Original Study

Outcome Differences Between First- and Second-generation EGFR Inhibitors in Advanced *EGFR* Mutated NSCLC in a Large Population-based Cohort

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Abstract

A review of patients with advanced non–small-cell lung cancer with *EGFR* activating mutations was conducted to investigate outcomes with different front-line tyrosine kinase inhibitors using a large population-based cohort. The survival benefits of a second-generation tyrosine kinase inhibitor appear generalizable to a real-world patients.

Introduction: Second-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) appear superior to first-generation TKIs in clinical trials, but at the cost of greater toxicity. It is unclear whether real-world patients, who often suffer worse outcomes, experience similar survival benefits. Using population-based data, we aim to characterize outcome differences by type of treatment. **Patients and Methods:** We reviewed all patients with advanced non–small-cell lung cancer who initiated treatment with an *EGFR* TKI at BC Cancer between 2010 and 2015. A propensity score was generated to account for imbalances in patient characteristics between treatment groups. A Cox proportional hazards model based on the propensity score was then used to estimate effects of treatment on survival. **Results:** A total of 484 patients were identified for analysis. Patients in the second-generation cohort were younger (62 vs. 67 years), had less baseline central nervous system metastases (9% vs. 22%), and more uncommon *EGFR* mutations (13% vs. 7%). Patients receiving a second-generation TKI had an improved overall survival (hazard ratio, 0.69; $P = .05$), driven by the subgroup with an *EGFR exon 19 deletion.* Patients with a *L858R* mutation did not appear to derive benefit from a second-generation TKI (hazard ratio, 0.91; $P = .74$). Overall, 40% of patients receiving a second-generation TKI required a dose reduction, but only 1% required discontinuation. **Conclusions:** Second-generation TKIs tended to be chosen over first-generation TKIs as frontline therapy in younger patients with uncommon *EGFR* mutations and without central nervous system metastases. The survival benefit of a second-generation TKI seen in clinical trials appeared to be generalizable to real-world patients and is a reasonable first-line therapy.

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Keywords: Afatinib, Erlotinib, Gefitinib, Real-world population, TKI

Introduction

The approval of tyrosine kinase inhibitors (TKIs) to selectively target tumors with activating epidermal growth factor receptor (EGFR) mutations marked a revolutionary milestone in the management of non–small-cell lung cancer (NSCLC) and signaled the dawn of the precision medicine era.[1,2] Approximately 25% of patients with NSCLC who were never- or ex-light smokers were found to have activating EGFR mutations, and this number can be up to 50% to 60% in Asian non-smoker patients whose tumors have adenocarcinoma histology.[3-5]

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Submitted: Feb 10, 2019; Revised: Apr 17, 2019; Accepted: May 3, 2019; Epub: May 11, 2019

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https://doi.org/10.1016/j.cllc.2019.05.003

There are multiple generations of EGFR TKIs approved for clinical use. First-generation EGFR TKIs, gefitinib and erlotinib, inhibit EGFR by competitive binding with ATP and demonstrate remarkable improvements in progression-free survival (PFS) over platinum doublet chemotherapy.[5-9] Subsequent generations of TKIs were designed to overcome treatment resistance. Second-generation TKIs, afatinib and dacomitinib, irreversibly inhibit all 4 ERBB receptors including EGFR. As such, they are more potent inhibitors of EGFR, but at the cost of increased toxicity.[10-14] Osimeritinib, the only available third-generation TKI, is specifically designed to target the *T790M* resistance mutation that emerges with EGFR TKI treatment but also shows activity against tumors harboring the *exon 19 deletion* and *exon 21 L858R* point mutations. Emerging evidence supports a role for afatinib,[10-12] dacomitinib,[13,14] and osimertinib in the upfront management of *EGFR*-mutated NSCLC.[15]

