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Challenges in the Management of Lung *Adenocarcinoma* in Elderly Patients: Case Report

I Nyoman Gede Witriadnyana[1], Putu Ayu Diah Puspita Sari1[2], Luh Dewi Rahayu1[3]

[1, 2, 3]Department/KSM Pulmonology and Respiratory Medicine, Mangusada Regional Hospital1, Badung, Bali Indonesia
[1]Corresponding Author Email: *nyomanwitriadnyana[at]gmail.com*
082147737160

Abstract: ***The management of elderly lung cancer patients has many challenges in providing therapeutic regimens. Diagnosis, patient performance status, tumour stage, and molecular mutations of lung cancer are key in providing drugs to NSCLC patients with very minimal side effects compared to chemotherapy. Rapid developments in molecular biology are currently having a positive impact on the maintenance and quality of life of patients. Epidermal Growth Factor Receptor - Tyrosine Kinase Inhibitors (EGFR - TKI) molecular therapy is a targeted therapy used in lung cancer patients with positive EGFR mutations to stop cancer cell growth. Adequate screening for EGFR mutations is necessary for optimal therapy. We report a 78 - year - old male patient with a diagnosis of non - small cell lung cancer (NSCLC) of the adenocarcinoma type. The diagnosis is based on anamnesis, physical examination, supporting examinations and examination of EGFR mutations. In the EGFR mutation, positive results were obtained with the Exon 19 Dels type. The target therapy plan provided is with the first generation EGFR - TKI, namely gefitinib. But before giving targeted therapy, the patient's condition worsened.***

Keywords: elderly lung cancer, therapeutic regimens, molecular mutations, EGFR - TKI targeted therapy, Lung Adenocarcinoma

1. Introduction

Lung cancer is a disease of uncontrolled cell growth in the lung tissue. This growth can lead to metastasis, invasion of adjacent tissues and infiltration outside the lung. Most primary lung cancers are lung carcinomas that originate from cellular bronchial epithelium. Lung cancer is the most common cause of cancer - related death in men and the second most common in women, and accounts for 1.3 million deaths worldwide each year.[1, 2] In the current era, the latest global statistical analysis estimates 1.8 million new cases were diagnosed worldwide in 2012, with 1.6 million deaths in the same year.3 This is up from 1.6 million new diagnoses and 1.4 million deaths from lung cancer in 2008.[4]

Lung cancer is commonly divided into *Non - small cell lung cancer (*NSCLC) and *Small cell lung cancer (*SCLC), with the former accounting for 80% of NSCLC cases and the latter 20%. Many NSCLC cases are managed with a combination of surgery and adjuvant therapy, whereas SCLC lung cancer shows an aggressive reaction and is treated without surgery. The introduction of different types of NSCLC has been subclassified in the 2004 and 2015 *World Health Organisation (*WHO) classifications.[5, 6] The main types of NSCLC include *Adenocarcinoma*, *Squamous cell carcinoma (*SCC), and *Large cell carcinoma (*LCC). Clinical manifestations that can be found include shortness of breath, cough, chest pain, spinal pain, haemoptysis, anorexia, significant weight loss, weakness, and vena cava obstruction.[7, 8, 9]

Lung adenocarcinoma is a malignant epithelial neoplasm of the bronchus with glandular differentiation.[10, 11, 12] Adenocarcinoma is one of the most common types of lung cancer, accounting for more than 40% of lung cancers, 60% of NSCLC, and more than 70% of surgically resected cases.[6, 13] The incidence of adenocarcinoma has been steadily increasing over the past few decades. Lung adenocarcinoma usually forms a mass located in the periphery of central fibrosis and pleural wrinkles. It can also see a variety of other bulky appearances, including centrally located masses, diffuse lobar consolidation, bilateral multinodular distribution, and pleural thickening.

Lung cancer can be caused by several risk factors. These risk factors are divided into two consisting of controllable and uncontrollable risk factors. Controllable risk factors include smoking, radon exposure, indoor and outdoor pollutants, chronic lung disease, and carcinogens in the workplace. Uncontrollable factors include age, gender and genetics.[14]

Smoking is the most common cause of lung cancer. An estimated 90% of lung cancer cases are caused by smoking. The risk is further compounded by exposure to other carcinogens, such as asbestos. There is no correlation between lung cancer and the number of packs smoked per year due to the influence of the cigarette.

