Article published online: 2025-10-30

Hospital-Based Observational Study of Mucocutaneous Adverse Reactions of Tyrosine Kinase Inhibitors

Sona C. Gowda[1] Tonita Mariola Noronha[1] Vijith Shetty[2]

[1] Department of Dermatology, K.S. Hegde Medical Academy, NITTE (Deemed to be University), Mangalore, Karnataka, India
[2] Department of Medical Oncology, K.S. Hegde Medical Academy, NITTE (Deemed to be University), Mangalore, Karnataka, India

Ind J Med Paediatr Oncol

Address for correspondence Sona C. Gowda, MD-DVL, Department of Dermatology, K.S. Hegde Medical Academy, NITTE (Deemed to be University), Mangalore, Karnataka 575018, India (e-mail: sonacgowda@gmail.com).

Tonita Mariola Noronha, MD-DVL, Department of Dermatology, K.S. Hegde Medical Academy, NITTE (Deemed to be University), Mangalore, Karnataka, India (e-mail: tones1980@yahoo.com).

Abstract

Introduction Tyrosine kinase inhibitors (TKIs), although considered less toxic than conventional chemotherapy, are not short of adverse drug reactions (ADRs). Cutaneous toxicities are among the most frequently reported ADRs; when severe, they can cause substantial morbidity, often requiring dose reduction or drug cessation.

Objectives 1. To estimate the frequency and pattern of mucocutaneous adverse reactions of TKI. 2. To grade the adverse reactions based on the severity scale of CTCAE v 5.0.

Materials and Methods This was a hospital-based observational study of 105 patients on TKI chemotherapy, attending the outpatient departments of dermatology and medical oncology, at Justice K.S. Hegde Charitable Hospital, Mangalore, from October 1, 2022, to April 30, 2024. Mucocutaneous adverse reactions after the initiation of TKI were recorded and graded according to the severity scale of CTCAE v 5.0. and causality was assessed using WHO-UMC criteria.

Results Among 105 patients, a majority of 34 (32.4%) patients belonged to the age group of 51 to 60 years, with a male predominance of 2:1. The most frequent cancer was lung in 38 (36.2%) patients, followed by CML in 21 (20.0%) patients. The most common class of TKI agent used was EGFR inhibitors in 51 (48.6%) patients, with gefitinib being the most common TKI agent in 46 (43.8%) patients. The most frequently reported ADRs were xerosis in 45 (42.9%) patients, followed by eczematous changes in 37 (35.2%) patients. The papulopustular rash was most commonly seen with EGFR inhibitors in 25 (49.0%) patients, eczematous changes with *BCR–ABL* inhibitors in 14 (50.0%), and hand–foot skin reaction with multikinase inhibitors in 12 (54.4%) patients. A statistically significant association was noted between papulopustular rash and paronychia among patients on EGFR inhibitors. Additionally, a statistically significant association was noted between hand–foot skin reaction and subsequent dose reduction.

Conclusion An awareness regarding the various ADRs of TKIs and interdisciplinary cooperation between oncologists and dermatologists will help in precise diagnosis and early identification of various cutaneous toxicities.

Keywords
- adverse drug reactions
- tyrosine kinase inhibitors
- EGFR inhibitors
- targeted chemotherapy

DOI https://doi.org/10.1055/s-0045-1812854.
ISSN 0971-5851.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

Introduction

Cancer chemotherapy is rapidly evolving from conventional intravenous cytotoxic agents to a class of newer molecular targeted therapies, namely tyrosine kinase inhibitors (TKIs). Targeted therapies are not short of adverse drug reactions (ADRs), and cutaneous toxicities are among the most frequently reported side effects, which, when severe, can lead to substantial morbidity, necessitating dose reduction or drug cessation.[1]

The FDA approved imatinib for the treatment of CML in 2001, following its discovery in 1998 that prevented the proliferation of the BCR–ABL oncogene. This marked the debut of TKIs in cancer chemotherapy.

