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Afatinib in advanced pretreated non-small-cell lung cancer—a Canadian experience

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ABSTRACT

Background Afatinib, an irreversible epidermal growth factor receptor tyrosine kinase inhibitor (EGFR TKI), is approved for first-line therapy in advanced *EGFR* mutation–positive non-small-cell lung cancer (NSCLC) and has previously demonstrated activity after failure of chemotherapy and reversible EGFR TKIs, with improved response and progression-free survival, compared with placebo. Outcomes in pretreated patients with advanced NSCLC receiving afatinib through a Canadian special access program (SAP) are reported here.

Methods Patients with NSCLC progressing after at least 1 line of chemotherapy and an EGFR TKI were eligible to enrol in the SAP. Characteristics of patients from the two largest accruing Canadian centres were retrospectively reviewed, including demographics, disease and treatment data, and patient outcomes.

Results The 53 patients who received afatinib (57% women, 51% never-smokers, 26% of East Asian ethnicity, and 66% with adenocarcinoma) had a median age of 59 years. *EGFR* mutations were documented in 25%, and *EGFR* wild-type in 8%. All patients had received prior EGFR TKI treatment, with 42% achieving a response. Patients took afatinib for a median of 2 months (range: 0–26 months); 17% required 1 or more dose reductions. Of 47 evaluable patients receiving afatinib, 10 experienced tumour shrinkage, and 11, stable disease. Median survival from afatinib initiation was 5 months (95% confidence interval: 2 months to 8 months). Grade 3 or greater diarrhea, rash, paronychia, and stomatitis were seen in 9%, 11%, 6%, and 4% of patients respectively.

Conclusions In an unselected population of pretreated patients with advanced NSCLC after TKI failure, median survival with afatinib therapy was 5 months. Through a SAP, afatinib demonstrated activity in clinical practice, with manageable toxicity.

Key Words Afatinib, non-small-cell lung cancer

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BACKGROUND

Afatinib, an oral irreversible epidermal growth factor receptor tyrosine kinase inhibitor (EGFR TKI), has demonstrated superiority compared with first-line chemotherapy in advanced *EGFR* mutation–positive non-small-cell lung cancer (NSCLC). The irreversible small-molecule TKIs have shown some promise in unselected patients with advanced NSCLC who have progressed on platinum-based chemotherapy or on erlotinib or gefitinib (or both)[1,2].

The LUX-Lung trials studied the efficacy of afatinib in both treatment-naïve and pretreated patients with advanced NSCLC[3,4]. In the treatment-resistant setting, the LUX-Lung 1 trial compared afatinib with placebo in unselected patients with advanced NSCLC in whom chemotherapy and first-generation EGFR TKI therapy had previously failed[5]. The trial showed improved progression-free survival, response rate, quality of life, and symptom control with afatinib treatment, but failed to show a difference between the two groups in its primary endpoint

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of overall survival (OS). However, a clear biologic effect of afatinib was demonstrated in pretreated patients with advanced NSCLC, with response rates of up to 50% reported in clinical trials[2,5].

The Canadian afatinib special access program (SAP) was designed to provide access to afatinib in jurisdictions in which the drug was then not approved or funded for use. There has been a paucity of real-world data reporting outcomes in the subgroup of pretreated patients with advanced NSCLC. In the present study, we report the outcomes of Canadian patients with advanced NSCLC who were treated with afatinib under the SAP after progressing on 1 or more lines of chemotherapy and on first-generation EGFR TKIs (gefitinib, erlotinib, or both). Patients accessed afatinib through the national SAP that was open between 2010 and 2013. We report our experience with afatinib at the 2 largest centres participating in the Canadian SAP.

METHODS

Patients and Treatment

Patients participating in the Health Canada SAP from July 2010 to June 2013 at 2 major Canadian cancer centres were retrospectively identified. Ethics approval and data-sharing agreements were obtained at the 2 centres, the BC Cancer Agency (Vancouver) and Princess Margaret Cancer Centre (Toronto). Eligibility criteria for the SAP were similar to those for the LUX-Lung 1 trial, previously published[5]. Patients were required to have a diagnosis of stage IIIB or IV NSCLC with measurable disease, failure of 1 or more lines of chemotherapy (including adjuvant chemotherapy), and disease progression after at least 12 weeks of prior treatment with erlotinib or gefitinib.

EGFR mutation testing methods have previously been described in detail[6]. Briefly, *EGFR* mutation testing was performed using fragment analysis for exon 19 deletions and restriction fragment-length polymorphism for exon 21 L858R mutations. *EGFR* mutation test results were reported as positive for exon 19 deletion, positive for exon 21 L858R mutation, or negative for exon 19 deletion or exon 21 L858R mutation. Testing for T790M was not routinely performed during the period of interest.

