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ORIGINAL ARTICLE

Multi-disciplinary proactive follow-up algorithm for patients with advanced NSCLC receiving afatinib

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Abstract

Purpose Afatinib is a standard first-line therapy for advanced EGFR-positive NSCLC. We implemented a pharmacist-led proactive follow-up algorithm to identify and manage early afatinib-related adverse events (AEs).

Methods We conducted a retrospective chart review of all patients treated with afatinib after implementation of the algorithm at the Sunnybrook Odette Cancer Centre (Toronto, ON, Canada) from April 1, 2015 to July 31, 2016. Our in-house algorithm involved consultations in person and proactive pharmacist-led callbacks on days 5, 10, and 17. All AEs were graded and documented in real time and management based on toxicity grade was standardized. This study evaluated the impact of our algorithm on real-world AEs.

Results and discussion Thirty-three patients were identified and reviewed. Median follow-up was 248 days. All patients experienced at least one drug-related AE; 18.2% were grade 3/4. The most common AEs were diarrhea 87.9%, rash 81.8%, stomatitis 57.6%, and paronychia 45.5%. Median dose of afatinib was 40 mg daily; 51.5% of patients had ≥ 1 dose reduction and 6.3% discontinued afatinib due to AEs. Proactive calls by the pharmacist identified 36.5% of all drug-related AEs, 33.3% of grade 3/4 AEs, 58.1% of first drug-related AEs and identified two patients that were non-compliant. Only 3.2% of AEs were identified by an emergency room/urgent clinic visit.

Conclusions This proactive multi-disciplinary AE management algorithm resulted in a low rate of urgent assessments and discontinuation due to toxicity while maintaining afatinib at ideal dose, thus providing a useful tool for centers prescribing afatinib.

Keywords NSCLC · EGFR · Afatinib · Adverse events · Proactive monitoring · Algorithm

Introduction

Lung malignancies are the leading cause of cancer-related mortality worldwide, with approximately 85% of these classified as non-small cell lung cancer (NSCLC) and the majority diagnosed as metastatic or stage IV [1]. Driver mutations in the epidermal growth factor receptor (EGFR), such as deletions in exon 19, point mutations in exon 21 (L858R), and less common EGFR mutations [2], activate oncogenic signal transduction pathways and result in pathogenic cell proliferation and survival [3]. These EGFR driver mutations are associated with approximately 9.4 to 17% of all NSCLC cases [4, 5] and 38% in Asian populations [6].

Oral EGFR tyrosine kinase inhibitors (TKIs) including gefitinib, erlotinib, and afatinib are standard of care first-line treatment for patients with advanced NSCLC whose tumors harbor sensitizing EGFR mutations [7, 8], based on numerous phase III trials demonstrating improved clinical outcomes compared to chemotherapy [9–14]. The second-generation EGFR TKI afatinib is an irreversible pan-human EGFR (HER) inhibitor [15] and is the only EGFR TKI that has demonstrated an improvement in overall survival compared to chemotherapy, particularly in patients whose tumors harbor EGFR exon 19 deletions [16]. In the randomized phase 2b LUX-Lung 7 trial, patients receiving afatinib ($n = 160$) had significantly improved progression-free survival (PFS;

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median 11.0 vs 10.9 months, HR: 0.74, $p = 0.0178$) and improved objective response rate (ORR; 72.5% vs 56.0%, OR 2.121, $p = 0.0018$) compared with those receiving gefitinib ($n = 159$), a first-generation EGFR TKI [17]. However, no improvement in overall survival was shown.

Afatinib is generally well tolerated, with equal rates of discontinuation due to treatment-related adverse events (AEs) as gefitinib in the LUX-Lung 7 trial (6.3% for each) [17]. In this study, however, afatinib was associated with higher rates of treatment-related grade ≥ 3 AEs overall (31.3% vs. 18.2%), in addition to increased grade ≥ 3 diarrhea (12.5% vs. 1.3%), rash/acne (9.4% vs. 3.1%), stomatitis (4.4% vs. 0%), and paronychia (1.9% vs. 0.6%) compared with gefitinib [18]. This indicates room for better AE management. A post hoc analysis of the LUX-Lung 3 and LUX-Lung 6 trials comparing afatinib to chemotherapy for EGFR-positive NSCLC showed that patients who received afatinib dose reductions due to toxicity (53.3% and 28.0% of patients in LUX-Lung 3 and LUX-Lung 6, respectively) showed similar PFS compared to patients that did not require dose reductions [16], providing a rationale for a proactive dose adjustment algorithm to improve the toxicity profile of this therapy. Moreover, a prospective study of 158 patients receiving TKIs for advanced NSCLC suggested that standardized grading and management of non-hematological adverse events can reduce the severity of diarrhea, rash, and stomatitis [19]. This study supports the rationale for the development of an interprofessional proactive follow-up algorithm for the management of TKI-related adverse events.