1. *BCR–ABL* inhibitors include imatinib, dasatinib, and nilotinib.
   Imatinib was the first TKI that was specifically designed to inhibit the tyrosine kinases c-KIT in gastrointestinal stromal tumors (GIST), *BCR–ABL* in CML, and several PDGFRs in various malignancies. It has demonstrated effectiveness in treating AIDS-related Kaposi's sarcoma, Ph+ ALL, hypereosinophilic syndrome, and metastatic dermatofibrosarcoma protuberans.[2]
   Cutaneous ADRs of imatinib therapy have been noted in 7 to 88.9% of patients across various datasets. Although they can occur at any dosage, ≥600 mg/day is frequently the dosage at which they manifest.[3] Because imatinib has a relatively low MW, the drug's pharmacological action rather than its immunogenicity is principally responsible for cutaneous side effects.[4]
   According to the study of 54 patients by Valeyrie et al,[5] the various cutaneous ADRs include erythematous maculopapular rash (in 66.7% of patients), eyelid edema (in 65% of patients), lichenoid reaction, psoriasiform rash, follicular mucinosis, pityriasis rosea-like eruption, and vasculitis.
2. EGFR inhibitors are classified as:
   - First generation: gefitinib, erlotinib, icotinib, lapatinib, vandetanib.
   - Second generation: afatinib, canertinib, dacomitinib, neratinib, pelitinib.
   - Third generation: osimertinib, avitinib, rociletinib, naquotinib, olmutinib.[6]

   Gefitinib: Following the failure of both docetaxel and platinum-based therapy, the FDA authorized gefitinib for the treatment of locally progressive or metastatic NSCLC.[2]
   Erlotinib: The FDA has authorized erlotinib for the treatment of locally progressive or metastatic NSCLC following the failure of at least one prior chemotherapy regimen. For pancreatic cancer that is metastatic, locally advanced, or incurable, it is also authorized when coupled with gemcitabine.[2]
   Lapatinib: The FDA approved lapatinib, the first dual inhibitor of HER2 and EGFR tyrosine kinases, to be used in conjunction with capecitabine for patients with overexpressed HER2 in advanced or metastatic breast cancer who have previously received treatment with anthracycline, taxane, and trastuzumab.[7]
3. *Multikinase or angiogenesis inhibitors* include sunitinib, sorafenib, and lenvatinib.
   Sunitinib targets the following receptors: CSF-1R, FLT3, RET, PDGFR, c-KIT, and VEGFR (-1,2,3). It is authorized by the FDA to treat GIST in individuals who do not respond well to imatinib or who are experiencing progression of the disease. In addition, it is also indicated for advanced or metastatic RCC and unresectable or metastatic pNETs.[8]
   Sorafenib is a dual-action MKI that inhibits angiogenesis and proliferation of tumor cells by targeting the tyrosine kinases VEGFR-2 and -3, PDGFR, and RAF kinase. It has been granted FDA authorization for the treatment of advanced RCC and unresectable HCC.[9]
   Lenvatinib targets proto-oncogenes such as RET, KIT, VEGFR (1-3), FGFR (1-4), and PDGFR-α. The FDA has authorized it for the treatment of differentiated thyroid cancer, unresectable HCC, advanced RCC, and advanced endometrial carcinoma.[10]

Materials and Methods

This was a hospital-based observational study conducted at Justice K.S. Hegde Charitable Hospital, Mangalore, from October 1, 2022, to April 30, 2024. According to the study by Naveed et al,[11] assuming a 95% confidence interval, the prevalence of at least one cutaneous ADR ($p = 84.51\%$) and an absolute precision of 7%, the sample size estimated for the study was 105. A convenience sampling method was used in this study. One hundred and five patients on TKI who presented with mucocutaneous adverse reactions and attended the outpatient departments of dermatology and medical oncology in the hospital were studied.

After obtaining informed written consent, a detailed history, general physical examination, systemic examination, and dermatological examination were carried out on all patients. All the relevant findings were recorded on a proforma (►**Supplementary Material**, available in the online version only), and adverse reactions were appropriately graded according to the severity scale of Common Terminology Criteria for Adverse Events (CTCAE) v 5.0.[12] Causality was assessed using the World Health Organization—Uppsala Monitoring Centre's WHO–UMC criteria.[13]

Inclusion criteria: Patients of both genders, diagnosed with cancer undergoing chemotherapy with TKI, presenting with mucocutaneous adverse reactions.

Exclusion Criteria

1. Patients having cutaneous manifestations because of internal malignancies.
2. Patients having cutaneous manifestations attributed to radiation therapy.
3. Patients already having cutaneous symptoms or infections before the initiation of TKI.
4. Patients on monoclonal antibodies.

Objectives

1. To study the incidence, distribution, severity, and dose dependence of mucocutaneous adverse reactions of TKI.
2. To estimate the frequency and pattern, and to grade the adverse effects based on the severity scale of CTCAE version 5.0.