There is a complex interaction between smoking, environmental and genetic factors. The risk of lung cancer from second - hand smoke increases by 20 to 30%.[15] Exposure to metals such as chromium, nickel, arsenic and polycyclic aromatic hydrocarbons is also associated with lung cancer. Lung diseases such as idiopathic pulmonary fibrosis increase the risk of lung cancer regardless of smoking.[16]

Supporting tests that can be used to diagnose lung cancer include laboratory tests, radiology such as thorax X - ray and CT - Scan, as well as diagnostic measures such as *Trans thoracal biopsy (*TTB), *Fine needle aspiration biopsy (*FNAB), and histopathological examination.[17]

Lung cancer treatment consists of several modalities. Common standard therapies for lung cancer are surgery, radiotherapy and chemotherapy. Optimal therapy with

surgery, radiation and chemotherapy only achieves a cure rate of <15%. Biomolecular research in recent decades has identified molecular pathways that are important in tumour development and growth.[18, 19, 20] These drugs have been developed by targeting mechanisms in lung tumours to improve outcomes and improve the quality of life of cancer patients with treatment called *Targeting Therapy*.[18]

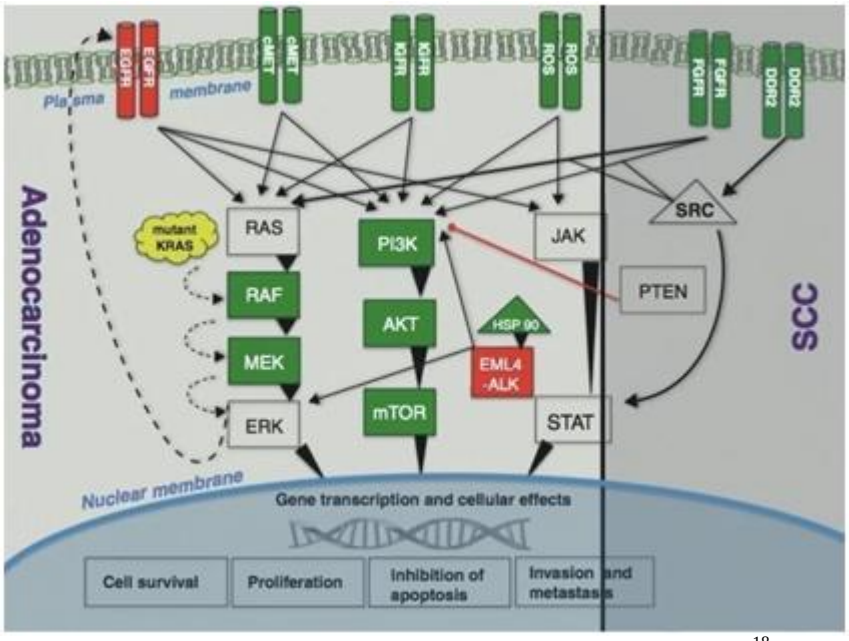

Figure 1: Molecular pathways and potential targets in NSCLC.[18]

EGFR is a group of receptor tyrosine kinases that can mediate molecular pathways that promote cell growth, proliferation and cell survival. The extracellular component of EGFR will bind to its ligand, where the intracellular component consists of a tyrosine kinase that acts as a signal transducer. After the ligand binds to the extracellular receptor, the receptor will be activated. This signal will be forwarded to several subsequent pathways, especially the RAS - RAF - MEK - ERK or MAPK, PI3K - AKTmTOR or JAK - STAT pathways. These pathways promote gene transcription and cell cycle disruption resulting in increased cell proliferation and angiogenesis, inhibited apoptosis and changes in migration, adhesion and invasion capacity.[18, 21, 22]

Regimen	Trials	Median PFS (Months)	References
Gefitinib	WJTOG3405, NEJ002, LUX-Lung 7, ARCHER 1050	9.2–10.9	[4,5,10,11]
Erlotinib	EURTAC, OPTIMAL, NEJ026	10.4–13.3	[6,7,12]
Afatinib	LUX-Lung 3, LUX-Lung 6, LUX-Lung 7	11.0–11.1	[8–10]
Dacomitinib	ARCHER 1050	14.7	[11]
Erlotinib + Bevacizumab	NEJ026	16.9	[12]
Osimertinib (second line)	AURA3	10.1	[13]
Osimertinib (first line)	FLAURA	18.9	[14]

Figure 2: Median progression - free survival (PFS) in clinical trials for patients with EGFR mutation positive advanced *Non - small cell lung cancer (*NSCLC) treated with EGFR - TKIs.

Rapid developments in molecular biology are providing evidence that driver mutations, such as the epidermal growth factor receptor (EGFR) 23, 24 and anaplastic lymphoma kinase (ALK) 25 genes, play an important role in *Non - small cell lung cancer* (NSCLC) cell oncogenesis. Studies revealed that first - line treatment with EGFR tyrosine kinase inhibitors (TKIs) provided better *Progression - Free Survival (*PFS) compared to standard chemotherapy in patients with advanced NSCLC, who were selected based on the presence of activating EGFR mutations (Figure 2).26, 27, 28, 29, 30, 31 Therefore, EGFR – TKI monotherapy has become the standard of care for patients with advanced NSCLC who are positive for the mutation. However, although most NSCLC patients with TKI - sensitive EGFR mutations show a clear initial response to EGFR - TKI treatment, resistance to these drugs may develop after 9 to 14 months of therapy.

