Editorial

Driver Mutations in Lung Cancer—Mapping the Way Forward

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In the latest issue of *South Asian Journal of Cancer* (*SAJC*), two articles by Khaddar et al[1] and Sharma et al[2] address the clinical and pathological aspects of rare driver mutations in nonsmall cell lung cancer (NSCLC). The first article assessed the prognostic impact of baseline liver metastasis in anaplastic lymphoma kinase (ALK)-positive metastatic NSCLC.[1] The study conducted at Tata Memorial Hospital, Mumbai, was a retrospective analysis of prospectively collected data. Lung cancer is the leading cause of cancer-related deaths the world over (18.4%) with NSCLC being the most common subtype (85%).[3] As per Indian data, liver metastasis is seen in 2 to 3% of patients of lung cancer at baseline.[4] Various Indian studies have shown that ALK positivity in NSCLC ranges from 3 to 7.6%[5] and that the incidence of liver metastasis in these patients can be as high as 24%.[6] When compared to the driver mutation negative patients, those with ALK gene rearrangements and epidermal growth factor receptor (EGFR) mutations were more likely to develop liver metastases.[7] So, the current article tries to address a common issue in an uncommon subgroup of NSCLC.

The presence of liver metastasis in lung cancer is considered a poor prognostic factor for survival. As per a Surveillance, Epidemiology, and End Results Program analysis, overall median survival time for patients with single site metastases in bone or brain for adenocarcinoma was 5 to 7 months, compared to 3 months for patients with solitary liver involvement. Similarly, for patients with multiple metastasis, survival was 4 versus 3 months in those without liver metastasis compared to those with liver metastasis. The authors concluded by stating that the presence of liver metastasis was found to be the worst prognostic factor in patients with lung cancer.[8] However, survival in specific subgroups of driver mutations was not looked for. This is important, as the outcomes of patients with ALK rearrangements are superior to patients without driver mutations.

Another study by Chang et al studied the impact of de novo liver metastasis on clinical outcomes of patients with NSCLC. Patients with liver metastasis, who also had poorer performance status and lymphocyte-to-monocyte ratio less than or equal to 3.1, had the worst outcomes. The authors also analyzed outcomes based on EGFR status. In patients with EGFR-mutant NSCLC, those with liver metastasis had worse progression-free survival (PFS) and overall survival (OS) than those without (PFS: 5.9 vs. 10.6 months, $p < 0.001$; OS: 11.9 vs. 20.2 months, $p < 0.001$).[9] This study showed that the presence of liver metastasis conferred a poorer prognosis in the EGFR subpopulation. Would similar results be seen with ALK driver mutations? The authors of the current study[1] should be commended on trying to answer this difficult question, especially as ALK rearrangements are much more infrequent than EGFR mutations. They reported no statistically significant differences in PFS or OS in the cohort of patients with liver metastasis compared to patients without liver metastasis. Another important point to note was that usage of an ALK inhibitor was associated with better outcomes when compared to chemotherapy alone. So, in clinical practice, the presence of liver metastases in ALK-positive lung cancer patients does not justify the use of chemotherapy and ALK inhibitors remain the most effective first-line option. The nonusage/ availability of newer ALK inhibitors is definitely a limitation, as they have been shown to be more effective that crizotininb,[10] but that is largely with regard to central nervous system metastasis. Another limitation in the study might have been the usage of only immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) for the detection of ALK rearrangements. A study by Nong et al[11] looked at the comparative efficacy of next-generation sequencing (NGS) and IHC, and reported that NGS could detect more ALK fusion samples than IHC staining (sensitivity of 83.33 vs. 33.33%). NGS also exhibits greater sensitivity in identifying ALK rearrangements than FISH.[12] Thus, employing a comprehensive/ hotspot NGS panels may help identify more patients with ALK rearrangements that could benefit from targeted therapy.

One of the issues faced in patients with liver metastasis is the presence of baseline transaminitis that may make administration of tyrosine kinase inhibitors (TKIs) difficult. Additional information regarding baseline liver functions, starting dose of crizotinib used in such patients, and whether there was a worsening of liver function in such cases would have been beneficial in guiding real-world practice. Also, the article does not report the baseline characteristics of the comparator cohort (362 patients), without liver metastases, that may have provided the readers with a better understanding of the burden of disease. Overall, the study reinforces the fact that all patients, irrespective of liver metastasis

should receive ALK inhibitors upfront, and can expect a near similar outcome to nonliver metastasis patients.

The second article by Sharma et al[2] studied the utility of IHC as a screening tool for ROS1 translocation/ rearrangements. ROS1 prevalence in India is around 2.8 to 4.1%,[13] which is higher when compared to the western population.[13,14] The study suggests that IHC may be a good screening tool for ROS1, as the test had high sensitivity. All positive cases, however, will have to undergo a confirmatory FISH, before labelling them as ROS1 positive. A limitation mentioned was a lower specificity when compared to other international studies (63.6 vs. 72.6–96.67%) that may have been due to differences in the clone used for IHC and variation in the study population. In a resource-poor setting, this screening methodology certainly has merit, especially in centers not equipped for FISH. The times, however, are changing.

Twenty years ago, the College of American Pathologists/ International Association for the Study of Lung Cancer/ Association of Molecular Pathology issued molecular testing guidelines that recommended testing only for EGFR mutations using polymerase chain reaction and ALK fusions using FISH.[15] Fast forward to 2022 and the current molecular landscape of NSCLC is undergoing rapid progress with multiple targetable mutations being identified. EGFR, KRAS, HER2, BRAF mutations, ALK, RET, ROS1, NTRK fusions, and MET exon 14 skipping mutations all have Food and Drug Administration-approved TKIs/monoclonal antibodies. More than half of the advanced lung cancers diagnosed today can harbor a targetable driver mutation. Newer predictive genomic and proteomic biomarkers are also under investigation that may further impact management of these cancers.[16] Thus, it is of paramount importance to test for all these molecular alterations using a technique that can provide maximum information. The most structured and efficient way to test for these mutations is with a comprehensive NGS panel, rather than other methods requiring larger tissue samples and perhaps further biopsies.[17]

The issue with using IHC or FISH only, in the near future, would be the lack of adequate tissue for conducting all the required tests, especially when there are over 10 targets to test for. With multiplex NGS, which is becoming more accessible and economical even in low- and middle-incomes countries,[18] we may be able to offer all our patients the best possible treatment strategies with minimal tissue. The use of liquid biopsies, that look for tumor cells/DNA in the blood, may also lead to omission of traumatic invasive procedures required to collect tissue for analysis.[19] Current international guidelines also recommend broad-panel NGS be used for the detection of molecular alterations, whenever feasible.[20] When NGS is unavailable or costly, ROS1 can instead be tested using IHC as a screening modality and confirmed by FISH if positive.

Conflict of Interest
None declared.

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