

The quality of life (QoL) of advanced stage lung adenocarcinoma patients receiving afatinib at Dr. Sardjito General Hospital, Yogyakarta

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ABSTRACT

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Lung cancer has the highest mortality rate of all cancers. In its advanced stages, this disease is associated with poor survival rates and quality of life. The most common subtype of lung cancer is adenocarcinoma which is frequently associated with mutations in the epidermal growth factor receptor (EGFR), a protein crucial for cell proliferation. The presence of EGFR mutations plays a key role in targeted therapy using tyrosine kinase inhibitors (TKIs). Afatinib is a second-generation TKI that offers several advantages over the first-generation. Afatinib is effective against complex and uncommon EGFR mutations, making it a commonly used option for patients with lung adenocarcinoma. However, afatinib is also associated with a higher incidence of adverse drug reactions (ADRs) compared to other TKIs, which may impact therapeutic outcomes. This study aimed to assess the quality of life (QoL) of advanced lung adenocarcinoma patients with EGFR mutations and the prevalence of ADRs associated with afatinib treatment at Dr. Sardjito General Hospital in Yogyakarta. The study employed an observational cross-sectional design. Prospective data collection was conducted for two months, from January to February 2025 at the Oncology Department following ethical approval. A total of 15 patients were enrolled in this study. The most commonly identified ADRs were acne (45%), diarrhea (20%), paronychia (20%), and oral mucositis (15%). The mean QoL scores was 81.38 ± 10.01 for the functional scale, 15.93 ± 8.48 for the symptom scale, and 72.78 ± 19.53 for global health status.

ABSTRAK

Kanker paru merupakan kanker dengan angka kematian paling tinggi dibandingkan kanker lain. Pada stadium lanjut, penyakit ini dikaitkan dengan angka ketahanan hidup yang rendah dan kualitas hidup yang buruk. Jenis kanker paru yang paling sering terjadi adalah adenokarsinoma yang sering membawa mutasi pada EGFR, suatu protein penting dalam proliferasi sel. Adanya mutasi pada EGFR memberikan peran penting terapi target dengan penghambat tirosin kinase (TKI). Afatinib adalah TKI generasi kedua yang mempunyai keunggulan dibandingkan generasi sebelumnya. Afatinib efektif pada adenokarsinoma dengan mutasi EGFR kompleks dan jarang terjadi, yang menjadikan obat ini sering digunakan untuk pasien adenokarsinoma paru. Namun, afatinib menyebabkan efek samping obat ADRs lebih tinggi dibandingkan TKI lain yang dapat mempengaruhi luaran terapi. Penelitian ini bertujuan untuk mengevaluasi kualitas hidup pasien adenokarsinoma paru stadium lanjut dengan mutasi EGFR serta prevalensi ADRs yang muncul akibat afatinib di RSUP Dr. Sardjito Yogyakarta. Desain penelitian yang digunakan adalah deskriptif observasional dengan rancangan potong lintang. Pengambilan data dilakukan secara prospektif selama dua bulan yaitu pada bulan Januari sampai Februari 2025 di Poliklinik Onkologi RSUP Dr. Sardjito Yogyakarta setelah mendapatkan persetujuan etik. Sebanyak 15 pasien masuk kedalam penelitian ini. ADRs yang teridentifikasi yaitu akne (45%), diare (20%), paronikia (20%), dan mukositis oral (15%). Skor kualitas hidup skala fungsional diperoleh rata-rata $81,38 \pm 10,01$, skala gejala $15,93 \pm 8,48$ dan kesehatan keseluruhan $72,78 \pm 19,53$.

