

Effectiveness of pharmacist-managed oncology ambulatory care for patients with non-small cell lung cancer in Taiwan

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Abstract

Non-small cell lung cancer (NSCLC) is commonly treated with tyrosine kinase inhibitors (TKIs). However, adverse events from such treatment can lead to treatment discontinuation and additional medical expenditures. Ambulatory care from oncology pharmacists in patient education and symptom management can benefit patients with NSCLC. In this study, we evaluated the effectiveness of an oncology pharmacy service at a medical center in Taiwan. We retrospectively enrolled 137 patients with NSCLC who initiated treatment with afatinib, gefitinib, or erlotinib between January 2017 and December 2021; 40 of them utilized the oncology pharmacy service (intervention group), and the remaining 97 did not (nonintervention group). To determine the effectiveness of the oncology pharmacy service, we analyzed the following outcomes: adverse event rates, number of hospital visits (unexpected outpatient department visits, emergency department visits, and hospitalization), and medical expenditure. The intervention group had significantly more skin-related adverse events (acneiform rash: 75% vs. 49%; mucositis: 40% vs. 21%; dermatitis: 30% vs. 9%; and paronychia: 85% vs. 28%) but significantly fewer monthly emergency department visits (0.04 vs. 0.17) and unexpected outpatient department visits (0.15 vs. 0.34). The intervention group also had significantly lower expenditure for emergency department visits (NT\$166.4 vs. NT\$734.8) and nonsignificantly lower expenditure for outpatient department visits. Our findings indicate the value of pharmacist-managed ambulatory oncology care. Although this service did not reduce the incidence rates of adverse events, it reduced the number of unplanned outpatient and emergency department visits and reduced the emergency department expenditure of patients with NSCLC receiving TKIs.

Keywords: Ambulatory care, Non-small cell lung cancer, Oncology pharmacist, Oral oncolytic therapy

1. Introduction

Lung cancer accounts for 11.4% of all cancer cases globally and is the leading cause of cancer death (18%) [1,2]. A previous study reported an incidence rate of 13.42% and a 5-year survival rate of 34.4% for lung cancer in Taiwan [3], and in 2020, it was the leading cause of cancer death (19%) [3,4]. Non-small cell lung cancer (NSCLC) accounts for approximately 78% of all lung cancer cases, and 56% of patients with NSCLC are diagnosed with this cancer in stage III or IV [3].

Approximately 50% of patients of Asian descent with NSCLC exhibit alterations in epidermal growth factor receptor (EGFR)—a rate higher than that in individuals of European descent [5]. Tyrosine kinase inhibitors (TKIs) targeting EGFR offer considerable advantages [6]. They have higher efficacy than chemotherapy in terms of the response rate and progression-free survival, and they have fewer side effects [7–10]. For these reasons, the usage rate of EGFR-TKIs, such as afatinib, erlotinib, and gefitinib, is high (56.7%) in Taiwan [4].

EGFR-TKI use is associated with adverse events (AEs) [7,9–11]. The most common AEs are diarrhea,

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acneiform rash, dermatologic reactions, and paronychia. These AEs can negatively affect patient quality of life [12], increase supportive care expenses, and reduce medication compliance [13].

The aforementioned AEs can be alleviated by oncology pharmacist-led ambulatory care. The Hematology/Oncology Pharmacist Association has advised pharmacists to educate patients regarding the self-management of oral oncolytic AEs and the importance of medication adherence [14,15]. For patients, the benefits of such interventions provided by pharmacists include the identification of more drug-related problems [16–20], a reduction in the severity of AEs [21,22], improvements to quality of life, and improvements in the outcomes of oral chemotherapy agents [19,22].