To be eligible for the SAP, patients were not required to have a tumour with an activating *EGFR* mutation (similar to the LUX-Lung 1 study). Patients were required to have no further treatment options available to them before SAP entry. The afatinib starting dose was determined at the discretion of the treating physician (up to 50 mg daily was available). Afatinib was continued until disease progression or development of intolerable adverse events.

Tumour response was assessed by oncologists (BM, NBL) who reviewed computed tomography imaging of chest to pelvis in the patients after 8 weeks of therapy, unless disease progression warranted earlier imaging. "Response" was classified as any tumour shrinkage. Stable disease was documented if tumours were unchanged in size, and progressive disease, if any tumour growth had occurred. Adverse events were assessed using the U.S. National Cancer Institute's *Common Terminology Criteria for Adverse Events* (version 3.0).

Retrospective chart review of SAP participants was performed at the 2 centres, including extraction of demographics, disease and treatment data, treatment duration, and OS. Toxicity, duration, and response data from both the prior EGFR TKI and afatinib were collected.

Statistical Analysis

The association between afatinib response or toxicity and prior therapy was investigated using chi-square and logistic regression tests, as appropriate. An odds ratio greater than 1 indicates greater odds of response to afatinib. Overall survival was determined from the date of treatment start to the date of death, regardless of cause. Survival analysis was performed using the Kaplan–Meier method. All tests of significance (p values) were 2-sided. Statistical significance was accepted at $p < 0.05$. The analysis was carried out using the SAS software application (version 9.3: SAS Institute, Cary, NC, U.S.A.).

RESULTS

Patient Characteristics

Between July 2010 and June 2013, 53 patients (57% women, 51% never-smokers, 66% with adenocarcinoma histology, 26% of East Asian ethnicity) were enrolled in the Health Canada SAP at the 2 participating centres and received afatinib. Median age in the group was 59 years (Table I). *EGFR* mutation data were available for only 17 patients, and 13 of those 17 had documented activating mutations.

Prior Therapy

Patients had received a median of 3 prior therapies, including a prior EGFR TKI (Table I). Most patients had been exposed to chemotherapy (almost 100%), mainly platinum-based regimens. Most had received prior erlotinib (81%), and some had received both erlotinib and gefitinib. Response to prior EGFR TKIs was 42%, with approximately one third of the group experiencing grade 2 or greater rash and 8% experiencing grade 2 or greater diarrhea with their first EGFR TKI.

Afatinib Treatment Outcomes and Adverse Events

The median time from metastatic diagnosis to afatinib start was 23.5 months (range: 3.0–94 months; Table II). Median duration of therapy was 2.0 months (range: 0–26 months). Most patients started at a dose of 40 mg daily, although 3 patients (5.7%) started at a dose of 50 mg daily. During afatinib therapy, 8 patients (15%) had 1 dose reduction, and 1 patient had 2 dose reductions (2%). Of the evaluable patients, best response to therapy was tumour shrinkage in 19%, stable disease in 21%, and progressive disease in 49%. Of the 10 patients who experienced tumour regression with afatinib, 2 had *EGFR* wild-type tumours, 3 had *EGFR* mutation–positive tumours, and the remaining 5 had an unknown genotype. Median survival in afatinib-treated patients was 5.0 months (95% confidence interval: 2.0 months to 8.0 months; Figure 1).

At the time of the analysis, 47 of the 53 patients (89%) had stopped afatinib therapy. The most common reasons for treatment discontinuation were disease progression (34%), deterioration in performance status (30%), and

TABLE I Demographics and treatment history for the study patients

Characteristic	Value[a]
Patients (*n*)	53
Age (years)	
Median	59.0
Range	37–88
Sex [*n* (%)]	
Men	23 (43)
Women	30 (57)
Smoking status [*n* (%)]	
Never-smoker	27 (51)
Light smoker[b]	4 (8)
Current smoker	2 (4)
Former smoker	19 (36)
Unknown	1 (2)
Histology [*n* (%)]	
Adenocarcinoma	35 (66)
Squamous cell	6 (11)
Large-cell	1 (2)
Not specified	11 (21)
East Asian ancestry [*n* (%)]	
Yes	14 (26)
No	39 (74)
EGFR mutation status [*n* (%)]	
Activating mutation	13 (25)
Exon 19	6 (11)
Exon 21	3 (6)
Other or unknown	4 (8)
Wild type	4 (8)
Unknown	36 (68)
EGFR TKI therapy [*n* (%)]	
Gefitinib	8 (15)
Erlotinib	43 (81)
Both	2 (4)
Lines of prior therapy [*n* (%)]	
1	3 (6)
2	13 (25)
>2	37 (70)
Median	3
Range	1–5
Best response to prior EGFR TKI [*n* (%)]	
Tumour shrinkage	22 (42)
Stable disease	11 (21)
Progressive disease	14 (26)
Unknown	6 (11)
Duration of prior EGFR TKI therapy (months)[c]	
Median	7
Range	1–53
Adverse events with prior EGFR TKI [*n* (%)]	
≥Grade 2 rash	17 (32)
≥Grade 2 diarrhea	4 (8)

[a] Percentages might not add to 100 because of rounding.
[b] <10 pack–year history.
[c] Gefitinib, erlotinib, or both.
EGFR = epidermal growth factor receptor; TKI = tyrosine kinase inhibitor.

