

Recent Management of Patients with Advanced Epidermal Growth Factor Receptor Mutation Non-small Cell Lung Cancer: Role of Afatinib and Lesson Learned for Developing Countries

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ABSTRAK

Kanker paru merupakan penyakit yang merugikan di dunia dengan angka insidensi, mortalitas dan morbiditas yang tinggi khususnya di negara berkembang. Pengobatan konvensional menggunakan kemoterapi sitotoksik memiliki kelemahan seperti kemungkinan resistensi dan toksisitas dari obat. Perkembangan terbaru menunjukkan bahwa Tyrosine Kinase Inhibitor generasi pertama, Gefitinib dan Erlotinib dan Tyrosine Kinase Inhibitor generasi kedua terbaru, Afatinib, memiliki potensi untuk menjadi pilihan pengobatan kanker paru bukan sel kecil (non-small cell lung cancer) metastatik/ lanjut EGFR (Epidermal Growth Factor Receptor) mutasi positif. Obat ini bekerja melalui ikatan yang ireversibel pada EGFR sehingga dapat menginaktivasi reseptor tirosin kinase. Beberapa studi menunjukkan bahwa Afatinib lini pertama dapat memperlama masa bebas progresivitas penyakit dan kontrol terhadap penyakit, serta dapat menjadi alternatif bagi pasien yang intoleran terhadap Gefitinib dan erlotinib. Di Indonesia, era Jaminan Kesehatan Nasional (JKN) telah terlaksana dan JKN menanggung penuh pengobatan kanker, termasuk TKI generasi pertama, Gefitinib dan Erlotinib, terhadap pasien-pasien kanker paru bukan sel kecil EGFR mutasi positif di Rumah Sakit Umum Pusat Nasional Dr. Cipto Mangunkusumo. Afatinib sebagai salah satu TKI generasi kedua terbaru, bisa juga diberikan sebagai alternatif apabila telah ditanggung JKN di masa datang. Akan tetapi, penilaian juga perlu dilakukan khususnya untuk mengetahui efektivitas dan efek samping yang dapat muncul pada pasien-pasien di negara-negara berkembang.

Kata kunci: kanker paru bukan sel kecil metastasis/ lanjut, EGFR mutasi positif, Afatinib.

ABSTRACT

Lung cancer is a devastating disease with a high incidence, mortality and morbidity rate, especially in developing countries. Conventional treatment with cytotoxic chemotherapy has some limitations attributed to chemoresistance and toxicity. Recent advances have shown that first generation Tyrosine Kinase Inhibitor (TKI), Gefitinib and Erlotinib, and the newest available second generation Tyrosine Kinase Inhibitor (TKI), Afatinib, have the potential to be an option in the management of patients with epidermal growth factor receptor/EGFR mutation positive advanced/ metastatic non-small cell lung cancer. Afatinib works by binding to EGFR irreversibly, thus inactivating the tyrosine kinase receptor. Some studies demonstrated that Afatinib first-line may result in longer progression free survival (PFS) and better disease control, and as an alternative for patients who intolerance to Gefitinib or Erlotinib. In Indonesia, the era of National Health Insurance has been implemented

and National Health Insurance has covered treatment for cancer, including first generation TKIs, Gefitinib dan erlotinib, for patients with EGFR mutation positive advanced/ metastatic non-small cell lung cancer at Cipto Mangunkusumo National Hospital. Afatinib, as one of the newest available second generation TKI, may be given free of charge too as an alternative if the National Health Insurance will be covered in the future. Further research is needed to know the efficacy and adverse effects that may occur in patients from developing countries.

