Editorial

Liquid biopsy for T790M mutation detection: A ray of hope?

Anant Mohan, Saurabh Mittal

Original Articles

A comparison of three strategies for withdrawal of noninvasive ventilation in chronic obstructive pulmonary disease with acute respiratory failure: Randomized trial

Kavitha Verkaivarayan, Gopi C Khinani, Vijay Hadda, Karan Madan, Anant Mohan, Ravindra M Pandey, Randeep Gulata

Clinical profile and course of children with postinfectious bronchiolitis obliterans from a tertiary care hospital

Krishna Mohan Gulla, Kana Ram Jat, Raakesh Lodha, Sushil K Kabra

T790M mutations identified by circulating tumor DNA test in lung adenocarcinoma patients who progressed on first-line epidermal growth factor receptor-tyrosine kinase inhibitors

Vinothi Menjila, Gatoool Soegiaro, Laksmi Wutandari

Predictors of mortality in acute exacerbations of chronic obstructive pulmonary disease using the dyspnea, eosinopenia, consolidation, acidemia and atrial fibrillation score

Avya Gopal Bansal, Gajanan S Gaude

Comparison of tuberculin skin test and QuantiFERON-TB Gold In-Tube test in Bacillus Calmette–Guerin-vaccinated children

Ira Shah, Jagdish Kathwala, Naman S Shelty

Regression equations of respiratory impedance of Indian adults measured by forced oscillation technique

Sajal De, Nilok Banerjee, Gagan Deep Singh Kushwah, Dhamendra Dharwary

And More...

ISSN : 0970-2113

Medknow
Editorial Board

Editor-In-Chief
Dr. Parvaiz Koul
Professor and Head
Pulmonary and Internal Medicine, Infectious Diseases/Geriatrics
SheriKashmir Institute of Medical Sciences,
Soura, Srinagar, J&K-190011,
INDIA

Deputy Editor
Dr. Bharat Bhushan Sharma

Associate Editors
Dr. Prashant Chhajed
Dr. Ritesh Agarwal
Dr. Sundeep Salvi

Assistant Editor
Dr. Sheetu Singh
Dr. Karan Madan

Editorial Board Members

International
Dr. Sonia Buist, USA
Dr. Surya Bhatt, USA
Dr. Jerry A. Krishnan, USA
Dr. R. Dhand, USA
Dr. S. Kalra, USA
Dr. D. Honeybourne, UK
Dr. P. Nair, Canada
Dr. B. Jonson, Sweden
Dr. R. Pawankar, Japan
Dr. M. Azizur Rahman, Bangladesh

National
Dr. Virendra Singh
Dr. A. A. Mahashur
Dr. D. Genguly
Dr. S. K. Jindal
Dr. S. K. Luhadia
Dr. R. Prasad
Dr. S. C. Matal
Dr. Rajesh Swarnakar
Dr. A. K. Janmeja
Dr. T. Mohan Kumar
Dr. V. Thanasekaraan
Dr. Surya Kant
Dr. Satil Bhargava
Dr. K. B. Gupta
Dr. Rajeev Gupta
Dr. R. Chowgule
Dr. J. C. Suri
Dr. N. K. Jain
Dr. J. M. Joshi
Dr. G N Srivastava

Section Editors

Alveolar diseases
Dr. C. Ravindran
Dr. M. Sabir

Critical care
Dr. G. C. Khilnani
Dr. Mradul K. Daga

Infectious diseases
Dr. A. G. Ghoshal
Dr. Ashok Shah

Lung cancer
Dr. D. Behera
Dr. Prasanta Mohapatra

Obstructive airway diseases
Dr. J. K. Samaria
Dr. Raja Dhar

Research methods
Dr. D.K. Mangal
Dr. Mohan Bainwa
Pictorial quiz
Dr. Alladi Mohan
Dr. R. Narasimhan

Pleural diseases
Dr. P. Baruwa
Dr. Arun Madan
Dr. Dharmesh Patel

Pulmonary circulation
Dr. P. Bhattacharyya
Dr. S. K. Chhabra

Sleep medicine
Dr. R. Gularia
Dr. Dhruv Chaudhary

Tuberculosis
Dr. S. K. Sharma
Dr. S. K. Katiyar

Surgical aspects of pulmonary medicine
Dr. S. K. Sarkar
Dr. Apar Jindal

Interventional Pulmonology
Dr. Nagarjun Maturu
Dr. Rakesh Chawla
Dr. Ramekant Dixit

Institutional affiliations: Editorial board members of Lung India

Editorial Board member  Affiliations
EDITOIR-IN-CHIEF

Dr. Parvaiz Koul  Professor & Head, Department of Internal & Pulmonary Medicine, Registrar, academics, Shar-i-Kashmir Institute of Medical Sciences, Srinagar, India

DEPUTY EDITOR

Dr. Bharat Bhushan Sharma  Professor of Medicine, Head of Allergy & Pulmonary Division, Department of Medicine, SMS Medical College, Jaipur, India

ASSOCIATE EDITORS

Dr. Prashant Chhajed  Fortis Hospitals, Mumbai and Navi Mumbai, Institute of Pulmonology, Medical Research and Development, Mumbai, India

Dr. Ritesh Agarwal  Professor, Dept of Pulmonary Medicine Postgraduate Institute of Medical Education and Research, Chandigarh, India

Dr. Sundeep Salvi  CRF - Chest Research Foundation, Marigold Premises, Behind Gold AD Labs, Kalyani Nagar, Pune, India

