CANCER DIAGNOSIS & PROGNOSIS
3: 251-256 (2023) doi: 10.21873/cdp.10209

Refusal of Subsequent Treatment in Patients With *EGFR*-mutant Non-small-cell Lung Cancer After Response to *EGFR*-TKIs

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Abstract. *Background/Aim: During the course of effective and long-term treatment with epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI), some elderly patients might decline further treatment after EGFR-TKI. We conducted a study to try and understand the reasons for this treatment decision. Patients and Methods: We analyzed the medical records of all patients diagnosed with non-small-cell lung cancer with EGFR mutations between 2016 and 2021. Results: There were 108 patients who received EGFR-TKIs. Of these, 67 patients responded to TKI. These responding patients were divided into two groups according to whether they received subsequent TKI treatment. At their request, 24 patients (group A) did not receive further anticancer treatment following TKI. The other 43 patients (group B) received anticancer therapy following TKI. Progression-free survival in group A patients was significantly longer (median=18 months, range=1-67 months) than in group B patients. The reasons for not wanting subsequent treatment after TKI were older age, reduced general condition, deterioration of physical comorbid disease and dementia. Dementia was the most common reason for patients over 75 years of age. Conclusion: Some elderly patients with well-controlled disease might express their refusal of all subsequent anticancer therapy after TKIs. Medical staff should respond seriously to these requests.*

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Key Words: Non-small cell lung cancer, elderly, epidermal growth factor inhibitor, tyrosine kinase inhibitor, response.

A high proportion of patients with non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (*EGFR*) mutations are relatively young, non-smoking, females, with adenocarcinoma (1). However, it is also known that a certain proportion of those with *EGFR*-mutated NSCLC are elderly (2, 3). *EGFR*-tyrosine kinase inhibitors (TKIs), which have a specific efficacy for *EGFR*-mutated NSCLC, have relatively easy-to-manage adverse effects compared with cytotoxic antitumor drugs, although lung damage can occur (4, 5). Response to EGFR-TKIs has a long duration (6), and some patients can continue treatment for more than 2 years (7). During long-term TKI treatment, some elderly patients can have exacerbation of comorbidities and dementia. Despite the success of EGFR-TKI therapy, healthcare professionals might encounter patients who declare that they do not wish to receive another cancer therapy after TKI.

For the elderly, decisions about whether to undergo examination for cancer diagnosis and receive anticancer therapy are problematic and have been for a long time. In recent research by Wieland *et al.* at the Mayo Clinic, it was reported that the decision to have no cancer-directed therapy seemed to have been made in a measured and thoughtful manner, in view of the comorbidities among elderly patients (8). In prostate and thyroid cancer which are slow-growing and more common in the elderly, there may be circumstances where patients do not wish to have a cancer diagnosis and anticancer therapy. On the other hand, in the diagnosis and treatment of lung cancer, while there are some patients

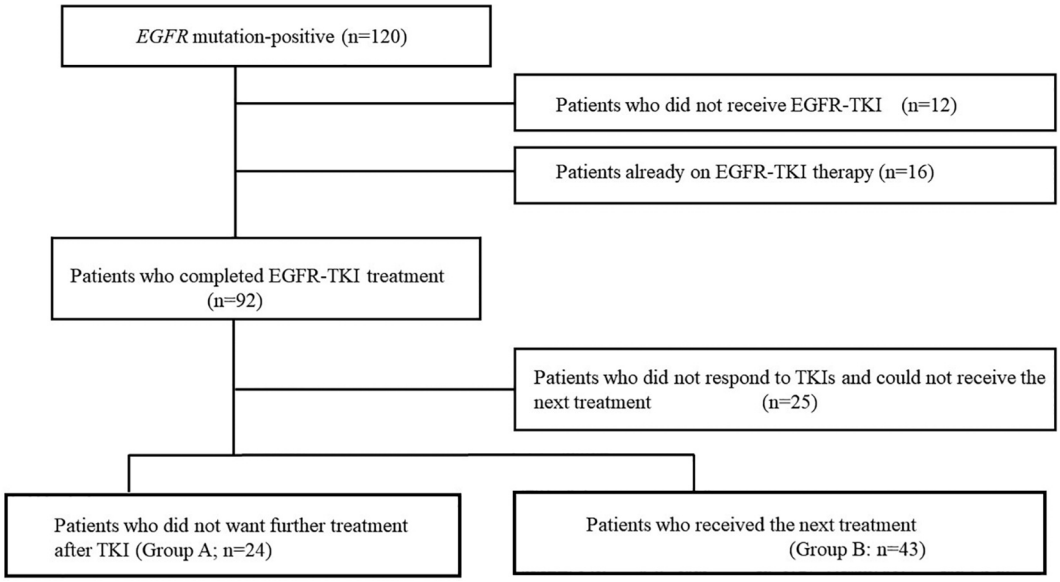

Figure 1. *Study flow chart. EGFR: Epidermal growth factor receptor; TKI: tyrosine kinase inhibitor.*