Several prospective studies have compared the different generations of EGFR TKIs against one another in treatment-naive patients. In the phase IIB LUX-Lung 7 study, afatinib demonstrated a non-significant improvement in median overall survival (OS) compared with gefitinib (27.9 vs. 24.5 months).[16,17] The larger phase III ARCHER 1050 study compared dacomitinib with gefitinib and found a significant improvement in PFS with the second-generation TKI.[13,14] This study also demonstrated a superior OS: median OS was 34.1 months in the dacomitinib group compared with 26.8 months in the gefitinib group (hazard ratio [HR], 0.7). Osimertinib was compared with first-generation TKIs in the FLAURA study, and also demonstrated a superior PFS.[15] Although the final OS data remains immature, interim results favored osimertinib.[18,19] Osimertinib has not been directly compared with second-generation TKIs in the first-line setting, and whether there is any benefit to using sequential therapy with a second-generation TKI followed by a third-generation TKI is unknown.

Clinically, the use of second-generation TKIs is limited by their relative toxicity over other TKIs. As such, they are often used in highly selected patients who tend to be young, have good performance status, and have no evidence of brain metastases. Based on subgroup analyses, treatment effects of EGFR TKIs may also be different depending on *EGFR* mutational subtype. Patients whose tumors have these common mutations derive benefit from EGFR TKIs, whereas the efficacy is less certain in the patients with uncommon *EGFR* mutations.[20,21] In the pooled analysis of LUX-Lung 3 and 6 studies, the superior OS of afatinib compared with chemotherapy was significant only in the *exon 19 deletion* subgroup.[10] Some clinicians may also favor the use of a second-generation TKI in subgroups of patients with the *EGFR exon 19 deletion* or with uncommon *EGFR* mutations.

Because only a selected group of patients are receiving second-generation TKIs in practice, it is unknown if similar survival benefits seen in clinical trials can be generalizable. Patients encountered in clinical practice often have a worse performance status and worse overall outcomes compared with those enrolled in clinical trials. It is important to ascertain that a survival benefit over first-generation TKIs can be observed in real-world patients to justify the increased toxicity of second-generation TKIs. To answer this question, we conducted a population-based retrospective review to compare differences in OS between patients with *EGFR* mutated NSCLC who were initially treated with first- or second-generation EGFR TKIs and examined the influence of *EGFR* mutation subtype on survival outcomes.

Patients and Methods

Study Patients

We conducted a retrospective review of all patients with advanced stage NSCLC over the age of 18 who initiated treatment with an EGFR TKI from 2010 to 2015 at BC Cancer, British Columbia, Canada. Patients with tumors of all histologies with a sensitizing *EGFR* mutation, including *exon 19* deletions, *L858R* point mutations, and other uncommon *EGFR* mutations, were included. Patients with *EGFR* mutations that conferred intrinsic resistance such as *exon 20* insertions and *HER2* insertions were excluded from the study. All patients who were included in the analysis had received at least 1 cycle of gefitinib, erlotinib, or afatinib in any line of therapy. Because prospective studies have not demonstrated OS differences based on the line of treatment,[5-12] patients who received an EGFR TKI in the first-, second-, or third-line setting following cytotoxic chemotherapy were included in our analysis.

Research ethics approval was obtained from the BC Cancer Institutional Research Ethics Board prior to study initiation.

Mutation Data

Prior to July 1, 2016, EGFR testing from tissue samples was conducted using polymerase chain reaction methods and was only capable of detecting *EGFR exon 19* deletions and *L858R* point mutations. After July 1, 2016, *EGFR* mutation testing was performed using next-generation sequencing, capable of detecting mutations in *EGFR exons 18-21*, including *exon 20* insertions and *T790M* mutations, as well as other uncommon *EGFR* mutations. All mutation testing was conducted in the Central Cancer Genetics Lab at BC Cancer.

Study Procedures

Patients were divided into 2 cohorts based on whether they received a first- or second-generation EGFR TKI as their initial TKI. Patients who received afatinib after progression on gefitinib or erlotinib were analyzed in the first-generation TKI cohort. The baseline clinical and pathologic characteristics of all patients was recorded, including age, gender, ethnicity, smoking status, Eastern Cooperative Oncology Group (ECOG) performance status, and the presence of baseline central nervous system (CNS) metastases. Baseline and follow-up CNS imaging was per physician discretion. Systemic treatment details on 6 or more lines of treatment were collected for all patients. Subsequent treatment with osimertinib was also documented.