2. Case Illustration

Patient IGNWP, male 78 years old, married, occupation retired TNI, with address Banjar Kaja, Buduk Village, mengwi District, Badung, Bali. The patient came to the Emergency Department of Mangusada Hospital on June 5, 2023 with complaints of shortness of breath approximately 10 hours ago before entering the hospital, previously the shortness was felt intermittently almost every day for the past 2 years, but it has worsened since yesterday. patients usually just sit at home because they complain of shortness. tightness worsens when walking and doing light activities.

when falling asleep patients usually use 2 to 3 pillows because they complain of tightness. tightness is also felt to improve when sleeping on the right or left side. The patient also complained of dry cough since the last 2 years. Coughing up blood was previously denied. Coughing is most often felt at night compared to morning or day. The frequency of coughing is rare. Patients sometimes feel pain in the right lower chest since the last 1 year. The pain is felt to be intermittent and recurrent.

The patient is a retired TNI approximately 20 years ago. In the past, the patient claimed to exercise regularly as a young man and adopt a healthy lifestyle, but besides that the patient was also an active smoker since the age of 20 until after retiring from the TNI. The patient admitted that he quit smoking 2 years ago because he complained that he often felt weak, had a short cough and right chest pain. since adolescence, the patient said he could use up to 1 to 2 packs of cigarettes a day. Before complaining of illness, the patient had a good posture and ideal weight, but after the last 2 years the patient felt that his weight had decreased by approximately 3 to 5 kilograms and also had no appetite. The patient's family said that the patient had a history of hypertension, heart swelling (May 2022), and lung infection and fluid in his lungs since 1 year ago. The patient often goes back and forth to the hospital because of his frequent complaints of tightness. Previously, the patient had been hospitalised twice since May 2023 and once in June 2023 with supporting examinations in the form of Thorax X - ray A/P and CT scan without contrast. The results of the supporting examination showed the impression of fluid in the lung cavity and mass in the right lung.

On examination the patient's consciousness was compos mentis, appeared slightly breathless, Glasgow coma scale (GCS) eye 4, verbal 5, motor 6 (E4V5M6), visual analogue scale (VAS) 1 right chest pain, with a general appearance of the patient (Karnofsky score) decreased 50 and *Eastern Cooperative Oncology Group Performance Score (ECOG/WHO) PS score 4* obtained

Blood pressure 165/116 mmHg, pulse 86 beats per minute, respiratory rate 26 beats per minute, axillary temperature 36 C, and oxygen saturation 92% with room air. The patient's weight was 50 kg, height 168 cm with a body mass index of 18.1 kg/m2 with an impression of underweight nutrition. On eye examination, the conjunctiva was not anemic, the sclera was not icteric, the pupillary reflex was normal, there was no enlarged lymph nodes in the neck and JVP + 2cm H2O. The patient's thorax was found to have a heart border exceeding CTR > 50%, there was heart enlargement, with inspection and palpation of icus cordis, single, regular S1 and S2 heart sounds and no additional sounds such as murmurs and gallops. Inspection of the thorax dynamic symmetrical static movement, found minimal chest wall retraction, palpation stem fremitus along the right lung field decreased, percussion of the right lower lung field is faint, auscultation The sound of both lung fields of the patient is vesicular, Abdominal examination inspection was symmetrical, flat, normal bowel sounds, murphy sign or mcburney negative, undulations negative, striae negative, distended or defans muscular negative, no palpable enlarged hepar and enlarged spleen. The pubic symphysis is within normal limits, the lower limbs are not found to be enlarged, the acral warm, CRT < 2 seconds.

Supporting examinations have been carried out on IGNWP patients, the results of the examination are presented in the table below (Table 1).

Table 1: Patient's laboratory examination results 05/06/2023

Type examination laboratory	Results	Reference	Unit
Whole Blood			
Leukocytes	13, 87	3.80 - 10.60	
Haemoglobin	15, 8	13.2 - 17.3	
Hematocrit	44, 5	40.0 - 52.0	
Platelets	321	150 - 440	
Neutrophils %	78, 7	50.0 - 70.0	
Lymphocytes%	10, 9	25.0 - 40.0	
Blood Glucose			
Current blood sugar	140	70 - 140	
Liver function			
SGOT (AST)	32	11- 33	
SGPT (ALT)	38	11- 50	
Renal function			
Ureum	37	15 - 45	
Serum creatinine	0.8	0.70 - 1.20	
eGFR	86		
Uric acid	4.4	4.4	
Electrolytes (na, k, cl)			
Sodium (Na)	131	136 - 145	
Potassium (K)	3.8	3.5 - 5.1	
Chloride (CL)	97	94 - 110	
Lipid Profile			
Total cholesterol	111	<200	
HDL cholesterol	36	35 - 60	
LDL cholesterol	61	<130	
Triglycerides	68	<150	