Since 2016, board-certified oncology pharmacists have been providing oncology ambulatory care at Taipei Medical University Wan Fang Hospital, a 733-bed tertiary hospital in northern Taiwan. The service process for the provided oncology ambulatory care is presented in [Supplementary Fig. 1](#). The pharmacists provide education to patients initially taking oral oncolytic agents and provide follow-up care at every oncology clinic visit. The follow-up care involves monitoring medication adherence and AE occurrence and helping with AE management. The pharmacists provide the service at an independent space in the oncology center. The service, which is mostly provided in collaboration with oncologists and pulmonologists, is offered seven times each week and for 3 h each time. After conducting a review of patients, pharmacists key in the pharmacy note, which may include advice to physicians, into the hospital information system. The system will alert physicians regarding the note upon the next visit of patients to the oncology clinic. Although studies [16–22] have highlighted the benefits of oncology ambulatory care, the effectiveness of such care for patients with NSCLC and its implications for the consumption of health-care resources remain unclear. Thus, we conducted a retrospective study to evaluate the effectiveness of pharmacist-managed oncology ambulatory care for patients with NSCLC receiving oral EGFR-TKIs in Taiwan.

2. Methods

This single-center retrospective study was conducted using data from the health-care information system of Wan Fang Hospital. We enrolled patients with advanced NSCLC who had initiated afatinib, gefitinib, or erlotinib treatment between January 2017 and December 2021. Patients who met the

following criteria were included: taking EGFR-TKIs for >1 month, receiving EGFR-TKIs as monotherapy, and visiting ambulatory care clinics at least twice within 3 months after the first TKI prescription. We excluded patients who had other cancers, who were aged <18 years, or who had insufficient medical information available for determining whether they met the inclusion criteria. Finally, this study included 137 patients with NSCLC on afatinib, gefitinib, or erlotinib treatment. They were divided into two groups: patients who used the pharmacy service (intervention group) and patients who did not (nonintervention group).

We recorded the patients' baseline characteristics, including their sex, age, body mass index, liver and renal function status, and underlying disease status. The TKI initiation date served as the index date. Moreover, patients were followed up until medication discontinuation, death, or March 31, 2022, whichever occurred first.

To determine the effectiveness of the oncology pharmacy service, the following outcomes were examined: AE rate, number of hospital visits (expected and unexpected outpatient department [OPD] visits, emergency department [ED] visits, and hospitalization), and medical expenditure. AEs were classified according to the Common Terminology Criteria for Adverse Events (CTCAE), version 6.0. For patients in the intervention group, we collected data on skin and gastrointestinal (GI)-related AEs from physician notes and pharmacy notes. The severity of these AEs was determined on the basis of the grades assigned by physicians in their notes. In the absence of such information, we merely recorded the AE without any grading. We collected data on liver function and blood counts from the hospital's laboratory information system, and for abnormal laboratory values, we assigned grades according to the CTCAE. In this study, we considered two categories of AEs: all grades and grade ≥ 3 (indicating severe AEs). The total AE rate was calculated as the number of patients experiencing any AE divided by the total number of patients in each group. The rate of AEs with grade ≥ 3 was calculated as the number of patients experiencing grade ≥ 3 AEs divided by the total population of a group.

We defined OPD visits as the number of visits made by a patient to the hospital to retrieve their TKI prescription. Moreover, unexpected OPD visits were defined as the number of visits made by a patient to the hospital for purposes other than for scheduled medication pick up. We also recorded ED visits and hospitalization during the treatment period. Because patients have unique treatment

durations, we calculated the average number of monthly hospital visits by dividing the number of visits by the treatment duration.

We also obtained data on the cost of each OPD visit, hospitalization, and ED visit from the hospital information system. We calculated the cost of medications prescribed for managing TKI-related AEs. The following supportive medications were considered in the analysis: antidiarrhea agents, topical steroids, antihistamines, oral antibiotics, topical antibiotics, and silymarin. The cost of each medication recorded in this study was based on the price announced by Taiwan's National Health Insurance Administration each year. Regarding medical expenditure in each OPD visit, hospitalization, and ED visit, we considered the labor cost of pharmacists (pharmacist hourly salary times the average duration of each visit).

