Benefits of Conventional Chemotherapy in Progressive Disease Patients with Tyrosine-Kinase Inhibitors: A Case Report

Ahmad Junaidi1*, Sabrina Ermayanti2, Afriani Afriani2

1Specialized Residency Training, Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Andalas, Padang, Indonesia
2Oncology Subdivision, Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Andalas, Padang, Indonesia

ARTICLE INFO

Keywords:
Lung adenocarcinoma
Chemotherapy
Epidermal growth factor receptor
Mutation
Tyrosine-kinase inhibitor

*Corresponding author:
Ahmad Junaidi

E-mail address:
yeahjuna@gmail.com

All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.37275/bsm.v6i14.657

1. Introduction

Treatment of advanced-stage lung cancer, non-small cell carcinoma (KPKBSK) has developed rapidly in recent years and is very decisive in the survival of lung cancer patients through conventional chemotherapy, targeted therapy, immunotherapy, and others. Therapies targeting specific oncogenic driver mutations can inhibit tumor progression and provide a favorable prognosis in clinical practice.1 Epidermal growth factor receptor (EGFR) mutations in KPKBSK are favorable predictive factors for the treatment of EGFR tyrosine kinase inhibitors (TKI). As many as 80% of KPKBSK adenocarcinoma patients have EGFR mutations.1-3 A study reported that in 205 CRCCC patients in China, 60% were women, 57% were non-smokers, and 43% had adenocarcinomas with mutations in exons 19 and 21 of 32.2%. EGFR mutations were also found to be lower in men at 14%, 10% in smokers, and 8% in European races.4

The guidelines of the American Society of Clinical Oncology (ASCO), the European Society for Medical
Oncology (ESMO), and the National Comprehensive Cancer Network (NCCN) recommend EGFR TKI as the first-line treatment for mutated EGFR patients. The most common mutations are exon 19 deletions and exon 21 single point mutations (Leu858Arg, L858R), both of which account for more than 80% of EGFR mutations. The standard first-line TKI treatment is a first-generation TKI (gefitinib, erlotinib) or second-generation (afatinib). EGFR TKI increased response rate (RR), time to progression (TTP), and overall survival (OS). Unfortunately, although patients receiving an EGFR-TKI have an RR of up to 80%, they will develop the progressive disease (PD) after a median of 10 to 14 months on an EGFR TKI.

Disease progression occurs in more than 60% of patients receiving first and second-generation TKI. The mechanism of resistance is a threonine-to-methionine amino acid substitution obtained at the gatekeeper position 790 of the EGFR in exon 20 or T790M, which increases the affinity of the EGFR kinase domain for ATP and thereby outperforms EGFR-TKI binding. Based on data from the AURA 2 Phase II trial and the AURA extension cohort, T790M-positive tumors were responsive to treatment with a third-generation TKI, osimertinib.

Progressive patient management after receiving EGFR TKI is currently still a polemic, even though the T790M examination is already available in Indonesia, but the EGFR of third-generation TKI osimertinib has not yet been covered by the National Health Insurance (JKN). The NCCN and ESMO guidelines recommend conventional chemotherapy with a doublet-platinum regimen as the treatment of choice for cases without an acquired T790M mutation or without tumor tissue accessible for repeat biopsy. There are not many studies investigating the optimal chemotherapy regimen as a treatment option in patients who are T790M mutation negative or have an unknown mechanism of acquired resistance after first-line TKI failure. This study aims to describe a case of progressive lung adenocarcinoma and its chemotherapy treatment.

2. Case Presentation

A woman, 54 years old, was diagnosed with adenocarcinoma of the left lung (Exon 21 mutation) in May 2020 and has received EGFR-TKI first-generation Gefitinib 1x250 mg targeted therapy by a pulmonary specialist at Dharmais Cancer Hospital. Treatment was then continued at Bengkulu General Hospital. After 17 months of treatment, the pulmonary specialist at the Bengkulu General Hospital concluded that the disease had worsened and the patient was then referred to Dr. M Djamil General Hospital.

The patient complained of shortness of breath which had worsened 2 weeks before admission to the hospital. Because of the tightness, the patient is more comfortable lying on the left side. Left chest pain has been felt since 4 months ago, does not spread, increases with activity, chest pain does not decrease with rest. The patient is a housewife, non-smoker, with no history of exposure to environmental cigarette smoke or history of cooking with firewood. The patient lives in a permanent house with tiled floors, no cracks, and no dug wells in the house.