Self-administered oral anticancer medications (OACMs) such as TKIs provide a convenient treatment option and decrease hospital resource utilization [20]. However, they are associated with unpredictable bioavailability, increased risk of medication interactions, and concerns regarding patient adherence, safety, monitoring, and follow-up [21, 22]. Self-administration also means that the severity of side effects can be greatly impacted by patient behaviors [22], highlighting the need for more proactive toxicity follow-up and side effect management. Emerging evidence indicates that regular proactive follow-up with patients receiving TKIs by oncology pharmacists improves adherence to TKIs [23]. Nurse-led proactive follow-up for patients on intravenous chemotherapy has also proven feasible and may improve symptom control [24]. While expert opinion guidelines on how to manage common TKI side effects also exist [25, 26], they do not detail the timing of specific AE occurrence and have yet to be validated in real-world patient populations.

A clinician level tool that outlines a proactive follow-up schedule to ensure timely AE identification and appropriate intervention(s) based on the grade of afatinib toxicity is an area of clinical need. The objective of this study was to determine whether implementation of a proactive pharmacist-led telephone AE management algorithm for afatinib was feasible and led to low rates of grade ≥ 3 AEs and treatment discontinuation. This study also provided information on the real-world characteristics of AEs experienced by patients receiving afatinib in an outpatient setting.

Methods

Algorithm development

A standardized follow-up algorithm was created by the oral chemotherapy pharmacist at the Sunnybrook Odette Cancer Centre (Toronto, ON, Canada, the second author on this paper). The algorithm was designed to dictate the timing of proactive, telephone-based toxicity assessment for patients on afatinib and to recommend interventions based on toxicity severity. Information from the Cancer Care Ontario (CCO) and the British Columbia Cancer Agency (BCCA) monographs on afatinib was used to inform the incidence and timing of specific toxicities associated with afatinib [27, 28]. Other resources used to develop the algorithm follow-up schedule included data from the LUX-Lung 3 and LUX-Lung 6 trials [12, 13] and a study by Yang et al. evaluating the timing of afatinib-related toxicities and dose reductions in these trials [16]. Published expert guidance on the management of common toxicities associated with EGFR TKIs [25, 26, 29] as well as feedback and clinical experience from Medical Oncologists at the Odette Cancer Centre were used to formulate grade-specific interventions. Assessment questions to determine the Common Terminology Criteria for Adverse Events (CTCAE) toxicity grade were adapted from the Canadian Oncology Symptom Triage and Remote Support (COSTaRS) tool [30] and the CCO symptom management guides [31]. Use of this algorithm as a new standard of care while prescribing afatinib was initiated on April 1, 2015, and at a minimum, included an initial pharmacist consultation on day 1, proactive calls from the oral chemotherapy pharmacist to patients on afatinib on days 5, 10, and 17, and in-clinic assessment by the medical oncologist on day 14 as per usual standard of care (Table 1) and then routine clinic follow-up with the medical oncologist thereafter. The major difference between this algorithm and other published AE algorithms was that afatinib was interrupted for grade 2 events until resolution to grade 1.

Study design

This was a retrospective chart review of patients treated with afatinib at the Odette Cancer Centre, Toronto, Canada, from April 1, 2015 to July 31, 2016. All patients with advanced EGFR-positive NSCLC who received one dose of afatinib during the study period were included in this study. Patients

Table 1 Pharmacist-led follow-up algorithm for patients prescribed afatinib

Time on drug	Day 1	Day 5	Day 10	Day 14	Day 17
Intervention	Face-to-face visit with pharmacist	Proactive call by pharmacist	Proactive call by pharmacist	Routine clinic visit with medical oncologist	Proactive call by pharmacist
Variables assessed	• Patient education on drug administration and side effects • Preventative measures discussed • Informed of nursing contact • Consent obtained for proactive pharmacist-led calls	• Adherence • Diarrhea • Stomatitis • Nausea	• Adherence • Rash • Diarrhea • Stomatitis • Paronychia • Nausea • Fatigue	• Clinical assessment • Laboratory: CBC, creatinine, liver function tests	• Adherence • Rash • Diarrhea • Stomatitis • Paronychia • Nausea • Fatigue • Anorexia

CBC, complete blood count

were identified using our computerized physician order entry system.

