated signaling pathway.[1]
- ROS1 tyrosine kinase phosphorylation and fusion proteins as drivers in non small cell lung cancer (NSCLC) were initially identified in 2007 [2].
- *ROS1* translocations are seen in 1%–2% of NSCLC patients and occur via a gene translocation between *ROS1* and other genes [3,4]
- Histologic and clinical features that are associated with *ROS1* translocations include adenocarcinoma histology, younger age, and never smokers, a profile similar to ALK positive cases [1,5]
- Crizotinib, a small molecule oral tyrosine kinase inhibitor (TKI) for ALK positive metastatic NSCLC (mNSCLC) patients, has activity against ROS1 due to a high degree of homology between ROS and ALK tyrosine kinase domains.
- There is limited data for *ROS1* transclocated mNSCLC from India.

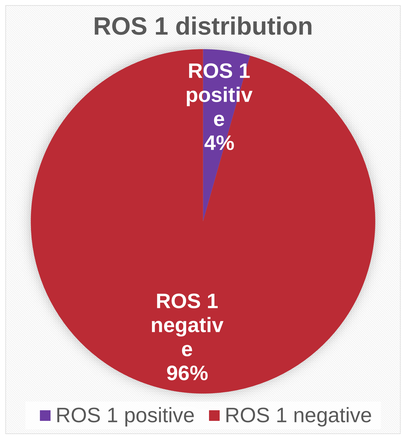
MATERIALS & METHODS

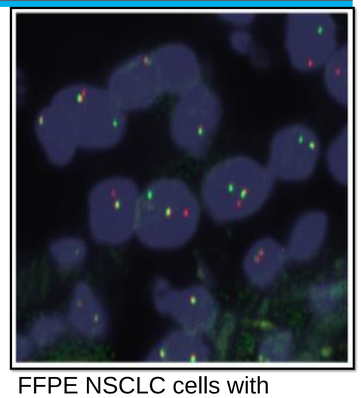
- In this retrospective study, we analyzed 409 samples of mNSCLC for *ROS1* rearrangements using the fluorescent in situ hybridisation assay (FISH) based test.
- ZytoLight SPEC *ROS1* Dual Color Break Apart FISH Probe (ZytoVision, Germany) was used according to the manufacturer's protocol and instructions
- Clinicopathologic and demographic characteristics of the *ROS 1* rearranged tumors were analysed.
- Institutional ethical committee approval was taken for this study.

RESULTS

- A total of 409 cases of mNSCLC (stage IV) were included.
- Eighteen patients (4.4%) were ROS1 positive by FISH of which there were 11 females (61%) and 7 males (39%).The age ranged between 28 years to 65 years.
- Nine patients were non smokers (50%) , 2 were smokers and the history of smoking was unknown in 7 patients.
- All patients had adenocarcinoma histology (solid 6 , acinar 2 , solid and acinar 3 , solid with micropapillary 1 , solid with macro nuclear 5 , mucinous 1)
- Fifteen patients received crizotinib ; all of which were in the first line .Four patients received crizotinib as their initial treatment and 11 patients received crizotinib as switch maintenance after 4 to 6 cycles of chemotherapy.
- None of the patients had complete response (CR) , 10 patients had a partial response (PR) to therapy , 4 had stable disease (SD) and 1 had progressive disease.
- The overall response rate (CR+PR) was 10/15 = 66.6% and the disease control rate (CR+PR+SD) was 93.3%.
- The duration of response (range) was 1 to 19 months.
- Overall crizotinib was well tolerated.

FIGURES





FFPE NSCLC cells with ROS1 gene rearrangement (FISH, 60x)

DISCUSSIONS

- Previous studies have shown *ROS 1 t*ranslocation to be present in 1% - 2% of mNSCLC [3,4]; however in our study the prevalence of *ROS 1* translocation was 4%.This could be due to a selection bias or could represent a higher prevalence in the Indian population. This needs to be validated in other studies.
- In our study 50% of the patients with *ROS 1* translocation were non smokers , 61% were females and all patients had adenocarcinoma histology; a clinical profile similar to patients with mNSCLC with driver mutations due to *EGFR* or *ALK* and *ROS1* translocation.[1,5]
- Crizotinib has demonstrated response rates upto 72% in mNSCLC with *ROS 1* translocation; which is similar to the response seen in our study (67%).
- Chemotherapy has low response in mNSCLC with driver mutations and hence targeted therapy is preferred.

CONCLUSION

- ROS 1 translocation is seen in 4% of mNSCLC .
- The patients are predominantly non smoker , females and have adenocarcinoma.
- Crizotinib has 70% response in mNSCLC with ROS 1 translocation and is well tolerated in this population.

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