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Retrospective Analysis of Skin Toxicity in Patients under Anti-EGFR Tyrosine Kinase Inhibitors: Our Experience in Lung Cancer

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Abstract

BACKGROUND: Tyrosine kinase inhibitors (TKIs) have been introduced for the treatment of lung cancer, improving progression-free survival, objective response rate, and quality of life. However, TKIs can lead to cutaneous toxicities, including papulopustular rash, xerosis, paronychia with/without pyogenic granulomas, scalp disorders, facial hair and/or eyelash growth.

AIM: In this study, we describe retrospectively all cases of mucocutaneous side effects in patients with lung cancer under TKIs referring to our outpatient for the skin care of oncological patients.

METHODS: We included patients referring from January 2016 to January 2018 affected by lung cancer and under TKIs. We collected data about the clinical exam, clinical photography, dermoscopy, histology and direct microscopic examination for each patient and we performed retrospectively descriptive analyses to assess whether a specific TKIs is linked significantly to particular cutaneous toxicity.

RESULTS: The majority of skin toxicities were due to afatinib, and the most common skin reaction was rash. We selected 60 patients with skin reactions, treated by TKIs for lung cancer. The majority of skin toxicities were due to afatinib (47/102 adverse reactions) and erlotinib (39/102). The most common skin reaction was rash (63% of patients), followed by xerosis (30%) and granulomas (30%). There was no significant relationship between a specific type of cutaneous reaction and specific EGFRi except for granulomas, developed more frequently in patients under afatinib ($p < 0.05$).

CONCLUSION: Most of our patients (63%) developed a cutaneous rash under TKIs. Most commonly afatinib was the drug involved, although it wasn't the most used EGFRi. Moreover, we noticed a significant correlation between afatinib therapy and appearance of granulomas.

Introduction

According to WHO data, lung cancer is the most common cause of cancer mortality (1.69 million deaths) [1].

The introduction of new therapeutic agents, with a different mechanism of action respect to traditional chemotherapy, led to a dramatic shift in patients' management [2]. In the last decades, several chemotherapeutic agents including target therapy have been introduced in the guidelines, impressively improving the survival rate of patients with lung cancer. Nowadays tyrosine kinase inhibitors (TKIs) have transformed the treatment of lung cancer, improving progression-free survival, objective response rate, and quality of life [3]. To date, three generations of TKIs are available: the first one includes gefitinib, erlotinib and icotinib; the second one afatinib, neratinib and dacomitinib; and the third one osimertinib, rociletinib and olmutinib [2].

However, TKIs can lead to several side effects. Skin toxicities are the most common and earliest reported. [4] Among them, papulopustular rash, xerosis, paronychia with/without pyogenic granulomas, scalp disorders, facial hair and/or eyelash growth frequently occur [5].

Studies suggest that cutaneous specificity for TKIs -associated adverse reactions might be due to the strong expression of EGFR [6] and to the multiple regulatory functions of EGFR/ligand system in the epidermis [7].

Currently, no studies exclusively on cutaneous toxicity of EGFRi in patients affected by lung cancer are available in recent literature.

Our study aims to describe retrospectively all cases of mucocutaneous side effects in patients with lung cancer under TKIs referring to our outpatient for the skin care of oncological patients.

Material and Methods

From January 2016 to January 2018, 263 patients referred to our outpatient for cutaneous side effects from oncological therapy. Seventy-six patients had lung cancer, and 60 of them were treated by TKIs (25 erlotinib, 22 afatinib, 10 gefitinib and 3 osimertinib). We excluded patients already suffering from mucocutaneous symptoms at the beginning of chemotherapy. All data were collected from the computerised database of our department.

We collected data about the clinical exam, clinical photography, dermoscopy, histology and direct microscopic examination results for each patient.

The analysed data also included personal and clinical characteristics such as gender, age, type of lung cancer, therapeutic agent, site and clinical presentation of skin reaction.

