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Editorial

Lung cancer: Prevalent trends & emerging concepts

Lung cancer is one of the commonest cancers and cause of cancer related deaths all over the world. It accounts for 13 per cent of all new cancer cases and 19 per cent of cancer related deaths worldwide. There were 1.8 million new lung cancer cases estimated to occur in 2012[1]. In India, lung cancer constitutes 6.9 per cent of all new cancer cases and 9.3 per cent of all cancer related deaths in both sexes, it is the commonest cancer and cause of cancer related mortality in men, with the highest reported incidences from Mizoram in both males and females (Age adjusted rate 28.3 and 28.7 per 100,000 population in males and females, respectively)[2]. The time trends of lung cancer show a significant rise in Delhi, Chennai and Bengaluru in both sexes. The incidence and pattern of lung cancer differ as per geographic region and ethnicity and largely reflect the prevalence and pattern of smoking. The overall 5-year survival rate of lung cancer is dismal with approximately 15 per cent in developed countries and 5 per cent in developing countries[3]. Screening by low dose computed tomography (CT) in high risk population demonstrated a relative risk reduction of 20 per cent in lung cancer mortality but with a false positive rate of 96 per cent[4]. In India where tuberculosis is prevalent, the applicability of such screening tool is questionable. Development of newer non invasive methods/ biomarkers for early diagnosis and screening of high risk population is warranted.

Over the years, our understanding of disease biology has evolved. The histological classification is now stretching to molecular classification. Newer molecular targets and driver mutations have been identified which play a major role in pathogenesis that can be addressed with therapeutic interventions[5]. These advancements have led to the development of more individualized treatment modalities, the so called era of "personalized medicine". There has been a new interest in the histological characterization of lung cancer in view of newer histology guided therapeutic modalities and genomic classification[6,7]. The use of generic terms non small cell and small cell lung cancer (NSCLC and SCLC), is being challenged[8]. In the Western countries and most of the Asian countries[9,10] adenocarcinoma has surpassed squamous cell carcinoma[9,10]. This shift might be attributable partly to the smoking habits, particularly filtered cigarettes; moreover, there is also increasing incidence of lung cancer in females and non smokers[9,11,12]. Most of the previous Indian studies have described squamous cell carcinoma as the commonest histology[13,14] however, some recent studies from two major centres are showing a changing pattern in India[15,16]. We have reported that adenocarcinoma has become the commonest subtype provided a careful pathology review is done[16]. The use of appropriate immunohistochemistry improves the histological sub-typing and should be used more often.

At present more than 50 per cent of lung adenocarcinomas and about a third of squamous cell carcinomas can be characterized based on the mutation profile[17]. This molecular classification has led to development of targeted therapeutic strategies. Mutations in epidermal growth factor receptors (EGFR) best illustrate the therapeutic importance of molecular classification. *EGFR* mutations strongly predict the efficacy of inhibitors of EGFR with response rates higher than 70 per cent seen in many studies[18]. Two prospective, randomized, phase 3 studies of patients with untreated metastatic NSCLC (Iressa Pan-Asia Study and WJTOG3405) have found that first-line gefitinib leads to longer progression-free survival (PFS) in patients with tumours positive for *EGFR* mutations than does platinum based doublet chemotherapy[18,19]. Similarly erlotinib has also shown better response rates and PFS as compared to chemotherapy for first

line treatment in EGFR mutation positive advanced NSCLC[20,21].

Genomic expression, mutational and proteomic profiling studies, as well as various mouse lung tumour models have led to the identification of additional molecular driver mutations[22,23]. Another such example of mutation driven therapy is targeting *EML4-ALK* (echinoderm microtubule-associated protein like 4-anaplastic lymphoma kinase) rearrangement. Biologically, EML4-ALK fusions result in protein oligomerisation and constitutive activation of the kinase[24]. The frequency of EML4-ALK translocation ranges from 3 to 7 per cent in unselected NSCLC[24]. Detection methods include reverse-transcriptase PCR, fluorescence *in-situ* hybridization, and immunohistochemistry. EML4-ALK translocations are generally found in tumours with wild type EGFR and KRAS[25]. Tyrosine kinase inhibitor targeting ALK, crizotinib has shown a response rate of 65 per cent in previously treated patients of NSCLC that harbour ALK rearrangement and has been approved for this indication[26,27]. Another ALK inhibitor certinib has also been recently approved based on its encouraging response rates of 56 per cent in patients who have progressed on crizotinib[28].

The prevalence of specific mutation varies among various ethnic and geographic populations. For example, the prevalence of *EGFR* mutation is around 10 per cent in Caucasians while it has been reported to be as high as 60 per cent in Asians[29,30]. In India the frequency of *EGFR* mutations has been found to be between 25-50 per cent in various studies[31-34].

With these advances, the validation of targeted therapeutic compounds should ideally parallel with the development of predictive biomarkers[35]. In this context, the availability of high quality molecular testing is pivotal and should be integrated into treatment guidelines. The accessibility of such testing to majority of our population is largely limited due to the high cost. Lack of quality control and uniformity of techniques and standards among various laboratories are also issues of concern. Bulk use of these new techniques are likely to reduce the cost of these tests. Adequacy of tumour tissue for molecular profiling is an important issue and even more relevant in lung cancer where the tissue yield is limited by small core biopsies. Judicious use of immunohistochemistry and conservation of samples for molecular testing would be helpful. Cell free circulating tumour DNA is also emerging as a useful tool in these situations and can be used for mutation testing and therapeutic monitoring[36]. The genetic heterogeneity among various ethnic populations has brought to the stage the issue of molecular characterizations in lung cancer and the need for regional studies.

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