

The Survival of Advanced Non-small Cell Lung Cancer Patients Treated with Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor in Thailand: A Single Institution Review

Archara Supavavej, MD, MSc¹, Manunya Tandhansakul, MD², Prakongboon Sungkasubun, MD, MSc¹, Jomtana Siripaibun, MD¹, Worawit Chaiwiriawong, MD¹, Teerapat Ungtrakul, MD, MSc³, Wisut Lamlerththong, MD, MPH³

¹ Medical Oncology Unit, Internal Medicine Department, Chulabhorn Hospital, HRH Princess Chulabhorn College of Medical Science, Chulabhorn Royal Academy, Bangkok, Thailand

² Pediatric Department, Chulabhorn Hospital, Princess Chulabhorn College of Medical Science, Chulabhorn Royal Academy, Bangkok, Thailand

³ Faculty of medicine and Public Health, HRH Princess Chulabhorn College of Medical Science, Chulabhorn Royal Academy, Bangkok, Thailand

Background: Epidermal Growth Factor Receptor (EGFR) Tyrosine Kinase inhibitor (TKI) can improve progression free survival in patients with treatment naive EGFR mutant metastatic non-small cell lung cancer (NSCLC) compared with platinum-based chemotherapy, but no statistically significant difference is observed in overall survival. The survival time of EGFR mutant NSCLC patients treated with at least two systemic chemotherapy regimens and one EGFR TKI was 34.8 months in a previous study.

Objective: The present study was to determine the median survival time of advanced NSCLC patients who received EGFR-TKIs in Chulabhorn Hospital.

Materials and Methods: We retrospectively reviewed the medical records of advanced NSCLC cases treated with EGFR TKIs in Chulabhorn Hospital during 2009 to 2011.

Results: Among 243 advanced NSCLC cases, 72 patients received EGFR TKIs. EGFR mutation status was positive in 14 (19.17%) patients. The median overall survival time was 30.04 months (95% CI: 18.71 to 49.48 months) in all patients, compared with 49.49 months (95% CI: 15.93 to NR) in EGFR mutation-positive patients (n=14). No statistically significant difference of overall survival was noted between EGFR mutation status groups (p=0.51).

Conclusion: The median survival time for Thai patients treated with EGFR TKIs was comparable to historical data and irrespective of EGFR mutation status.

Keywords: Metastatic non-small cell lung cancer, EGFR TKIs, Survival

J Med Assoc Thai 2021;104(Suppl2): S40-4

Website: <http://www.jmatonline.com>

Lung cancer is the second most common cause of cancer-related death in Thailand⁽¹⁾. Non-small cell lung cancer (NSCLC) is the most common histological subtype of lung cancer, with adenocarcinoma cell type representing the majority of NSCLC. The median survival of advanced NSCLC

in the 1990s was nearly 1 year.

Multiple clinical studies have shown that epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) showed clinical efficacy in terms of progression-free survival (PFS) benefit in EGFR mutant NSCLC patients compared with standard platinum doublets chemotherapy⁽²⁻⁶⁾. The median PFS in these studies ranged from 7 to 13 months. A meta-analysis revealed that all examined EGFR-TKIs improved PFS and overall response rate to chemotherapy in EGFR mutated NSCLC⁽⁷⁾. In contrast, two studies^(8,9) showed no significant differences of overall survival between patients treated with EGFR TKIs versus chemotherapy. Furthermore, these studies found that patients who received sequential therapy of EGFR-TKI and chemotherapy throughout the course of treatment had improved overall survival up to 29 to 30 months compared with chemotherapy alone.

The aim of the present study was to assess the median survival time of advanced NSCLC patients treated with EGFR TKIs in Chulabhorn Hospital, Thailand in 2009

Correspondence to:

Supavavej A.

Medical Oncology Unit, Internal Medicine Department, Chulabhorn Hospital, HRH Princess Chulabhorn College of Medical Science, Chulabhorn Royal Academy, Bangkok 10210, Thailand

Phone & Fax: +66-2-5766791

Email: archara.sup@pccms.ac.th

How to cite this article:

Supavavej A, Tandhansakul M, Sungkasubun P, Siripaibun J, Chaiwiriawong W, Ungtrakul T, Lamlerththong W. The Survival of Advanced Non-small Cell Lung Cancer Patients Treated with Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor in Thailand: A Single Institution Review. J Med Assoc Thai 2021;104 (Suppl2): S40-4.

doi.org/10.35755/jmedassocthai.2021.S02.12556

to 2011. During that time, EGFR mutation test was not routinely assessed in Thailand; the majority of cases treated with EGFR TKIs were selected by clinical characteristics. We also examined the differences in median survival among patients according to EGFR mutation status.

