Original Article

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The profile and clinical predicting effect of non-rash dermatologic toxicity related to targeted therapy in stage-IV non-small cell lung cancer patients

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SUMMARY: Dermatologic toxicities associated with targeted therapies may impact drug intolerance and predict drug response, among which rash is most frequently reported and well delineated. However, the profile and effect of non-rash dermatologic toxicity are not fully understood. We identified stage-IV non-small cell lung cancer patients diagnosed at Mayo Clinic in 2006-2019 and systematically analyzed demographics, targeted agents, toxicity, response, and survival outcomes of patients who received targeted therapy. Five toxicity subgroups-none, only non-rash dermatologic, concurrent non-rash and rash (concurrent) dermatologic, only rash, and others-were compared; multivariable survival analyses employed Cox Proportional Hazard models. This study included 533 patients who had taken targeted therapies: 36 (6.8%) had no toxicity, 26 (4.9%) only non-rash dermatologic, 193 (36.2%) only rash, 134 (25.1%) concurrent dermatologic, 144 (27.0%) other toxicities. Non-rash dermatologic toxicities predominately included xerosis (12.8%), pruritus (8.5%), paronychia (7.0%). Rash was the most frequent (59.4%) and the earliest occurring (21 median onset days [MOD]) dermatologic toxicity; paronychia was the latest (69 MOD) occurring. In 329 epidermal growth factor receptor inhibitors-treated patients with dermatologic toxicity, mild toxicity occurred the most frequently in patients with only non-rash (81.8%), then those with only rash (64.8%), and the least in the concurrent (50.4%, P=0.013). Patients with concurrent dermatologic toxicities had a significantly higher response rate (67.9%) than those with only non-rash (53.8%) or only rash (41.1%, $p < 0.001$). Multivariable analysis demonstrated concurrent dermatologic toxicity independently predicted a lower risk of death (harzard ratio [HR] 0.48 [0.30-0.77], $p < 0.001$). Compared to rash, non-rash dermatologic toxicity might be a stronger predictor of better treatment response and longer survival in patients who received targeted therapy.

Keywords: lung cancer, target therapy, dermatologic toxicity, non-rash, survival

1. Introduction

Lung cancer accounts for approximately 21% of cancer deaths in the United States; however, the mortality has been declining with advances in targeted therapy, partly driven by improved overall survival time of stage-IV non-small cell lung cancer (NSCLC) (*1*). Meanwhile, certain adverse effects associated with these novel anti-cancer agents, particularly dermatologic toxicity, have been significant and draw attention of care providers (*2-4*).

NSCLC accounts for 85% of lung cancer (*5*), predominantly consisting of adenocarcinoma and squamous cell carcinoma. Approximately 78% of Asian populations and 60% of Western populations of lung adenocarcinoma patients have driver gene mutations, including *epidermal growth factor receptor* (*EGFR*), *anaplastic lymphoma kinase* (*ALK*), *c-ros oncogene 1* (*ROS1*), *Kirsten rat sarcoma virus* (*KRAS*), *V-raf murine sarcoma oncogene homolog B1* (*BRAF*), *MET*,

and *human epidermal growth factor receptor* (*HER2*), rearranged during transfection *(RET)* and other genetic alterations (*6*). Other targeted agents included anti-*vascular endothelial growth factor* (*VEGF*) therapy, widely used for targeting tumor angiogenesis (*7*), and *mammalian target of rapamycin* (mTOR) inhibitors, which targets a cellular pathway driving oncogenesis and tumor progression (*8*) independent of specific gene mutations.

Dermatologic toxicity was mostly reported in *EGFR* inhibitors compared to other targeted drugs, typically presenting as papulopustular (acneiform) rash, xerosis, pruritus, paronychia, hair changes, and mucositis, and their incidences ranged from 47% to 100%, 10% to 49%, 8% to 57%, 3% to 25%, 0 to 13%, and 0 to 44% (*9*), respectively. Even though most dermatologic toxicities are not life-threatening, their symptoms are unfavorably correlated with quality of life (*10*). One of the earlier clinical studies to explore the relationship between rash and clinical outcomes showed patients who developed cutaneous rash were associated with better response and prolonged survival in 57 NSCLC patients treated with erlotinib, a classic *EGFR* inhibitor (*11*). A similar result between rash and survival has been observed in a real-world cohort of 79 patients with erlotinib (*12*). Higher severity of rash was also found to be a potential marker for the long-term efficacy of afatinib in 32 NSCLC patients (*13*). We also validated that dermatologic toxicity was a protective predictor for treatment response and survival (*14*). However, the specific relationship between non-rash dermatological and drug response, as well as survival length, is not documented, especially from real-world settings.

Our current study was designed to provide additional perspectives to fulfill the knowledge gap on the profile and predictive value of non-rash dermatologic toxicities in stage-IV lung cancer patients based on a 14-year prospectively enrolled and followed clinical cohort.

2. Patients and Methods

2.1. Study population and grouping

A total of 3,767 patients with newly diagnosed stage-IV NSCLC were identified from January 1, 2006 to December 31, 2016 (*15-17*) in Mayo Clinic Lung Cancer Cohort and consecutive case series from January 1, 2017 to December 31, 2019 (*18*). Patients were staged at the time of original diagnosis according to the 5th (*19*) or 7th (*20*) edition of TNM staging system. Inclusion criteria were *i*) patients were newly diagnosed stage-IV NSCLC from January 1, 2006 to December 31, 2019, *ii*) patients were treated with targeted therapy at Mayo Clinic, and (iii) patients signed content form. Exclusion criteria were *i*) patients had no documented toxicity information relevant to targeted therapy, *ii*) patients were lost to follow-up or terminated targeted therapy within one month from treatment initiation, and *iii*) patients were treated with concurrent chemoradiation and targeted therapy. Targeted agents targeted specific driver genes (*e.g.*, *EGFR*, *ALK*/*ROS1*) and other antagonists targeting mTOR and *VEGF/VEGFR*.