The primary outcome of interest was a comparison of OS between patients who received a first-generation TKI or a second-generation TKI. In addition, we examined survival differences within the *EGFR* mutation subtypes: *exon 19* deletion, *L858R* point mutation, and uncommon *EGFR* mutations. Because patients with *EGFR*- mutated NSCLC have a long duration of disease, survival data was updated in March 2018 to ensure adequate follow-up.

To characterize the tolerability of the second-generation TKIs in a real-world setting, adverse events were collected, and any dose reductions or modifications were documented for patients who were treated with afatinib. The adverse event profile of gefitinib and erlotinib are well-established, so the toxicity data for this group of patients was not collected in this study.

Statistical Analysis

The baseline characteristics of patients who received a first- or second-generation TKI were summarized using descriptive statistics and compared using the χ^2 test. Survival was estimated from the time of diagnosis of metastatic disease. Patients who remained alive at the end of the study were censored. OS was estimated using the Kaplan-Meier method in the unweighted cohort, and differences between the first and second-generation TKI cohorts were tested using the log-rank test. A propensity score was generated to adjust for confounding using the following variables: age, gender, ECOG performance status, ethnicity, smoking status, baseline CNS metastases, and *EGFR* mutation subtype. A Cox proportional hazards model based on the propensity score was used to examine for differences in treatment effect of the TKI used and *EGFR* mutation subtype. As there may be effect modification among different *EGFR* mutations, survival analysis was repeated by mutation subgroup: *exon 19* deletion, *L858R*, and uncommon *EGFR* mutations. Sensitivity analysis was performed using patients with adenocarcinoma who received a second-generation TKI at any treatment line. All *P*-values were 2-sided, and a *P*-value of $< .05$ was considered statistically significant. All analyses were performed using Stata/IC 15.1.

Results

We identified 484 patients with a known *EGFR* sensitizing mutation who received at least 1 cycle of EGFR TKI. Of these, 414 patients initially received first-generation gefitinib or erlotinib. The remaining 70 patients initially received afatinib, the only second-generation EGFR TKI that is available for first-line use in Canada.

Baseline characteristics of the 2 cohorts are summarized in Table 1. ECOG performance status, smoking history, and ethnicity were similar between the 2 groups. However, there were significant differences in age, CNS metastases, and *EGFR* mutation subtype, which may bias survival results. Patients receiving a second-generation TKI were significantly younger (median age, 62 vs. 67 years; $P = .001$). The distribution of *EGFR* mutations was also different between the 2 groups ($P < .001$). Patients were more likely to receive a second-generation TKI with uncommon *EGFR* mutations. Of the 16 patients who were identified as having uncommon *EGFR* mutations, 4 patients had a *G719X* mutation, and 3 patients had complex *G719X* plus *L861Q* or *S768I* mutations. Among the 2 common activating mutations, patients with *exon 19 deletions* were more frequent in the second-generation TKI group. There was a significant difference in baseline CNS metastases between the 2 groups. In the first-generation EGFR TKI cohort, 22% had brain metastases at presentation compared with 9% in the afatinib cohort ($P = .008$).

Most patients in both cohorts received their initial EGFR TKI in the first-line setting. In the first-generation TKI cohort, 97% (n = 403) of patients received erlotinib or gefitinib as first-line treatment, and only 3% (n = 11) received this in the second line, after chemotherapy. In the second-generation TKI cohort, 90% (n = 63) of patients received afatinib as a first-line treatment, 9% (n = 6) as a second-line treatment, and 1% (n = 1) as a third-line treatment after chemotherapy.

At the time of data analysis, 75% of patients had died, and the median duration of follow-up of the censored patients was 31.7 months. The median OS in the entire cohort of patients who were *EGFR* mutation-positive and treated with an EGFR TKI was 25.9 months (95% confidence interval [CI], 24.1-28.8 months). The outcomes were significantly better in the second-generation TKI group, with a median OS of 39.0 months (95% CI, 25.6-48.8 months) compared with the first-generation TKI group, with a median OS of 25.0 months (95% CI, 23.1-27.5 months) (Table 2, Figure 1). This remained statistically significant in the regression analysis using the propensity score (hazard ratio [HR], 0.694; 95% CI, 0.47-1.00; $P = .05$).

