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Original Research Article

An analysis of studies on non-small cell lung cancer registered on clinical trials registry of India

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ABSTRACT

Background: Lung cancer is the most common cancer in males, of which non-small cell type is more prevalent. It is an active area of research owing to the limited available treatment modalities with several studies registered on CTRI. Objectives of current study was to analyse randomized control trials for non-small cell lung cancer registered on clinical trial registry India.
Methods: Studies registered on CTRI were reviewed in this registry-based audit using the keywords lung cancer and non-small cell lung cancer. Parameters such as type of study, nature of intervention, phase of study, primary and secondary endpoints used, etc, were analysed and summarised using descriptive statistics in Microsoft Excel 365.
Results: Out of 230 trials for lung cancer, 121 studied non-small cell lung cancer, of which 103 studies (85.1%) were interventional studies. Most common intervention under study was drug 97 studies (94.2%) followed by radiation 4 studies (3.3%). Majority of trials were phase 3, 48 trials (39.7%) and only 4 (3.3%) studies were phase 1. Five most common primary and secondary endpoints observed were survival, response rate, safety, pharmacokinetic data & quality of life. Maximum patients were in the advanced stage of cancer(52.1%) and pemetrexed (9.9%) was the most common drug used.
Conclusions: We observed an increasing trend in studies registered on CTRI, with maximum studies in phase 3 with patients in the advanced stage of cancer having overall survival as the endpoint.

Keywords: Lung carcinoma, Trial registry, EGFR mutation, Pemetrexed, Radiation therapy

INTRODUCTION

Lung cancer remains to be the leading cause of cancer related deaths worldwide with estimated 1.8 million deaths, and the second most diagnosed cancer, after breast cancer, according to Globocon 2020 estimates of cancer.[1] In India however, Lung cancer ranks as the fourth most common cancer overall, and the second most common in males for incidence and death rates both.[2] As such, lung cancer is broadly divided into small-cell and non-small cell types. Small cell lung cancer is a fast-growing tumour usually associated with a history of smoking. Non-small cell lung cancer (NSCLC) is an umbrella term for squamous cell carcinoma, adenocarcinoma, large cell carcinoma and other poorly differentiated variants now grouped as NSCLC-NOS (not otherwise specified) of which, squamous cell carcinoma is tobacco-dependent and the rest are grouped as non-squamous cell carcinoma, that are usually tobacco-independent.[3] The incidence of tobacco related cancers comes to 27.1% of all cancers, and rightly so, since 76% of those developing lung cancer are smokers.[4,5] Since, smoking leads to small cell and squamous cell types,

these were the most common lung cancers encountered up until the last decade or so. But this past decade has seen a shift in the incidence from tobacco dependent lung cancer to tobacco-independent lung cancers, making adenocarcinoma the dominant histologic type.[6] This shift could be a result of the decrease in prevalence of tobacco use by about 81 lakhs from global adult tobacco survey-1 (2009-10) to global adult tobacco survey-2 (2016-17) in India, and improvements in histologic typing subtype analysis for molecular mutations such as epidermal growth factor receptor (EGFR), BRAF, MET, ERBB2, & fusion markers such as anaplastic lymphoma kinase (ALK), ROS-1, RET, NTRK rearrangements.[7] The rising number of accredited facilities for gene sequencing have considerably made the testing faster, cheaper, and more frequent leading to an increasing need for newer modalities that provide specific treatment. ICMR has also launched a national DHR-ICMR advanced molecular oncology diagnostic services project to provide for free of cost biomarker testing of lung cancer throughout India.[6] All these factors have led to an increase in the randomised control trials being conducted for non-small cell lung cancer. Hence, we aimed to analyse those registered on clinical trial registry of India.