ASSISTANT EDITOR

Dr. Sheetu Singh  Assistant professor, Department of Chest & Tuberculosis, Institute of Respiratory Diseases, SMS Medical College, Jaipur, India
EDITORIAL BOARD MEMBERS

International

Dr. Sonia Buist
Professor Emeritus of Medicine, Pulmonary & Critical Care Medicine, Oregon Health & Science University, 3181 SW Sam Jackson Park Rd. MC:UHN67, Portland, OR, USA.
Assistant Professor, Medical Director, Pulmonary Function and Exercise Physiology Lab, Medical Director, Remote Pulmonary Rehabilitation Program Director, UAB Lung Imaging Core231 Kracke Building, Division of Pulmonary, Allergy and Critical Care Medicine, University of Alabama at Birmingham
Pulmonologist in Knoxville, Tennessee University of Tennessee Medical Center, USA.
University of Illinois Hospital, Chicago, National Institutes of Health (NIH), 1801 West Taylor Street, Chicago, IL, USA.

Dr. Surya Bhatt
Rush-Copley Medical Center, Aurora, IL, USA.
Consultant physician at Birmingham Heartlands Hospital, UK.
Professor of Medicine, Division of Respiriology, Adjunct Professor of Medicine, McGill University, Staff Respirologist, Firestone Institute for Respiratory Health, Canada.

Dr. R. Dhand
University Hospital, Lund, Sweden.

Dr. Jerry A. Krishnan

Dr. S. Kalra
Rush-Copley Medical Center, Aurora, IL, USA.

Dr. D. Honeybourne
Consultant physician at Birmingham Heartlands Hospital, UK.
Professor of Medicine, Division of Respiriology, Adjunct Professor of Medicine, McGill University, Staff Respirologist, Firestone Institute for Respiratory Health, Canada.

Dr. P. Nair

Dr. B. Jonson
University Hospital, Lund, Sweden.

Dr. R. Pawankar
Prof. Ruby Pawankar, Prof. Allergy, Dept. of Pediatrics, Nippon Medical School, Tokyo, Japan.

Dr. M. Azizur Rahman
Associate Professor, Respiratory Medicine, Under Faculty of Medicine, Dhaka University, Dhaka, Bangladesh.

National

Dr. Virendra Singh
Specialist in Respiratory Diseases and Director of Asthma Bhawan, Jaipur, Rajasthan, India
Consultant Chest Physician, P.D. Hinduja National Hospital and MRC, II Floor, OPD Building, Veer Savarkar Marg, Mahim (W), Mumbai, India

Dr. A. A. Mahashur
1. G D Hospitals & Diabetic Institute, Kolkata 2. Calcutta Heart Clinic & Hospital - Salt Lake Kolkata, India
Emeritus Professor, Pulmonary Medicine Postgraduate Institute of Med Edu & Res, Chandigarh, India, Medical Director, Jindal Clinics, Chandigarh, India.
Professor and Head, Department of Respiratory Medicine, Geetanjali Medical College and Hospital, Udaipur, Rajasthan, India
King George's Medical University, (Erstwhile Chhatrapati Shahruji Maharaj Medical University), Chowk, Lucknow, Uttar Pradesh, India

Dr. Prasad
Professor of Chest Diseases, Department of TB & Chest Diseases, SSH, IMS BHU.

Dr. S. C. Matal
Director & Chief Consultant Pulmonologist, Department of Respiratory, Critical Care & Sleep Medicine with Interventional Pulmonology, Getwell Hospital & Research Institute, Dhatolli, Nagpur – 440012, Maharashtra, India

Dr. Rajesh Swarnakar
Dr. A. K. Janmeja
Government Medical College & Hospital, Sector- 32, Chandigarh Punjab-Haryana, India
Senior Consultant Pulmonologist & HOD, Sri Ramakrishna Hospital Avarampilayam road, Coimbatore 641046, Tamilnadu, India
Emeritus Professor of Pulmonology, Sri Ramachandra University, Head of Clinical Services, Respiratory (Pulmonary) Medicine, Sri Ramachandra Medical Centre, Porur, Chennai, India
King Georges Medical University, Lucknow, Chowk, Lucknow, Uttar Pradesh, India
Professor & Head of Pulmonary Medicine, M.G.M Medical College, Indore, MP, India
Head, Dept. of Respiratory Medicine, Post Graduate Institute of Medical sciences, Rohtak, Haryana, India
Chairman- Preventive Cardiology, General Medicine & Research Eternal Hospital, 3 A Jagatpura Road, Near Jawahar Circle, Jaipur, India
Head, Lung Care Clinic, Sukh Sagar Building, N S Patkar Marg, Grant Road, Mumbai, Former Professor and Head of Medicine Department, Bombay Hospital Institute of Medical Sciences, Mumbai, India
Consultant, Professor & Head, Dept. of Pulmonary, Critical Care & Sleep Medicine, Vardhman Mahavir Medical College & Safdarjung Hospital, New Delhi, India
Director, Jain Chest Care Center, H. 28-32, Subhash Nagar Shopping Center, Jaipur, India
Professor and Head, Department of Pulmonary Medicine, TN Medical College, BYL Nair Hospital, Mumbai, India
Head and professor, Department of TB & Respiratory Disease, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India, and Deputy Medical Superintendent (MM), SSL Hospital IMS, BHU, Varanasi, Uttar Pradesh, India

SECTION EDITORS

Alveolar diseases
Dr. C. Ravindran
Professor & Head of Pulmonary Medicine and Vice Dean, DM Wayanad Institute of Medical Sciences, Wayanad, Kerala, India
Visiting Prof., Dept. of Medicine, MAMC, Agroha, Rtd.
Prof. and Head, Resp. Div., Dept. of Medicine, S.P. Medical College, Bikaner, Senior Consultant Physician & Pulmonologist, KMRI, Bikaner, Rajasthan, India