Data collection

Proactive interactions with the oral chemotherapy pharmacist were documented real time in the electronic patient record (Sunnycare). They outlined (1) day of therapy, (2) afatinib dose, (3) AEs identified along with CTCAE v. 4.0 grading (Table 2), (4) recommended interventions, and (5) whether treatment was interrupted, discontinued, and/or dose-reduced. If an AE was noted, a second call was made to the patient by the oral chemotherapy pharmacist following recommended intervention(s) to document: (1) interventions carried out by the patient, (2) time of side effect resolution, (3) any additional interventions recommended/reinforced, and (4) if treatment was held, discontinued, or dose-reduced. In addition, if patients reactively called to self-report a side effect to the pharmacist or oncology nursing line, the interaction was documented as described above.

Statistical analysis

Patient demographics and adverse events were reported using descriptive statistics expressed as percentages and frequencies for categorical factors, and medians and interquartile ranges for continuous factors such as days to onset or resolution of adverse events. Unadjusted logistic regressions were conducted to identify putative risk factors for each AE and determine odds ratios and 95% confidence intervals to express the impact of potential risk factors on the likelihood of AE.

Results

Thirty-three patients met the inclusion criteria and were included in the analysis. The median follow-up period was 248 days. The median age of patients was 64 years (interquartile range [IQR] 59–70), 59.4% were of Asian ethnicity, 33.3% ($n = 11$) were Caucasian, 21.3% ($n = 7$) were ECOG>1, and 87.9% of patients were receiving afatinib as first-line therapy. Of the EGFR mutations, 54.6% ($n = 18$) were an exon 19 deletion, 39.4% ($n = 13$) L858R mutation, and 6.1% ($n = 2$) uncommon mutations. Oral tetracycline and steroid/clindamycin cream were prescribed as primary prophylaxis in 45.5% ($n = 15$) and 54.6% ($n = 18$) of patients, respectively. Seventy-nine percent ($n = 26$) had ≥ 3 concomitant medications.

The median exposure to afatinib was 157 days, and the median dose of afatinib on the study was 40 mg. Twenty-six patients (78.8%) started at the ideal dose of 40 mg, five patients (15.2%) started at 30 mg, and two patients (6.1%) started at 20 mg. Two out of the seven patients for which the initial dose of afatinib was less than 40 mg had a dose escalation during the study, and one of these two patients maintained the dose escalation.

All 33 patients experienced at least one drug-related AEs of any grade, with diarrhea (87.9%), rash (81.8%), stomatitis (57.6%), and paronychia (45.5%) being the most common AEs (Table 3). Transaminitis (6.1%) and anorexia (6.1%) were the most common grade 3/4 AEs. The median number of different AEs per patient was 5 (IQR 3 to 6), and the median time to onset of the first AE of any grade was 17 days (IQR 7 to 126; Table 3). Diarrhea occurred earliest, with a median time to onset of 8 days (IQR 6 to 16), and stomatitis occurred second with a median time to onset of 13 days (IQR 9 to 21; Table 3). AEs with later median times to onset included paronychia (74.5 days, IQR 41.5 to 143) and anorexia (132.5 days, IQR 16 to 263). Logistic regression analysis did not identify any major risk factors for AEs, with the exception of nausea which was associated with prophylactic oral tetracycline use (odds ratio [OR] 10.0, 95% CI 1.94 to 51.54).