In May 2023, sputum culture and TCM were examined because there was an increase in vascular cores accompanied by extensive infiltrates in the right and left lung fields, as well as excluding possible differential diagnoses. The results obtained in the patient were normal sputum flora with MTB not detected. On 26 May 2023, pleural puncture and *Trans - Thoracal Needle Aspiration (*TTNA) with *CT - Scan guiding* were performed. During pleural puncture, 10 cc of ceroxantochrom - coloured fluid came out for pleural fluid analysis and pleural fluid cytology tests with the results of *seeding adenocarcinoma with a* background of *Reactive Mesothelial Hyperplasia. Trans - Thoracal Needle Aspiration (*TTNA) was performed with cytological results in the form of an impressive *Non - Small Cell Lung Carcinoma Adenocarcinoma.*

An examination for the eGFR mutation test for lung cancer has been carried out with the receipt of a sample on **28/06/2023 with** a cell percentage of > 50% using the DNA Extraction method (GeneAll Exgene TM Clinic SV), q - RT - PCR (High Resolution Melt) AmoyDx EGFR ADx - ARMS. Results were obtained on **03/07/2023** with the conclusion of EGFR mutation detected on EXON 19 deletions.

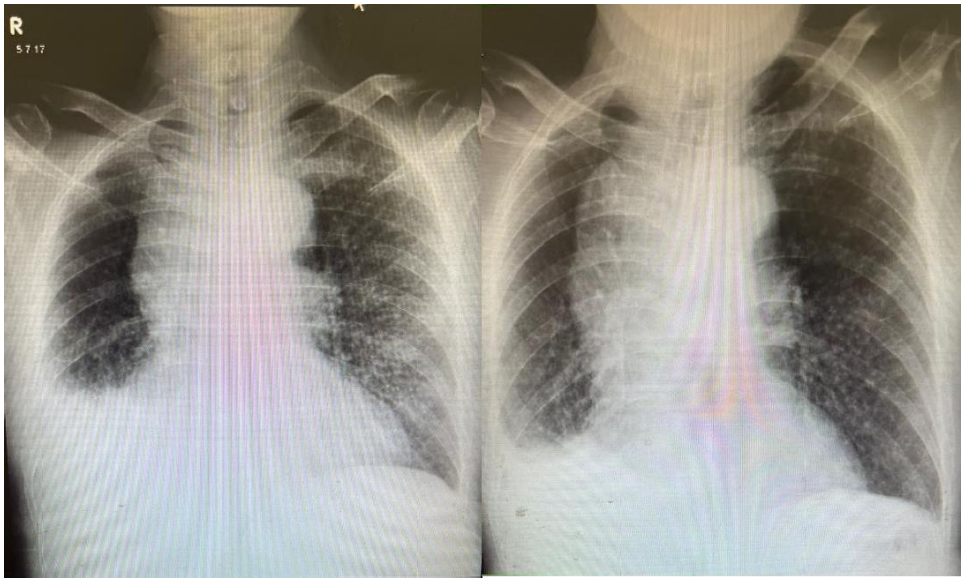

Figure 3: Results of AP thorax photographs on 09/05/23 and 26/05/23 pre and post plerural puncture.