Statistical analysis: The data were tabulated in an MS Excel worksheet, and descriptive statistics were expressed in terms of mean (±standard deviation) for continuous data and frequency (percentage) for categorical data. The data were analyzed using SPSS software version 25. A *p*-value of <0.05 was considered statistically significant.

Ethics: Ethical clearance was obtained from the Institutional Ethics Committee, KS Hegde Medical Academy, Mangalore, INST.EC/EC/103/2022 on July 5, 2022. This study was in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Results

Of 105 patients on TKI, 35 (33.3%) were females and 70 (66.7%) were males with a male-to-female ratio of 2:1. A majority of 34 (32.4%) patients were aged between 51 and 60 years. The average age was recorded as 55.20 ± 11.82 years. Lung cancer 38 (36.2%) was the most common cancer, followed by CML 21 (20%). The frequency of distribution of various cancers is depicted in ►**Fig. 1**.

A majority of 51 (48.6%) patients received EGFR inhibitors, with gefitinib being the most frequently used TKI agent in 46 (43.8%) patients. The distribution of patients based on the TKI agent received is shown in ►**Fig. 2**.

►**Fig. 3** shows the various mucocutaneous adverse reactions of TKI agents. Xerosis was the most common ADR, seen in 45 (42.9%) patients, with 40 (88.8%) patients having grade 1 disease, while the remaining 5 (11.2%) had grade 2. Gefitinib was the most common TKI agent, accounting for xerosis in 18 (40.0%) patients (►**Fig. 4**).

This was followed by eczematous changes in 37 (35.2%) patients, with seborrheic dermatitis being the most common type seen in 7 (18.9%) patients. They were most frequently reported with imatinib, affecting 13 (35.1%) patients. Forty (88.8%) patients had grade 1 disease, while the remaining 5 (11.2%) had grade 2.

Papulopustular rash occurred in 27 (25.7%) patients, out of which 23 (85%) patients had gefitinib as the TKI agent (►**Figs. 5** and **6**). Twenty-two (81.5%) patients had grade 1, and 5 (18.5%) had grade 2 rash. Among EGFR inhibitors, a statistically significant association ($p = 0.001$) was noted between papulopustular rash and paronychia (►**Table 1**).

Maculopapular rash occurred in 16 (15.2%) patients and was most frequently seen with imatinib in 9 (56.3%) patients. Fourteen (87.5%) patients had grade 1 rash, while 2 (12.5%) had grade 2.

Nail changes were reported in 29 (27.6%) patients, of which 4 had nail discoloration, and 11 had nail ridging. Of 29 patients with nail changes, a majority of 15 (51.7%) patients were on EGFR inhibitors. Seventeen patients reported paronychia, with 12 cases being acute and 5 chronic (►**Fig. 7**).

Pigmentary changes were reported in 23 (21.9%) patients, with hyperpigmentation in 17 (73.9%) and hypopigmentation in 6 (26.1%) patients. Imatinib was the most common TKI agent, causing pigmentary changes in 11 (47.8%) patients (►**Fig. 8**). ►**Table 2** shows the various patterns of hyperpigmentation.

Hand–foot skin reaction (HFSR) was reported in 14 (13.3%) patients, of which 8 (57.1%) had grade 1 HFSR, while 6 (42.9%) had grade 2 HFSR. Of 14 (13.3%) patients with HFSR, 11 (78.6%) patients had a dose reduction, and 3 (21.4%) patients did not (►**Figs. 9** and **10**). A highly statistically significant association ($p \leq 0.001$) was noted between the HFSR and a subsequent dose reduction.

Seventeen (16.2%) patients reported mucosal changes, of which 16 had oral mucosal changes (►**Table 3**; ►**Fig. 11**). One had genital mucosal changes (seen as candidiasis).

Seventeen (16.2%) patients reported infections, with 8 patients having bacterial infections (pyoderma), and 9 having fungal infections, including 2 with candidiasis and 7 with intertrigo (►**Fig. 12**).