METHODS

The Clinical trials registry India is a publicly available database established and maintained by the National institute of medical statistics of the Indian council of medical research (ICMR) since July 2007, where registration of any new clinical trial is mandatory. The trial must be registered before patients are recruited. We conducted a registry-based audit to analyse studies focusing on non-small cell lung cancer conducted from February 2008 to May 2022. We extracted 230 lung cancer trials from this website database using the keyword - lung cancer and non-small cell lung cancer, of which 121 studies were on non-small cell lung cancer. These 121 trials were manually screened and analysed for parameters such as frequency of studies per year, type of study, nature of the intervention, histologic subtype and stage of cancer, phase of the study, study design, randomization and blinding, sample size, primary and secondary endpoints used. The data was analysed by descriptive statistics using Microsoft Excel version MS Office 365.

RESULTS

An average of 8 studies were conducted per year, with a sharp fall in the year 2015 with only 2 studies, following a steady rise with a peak of 17 studies in 2020, details of which are given in (Figure 1). Of 121 studies, 103 were interventional in nature with drug being the most common intervention 97 (94.2%), other interventions were radiation 4 (3.3%) and vaccine 2 (1.7%), as seen in (Figure 2). The 2 vaccines were Stimuvax and allogenic B7.1/HLA-A1 transfected NSCLC tumor cell vaccine. Observational studies comprised 14 studies, with 2 studies on bioequivalence, one study comparing 2 brands of pemetrexed - Pemgem vs Alimta, the other study comparing lyophilised docetaxel powder to Txotere R-doxetaxel injection. And 2 questionnaire-based studies, one study assessing quality of life in only chemotherapy versus chemotherapy with oral-Tyrosine Kinase Inhibitor arms and other study assessing ADRs and SAEs with the use of drug nintedanib.

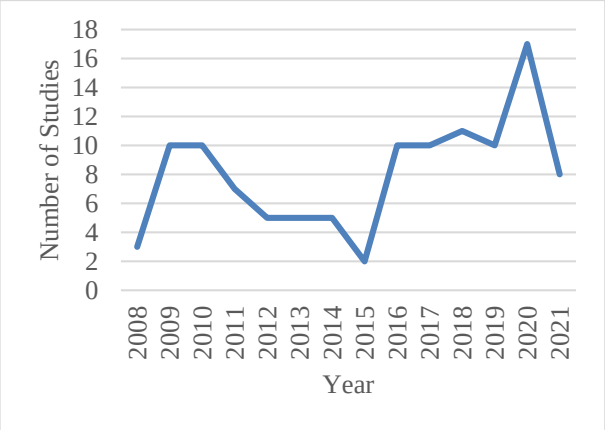

Figure 1: Year wise distribution of number of studies.

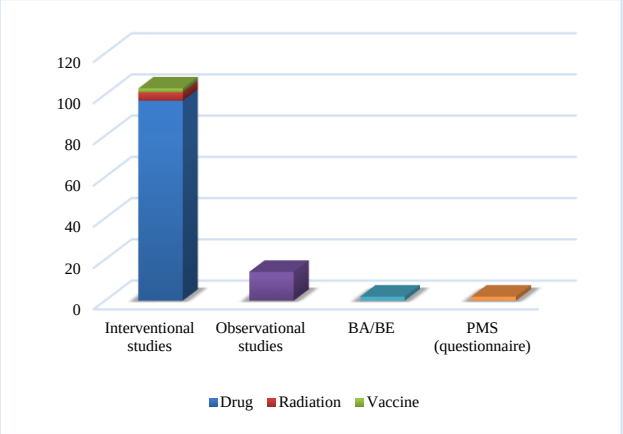

Figure 2: Type of trial with intervention.

The most common drug used was pemetrexed, in 9.9% trials and the most common combination used was paclitaxel + carboplatin in 8.3% studies. Other drugs used were bevacizumab in 8.3%, docetaxel in 6.6%, and the least common drugs used were sorafenib, ramucirumab and afatinib, among others. The population chosen included advanced stage in 63 (52.1%) studies, all stages in 15 (12.4%) studies, metastasis in 14 (11.6%) studies, recurrent disease and stage 3 in 9 studies (7.4%) each, stage less than 3 in 8 (6.6%) studies, others in 3 (2.5%) studies, as in (Table 1). The histologic subtype of non-small cell lung cancer studied included- both squamous and non-squamous types in 46 studies, only non-squamous types (adenocarcinoma, large cell, NSCLC-NOS) in 29 studies, mutations in 33 studies including molecular markers in 20 studies, fusion markers in 7 studies and both in 6 studies, NSCLC with other cancers

in 11 studies and only squamous type in 2 studies, as in (Figure 3).