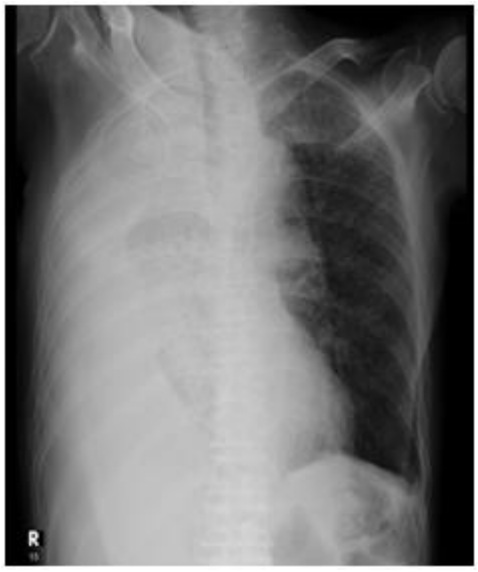

Figure 4: Results of AP thorax examination on 15/7/23

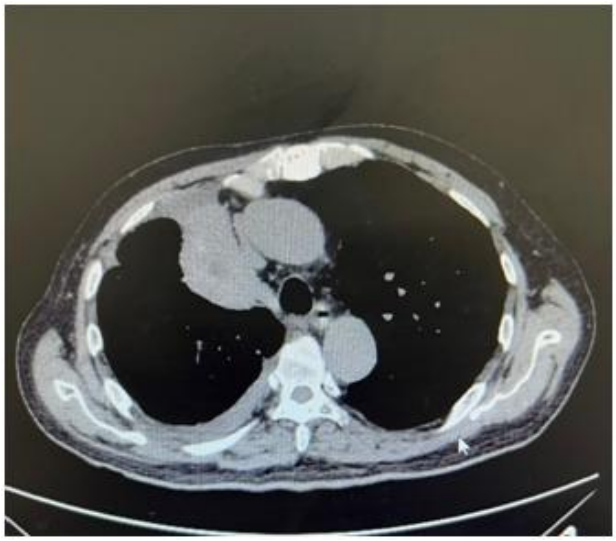

Figure 5: Examination results with CT - Scan thorax without contrast on 11/05/23

Chest X - ray examination revealed an enlarged heart with a cardio thorax ratio (CTR) of 57% accompanied by increased vascular patterning and mediobasal infiltration of the right and left lung fields. There was dense ridge in the right upper lung field suspicious of lung mass and mediastunal mass. There is fluid in the right lower lung cavity as high as ICS 5 before and after pleural puncture. From the results of the above thorax photos, it is concluded that there is bilateral pneumonia, pleural effusion, dextra lung mass and cardiomegaly.

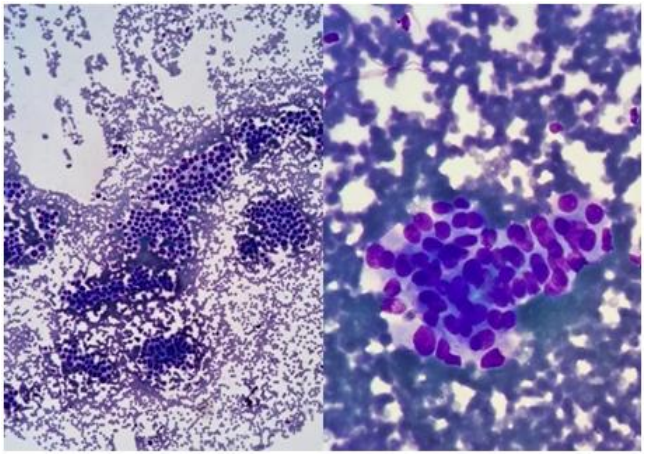

Figure 6: Microscopic results of Post TTNA cytology with Papanicolaou staining

Apical CT - Scan without contrast showed consolidation in the right lung segment measuring 4.7 x 6 cm, heterogeneous density, no visible calcification, accompanied by nodules in the inferior lobe of the right lung irregular. Right

parabronchial nodule spleen gland enlargement measured 1.4x1.1 cm and 1.4x1cm. Impression of T4N1M1a with right pleural effusion and atherosclerotic aorta.

Based on the clinical and supporting data above, the patient was diagnosed with *Non - Small Cell Lung Cancer (*NSCLC) *type Adenocarcinoma Stage* dextra lung tumour.

*IV A PS score 4 with EGFR Mutation Exon 19 dels, Chronic Obstructive Pulmonary Disease (*COPD), *Atelectasis, Health - Care Associated Pneumonia (*HCAP), *Encapsulated Pleural Effusion dt Massive Dextra, Bronchiectasis, Acute Coronary Syndrome (*ACS) *et causa Unstable Angina Pectoralis (*UAP), *Chronic Heart Failure (*CHF), *Hypertension Heart Disease (*HHD).

The patient received treatment in the form of O2 NRM 8 lpm, administration of NaCL 0.9% infusion fluid combined with Bfluid 1: 1 rate of 20 drops per minute, administration of antibiotics levofloxacine 750 mg every 24 hours intravenously, methylprednisolone 62.5mg intravenously every 12 hours, cough mucolytics and antioxidants in the form of n - acetylcysteine 200mg tablets every 8 hours orally, nebu combivent combined with flixotide every 8 hours by inhalation, pantoprazole 40mg every 12 hours intravenously, cernevit multivitamin 1 vial injection every 24 hours intravenously.

3. Discussion

Lung cancer is a disease of uncontrolled cell growth in the lung tissue. This growth can lead to metastasis, invasion of adjacent tissues and infiltration outside the lung. Most primary lung cancers are lung carcinomas originating from bronchial epithelial cells. Lung cancer is the most common cause of cancer - related death in men and the second most common in women, and accounts for 1.3 million deaths worldwide each year. In the current era, recent global statistical analyses estimate 1.8 million new cases were diagnosed worldwide in 2012, with 1.6 million deaths in the same year. This is an increase from 1.6 million new diagnoses and 1.4 million deaths from lung cancer in 2008.1, 2, 3, 4 In this case, the patient was a 78 - year - old male.