We also collected data on TKI usage, the types of pharmacy service provided, and progression-free survival (PFS). To determine TKI usage, we considered medication discontinuation or interruption, dose adjustment, treatment duration, and relative dose intensity (RDI). We also obtained the reasons for medication discontinuation or interruption and dose adjustment. If physicians documented that these medication-related factors occurred because of AEs, the reason was defined as intolerance. The RDI was defined as the total actual dosage received by the patient divided by the sum of the standard dosage during the treatment period. From the ambulatory pharmacy service database, we collected data on the types of pharmacy service provided. Pharmacy services were categorized as either patient counseling or physician advice. Patient counseling was classified into the following subcategories: management of side effects, education on side effects, support on food interaction, supportive care, guidance on drug interactions and drug administration, and others. Physician advice was classified into the following subcategories: patient monitoring using laboratory data, provision of supportive medications, evaluation of symptoms, management of abnormal laboratory data, guidance on drug interactions, dose adjustment, and others. To determine PFS, we analyzed the survival data of patients who used EGFR-TKI as first-line therapy.

This study was approved by the Institutional Review Board of Taipei Medical University (Approval No. N202103096); the requirement for informed consent was waived.

Regarding statistical analysis, continuous and categorical data were compared using independent sample *t* tests and chi-square tests, respectively. A *p* value of <0.05 was considered significant. All

statistical analyses were performed using SPSS, version 19 (SPSS, Chicago, IL, USA).

3. Results

We initially enrolled 218 patients with advanced NSCLC and then excluded noneligible patients to form a final sample of 137 patients (40 and 97 in the intervention and nonintervention groups, respectively; Table 1). The demographic and clinical characteristics of these patients are presented in Table 1. The two groups differed only in terms of the site of metastasis.

The total AE rate was higher in the intervention group (Table 2). Moreover, the rates of acneiform rash (75% vs. 49%, *p* = 0.004), mucositis (40% vs. 21%, *p* = 0.021), dermatitis (30% vs. 9%, *p* = 0.002), paronychia (85% vs. 28%, *p* < 0.001), and diarrhea (78% vs. 52%, *p* = 0.005) of any grade were higher in the intervention group. With regard to AEs of grade ≥3, the two groups only significantly differed in the rates of diarrhea (intervention group: 13%; nonintervention group: 2%; *p* = 0.017).

Overall, the intervention group had fewer hospital visits (Table 3), fewer hospitalizations (0.13 vs. 0.22, *p* = 0.062), and significantly fewer ED visits (0.04 vs. 0.17, *p* = 0.005). The number of expected OPD visits was similar between the groups. The number of unexpected OPD visits was significantly lower in the intervention group than in the nonintervention group (0.15 vs. 0.34, *p* = 0.017).

Relative to the nonintervention group, the intervention group had lower overall medical expenditure (Table 3) and lower medical expenditure in ED visits (NT\$230.7 vs. NT\$782.4, *p* = 0.01). In addition, the cost of OPD visits and supportive medications was lower in the intervention group.

The two groups did not differ significantly in terms of the rates of dose adjustment, dose interruption, and permanent discontinuation (Table 4). The rates of dose adjustment and permanent discontinuation owing to intolerance were significantly lower in the intervention group than in the nonintervention group (30% vs. 72%, *p* = 0.031).

Compared with the nonintervention group, the intervention group had a nonsignificantly higher treatment duration (17.3 months vs. 12.8 months, *p* = 0.078), nonsignificantly lower RDI (0.938 vs. 0.956, *p* = 0.637), and numerically higher median PFS (13.1 months vs. 12.9 months, *p* = 0.759).

Physician advice was most common in the subcategory of patient monitoring using laboratory data (Fig. 1), followed by the provision of supportive medications and the evaluation of symptoms. Patient counseling was most common in the

Table 1. Sample baseline characteristics.