Thirteen (39.4%) and four (12.1%) patients had one and two dose reductions, respectively. The most common reasons for dose reductions were diarrhea (20.5%), rash (18.0%), stomatitis (10.3%), and nausea (10.3%). The median number of

Table 2 Common afatinib-associated adverse events, CTCAE grading, suggested interventions, and counseling tips [12, 13, 16, 25, 26, 29–35]

CTCAE 4.0	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Diarrhea	Patient is experiencing no increase in number of stools or ostomy output from baseline	Increase of less than 4 stools per day over baseline or mild increase in ostomy output	Increase of 4-6 stools over baseline or moderate increase in ostomy output	Increase of more than 6 stools from baseline Hospitalization indicated	Life-threatening consequences Urgent intervention required

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Suggested Interventions	n/a	• Non-pharmacological interventions and loperamide (2 tablets of 2 mg loperamide should be taken immediately, followed by 1 tablet of 2 mg loperamide with every loose bowel movement, up to a maximum daily dose of 10 tablets)	• Hold afatinib and add Lomotil® (0.025mg Atropine/2.5mg Diphenoxylate) 1 tablet bid with standard dose loperamide or increase loperamide to 4 mg then 2 mg every 2 hours until diarrhea free for 12 hours • Once diarrhea improves to grade 1, patient may restart afatinib at the same dose, continuing on Lomotil® as prophylaxis or restart afatinib at 1 dose level reduction • Follow-up with patient within 24 hours to ensure improvement	• Stop afatinib • Notify MD and nursing • Refer patients to emergency care in consultation with the medical team • Refer all patients to emergency care if symptoms worsen

Counseling points:

- Ensure the patient has stopped use of all laxatives
- Adequate rehydration using broths and/or oral rehydration solution
- Avoid high fiber foods, dairy, high sugar sport drinks, fatty or spicy foods
- Advise on the BRAT diet (unripe bananas, white rice, applesauce and white toast) and avoid dairy while experiencing diarrhea
- Patients should be advised to hold afatinib on their own and call the appropriate healthcare professional if experiencing grade ≥2 diarrhea
- Advise on appropriate use of over the counter loperamide (see CCO diarrhea symptom management sheet) [7]
- If symptoms intolerable, patient is experiencing signs of dehydration, or diarrhea has not completely resolved or reduced to grade 1 despite appropriate management, contact MD

CTCAE 4.0	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Stomatitis	Patient is experiencing no mouth soreness, no ulcers	Painless ulcers or mild soreness but patient can maintain normal diet	Painful redness, swelling, or ulcers, but can eat a modified diet	Erythema, edema, or ulcers requiring IV hydration. Patient is	Severe ulceration or requires parenteral or enteral nutritional support

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				unable to hydrate orally	
Suggested Interventions	• Rinse with salt water four times a day for prophylaxis (1 teaspoon salt, 1 teaspoon baking soda in 1 liter/4 cups of water)[10] • May consider a steroid based mouthwash as prophylaxis	• Salt water mouth rinse several times a day • Initiate a steroid based mouthwash (e.g., dexamethasone 0.1% mouthwash, 0.1-0.5 mg/ml hydrocortisone) and rinse four times daily • If patient is experiencing cheilitis or tender gums, use triamcinolone 0.1% paste (Oracort®) once to twice daily	• Hold afatinib • Initiate steroid based mouthwash if not already receiving. • Consider increasing potency of steroid (dexamethasone) or adding topical corticosteroid paste (triamcinolone 0.1%) if localized ulcers or tender gums • nystatin indicated only if fungal infection • Re-initiate afatinib at the same dose while continuing with steroid mouthwash as prophylaxis or reduce afatinib by one dose level	• Stop afatinib • Notify MD and nursing • Refer patients to emergency care in consultation with the medical team • Refer all patients to emergency care if symptoms worsen	
Counselling points: • Avoid agents containing alcohol or hydrogen peroxide • Rinse with salt water several times a day (prophylaxis) • Use a soft bristle toothbrush with sodium lauryl sulfate-free toothpaste (e.g.Biotene®) and floss daily • Drink lots of water to alleviate mouth dryness • Avoid alcohol and hot, acidic and/or spicy foods. Avoid foods with sharp edges (i.e., potato chips) that may result in mouth injury • Use Blistex® or petrolatum jelly for dry lips multiple times a day as prophylaxis					
CTCAE 4.0	**Grade 0**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Skin Rash	n/a	Macules/papules with or without symptoms of burning, pruritus or tenderness covering less than 10% BSA	Macules and/or pustules covering 10-30% BSA, which may or may not be associated with symptoms of pruritus or tenderness	Macules and/or pustules covering greater than 30% of BSA; impacting self-care; superinfection;	Macules and/or papules covering any % BSA associated with superinfection