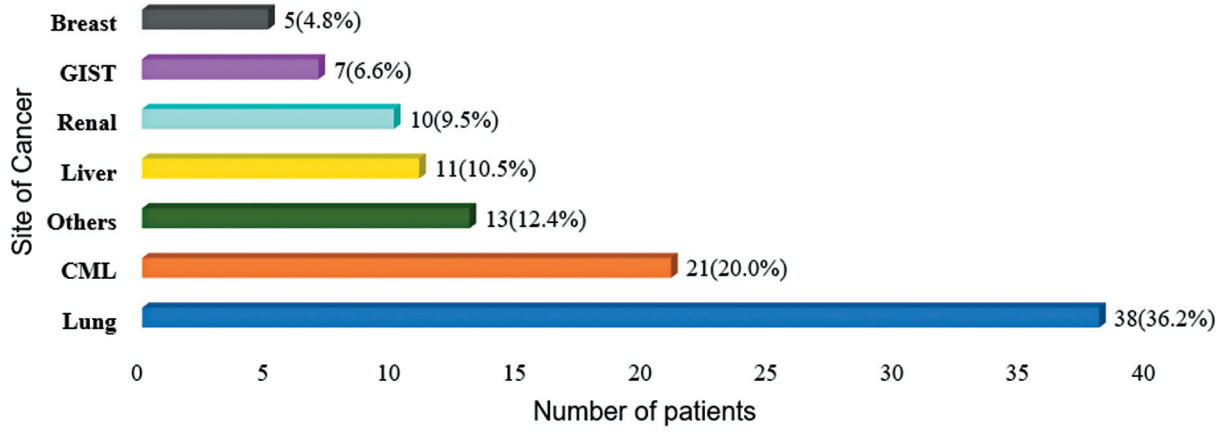

Fig. 1 Frequency of distribution of various cancers.

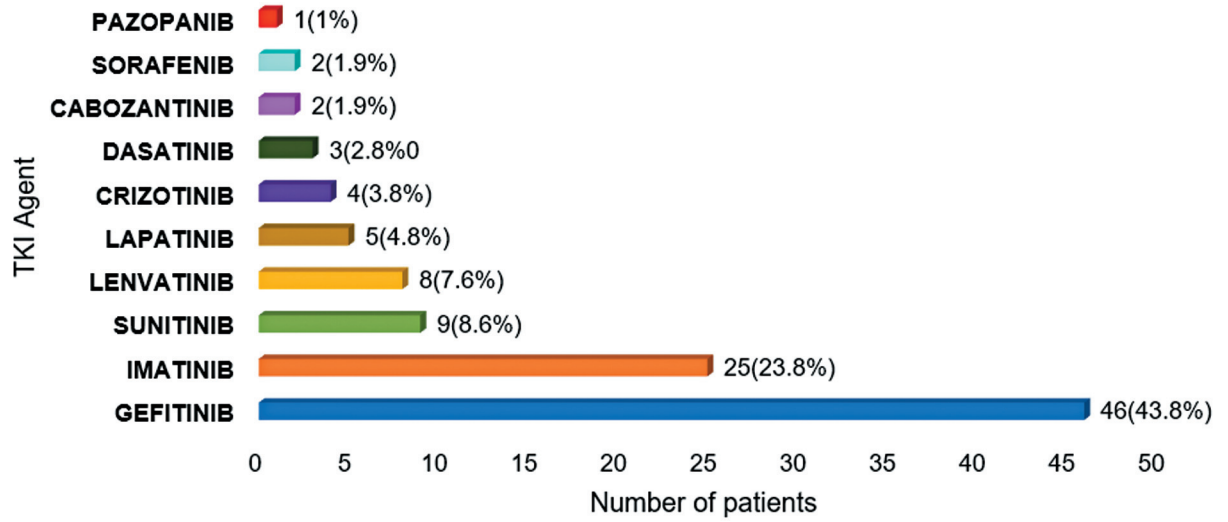

Fig. 2 Distribution of patients based on the TKI agent received.