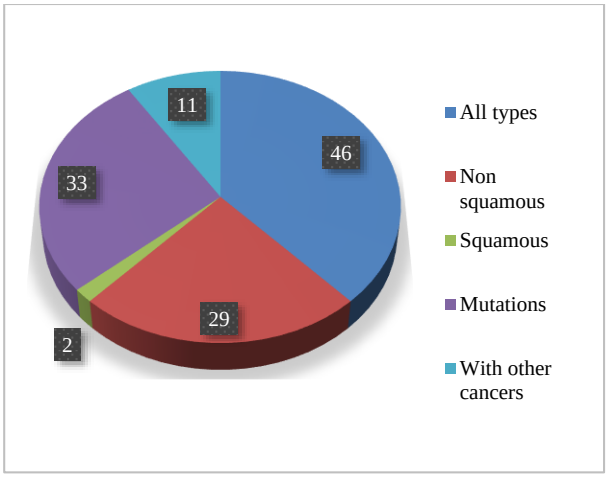

Figure 3: Type of non-small cell lung cancer.

Maximum trials were in Phase 3, 48 studies (39.7%), 26 studies were in phase 2 (21.5%), 17 studies were in phase 4 (14%), 6 studies were in phase 2 or 3 (5%), and only 4 studies were in phase 1 (3.3%). Phase of trial was not applicable to 20 studies (16.5%). The most common study design was parallel arm in 79 (65.3%) studies, single arm in 23 (19%) studies, and other designs in 19 (15.7%) studies.

Table 1: Stage of non-small cell lung cancer.

Stage of cancer	Number of studies
Advanced stage	63
All stages	15
Stage 4	14
Stage 3	9
Stages less than 3	8
Recurrent cancer	11
Total	121

Table 2: Primary and secondary endpoints

Endpoint	Number of trials as primary endpoint	Number of trials as secondary endpoint	Total
Survival	57	90	147
Response rate	19	42	61
Safety	8	38	46
Pharmacokinetic data	12	28	40
Quality of life	8	28	36

Randomisation was done in 85 studies (70.3%), with 46 (54.1%) studies using simple randomisation by computer generated numbers, stratified block randomisation in 30 (35.3%) studies, permuted block randomisation in 2 studies (2.4%), random number table in 1 (1.2%) study and other methods in 6 studies. (7%). From the 85 randomised studies, 41 (48.2%) were open label, and 44 (51.8%) underwent blinding maximum studies used double blinding 36 (81.8%), 6 studies (13.6%) used triple blinding and 2 studies (4.6%) used single blinding. The minimum sample size observed was 10 and maximum was 2600. The mean sample size was 372.8 and median was 220.5. The data had bimodal peaks, at 100 and 300, as seen in 7 studies each. Multiple intervention arms were observed in 84 studies, single intervention arm in 27 studies and intervention arm was not applicable in 10 studies. Multicentric studies were 91, and single centre studies were 30. Clearance was obtained from DCGI in 87 studies, and it was not needed in 34 studies. Multiple primary and secondary endpoints were seen in each study. The five most common endpoints seen were survival, response rate, safety, pharmacokinetic data & quality of life. Survival was the primary endpoint in 57 studies and secondary endpoint in 90 studies. Response rate was the primary endpoint in 19 studies and the secondary endpoint in 42 studies. Safety was the primary endpoint in 8 studies and secondary endpoint in 38 studies. Pharmacokinetic data such as % drug absorbed, bioavailability, half-life of drug, clearance, etc was the primary endpoint in 12 studies and secondary endpoint in 28 studies. Quality of life was the primary endpoint in 8 studies and secondary endpoint in 28 studies, refer to (Table 2).