whose disease progresses slowly, it is more common for the disease to progress rapidly. In these types of cancer, it is rare for patients to be unwilling to receive subsequent therapy after effective first-line therapy. This has likely led to there being little discussion of how to deal with patients who decline therapy after having a long duration of response to TKIs with no serious side-effects. In this retrospective study, we conducted a chart review of patients with *EGFR*-mutated NSCLC to better quantify and understand refusal of all subsequent anticancer therapy after TKIs in responding patients with NSCLC, with the aim of informing future medical care practices.

Patients and Methods

Patients. We analyzed the medical records of all patients diagnosed with *EGFR*-mutated NSCLC at two tertiary hospitals in Japan (Ryugasaki Saiseikai Hospital and Mito Medical Centre, University of Tsukuba) between February 2016 and June 2022. NSCLC was diagnosed based on the World Health Organization classification (9). The tumor-node-metastasis staging (TNM classification, eighth edition) (10) using cranial computed tomography or magnetic resonance imaging, bone scans and ultrasonography/computed tomography of the abdomen was performed for all patients prior to *EGFR*-TKI therapy initiation. Patients with the following comorbidities and with a history of treatment for these conditions were excluded: Parasitic infestations, allergic diseases, autoimmune diseases, and hematological malignancies. Patients with chronic obstructive pulmonary disease and those with both bronchial asthma and chronic obstructive pulmonary disease requiring systemic steroid use were also excluded. Patient demographic data, including age, sex, histopathology, disease stage, objective tumor response and duration of TKI therapy, were obtained from the patients' medical charts. Tumor response was evaluated according to the Response Evaluation Criteria in Solid Tumors (Version 1.1) (11).

Expression of unwillingness to receive subsequent anticancer therapy after TKI. Following the charting format of SOAP (subject, object, assessment, and plan) (12), the patient's/family's expression of refusal of all subsequent anticancer therapy after TKIs was described in the patient's chart as it was given. The reason for the refusal was also described as it was given. In this study, those descriptions were examined for each patient. When the patient/family gave 'decline in systemic physical function due to aging' as a reason for refusal of all subsequent anticancer therapy after TKIs, we treated the reason as being 'older age'. On the other hand, when the patient/family cited 'declining cognitive function' as the reason, we treated the reason as 'dementia'. Among the patients who responded to TKI treatment, patients who did not wish to undergo subsequent anticancer treatment after TKI during the TKI response period were classified as group A patients; group B patients were those who received subsequent therapy after successful TKI therapy.

Statistical analysis. The chi-squared test was used to compare nominal variables. The nonparametric Mann-Whitney test was used to compare values with unknown population variance. All statistical analyses were conducted using SPSS version 23 (IBM Corporation, Armonk, NY, USA). A p-value of less than 0.05 was considered significant.

Ethics. This study conformed to the Ethical Guidelines for Clinical Studies issued by the Ministry of Health, Labor, and Welfare of Japan. Written informed consent for a non-interventional retrospective study was obtained from each patient. The analysis of the medical records of patients with lung cancer was approved by the Ethics Committee of the Mito Medical Centre, University of Tsukuba (no. 20-57).

Table I. *Clinical features in patients aged 75 years and older and those less than 75 years.*

Characteristic		Age		*p*-Value*
		75 Years and older	Less than 75 years	
Patients	Number	51	57	
Sex, n (%)	Male	17	25	0.52
	Female	34	32	
Age, years	Median (range)	80 (75-92)	65 (40-74)	
Pathology, n	Adenocarcinoma	50	54	0.62
	Other	1	3	
Stage, n	IIIA-C	18	11	0.08
	IVA-B	33	46	
EGFR, n	Exon 19 deletion	25	38	0.08
	Other	26	19	

EGFR: Epidermal growth factor receptor.