Keywords: *advanced/metastatic non small cell lung cancer, EGFR mutation, afatinib.*

INTRODUCTION

Being the most common for decades, there were 1.8 million new cases of lung cancer in 2012, forming 12.9% of all cancers. Among 58% or 1.066 million cases occurred in less developed regions. In some developing countries such as Indonesia, lung cancer is on the top with 25,322 new cases or 18.2% in 2012.¹ Data from Dharmais National Cancer Center in Indonesia also showed that lung cancer was one of the top three most prevalent cancers in 2010-2013 continuously with around 117 to 173 new cases.² In India, with a population of around 1.258 billion population, lung cancer was also ranked the highest number of new cancer cases in 2012, with 53,728 people diagnosed.¹

Besides its high incidence, lung cancer is also the deadliest cancer in the world causing 21.9% of all cancer-related mortality. Focusing on developing countries, Indonesia and India also claimed lung cancer as the highest cause of cancer-related mortality, with 22,525 and 48,697 fatal cases in 2012.² Moreover, lung cancer had cost \$12.1 billion to The U.S. health fund in 2010 and loss of productivity due to early death.³ Thus, research has been done to find the best way of curing these diseases.

There are many treatment options for cancer management, however, traditional treatment such as chemotherapy, which rely on the histopathologic subtype has limited efficacy attributed to chemoresistance and toxicity (e.g. nausea and vomiting, alopecia, fatigue, cytopenias, febrile neutropenia, nerve, and kidney damage, as well as death).⁴ Recent advances have shown that understanding the basic molecular of cancer has led to a new paradigm in curing cancer, the era of personalized medicine. One of them is the development of Tyrosine Kinase Inhibitors (TKIs) as targeted therapies in cancer

management. This review will explore more on the role of TKIs especially Afatinib as the newest available targeted therapy in Non-Small Cell Lung Cancer (NSCLC) management and what can be learned for developing country.⁵

LUNG CANCER

Lung cancer is divided into two main histological subtypes, Small Cell Lung Cancer and Non Small Cell Lung Cancer (NSCLC). The latter is further classified into three major histologic subtypes, squamous-cell carcinoma with keratin expression, adenocarcinoma with glandular expression, and large-cell carcinoma. Among those types of cancer, NSCLC (86%) with adenocarcinoma and squamous cell carcinoma is the most common subtype of lung cancer. Moreover, perihilar mass with peribronchial compression and obstruction is the most common presenting symptom.⁶

To diagnose lung cancer, there are several diagnostic methods which may be used. First, clinical history and recognizing the typical, non-specific signs and symptoms of lung cancer, is needed. Then, further evaluation of the risk factors such as age, tobacco use, family history of cancer (especially lung cancer or oropharyngeal cancers) and exposure to asbestos. Next, the patient should be referred to a multidisciplinary team for diagnosis and evaluation. The patient will undergo a chest radiograph and Computed Tomography (CT) scan for diagnosing and staging of lung cancer if there is a suspicion of malignancy. Positron Emission Tomography (PET)-scan can be an additional combination tool to CT-scan, to diagnose and characterize the primary nodule, stage, and to treat lung cancer. Since surgery is the best treatment option, especially for patient in the early stage, preoperative evaluation may

be needed for lung cancer patients. Patients will have his/her cardiovascular risk quantified and their lung function assessed by using the Thoracic Revised Cardiac Risk Index (ThRCRI) and spirometry, respectively. Sputum cytology testing, tumor marker evaluation, and biopsy by using Transbronchial Needle Aspiration (TBNA), Endobronchial Ultrasound (EBUS) with Fine-Needle Aspiration (FNA), Endoscopic Ultrasound (EUS) and transthoracic FNA or mediastinoscopy is also necessary for the diagnosis and treatment evaluation.⁷

There are two types of staging in lung cancer, pathological/surgical and clinical staging. Pathologic staging has been mentioned in the previous paragraph.⁸ The newest edition of clinical staging is the eighth revision and it will be implemented in January 2017 by The International Association for the Study of Lung Cancer (IASLC). Further clinical staging is classified based on size of Tumor, Nodes, Metastasis (TNM) Classification. From the state of T, N and M, lung cancer is further classified into different stages and this affects the treatment and prognosis of disease.⁹