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INTRODUCTION

In Indonesia ini 2020, lung cancer was the most commonly diagnosed cancer among, accounting for 34,783 new cases (14.1%) and it remains the leading cause of cancer-related death.¹ Globally, lung cancer deaths have decreased by 59% among men since 1990 and by 36% among women since 2002. However, lung cancer still causes more deaths each year than colorectal, breast, and prostate cancers combined.² Adenocarcinoma is the most frequently diagnosed subtype of non-small cell lung cancer (NSCLC), accounting for approximately 39% of cases, followed by squamous cell carcinoma (25%) and large cell carcinoma (8%). Small cell lung cancer (SCLC) accounts for around 11% of all lung cancer cases. Among women, adenocarcinoma represents 57% of cases, followed by squamous cell carcinoma (12%), large cell carcinoma (6%), and small cell lung cancer (9%).³

Patients with advanced lung adenocarcinoma are treated systemically with chemotherapy, immunotherapy, and/or targeted therapy, depending on the genetic characteristics of the disease. Tyrosine kinase inhibitors (TKIs) are standard therapy for patients with lung adenocarcinoma with mutations in the epidermal growth factor receptor (EGFR). Afatinib is a second-generation TKI that has a higher potential for inhibiting EGFR through irreversible covalent binding. Compared to gefitinib, first-generation TKI, afatinib has a significantly longer progression free survival (PFS). However, this second-generation TKI is associated with a higher toxicity profile which in some cases can be severe enough to require dose reduction or even discontinuation of therapy.^{4,5}

In advanced cancer, one of the main focuses of therapy is maintaining the patient's quality of life (QoL). Adverse drug reactions (ADRs) associated with TKIs are known to significantly affect QoL. When assessed using the Skindex-16

questionnaire for dermatological ADRs, both the symptom and functional domains were markedly affected, with the emotional domain being the most impacted.⁶

In Indonesia, data on the incidence of ADRs related to afatinib use are still limited. Several studies conducted in other countries have demonstrated that TKI-induced ADRs can have a substantial impact on therapeutic outcomes in cancer patients. Dr. Sardjito General Hospital serves as a central referral hospital for lung cancer cases in Yogyakarta,¹ which highlights the need for research to determine the incidence of ADRs caused by afatinib and their impact on the QoL of patients with advanced lung adenocarcinoma.

MATERIAL AND METHODS

Design and subjects

This study was a descriptive observational study with a cross-sectional design, conducted at the Polyclinic of Dr. Sardjito Hospital, Yogyakarta, after ethical approval had been obtained. The study subjects were male and female patients aged ≥ 18 yr who were diagnosed with advanced-stage positive lung adenocarcinoma EGFR mutations and had received afatinib therapy for at least one month. Patients who were willing to participate and provided written informed consent were included. The exclusion criteria were patients who had received other EGFR inhibitor drugs or conventional chemotherapy. This study was approved by the Medical and Health Research Ethics Committee, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Yogyakarta (Ref. No. KE/FK/0008/EC/2025).

QoL assessment

Primary data, the QoL based on filling out the EORTC QLQ-C30 questionnaire which has been validated

by Perwitasari *et al.*,⁷ and interviewed related to complaints and suspicions of ADRs. Interviews were conducted when patients visit the outpatient clinic of Dr. Sarjito General Hospital. Interviews could be conducted directly to the patients or assisted by the patient's closest family. Subjects were allowed to ask researchers to read the questionnaire, but researchers were not allowed to direct the patient's answers. While secondary data came from medical records.

ADRs assessment

The ADRs assessment was based on the Naranjo scale assessment of complaints, examination data, and/or the presence of a medical doctor's diagnosis in medical records. Only a total score of 5-8 (possible) and 9 + (very likely) from the Naranjo scale were included in this study. This study was approved by the Medical and Health Research Ethic Committee, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada/Dr. Sardjito General Hospital, Yogyakarta with letter number KE/FK/0008/EC/2025.

Data analysis

Data were presented as mean $\pm$ standard deviation (SD) or as percentages and descriptive analysis was performed.

RESULT

Data were collected from January to February 2025, including patient characteristics and scores from the EORTC QLQ-C30 questionnaire. Characteristic data included gender, age, cancer stage, EGFR mutation status, location of metastasis for stage 4 cases, afatinib dose, and suspected ADRs assessed during the previous week using the Naranjo scale and/or confirmed by a medical doctor's diagnosis.