The included patients were divided into five toxicity subgroups-none, only non-rash dermatologic, concurrent non-rash and rash (concurrent) dermatologic, only rash, and others based on the targeted therapy status. Patients without any targeted therapy-induced toxicity were grouped into none group; those who had dermatologic toxicity but not rash were put into only non-rash dermatologic group, and they could also have non-dermatologic toxicity or not; those who had dermatologic toxicity with concurrent rash and other dermatologic toxicities that included but not limited to xerosis, pruritus, paronychia, erythema, mucositis, and nail changes were put into concurrent dermatologic group; those with only rash rather than other dermatologic toxicities were put into only rash group, and they could also have non-dermatologic toxicity or not; and those with only non-dermatologic toxicity were put into others group.

2.2. Data collection

The electronic medical records were reviewed, including detailed information on demographics, smoking history, lung cancer diagnosis, treatment, targeted therapy-associated toxicity, treatment response, and vital status under the approval of the Mayo Foundation Institutional Review Board approval (IRB# 225-99).

Dermatologic toxicities were identified and categorized into rash and non-rash toxicities. Rash referred to acneiform, maculopapular, erythematous papular/pustular; non-rash dermatologic toxicity included xerosis, pruritus, paronychia, erythema, mucositis, nail changes, and other dermatological reactions that have been reported previously (*21*). The severity of dermatologic toxicities was evaluated by Common Terminology Criteria for Adverse Events (CTCAE) v5.0 (*22*), were graded into mild (grade 1), moderate (grade 2), severe (grade 3), life-threatening (grade 4) and death (grade 5). If the grade of toxicity based on CTCAE was not documented, descriptions related to severity were employed. Definitions of severity in medical records were identified by oncologists as follows: "tolerable or tolerated, sporadic, some, notable, occasional, manageable, faint (skin disorders)" were graded as mild; "intermittent, some continued, some modest, worsen" were categorized as moderate; "extremely, profound, generalized, faint (anemia, weak, fatigue), generalized, outstanding, persistent, quite a bit, really bad, significant, prominent, considerable, substantial, very" were considered as severe. The toxicity onset time was defined as the time from targeted drug initiation to toxicity occurrence.

Treatment response was determined by the best response to targeted drugs, evaluated by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (*23*), categorized by complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). Objective response rate was the percentage of CR and PR (abbreviated as "response"). If original imaging tests and biopsy of the new suspected disease were not available, descriptions of response noted in medical records were utilized to define the best response. Definition of the descriptions for response were identified by oncologists based on the following criteria: "Totally resolved, complete remission, complete response, free of disease, negative bronchial margins, negative for tumor, no evidence of disease" were classified as CR; "Interval response, near complete response, good response, nice response, a remarkable response, nice regression, responded well, reduction, improvement of disease, and dramatic shrinkage" were categorized as PR; "Stable, stable disease, and good control" were considered as SD; "Disease progression, recurrent, progressive, recurrence, and new metastatic" were identified as PD.

2.3. Statistical methods

Age was analyzed by Kruskal-Wallis test; sex, race, smoking status, cell type, treatment modality, treatment line, treatment response, toxicity severity and gene status were evaluated by Chi-Square test to identify differences in five toxicity groups: none, only non-rash dermatologic, concurrent non-rash and rash (concurrent) dermatologic, only rash, and other (non-dermatologic toxicities), as well as the subgroup analysis in three dermatologic toxicity groups (only non-rash, concurrent, only rash). A Logrank test assessed overall survival (OS), defined as the date of targeted drug initiation to the date of last follow-up or patient death with the endpoint on April 30, 2022. A Cox proportional hazards model was developed for multivariable analysis to evaluate the toxicity status and known prognostic factors, including age, sex, race, smoking status, cell type, treatment modality, treatment line and treatment response. Hazard ratios (HR) with 95% confidence intervals (CI) were calculated. Statistical analyses were performed using SAS, v.9.4 (SAS Institute Inc., Cary, NC, USA). Means (standard deviation, SD) and medians were reported for continuous data, and counts (*n*) and frequency (%) were used for categorical data. A two-sided $p < 0.05$ was statistically significant.

3. Results

In 3,767 stage-IV NSCLC patients, 1,856 (49.3%) received systemic therapy. Among the remaining 1,911 (50.7%) patients who did not receive systemic therapy, 185 had surgery and 625 had radiation. Excluding 1,224 patients that were treated only with chemotherapy, immunotherapy, or concurrent chemoradiation. Six hundred and thirty-two (34.1%) of the 1856 patients were treated with targeted therapy. After excluding 99 patients without information on toxicity, 533 were included in the analyses (Figure 1): dermatologic toxicity occurred in 353/533 (66.2%), including 26/533 (4.9%) only non-rash, 193 (36.2%) only rash, 134 (25.1%) concurrent, other toxicity in 144 (27.0%), and none in 36