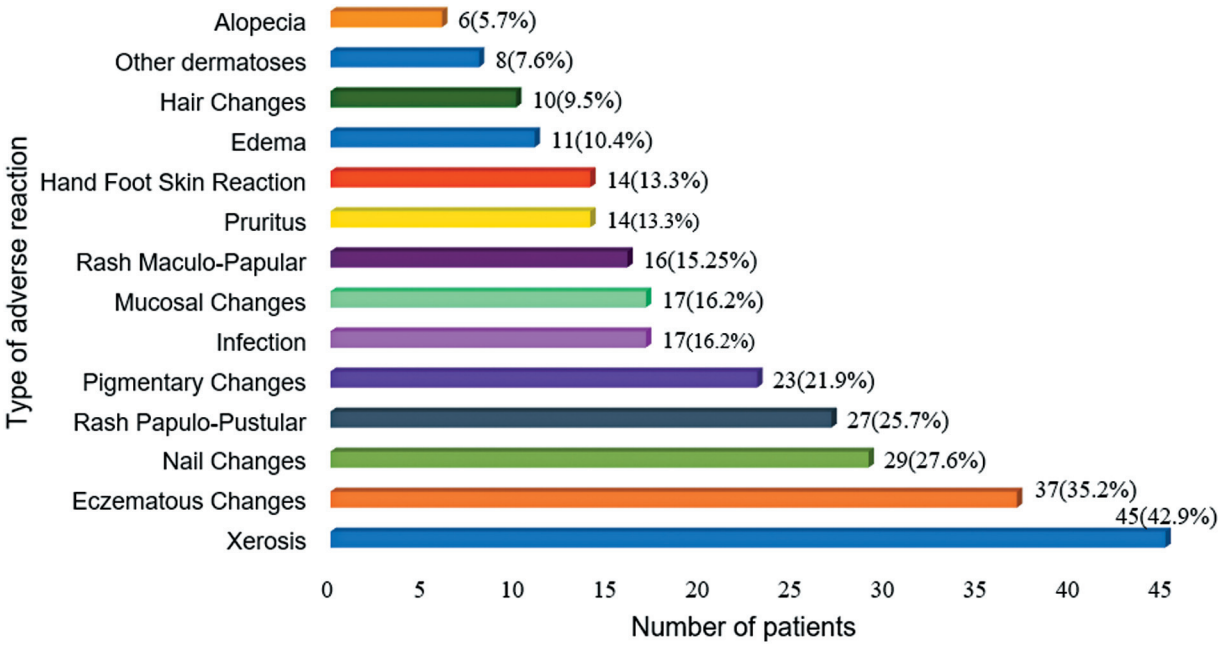

Fig. 3 Various mucocutaneous adverse reactions of TKI.

Of 8 (7.6%) patients with other dermatoses, 5 had keratolysis exfoliativa, 1 had palmar hyperhidrosis, 1 had pyoderma gangrenosum, and 1 had pyogenic granuloma.

The causality assessment using WHO–UMC criteria showed that the ADRs to TKIs were probable in 70 (66.7%) cases and possible in 35 (33.3%) cases.

Of 105 patients, 46 (42.8%) were on gefitinib. ►**Table 4** depicts the various ADRs with gefitinib, with the most common adverse effect being papulopustular rash, in 23 (50%) patients. Pigmentary changes included post-inflammatory hyperpigmentation in seven patients, lichen planus pigmentosus in one, flagellate in one, and melasma-like in one patient. Five patients had keratolysis exfoliativa, and one patient each had a pyogenic granuloma affecting the nail fold and PRIDE complex.

Of 105 patients, 25 (23.8%) were on imatinib. ►**Table 5** shows the various ADRs with imatinib. The most common adverse effect noted was eczematous changes affecting 13 (52.0%) patients, with seborrheic dermatitis in 5 patients, photodermatitis in 4, lichenoid dermatitis in 3, and psoriasiform dermatitis in 1 patient. Pigmentary changes were the next most common, affecting 11 (44.0%) patients with diffuse hypopigmentation in 6 patients and melasma-like pigmentation in 5 patients.

A total of 21 patients had a dose reduction. Among these, 6 (28.6%) patients were on lenvatinib, 5 (23.8%) were on gefitinib, 4 (19%) were on sunitinib, and 2 (9.5%) each were on cabozantinib, sunitinib, and lapatinib. The two patients on lapatinib and cabozantinib had HFSR and eczematous changes as dose-dependent ADR. Both patients on sorafenib

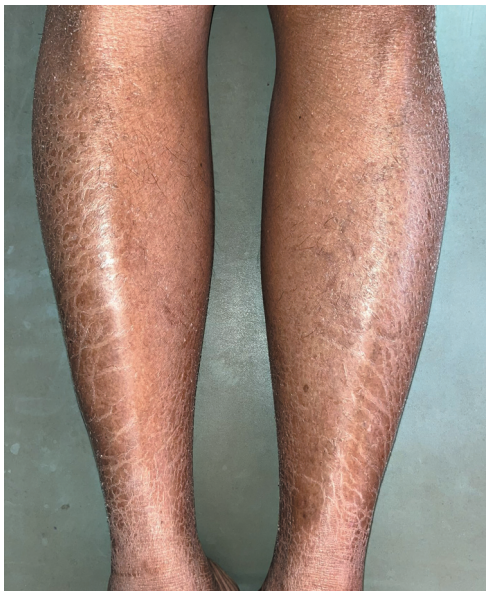

Fig. 4 Acquired ichthyosis over bilateral lower legs caused by gefitinib.