	Intervention (n = 40)	Nonintervention (n = 97)	p value
Sex, no. (%)			
Female	29 (72)	62 (64)	0.333
Male	11 (28)	35 (36)	
Age, year (mean \pm SD)	71 \pm 10.4	72.2 \pm 13.8	0.675
BMI, kg/m ² (mean \pm SD)	23.8 \pm 4.1	23.2 \pm 4.1	0.471
Laboratory data (mean \pm SD)			
Total bilirubin (mg/dL)	0.3 \pm 0.4	0.4 \pm 0.4	0.870
Glutamic oxaloacetic transaminase (U/L)	18.3 \pm 9.4	17.9 \pm 10.7	0.824
Glutamic pyruvic transaminase (U/L)	16.2 \pm 14.1	14.5 \pm 11.1	0.463
Blood urea nitrogen (mg/dL)	16.4 \pm 5.1	17.5 \pm 12.6	0.450
Serum creatinine (mg/dL)	0.8 \pm 0.2	1.0 \pm 1.3	0.392
Creatinine clearance (mL/min)	68.5 \pm 22.6	64.9 \pm 27.5	0.462
EGFR-TKI, no. (%)			
Afatinib	13 (32.5)	26 (27)	0.502
Erlotinib	7 (17.5)	23 (24)	0.424
Gefitinib	20 (50)	48 (49)	0.956
Comorbidity, no. (%)			
Hypertension	23 (58)	48 (50)	0.590
Hyperlipidemia	8 (20)	31 (32)	0.285
Diabetes mellitus	7 (18)	25 (26)	0.457
Hyperuricemia	1 (3)	6 (6)	0.540
Valvular heart disease	8 (20)	24 (25)	0.667
Osteoporosis	3 (8)	4 (4)	0.588
Chronic kidney disease	2 (5)	11 (11)	0.410
Hepatitis B	2 (5)	11 (11)	0.410
Atrial fibrillation	1 (3)	6 (6)	0.540
Heart failure	3 (8)	4 (4)	0.588
Metastasis, number/patient	1.40	1.39	0.937
Site of metastasis, no. (%)			
Liver	7 (18)	8 (8)	0.241
Lung	10 (25)	26 (27)	0.787
Bone	15 (38)	33 (34)	0.765
Brain	15 (38)	29 (30)	0.576
Pleural	6 (15)	34 (35)	0.047
Other	3 (8)	11 (11)	0.639

Table 2. Adverse events after initiating oral chemotherapy.

	Intervention (n = 40)	Nonintervention (n = 97)	p value	Intervention (n = 40)	Nonintervention (n = 97)	p value
Event	Any grade			Grade \geq 3		
All events	40 (100)	88 (91)	0.046	1 (3)	3 (3)	0.807
Skin-related adverse events, no. (%)						
Acneiform rash	30 (75)	47 (49)	0.004	1 (3)	3 (4)	0.709
Mucositis	16 (40)	20 (21)	0.021	1 (3)	1 (1)	0.545
Dermatitis	12 (30)	9 (9)	0.002	1 (3)	1 (1)	0.502
Paronychia	34 (85)	27 (28)	0.000	—	—	—
Skin itching	9 (23)	12 (12)	0.135	—	—	—
Skin reaction	14 (35)	40 (41)	0.497	2 (6)	8 (8)	0.607
Hand–foot syndrome	9 (23)	18 (19)	0.598	—	—	—
Gastrointestinal adverse events, no. (%)						
Nausea	7 (18)	19 (20)	0.777	2 (5)	3 (3)	0.585
Diarrhea	31 (78)	50 (52)	0.005	5 (13)	2 (2)	0.017
Vomiting	3 (8)	14 (14)	0.263	1 (3)	2 (2)	0.901
Adverse events related to the liver and kidneys, no. (%)						
Elevated creatinine	19 (48)	33 (34)	0.139	1 (3)	1 (1)	0.515
Abnormal liver function	19 (48)	43 (47)	0.979	2 (5)	3 (3)	0.639

Table 3. Hospital visits and medical costs for the two groups.

	Intervention (n = 40)	Nonintervention (n = 97)	p value
Hospital visits (times/month)			
Hospitalization	0.13 ± 0.20	0.22 ± 0.36	0.062
Emergency department visits	0.04 ± 0.08	0.17 ± 0.40	0.005
Outpatient department visits	2.77 ± 1.46	2.93 ± 1.70	0.609
Unexpected outpatient department visits	0.15 ± 0.24	0.34 ± 0.68	0.017
Cost, NT\$/month (mean ± SD)			
Outpatient department	48848.55 ± 25315.39	70694.21 ± 13721.48	0.134
Emergency department	230.71 ± 339.17	782.44 ± 1992.57	0.01
Hospitalization	105795.02 ± 153794.72	101341.06 ± 209669.21	0.903
Supportive medications	202.89 ± 144.41	224.19 ± 398.01	0.743

Table 4. Statistics of oral targeted therapy for the two groups.