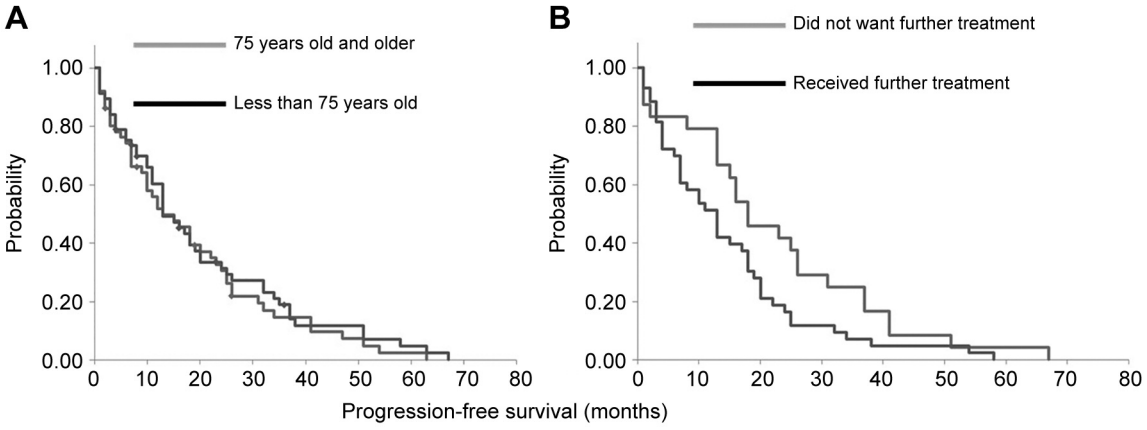

Figure 2. *Comparison of progression-free survival (PFS) between patients aged 75 years and older and patients younger than 75 years (A). There was no significant difference in the progression-free survival (PFS) of patients aged 75 years and older and those younger than 75 years (median of 12.0 vs. 13.0 months, respectively, p=0.29). Comparison of PFS between patients who did not want further treatment after tyrosine kinase inhibitor (TKI) treatment and those who received the next treatment after TKI (B). The PFS of those who refused subsequent treatment (median=18.0 months, range=1.0-67.0 months) was significantly longer than that of patients who did not (median=13.0 months, range=1.0-58.0 months; p=0.04).*

Results

Patient cohort. A total of 120 patients with *EGFR* mutation-positive NSCLC were diagnosed during the study period. The median age of this study population was 73 years, and 54 (45%) were aged 75 years or older. Figure 1 shows the study flowchart.

In all, 108 out of 120 patients received *EGFR*-TKI therapy. These 108 patients were divided into those aged 75 years and over, and those under 75 years, and the clinical backgrounds of these patients are shown in Table I. There were no differences between these two age groups. In addition, we found that there was no significant difference in the progression-free survival (PFS) of patients aged 75 years and older and those younger than 75 years (median of 12.0 *vs*. 13.0 months, respectively, *p*=0.29; Figure 2A). Ninety-two out of the 108 patients completed *EGFR*-TKI therapy during the study period. Of these, 67 patients responded to TKIs: Group A consisted of 24 patients who did not wish to and then did not receive anticancer treatment following TKI; and group B, who did receive anticancer therapy following TKI, comprised 43 patients.

Comparison between group A and group B patients. The clinical backgrounds of the two groups of patients are shown in Table II. There was no significant difference in the clinical features between these two groups. The PFS of group A patients (median=18.0 months, range=1.0-67.0 months) was significantly longer than that of group B patients (median=13.0 months, range=1.0-58.0 months; *p*=0.04. Figure 2B).

Table II. *Clinical features in patients who refused all subsequent therapy after therapy with tyrosine kinase inhibitor (group A) and those who received the next treatment after tyrosine kinase inhibitor (group B).*

		Group A	Group B	*p*-Value
Patients	Number	24	43	
Sex, n	Male	7	19	0.30
	Female	17	24	
Age, years	Median (range)	73 (58-85)	69 (44-86)	0.11
Pathology, n	Adenocarcinoma	23	42	0.99
	Other	1	1	
Stage, n	IIIA-C	7	10	0.99
	IVA-B	17	33	
EGFR, n	Exon 19 deletion	13	25	0.80
	Other	11	18	

EGFR: Epidermal growth factor receptor.

Reasons for not wishing to receive subsequent treatment after TKI. The reasons given for not wanting to receive subsequent treatment after TKI often comprised multiple reasons and were as follows: 'older age' (12 patients); 'decreased general condition' (10 patients); dementia (9 patients); and 'deterioration of physical comorbid disease' (two patients). Dementia was the reason for refusing further therapy in eight out of 13 patients aged 75 years and older, and one of 11 persons aged <75 years; this difference between age groups was significant (p=0.01).

A preference for no subsequent TKI treatment was expressed by 'patients and their family' in 20 cases, 'patients' in three cases, and 'family' in one case.

Discussion

This study had five key findings. Firstly, the median age of the 120 *EGFR*-positive patients was 73 years, and 45% were 75 years and older. When divided by age into older or younger than 75 years, there was no difference in patient clinical characteristics and no difference in PFS. Secondly, of the 67 patients who responded to TKIs, 24 (35.8%) (group A) expressed that they did not wish to receive subsequent treatment after TKI while still within their TKI response period. Thirdly, there was no difference in patient backgrounds between the 43 patients who responded to TKI and underwent subsequent treatment after TKI (group B) and group A. However, the PFS of group A patients was longer than that of group B patients. Fourthly, reasons for not wanting the next treatment after TKI were 'poor performance status', 'exacerbation of physical complications', 'old age' and 'dementia'. Finally, the percentage of patients who expressed 'dementia' as the reason for not wanting further treatment was higher in patients aged 75 years and older.