Management of lung cancer differs from one subtype to another. In stage I and II of the disease, surgery, especially lobectomy, is the treatment of choice. Patients with stage II and III NSCLC may be offered a two-drug combination adjuvant chemotherapy, preferably with cisplatin.¹⁰ In patients with locally advanced or stage III disease, surgery with lung-sparing and minimal invasive technique may be indicated; added by adjuvant or neoadjuvant chemotherapy to improve cure rates by killing the micrometastases. In addition, radiotherapy may also be used for preoperative chemoradiotherapy, concurrent chemoradiotherapy or induction therapy followed by high-dose radiotherapy in patients with inoperable stage III NSCLC.¹¹ In managing patients with stage IV disease, there will be a discussion among the multidisciplinary tumour board to choose the best treatment option based on the cancer histology, molecular pathology, age, performance status (PS), comorbidities, and patient preferences. Several approaches to management in stage IV patients are smoking cessation due to interaction with systemic therapy;

systemic therapy with platinum-based doublet (i.e. cisplatin/carboplatin and gemcitabine/taxanes/pemetrexed) as the first line, especially if the patient has PS 0-2; Tyrosine Kinase Inhibitors (TKIs), especially in patients with a mutation or rearrangement in the Epidermal Growth Factor Receptor (EGFR) or Anaplastic Lymphoma Kinase (ALK); and radiotherapy or surgery in patient with oligometastatic NSCLC.¹² Recent advances also highlight the usage of antibodies to Vascular Endothelial Growth Factor (VEGF) such as Bevacizumab.¹³

RECEPTOR TYROSINE KINASE (RTK)

Receptor tyrosine kinase is one of cell surface receptors, which play a key role in cell proliferation and differentiation, cell survival and metabolism, cell migration and cell cycle control. There are 20 subfamilies of RTK with 58 types in total, however, all of them have a similar configuration which consists of a ligand-binding region, a single transmembrane helix, and a cytoplasmic region. The carboxy (C-) terminal and juxtamembrane regions of receptor tyrosine kinase may be found in the cytoplasmic region. During inactive periods, RTKs will form monomers or oligomers. When there is a growth factor or ligand binding, the receptors will undergo auto-phosphorylation, creating an activated kinase and phosphotyrosine-based binding site that can recruit Src homology-2 (SH2) and phosphotyrosine-binding (PTB) domains from the cytoplasm. Next, the RTK 'active' dimer or oligomers may further initiate the recruitment of other downstream signaling molecules. Being an 'active' receptor, RTKs will lead to a subsequent activation of downstream a signalling pathway.

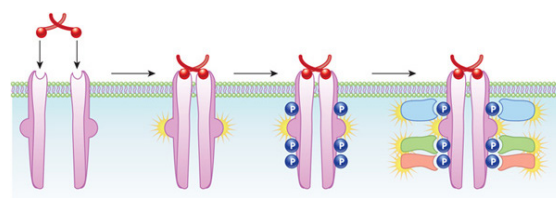


Figure 1. Schematic diagram depicting the process of RTK activation. Firstly, the ligand will bind to an inactive RTK receptor and the dimerization process begin. Then, auto-phosphorylation of the tyrosine residues occur (third part) and the phosphorylated RTKs may attract intracellular proteins for further activation of the signaling cascades.¹⁶

Some of the pathways which may be involved are the mitogen-activated protein kinase (MAPK), phosphatidylinositol 3-kinase (PI3K), protein kinase C and GTPases (e.g. Ras and Rho). All of these signalling cascades leads to a specific function of the cell.^{14,15}