Materials and Methods

We retrospectively reviewed the medical records of advanced NSCLC cases treated with EGFR TKIs in Chulabhorn Hospital during 2009 to 2011. The authors collected demographic data including race, sex, smoking history, co-morbidity illness, histology cell type and EGFR mutation status. The authors also recorded date of diagnosis of advanced NSCLC, date of treatment start and date of treatment completion for each line of systemic treatment.

The median overall survival was calculated from the date of diagnosis of advanced NSCLC until death from any cause or last follow-up visit. The duration of treatment of EGFR TKIs was calculated from the date of treatment start until date of treatment completion, death or last follow-up visit.

The primary objective was to determine the median survival time of patients with advanced NSCLC who received EGFR-TKIs in Chulabhorn Hospital.

The secondary objective was to identify the differences in median survival between EGFR mutation status groups.

The protocol of this research was reviewed and approved by the Human research ethics committee Chulabhorn Research Institute No. 029/2561.

Statistical analysis

In a 10 year retrospective population-based review of advanced non-small cell lung cancer patients treated with EGFR TKIs that was published in 2014⁽¹⁰⁾, 123 (16.4%) of 750 patients received EGFR TKIs. Sample size calculation was performed with the Levy and Lemeshow method. The sample size required to achieve a 95% confidence interval of width $\pm 5\%$ was 210.

Descriptive statistics (frequency, percentage, mean, median and standard deviation) were used for demographic and clinical characteristics. The overall survival and duration of treatment with EGFR TKIs was estimated by Kaplan-Meier method. The overall survival in groups according to EGFR mutation status was compared by log rank test. A p-value less than 0.05 was considered statistically significant. The statistical analysis was performed using STATA version 12 statistical software.

Results

From 2009 to 2011, there were 243 cases of advanced NSCLC in Chulabhorn Hospital. Among these patients, 72 cases were treated with EGFR TKIs. The median follow-up time in these patients was 17.09 months. The demographic data of the patients are presented in Table 1. Among the total patient group, 47.2% were female patients. The median age at diagnosis was 60 years old. Nearly one-

Table 1. Demo-graphic data

Characteristic	n=72 (%)
Sex	
Male	38 (52.8)
Female	34 (47.2)
Age, years	
Mean	61.83
Median	60.00
SD	11.56
Smoking history	
Non-smoker	19 (26.4)
Ex-smoker	14 (19.4)
Current-smoker	12 (16.7)
Unknown	27 (37.5)
Type of histology	
Adenocarcinoma	52 (72.2)
Squamous cell carcinoma	10 (13.9)
Large cell carcinoma	1 (1.4)
Adenosquamous cell carcinoma	2 (2.8)
Carcinoma unspecified	4 (5.6)
Other: sarcomatoid carcinoma, mucinous neoplasm, large cell neuroendocrine carcinoma	3 (4.2)
Staging at first diagnosis	
I	1 (1.4)
III	7 (9.7)
IV	64 (88.9)
EGFR mutation status	
Positive for exon 19 deletion	8 (11.1)
Positive for exon 21 L858R	5 (6.9)
Positive for exon 20 T790M	0 (0)
Positive for uncommon mutation	1 (1.4)
Negative for EGFR mutation	15 (20.8)
Unknown	43 (59.7)
EGFR-TKIs	
Gefitinib	19 (26.4)
Erlotinib	53 (73.6)
Line of EGFR TKIs treatment*	
First line	18 (24.7)
Second line	29 (39.7)
Third line	22 (30.1)
Fourth line	3 (4.1)
Fifth line	1 (1.4)
Status	
Last follow-up	40 (55.6)
Still on treatment	1 (1.4)
Death	31 (43)

fourth of this population was never smokers. Adenocarcinoma was the major histology (approximately 72.2% of the overall group). Eighty-nine percent of the population presented with advanced stage at diagnosis. EGFR mutation status was tested in 30 patients (40.3%), and 14 patients were positive for EGFR mutation. Exon 19 deletion mutation was present in eight (11.1%) patients while five (6.9%) patients presented with exon 21 L858R mutation. One patient showed exon 19 G729E substitution mutation. No patient presented with primary exon 20 T790M mutation.

At the time of treatment, the hospital used two first generation EGFR TKIs (Erlotinib or Gefitinib). Erlotinib was prescribed in 53 (73.6%) patients. EGFR TKIs were prescribed as first line, second line and third line treatment in 18 (24.7%), 29 (39.7%) and 22 (30.1%) patients, respectively. 31 patients (43%) died; 40 patients were alive at the last follow-up and one patient was still on treatment.