We performed retrospective descriptive analyses, and we classified data by patients' clinical characteristics, types of lung cancer, treatment and adverse reactions. The study was conducted by ethical guidelines and providing informed consent from the subjects enrolled.

Statistical analysis

We carried out statistical analysis to assess whether a specific EGFRi is linked significantly to particular cutaneous toxicity. We excluded patients treated with osimertinib because of the insufficient sample size.

Categorical variables were reported as absolute number and percentage and compared using the exact chi-square test. A two-tailed P-value < 0.05 was considered significant. Data were analysed using SAS version 9.4 (SAS Inc, Cary, NC).

Results

We selected 60 treated by TKIs of 76 patients with lung cancer and skin reactions.

A group of 31/60 were males (51.67%), and 29/60 (48.33%) were females. Patients aged from 41 to 80 years (mean age 64.60 ± 10.85 DS). The lung cancer type diagnosed was: 41/60 (68.33%) adenocarcinoma, 6/60 (10.00%) squamous cell carcinoma, 6/60 (10.00%) Small Cell Lung cancer (SCLC) and in 7/60 (11.67%) patients the lung cancer type was not specified nor included in the previous categories.

The most frequent TKIs were erlotinib (25/60, 41.67%) followed by afatinib (22/60, 36.66%) Table 1.

Table 1: Characteristics of patients included in our analysis

Sex	Mean age (years ± DS)	Cancer type	Treatment
31 M (51.67%)	64.60 ± 10.85	41 adenocarcinoma	25 erlotinib
29 F (48.33%)		6 squamous cell carcinoma	22 afatinib
		6 SCLC	11 gefitinib
		7 other or not specified	2 osimertinib

The majority of skin toxicities were due to, in order of frequency: afatinib (47 reported adverse reactions), erlotinib (39), gefitinib (13) and osimertinib (3). The most common skin reaction was rash (63% of patients), followed by xerosis (30%), granuloma (30%), mucositis (18%), psoriasis (8%), fingertips fissures (7%), itching (5%). Alopecia (5%), hand-foot syndrome (2%), and trichomegaly (2%) (Figure 1).

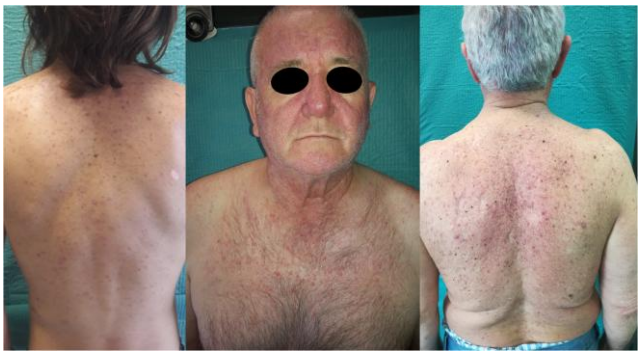

Figure 1: Papulo-pustular rash under EGFRi in its typical localization (trunk and head)

Data and frequency distribution are reported in Table 2.

Table 2: Frequency of adverse cutaneous events related to TKIs' administration

	Erlotinib 25 patients	Afatinib 22 patients	Gefitinib 11 patients	Osimertinib 2 patients	Total ADR/reaction	% ADR/patient
Rash	14 (56%)	17 (77%)	6 (55%)	1 (50%)	38	63%
Xerosis	7 (28%)	7 (32%)	4 (36%)	0 (0%)	18	30%
Granuloma	6 (24%)	11 (50%)	1 (9%)	0 (0%)	18	30%
Psoriasis	3 (12%)	2 (9%)	0 (0%)	0 (0%)	5	8%
Mucositis	2 (8%)	7 (32%)	1 (9%)	1 (50%)	11	18%
Pruritus	1 (4%)	1 (5%)	0 (0%)	1 (50%)	3	5%
Fingertips fissures	2 (8%)	2 (9%)	0 (0%)	0 (0%)	4	7%
Alopecia	3 (12%)	0 (0%)	0 (0%)	0 (0%)	3	5%
Hand-foot syndrome	0 (0%)	0 (0%)	1 (9%)	0 (0%)	1	2%
Trigomegaly	1 (4%)	0 (0%)	0 (0%)	0 (0%)	1	2%
Total ADR/drug	39	47	13	3		

Statistical data revealed that there was no significant relationship between a specific type of cutaneous reaction and specific EGFRi except for granulomas, appearing significantly more frequently in patients under afatinib ($p < 0.05$).