EPIDERMAL GROWTH FACTOR RECEPTOR

Epidermal Growth Factor Receptor (EGFR) is a protein which belongs to the ErbB receptor tyrosine kinases' family along with HER2/c-neu (ERBB2), HER3 (ERBB3) and HER4 (ERBB4). This transmembrane receptor, also called as ERBB, ERBB1, and HER1, is encoded by the EGFR gene located on the short arm (p) of chromosome 7 position 12 (chr band 7p12.1), base pair 55,019,031 to 55,207,337 with ~2115 nucleotides length analyzed. Based on high-resolution X-ray crystal analysis, there are two ligand binding domain (domains I and III) and two cysteine rich domains (domain II and IV) in the EGFR family members which may be used in various extracellular or intracellular signalling pathways.^{17,18} To activate this receptor, there are a lot of ligands in this pathways, including the epidermal growth factor (EGF), betacellulin, amphiregulin, epigen, epidregulin and heparin binding EGF-like growth factors. The binding of these ligands will change the conformation of the receptor, leading to dimerization and auto-phosphorylation of tyrosine in the intracellular domain. Then, auto-phosphorylated intracellular tyrosine residues will regulate the activation of downstream proteins and promote nucleus signal transduction.¹⁸ Some of the downstream target of EGFR are PI3K, RAS, mammalian target of rapamycin (mTOR), mitogen-activated protein kinase (MAPK), Janus Kinase (JAK), extracellular signal-regulated kinase (ERK), signal transducer and activator of transcription (STAT) signalling pathways.¹⁷ Moreover, activated EGFR also shown to have function in regulating the process of transcription, DNA synthesis and repair.¹⁹

Since the development EGFR-TKI was found found to be useful in treating NSCLC, the mutation status of EGFR has become more and more important. Mutation of EGFR will lead to NSCLC by increasing EGFR expression,

enhancing ligand production and activating the mutation of EGFR (exon 18-21 especially exon 19 deletion, exon 21 L858R substitution, exon 18 G719X missense mutation as the most common mutation) in malignant cell.^{5,13} Upregulation of EGFR pathways will activate downstream proto-oncogene such as RAS and RAF, resulting in activation of other signaling pathway, tumor growth and proliferation.⁵ Study done by Nakamura et al.²⁰ showed that there may be an association between mutation status of EGFR and volume doubling time (VDT) of adenocarcinoma. People with mutant EGFR had a longer VDT and this mutation may lead to a better patient prognosis. Other common mutation in EGFR is a point mutation in exon 20 of T790M which has an association with resistance to tyrosine kinase inhibitor. Research done by Costa et al.²¹ showed that patients with the T790M mutation had a shorter progression free survival (9.7 months vs 15.8 months in patients with no mutation) during treatment with erlotinib.

TYROSIN KINASE INHIBITORS

Tyrosine kinase inhibitors (TKIs) have made a breakthrough in lung cancer management. Previously, some patient groups, especially the elderly who were diagnosed with lung cancer, had a poor prognosis and high incidence of death due to their inability to receive treatments such as operations or cytotoxic agents which have a lot of side effects. However, as the development of medicine continued, in this TKI era, even patients with poor PS but positive EGFR mutation can receive therapy to extend their life. Chen et al.²² showed that elderly patients with positive EGFR mutation have significantly better overall survival compared to the wild type patients (13.2 vs 4.9 months, $p=0.003$). Patients treated with erlotinib, a TKI, also had longer median progression-free survival than those by chemotherapy (13.1 [95% CI 10.58-16.53] vs 4.6 months [95% CI 4.21-5.42] respectively) as shown in a study by Zhou et al.²³ These result indicate that positive EGFR mutation status and use of TKIs may reverse the patient's poor prognosis.