Critical care
Dr. G. C. Khilnani
Professor & Head Department of Pulmonary Medicine & Sleep Disorders, All India Institute of Medical Sciences, Ansari Nagar, New Delhi, India
Director Professor of Medicine, And Incharge Medical ICU, Maulana Azad Medical College and attached Lok Nayak and GB Pant hospital, New Delhi, India

Infectious diseases
Medical Director, National Allergy Asthma Bronchitis Institute, 11/3, Dr. Biresh Guha Street, 2nd Floor, IMA House, Park Circus, Kolkata, India

Dr. A. G. Ghoshal

Dr. Ashok Shah

Prof. Ashok Shah, Senior, Consultant. Department of Pulmonology, Max Super Specialty Hospital, Shalimar Bagh, Delhi, India

Lung cancer

Senior Professor & Head, Dept. of Pulmonary Medicine, Postgraduate Institute of Medical Education & Research, Chandigarh, India

Dr. D. Behera

Professor and Head, Dept. of Pulmonary Medicine, All India Institute of Medical Sciences, Bhubaneswar, Odisha, India

Dr. Prasanta Mohapatra

Obstructive airway diseases

Ex-Professor & Head, Department of Chest Diseases, Institute of Medical Sciences, B.H.U., Varanasi, India

Dr. J. K. Samaria

Director, Department of Pulmonology, C K Birla group of Hospitals, Kolkata, India

Dr. Raja Dhar

Research methods

Professor and Dean Research, IIHMR University, Jaipur, 1, Prabhu Dayal Marg, Near Sanganer Air Port, Jaipur-302029, Rajasthan, India

Dr. D.K. Mangal

Affiliation 1: Assistant Professor of Epidemiology, Department of Public Health, IIHMR University, Jaipur, India, Affiliation 2: Associate, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, USA.

Dr. Mohan Bainwa

Pictorial quiz

Professor and Head, Department of Medicine; Chief, Division of Pulmonary, Critical Care and Sleep Medicine, Sri Venkateswara Institute of Medical Sciences, Tirupati 517 507 Andhra Pradesh, India

Dr. Alladi Mohan

Senior Respiratory Physician, Apollo Hospitals, Chennai, India

Dr. R Narashiman

Pleural diseases

Module no. 1, 1st floor, Astha Towers, C K Road, Panbazar, Near Hari Sabha Guwahati, Assam, India

Dr. P. Baruwa

Professor & HOD, Dept. of Pulmonary Medicine, NDMC Medical College, HRH, Civil Lines, New Delhi, India

Dr. Arun Madan

Consultant Respiratory Physician, City Clinic & Bhailal Amin General Hospital, Vadodara, Gujarat, India

Dr. Dhamesh Patel

Pulmonary circulation

Consultant, Institute of Pulmocare and Research, Kolkata. Add: DG8, Action area 1, New Town, Kolkata, India

Dr. P. Bhattacharyya

Head, Dept. of Pulmonary, Sleep & Critical Care Medicine, Primus Super Specialty Hospital, Chanakyapuri, New Delhi, Former Director-Prof. Vallabhbhai Patel Chest Institute, Delhi, India

Dr. S. K. Chhabra

Sleep medicine
Tuberculosis

Adjunct Professor, Dept. of Molecular Medicine, Jamia Hamdard Institute of Molecular Medicine, Hamdard University, Hamdard Nagar, Delhi & Director Research, & Adjunct Professor, Departments of General Medicine & Pulmonary Medicine, JNMC, Datta Meghe Institute of Medical Sciences (DMIMS), Sawangi (M), Wardha (Maharashtra), India
Former Principal & Dean, Professor & Head, Dept. of Tuberculosis & Respiratory Diseases. GSVM Medical College, Kanpur, India

Surgical aspects of pulmonary medicine

C-24, Vaishali Marg, Vaishali Nagar, Jaipur, Rajasthan 302021, India
Director - Advanced Lung Failure, Transplant Pulmonology, Yashoda Hospital, Hyderabad, India

Interventional pulmonology

Dr. Nagarjun Maturu
Sr. Consultant Respiratory Medicine, Critical Care and Sleep Medicine, Interventional Pulmonologist, Jaipur Golden Hospital, Saroj Hospital & Rajiv Gandhi Cancer Institute, Delhi, India

Dr. Rakesh Chawla
Professor & Unit Head, Department of Respiratory Medicine, J. L. N. Medical College & Associated Group of Hospitals, Ajmer, Rajasthan, India

Dr. Ramakant Dixit

Never Miss an Issue

Get new journal Tables of Contents sent right to your email inbox

Get New Issue Alerts

Browse Journal Content
Liquid biopsy for T790M mutation detection: A ray of hope?

Mohan, Anant; Mittal, Saurabh

Lung India. 37(1):1-2, Jan-Feb 2020.
A comparison of three strategies for withdrawal of noninvasive ventilation in chronic obstructive pulmonary disease with acute respiratory failure: Randomized trial

Venkatnarayan, Kavitha; Khilnani, Gopi C; Hadda, Vijay; More

Lung India. 37(1):3-7, Jan-Feb 2020.

Clinical profile and course of children with postinfectious bronchiolitis obliterans from a tertiary care hospital

Gulla, Krishna Mohan; Jat, Kana Ram; Lodha, Rakesh; More

Lung India. 37(1):8-12, Jan-Feb 2020.