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				and oral antibiotics required	requiring IV antibiotics
Suggested Interventions	• Reinforce sun protection and skin care measures outlined in counseling points below • Consider tetracycline antibiotic as prophylaxis (doxycycline 100 mg once to twice daily or minocycline 100 mg once to twice daily)[12,13]	• Non-pharmacological interventions and hydrocortisone acetate 1% with clindamycin 1%-2% in glaxal base or mix clindamycin 2% powder in hydrocortisone valerate 0.2% ointment. • Consider treatment with tetracycline antibiotic • If patient is on tetracycline antibiotic for prophylaxis ensure adherence to antibiotic. Consider increasing to twice daily if taking once daily	• If grade 1 symptoms persist despite treatment or grade 2 rash, an oral doxycycline or minocycline should be added if not already receiving, at therapeutic doses of 100 mg twice daily • Switch to a more potent corticosteroid such as betamethasone valerate (Betaderm®) 0.1% ointment or fluocinonide 0.05% (Lyderm®) ointment/cream twice to three times daily. • If rash painful/tender, , hold afatinib in consultation with physician until ≤grade 1. • For scalp rash, consider Derma-Smoothe/FS Scalp Oil® (fluocinolone acetonide) 0.1% oil, once to twice daily – *cannot use if peanut allergy* • Consider holding afatinib until resolution to ≤grade 1 • If afatinib held, restart at 1 dose level reduction	• Stop afatinib • Non-pharmacological interventions and MD notification required • Oral steroids and broad spectrum antibiotics indicated • If restarting afatinib, reduce dose 1 level; consider switching to another therapy	• Stop afatinib • Notify MD and nursing • Refer patients to emergency care in consultation with the medical team • Refer all patients to emergency care if symptoms worsen
Counselling tips:					

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- Use unscented, alcohol-free moisturizing creams (e.g., Eucerin®, Aquaphor®, or Cetaphil®) and moisturize twice daily to entire body, including the face
- Avoidance of direct sunlight, detergents, antibacterial soaps, alcohol-based perfumed lotion
- Use sun protection of at least SPF 30
- Wear loose fitting clothing
- If rash/itch present, bath treatment or lotion containing colloidal ointment can provide relief and short lukewarm showers can prevent further irritation.
- Avoid hot showers
- Patients should be advised that if rash is tender to the touch or widespread, they should stop afatinib and call appropriate healthcare professional

CTCAE 4.0	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Paronychia	n/a	Nail fold edema or erythema; disruption of the cuticle	Nail fold edema or erythema with pain; associated with discharge or nail plate separation; limiting instrumental ADL	Limiting self-care ADL	n/a
Suggested Interventions	n/a Reinforce patient education and non-pharmacological preventative measures outlined in counseling points below	• Continue afatinib • Apply betamethasone valerate 0.1% ointment to the nail bed and cuticle liberally twice daily	• If grade 2 symptoms are present or grade 1 symptoms persist despite treatment, switch patient to a high-potency steroid such as clobetasol 0.05% ointment twice daily and encourage protective finger/toe cover or cellophane wrap to increase absorption • An oral tetracycline should be added (doxycycline or minocycline 100 mg twice daily) • If pain with grade 2 paronychia is not tolerable	• Hold afatinib • Surgical intervention or culture for antibiotics required • Continue topical steroids and add the appropriate antibiotic if organism is cultured • Often empiric initiation of cephalexin, clindamycin or cloxacillin is indicated • Long term paronychia may be	n/a

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			or improvement not seen in 1 week, hold afatinib until complete resolution of symptoms or until grade 1 • *If afatinib to be held beyond 5 days MD to be notified, close monitoring for disease flare* • If paronychia not resolving, provide podiatry referral • If ingrown toenail, apply silver sulfadiazine (Flamazine®) twice daily to affected toe and refer to podiatry	fungal and addition of creams such as Lamisil® (terbinafine) or oral terbinafine may be helpful in consultation with podiatry • Re-initiate afatinib at one dose level reduction with continuation of tetracycline antibiotics and medium to high potency steroid ointment as required	
Counselling tips To prevent: • Wear comfortable shoes and trim nails • Wear gloves while cleaning • Use petrolatum jelly along nail bed and cuticle To treat: • Soak affected nails and toes in a mixture of Epsom salts in water or diluted bleach in water as needed to prevent superinfection • Use thick moisturizers or zinc oxide (13-40%) creams to seal cracks when not applying steroid ointments (steroid ointments preferred over creams for greater penetration)					