The first ever recognition of TKIs' usage began in 2004, where a group of researchers found that a small group of patients who responded

to Gefitinib had distinct characteristics. These groups were those of Asian ethnicity, females, adenocarcinoma and never smoking status. Since then, trials were done and Gefitinib became the pioneer in treating EGFR-mutated NSCLC patients after publication of the Iressa Pan-Asia Study (IPASS). In that study, Gefitinib exhibited a superiority on progression-free survival and overall response rate to Carboplatin/Paclitaxel. Then, other TKIs such as erlotinib, emerged and TKIs become one of the treatment option in lung cancer.²⁴

Unfortunately, as time goes by, resistance was developed following one or two years treatment with first generation TKIs. The emerging of resistance towards TKIs were due to several mechanisms, one of which is rapid changes of cancer cells' genome. Moreover, three pathways were responsible in acquiring resistance towards EGFR TKIs in lung cancer: 1) Growth factor receptor activation, 2) EGFR related protein and ligands activation, and 3) downstream signaling molecules activation. One of the most widely study mechanism was related to T790M, where this mutation may reduce the affinity of TKI towards EGFR and resistance occurred. Other examples are HER2 amplification, expression of integrin β 1, altered expression B-cell lymphoma 2 (Bcl2), Bcl2 interacting apoptosis mediator of cell death (BIM), p53 and nuclear-factor-kappa B (NF-kB) which related to apoptosis.^{24,25}

In order to fight the evolution of this new subtype of lung cancer, the second generation of lung cancer medication was developed. This second generation has a better efficacy against the variation of an EGFR oncogene (such as the mutated EGFR-L858R/T790M). Afatinib and dacomitinib as some example of the newest market available generation may have a better suppression towards tyrosine kinase receptor by preventing the dimerization which promote receptors' activity.²⁶ The third generation (e.g. osimertinib and rociletinib) also emerge to accommodate neediness of competitive inhibition towards T790M mutant kinases.²⁴ Since only first and second generation are available on market, further explanation will focus more on Gefitinib, Erlotinib and Afatinib. The comparison between those drugs can be seen in **Table 1**.

In general, Gefitinib, Erlotinib and Afatinib are oral medications which may inhibit EGFR tyrosine kinase, but only Afatinib can inhibit the receptor irreversibly. In terms of efficacy and side effects, all TKIs had a better efficacy compared with chemotherapy and shared almost similar types of side effects such as skin or gastrointestinal problems.²⁶⁻³⁴

In general, there are three TKIs: gefitinib, erlotinib, and afatinib as oral targeted agent which inhibit EGFR tyrosine kinase, however only afatinib can inhibits the receptor irreversibly. In term of efficacy, all TKIs had a significant response rate and progression free survival compared to chemotherapy in patients with EGFR mutation advanced/metastatic non small lung cancer and shared comparable side effects such as skin or gastrointestinal problem based on many large clinical trial.²⁶⁻³⁴

Mok et al.³⁵ reported a phase 3, multicenter, randomized, open-label, parallel-group IPASS (Iressa Pan Asia) study that first-line gefitinib is more superior to carboplatin-paclitaxel for the treatment of clinically selected patients in east asia who had EGFR mutated advanced non-small cell lung cancer in terms of progression free survival (9.5 vs 6.3 months; HR 0.48, 95% CI: 0.36-0.64; $p < 0.001$) and response rate (71.2% vs 47.3%; $p < 0.001$). In Japan, Mitsudomi et al.³⁶ also reported an open label phase 3 WJTOG3405 study that gefitinib has longer progression free survival (9.2 months; 95% CI: 8.0-13.9 vs 6.3 months; 95% CI 5.8-7.8; HR 0.489; 95% CI 0.336-0.710; log rank $p < 0.001$) in patients with lung cancer who are selected by EGFR mutations compared to cisplatin plus docetaxel significantly.