T790M mutations identified by circulating tumor DNA test in lung adenocarcinoma patients who progressed on first-line epidermal growth factor receptor-tyrosine kinase inhibitors

Merinda, Vinodini; Soegiarto, Gatot; Wulandari, Laksmi

Lung India. 37(1):13-18, Jan-Feb 2020.
Predictors of mortality in acute exacerbations of chronic obstructive pulmonary disease using the dyspnea, eosinopenia, consolidation, acidemia and atrial fibrillation score
Bansal, Avya Gopal; Gaude, Gajaman S

Comparison of tuberculin skin test and QuantiFERON-TB Gold In-Tube test in Bacillus Calmette–Guerin-vaccinated children
Shah, Ira; Kathwate, Jagdish; Shetty, Naman S

Regression equations of respiratory impedance of Indian adults measured by forced oscillation technique
De, Sajal; Banerjee, Nalok; Kushwah, Gagan Deep Singh; More

Endoscopic ultrasound-guided-fine-needle aspiration/fine-needle biopsy in diagnosis of mediastinal lymphadenopathy – A boon
Junare, Parmeshwar Ramesh; Jain, Samit; Rathi, Pravin; More
Systematic Review

Prevalence of pulmonary tuberculosis in India: A systematic review and meta-analysis
Sathiyamoorthy, Ramadass; Kalaivani, Mani; Aggarwal, Praveen; More
Lung India. 37(1):45-52, Jan-Feb 2020.

Case Report

Case of urinothorax – A rare presentation
Chawla, Aditya Kumar; Chaudhary, Gaurav; Chawla, Madhav Kumar; More
Lung India. 37(1):53-56, Jan-Feb 2020.
A novel procedure of endobronchial ultrasound-guided transbronchial needle aspiration for pulmonary parenchymal lesions: The ZUTAM technique

Tamburini, Mario; Reddy, Siva Prasad; Gundappa, Vivek; More
Lung India. 37(1):63-65, Jan-Feb 2020.

Mediastinal mass mimic

Datta, Ananda; Patro, Mahismita; Gothi, Dipti
Lung India. 37(1):66-68, Jan-Feb 2020.

A rare case of lung adenocarcinoma: Unusual presentation with miliary mottling

Goyal, Pankaj; Bothra, Sneha J; Jain, Parveen; More
Gefitinib-induced pyogenic granuloma in a patient with lung cancer
Sahoo, Satyajeet; Sirka, Chandra Sekhar; Majumdar, Saroj K Das; More
Lung India. 37(1):71-72, Jan-Feb 2020.

From symptom and sign to diagnosis in a case of pulmonary plasmacytoma and pulmonary metastasis
Ghinea, Mihaela Maria; Stoica, Andreea Georgiana; Ciocodei, Sabina Livia
Lung India. 37(1):72-74, Jan-Feb 2020.

Osteosarcoma mimicking fibrous pleurisy with dystrophic calcification!!
Kumar, Tahiria Sultana; Chawla, Ashish
Lung India. 37(1):75-76, Jan-Feb 2020.

Osimertinib as an emerging therapeutic modality in nonsmall cell lung cancer: Opportunities and challenges in Indian scenario
Thakur, Sayanta; Chakraborty, Dwaipayan Sarathi; Lahiry, Sandeep; More
Lung India. 37(1):77-78, Jan-Feb 2020.

Intercostal chest drain clamping
Flores-Franco, René Agustín
Lung India. 37(1):79-80, Jan-Feb 2020.

The effects of obesity on pulmonary function in adults with asthma
Al-Mendaliawi, Mahmood Dhahir
Lung India. 37(1):80-81, Jan-Feb 2020.
Assessing the flat diaphragm in chronic obstructive pulmonary disease: Deep-diving is a better approach

Devaraj, Uma; Venkatnarayan, Kavitha; Krishnaswamy, Uma Maheswari; More
Lung India. 37(1):82-83, Jan-Feb 2020.
General Perspective

Bronchial Thermoplasty for Severe Asthma: A Position Statement of the Indian Chest Society
(Madan, Karan; Mittal, Saurabh; Suri, Tejas M; More)
T790M mutations identified by circulating tumor DNA test in lung adenocarcinoma patients who progressed on first-line epidermal growth factor receptor-tyrosine kinase inhibitors

Vinodini Merinda¹, Gatot Soegiarto², Laksmi Waulandari²

¹Department of Pulmonology and Respiratory Medicine, Faculty of Medicine Universitas Airlangga, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia; ²Division of Clinical Immunology, Department of Internal Medicine, Faculty of Medicine Universitas Airlangga, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia.

ABSTRACT

Background: Plasma circulating tumor deoxyribonucleic acid (ctDNA) test is an alternative method to detect the T790M mutation. Compared to conventional tumor rebiopsy, ctDNA possesses several advantages including less invasive, faster, lower costs, and having minimal risk of complications for patients. Objective: The main objective of the study is to identify the prevalence of T790M mutations in lung adenocarcinoma patients who progressed after tyrosine kinase inhibitors (TKIs) therapy using ctDNA examination. Materials and Methods: This was a retrospective cohort study based on medical records of lung adenocarcinoma patients in the Oncology Outpatient Clinic of Dr. Soetomo General Hospital within the period of January 2017–June 2018. Patients who progressed after receiving first-line epidermal growth factor receptor-TKI (EGFR-TKI) undergone plasma ctDNA examination and genotyping using digital platforms (DropletDigital™ PCR) method. Results: In total, there were 39 patients who met the criteria for ctDNA testing. Thirty-three patients (84.6%) received first-line gefitinib, while the other six (15.4%) received erlotinib. The T790M mutations were detected in 46.2% of patients. In addition, EGFR common mutation in exon 19 and exon 21 were detected in 87.2% of patients. Median progression-free survival of patients receiving first-line gefitinib or erlotinib were both around 9 months and did not differ significantly. Conclusions: ctDNA examination successfully detected T790M mutation in a certain proportion of lung adenocarcinoma patients who progressed after first-line EGFR-TKI without the need for difficult and invasive rebiopsy.