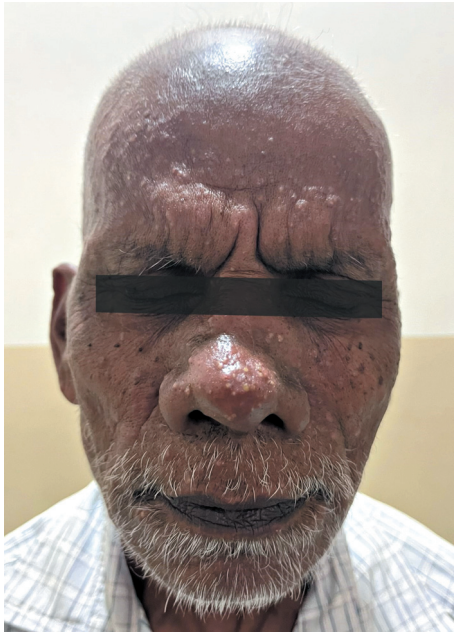

Fig. 5 Papulopustular rash involving the face caused by gefitinib.

had HFSR as the dose-dependent ADR. Of 6 patients on lenvatinib, 5 had HFSR and 1 had pyoderma gangrenosum. Of five patients on gefitinib, four had papulopustular rash with paronychia, and one had a pyogenic granuloma of nail folds. Of four patients on sunitinib, three had HFSR and one had eczematous changes.

Discussion

In the current study, 51 (48.6%) patients were on EGFR inhibitors, with 46 patients on gefitinib and 5 on lapatinib. Twenty-eight (26.6%) patients were on *BCR–ABL* inhibitors, with 25 on imatinib and 3 on dasatinib. Twenty-two (21%) patients were on MKIs, with 8 on lenvatinib, 9 on sunitinib, 2

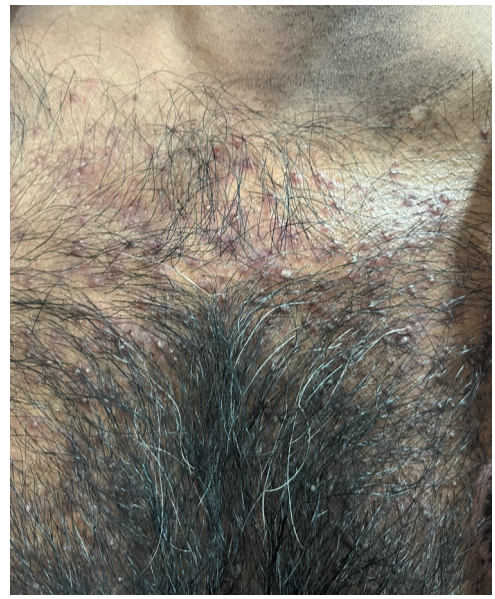

Fig. 6 Papulopustular rash involving the chest caused by gefitinib.

Table 1 Statistically significant association between papulopustular rash and paronychia

Rash papulopustular	Paronychia		*p*-Value
	Yes	No	
	Number (%)		
Yes (27)	10 (37.0)	17 (63.0)	0.001
No (78)	7 (8.9)	71 (91.1)	

on sorafenib and cabozantinib each, and 1 on pazopanib. Four (3.8%) patients were on an ALK inhibitor, namely crizotinib (►**Table 6**).

There are individual studies highlighting the cutaneous ADRs of each TKI agent class, but a pooled analysis of all TKI agents is quite uncommon in the literature, which makes our study unique.

Of 51 patients on EGFR inhibitors, the most common ADRs noted were papulopustular rash in 25 (49.0%) patients, xerosis in 22 (43.1%), nail changes in 15 (29.4%), eczematous and pigmentary changes in 11 (21.6%) patients each, infections in 9 (17.6%), and mucosal changes in 6 (11.8%) patients.

In the study by Chanprapaph et al,[14] of 99 patients on EGFR inhibitors, the most common ADR was xerosis in 52.5% of patients, which was comparable to our study. Enhanced inflammation, keratinocyte apoptosis, increased UV sensitivity, and altered keratinocyte differentiation are the various outcomes of EGFR suppression. The disruption of the stratum corneum and dysfunctional sebaceous glands causes the epidermis to lose its ability to retain water. Drug buildup can interfere with the secretory function of eccrine sweat glands, which can cause dryness.[15]

Since the majority of patients were on EGFR inhibitors and the most common age group was 51 to 60 years, this could explain the higher incidence of xerosis in the current study.