DISCUSSION

Adenocarcinoma is the most common histologic subtype of lung cancer in most countries, accounting for almost half of all lung cancers, usually seen in never-smokers and associated with EGFR mutations.[8-10] In our study, we found 46 studies included all histologic types, 29 studies included non-squamous types- adenocarcinoma, large cell carcinoma and NSCLS-NOS of which only 4 exclusively studied adenocarcinoma. Studies on EGFR mutation in NSCLC started to rise after 2017, owing to increased awareness by global adults tobacco survey-2 (2016-17), and establishment of DHR-ICMR advanced molecular oncology diagnostic services (DIAMOnDS) in 2019.[7-11] In accordance to this, in our study, we observed total 19 studies on EGFR, with a maximum of 4 studies in the year 2018 and 2020, and the least of 1 study in 2014, 2015, 2016 and 2021. There were no studies observed in the years before 2014. A global systemic review of EGFR mutation in non-small cell lung cancer of adenocarcinoma histology by Midha et al conducted a Medline database search to identify journal articles reporting studies of *EGFR* mutation frequency/incidence in patients with NSCLC/ADC on February 18, 2014. Only 3 studies were found in India that satisfied the inclusion criteria.[10] This highlights the lack of trials conducted in India before the year 2014-15 on non-small cell lung cancer, as consistent with our finding of least number of studies conducted in 2015. As per a study conducted by Yoon et al majority of newly diagnosed

lung cancers are NSCLC, half of which are locally advanced and inoperable at time of diagnosis.[12] Distant metastasis was the commonest presentation followed by locoregional spread, as observed in the report of National cancer registry programme by ICMR and NCDIR in 2020.[13] In our study, the most common stage of cancer was advanced stage (that includes locally advanced stage and metastasis) seen in 52.1% of studies. Treatment options for patients that present early with resectable disease include surgery followed by chemotherapy, with or without radiation therapy for control of local spread. Patients with locally advanced unresectable disease may achieve long-term survival with chemotherapy combined with radiation therapy, most patients present at this stage of disease. Patients with advanced metastatic disease may achieve improved survival and palliation of symptoms with chemotherapy, targeted agents, and other supportive measures.[14] In clinical practice, pemetrexed maintenance therapy often follows first-line treatment with platinum-based chemotherapy in patients with non-squamous-cell NSCLC.[15] In accordance to this, in our study, the most common drug for chemotherapy used was pemetrexed, in 9.9% trials and the most common combination used was paclitaxel+carboplatin in 8.3% trials. We observed the use of radiation therapy in only 6 trials, and the methods used were local ablation technique in two studies, hypofractionated radiation, radiation with oral tyrosine kinase inhibitors, fractionated stereotactic radiotherapy, radiotherapy with oral resveratrol copper. A systemic review and meta-analysis by Cao et al observed that stereotactic body radiation therapy is the preferred treatment modality for patients with inoperable early-stage non–small cell lung cancer, but surgery is superior to stereotactic body radiation therapy in terms of mid- and long-term clinical outcomes.[16] Most of the trials using radiation in our study had patients with brain metastasis, and the maximum studies were conducted with patients in advanced stage: these factors could account for the sparse use of radiation in the lung cancer trials we analysed. The most common endpoint, also regarded as 'gold standard' primary clinical endpoint in cancer studies is overall survival.[17,18] Our study also shows survival as the most common endpoint, seen as the primary objective in 57 studies and secondary objective in 90 studies where survival includes overall survival, progression free survival and disease-free survival, in decreasing order of their frequencies. Majority of the studies observed are randomised control trials in phase 3 with a large patient population, all of which increase the quality of the study. Significance of having abundant multicentric trials is that they diversify the population under study.

CONCLUSION

A lot of lacunae surround the treatment of non-small cell lung cancer due to the discovery of newer molecular targets, the unpredictable response of the tumour to older medications because of variations in ethnicity form the tip of the iceberg. Targeted therapies, intensity-modulated radiotherapy and proton therapy are newly emerging promising treatment modalities that need further research. The treatment approaches for NSCLC are large and constantly evolving. Thus, the need for more trials and newer molecules in this area is ever increasing, especially in the Indian subcontinent.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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