ADL, activities of daily living; *BRAT*, bananas, rice, applesauce, toast; *BSA*, body surface area; *CCO*, Cancer Care Ontario; *CTCAE*, Common Terminology Criteria for Adverse Events version 4.0; *IV*, intravenous; *MD*, medical doctor; *n/a*, not applicable; *OTC*, over the counter; *Non-pharms*, non-pharmacological interventions; *qid*, 4 times a day; *Rx*, prescription; *S&W*, salt and water; *SPF*, sun protection factor; *tid*, 3 times a day

dose interruptions was 1, the median duration of the first dose interruption was 4 days, and the median time to first interruption was 20.5 days. Diarrhea led to 24.5% of all dose interruptions, followed by rash (17.0%), stomatitis (13.2%), and paronychia (11.3%). No cases of disease flare were observed during treatment interruptions. Two patients (6.3%) discontinued afatinib due to AEs; one was due to transaminitis and the other was due to diarrhea.

Results showed that 58.1% of first AEs were identified by proactive pharmacist telephone assessment, with 3.2% of first AEs identified via reactive patient reporting. The proactive callback procedure identified 37.3% of any grade AEs and 33.3% of grade ≥ 3 AEs, whereas patient reactive calls identified 14.3% and 11.1%, respectively. The rate of AEs that required an emergency room visit or urgent clinical

Table 3 Incidence and time to onset and resolution of adverse events

Adverse events	Any grade *N* (%)	Grade 3+ *N* (%)	Time of onset median days (IQR)	Time to resolution median days (IQR)
Incidence of drug-related AEs				
First any AE	–	–	17 (7 to 126)	–
Any drug-related AE	33 (100.0)	6 (18.2)	–	–
Diarrhea	29 (87.9)	1 (3.0)	8 (6 to 16)	9 (5 to 22)
Rash	27 (81.8)	0 (0.0)	15 (9 to 41)	13 (5 to 29)
Stomatitis	19 (57.6)	1 (3.0)	13 (9 to 21)	8 (7 to 14)
Paronychia	15 (45.5)	1 (3.0)	75 (42 to 143)	59 (7 to 63)
Nausea	13 (39.4)	0 (0.0)	25 (18 to 52)	11 (5 to 28)
Fatigue	13 (39.4)	0 (0.0)	18 (14 to 46)	6 (4 to 10)
Anorexia	10 (30.3)	2 (6.1)	133 (16 to 263)	34 (7 to 39)
Transaminitis	4 (12.1)	2 (6.1)	114 (54 to 192)	21 (8 to 29)

AE, adverse event; *IQR*, interquartile range; *N*, number

assessment was 3.2%. Two patients were identified as non-compliant by proactive calls.

Discussion

To our knowledge, this is the first study that evaluates the impact of an interprofessional, proactive follow-up algorithm on the incidence of dose interruptions, reductions, and the severity of AEs in patients on afatinib. Another study demonstrated the value of standardized interventions, but this was driven by patient self-reported AEs and reaction by the medical oncologist [19]. Our study demonstrates that implementation of a pharmacist-led, proactive primarily phone-based follow-up algorithm is feasible, allowing for the early identification and management of afatinib-related AEs. Over half of first drug-related AEs and approximately a third of all grade and grade ≥ 3 treatment-related AEs in our real-world patient population were identified via proactive follow-up. Far fewer first AEs, all grade AEs, and grade 3 AEs were identified reactively in our study, indicating that patient self-reporting may be unreliable and could result in delayed toxicity management. Safety outcomes for our pharmacist-led treatment algorithm cohort were improved compared with the afatinib arm of the LUX-Lung 3 trial [12], which reported a 48.9% overall rate of grade ≥ 3 drug related AEs compared with 18.2% in our study. This was largely driven by a reduced rate of more common grade ≥ 3 AEs like diarrhea, rash, stomatitis, and paronychia. In addition, rates of treatment discontinuation and patients who maintained the ideal dose were similar in our cohort compared with the LUX-Lung 3 trial population [12].