A total of 15 patients who met the inclusion criteria were evaluated in this study. The patient characteristics are

presented in TABLE 1. The distribution of adult and elderly patients, as well as male and female patients, was generally balanced, with a slightly higher proportion of elderly and male patients (46.67% and 53.33%, respectively, compared to 53.33% and 46.67% for adults and females).

Only one patient receiving afatinib therapy had stage III disease, while the remaining patients were in stage IV (6.67% vs. 93.33%). Among stage IV patients, the most common metastatic sites were the pleura, brain, bone, and liver (35.71%, 28.57%, 28.57%, and 7.14%, respectively). The most frequent EGFR mutation was exon 19 deletion, followed by exon 21 L858R (33.33% and 27.78%, respectively). The standard afatinib dose is 40 mg once daily, which was administered to most patients (80%), while three patients (20%) received a lower dose. The suspected ADRs included acne, diarrhea, paronychia, and stomatitis, with acne being the most frequent (45%), followed by diarrhea and paronychia (20% each).

QoL score

This study employed the EORTC QLQ-C30 questionnaire, which has been validated in the Indonesian language, making it suitable for assessing the quality of life of Indonesian patients. Score calculations were performed according to the EORTC QLQ-C30 Scoring Manual version 3.0. The QoL score of patients are presented in TABLE 2. The mean scores for the functional, symptom, and global health scales were 81.38 ± 10.01 , 15.93 ± 8.48 , and 72.78 ± 19.53 , respectively. Among the functional scales, the highest score was observed in the emotional function domain (93.42 ± 9.45), while the lowest was in physical function (64.2 ± 25.51). On the symptom scale, fatigue had the highest score (33.33 ± 27.23), whereas nausea and vomiting and constipation had the lowest (6.67 ± 17.59 and 6.67 ± 18.68 , respectively).

TABLE 1. Patient characteristics

Characteristics	Number	Percentage (%)
Age (yr; n=15)		
Adult (18-59)	7	46.67
Elderly (≥ 60)	8	53.33
Gender (n=15)		
Male	8	53.33
Female	7	46.67
Lung cancer stage (n=15)		
III	1	6.67
IV	14	93.33
Metastasis location (n=14)		
Pleural	5	35.71
Brain	4	28.57
Bone	4	28.57
Liver	1	7.14
EGFR mutation (n=18)		
Exon 18 G719S	3	16.67
Exon 18 G179A	1	5.55
Exon 18 G719C	1	5.55
Exon 19 deletion	6	33.33
Exon 20 T790M	1	5.55
Exon 21 L858R	5	27.78
Exon 21 L861Q	1	5.55
Afatinib dose (n=15)		
40 mg/24h	12	80
< 40 mg/24h	3	20
Identified ADRs (n=20)		
Diarrhea	4	20
Acne	9	45
Paronychia	4	20
Oral mucositis	3	15



FIGURE 1. Acne on the back area (left), and paronychia (right)

TABLE 2. The QoL's score of patients

Scale	Mean ± SD			
Functional scales				
Physical functioning	64.2	±	25.51	
Role functioning	77.8	±	35.43	
Fungsi emosional	93.42	±	9.45	
Emotional functioning	88	±	18.31	
Social functioning	83.47	±	21.82	
Mean	81.38	±	10.01	
Symptom scales				
Dyspnoea	11.11	±	20.57	
Pain	25.55	±	29.45	
Fatigue	33.33	±	27.23	
Insomnia	8.89	±	23.45	
Nausea and vomiting	6.67	±	17.59	
Appetite lost	15.55	±	30.51	
Constipation	6.67	±	18.68	
Diarrhea	17.78	±	27.79	
Financial difficulties	17.78	±	21.33	
Mean	15.93	±	8.48	
Global health status				
Quality of life	72.78	±	19.53	
Mean	72.78	±	19.53	