The results of the *Global Cancer Observatory (*GLOBOCAN) research related to Cancer Incidence and Mortality Worldwide in 2012 showed Asia as the largest contributor to lung cancer. More than 51.4% of the world's lung cancer cases occur in Asia. According to the WHO cancer profile report, lung cancer contributes to the highest incidence of cancer in men in Indonesia, and is the number 5 contributor to cases in women. From the Ministry of Health data, the percentage of new cases in Indonesia reached 34.2% with a mortality rate of 30%.32, 33, 34 In this case the patient is a male from Asia, Indonesia.

Lung cancer can be caused by several risk factors. The risk factors are divided into two consisting of risk factors that can be controlled and cannot be controlled.

Controllable risk factors include smoking, radon exposure, indoor and outdoor pollutants, chronic lung disease, and carcinogens in the workplace. Uncontrollable factors include age, gender and genetics.[14] Smoking is the most common cause of lung cancer. It is estimated that 90% of lung cancer cases are caused by smoking.[15] Chemical substances contained in cigarette smoke are in the form of gas or particles that have been decomposed. These toxic materials can be in the form of chemicals, such as formaldehyde, nitrosamines, or in the form of gases, such as carbon monoxide, oxides of nitrogen, and hydrogen cyanide. In addition, cigarettes also contain free radicals that can stimulate cells to quickly undergo damage due to oxidative stress.[35] The risk is further exacerbated by exposure to other carcinogens, such as asbestos. There is no correlation between lung cancer and the number of packs smoked per year due to the complex interactions between smoking, environmental and genetic factors. The risk of lung cancer from second - hand smoke increases by 20 to 30%.[15] Exposure to metals such as chromium, nickel, arsenic and polycyclic aromatic hydrocarbons is also associated with lung cancer.16 In this case, the patient had a history of smoking for more than 50 years with 1 - 2 packs of cigarettes/day.

In general, almost 70% of lung cancer patients present with local symptoms due to tumour and metastasis. This is because the initial clinical course is usually asymptomatic. If the patient has shown symptoms, it means that the patient is already at an advanced stage.[36]

Clinical manifestations that can be found include shortness of breath, cough, chest pain, spinal pain, haemoptysis, anorexia, significant weight loss, weakness, and vena cava obstruction. Lung cancer with intrathoracic spread presents symptoms such as decreased breath sounds and shortness of breath, decreased heart sounds with heart enlargement, difficulty swallowing, elevation of the diaphragm, facial swelling, oedema of the extremities, hoarseness, infrequent cough, pleural chest pain, ptosis, miosis, facial anhidrosis, and pain in the spine and muscles along cervical 8 - thoracic 3. Cancer with distant metastases is usually characterised by weakness, weight loss, anorexia, hepatomegaly, pain, bone fractures, elevated alkaline phosphatase, lymphadenopathy, headache, seizures, nausea, vomiting, altered mental status, adrenal insufficiency, and subcutaneous nodules. This patient had symptoms such as shortness of breath, coughing, chest pain radiating to the back, decreased right lung breath sounds, and diaphragm elevation. The patient also experienced noticeable weight loss so the cancer in this case was suspected to have metastasised.[7, 8, 9]

Screening for lung cancer has concluded that *computed tomography (*CT) is more useful than chest X - ray, especially for high - risk smokers. A computed tomography chest X - ray examination more accurately supports the possibility of a lung tumour, when a normal chest X - ray cannot confirm the presence of a tumour. CT scan examination of the thorax is more sensitive than plain chest X - ray examination, as it can detect abnormalities or nodules with a diameter of at least 3 mm, although false positives for abnormalities of this size are 25 - 60%. Other supporting radiological examinations that are sometimes required are bronchography, fluoroscopy, superior venous cavography, ventilation/perfusion scanning, and *ultra - sound sonography (*USG).37 Other cytological examinations

for the diagnosis of lung cancer can be performed on pleural fluid, cervical and supraclavicular lymph node aspirates, and bronchial rinses and scrapings on bronchoscopy. For early diagnosis of lung cancer, histopathological examination is the gold standard. Diagnosis of lung cancer to obtain specimens can be by biopsy through: bronchoscopy, trans thoracic biopsy, thoracoscopy, mediastinoscopy and thoracotomy. Biopsy with TTB, especially for peripheral lesions with a size of >2 cm, has a sensitivity of 90 - 95%. The results of the examination will be better if there is guidance from CT scan, ultrasound, or fluoroscopy.[7, 38] This patient has been examined to diagnose in the form of CT scan, thorax photo, sputum culture, TCM, pleural fluid analysis, pleural fluid cytology, and TTNA.