Fig. 7 Subungual splinter hemorrhages involving fingernails caused by sorafenib.

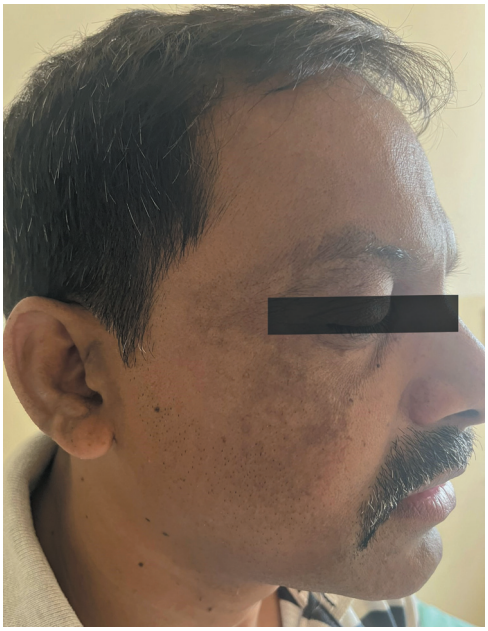

Fig. 8 Melasma-like hyperpigmentation caused by imatinib.

Table 2 Various patterns of hyperpigmentation

Type of hyperpigmentation	Frequency	Percentage
Post-inflammatory hyperpigmentation	8	47.1
Melasma-like	6	35.2
Lichen planus pigmentosus	2	11.8
Flagellate	1	5.9
Total	**17**	**100.0**

In a study conducted by Saini et al,[16] papulopustular rash was the most frequent cutaneous ADR seen in 21 (26.25%) patients, which correlated with our study.

Of 27 patients with papulopustular rash, 20 (74%) had an onset at or before 3 weeks. Similar findings were noted in the study by Chanprapaph et al,[14] where the onset ranged between 8 and 25 days.

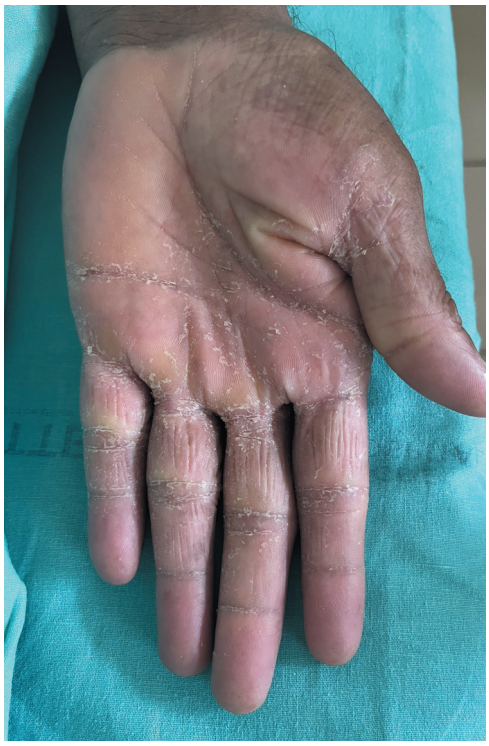

Fig. 9 Hand–foot skin reaction over palms caused by sunitinib.

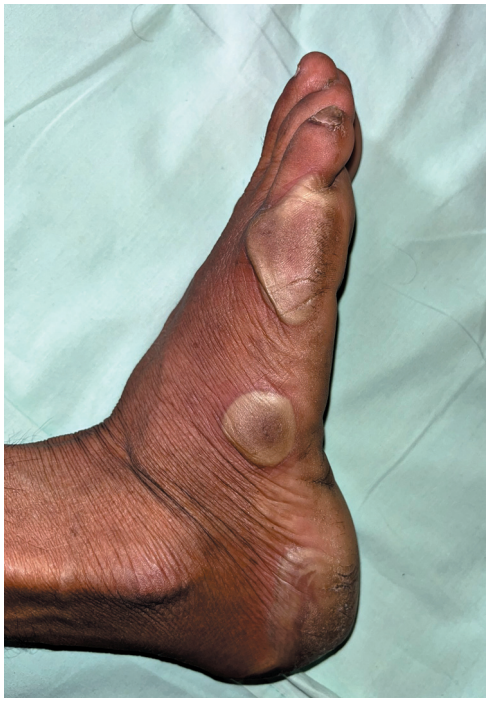

Fig. 10 Hand–foot skin reaction over soles caused by sunitinib.