In China, Zhou et al.³⁷ reported a multicentre, open label, randomised, phase 3 first-line treatment for patients with advanced EGFR mutation-positive non-small cell lung cancer OPTIMAL, CTONG-0820 study that median progression free survival of erlotinib-treated patients was significantly longer than in those on gemcitabine plus carboplatin (13.1 months; 95% CI: 10.58-16.53 vs 4.6 months; 95% CI 4.21-5.24; HR 0.16; 95% CI 0.10-0.26; $p < 0.0001$). In Europe, Rossel et al.³⁸ also reported a multicentre, open-label, randomised

Table 1. Comparison between Gefitinib, Erlotinib, and Afatinib

Drugs	Mechanism of Action	Administration	Efficacy	Side Effects	Price
Gefitinib	Reversible inhibition of EGFR tyrosine kinase by competing with adenosine triphosphate at EGFR kinase binding sites. Then, EGFR signal transduction will be blocked.	Oral, tablet 250 mg.	As the first line treatment to EGFR mutated patients, Gefitinib had a better median progression free survival compared to platinum-based doublet chemotherapy (10 months vs 5-6 months). No significant difference in overall survival.	Mild to moderate toxicities. Main adverse reactions: skin rash/acneiform rashes, dry skin, pruritus, paronychia, diarrhea, elevated aminotransferase, neutropenia, anemia, interstitial lung disease.	IDR 802,595.2 or 54 USD per tablet 250 mg.
Erlotinib	Competitive inhibitor at ATP-binding pocket in intracellular domain of EGFR (same mechanism with Gefitinib).	Oral, tablet 25 mg, 100 mg and 150 mg.	Compared to docetaxel/pemetrexed, erlotinib had 0.71 hazard ratio (0.13 to 3.97) in patient with positive EGFR mutation. Moreover, longer median overall survival also observed in comparison with best supportive care patients (10.9 and 8.3 months).	Low incidence of myelosuppression, nausea, vomiting, fatigue, neurotoxicities. Mild to moderate rash, diarrhea, and asymptomatic hypertransaminasemia.	IDR 900,000 or 60 USD per tablet 150 mg.
Afatinib	Irreversible binding of EGFR, inactivate dimerization process that promote the activity of tyrosine kinase receptor. Moreover, afatinib may inhibit enzymatic activity of wild-type EGFR, HER2, EGFR L858R and T790M mutant.	Oral, tablet 20 mg, 30 mg and 40 mg.	Compared with Cisplatin + Pemetrexed, Afatinib had a superiority in terms of progression free survival and overall survival with 11.1 vs 6.9 months and 31.6 vs 28.2 months (HR: 0.58, p=0.0004 and 0.78, p=0.1) respectively in advanced lung adenocarcinoma-EGFR positive patients.	Diarrhea, rash/dermatitis acneiform, stomatitis, paronychia, dry skin, decreased appetite, pruritus.	IDR 1,255,979.91 or 83.73 USD per tablet.

phase 3 European patients with advanced EGFR mutation-positive non-small cell lung cancer (EURTAC) trial that median progression free survival of erlotinib group was 9.7 months (95% CI: 8.4-12.3) compared with 5.2 months (95% CI: 4.5-5.8) standard chemotherapy cisplatin plus docetaxel group (HR 0.37; 95% CI: 0.25-0.54; $p < 0.0001$).

Sequist et al.³⁹ reported phase III of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations LUX-Lung 3 study that median progression free survival among those with exon 19 deletions and L858R EGFR mutations was 13.6 months for afatinib and 6.9 months for chemotherapy (HR 0.47; 95% CI 0.34-0.65; $p = 0.001$). Wu et al.⁴⁰ also reported an

open-label, randomised phase 3 trial of LUX-Lung 6 that median progression free survival was significantly longer in the afatinib group (11.0 months; 95% CI: 9.7-13.7) than in the gemcitabine and cisplatin group (5.6 months; 95% CI: 5.1-6.7; HR 0.28; 95% CI: 0.20-0.39).