	Intervention (n = 40)	Nonintervention (n = 97)	p value
Dose adjustment, no. (%)	10 (25)	18 (19)	0.395
Reason, no. (%)			
Intolerance	3 (30)	13 (72)	0.031
Disease progression	2 (20)	4 (22)	
Other	5 ^a (50)	1 (6)	
Dose interruption, no. (%)	7 (18)	23 (24)	0.424
Reason, no. (%)			
Intolerance	6 (86)	18 (78)	0.666
Other	1 (14)	5 (22)	
Permanent discontinuation, no. (%)	25 (68)	66 (76)	0.166
Reason, no. (%)			
Intolerance	1 (4)	14 (21)	0.048
Disease progression	22 (88)	41 (62)	
Death	0 (0)	8 (13)	
Other	2 (8)	3 (5)	
Treatment duration (mean ± SD)	17.3 ± 2.1	12.8 ± 1.3	0.078
Relative dose intensity (mean ± SD)	0.938	0.956	0.637

^a All of them increased the dose of tyrosine kinase inhibitors. Three of them increased the afatinib dose from 30 mg/day to 40 mg/day, and two of them increased the gefitinib dose from 250 mg every other day to 250 mg per day.

subcategory of the management of side effects (Fig. 2), followed by education on side effects.

4. Discussion

This retrospective study revealed that the oncology ambulatory care provided by pharmacists for patients with advanced NSCLC may not reduce the rate of skin-related AEs and may reduce medical costs and the number of hospital visits. Moreover, this care can lead to a low rate of dosage adjustment owing to drug intolerance. The service most commonly provided by the pharmacists at the hospital was the management of side effects.

EGFR-TKIs can prolong the survival of patients with advanced NSCLC. However, this treatment commonly leads to AEs, which can affect patients' quality of life. At this study's hospital, AEs were treated through the provision of regular interventions by board-certified oncology pharmacists. In this study, we comprehensively analyzed

the effectiveness of the oncology ambulatory care provided in terms of the rates of AEs, number of hospital visits, and medication use among patients with advanced NSCLC. Moreover, we analyzed the types of services provided as a part of ambulatory oncology care and the effects of such care on reducing medical expenditure.

In this study, the incidence rates of AEs were higher in the intervention group, with AEs related to the skin and GI tract being particularly prevalent. Some reasons for this finding can be given. First, we collected AE data from physician notes for both groups and from pharmacy notes for the intervention group. Therefore, the AE records for the intervention group are likely to be more comprehensive than those of other studies. Similarly, Patel et al. revealed that a pharmacist-led oral chemotherapy monitoring program led to the identification of more complications from treatment and the reporting of more AEs, enabling timely intervention for addressing these problems [17]. Second, the incidence rates of rash,