Subgroup analyses were performed according to mutation subtype (Table 2, Figure 2). Among patients who had an *exon 19* deletion, treatment with a second-generation TKI was superior compared with that of a first-generation TKI (median OS, 48.8 months; 95% CI, 48.8 months to not reached [NR] vs. 26.4 months; 95% CI 23.8-31.7 months). Only a trend to significance remained in regression models using the propensity score (HR, 0.59; 95% CI, 0.35-1.01; $P = .052$). However, in the subgroup analysis of patients with a *L858R* point mutation, there was no difference in survival between a second- and a first-generation EGFR TKI (median OS, 25.4 months; 95% CI, 18.0-38.3 months vs. 20.6 months; 95% CI, 17.8-25.0 months; HR, 0.90; 95% CI, 0.52-1.60; $P = .74$). Among the patients with uncommon EGFR mutations, the survival outcome of patients treated with second- and first-generation TKI does not appear to be different (median OS, 48.5 months; 95% CI, 6.4 months to NR vs. 32.7 months; 95% CI, 1.1 months to NR; HR, 0.33; 95% CI, 0.06-1.92; $P = .22$).

After progression on first-line TKI, 93 patients had *T790M* mutation testing done, and 70% (n = 66) tested positive. Of these, 53 patients received post-progression treatment with osimeritinib, 46 in the first-generation TKI cohort, and 7 in the second-generation TKI cohort. The median OS for patients who received osimertinib had not yet been reached at the time of our study analysis; however, the 24-month survival rate among these 53 patients who received osimertinib was 90%. All of the patients who received osimertinib after afatinib were still alive at the time of study analysis.

In this study, a total of 93 patients received afatinib at some point in their treatment; 70 received it as their first-line treatment and 23 after either erlotinib or gefitinib. The median starting dose of afatinib in this study was 40 mg, and the median tolerated dose was 30 mg. Among these patients, 40% (n = 37) required dose reductions or interruptions for adverse events, but only 1 patient required permanent discontinuation of afatinib owing to toxicity. Clinically relevant adverse events that led to a dose reduction were typical EGFR TKI side effects and included rash, paronychia, diarrhea, and mucositis. Transaminitis is uncommon with afatinib, and no dose reductions or interruptions in treatment were related to this side effect in our cohort.

Table 1 Baseline Demographic Characteristics of Patients in the First-generation and Second-generation TKI Cohorts

	First-generation TKI (N = 414)	Second-generation TKI (N = 70)	*P* Value
Age, y			
Median	67 (30-90)	62 (34-84)	.001
Age, y			.002
≤65	188 (45)	46 (66)	
>65	226 (55)	24 (34)	
Gender			.36
Female	283 (68)	44 (63)	
Male	131 (32)	26 (37)	
Ethnicity			.88
Asian	211 (51)	35 (50)	
Non-Asian	203 (49)	35 (50)	
ECOG PS			.15
0	86 (21)	14 (20)	
1	195 (47)	41 (59)	
2	89 (21)	13 (19)	
3	40 (10)	1 (1)	
4	4 (1)	1 (1)	
Smoking			.56
Never	277 (67)	47 (67)	
Former	97 (24)	19 (27)	
Current	38 (9)	4 (6)	
Histology			.16
Adenocarcinoma	367 (89)	66 (94)	
Squamous or adenosquamous	47 (11)	4 (6)	
Baseline CNS metastases			.008
No	321 (78)	64 (91)	
Yes	93 (22)	6 (9)	
Overall incidence of CNS metastases			<.001
No	209 (51)	52 (74)	
Yes	205 (49)	18 (26)	
De novo metastatic disease			.35
Yes	355 (86)	57 (81)	
No	59 (14)	13 (19)	
EGFR mutation			<.001
Exon 19 deletion	242 (58)	41 (59)	
L858R	165 (40)	20 (28)	
Uncommon mutations	7 (2)	9 (13)	
First EGFR TKI used			
Gefitinib	403 (97)	0	
Erlotinib	11 (3)	0	
Afatinib	0	70 (100)	

Data are presented as n (%).
P values of < .05 are significant.
Abbreviations: CNS = central nervous system; ECOG PS = Eastern Cooperative Oncology Group performance status; EGFR = epidermal growth factor receptor; TKI = tyrosine kinase inhibitor.