KEY WORDS: T790M mutation, first-line epidermal growth factor receptor-tyrosine kinase inhibitors, lung adenocarcinoma, plasma circulating tumor deoxyribonucleic acid

Address for correspondence: Mr. Laksmi Waulandari MD, PhD, FCCP, Division of Thoracic Oncology, Department of Pulmonology and Respiratory Medicine, Faculty of Medicine Universitas Airlangga, Dr. Soetomo General Academic Hospital, Jl. Mayan Prof. Dr. Moestopo No. 6-8, Surabaya 60285, Indonesia.

E-mail: laksmi.waulandari@fkm.uis.ac.id

Received: 23-04-2019 Revised: 08-08-2019 Accepted: 12-10-2019 Published: 31-12-2019

INTRODUCTION

Lung cancer is one of the most common causes of cancer mortality in the United States. In 2018, the incidence of new lung cancer cases was estimated to be 234,030 (121,680 of men and 112,350 of women), and the mortality of lung cancer was estimated at 154,050 (83,550 of men and 70,500 of women).
Non-small-cell lung cancer (NSCLC) is considered as the most common type, which comprised more than 65% of all lung cancer cases.[2] Adenocarcinoma is the most common type of lung cancer and is associated with the presence of epidermal growth factor receptor (EGFR) mutation in about 14%-19% of patients in the Western countries and in 40%-48% of patients in Asia.[2]

The EGFR-tyrosine kinase inhibitors (EGFR-TKI), including gefitinib, erlotinib, and afatinib, are recommended as the first-line treatment for patients with positive EGFR-mutation. Despite achieving notable efficacy from EGFR-TKI treatment, a majority of patients eventually develop resistance after a median progression-free survival (PFS) of approximately 1-year (8-14 months). The progressive disease could be accounted to different resistance mechanisms to TKI. The most common resistance mechanism (approximately 60%) is the T790M secondary mutation. Consequently, patients who progressed after receiving first-line TKI therapy were subjected to biopsies of tumor tissue to determine the presence of T790M mutation. However, biopsy is not always feasible for many of the patients.[3]

One alternative method that could be employed for the detection of T790M is the circulating tumor deoxyribonucleic acid (ctDNA) test. The ctDNA genotyping is a specific and sensitive biomarker test that can be used for the detection of EGFR mutation. The ctDNA can be extracted from plasma and used for tumor-specific molecular marker detection. Compared to conventional biopsy of tumor tissue in patients who have progressed, ctDNA possesses several advantages such as less invasive, faster, lower costs, and having minimal risk of complications for patients. The concordance between plasma ctDNA test and tumor biopsy result in NSCLC patients in Asia Pacific was found to be 78%, with a sensitivity of 50% and specificity of 97%. T790M was detected in 47% of NSCLC patients with acquired EGFR-TKI resistance using the plasma ctDNA test and can be found either before or after disease progression. Hence, it can be regarded as a poor prognostic factor.[3]

Until now, the T790M mutation in NSCLC patients in Dr. Soetomo General Hospital, Surabaya, Indonesia, had never been reported. The aim of this study is to determine the prevalence of T790M and other EGFR mutations in lung adenocarcinoma patients who progressed after the first-line EGFR-TKI using ctDNA test.

MATERIALS AND METHODS

This was a retrospective cohort study based on the medical records of lung adenocarcinoma patients in the Oncology Outpatient Clinic of Dr. Soetomo General Hospital, Surabaya, Indonesia, a tertiary referral hospital in Indonesia, within the period of January 2017 to June 2018. Eligible participants must fulfill the inclusion criteria: those who had been diagnosed with pulmonary adenocarcinoma Stage IV, had positive EGFR mutation, treated and followed-up at the Oncology Outpatient Clinic of Dr. Soetomo General Hospital Surabaya, Indonesia, received first-line EGFR-TKI as treatment, had their disease progressed as evident by radiological (RECIST version 1.1) and/or physician’s clinical judgment, and subsequently undergone plasma ctDNA examination. All of the participants characteristic and demographic data, EGFR mutation status, types of first-line EGFR-TKI received, and survival data were recorded. All of the data were obtained from the patient’s medical record. Participants with incomplete data or who had their plasma ctDNA examination done while on chemotherapy were excluded from the study. This study was approved by the Ethical Committee of Dr. Soetomo General Hospital, Surabaya, Indonesia (0632/KEPK/Ix/2018).

During the study period, from the first screening, there were a total of 50 patients who had their plasma ctDNA tested and were recorded in the medical records. Eleven patients were excluded due to several reasons, leaving 39 patients who met the inclusion criteria and included in the study as described in Figure 1. We describe our study and the participants filled out the consent form.