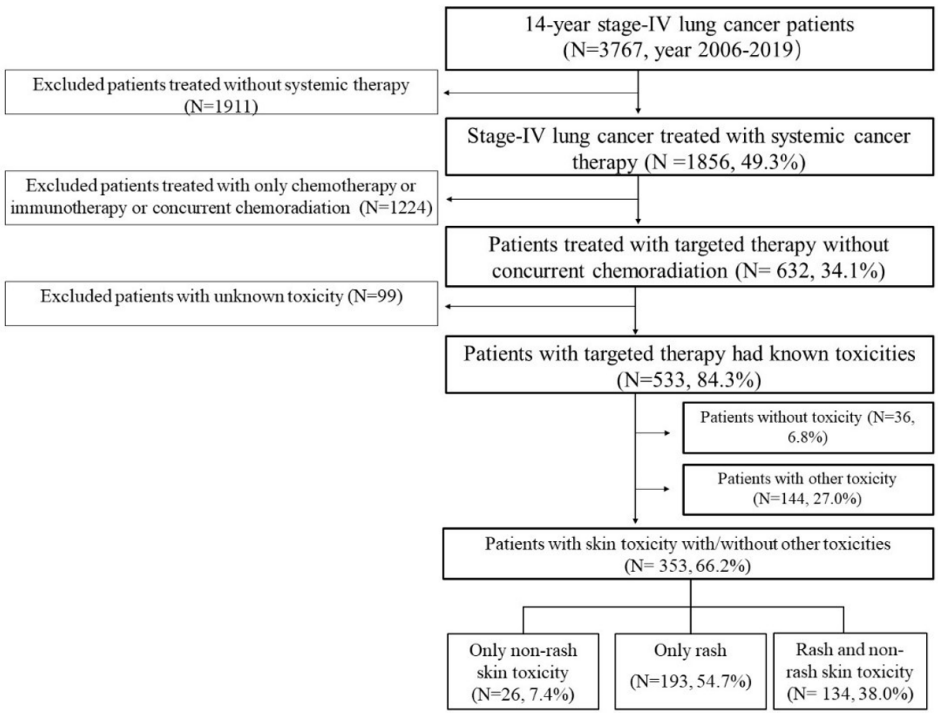


Figure 1. The flow chart for the study population with patient inclusion and exclusion criteria.

(6.8%). Of the 533 patients, the mean age (± SD) at lung cancer diagnosis was 62.4 (± 12.74) years, with 58.9% being female, 87.4% Whites, and 90.4% adenocarcinoma (Table 1). We observed that dermatologic toxicity was more frequent in *EGFR*+ than *EGFR*- patients (73.4% *vs.* 45.0%; $p < 0.001$). Among 353 patients with dermatologic reactions, 26/353 (7.4%) had only non-rash, 193 (54.7%) only rash, 134 (38.0%) concurrent (Supplemental Table S1, *https://www.biosciencetrends.com/action/getSupplementalData.php?ID=245*); concurrent dermatologic toxicity was more frequent in patients with EGFR+ than EGFR- tumors (44.0% *vs.* 22.0%, $p = 0.014$), and in those who received targeted therapy as the first-line treatment than other lines (45% *vs.* 30.8%, $p = 0.005$). A total of 727 dermatological events were observed among 353 patients; the frequencies (*n*, %) from the highest to the lowest were rash (432, 59.4%), xerosis (93, 12.8%), pruritus (62, 8.5%), paronychia (51, 7.0%), erythema (36, 5.0%), mucositis (12, 1.7%), nail changes (12, 1.7%) and others (30/727, 4.1%), predominately included dermatitis, skin pigmentation, and eyelash changes (Table 2A). When comparing the distribution of non-rash dermatologic toxicities, more patients had xerosis in the only non-rash dermatologic group (14/26, 53.8%) than those in the concurrent dermatologic group (68/134, 50.7%); conversely, more patients had pruritus (58/134, 43.3%), paronychia (31, 23.1%) and mucositis (7, 5.2%) in the concurrent dermatologic group compared with those in only the non-rash dermatologic group (both pruritus and paronychia 1/26, 3.8%; mucositis 0; $p = 0.003$).

In 353 patients with dermatologic toxicity, 348 (98.6%) had known severity of toxicity: 206/353 (59.2%) patients experienced grade 1 toxicity, 49 (14.1%) grade 2, 93 (26.7%) grade 3-4. Grade 1 toxicity was found in the most patients with only non-rash (76.0%), then those with only rash (62.4%), and the least in those with concurrent (51.5%) dermatologic toxicity, though significance did not reach the p-value threshold ($p = 0.069$). The incidence, severity, and onset days for the common dermatologic toxicities varied by drugs were identified (Table 3). Rash was found the earliest occurring (21 median onset days [MOD]) while paronychia the latest (69 MOD). A similar distribution of incidence, severity and onset time were observed in patients with *EGFR* inhibitors. The responsible drugs associated with the common dermatologic toxicities were scrutinized (Figure 2). Erlotinib (64.5%), then osimertinib (11.3%) and afatinib (11.1%) were preponderantly drugs associated with these dermatologic events but occurrence rates varied, Figure 2A. Rash occurred more frequently in erlotinib (66.5%) than in afatinib (58.9%) and osimertinib (44.8%); and paronychia was more associated with osimertinib (14.9%) and afatinib (10.7%) than erlotinib (4.0%), Figure 2B. Other non-skin toxicities mainly reported fatigue (14.0%), diarrhea (14.9%), nausea (10.8%), anorexia (5.7%), vomiting (4.1%) and anemia (3.4%) (Table 2B).