Discussion

Our study demonstrates that real-world patients with *EGFR*-mutated advanced NSCLC benefit from initial treatment with a second-generation TKI. A statistically significant survival benefit is seen after propensity score-based regression analysis (HR, 0.69; 95% CI, 0.47-1.00; $P = .05$). These findings are similar to those from the ARCHER 1050 study, which compared dacomitinib with gefitinib.[13,14] Given concerns about toxicity, patients who receive a second-generation EGFR TKI in clinical practice are highly selected and often differ from a clinical trial population. Our results are

Table 2 Median Overall Survival Values

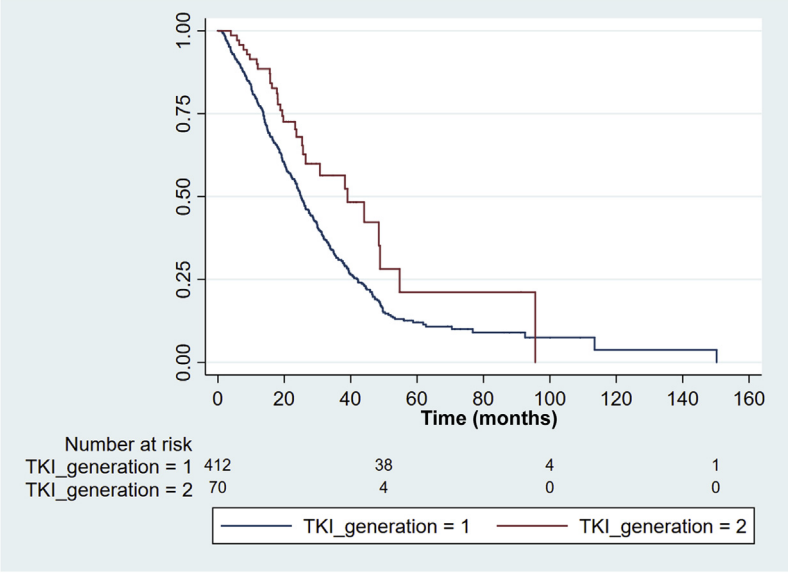
Cohort	Median OS, mos	95% CI	HR (95% CI)
Entire cohort	25.9	(24.1-28.8)	
Second-generation TKI	39.0	(25.6-48.8)	0.69 (0.47-1.00)
First-generation TKI	25.0	(23.1-27.5)	
Exon 19 deletion subgroup			
Second-generation TKI	48.8	48.8 to NR	0.59 (0.35-1.00)
First-generation TKI	26.4	23.8-31.7	
L858R subgroup			
Second-generation TKI	25.4	18.0-38.3	0.91 (0.52-1.60)
First-generation TKI	20.6	17.8-25.0	
Uncommon *EGFR* mutation subgroup			
Second-generation TKI	48.5	6.4 to NR	0.33 (0.06-1.92)
First-generation TKI	32.7	1.1 to NR	

Abbreviations: CI = confidence interval; EGFR = epidermal growth factor receptor; HR = hazard ratio; NR = not reached; TKI = tyrosine kinase inhibitor.

reassuring that the benefits of second-generation TKIs are generalizable to real-world patients.

