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Editorial - T790M Mutation and Clinical Outcomes with Genuine Osimertinib

The tyrosine kinase inhibitor (TKI) revolution, in the management of lung cancer, is now more than 10 years old.[1] The insight that molecular testing and identification of driver mutations is key to the selection of the right treatment is also well established and led to the era of precision medicine and personalized therapy. It also led to the recognition that there were significant geographic and ethnic variations in the incidence of epidermal growth factor receptor (EGFR) mutations.[2] Suddenly, our patients with lung cancer had a bouquet of options that would give them longer survival and better quality of life.[3] Accumulation of cumulative data and improvement in laboratory techniques refined our understanding and threw up new questions.[4] We also noted the experience with imatinib and chronic myeloid leukemia being replicated in lung cancer as well.[5] Patients who responded well to initial treatment of gefitinib invariably develop progressive disease.[6]

The specific mutation T790M was quickly recognized as the main reason for progression in patients with lung cancers who had presented with EGFR mutation and were treated with oral first-generation TKIs.[6] Availability of second- and third-generation TKIs rekindled hope.[7] Both afatinib and osimertinib quickly gained a prominent place in the management of EGFR-mutated lung cancer. The AURA3 trial showed that in T790M mutation-positive advanced lung cancer, osimertinib provided median progression-free survival (PFS) of 10.1 months as compared to 4.4 months with platinum-pemetrexed combination chemotherapy.[6] The first Indian report of 13 patients showed good symptom control as well as an overall response rate of 55% (6/11 evaluable patients).[8] This was comparable to the objective response rate to osimertinib of 71% in AURA3.[6]

This issue of IJMPO presents prospective observational data on 90 patients who had progressive disease while on EGFR TKI.[9] They were evaluated by molecular testing on rebiopsy or ctDNA for T790M mutations, which were detected in 52.2% (47/90 patients). T790M mutation was identified on repeat tissue biopsy in 82.9% (39/47) and with CTDNA in 17% (8/47). For the whole group, at progression, biopsy was feasible in 77/90 (85%) patients.[10] Interestingly, the incidence of T790M mutation was similar in tissue (50.6%) and liquid biopsy (52.9%), giving the reassurance that liquid biopsy is robust enough to be relied upon for clinical decisions.

Among the T790M-mutated patients with progressive disease, 46 could be commenced on osimertinib. At 15-month follow-up, the overall response rate and median PFS were 65.21% and 12.45 months, respectively. The median overall survival was not reached (67.3%; 33/46 patients being alive in the osimertinib cohort). There was also no therapy discontinuation related to adverse effects. This is encouraging news for our patients with lung cancer. Several years of survival with good quality of life is possible by judicious sequencing of therapy. Surrogate markers to fine tune the decision-making process further will be beneficial. The authors have identified that PFS was significantly better with second-line osimertinib if patients had achieved a complete response to first-line oral TKI therapy.

However, there are certain unscrupulous businesses and people, who are fooling lung cancer patients in India with the promise of cheap TKIs - at a fraction of the cost of the original genuine medicine.[11] We have previously described how our patients are becoming victims of fake, illegal "generic medicines" made available in the grey market without bill, without approval by the Drug Controller General of India, without any testing in the laboratory or humans, from across our borders and without even the permission to market or sell in their own country. This is a scam allegedly of value of 500 crore rupees every month! Our patients' lives are being put at risk by being sold attractively packaged smart looking plastic containers with seemingly authentic labels whose contents have not been tested by any regulatory authority anywhere in the world. Unless our lung cancer patients are alert, they will continue to deteriorate while consuming material that at best is placebo and could potentially contain chemicals or impurities that could put their lives at immediate risk. Under the circumstances, how can we provide them with the benefit of genuine medicines and the improved response, survival, and quality of life that have been proven with the use of genuine official TKIs?

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