When looking into the 442 *EGFR* inhibitors-treated patients, 24 (5.4%) patients had none, 23 (5.2%) only non-rash dermatologic, 127 (28.7%) concurrent dermatologic, 179 (40.5%) only rash, and 89 (20.1%) other toxicities. Among them, more patients (315/442, 71.3%) had *EGFR*+ tumors. Dermatologic toxicity subgroup analysis showed patients with only non-rash (81.8%) were the most frequently observed grade 1 toxicity, then those with rash (64.8%), and the least in those with concurrent (50.4%, $p = 0.013$). In 63 patients treated with *ALK/ROS1* inhibitors, 6 (9.5%) patients had no toxicity, 2 (3.2%) only non-rash dermatologic toxicity, 3 (4.8%) concurrent dermatologic toxicity, 5 (7.9%) only rash and 47 (74.6%) other toxicities. *ALK* and *ROS1* mutations were identified in 41/63 (65.1%) and 4/63 (6.3%), respectively. Comparison of variables was limited by sample size.

Patients with dermatologic toxicity (52.3%) had similar ORR compared with those without (43.8%, $p = 0.127$). However, when focusing on dermatologic toxicity subgroups, we found patients with concurrent dermatologic (67.9%) had a significantly higher ORR than those with only non-rash dermatologic (53.8%) and only rash (41.1%, $p < 0.001$) toxicities. Similar differences were also identified in those with *EGFR* inhibitors ($p < 0.001$), indicating non-rash dermatologic toxicity was more likely to enhance the drug-efficacy predictor (Supplemental Table S2, *https://www.biosciencetrends.com/action/getSupplementalData.php?ID=245*). For all patients with targeted therapy, multivariable analysis showed patients in concurrent dermatologic toxicity group had longer median survival years (2.6 years) than those in other groups (1.5-1.9 years) and lower risk of death (HR 0.71, 95% CI [0.46-1.10], $p = 0.009$) adjusting for smoking status, cell type, treatment modality, treatment response and age (Supplemental Table S3, *https://www.biosciencetrends.com/action/getSupplementalData.php?ID=245*). Furthermore, when focusing on dermatologic toxicity subgroups, the concurrent group was an independent predictor of a lower risk of death (HR 0.48, 95% CI [0.30-0.77]) ($p < 0.001$, Figure 3A) adjusting for cell type, treatment modality, treatment response, and age (Table 4). Severity of drug-related dermatologic toxicities showed no correlation with drug efficacy. A similar association with dermatologic toxicity and survival benefits was found in anti-*EGFR* agents (Figure 3B). However, the limited amount of patients with anti-*ALK*/*ROS1* agents could not be used for Cox model analysis.

These results highlighted the importance of non-rash dermatologic toxicities in the drug-efficacy predictive value of dermatologic toxicities in targeted therapy-treated and *EGFR* inhibitors-treated patients. Concurrent dermatologic toxicity predicted a strengthened efficacy and longer survival.

Table 1. The characteristics of 533 patients with targeted therapy in five toxicity status groups

	Toxicity					Total (n = 533)	p value
	None (n = 36)	Only Non-rash (n = 26)	Non-rash and rash (n = 134)	Only rash (n = 193)	Other (n = 144)		
Age at diagnosis							0.955
Mean (SD)	62.8 (13.53)	63.0 (14.55)	62.9 (12.71)	62.3 (13.04)	61.9 (11.97)	62.4 (12.74)	
Median	65	65	64	63	64	64	
Range	29.0, 94.0	36.0, 84.0	31.0, 87.0	26.0, 86.0	34.0, 94.0	26.0, 94.0	
Sex, n (%)							0.709
0 = Female	18 (50.0)	14 (53.8)	81 (60.4)	112 (58.0)	89 (61.8)	314 (58.9)	
1 = Male	18 (50.0)	12 (46.2)	53 (39.6)	81 (42.0)	55 (38.2)	219 (41.1)	
Race, n (%)							0.923
White	31 (88.6)	24 (92.3)	116 (86.6)	166 (86.5)	126 (88.1)	463 (87.4)	
Other	4 (11.4)	2 (7.7)	18 (13.4)	26 (13.5)	17 (11.9)	67 (12.6)	
NA	1	0	0	1	1	3	
Smoking history, n (%)							0.451
Never	19 (52.8)	18 (69.2)	85 (63.4)	121 (62.7)	81 (56.3)	324 (60.8)	
Ever	17 (47.2)	8 (30.8)	49 (36.6)	72 (37.3)	63 (43.8)	209 (39.2)	
Cell type, n (%)							0.876
Adenocarcinoma	34 (94.4)	24 (92.3)	121 (90.3)	172 (89.1)	131 (91.0)	482 (90.4)	
Other	2 (5.6)	2 (7.7)	13 (9.7)	21 (10.9)	13 (9.0)	51 (9.6)	
Treatment modality, n (%)							0.846
Drug therapy	28 (77.8)	20 (76.9)	100 (74.6)	132 (68.4)	113 (78.5)	393 (73.7)	
Surgery & drug	1 (2.8)	1 (3.8)	8 (6.0)	12 (6.2)	6 (4.2)	28 (5.3)	
Surgery, rad, drug	1 (2.8)	0	4 (3.0)	4 (2.1)	3 (2.1)	12 (2.3)	
Radiation & drug	6 (16.7)	5 (19.2)	22 (16.4)	45 (23.3)	22 (15.3)	100 (18.8)	
Treatment line of targeted therapy, n (%)							0.004
First line	19 (52.8)	16 (66.7)	86 (64.2)	89 (47.1)	62 (44.0)	272 (51.9)	
Other	17 (47.2)	8 (33.3)	48 (35.8)	100 (52.9)	79 (56.0)	252 (48.1)	
NA	0	2	0	3	4	9	
EGFR mutation, n (%)							< 0.0001
Negative	12 (42.9)	5 (26.3)	11 (9.6)	34 (22.5)	49 (41.5)	111 (25.8)	
Positive	16 (57.1)	14 (73.7)	103 (90.4)	117 (77.5)	69 (58.5)	319 (74.2)	
ALK mutation, n (%)							
Negative	4 (40.0)	2 (100.0)	2 (33.3)	8 (72.7)	11 (28.2)	27 (39.7)	0.036
Positive	6 (60.0)	0	4 (66.7)	3 (27.3)	28 (71.8)	41 (60.3)	
ROS1 mutation, n (%)							
Negative	1 (100.0)	1 (100.0)	2 (100.0)	3 (60.0)	4 (57.1)	11 (68.8)	-
Positive	0	0	0	2 (40.0)	3 (42.9)	5 (31.3)	
Other genetic mutation, n (%)							
Negative	0	0	1 (20.0)	4 (57.1)	6 (50.0)	11 (42.3)	-
Positive	1 (100.0)	1 (100.0)	4 (80.0)	3 (42.9)	6 (50.0)	15 (57.7)	