DISCUSSION

In this study, NSCLC sufferers were predominantly elderly and male. The increase in lung cancer incidence is indeed in line with increasing age. The male gender is also known to still dominate this cancer.⁸ The number of patients with stage IV lung cancer is also known to be much more dominant than stage III. This is likely because lung cancer often does not show clear symptoms until the cancer spreads to other parts of the body. Thus, when patients already experience symptoms, the prognosis is usually poor.⁹ The location of the metastasis in this study is also in accordance with various other literature, where the most common locations for the spread of non-small cell lung cancer are the pleura, bones, brain, and liver.¹⁰

As in many other studies, mutations in exons 19 deletion and 21 L858R are

most frequently identified in NSCLC.¹¹ Mutations in exon 19 deletion result in a conformational shift in the EGFR helical axis, thereby increasing ligand-dependent EGFR activation. Not that different, the L858R mutation stabilizes the receptor activation loop and increases the duration of EGFR activation.¹² However, afatinib is known to be very effective in exon 19 deletion mutations compared to exon 21 L858R.¹³

The standard dose of afatinib therapy is 40 mg/24 hr. Mainly patients received that dose, but some patients received a dose below that. Patients who were given doses below the standard were due to experiencing severe adverse effects that could not be tolerated, so the dose was reduced to 20 mg/24 hr, 30 mg/24 hr or 40 mg/48 hr, respectively based on the oncologist's decision. This is because most of the adverse effects of afatinib are dose-dependent. Dose reduction strategies have been shown to

be effective in reducing adverse effects without reducing therapeutic efficacy.¹⁴

The adverse effects due to afatinib identified in this study were acne, diarrhea, paronychia, and oral mucositis. These adverse effects do have a very high incidence rate with afatinib, especially in Asians. The causal mechanism is likely the same, due to inhibition of EGFR in the epidermis and gastrointestinal tract.⁵

Afatinib is a TKI that is still relied on in cases of lung adenocarcinoma with EGFR mutations. This drug has activity on complex and uncommon mutations. Afatinib also shows little benefit in lung adenocarcinoma patients who experience disease progression while receiving other TKIs, and patients who experience resistance to erlotinib, gefitinib, or both. However, afatinib often causes ADRs that are even more severe than other TKIs. In this study, ADRs were detected as many as 24 events. The most common ADRs were acne, followed by diarrhea and paronychia. The presence of ADRs is known to diminish the quality of life.¹⁶ Nevertheless, this study did not evaluate how ADRs impact quality of life because the number of subjects was inadequate.

The EORTC QLQ-C30 questionnaire is a widely utilized tool for evaluating cancer patients' quality of life. This questionnaire assesses QoL by considering many aspects. This questionnaire consists of 30 questions with 3 scales: functional, symptom and global health. On the functional scale there are questions related to physical function, including difficulty in doing heavy activities, difficulty walking, intensity of lying in bed or sitting in a chair, and the need for help from others when doing personal activities. In this study, physical function had the lowest score among all functional scales. High physical function is associated with better survival.¹⁷ Cancer patients often experience weakness, which can be caused by loss of muscle mass. Some contributing factors include malignancy and the tumor environment,

chemotherapy, radiotherapy, and malnutrition.¹⁸ In late-stage lung cancer, patients generally have received various previous therapies, which will certainly affect the loss of muscle mass.

In contrast to physical function, emotional function has the highest score. The assessment of emotional function in this questionnaire is divided into 4 questions: tension, worry, irritability, and depression. Depression can occur due to stress that overcomes a person's ability to adjust to changes in life, causing bad mood, hopelessness, anhedonia, and feelings of helplessness. Emotional stress can come from a poor prognosis or uncertainty experienced by the patient. This is exacerbated by the negative effects caused by the diagnosis and treatment of cancer on the patient's work, family, physical appearance, ability, independence, and finances.¹⁹ In this study, most of the patients were no longer working. Still, they had sufficient income ($\geq$ minimum regional wage) and family support, which can be seen from the status of most patients who were still in pair, so the overall average score for emotional function was high.