Statistical data are reported on Table 3.

Table 3: Statistical analysis

	Rash	Xerosis	Granuloma	Psoriasis	Mucositis	Pruritus	Fingertips fissures	Alopecia	Hand-Foot Syndrome	Trichomegaly
Erlotinib 25 patients	14 56%	7 28%	6 24%	3 12%	2 8%	1 4%	2 8%	3 12%	0 0%	1 4%
Afatinib 22 patients	17 77%	7 32%	11 50%	2 9%	7 32%	1 5%	2 9%	0 0%	0 0%	0 0%
Gefitinib 11 patients	6 55%	4 36%	1 9%	0 0%	1 9%	0 0%	0 0%	0 0%	1 9%	0 0%
p-value	0,268	0,932	0,037	0,620	0,076	0,999	0,679	0,214	0,190	0,999

Discussion

In our study, the rash was the most common dermatological side effects reported (38 patients), followed by xerosis (18), granuloma (18), mucositis (11), psoriasis (5). Our data showed that only a few patients complaint of fingertips fissures (4), pruritus (3), alopecia (3). Only one patient developed hand-foot syndrome and another one trichomegaly.

The majority of skin toxicities were due to afatinib (47 reported adverse reactions), erlotinib (39), gefitinib (13) and osimertinib (3).

Afatinib was the drug causing more adverse reactions although it wasn't the most used therapy in our patient's sample, confirming *Derrick Chen-Wee Aw et al.* review data [8].

In our experience, no statistical difference linking a type of cutaneous reaction and specific EGFRi were observed except for granulomas.

The majority of anti-cancer drugs can induce rash because they act on rapidly growing cells and hence the skin, but also hair follicles and nail matrix. TKIs may interfere in the epidermal structure, antimicrobial and inflammatory response, leading to dysfunction of normal epidermal barrier and dysregulated cytokines patterns [4].

A papulopustular eruption is the most frequent side effect of anti-EGFR drugs reported in the literature. The eruption may be asymptomatic or accompanied by pruritus, and it tends to improve over time despite the continuation of therapy. It is generally distributed in the seborrheic areas, where EGFR is more expressed [9].

The incidence of rash from TKIs observed in our study is similar to those of several clinical studies: it is more frequent in first or second generation TKIs (44.73% of rash due to afatinib, 36.84% in erlotinib, 15.78% in gefitinib), when compared with third-generation TKI treatment (2.63% in osimertinib) [9], [10].

As already reported by Derrick Chen-Wee Aw et al., our study confirms that afatinib causes rash more frequently than erlotinib, gefitinib and osimertinib [8], [11]. We only had two patients under osimertinib therapy, and one of them developed a rash (50% of total patients), but we cannot conclude that osimertinib causes rash as frequently as first or second generation TKIs since our data were conducted on a few numbers of patients.

In our study, we observed xerosis in 18 patients (7 afatinib and erlotinib, 4 gefitinib). Comparing to Derrick Chen-Wee Aw et al., we didn't find xerosis in the two patients treated with osimertinib, but we cannot consider our percentage statistically significative for the limited number of patients. The rate of body surface area involved can be variable like also the time of onset that can variate from 15 days to 60 days [12].

Xerosis, also known as xeroderma or dry skin, can occur independently or associated with other adverse reactions, particularly pruritus [13].

In our study, pruritus was found in three patients (1 afatinib, 1 erlotinib and 1 osimertinib), but no patient treated with gefitinib complaint of itching. Our results disagree partially with published literature since we didn't observe gefitinib-induced pruritus [8].