Briefly, the procedure for ctDNA test in our hospital was as follows: blood samples were taken from all of the patients and put in ethylenediaminetetraacetic acid tubes. The samples were processed for DNA extraction and complimentary DNA (cDNA) synthesis. The cDNA samples were then analyzed for the presence of T790M mutation.
were then directly sent to a central referral laboratory for further processing within 2 h of blood drawing. Plasma was obtained after a series of centrifugations according to the standard protocol. Fresh plasma were stored at −80°C until further examination. DNA extractions were carried out by using spin column method with QIAamp® circulating nucleic acid kit (QIAGEN, Manchester, UK). Extracted ctDNAs were tested for EGFR mutations using digital detection with the highly sensitive and quantitative Droplet Digital PCR (ddPCR™; Bio-Rad Molecular MD, Hercules, CA, USA). Assays were performed according to the manufacturer’s protocol.

The collected data were assessed using the Shapiro–Wilk test for normality of the distribution. We use the Mann–Whitney U-test or Independent t-test to assess the difference between patients who received first-line gefitinib or erlotinib in terms of PFS, with P < 0.05 considered as statistically significant. All of the statistical analysis was done using IBM SPSS Statistics Software Version 23.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Subjects characteristics

The characteristics of the study participants were summarized in Table 1. The average age of the participant was 57.80 ± 11.29 years (ranged from 35 to 83 years). The majority of them (20 individuals, 51.3%) were in 41–60 years age group. Most of them were female (28 individuals, 71.8%) and nonsmokers (29 individuals, 74.4%). Based on the data of the initial performance score (PS), the majority of the study participants had PS 1 condition (34 individuals, 87.2%).

Most of the histopathology specimens were taken from lung mass (30 samples, 76.9%), mostly by fine-needle aspiration biopsy (FNAB) techniques (in 23 participants, 59.0%). The first-line EGFR-TKI treatment received by the participants was mostly gefitinib (in 33 patients, 84.6%). With respect to EGFR mutation type, EGFR common mutations were a dominant finding (87.2%), consisted of 23 patients with exon 19 deletion mutation (59.0%) and 11 patients with exon 21 L858R mutation (28.2%).

T790M mutation status

The result of the T790M mutation status obtained from plasma ctDNA test in this study was illustrated in Table 2. Eighteen out of 39 patients (46.2%) showed positive T790M mutation. Comparing participants with T790M-positive and T790M-negative mutations, there were no significant differences in patients’ characteristics in terms of age group, sex, smoking history, and first-line EGFR-TKI treatment received [Table 3].

Progression free survival

In this study, 3 out of 39 participants who fulfill the inclusion criteria had incomplete survival data, so they were not included in the analysis of the PFS. With regard to patients who had disease progression, the median PFS was 9 months and the 12 months survival rate was 36.1% [Table 4]. There was no difference in the median PFS between the two types of EGFR-TKI treatment (gefitinib or erlotinib). The median PFS value for both types of EGFR-TKI treatment was around 9 months (P = 0.932) as shown in Table 5.
DISCUSSION

Plasma ctDNA test in lung adenocarcinoma patients who had progressive disease following the first-line EGFR-TKI in Dr. Soetomo General Hospital Surabaya, Indonesia, revealed 46.2% prevalence of positive T790M mutation. This result is encouraging because our study confirmed the conclusions of many other previous studies done in similar circumstances elsewhere. It has long been known that EGFR-mutant lung cancer patients who received EGFR-TKI treatment will eventually come to a disease progression due to secondary resistance to EGFR-TKI. Current guidelines recommended tumor tissue relpobiology to analyze the mechanisms of resistance and identify new targets for further therapy. However, it is not easy to obtain tumor samples from patients with EGFR mutation-positive NSCLC that has relapsed after treatment with EGFR-TKIs. The confirmation that plasma ctDNA analysis using digital assay can be used as an alternative and noninvasive method to assess EGFR secondary mutation is a major advance in the management of NSCLC patients. It diverts the necessity of other cumbersome and invasive method which is also vulnerable to false-negative results.

Table 3: Characteristics of T790M-positive and T790M-negative mutant patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>T790M (-)</th>
<th>T790M (+)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age category (years), n (%)</td>
<td>0</td>
<td>3 (16.7)</td>
<td>0.237</td>
</tr>
<tr>
<td>21-40</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>41-60</td>
<td>12 (57.1)</td>
<td>8 (44.4)</td>
<td></td>
</tr>
<tr>
<td>61-80</td>
<td>4 (18.2)</td>
<td>7 (37.9)</td>
<td></td>
</tr>
<tr>
<td>≥80</td>
<td>1 (4.8)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td>13 (71.4)</td>
<td>13 (72.2)</td>
<td>1.0</td>
</tr>
<tr>
<td>Woman</td>
<td>6 (38.6)</td>
<td>5 (27.8)</td>
<td></td>
</tr>
<tr>
<td>Man</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking history, n (%)</td>
<td>16 (76.2)</td>
<td>13 (72.2)</td>
<td>0.792</td>
</tr>
<tr>
<td>Non-smoker</td>
<td>2 (9.5)</td>
<td>2 (11.1)</td>
<td></td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>3 (14.3)</td>
<td>3 (16.7)</td>
<td></td>
</tr>
<tr>
<td>First-line EGFR-TKI treatment, n (%)</td>
<td>18 (85.7)</td>
<td>15 (83.3)</td>
<td>1.0</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>15 (83.3)</td>
<td>15 (83.3)</td>
<td></td>
</tr>
<tr>
<td>Erlotinib</td>
<td>3 (14.3)</td>
<td>3 (16.7)</td>
<td></td>
</tr>
</tbody>
</table>