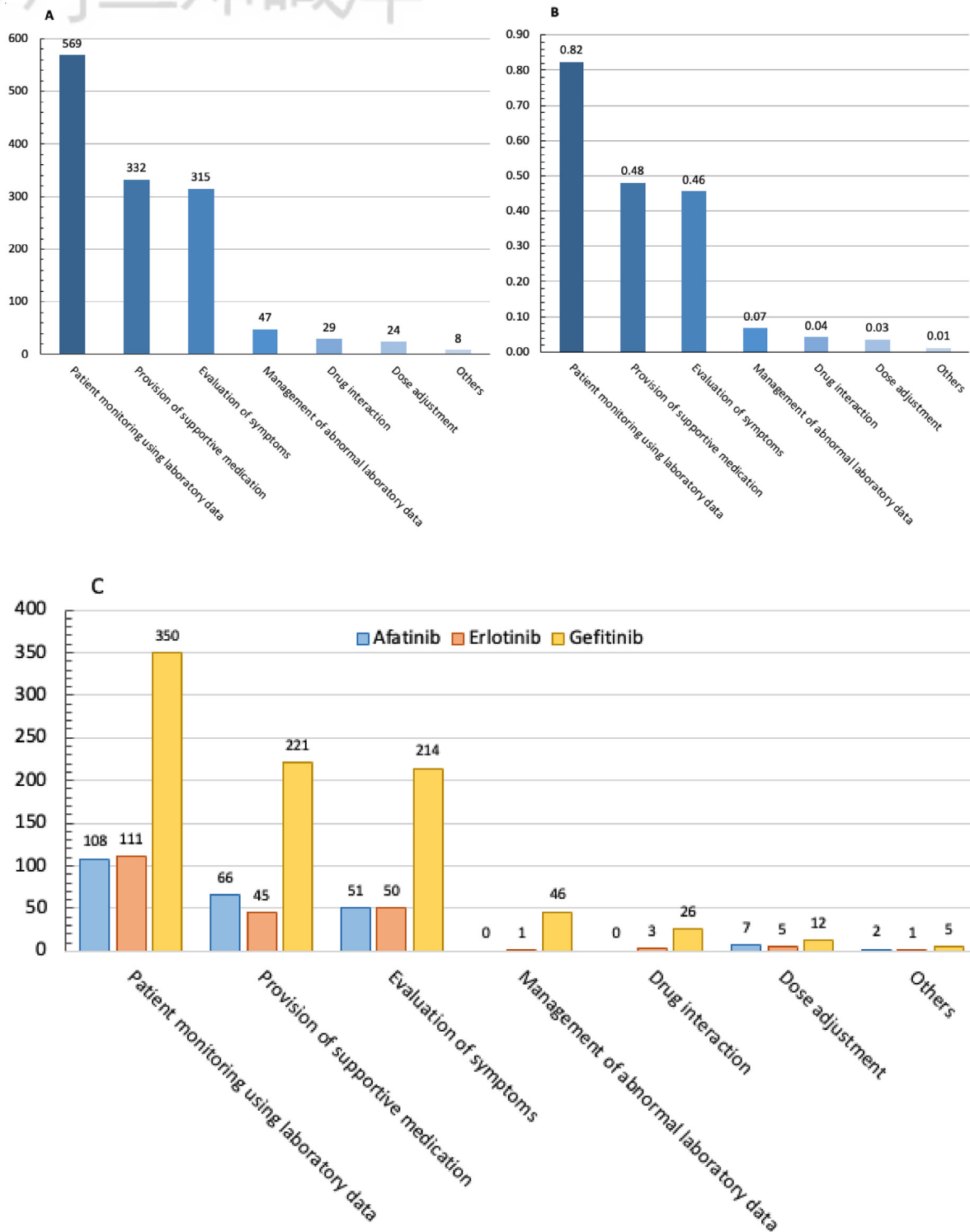


Fig. 1. Categories of physician advice in the pharmacy service. A, total number of advice instances in each category; B, the average monthly number (per patient) of physician advice instances in each category; C, the number of physician advice instances grouped by three tyrosine kinase inhibitors.

mucositis, and paronychia in the nonintervention group are lower in our study than in the FLAURA study in an Asian cohort [23]. The FLAURA study did not enroll afatinib users. Given the higher incidence

of skin-related AEs resulting from afatinib [16], the AE rate may be higher when afatinib users are included in an analysis. Hence, the skin-related AEs might have been underestimated in our study. Third,