Our study did reported increased rates of any grade nausea [12, 18], which may have been associated with high use of prophylactic oral tetracycline. As such, our algorithm will be modified to include dosing of tetracycline antibiotics at a frequency of once daily as opposed to twice daily for the prevention of rash, or alternatively initiated at the onset of grade 1 rash or paronychia as opposed to prophylaxis. Our study reported rates of any grade anorexia (30.3%) and transaminitis (12.2%), which were either not reported or reported at lower levels in the LUX-Lung trials [12, 18]. This may represent an example of how real-word data might elucidate side effects that are different from clinical trials due to the uncontrolled patient population and might also represent an increased capture rate due to proactive AE follow-up.

Nevertheless, the over two and a half-fold reduction in grade ≥ 3 drug-related toxicities compared with the afatinib arm of the LUX-Lung 3 trial using our proactive algorithm is notable, as toxicity profiles in real-world patient populations are often worse than those experienced by clinical trial participants due to the stringent inclusion criteria of clinical trials which often exclude patients with certain comorbidities and concomitant medications [36]. Also, patients in clinical studies are often more closely monitored than patients in the real-world context [36]. Outcomes may further be improved with our algorithm by adding a callback on day 20, as this was the median time to dose interruption in our real-world data set.

Despite the earlier dose modification mandated by our protocol, the median afatinib dose was 40 mg daily, suggesting that ideal afatinib dosing was maintained. Similar overall dose reductions below 40 mg observed in our study (51.5%) compared with those reported in the LUX-Lung 3 trial (52%) [12] suggests that proactive AE identification and management are unlikely to compromise treatment efficacy.

The major difference between published AE algorithms [25, 26, 29] and ours was that afatinib was interrupted for grade 2 AEs and reinitiated after resolution to grade 1. The main concern with holding afatinib is inducing a disease flare, which is a well-described phenomenon of accelerated progression of disease after withdrawal of an EGFR TKI in EGFR-positive NSCLC patients [37]. However, no cases of disease flare were reported, likely due to the short length of required treatment interruption (median of 4 days). Despite longer recovery periods for paronychia and transaminitis (Table 3), disease flare was also not seen in these patients.

Our study was retrospective in nature and lacked randomization, so it is possible that the observed lower rates of grade ≥ 3 AEs were influenced by more favorable patient and/or disease characteristics and/or better standards of care at our institution. Additionally, our study was small and may not have been sufficiently robust to identify less common toxicities associated with afatinib or identify factors associated with AEs. A recent randomized trial showed that patients with advanced cancer had improved survival with real-time web-based toxicity reporting and intervention [38]. We did not compare our proactive follow-up program to this method or other electronic AE notification systems. A major strength of our study was the real-time capturing of AE data and management through proactive calls, supporting the robustness of our retrospective analysis.

Despite limitations, our data suggest that earlier intervention prompted by this proactive follow-up algorithm is feasible and reduces the incidence of severe AEs and the need for costly emergency room or urgent clinic visits. The average time spent by the oral chemotherapy pharmacist to provide a symptom intervention for a patient was 30 min. Published data indicates that the cost of a single hospital admission can range anywhere from $8900 to $24,000 USD [39, 40], which easily justifies the additional resources required for proactive callback. Although this study focused on pharmacists providing proactive follow-up, we would expect similar outcomes if this was delegated to other health care providers such as nurses, as it would not have changed the management algorithm.

This study highlights the importance of proactive follow-up rather than relying on patient self-reporting between clinical visits. It also underscores the importance of managing

patients receiving OACMs in a multi-disciplinary manner [41] and shows how use of a standardized tool can facilitate interprofessional engagement in routine clinical practice. This algorithm is an easily generalizable and viable model for use in other institutions seeking to improve the AE management of afatinib.

Conclusion

Implementation of our proactive follow-up algorithm for patients with advanced EGFR-positive NSCLC allowed the early identification and management of afatinib-related toxicities and resulted in a low rate of urgent assessments and discontinuation due to toxicity while maintaining an ideal dose of afatinib. This study underscores the importance of multidisciplinary management of patients receiving oral afatinib and represents a generalizable and viable model for use in other institutions seeking to optimize care for patients on afatinib.

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Compliance with ethical standards

Conflict of interest Boehringer Ingelheim Canada supported this study with an unrestricted educational grant. Funds were used for data collection, statistical analysis, and writing of our retrospective analysis. Boehringer Ingelheim had no input on the follow-up algorithm, the data results, or interpretation of the analysis. We have full control of the primary data and will allow the journal to review our data if requested. Dr. Cheema, Alia Thawer, and Dr. Suneil Khanna have participated in advisory boards for Boehringer Ingelheim.

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