EGFR: Epidermal growth factor receptor, TKI: Tyrosine kinase inhibitors

Table 4: Progression-free survival analysis

<table>
<thead>
<tr>
<th>Analysis of patient’s survival</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS-months</td>
<td>9</td>
</tr>
<tr>
<td>Median</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>2-48</td>
</tr>
<tr>
<td>PFS in 12 months, n (%)</td>
<td>23 (63.9)</td>
</tr>
<tr>
<td>&lt;12</td>
<td></td>
</tr>
<tr>
<td>≥12</td>
<td>13 (36.1)</td>
</tr>
</tbody>
</table>

PFS: Progression-free survival

Table 5: Median progression-free survival of first-line gefitinib or erlotinib treatment

<table>
<thead>
<tr>
<th>First-line EGFR-TKI treatment</th>
<th>Median PFS months (range)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gefitinib</td>
<td>9 (2-48)</td>
<td>0.952</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>9 (3-16)</td>
<td></td>
</tr>
</tbody>
</table>

PFS: Progression-free survival, TKI: Tyrosine kinase inhibitors, EGFR: Epidermal growth factor receptor

Plasma ctDNA analysis is now approved as a robust and accurate method for the detection of actionable mutations prior treatment, selection of first-line TKI, predicting and monitoring response to treatment, and emerging drug resistance mechanisms in NSCLC. Many studies had confirmed the high sensitivity and specificity of plasma ctDNA analysis, which also showed high overall concordance with tumor tissue samples. NSCLC patients from our hospital had previously been involved in a large multicenter IGNITE study conducted in 90 centers from Asia-Pacific and Russia. In that study, plasma ctDNA also had a high concordance with matched tissue/cytology samples (80.5%) albeit with somewhat lower sensitivity (46.5%), specificity 98.6%). EGFR mutation frequencies for evaluable tissue/cytology samples in Asia-Pacific in that study were 49.3% (862/1749).

The prevalence of EGFR mutation in our study is dominated by EGFR common mutation (87.2%) which consisted of exon 19 (69.0%) and exon 21 L858R mutation (28.2%). This result is consistent with other major researches in the field which found that the prevalence of EGFR common mutation was around 85%-90%, consisting of exon 19 deletion and exon 21 L858R mutation. Similarly, in the IGNITE study, the proportion of EGFR common mutation was 91.2% in the Asia-Pacific population, which consisted of exon 19 deletion (48.7%) and exon 21 L858R mutation (42.5%). In our study, exon 18 G719S mutation comprised 5.1% of the mutation pool, whereas combination of exon 19 deletion and exon 21 L858R mutation, exon 20 and exon 21 L858R mutation, and triple mutation of exon 19 deletion, exon 20 and exon 21 L861Q mutation were each 2.6% of our study participants, respectively. The result of our study is also consistent with the common findings as summarized by Sharma et al. and Pirker et al., where exon 18 mutation was found to be 5% for the total mutation pool and mutation in exon 20 were <1% in proportion. In the IPASS study, several patients were found to possess either EGFR mutation in exon 20, other types of mutations, and/or multiple combinations of mutations. The mutation in exon 20 is associated with primary resistance to EGFR-TKI.

The presence of EGFR mutation in NSCLC of adenocarcinoma histology warrants EGFR-TKI as the first-line treatment. With regard to the patient’s demographic data, our study results were closely resembled or comparable to the IPASS and WJTOG3405 studies. The subject’s median age in our study was 55 years (ranged from 35 to 83 years), while in the IPASS study, the median age of the participants was 57 years (range: 24-84 years) and in WJTOG3405 study, it was 64 years (range: 34-74 years). A higher proportion of female patient (71.8%) was found in our study. This result was also similar with NEJ002 and WJTOG3405 studies. In NEJ002 study, the female participants made up 63.2% of the study population, while in WJTOG3405 study, it was 68%. In terms of smoking history, there were more non-smokers (74.4%) compared to active and ex-smokers. The result of our study is similar to the WJTOG3405 study.
study where nonsmokers were found to be 70.9%. Most participants in our study were in PS 1 condition, which made up 87.2% of the total study population. In comparison, only 64.2% of study participants in IPASS study had PS 1 condition. With regard to the sampling site of histopathological examination for the diagnosis of adenocarcinoma, most specimen samples in our study were obtained from lung mass (76.9%). The most common sampling method for histopathological examination was by FNA (59%). This finding is consistent with the IGNITE study, where fine-needle aspiration was also identified as the most common method for obtaining samples (51%).

Three types of EGFR-TKI available in Indonesia for first-line treatment of EGFR-mutant NSCLC were gefitinib, erlotinib, and afatinib. Gefitinib was more widely used (84.6%) than erlotinib. This could be due to the fact that gefitinib was the first EGFR-TKI received the approval by National Health Insurance issued by the Indonesian government. Until the end of this study, there were no patients receiving afatinib as the first-line treatment that suffered from disease progression, and therefore, no plasma ctDNA examination done for these patients.

Among patients who had progressed after first-line gefitinib or erlotinib, our study detected 46.2% participants positive for T790M mutation. This result is comparable with the study conducted by Zheng et al., which found that the prevalence of T790M-positive mutation patients was 47%. In their study, the combination of T790M-positive mutation with either exon 19 deletion or exon 21 L858R mutation was found to be 29.3%, which is higher compared to single T790M mutation (17.9%). Our result was in contrast to Socinski et al., which found that the prevalence of T790M mutation was 60%, aside from other types of non-EGFR mutations. This difference might be accounted to the difference in race and genetic factors between the Caucasian and Asian population. Further research is needed to confirm this assumption.