TABLE II Afatinib treatment and outcomes in 53 patients

Therapy characteristic	Value
Treatment duration (months)	
Median	2.0
Range	0–26
Starting daily dose [*n* (%)]	
40 mg	49 (92)
50 mg	3 (6)
Other	1 (2)
Dose reductions [*n* (%)]	
None	44 (83)
1	8 (15)
2	1 (2)
Best response to therapy [*n* (%)]	
Tumour shrinkage	10 (19)
Stable disease	11 (21)
Progressive disease	26 (49)
Non-evaluable	6 (11)
Treatment discontinued [*n* (%)]	47
Disease progression	16 (34)
Toxicity	8 (17)
Clinical deterioration	14 (30)
Other	9 (19)
Adverse events (*n* Gr.≥2/Gr.≥3)	
Diarrhea	17/9
Rash	17/11
Paronychia	9/6
Stomatitis	6/4

Gr. = grade.

afatinib toxicity (17%). Grade 3 rash was seen in 11% of the patients, diarrhea in 9%, paronychia in 6%, and stomatitis in 4%.

Predictors of Afatinib Response and Toxicity

The association between response to a prior EGFR TKI and subsequently to afatinib was not statistically significant (chi-square $p = 0.12$). No association between duration of prior EGFR TKI therapy and afatinib response was observed (odds ratio: 1.02; 95% confidence interval: 0.96 to 1.09). No significant association between afatinib response and other variables such as rash or diarrhea during prior EGFR TKI therapy was observed (chi-square $p = 0.10$).

DISCUSSION

Heavily pretreated patients with advanced NSCLC present a challenge because of a lack of effective treatment options. Afatinib was approved by the U.S. Food and Drug Administration, the European Medicines Agency, and Health Canada, among other jurisdictions, for the first-line treatment of patients with advanced *EGFR*-mutated NSCLC[3,8,9].

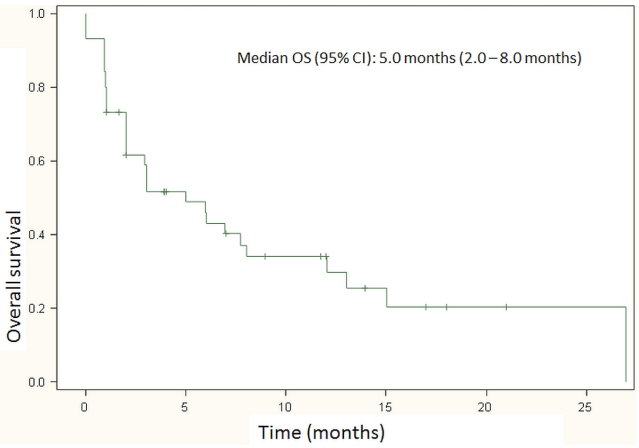

FIGURE 1 Median survival in patients treated with afatinib in a Canadian special access program.

Our analysis describes a Canadian experience of afatinib use in pretreated patients with advanced NSCLC at 2 large cancer centres.

We found that up to 40% of our patients achieved either tumour regression or stable disease with afatinib therapy and that median survival from the start of afatinib therapy was 5 months. In the pivotal LUX-Lung 1 trial and other similar populations, response rates of 10%–20% were reported[5,10]. The LUX-Lung 1 trial reported a median OS of 10.8 months in afatinib-treated patients. Additionally, LUX-Lung 1 reported rates of grade 3 or greater diarrhea that were higher than were found in our study, although the rash and stomatitis rates were similar. Given that the real-world patient population in our analysis was more heavily pretreated (70% received >2 lines of prior therapy) and more heterogeneous than that in the LUX-Lung 1 trial, those differences in outcome are explainable. It should also be noted that these data all precede the advent of immunotherapy. Given that first-line immunotherapy has now become the standard of care in the treatment of advanced NSCLC with high PD-L1 expression, the role of afatinib therapy in an unselected heavily pretreated NSCLC population remains to be determined.