Treatment guidelines for *EGFR*-mutated NSCLC do not provide a separate framework for elderly patients (13-15). *EGFR*-TKIs became available in many countries in the early 2000s. Initially, lung injury was a side-effect but stricter indications and the establishment of appropriate countermeasures have made it possible to manage side-effects sufficiently (4, 5). Due to the combination of a long-lasting clinical efficacy and a low frequency of serious side-effects, except for pulmonary damage, TKIs have enabled long-term disease control that was not possible with conventional cytotoxic chemotherapeutic treatments (7). Moreover, since it is an oral treatment, this is considered a major improvement in the treatment of NSCLC in terms of patient quality of life, as patients do not require long-term hospitalization.

For TKI treatment in elderly patients, the median PFS has been reported to be 11.7 to 19.4 months (16-18). The median PFS for TKI treatment in patients aged 75 years and older in this study was 13.0 months, which is consistent with these previous reports, suggesting the patients in this study likely represent average patients seen in routine practice. Among these patients, the median PFS for patients who did not wish to receive subsequent TKI treatment despite a TKI response was 18.0 months. These results suggest that among elderly patients with a long duration of response, there might be some patients who do not wish to receive subsequent TKI therapy even if they respond to TKI.

Most patients with *EGFR*-mutated NSCLC have been reported to be young, female, non-smoker and have adenocarcinoma (1). Indeed, it has already been reported that the age of onset of *EGFR*-mutated NSCLC is significantly younger than in patients with wild-type EGFR, but it is also known that a certain percentage of elderly patients have *EGFR*-mutated NSCLC (2, 3). Many elderly patients have several physical comorbidities, such as lifestyle-related

diseases associated with aging (19). In elderly patients, it is necessary to consider not only such physical illnesses but also cognitive decline (20-22). In the present study, the most common reasons for refusing post-TKI treatment were 'old age', 'decreased performance status and 'dementia' (8, 23). There are no reports indicating a specific age for 'old age', and the term is vague. However, 'old age' was the reason chosen by 12 patients/families in our study. Among our patients, there was a patient whose physical and mental condition made it impossible to continue taking oral TKI; the family described it as 'old age'. An interesting finding in our study was that dementia was given as the reason for stopping treatment at a higher rate in patients aged 75 years and older than in those younger than 75 years. Even if TKIs are started before the age of 75 years, it might be necessary to consider the patient's likely cognitive function at the next cancer treatment after the age of 75 years.

In 20 out of 24 patients in our study, the patients and their families expressed a wish to the attending physician not to receive subsequent anticancer therapy. We interpreted this to mean that the decision was made after full discussion between the patient and their family. To the best of our knowledge, there are no reports concerning who makes this decision and under what circumstances, but previous research investigating refusal of diagnostic measures/treatment has reported that there is sufficient consultation within the family (8, 23, 24). There is currently no established 'correct' response to a request from the patient and their family to not receive subsequent treatment during the *EGFR*-TKI response period. There is no one-size-fits-all answer, and a response according to the situation of each patient should be made. Understanding 'patient refusal' among very elderly patients with cancer or presumed cancer is discussed by Wieland *et al*. (8), and the decision not to have additional anticancer therapy after TKI therapy should be made after careful and thoughtful consideration of a wide range of medical facts, including the risks and benefits of subsequent anticancer therapy, and information from healthcare providers and family members, and ultimately, where possible, the patient's opinion should be trusted and respected.

There are some limitations in this study. This study was retrospective, involving results from a small number of patients at two hospitals, and included treatment with several TKIs. As such, while these results could provide some clarification in situations where patients refuse subsequent treatment despite a response during TKI treatment, a larger survey needs to be conducted involving a larger number of patients. A long duration of response with no serious adverse effects may also occur with other TKI treatments and treatments using immune checkpoint inhibitors (25). Therefore, a similar situation of refusing the next treatment despite a response might also be a problem for patients under these treatments in the future.

Conclusion

Some elderly patients with *EGFR*-mutated NSCLC whose disease has been under good long-term control with TKIs may express a wish not to receive subsequent treatment after TKIs. To date, the optimal response to such a request has not been determined but it should consider the physical and cognitive function of the patient and involve fully explaining the situation to both the patient and their family.

Conflicts of Interest

None declared.

Authors' Contributions

SH, KM, and HS designed the study. SH, YF, MU, KM, SS, TK, and HS collected the data. NT, NK, and HS analyzed the data. SH, KM, and HS prepared the article. All Authors approved the final version for submission.

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Received November 3, 2022
Revised November 23, 2022
Accepted November 25, 2022