None of gefitinib and erlotinib demonstrated longer overall survival compared to standard chemotherapy. Yang JC et al.⁴¹ performed analysis of overall survival data from two randomised, phase 3 trials (LUX-Lung 3 and LUNG-Lux 6) that showed eventhough none of both trial there were no significant benefit in overall survival, however in preplanned analysis, overall survival was significantly longer for patients with del 19 positive tumours in the afatinib group than in the chemotherapy group

in both trials. In LUX-Lung 3, median overall survival was 33.3 months (95% CI: 26.8-41.5) in the afatinib group versus 21.1 months (95% CI: 16.3-30.7) in the chemotherapy cisplatin plus pemetrexed group (HR 0.54; 95% CI: 0.36-0.79; $p = 0.0015$). In LUX-Lung 6, median overall survival was 31.4 months (95% CI: 24.2-35.3) in the afatinib group versus 18.4 months (95% CI: 14.6-25.6) in the chemotherapy cisplatin plus gemcitabine group (HR 0.64; 95% CI: 0.44-0.94; $p=0.0023$).

Based on many clinical trials, in patients with advanced/metastatic non-small cell lung cancer when EGFR mutations are diagnosed in the first line setting, we have three options to administer EGFR TKIs: the first generation TKIs: Gefitinib and Erlotinib, and the second generation TKI: Afatinib. The question is which parameters should be taken into consideration regarding the choice of EGFR TKIs?

Park et al.⁴² performed a phase 2b, open-label, randomised controlled trial afatinib versus gefitinib as first-line treatment of patients with EGFR mutation-positive non-small cell lung

cancer (LUX-Lung 7). According to Park et al.⁴², LUX-Lung 7 is the first prospective head-to-head trial to assess an irreversible EGFR TKI afatinib and a reversible EGFR TKI gefitinib, as first-line treatment of patients with EGFR mutation-positive non-small cell lung cancer in both Asians and non-Asian patients. Although it was an extrapolatory trial, the data indicated that afatinib might offer improved progression free survival compared with gefitinib. Progression free survival by blinded independent assessment was significantly longer with afatinib (11.0 months; 95% CI: 10.6-12.9) versus gefitinib (10.9 months; 95% CI: 9.1-11.5).

The progression free survival curves separated more substantially with time, starting at the median. This phenomenon might reflect the broader and more durable inhibitory profile of afatinib and its potential to delay possible resistance mechanism when compared with gefitinib.

The proportion of patients who achieved an objective tumour response was significantly higher with afatinib (70%) than with gefitinib