Examination of the patient’s chest X-ray in December 2021 at Dr. M Djamil General Hospital found the impression of a left pleural effusion. When compared to the previous chest X-ray when receiving EGFR-TKI in the 13th month (September 2021), the impression worsened due to the appearance of a left pleural effusion (Figure 1). This is concluded because the patient could not show a serial chest X-ray or a chest CT scan at the time the EGFR-TKI was initially given.
Based on the results of the current examination, the patient was diagnosed with left lung adenocarcinoma (Exon 21 mutation) progressive disease with TKI. TKI therapy in the patient was discontinued, and rediagnostic was performed. The patient underwent a chest CT scan with contrast, and an enhanced lung mass was found after contrast administration in segment 8 of the left lung with a size of 6.8x6.2x4.1 cm, nodules in the right lung, lytic lesions on the left anterior II-III ribs, pleural effusion. Left, enlarged lymph nodes (KGB) in the left bronchus and metastatic lesions in both adrenal glands. Bronchoscopy examination found irregular mucosa that bleeds easily with narrowing of the lumen in the left lower lobe, then bronchial brushing and rinsing were performed, while other branches were found to have an open lumen, regular mucosa. The results of the anatomical pathology of bronchial brushing and bronchial washings showed the impression of adenocarcinoma. The patient was advised to undergo a molecular biology examination to determine the presence of the T790M mutation, but because the examination was not covered by JKN, the examination was not carried out. Based on these diagnostic results, the patient was diagnosed with progressive disease T3N1M1c left lung adenocarcinoma (pleura, contralateral nodule, ribs, suprarenal) Stage IVb PS ECOG 0. The patient was then treated with conventional doublet-platinum-based chemotherapy with the Carboplatin-Paclitaxel combination.

After the third cycle of chemotherapy, the Response Evaluation Criteria in Solid Tumor (RECIST) was conducted. The subjective response assessment of complaints of shortness of breath and chest pain was reduced after chemotherapy was given, the semi-subjective response was increased, and the objective response was using a chest CT scan with contrast to suprarenal, compared with conventional prechemotherapy CT-scan, solid mass was found to be reduced by 43% (partial response), so it was decided to continue chemotherapy until the sixth cycle. The patient has currently completed conventional chemotherapy and is under post-therapy monitoring.
3. Discussion

Asian female non-smoker patient has been diagnosed with progressive disease T3N1M1c left lung adenocarcinoma (pleura, contralateral nodule, rib, suprarenal) Stage IVb PS ECOG 0, after administration of EGFR TKI therapy on the indication of exon 21 EGFR mutation. This is in accordance with several studies that show EGFR mutations are common in women, East Asian races, and non-smokers. Previous studies have reported that EGFR mutations occur in 44%-55% of adenocarcinoma patients, 51%-68% in non-smokers, 42-62% in women, and 30-50% in Asian races. EGFR mutations, to a lesser extent, were also found in 8% of adenocarcinomas, 10% of smokers, and 14% of men of the European race.

Shigematsu et al. reported a higher frequency of lung cancer from East Asians than from non-Asians (30% versus 8%, p<0.001), women compared to men (59% versus 26%, p<0.001), and non-smokers versus smokers. (66% versus 22%, p<0.001). And in adenocarcinoma compared with other histology of KPKBSK (49% versus 2%).

Lung cancer treatment has entered the era of individualized therapy based on histology and genotype, which allows patients to receive targeted therapy. Targeted therapy is therapy with a type of drug that can inhibit the growth and spread of cancer cells by intervening against specific molecular targets involved in the growth, progression, and spread of cancer cells. Mutations in the EGFR gene cause signals that trigger cells to turn into malignancy. Tyrosine kinase inhibitor (TKI) inhibits the action of tyrosine kinase, which is a component of the EGFR gene.

Based on the results of the pleural fluid EGFR examination, the patient found a positive mutation in exon 21, and the patient was given first-generation TKI target therapy Gefitinib 1x250 mg according to the 2022 NCCN guidelines for lung cancer patients with adenocarcinoma types with EGFR mutations in exons 19 and 21 receiving first-line therapy in the form of targeted therapy. EGFR TKI. Peter et al. reported that EGFR mutations at exon 19 (47%) and at exon 21 (41%) predominate in the type of mutation in adenocarcinoma. Maruyama et al. reported that in non-smoker Asian female patients with adenocarcinoma, gefitinib had a better PFS than placebo (5.6 months versus 2.8 months, p<0.0001).