Abbreviations: SD, standard deviation; *EGFR,* epidermal growth factor receptor; *ALK,* anaplastic lymphoma kinase; *ROS1,* c-ros oncogene 1.

Table 2 (A). The distribution of common dermatologic toxicities in patients with different type of drugs

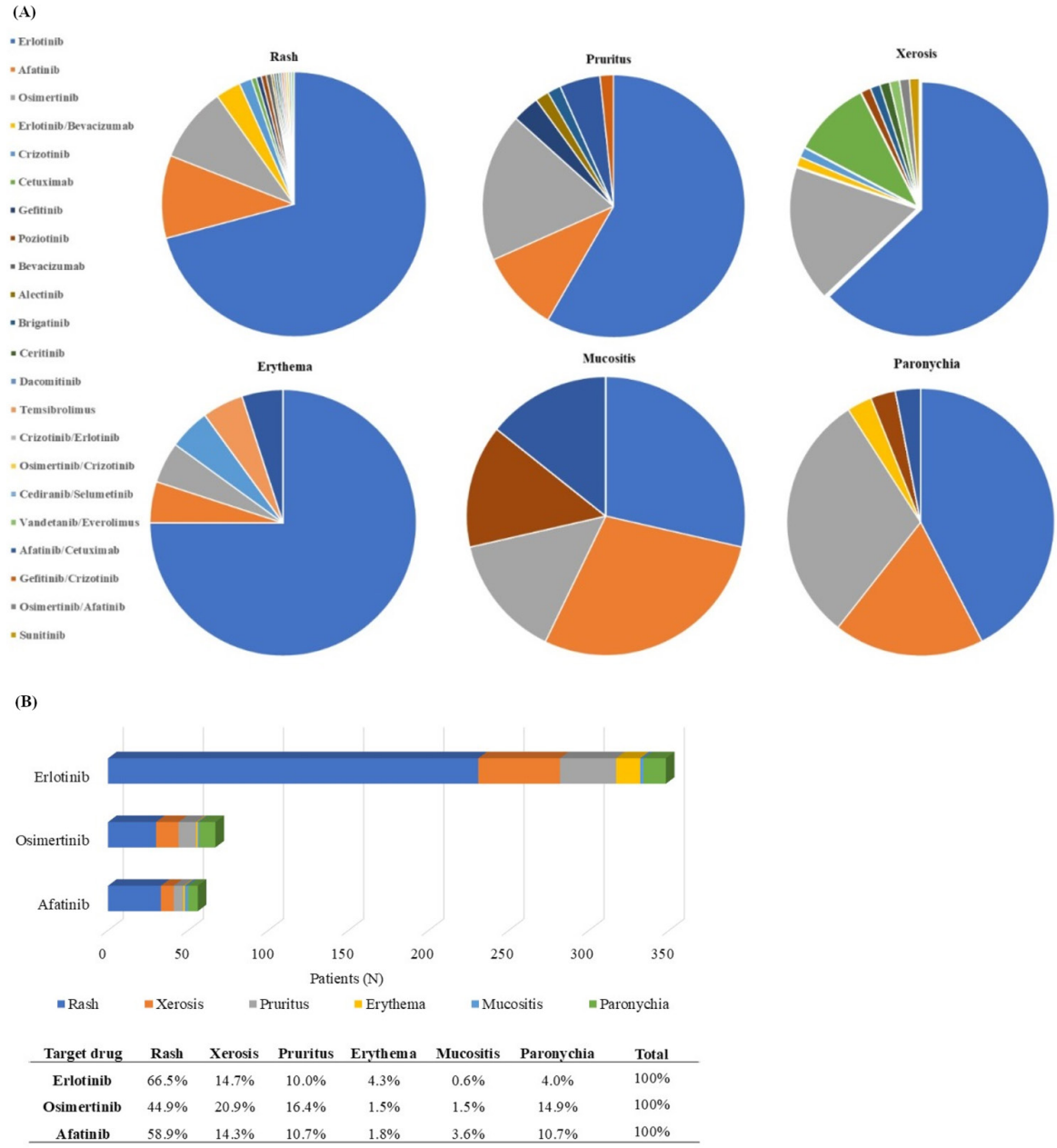
Most common toxicities (N*, %)	Target therapy N = 353 patients with 727 toxicities*	*EGFRIs* N = 329 patients with 681 toxicities*	*ALK/ROS1* inhibitors N = 10 patients with 40 toxicities*
Rash	432 (59.4)	403 (59.2)	27 (67.5)
Xerosis	93 (12.8)	87 (12.8)	7 (17.5)
Pruritus	62 (8.5)	60 (8.8)	4 (10.0)
Paronychia	51 (7.0)	51 (7.5)	0
Erythema	36 (5.0)	30 (4.4)	2 (5.0)
Mucositis	12 (1.7)	11 (1.6)	0
Nail changes	12 (1.7)	12 (1.8)	0

**N means the observed toxicities rather than the patient number. *Abbreviations*: EGFRIs, epidermal growth factor receptor inhibitors; ALK/ROS1, anaplastic lymphoma kinase/ c-ros oncogene 1.