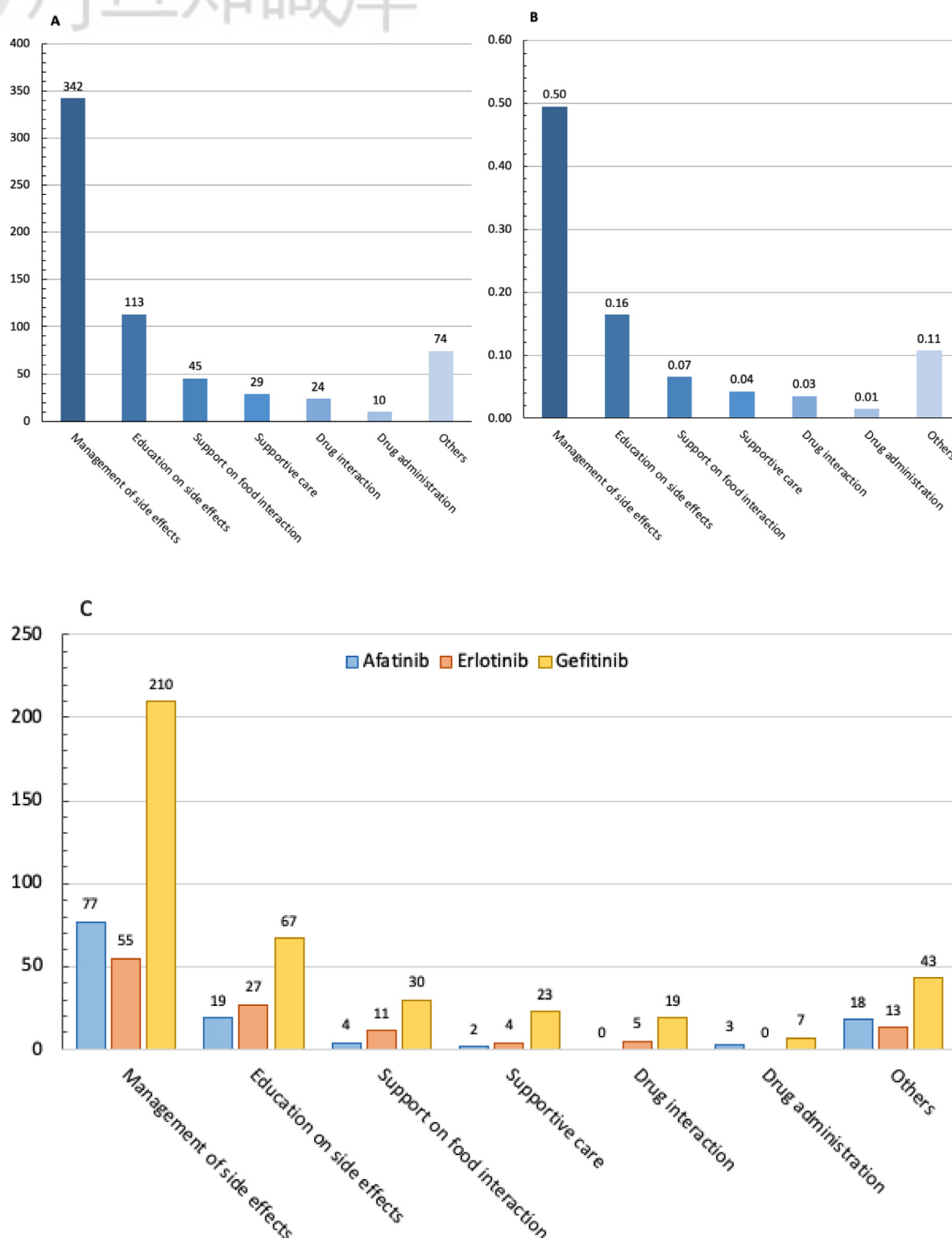


Fig. 2. Categories of patient counseling in the pharmacy service. A, total number of counseling sessions in each category; B, the average monthly number (per patient) of counseling sessions in each category; C, the number of patient counseling sessions grouped by three tyrosine kinase inhibitors.

the percentage of afatinib users was higher in the intervention group than in the nonintervention group (32.5% vs. 26.4%). Therefore, this may also contribute higher skin AE rate.

Although the oncology ambulatory service led to a higher rate of AEs in the treatment group, the supportive medication costs and overall health-care costs were lower in the intervention group

than in the nonintervention group in this study. Oncology pharmacists play essential roles in reducing the cost of cancer treatment. Wong et al. revealed that pharmacist-led interventions for oral chemotherapy decreased the cost of outpatient care associated with drug-related AEs and drug interactions and reduce the adjustment rate of dosage or frequency [24]. Iihara et al. indicated that pharmacy interventions at cancer chemotherapy clinics resulted in a 16% decrease in antiemesis costs [25]. Furthermore, Dranitsaris et al. reported that following a pharmacist-led intervention, the costs of ondansetron treatment in patients with cancer reduced by 58% [26]. Our results also revealed significant decreases in the number of ED visits and unexpected OPD visits; the overall OPD and ED expenditure was lower in the intervention group than in the nonintervention group. Consistent with our results, Walter et al. reported a 13% reduction in the number of unplanned admissions and a 10% reduction in the clinic attendance rate after specialist clinical cancer pharmacists joined multidisciplinary lung cancer clinics [19]. The decreases in medication costs, number of unplanned visits, and health-care expenditure may be attributed to the patient education provided by oncology pharmacists. Patient education on the day-to-day management of side effects and the correct use of supportive medications can prevent unnecessary drug use, leading to fewer hospital visits and greater cost savings [27,28].