Our data demonstrate afatinib activity not only in patients with *EGFR* sensitizing mutations (25%), but also in patients with wild-type *EGFR* (8%). It is possible that *EGFR* sensitizing mutations other than the common mutations detected by earlier institutional assays might have been present in the population classified as "wild type" in our analysis. In patients with uncommon *EGFR* mutations (specifically, subtypes such as G719X, L861Q, and S768I), response rates of 56%–100% have been described with first-line afatinib therapy[11]. Shen *et al.*[12] reported superior response rates for afatinib compared with erlotinib or gefitinib in patients with uncommon mutations. In heavily pretreated patients, Heigener *et al.*[10] reported clinical activity for afatinib in patients with uncommon mutations, but inferior efficacy for those with the common exon 19 and 21 mutations.

Use of afatinib in a SAP for pretreated patients with advanced NSCLC in Germany and the United Kingdom achieved response rates similar to those we found (15%–20%)[13,14]. Those prior data showed that an *EGFR* mutation was present in up to 80% of the population receiving afatinib therapy. Although most patients in our SAP had an unknown *EGFR* mutation status, the clinical characteristics in most of our cohort raise the possibility of a predominantly *EGFR*-mutated population. Response rates comparable to those demonstrated by prior data further strengthen that possibility.

Most patients in our cohort had previously received an EGFR TKI. Unlike the first-generation EGFR TKIS, afatinib is an irreversible pan-EGFR inhibitor, which is theoretically able to overcome acquired first-generation EGFR TKI resistance. Indeed, afatinib has shown some activity in overcoming such resistance[10,15]. That action could potentially be augmented if afatinib is combined with other EGFR-targeted agents such as EGFR-directed monoclonal antibody therapy[16].

Recently, acquired resistance to first-generation EGFR TKIS has been shown to occur by multiple mechanisms, the most common being the development of a T790M mutation in the *EGFR* gene, which causes resistance of the EGFR protein to gefitinib and erlotinib[17]. That mutation occurs in 50%–60% of patients with acquired resistance to first-generation EGFR inhibitors. Osimertinib is a third-generation EGFR TKI with activity against tumours with the T790M mutation and other somatic TKI-sensitizing *EGFR* mutations. It has been approved for the treatment of patients with metastatic *EGFR* T790M mutation–positive NSCLC whose disease has progressed on or after initial EGFR TKI therapy[8,9,18]. Emerging data have demonstrated the safety and efficacy of osimertinib as first-line therapy in *EGFR* mutation–positive NSCLC, with upcoming data comparing third-generation osimertinib with first-generation gefitinib or erlotinib as initial therapy[19]. In preclinical models, greater activity in *EGFR*-mutant NSCLC brain metastases has been shown for osimertinib than for other TKIS (gefitinib, afatinib, rociletinib)[20]. After development of resistance to osimertinib therapy, some response to gefitinib has been described[21]. Ultimately, the optimal sequencing of the second- and third-generation EGFR inhibitors is not well understood. Future studies should delineate the ideal sequencing of the EGFR TKIS and should examine whether there remains a role for afatinib after failure of osimertinib or in *EGFR* T790M–negative disease that is still driven by the EGFR signalling pathway.

Some limitations of our study should be noted. The percentage of patients with an unknown *EGFR* genotype did not allow for optimal characterization of the specific *EGFR*-mutant population that achieved some tumour shrinkage with prior EGFR TKIS and with afatinib therapy. Regardless, the population of patients analyzed in this study were pretreated and might represent a heterogeneous group with respect to acquired oncogenic driver mutations, with only limited molecular analysis (mutations in exons 19 and 21) available during the study period.

In the pre-osimertinib era (or the present day T790M-negative setting), patients with progressive NSCLC who develop acquired resistance to EGFR TKIS are often treated with cytotoxic chemotherapy. There are some reports of efficacy with EGFR TKI rechallenge after development of

resistance to first-line TKIs[22–24]. Response to EGFR TKI rechallenge appears to be associated with a sufficient TKI-free interval and prior exposure to cytotoxic chemotherapy[22]. Although the mechanisms for sensitization to EGFR TKI rechallenge are not fully understood, such sensitization might be attributable to alteration, by cytotoxic chemotherapy, of the initial genetic changes that resulted in TKI resistance. An alternative mechanism might be repopulation by the EGFR TKI–sensitive clones. Future studies elucidating the role of afatinib rechallenge in patients with *EGFR*-mutated T790M-negative advanced NSCLC will be of importance[25].

Our data relate to the activity of afatinib in heavily pretreated patients with advanced NSCLC. Specifically, afatinib rechallenge might have a role to play in patients with T790M-negative disease.

CONCLUSIONS

The present analysis provides real-world evidence of the activity of afatinib in unselected patients with advanced NSCLC who have progressed on chemotherapy and prior EGFR TKIs. Of 47 evaluable patients, 10 experienced tumour shrinkage with afatinib, and median survival was 5.0 months in this heavily pretreated patient population.

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have no relevant conflicts.

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