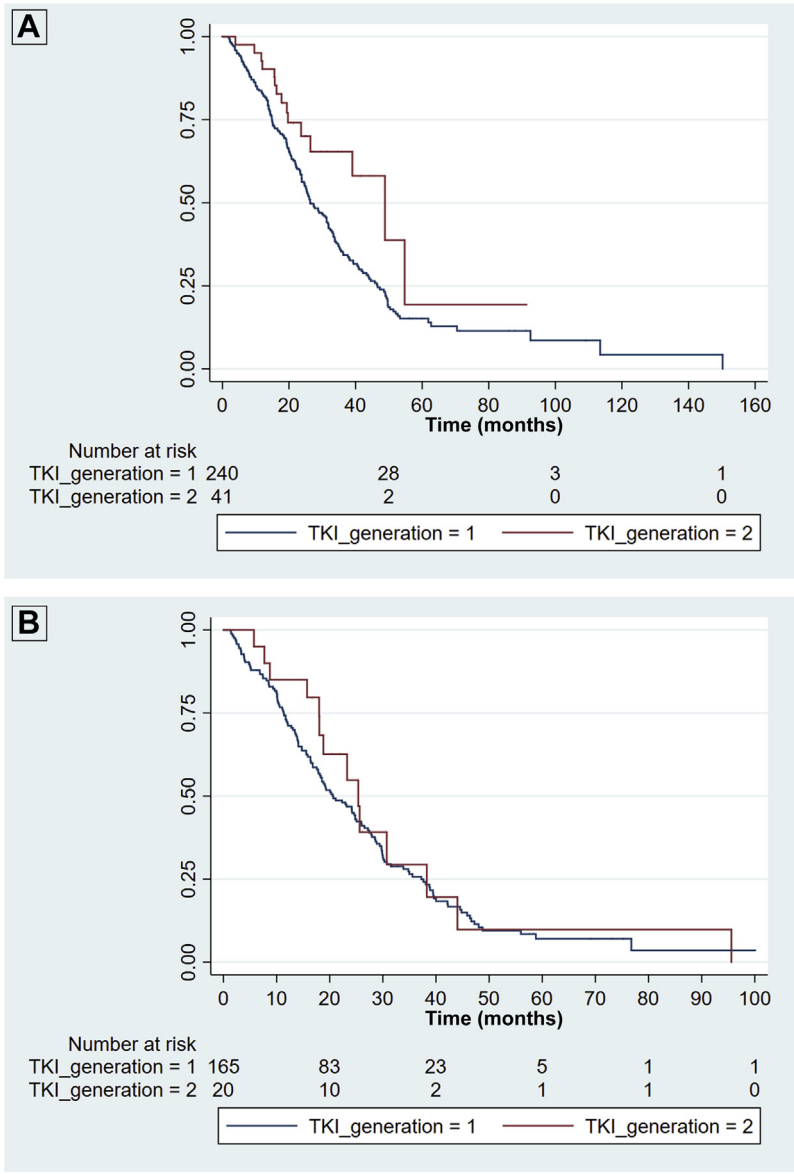
There were statistically significant differences that were noted in our cohort at baseline, which is a reflection that only select patients are prescribed a second-generation TKI, which may bias interpretation of survival results in favor of second-generation TKIs. Younger patients were more likely to receive a second-generation TKI (median 62 vs. 67 years; $P = .001$). This practice was consistent with the results of 2 observational studies, in which practice patterns revealed a higher likelihood of using aggressive treatment plans for younger patients, especially for those fit enough to tolerate greater toxicity.[22,23] However, the impact of younger age on survival is less clear. A large retrospective study in Japan found that younger age was a significant predictor of better OS.[24] But another study performed in Taiwan found that younger age predicted for worse response and survival.[25] In this cohort, younger age was also associated with a higher frequency of uncommon EGFR mutations.[25] Another important baseline difference that we observed was the significantly higher incidence of

Figure 1 Kaplan-Meier Curve of OS of Second Versus First-generation TKI as Primary Treatment. Median OS in the Entire Cohort of EGFR Mutation Positive Patients Treated With an EGFR TKI Was 25.9 Months. OS of Patients Receiving a Second-generation TKI as Primary Treatment is Better Compared With a First-generation TKI (Median OS, 39.0 Months vs. 25.0 Months; Propensity Score-adjusted HR, 0.69; 95% CI, 0.47-1.00)



Abbreviations: CI = confidence interval; EGFR = epidermal growth factor receptor; HR = hazard ratio; OS = overall survival; TKI = tyrosine kinase inhibitor.