Supporting examinations that can be used to diagnose lung cancer include laboratory examinations, radiology such as thorax X - ray and CT - Scan, as well as diagnostic measures such as *Trans thoracal biopsy (*TTB), *Fine needle aspiration biopsy (*FNAB), and histopathological examination.17 This patient was upright with a diagnosis of *Non - small cell* lung *cancer (*NSCLC) right lung tumour with adenocarcinoma impression.

The stage of lung cancer can be determined by clinical diagnosis (cTNM), pathological - surgical resection (pTNM), surgical evaluation (sTNM), retreatment (rTNM), and autopsy (aTNM). For lung cancer staging, at least thoracic CT scan, abdominal ultrasound (or abdominal CT scan), as well as brain CT scan and bone scanning are required. For Tx information: 1) Tumour evidently malignant from bronchopulmonary secretions, but not bronchoscopically and radiologically visible; 2) The tumour cannot be assessed at staging retreatment. Tis: carcinoma in situ (pre invasive carcinoma), T1: tumour, 3 cm in diameter or atelectasis at distal hilum. T3: any size tumour extending to pleura, chest wall, diaphragm, pericardium, <2cm from carina, total atelectasis present. T4: any size tumour invades the mediastinum or there is malignant pleural effusion. N0: no lymph nodes involved, N1: bronchopylmonary or ipsilateral hilum lymph node metastasis. N2: contralateral mediastinal or hilus metastasis or scaleneus or supraclavicular. M0: no benign metastasis, M1: benign metastasis to organs (brain, liver, bone etc.). (54, 55) This patient was staged as T4N1M1a. T4 because of the thoracic CT - scan image with a consolidated mass in the apical segment of the right lung measuring 4.7x6 cm, heterogeneous density, no visible calcification, extending to the mediastinal cavity with the presence of right pleural effusion. N1 because there was a nodule in the inferior lobe of the right lung, irregular, enlarged right parabronchial lymphodule measured 1x4x1.1 cm and 1.4x1 cm. M1a because there is already metastasis in the form of pleural effusion in the lung cavity.[8, 17]

Lung cancer treatment consists of several modalities. Common standard therapies for lung cancer are surgery, radiotherapy and chemotherapy. Optimal therapy with surgery, radiation and chemotherapy only achieves a cure rate of <15%. Biomolecular research in recent decades has identified molecular pathways that are important in tumour development and growth.18, 19, 20 These drugs have been developed by targeting mechanisms in lung tumours to improve outcomes and improve the quality of life of cancer patients with treatment called ***Targeting Therapy***.[18] Rapid developments in molecular biology provide evidence that driver mutations, such as epidermal growth factor receptor (EGFR) 23, 24 and anaplastic lymphoma kinase (ALK) genes25 , play an important role in *Non - small cell lung cancer (*NSCLC) cell oncogenesis. Studies revealed that first - line treatment with EGFR tyrosine kinase inhibitors (TKIs) provided better *Progression - Free Survival (*PFS) compared to standard chemotherapy in patients with advanced NSCLC, who were selected based on the presence of activating EGFR mutations (Figure 2).26, 27, 28, 29, 30, 31 Therefore, EGFR – TKI monotherapy has become the standard of care for patients with advanced NSCLC who are positive for the mutation. However, although most NSCLC patients with TKI - sensitive EGFR mutations show a clear initial response to EGFR - TKI treatment, resistance to these drugs may develop after 9 to 14 months of therapy.

Lung cancer, especially non - small - cell lung cancer (NSCLC), remains the leading cause of cancer death worldwide.39 Unfortunately, few treatment options are available for most patients with advanced or metastatic disease.40 Despite improvements in survival, most advanced patients require systemic therapy.41 Recent advances in genetic discoveries have proven that the pathways EGFR activation - dependent pathways occur in more than half of patients with NSCLC and play a critical role in epithelial cell development and progression.42 Small molecule tyrosine kinase inhibitors (TKIs), including gefitinib and erlotinib, which specifically block the EGFR - dependent pathway, were the first targeted drugs to enter clinical use for the treatment of lung cancer.43 It has been extensively demonstrated that NSCLC patients harbouring sensitive EGFR mutations, which mainly refer to exon 19 deletion or L858R substitution in exon 21, usually benefit more from EGFR - TKIs than wild - type patients.[44, 45] However, whether the efficacy of EGFR - TKIs varies among different sensitive EGFR mutations is still controversial. Some studies have reported that advanced NSCLC patients with EGFR exon 19 deletion have longer overall survival (OS) and/or progression - free survival (PFS) after treatment with gefitinib or erlotinib compared to those with L858R mutation but these results have not been shown in all reports.[46, 47, 48, 49, 50, 51, 52, 53]