Table 3. The incidence, severity, and onset days for skin toxicity in patients with different type of drugs

	Targeted therapy (*n* = 353)	*EGFR* inhibitors (*n* = 339)	ALK/ROS1 inhibitors (*n* = 10)
Rash, *n* (incidence, %)	327 (92.6)	306 (93.0)	8 (80.0)
Severity, *n* (%)			
Grade 1	170 (60.7)	161 (61.7)	4 (66.7)
Grade 2	44 (15.7)	43 (16.5)	1 (16.7)
Grade 3-4	65 (23.2)	56 (21.5)	1 (16.7)
NA	48	46	2
Onset days (median)	21	21	44
Xerosis, *n* (incidence, %)	82 (23.2)	76 (23.1)	3 (30.0)
Severity, *n* (%)			
Grade 1	45 (73.8)	41 (71.9)	3 (100.0)
Grade 2	4 (6.6)	4 (7.0)	-
Grade 3	12 (19.7)	12 (21.1)	-
NA	21	19	-
Onset days (median)	47	47	177
Erythema, *n* (incidence, %)	20 (5.7)	18 (5.5)	1 (10.0)
Severity, *n* (%)			
Grade 1	12 (75.0)	11 (73.3)	-
Grade 2	1 (6.3)	1 (6.7)	-
Grade 3	3 (18.8)	3 (20.0)	-
NA	4	3	-
Onset days (median)	30.5	28.5	109
Mucositis, *n* (incidence, %)	7 (2.0)	7 (2.1)	-
Severity, *n* (%)			
Grade 1	1 (20.0)	1 (20.0)	-
Grade 2	1 (20.0)	1 (20.0)	-
Grade 3	3 (60.0)	3 (60.0)	-
NA	2	2	-
Onset days (median)	34	34	-
Pruritus, *n* (incidence, %)	60 (17.0)	57 (17.3)	2 (20.0)
Severity, *n* (%)			
Grade 1	35 (74.5)	34 (77.3)	1 (50.0)
Grade 2	3 (6.4)	3 (6.8)	-
Grade 3	9 (19.1)	7 (15.9)	1 (50.0)
NA	13	13	-
Onset days (median)	36	34	163.5
Paronychia, *n* (incidence, %)	33 (9.3)	33 (10.0)	-
Severity, *n* (%)			
Grade 1	21 (84.0)	21 (84.0)	-
Grade 2	1 (4.0)	1 (4.0)	-
Grade 3	3 (12.0)	3 (12.0)	-
NA	8	8	-
Onset days (median)	69	69	-

Abbreviations: EGFR, epidermal growth factor receptor inhibitors; ALK/ROS1, anaplastic lymphoma kinase/ c-ros oncogene 1.



Target drug	Rash	Xerosis	Pruritus	Erythema	Mucositis	Paronychia	Total
Erlotinib	66.5%	14.7%	10.0%	4.3%	0.6%	4.0%	100%
Osimertinib	44.9%	20.9%	16.4%	1.5%	1.5%	14.9%	100%
Afatinib	58.9%	14.3%	10.7%	1.8%	3.6%	10.7%	100%

Figure 2. (A) The proportion of responsible drugs for skin toxicities. A total of 22 single agent or combined therapies were related to 6 primary skin toxicities. Erlotinib, afatinib and osimertinib were the most frequent associated drugs for rash, pruritus, erythema, mucositis, and paronychia. However, erlotinib, osimertinib and cetuximab were more common to cause xerosis. **(B)** The distribution and proportion of dermatologic toxicity in erlotinib, osimertinib, and afatinib. The skin toxicities had different distributions among the three predominate responsible drugs: rash was the most common skin toxicity and occurred more frequently in erlotinib (66.5%) than osimertinib (44.9%) and afatinib (58.9%), however, paronychia had a lower rate with erlotinib (4.0%) than osimertinib (14.9%) and afatinib (10.7%).

Table 2 (B). The distribution of common non-dermatologic toxicities in patients with different type of drugs

Most common toxicities (N*, %)	Target therapy N = 144 patients with 2,383 toxicities**	EGFRIs N = 89 patients with 1,857 toxicities**	ALK/ROS1 inhibitors N = 47 patients with 377 toxicities**
Fatigue	334 (14.0)	273 (14.7)	48 (12.7)
Diarrhea	355 (14.9)	321 (17.3)	36 (9.5)
Nausea	257 (10.8)	202 (10.9)	39 (10.3)
Anorexia	137 (5.7)	114 (6.1)	16 (4.2)
Vomiting	97 (4.1)	74 (4.0)	16 (4.2)
Anemia	81 (3.4)	60 (3.2)	17 (4.5)

**N means the observed toxicities rather than the patient number. *Abbreviations*: EGFRIs, epidermal growth factor receptor inhibitors; ALK/ROS1, anaplastic lymphoma kinase/ c-ros oncogene 1.