A unique common site of xerosis is the fingertips, especially in patients treated with EGFR inhibitors. Dry fingertips commonly prove in pulpitis with painful fissures [9]. In literature, the incidence is 18-25% and the onset time is around 30-60 days [12]. In our study, fingertips xerosis with fissures was seen in 4 cases, two treated with afatinib and two with erlotinib, in agreement with already reported severe cases of pulpitis sicca and painful rhagades [8].

From 4% through 56.8% of patients under TKI can present nails changes, including paronychia, painful fissures, swelling, and noninfectious granuloma [12], [14]. In our experience, we have reported granulomas in 18 patients, and we found that, together with xerosis, the periungual involvement is the second most frequent adverse reaction in patients under TKIs. Our statistical data show that afatinib causes more frequently granulomas.

Psoriasis, both with diffuse or localised involvement of the skin, has been often reported in literature during anti-cancer treatment.

We observed psoriasis in two patients treated with afatinib and in three treated with erlotinib; all of these patients were affected in the scalp area. In literature, there are some contrasting data: there are case reports that describe the positive effect of EGFR inhibitors in psoriasis. Overbeck presented cases of patients with psoriasis treated with tyrosine kinase inhibitors; instead, Zorzou observed that psoriasis

recurred after treatment with anti-EGFR [15], [16].

Mucositis has also been reported with TKIs, more frequently with the second generation of TKIs than the first one. Incidence of mucositis induced by afatinib varies from 29 to 64%, while mucositis induced by erlotinib and gefitinib ranges between 8 and 20% and 19 to 24%, respectively [17]. We observed 11 cases (7 afatinib, 2 erlotinib, 1 gefitinib and osimertinib) and our results confirm that mucositis is more frequently reported with second-generation TKIs than the others.

TKIs can induce hair changes such as hair loss (scarring or non-scarring alopecia), scalp inflammation or hirsutism including hair rigidity and curling, trichomegaly and facial hypertrichosis [8]. In literature, it was reported that TKIs cause androgen-like frontal alopecia with progressive growth of facial hair and eyelashes, more evident in female patients [18], [9]. In our study, alopecia has been reported in three female patients treated with erlotinib, and one of them also showed trichomegaly of the malar region.

Hand-foot syndrome (HFS) or Erythrodysesthesia by TKi has been rarely reported in the literature [19], [20]. In our study, this reaction was found in only one patient treated with gefitinib and not exposed to precedent therapy, contrary to 'recall reactions' which Razis et al., consider in patients previously treated with liposomal doxorubicin and then with gefitinib [19].

Pigmentation disorders (hypo- and hyperpigmentation) [21] photosensitivity and also telangiectasia [22] have been reported, but, hereinbefore, we didn't find these dermatologic toxicities in our patient sample.

Limitations of the study

The main limitation of our study was the limited sample size that leads us to exclude osimertinib in the statistical analysis. Moreover, we cannot conclude completely that there is no association between type of EGFRi and skin reactions, but it's a good start point of view for future guidelines. Future studies should include a higher number of patients treated with different EGFRi.

We can conclude that 63% of our patients presented rash, most commonly those treated by afatinib, although it wasn't the most used EGFRi. Moreover, we noticed a significant correlation only between afatinib therapy and appearance of granulomas.

It is already known that skin reactions occur with different severity and frequency for each drug.

Cutaneous EGFRi-induced side effects, generally classified as moderate, may become chronic, impacting patient's quality of life and requiring therapy reduction or even interruption [23]. As a consequence, the appearance of an adverse reaction may compromise treatment efficacy and cancer response [24].

So, we assume that the knowledge and the correct management of drug reactions are important to prevent their appearance and to avoid unnecessary interruption of drugs, especially of those giving a higher survival rate to oncological patients.

The management of cutaneous toxicities in lung cancer patients should also include patient and family support, self-esteem maintenance and quality of life improvement for 360-degree patient care.

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