On the symptom scale, the highest score was fatigue (33.33 ± 27.23) followed by pain (25.55 ± 29.45). A high score on the symptom scale indicates a high level of patient problems or complaints. Fatigue is known to be one of the strong factors that can reduce the QoL of patients.²⁰ However, despite its high prevalence and significant effects, the underlying etiology of cancer fatigue remains poorly understood. Evidence suggests the involvement of complex multifactorial processes associated with a variety of molecular/physiological, clinical, and psychological factors.²¹ Poor performance status, chemoradiotherapy, female gender, insomnia, pain, and depression are some of the identified risk factors for cancer-related fatigue.²² This suggests that the high pain scores in this study may cause the high fatigue scores. On the other hand, a survey by Riccetti *et al.*²³ found that fatigue on the symptom

scale in patients with TKI therapy was higher than in those receiving chemotherapy. The study also presented data on pain as the third highest ranking on the symptom scale after fatigue and shortness of breath.

Lung cancer patients often experience pain, especially in the advanced stages. Pain in these patients is mainly caused by metastatic lesions in the bones, Pancoas tumors (a rare lung cancer that usually occurs in the upper area of the lungs), and chest wall disease (a condition where lung cancer infiltrates the chest wall).²⁴ The high pain score in this study could be caused by 28.57% of patients having experienced bone metastases. In a similar survey conducted by Ariantika *et al.*²⁵ at the University of North Sumatra Hospital, pain scores in lung cancer patients ranked first on the symptom scale (52.66 ± 29.95). Pain is known to have a strong correlation in reducing the QoL of patients.²⁶

The lowest score on the symptom scale in this study was nausea, vomiting, and constipation. Afatinib is known not to cause ADRs of nausea, vomiting or constipation. Some ADRs in several previous clinical trials included diarrhea, stomatitis, paronychia and skin rash, as identified in this study.^{18,19} ADRs are thought to be related to inhibition of EGFR in the digestive tract and epidermis.²⁰

In a similar study conducted in 2009 on palliative care patients with lung cancer and colorectal cancer regardless of the therapy received, the results also showed that no patients experienced constipation and nausea or vomiting, but no diarrhea either.²⁷ The absence of diarrhea is likely because none of the lung cancer patients in the study received TKIs. In 2009 and earlier, these drugs were not FDA approved for treatment of late-stage lung cancer. Another multicenter study in 2022 found that patients treated with TKI therapy had higher diarrhea symptom scores than chemotherapy.²³ In line with this study, a similar survey was conducted in Germany in 2020, specifically on

lung cancer patients receiving TKI, and diarrhea scores ranked highest on the symptom scale after fatigue.²⁸

Based on the global health status, the average score of advanced lung adenocarcinoma patients receiving afatinib in this study was 72.78 ± 19.53 . This score is higher than a similar survey by Ariantika *et al.*²⁵ with an average score of 59.11 ± 12.86 . However, the study did not compare patients who received targeted therapy with chemotherapy, so it is unknown what the score was in patients who received TKI alone. In Riccetti *et al.*²³ study, the average global health status score of stage IV lung cancer patients with TKI was below that of patients who received therapy other than TKI (57.1 ± 21.4 vs 68.8 ± 22.8). Still, this study did not specifically assess afatinib because several other studies have shown an increase in global health status in the administration of afatinib, especially among those who previously received other therapies.^{26,29}

There are several shortcomings of this study. The number of patients is too small, so the data cannot be analyzed statistically. For example, the study will not be able to see the influence of patient characteristics and ADR events on the QoL's scores. The occurrence of ADRs identified in this study is primarily still based on the researcher's assessment using the Naranjo scale. Only two types of ADRs are enforced by doctors, diarrhea and pyoderma, so the accuracy of determining ADRs can be wrong.

CONCLUSION

In conclusion, patients with advanced lung adenocarcinoma at Dr. Sardjito General Hospital, Yogyakarta have an average QoL score on a high functional scale and global health status, with a low symptom scale. Although third-generation TKIs are currently available, afatinib is still very good at maintaining the QoL of patients with advanced lung adenocarcinoma, so it can still be relied on in some instances,

such as complex or uncommon EGFR mutations. Further research is needed to determine the impact of ADRs from afatinib on patient QoL.

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