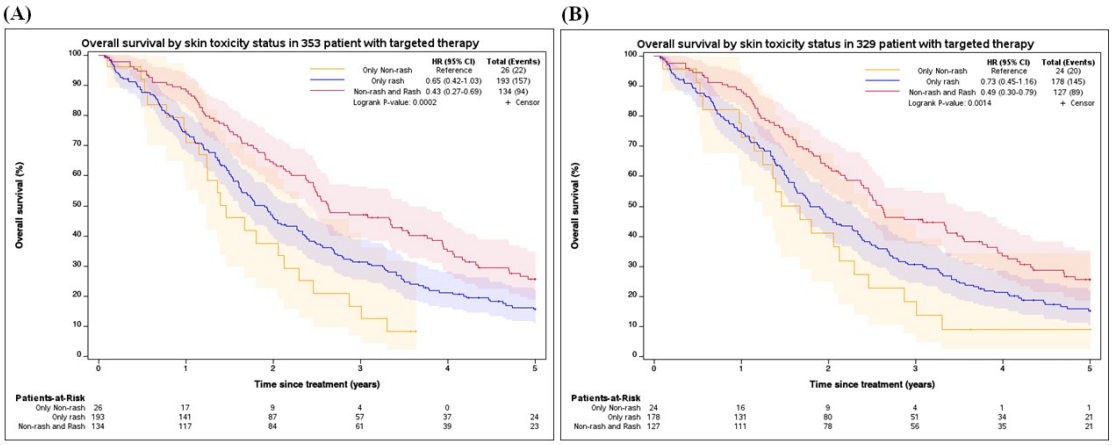


Figure 3. Kaplan-Meier curves of overall survival in targeted therapy-treated and *EGFR* inhibitors-treated patients with dermatologic toxicity respectively truncated at 5 years. (A) In all 353 targeted therapy-treated patients, patient with concurrent non-rash and rash had better survival than those with only non-rash or only rash dermatologic toxicity. **(B)** In 329 *EGFR* inhibitors-treated, patient with concurrent non-rash and rash had better survival than those with only non-rash or only rash dermatologic toxicity.

4. Discussion

Dermatologic toxicity is a commonly observed adverse effect of targeted therapy, reporting a frequency of 60.6% among NSCLC patients in our study. As is known, we observed that rash (59.3%) is the most frequent dermatologic toxicity associated with targeted therapy, consistent with that in the literature (*24*). Furthermore, we delineated the profile of non-rash dermatologic toxicities and discovered the strengthened prognostic predicting value of concurrent dermatologic toxicities in targeted therapy-treated patients.

Administration of targeted drugs is standard treatment for driver gene-mutated patients (*25*). Meanwhile, gene tests have become a routine recommendation by conventional methods, even novel next-generation sequencing for screening oncogenic targets (*26*). *EGFR* mutation is the most common targetable genetic driver alteration in lung adenocarcinoma, accounting for approximately 40% and 20% of NSCLC patients in Asian and non-Asia populations, respectively (*27*). Frequently administered *EGFR* inhibitors are divided into intracellular tyrosine kinase inhibitors (TKIs) and monoclonal antibodies inhibitors (mAbs) against the extracellular domain of *EGFR* (*28*). The main mechanism of *EGFR* inhibitors-related dermatologic toxicities is due to the prominent role of *EGFR* in maintaining dermatological homeostasis; *EGFR* inhibitors instigate pathological changes of growth and migration arrest and apoptosis, chemokine expression, and abnormal maturation and differentiation in skin cells, eventually, causing skin disorders (*29*).

In our study, dermatologic toxicity was mostly prevalent in erlotinib, afatinib, and osimertinib, which were typical three generations of EGFR tyrosine kinase inhibitors (EGFR-TKIs). To date, first-generation (gefitinib, erlotinib), second-generation (afatinib, dacomitinib), and third-generation (osimertinib) EGFR-TKIs are approved as standard management for sensitive *EGFR* mutations (*30*). The frequency of various dermatologic toxicities differed in first-, second-, third- generation of EGFR-TKIs in phase III trials were reported rash at 51.3%, 75.2%, 45.7%, stomatitis or mucositis at 11.2%, 27.5%, 21.7%, paronychia at 9.2%, 30.7%, 28.3%, respectively; additionally, xerosis occurred at 23%-36% in osimertinib and pruritus at 7% in gefitinib (*31*). Our results showed a higher frequency of rash in erlotinib than afatinib, and similar incidences of xerosis and pruritis with those in clinical trials. For non-dermatologic toxicities, most notably, diarrhea occurred at any grade (grade $\geq$ 3) was 45.3% (2.6%), 79.2% (6.8%), 49.1% (1.6%) for first-, second-, third-generation of EGFR-TKIs respectively, as validated by our study (*31*).

We validated that rash was the earliest occurring and most frequent dermatologic toxicity caused by *EGFR* inhibitors, and median onset time was in the range of 2-4 weeks (*32*). Further subgroup analysis on the patients showed that less patients had non-rash (7.4%) than only rash (54.7%) or concurrent (38.0%) dermatologic toxicities. More specifically, we found that pruritus, paronychia, and mucositis tended to occur with rash. Pruritus concurrent with rash may be related to the inflammatory response and probably increased keratinocyte expression in growth factors significant to mast cells (*33*). Paronychia is a disorder characterized by an inflammatory process involving the soft tissues around the nail (*34*), which emerged latest at a median onset 69 days in our study.