Figure 2 Survival of Patients by Mutation Subtype. A, Comparison of Second and First-generation TKI in the *exon 19 deletion* Subgroup Only (Median OS, 48.8 vs. 26.4 Months; Propensity Score-adjusted HR, 0.59; 95% CI, 0.35-1.00). B, Comparison of Second and First-generation TKI in the *L858R* Subgroup (Median OS, 25.4 vs. 20.6 Months; Propensity Score-adjusted HR, 0.91; 95% CI, 0.52-1.60)



Abbreviations: CI = confidence interval; HR = hazard ratio; OS = overall survival; TKI = tyrosine kinase inhibitor.

baseline CNS metastases in the first-generation TKI cohort (22%) compared with the second-generation cohort (9%). The overall incidence of CNS metastases in the first-generation group (49%) is also much higher than expected. There is no clear explanation from our data for this observation, and it may be owing to chance alone given the retrospective nature of our study. However, an imbalance in CNS metastases can skew the survival results in favor of second-generation TKIs. Despite differences in age and presence of brain metastases, ECOG performance status was similar between the 2 groups. The distribution of mutation subgroups were also different between patients in the first-generation compared with the second-generation cohort and again likely reflect clinician preferences. Post-hoc analyses from prospective trials have suggested a better treatment effect in patients with *EGFR exon 19 deletion* and uncommon *EGFR* mutations.[10,11,26] In addition to adjusting for age and ECOG performance status in the multivariate analysis, we also adjusted for the total lines of treatment as a proxy for unmeasured factors such as disease biology. Because the choice of an upfront TKI treatment is highly influenced by clinician preference, which in turn reflects differences in baseline characteristics of patients, a propensity

score-based analysis was used for theses imbalances. However, residual bias may remain owing to unmeasured confounding.

The survival benefits from second-generation EGFR TKIs that we observed in our study appear to be driven by the *exon 19* deletion subgroup. Several retrospective studies have reported that that mutation subtype is a prognostic factor, and patients with *EGFR exon 19* deletions have better survival outcomes.[27-30] The predictive value of *EGFR* mutation subtypes with specific generations of TKIs is more controversial. In a recent meta-analysis, Lee et al analyzed 7 different EGFR TKI studies and concluded that EGFR TKIs prolonged PFS in all mutational subtypes, but the degree of benefit was greater in those with *exon 19* deletions and statistically significant only for afatinib.[31] Another meta-analysis performed by Kuan et al found that second-generation, but not first-generation, TKIs were associated with a survival advantage in patients with an *EGFR exon 19* deletion mutation.[32] Contrarily, the ARCHER 1050 study did not identify any differences in survival with respect to mutation subtype, but may be limited by sample size of mutational subgroups.[13,14] Our study results favor using afatinib in *EGFR exon 19 deletion* but not *L858R* mutated patients. Given the small number of patients with uncommon *EGFR* mutations, meaningful interpretation of this subgroup cannot be made.

The impact of subsequent treatment with osimertinib was not analyzed in this study because only 53 (10%) patients in the entire cohort received subsequent osimeritinib; we do not expect this to significantly impact the overall results. There was an equal distribution in the first- and second-generation cohort (11% vs. 10%) who received osimertinib. All the patients who received osimertinib after afatinib remain alive at the time of study analysis. The prolonged survival of patients who received sequential therapy with afatinib (second- followed by third-generation EGFR TKI) has also been reported. Park et al reported on the patients in the LUX-Lung 7 study who were treated with subsequent osimeritinib demonstrating superiority in the afatinib group (3-year OS rates of 96% in the afatinib group compared with 89% in the gefitinib group).[33] In the ARCHER 1050 study, 22 patients received dacomitinib followed by osimeritinib and demonstrated a median OS of 36.7 months.[14] These results highlight the need to study the different sequencing strategies as osimertinib moves into first-line treatment.