Drugs belonging to the TKI class include; The first generation is gefitinib and erlotinib, the second generation is afatinib and dacomitinib, and the third generation is osmeratinib. The management of this patient was in accordance with the guidelines, where the patient was diagnosed as advanced stage left lung adenocarcinoma with exon 21 mutation EGFR, so she was treated with EGFR target therapy for TKI Gefitinib, and had been taken for 17 months.

First-generation TKIs such as gefitinib, and erlotinib have been shown to increase objective response rates and prolong progression-free survival (PFS) compared to standard chemotherapy in large phase III trials. Unfortunately, almost all patients become resistant to the treatment within 10-14 months. The first-generation TKI (gefitinib and erlotinib) reversibly bind and inhibit EGFR signaling, while the second-generation TKI (afatinib) can inhibit the erythroblastosis oncogene B (ErB) family irreversibly inhibiting the signaling of all homodimers and heterodimers of the ErB family receptor (EGFR). /ErB1, HER2/ErbB2, ErbB3, and ErbB4), compared with gefitinib in the first-line regimen, afatinib prolongs PFS and time to treatment failure. Afatinib has been shown to prolong overall survival (OS) in a subset of patients with exon 19 EGFR deletions compared with chemotherapy.

The patient experienced disease progression at the 17th month of EGFR TKI treatment in the form of
clinical worsening and the finding of contralateral nodules, pleural effusions, and bilateral suprarenal metastases, so it was decided that the patient had systemic progression and underwent rediagnostics. Impression of adenocarcinoma, according to the histopathological results at the start of the diagnostic investigation. Yang et al. reported that 72.5% of patients with mutated EGFR had pleural effusion and had a better OS than wild-type (WT) EGFR (7.33 months versus 2.07 months, p=0.032).25 Jian et al. reported that patients with lung adenocarcinoma with pleural effusion had a better RR if there was a mutation in EGFR (90.9%) compared to EGFR WT (9.1%).26 Suprarenal metastases from cells of lung cancer origin are quite rare.27,28 Suprarenal metastases originating from KPKBSK are common at autopsy while being diagnosed quite rarely in living patients and are usually unilateral.29,30 Numan et al. found that 38% of suprarenal metastases were from lung cancer out of the total suprarenal metastases found in the study.31 The route of the spread of lung cancer to the suprarenal is still a matter of debate, originating from the hematogenous or lymphogenous route. Secondary tumors can interfere with suprarenal structure and function. Suprarenal metastases from lung cancer can lead to adrenal insufficiency to adrenal failure.32,33

![Figure 3. Schematics of different treatment scenarios for adenocarcinomas with EGFR mutations.](image)

Patients were then recommended to undergo a T790M examination because, in more than 60% of patients who received first and second-generation TKI, disease progression was due to the resistance mechanism of the T790M mutation.8,34,35 A study by Oxnard GR et al. shows that after initial treatment with EGFR TKI (Gefitinib, Erlotinib), adenocarcinoma EGFR mutations can shrink dramatically (blue cells; left). In most cases, disease progression was due to the acquired mutation T790M (red cell; center). After discontinuation of EGFR TKI, faster-growing TKI-sensitive cells can regenerate (sometimes causing flares), allowing the tumor to re-respond to EGFR TKI for a second time after the drug holiday (right). If the resistant tumor is indeed a heterogeneous mixture of TKI-sensitive and resistant cells (middle), a continuation of TKI therapy together with chemotherapy after progression (bottom) will target both cell populations more effectively than chemotherapy alone (top).34 Based on data from the AURA 2 Phase II trial and the AURA extension cohort, T790M-positive tumors were responsive to treatment with a third-generation TKI, osimertinib.9 Until now, JKN has not covered the third-generation target therapy for osimertinib, so testing for T790M mutations in patients has not been carried out. The NCCN recommends that for cases without an acquired T790M mutation, without accessible tumor tissue for repeat biopsy, or without access to treatment using a third-generation EGFR TKI, chemotherapy remains the next important therapy after a first-line TKI.10,11,19 There are not many studies investigating the optimal chemotherapy regimen as second-line treatment in patients with T790M mutation negative
or who have an unknown mechanism of acquired resistance after failure of first-line TKI. Based on the NCCN guidelines above, the patient decided to continue therapy with conventional doublet-platinum chemotherapy with the Carboplatin-Paclitaxel regimen. Masuda et al., in a study comparing doublet platinum chemotherapy regimens for patients who were progressive after receiving gefitinib, compared the RR of Cisplatin and Carboplatin (38.4% and 20.6%, p=0.22), PFS (5.1 months) and OS (17.8 months) after starting conventional chemotherapy as second-line therapy. The Goldberg et al. study compared chemotherapy+erlotinib and chemotherapy in progressive adenocarcinoma with EGFR TKI, finding RR in the chemotherapy+erlotinib and chemotherapy groups (41% and 18%, p=0.02), with PFS in both groups at 4.4 months and 4 months respectively. 2 months (p=0.34), there was no significant difference in OS. Wu JY et al. in a study comparing groups receiving various conventional chemotherapy regimens with erlotinib after progressing with gefitinib, RR doublet-platinum, and erlotinib groups (50% and 5.6%), PFS (4.0 months and 4.2 months), OS (21.7 months p=0.011 months and 12.2 months p=0.603).