In our study, the proportion of patients with negative T790M mutation was 53.8%, in which 38.5% patients had no T790M mutation and 15.3% had no T790M mutation but were positive for either exon 19 deletion or exon 21 L858R mutation. This is consistent with Zheng et al., where the proportion of patients with negative T790M mutation but were positive for either exon 19 deletion or exon 21 L858R mutation was 6.3%-14.3%. Based on the characteristics of patients, there were no significant differences between T790M positive and T790M negative mutation in terms of age, gender, smoking history, and EGFR-TKI treatment (P > 0.05). This is also consistent with the previous study by Zheng et al., which had the same findings.

Patients with positive T790M mutations from ctDNA test following EGFR-TKI are associated with poor prognosis. It could indicate that tumor cells have exceeded the threshold for tumor growth, and reflect an increase in tumor burden and also metastasis.

PFS in this study was calculated from the time EGFR-TKI treatment was started until the earliest signs of disease progression assessed using RECIST version 1.1 and/or clinical worsening. Socinski et al. mentioned that resistance to EGFR-TKI will develop in patients after a median PFS of approximately 1-year (average 8–14 months). In the current study, the median PFS was 9 months for both gefitinib and erlotinib. The result of our study is very similar to the WJOG3405 study which asserted that the median PFS was 9.2 months. Our previous study (thesis, unpublished data) found that the median PFS was 7 months, while the IFUM study reported the median PFS of 9.7 months. Twelve months survival rate in the current study was 36.1%, whereas in our previous study, it was 15.25%. This might be due to immature data in our previous report.

In the current study, there was no difference in median PFS between the two types of EGFR-TKI treatment (gefitinib or erlotinib). The median PFS of gefitinib and erlotinib were 9 months, respectively (P = 0.932). In WJOG5018 L study comparing gefitinib and erlotinib, it was found that the median PFS for gefitinib was 8.3 months, while the median PFS for erlotinib was 10 months.

There are several mechanisms of resistance to EGFR-TKI which result in disease progression. The T790M mutations are presumed to cause resistance to EGFR TKI through a variety of mechanisms. One of which is by steric hindrance, which results in the decrease of reversible TKI binding, increased bound affinity with ATP and increased phosphorylation levels, which ultimately result in the decrease of EGFR-TKI potential. Other review suggests that the mutation causes changes in the tridimensional tyrosine kinase domain structure and prevents gefitinib or erlotinib from binding to EGFR.

CONCLUSIONS

In EGFR-mutated lung adenocarcinoma patients who had disease progression after the first-line EGFR-TKI, plasma ctDNA examination is a valid alternative method for tumor rebiopsy. Our study confirmed the conclusions of many other previous studies done in the same circumstances elsewhere. Using plasma ctDNA test in Dr. Soetomo General Hospital Surabaya, Indonesia, the proportion of T790M mutation in such patients was 46.2%. There were no significant differences between T790M-positive and T790M-negative mutations in terms of the age, sex, smoking history, and the type of EGFR-TKI used. Prior to the first-line EGFR-TKI treatment, EGFR common mutation in exon 19 and exon 21 was detected in 87.2% of the patients. The median PFS of patients receiving gefitinib or erlotinib as the first-line treatment was 9 months.

Acknowledgment

All authors would like to thank Ms. Roselini Ngiono B.Sc for manuscript proofread and her recommendations to
improve our manuscript. The plasma ctDNA test was supported by AstraZeneca Ltd, Indonesia but it does not interfere in manuscript design and preparation.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

REFERENCES

KOMITE ETIK PENELITIAN KESEHATAN
RSUD Dr. SOETOMO SURABAYA

KETERANGAN KELAIKAN ETIK
("ETHICAL CLEARANCE")

0632/KEPK/Ix/2018

KOMITE ETIK RSUD Dr. SOETOMO SURABAYA TELAH MEMPELAJARI
SECARA SEKSAMA RANCANGAN PENELITIAN YANG DIUSULKAN, MAKA
DENGAN INI MENYATAKAN BAHWA PENELITIAN DENGAN JUDUL :

"Profil Mutasi T790M Pasien Kanker Paru Adenokarsinoma yang Mengalami
Progresivitas Setelah Mendapatkan Inhibitor Tirosin Kinase Sebagai Terapi Lini
Pertama dengan Pemeriksaan Circulating Tumor DNA"

PENELITI UTAMA : Dr. Laksmi Wulandari, dr., Sp.P (K), FCCP
PENELITI LAIN : 1. Vinodini Merinda, dr
UNIT / LEMBAGA / TEMPAT PENELITIAN : RSUD Dr. Soetomo

DINYATAKAN LAIK ETIK

Berlaku dari : 16/09/2018 s.d 16/09/2019
Surabaya, 16 September 2018

KETUA

(Dr. Elizeus Hanindito, dr., Sp.An, KIC,KAP)
NIP. 19511007 197903 1 002

*) Sertifikat ini dinyatakan sah apabila telah mendapatkan stempel asli dari Komite Etik
Penelitian Kesehatan
Lung India

Country: India

Subject Area and Category: Medicine, Pulmonary and Respiratory Medicine

Publisher: Walters Kluwer Medknow Publications

Impact Factor: 25

Publication Type: Journals

ISSN: 0970-0113, 0974-959X

Coverage: 2001-2020

Scope:

I hope that you find Lung India useful in boosting your academic pursuits. The editorial team and the leadership of the Indian Chest Society are interested and engaged in improving the journal and its rating. Nothing is possible without your active involvement and inputs. It is a continued request to you all to spare some of your time and contribute to the journal, especially with your original research and observations. We also need your help in the peer review process of the articles submitted to the journal.

Join the conversation about this journal.