In our study, the toxicity profile of second-generation EGFR TKIs was manageable. Despite frequent dose reductions, only 1 patient in the second-generation cohort discontinued the drug. The median tolerated dose of afatinib in our cohort was 30 mg daily, which is consistent with the reduced dose levels reported in the literature.[10-12] Importantly, in our study, the OS benefit of afatinib was maintained even with treatment reductions and interruptions. Overall, side effects from second-generation TKIs can be very effectively managed with dose reductions while maintaining its survival superiority over first-generation TKIs. In the prospective ARCHER 1050 study, quality of life assessments showed stable to improved symptoms in patients receiving dacomitinib.[14]

There are several limitations to our real-world study. First, this study is retrospective in nature, and patients received a first- or second-generation EGFR TKI per the recommendation of their treating physician based on their functional status and clinical features. Although we tried to account for baseline differences by using a propensity score regression analysis, the risk of residual confounding bias still exists. Second, the treatment strategies were heterogeneous. We categorized patients into 2 cohorts based on the initial TKI received, but some patients received a first-generation TKI followed by a second-generation TKI upon progression. Because second-generation TKI after progression on first-generation targeted therapy has not been shown to be statistically effective in prospective trials, we believe that this categorization in our study remains reasonable.[34] In addition, sensitivity analyses were done to include patients who had 1 line of EGFR TKI, and only in the first-line setting, to ensure that the results are consistent. These limitations should be balanced with the relative strengths of this study, which include the relatively large sample size and a long duration of follow-up to detect differences in OS. Importantly, the population-based nature of this study provides insight into the treatment effects of second-generation EGFR TKIs in real-world patients.

Conclusion

Real-world patients who received a second-generation TKI as upfront treatment are highly selected and tended to be younger patients with uncommon *EGFR* mutations and without CNS metastases. Despite an increase in treatment-related adverse events, toxicity can be managed with dose reductions with a low discontinuation rate of the drug. Our results provides support that the survival benefit of first-line second-generation TKIs seen in clinical trials can be generalized to real-world patients. Overall, second-generation TKIs in otherwise fit patients who can manage the toxicity remain a reasonable upfront treatment choice.

Clinical Practice Points

- TKIs are effective at selectively targeting tumors with activating *EGFR* mutations. The optimal sequencing of TKIs is controversial, and *EGFR* mutational subtypes may influence TKI efficacy. It is unknown whether the survival benefit of second-generation TKIs is generalizable to real-world patients who often have a worse performance status compared with those enrolled in clinical trials.
- In a population-based cohort, use of a second-generation TKI in patients with advanced NSCLC is associated with improved survival using propensity score-based regression analysis (HR, 0.69; $P = .05$).
- Improvement in OS is driven by the exon 19 deletion subgroup (HR, 0.59; $P = .052$).
- Patients with a L858R mutation do not appear to derive any benefit from afatinib (HR, 0.91; $P = .74$).
- The toxicity of the second-generation TKI was common; 40% of patients receiving afatinib required a dose reduction. However, toxicity is manageable, with only 1% discontinuation rate after dose adjustments.
- Using a population-based cohort, we demonstrate that survival benefit of a second-generation TKI is generalizable to real-world patients. The use of a second-generation TKI as front-line treatment is reasonable for otherwise fit patients harboring an EGFR exon 19 deletion mutation who can manage the toxicity.

Acknowledgments

The authors wish to acknowledge Chrystal Palaty from Metaphase Health Research Consulting Inc for assistance with preparing and submitting the manuscript, and Jenn Currie for assistance with proofreading. Writing support was provided by Boehringer Ingelheim Canada.

Disclosure

Dr Ho reports grants and personal fees from AstraZeneca, personal fees and other from Boehringer Ingelheim Canada, personal fees and other from Pfizer, personal fees from BMS, personal fees and other from Roche, personal fees from Lilly, grants from Genzyme, grants from Eisai, and personal fees from Merck, outside the submitted work. Dr Melosky reports advisory board/honorarium from Bayer, Pfizer, Astra Zeneca, Boerhinger Ingleheim Canada, and Roche. Dr. Chooback received advisory board honorarium from BMS. The remaining authors have stated that they have no conflicts of interest.

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