This study recorded patients' objective response to chemotherapy based on RECIST, both after cycle 3 and cycle 6 chemotherapy. In this study, PDPI RECIST was used, namely

1) Complete response (CR) if at evaluation, the tumour disappeared 100% and this condition persisted for more than 4 weeks;
2) Partial response if the tumour size reduction was >50% but 25% but <100%; 3. Stable disease if the tumour size does not change or decreases by >25% but <50%; and 4. Progressive disease if the tumour size increases by <25% or new tumours/lesions appear in the lung or elsewhere.[54]

Four EGFR TKIs, erlotinib (Tarceva), gefitinib (Iressa), afatinib (Gilotrif), and osimertinib (Tagrisso), have been approved by the *Food and Drug Administration (*FDA) in

the treatment of advanced lung cancer in the United States. Compared to standard cytotoxic chemotherapy doublets, these drug classes have been shown to prolong *progression - free survival (*PFS) in advanced NSCLC patients with positive EGFR mutations. Gefitinib showed an impressive improvement in PFS compared to carboplatin (Paraplatin) and paclitaxel (Taxol) in the Iressa Pan - Asia Study trial in 2009. In this study, PFS was doubled with gefitinib at 10.8 months compared to 5.4 months for the standard cytotoxic chemotherapy doublet.55 Gefitinib was approved for patients whose tumours contained deletions of exon 19

EGFR or exon 21 L858R. Erlotinib was also compared to standard cytotoxic chemotherapy in the OPTIMAL trial, an impressive improvement in *progression - free survival (*PFS) of 8 months was noted when erlotinib compared to gemcitabine (Gemzar) plus carboplatin.56 Afatinib is an irreversible oral EGFR and HER2 inhibitor. In the LUX - Lung 3 trial, afatinib showed a significant improvement in PFS over 6.7 months compared with cisplatin (Platinol) and pemetrexed (Alimta) in treatment patients with EGFR exon 19 deletion and L858R point mutation.[57]

Afatinib is an FDA - recommended first - line treatment for patients with metastatic NSCLC whose tumours have EGFR exon 19 deletion or exon 21 substitution mutations.58 The EGFR T790M mutation in exon 20 is associated with acquired resistance to TKI therapy and has been reported in up to 63% of patients with disease progression after an initial response to a first - line TKI.59, 60 Osimertinib and rociletinib are third - generation EGFR inhibitors that are active in preclinical models of EGFR T790M mutated NSCLC.[61, 62]

In the prognosis of NSCLC cases, the most important thing is to determine the stage of the disease. About 40% of adenocarcinomas and large cell carcinomas die from thoracic complications, 55% from extra - thoracic, 15% of adenocarcinomas and large cell carcinomas metastasise to the brain, and 8 - 9% die from central nervous system disorders. The average life expectancy of patients with metastatic tumours varies from 6 months to 1 year. It is highly dependent on performance status (Karnofsky scale), extent of disease, and presence of weight loss in the last 6 months.63, 64, 65 The prognosis in this patient for vitam is dubia ad malam due to possible complications of the cancer itself which has metastasised can be life - threatening from the patient, age and other comorbid factors. For functionam is dubia ad malam, because in carrying out daily activities requires the help of others, because they cannot carry out activities independently. For ad sanactionam is dubia ad malam, because there can be enlargement of the tumour and metastases in certain organs. The main prevention is not smoking, quitting smoking and avoiding cigarette smoke early on to reduce the occurrence of lung cancer. Recently, chemoprevention has been done, using retinoid acid derivatives, carotenoids, vitamin C, selenium, and others.[7, 8]

4. Conclusions

The management of lung cancer in the elderly has been controversial in various studies around the world, especially the high mortality rate in patients with chemotherapy treatment. Certain patients with positive EGFR mutations have a higher *progression - free survival (*PFS) than those with negative EGFR mutations. In some cases, adjuvant chemotherapy treatment has been found to be more aggressive in terms of side effects than active EGFR TKI monotherapy. Many risk factors can lead to failure in lung cancer treatment including comorbidities of other diseases in patients, especially patients with advanced age. This study explains the importance of early screening and diagnosis based on history, physical examination, complete support and appropriate measures to determine the type of mutation of lung cancer. The challenge to management in elderly patients is the accuracy in determining the diagnosis based on the type of EGFR mutation to get the right target therapy treatment. This case reports an elderly male patient with a diagnosis of *Non - Small Cell Lung Cancer (*NSCLC) *type Adenocarcinoma Stage IV A PS score 4 with EGFR Mutation Exon 19 dels* with a treatment plan in the form of the first generic target therapy, gefitinib. However, the patient experienced worsening of the condition before being given the target therapy.

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