Median survival time

The median survival time for all patients treated with EGFR TKIs was 30.01 months (95% CI; 18.71 to 49.49), as shown in Kaplan-Meier curves in Figure 1. The median survival time for the EGFR mutation-positive group was 49.49 months (95% CI; 15.93 to NR), compared with 20.96 months (95% CI; 10.64 to NR) for the EGFR mutation-negative group and 27.74 months (95% CI; 18.01 to NR) for the EGFR mutation unknown group (Figure 2). The median survival time in the groups with different EGFR mutation status showed no statistically significant difference by log rank test ($p > 0.05$).

Duration of treatment

The median duration of treatment with EGFR TKIs in all patients was 7.07 months (95% CI; 4.19 to 12.4 months) (Figure 3). The median duration of treatment with EGFR TKIs in the EGFR mutation-positive group was 12.4 months (95% CI; 6.18 to NR) compared with 6.21 months (95% CI; 1.85 to NR) in the EGFR mutation-negative group and 5.55 months (95% CI; 2.35 to NR) for the EGFR mutation unknown group. The median duration of treatment did not show any statistical significance between groups ($p = 0.2269$) (Figure 4).

Discussion

This is the first retrospective cohort study of patients with advanced NSCLC treated with first generation EGFR TKIs at our institution. Our institution previously used clinical characteristic selection to identify patients who can benefit from EGFR TKIs. Nearly 60% of all patients had unknown EGFR mutation status. This group showed an impressive median duration of treatment and overall survival, which may be because most of these patients had adenocarcinoma histology and were never or light smokers.

Thai NSCLC patients receive EGFR TKIs in one of the lines of treatment. Most patients receive second or third lines of treatment after platinum-based chemotherapy.

Second line chemotherapy such as docetaxel or pemetrexed can prolong the median survival time of patients. Most patients in our institute received systemic treatment up to third line treatment, and a few patients received fourth or fifth lines of systemic treatment. This strategy can prolong median overall survival by a few months.

Our study found that the median overall survival was 30.01 months irrespective of EGFR mutation status. In EGFR mutation-positive patients, the median survival was more than 4 years (49.49 months). In a previous study⁽⁸⁾, the median survival time for EGFR mutated advanced NSCLC with three lines of systemic treatment was 34.8 months. The median overall survival in all patients at our hospital was comparable to that of a previous study⁽⁸⁾ with EGFR mutation-positive patients; this is because 60% of the patients were not tested for EGFR mutation. From the clinical characteristics, these patients were likely to be positive

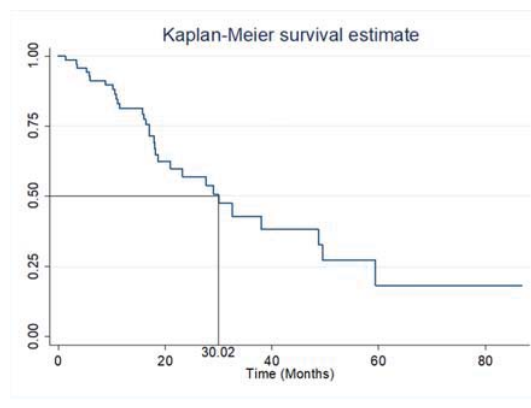


Figure 1. Kaplan-Meier survival estimate of the overall population.

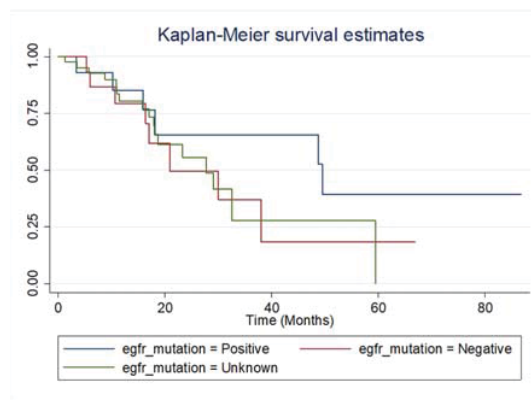


Figure 2. Kaplan-Meier survival according to EGFR mutation status.

for EGFR mutation. Furthermore, our patients received multiple lines of systemic treatment, which can affect the median overall survival time.

One of the limitations of our study is the unknown death date of patients; more than 50% of our cases only had the last follow-up date in records. Further study should exclude cases with an unknown death date to better clarify exact overall survival data.

EGFR TKIs can now be widely used as first line treatment for EGFR mutation-positive advanced NSCLC in Thailand. Additionally, third generation EGFR TKIs have been shown to reverse the acquired resistance of NSCLC to first generation EGFR TKIs such as with exon 20 T790M mutation⁽¹¹⁾. Because of these improvements in treatment, we may see longer survival times for patients with advanced NSCLC with EGFR mutation.