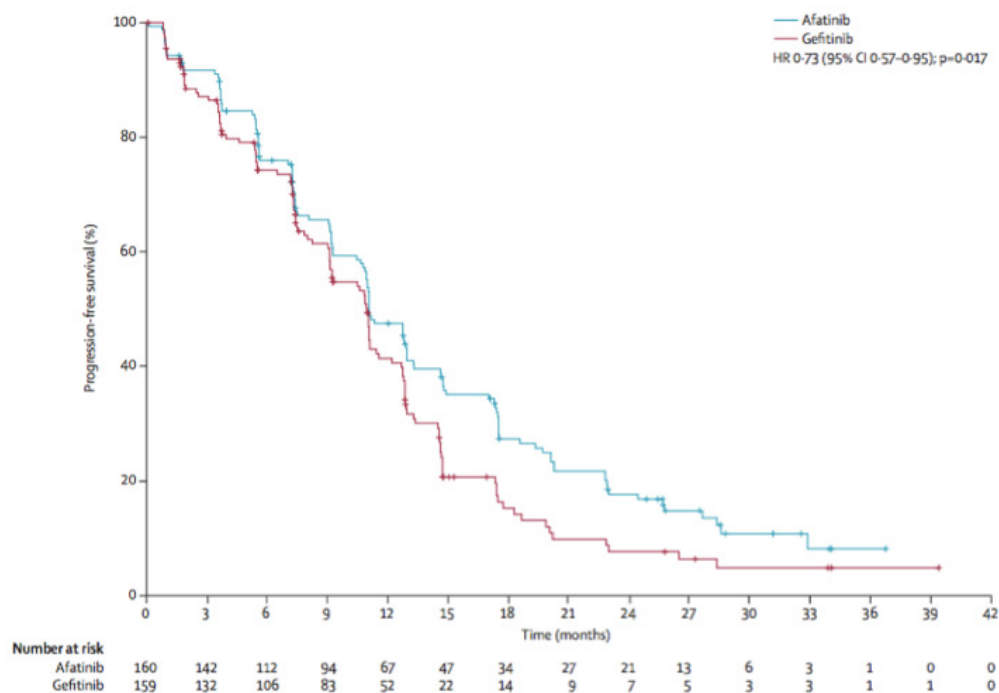


Figure 2. Progression free survival of afatinib vs gefitinib by independent review.⁴² (Published under permission from original article entitled "Afatinib versus gefitinib as first-line treatment of patients with EGFR mutation-positive non-small-cell lung cancer (LUX-Lung 7): A phase 2B, open-label, randomised controlled trial", published in *Lancet Oncology* 2016).

(56%) by independent review (OR: 1.87; 95% CI: 1.18-2.99) and a longer median duration of response for patients treated with afatinib than gefitinib (10.1 months vs 8.4 months).⁴² Peled⁴³, Head of the Thoracic Cancer unit, Davidoff Cancer Center, Petah tikva, Israel recommended that in daily clinical practice, we take into account the type of the mutation, age, physical appearance of the patient, the side effects of TKIs, and comorbidity. If the patient is an old lady with many comorbidities, afatinib would not be the first choice, but a younger or middle-aged person with Exon 19 mutations can get benefit from afatinib. Afatinib also covers uncommon mutation, especially those in exon 18. Another consideration is brain metastases. Afatinib shows a favourable response rate with regard to brain lesions, even though the other TKIs elicit brain responses too. As the EGFR TKIs showed comparable progression free survival based on many trials, toxicity is one of the selection criteria. Diarrhea tends to occur more frequently with afatinib, as well as nail abnormalities, which can become a significant burden for many patients, forcing the doctor to decrease the afatinib dose. Even though dose reductions occurred more often with afatinib than with gefitinib due to adverse events, however afatinib still preserved efficacy with dose reductions.

AFATINIB IN INDONESIA AND LESSON LEARNED

The fight against cancer in Indonesia started in the early 1920s during the Dutch Colonial Government with the Institution for Cancer Control. However, during the Japanese Colonization, this institution was closed and rebuilt again in 1962 under the name of The Cancer Control Foundation. Since then, many efforts have been done to handle the cancer problems such as establishment of Dharmas Cancer Center and cancer data collection.⁴⁴ However, before the National Health Insurance/*Jaminan Kesehatan Nasional* (JKN) was implemented, cancer was a huge problem, especially due to the lack of funds.⁴⁵

Since the era of JKN, cancer patients have a better/longer chance of survival. Under the principle of social insurance and equality of

services, JKN aims to ensure health care coverage of every Indonesia citizen.⁴⁶ This includes services such as accommodation, diagnostic procedures, laboratory examinations, and other procedures related to cancer management.⁴⁷ Regarding cancer treatment in patients with positive EGFR mutation, first line Gefitinib and Erlotinib is covered by JKN and may be used as one of the treatment modalities. However, Afatinib in JKN is yet to be free of charge, yet it can be used as first line treatment options in EGFR mutation positive NSCLC management.^{43,48}

CONCLUSION

Lung cancer is an iceberg phenomenon, where even with proper cancer management, high incidence and rate of mortality are still the norm. One of the recent advances in cancer management is the development of second generation TKIs, especially Afatinib as the newest available drug. This drug inhibits EGFR irreversibly compared with first generation TKIs, Gefitinib and Erlotinib. Thus, Afatinib may be an alternative drug with a superior effect in patients with mutated EGFR. To be free of charge, this drug should be registered to JKN's national formulary. Moreover, further research is needed, regarding the efficacy and adverse effects in the Indonesian population.

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