Platinum-based regimens were preferred over non-platinum-based combinations because they were superior in terms of response rate and survival, while combination therapy with non-platinum was used when there were contraindications to platinum-based regimens. One of the conventional chemotherapy regimens for progressive KPKBSK with EGFR TKI is a combination of platinum carboplatin or cisplatin with one of the third-generation anticancer drugs, namely gemcitabine, paclitaxel, docetaxel, and vinorelbine. Various studies have found that the therapeutic response to the various regimens is almost the same. Overall response rates for the four first-line regimens ranged from 17-22%. The survival rate, which is the basis for the effectiveness of the combination regimen of carboplatin/cisplatin with these four third-generation anticancer drugs, shows no different results. The median survival time was 8.2 months and 9.8 months, respectively. Anwar J et al. reported the efficacy of the regimen of docetaxel + carboplatin in patients with KPKBSK in Jakarta and obtained no different results. The results are almost the same as the efficacy of the paclitaxel + carboplatin regimen for KPKBSK from the results of the study of Kosmidis P et al.

The goal of treatment in advanced stage KPKBSK is palliative so that the choice of type of treatment should not cause other complaints that can reduce the patient’s quality of life. The results of Syahrudin E’s research at Persahabatan Hospital showed that chemotherapy paclitaxel 175 mg/m2 + carboplatin AUC-5 in patients with KPKBSK, especially adenocarcinoma, gave a good clinical response (clinical response). The clinical implication of the clinical response is the ability of chemotherapy not to cause progression in a certain period of time even though the size of the tumor remains or does not change. The best choice of chemotherapy regimen for advanced-stage KPKBSK is a regimen that has a long time to progress and, more importantly, has mild toxicity.

A study conducted by Rosell et al. directly compared the combination chemotherapy of carboplatin/paclitaxel with cisplatin/paclitaxel in patients with KPKBSK. Overall responses to the two combinations above were 28% and 25%, with the same trend of results. However, significantly OS in patients with COPD, it was longer (9.8 months) in the cisplatin/paclitaxel group than in the carboplatin/paclitaxel (8.2 months). The effectiveness of cisplatin and its combination with cytotoxic drugs has been shown to increase. However, there are clinical trial studies of the combination of carboplatin/paclitaxel with doses varying from 135 mg/m2 to 250 mg/m2, which have shown promising effects as a chemotherapeutic agent in patients with KPKBSK. Treatment with this regimen has also been shown to improve the OS and quality of life of KPKBSK patients. Although the advantages of the cisplatin/paclitaxel combination are widely reported, the use of chemotherapy regimens is still returned to
the individual patient’s condition, one of which is renal impairment due to renal toxicity and neurotoxicity reported with cisplatin use.\textsuperscript{41-43} The indication for the use of carboplatin/paclitaxel in this case, was due to the finding of suprarenal metastases. The study of Kimura et al. concluded that the response to carboplatin, combined with paclitaxel in patients with EGFR mutations was higher than in patients without EGFR mutations.\textsuperscript{44}

Patients who have currently completed conventional chemotherapy and KPKBSK patients who have completed conventional chemotherapy are recommended for routine control for evaluation from the pulmonary polyclinic. The patient managed to survive 24 months since the initial diagnosis. This is very good compared to the average survival time after diagnosis of stage four lung cancer, which ranges from 6.3 months to 11.4 months.\textsuperscript{15} Patients managed to pass the one-year survival rate, which was statistically only 15 – 19%.\textsuperscript{45} The relatively young age at diagnosis (53 years), good performance status at baseline and during treatment, the presence of mutations in the EGFR gene, and the absence of comorbidities may be other factors that can affect the good survival rate in these patients.

4. Conclusion

Systemic chemotherapy with doublet-platinum is an option in patients with progressive adenocarcinoma with EGFR-TKI who are unable to obtain tissue for histopathological examination at rebiopsy or do not have access to advanced molecular biology (e.g., T790M) or follow-up therapy (third-generation TKI, osimertinib).

5. References