In our study, oncology pharmacist-led ambulatory care led to improved patient adherence to TKIs. Moreover, we observed fewer changes in patient behavior related to medication discontinuation or interruption owing to intolerance in the intervention group. Yeoh et al. reported that 92% of patients with cancer experience drug-related problems, with drug–drug interactions (32.4%) and drug-related AEs (31.6%) being the most common [16]. In Taiwan, oncology ambulatory pharmacists can help treat these two common problems [16,29]. In our study, the management of side effects was the most common subcategory of counseling provided to patients and the second-most common subcategory of advice provided to physicians in the pharmacy note. Moreover, patient monitoring using laboratory data was the most common subcategory of advice provided by pharmacists to physicians. TKIs may induce some

laboratory AEs such as abnormal liver function test and increased serum bilirubin levels. Patient monitoring using laboratory parameters enables the early identification and management of side effects due to oral cancer therapy [29]. Thus, oncology pharmacy services can help prevent more severe problems that cause drug intolerance in patients with cancer, thereby supporting the management of side effects from medications.

Our study has some limitations. First, because we focused on patients with NSCLC, our results may not be generalizable to patients with other types of cancer. However, NSCLC is the most common cancer in Taiwan, and half of the Taiwanese population with NSCLC has alterations in EGFRs, which highlights the importance of this research topic. Second, documentation bias related to AEs may have occurred in the results because we collected data from electronic clinical notes. In physician notes, the recording of AEs is not mandatory. In pharmacy notes, the AEs may be recorded either on the basis of subjective clinical judgment or objective measurements. Therefore, for the intervention group, we collected AE data not only from physician notes but also from pharmacy notes. Finally, during the COVID-19 pandemic, patients may have avoided hospital visits, which may have affected their RDI. However, instead of patients, their family members commonly visited the hospital to refill their prescriptions. Thus, COVID-19 is unlikely to have substantially affected patient RDI.

In conclusion, our study demonstrated the value of oncology pharmacist-led ambulatory care for patients with NSCLC receiving EGFR-TKIs. Although this oncology pharmacy service did not reduce the incidence rates of AEs, it reduced the number of unplanned outpatient and ED visits and the emergency department expenditure of patients with NSCLC receiving TKIs.

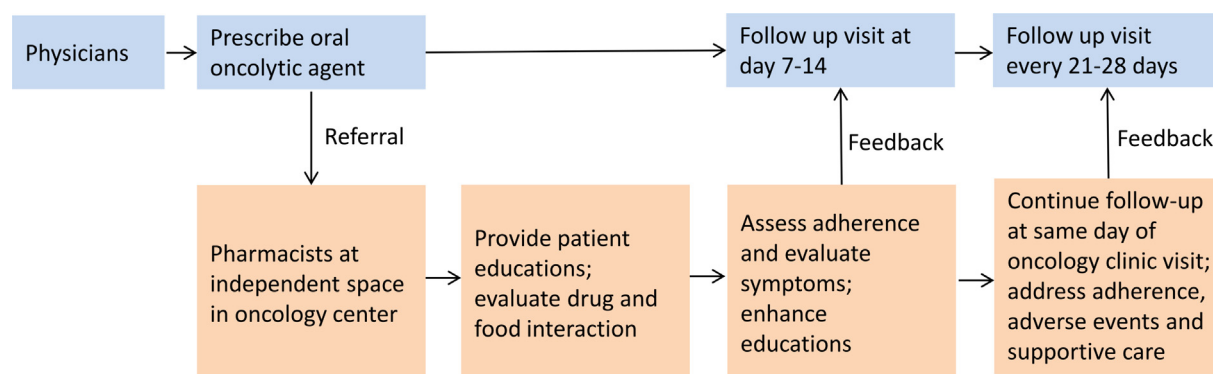
Conflict of interest

None.

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Appendix



Supplementary Fig. 1. The process of pharmacist-managed oncology ambulatory care.

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