Although dermatologic symptoms induced by *EGFR* inhibitors appeared to be significantly correlated with poor quality of life and compliance (*35*), rash in *EGFR* inhibitors has been varied to be a surrogate biomarker of therapeutic efficacy and improved survival for *EGFR*-mutated patients (*36,37*) and validated our previous study (*14*). This study highlighted that non-

Table 4. The characteristics of 353 patients with targeted therapy in three dermatologic toxicity groups

Variable	*n*	Events (%)	Median Years	5-year survival % (95% CI)	Cox univariate hazard ratio (95% CI)	Cox univariate score *p* value	Cox multivariate hazard ratio (95% CI)	Cox multivariate likelihood ratio *p* value (*n* = 352)
Toxicity						< 0.001		< 0.001
Only Non-rash	26	22 (85)	1.5	8.4 (0, 19.6)	-		--	
Non-rash and Rash	134	94 (70)	2.6	27.7 (19.9, 35.6)	0.45 (0.28, 0.72)		0.48 (0.30, 0.77)	
Only rash	193	157 (81)	1.9	16.3 (11.0, 21.7)	0.70 (0.45, 1.09)		0.75 (0.48, 1.18)	
Sex						0.444		
0 = Female	207	174 (84)	2.3	21.9 (16.0, 27.7)	-			
1 = Male	146	126 (86)	2.0	17.8 (11.5, 24.1)	1.09 (0.87, 1.38)			
Race						0.670		
White	306	263 (86)	2.1	20.0 (15.4, 24.6)	-			
Other	46	36 (78)	2.3	21.7 (9.1, 34.4)	0.93 (0.65, 1.31)			
Ever smoke cigarettes						0.019		0.074
0 = Never	224	165 (74)	2.3	24.1 (18.3, 29.9)	-		-	
1 = Ever	129	108 (84)	2.0	13.3 (7.3, 19.4)	1.34 (1.05, 1.70)		1.26 (0.98, 1.62)	
Cell type						< 0.001		< 0.001
Adenocarcinoma	317	240 (76)	2.3	21.5 (16.8, 26.2)	-		-	
Other	36	33 (92)	1.3	8.3 (0, 17.4)	1.97 (1.37, 2.84)		2.04 (1.40, 2.96)	
Drug treatment/combination						< 0.001		< 0.001
Drug therapy	252	209 (83)	1.9	14.1 (9.7, 18.6)	-		-	
Drug therapy & other	101	64 (63)	3.3	34.8 (25.3, 44.3)	0.54 (0.41, 0.71)		0.57 (0.42, 0.75)	
Treatment line of targeted therapy, *n* (%)						0.011		0.087
First line	191	141 (74)	2.5	23.7 (17.5, 29.9)	-		-	
Other	156	129 (83)	1.8	15.0 (9.2, 20.8)	1.36 (1.07, 1.73)		1.24 (0.97, 1.60)	
Treatment response						< 0.001		< 0.001
Response	184	128 (70)	2.6	27.2 (20.6, 33.9)	-		-	
No response	168	145 (86)	1.6	12.4 (7.3, 17.5)	1.79 (1.41, 2.28)		1.53 (1.20, 1.96)	
Toxicity severity						0.937		
Mild	206	176 (85)	2.1	20.3 (14.6, 25.9)	-			
Moderate & Severe & life threatening	142	120 (85)	2.4	19.4 (12.6, 26.2)	1.01 (0.80, 1.27)			
Age at diagnosis	353	273 (77)	2.1	20.1 (15.8, 24.5)	1.017 (1.007, 1.027)	0.001	1.013 (1.003, 1.023)	0.010

rash dermatologic toxicity played a critical role in predicting better response to treatment when looking into the higher ORR in patients with concurrent (67.9%) or only non-rash (53.8%) dermatologic toxicities than those with only rash (41.1%). Furthermore, the relationship between dermatologic toxicity and survival analysis showed longer survival among patients with concurrent toxicity, providing more detailed evidence of targeted therapy-induced dermatologic toxicity predicting positive treatment response and OS benefit (*38*). Considering prevalence of non-rash dermatologic toxicity in the concurrent dermatologic toxicity group, rash with pruritus, paronychia or mucositis appeared to be associated with improved outcomes. Therefore, dermatologic toxicity as a drug-efficacy marker for patients with treated therapy called for further investigations to differentiate various toxicities, especially non-rash dermatologic toxicities.

ALK and *ROS1* define unique subsets of NSCLC patients highly sensitive to *ALK*/*ROS1* targeted drugs. However, *ALK*+ and *ROS1*+ have a low frequency of 1.7% and 2.9% among NSCLC patients, respectively (*39*). Therefore, only 63 patients who received *ALK*/*ROS1* inhibitors were included in our study. Dermatologic toxicity was uncommon in the toxicity profile of *ALK/ROS1* inhibitors. Rash was the primary complaint of dermatologic side effects, reporting rates of any grade (grade ≥ 3) at 8.4% in crizotinib, 14.7% (0.9%) in alectinib, 15.4% (0.7%) in brigatinib, 12.4% in ceritinib, 62.9% (8.0%) in ensartinib, 6.6% (0.2%) in lorlatinib (*40*). We found that *ALK/ROS1* inhibitors had a low incidence of dermatologic toxicity (15.9%), as reported in previous studies.

Due to the nature of back-reviewed information, clinical data unavoidably produced some bias, such as the inaccurately reported and recorded toxicity information, even though we have carefully defined each variable. Additionally, patients with unavailable or unjudgeable toxicity were not included because of outside medical records, less than one-month treatment duration and loss of follow-up, which might lead to underestimation of the occurrence and effects of dermatologic toxicity.

In conclusion, non-rash dermatologic toxicity appeared to be milder than rash compared to rash toxicity, but might be a stronger protective indicator for treatment response and survival length in patients who received targeted therapy or *EGFR* inhibitors. Severity of dermatologic toxicity showed no correlation with survival length. Oncologists and dermatologists need to collaborate effectively on the awareness, prevention, and treatment of dermatologic toxicity associated with targeted drugs.

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