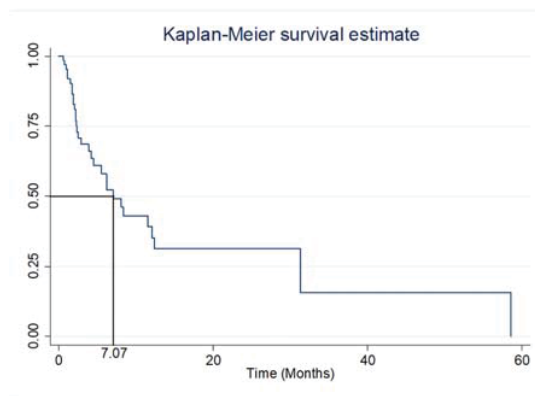


Figure 3. Median duration of treatment with EGFR TKIs in all patients.

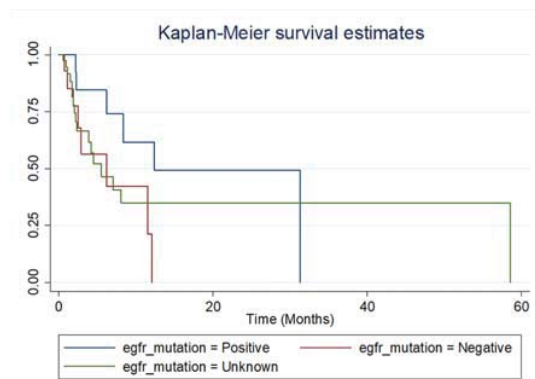


Figure 4. Median duration of treatment with EGFR TKIs in groups according to EGFR mutation status.

What is already known on this topic?

The median survival of NSCLC patients with EGFR TKIs from previous studies was 30.4 months.

What this study adds?

This is the first study to examine the median survival of NSCLC patients treated with EGFR TKIs in a Thai population; the median survival of Thai patients with EGFR TKIs in this study was 30.04 months.

Acknowledgements

Thanks go to my medical oncology team, Multidisciplinary tumor board team and all Chulabhorn Hospital lung cancer patients.

Potential conflicts of interest

The authors declare no conflict of interest.

References

1. Imsamran W, Chaiwerawattana A, Wiangnon S, Pongnikorn D, Suwanrung K, Sangrajrang S, et al. Cancer in Thailand, Vol. VIII, 2010-2012. Bangkok: Cancer Registry Unit, National Cancer Institute Thailand; 2015.
2. Mok TS, Wu YL, Thongprasert S, Yang CH, Chu DT, Saijo N, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med* 2009;361: 947-57.
3. Maemondo M, Inoue A, Kobayashi K, Sugawara S, Oizumi S, Isobe H, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. *N Engl J Med* 2010;362:2380-8.
4. Mitsudomi T, Morita S, Yatabe Y, Negoro S, Okamoto I, Tsurutani J, et al. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. *Lancet Oncol* 2010;11:121-8.
5. Zhou C, Wu YL, Chen G, Feng J, Liu XQ, Wang C, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. *Lancet Oncol* 2011;12:735-42.
6. Rosell R, Carcereny E, Gervais R, Vergnenegre A, Massuti B, Felip E, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EORTAC): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol* 2012;13:239-46.
7. Haaland B, Tan PS, de Castro G Jr, Lopes G. Meta-analysis of first-line therapies in advanced non-small-cell lung cancer harboring EGFR-activating mutations. *J Thorac Oncol* 2014;9:805-11.
8. Inoue A, Kobayashi K, Maemondo M, Sugawara S, Oizumi S, Isobe H, et al. Updated overall survival re-

- sults from a randomized phase III trial comparing gefitinib with carboplatin-paclitaxel for chemo-naïve non-small cell lung cancer with sensitive EGFR gene mutations (NEJ002). *Ann Oncol* 2013;24:54-9.
9. Zhou C, Wu YL, Chen G, Feng J, Liu XQ, Wang C, et al. Final overall survival results from a randomised, phase III study of erlotinib versus chemotherapy as first-line treatment of EGFR mutation-positive advanced non-small-cell lung cancer (OPTIMAL, CTONG-0802). *Ann Oncol* 2015;26:1877-83.
 10. Ho C, Ramsden K, Zhai Y, Murray N, Sun S, Melosky B, et al. Less toxic chemotherapy improves uptake of all lines of chemotherapy in advanced non-small-cell lung cancer: a 10-year retrospective population-based review. *J Thorac Oncol* 2014;9:1180-6.
 11. Mok TS, Wu YL, Ahn MJ, Garassino MC, Kim HR, Ramalingam SS, et al. Osimertinib or platinum-pemetrexed in EGFR T790M-positive lung cancer. *N Engl J Med* 2017;376:629-40.