These follicle-centric erythematous papules and pustules mostly affect the seborrheic regions, while sparing the periorbital and palmoplantar areas. The onset is within the first 2 weeks of treatment and is characterized by waxing and waning of lesions. In contrast to acne, comedones are

Table 3 Oral mucosal changes after the initiation of TKI

Oral mucosal changes	Frequency	Percentage
Mucositis	10	62.4
Cheilitis	4	25.0
Mucosal melanosis	1	6.3
Oral lichen planus	1	6.3
Total	**16**	**100.0**

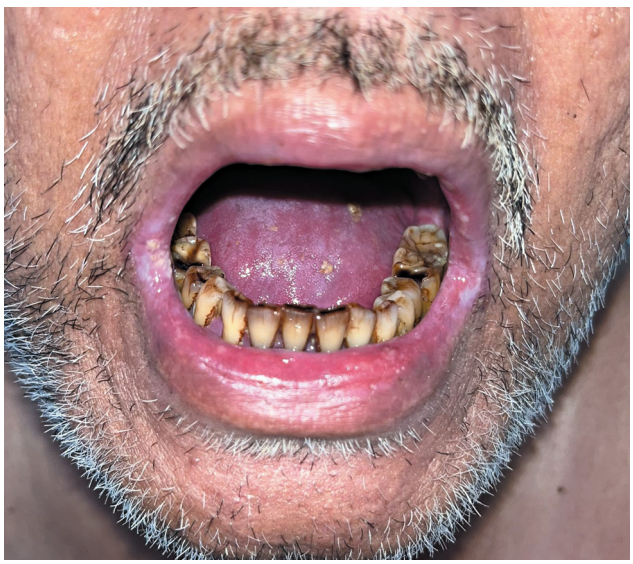

Fig. 11 Angular cheilitis caused by imatinib.

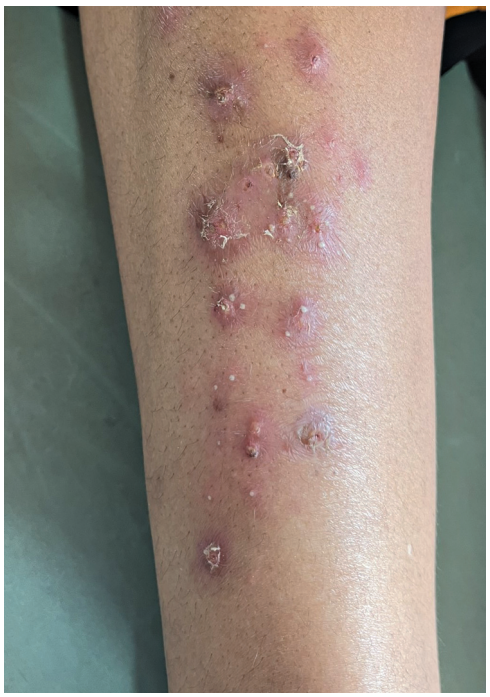

Fig. 12 Pyoderma involving the right thigh caused by gefitinib.

noticeably absent, the lesions are associated with pruritus, and the scalp is usually involved. EGFR inhibitors block the expression of EGFR in normal epidermal cells as well as in tumor cells. As a result, there is enhanced cell differentiation, apoptosis induction, and cell growth arrest, which causes keratinocytes to produce inflammatory chemokines, namely, CCL2, CCL5, and CXCL10.[17]

In the current study, a rare case of pyogenic granuloma affecting lateral nail folds was reported, after nearly 21 months of gefitinib initiation (►**Fig. 13**). Most patients

Table 4 ADRs with gefitinib

Adverse reaction	Frequency	Percentage
Rash papulopustular	23	50.0
Xerosis	18	39.1
Nail changes	12	26.1
Pigmentary changes	10	21.7
Eczematous changes	9	19.6
Infection	9	19.6
Mucosal changes	6	13.0
Other dermatoses	6	13.0
Pruritus	5	10.9
Rash maculopapular	4	8.7
Hair changes	4	8.7

Table 5 ADRs with imatinib

Adverse reaction	Frequency	Percentage
Eczematous changes	13	52.0
Pigmentary changes	11	44.0
Rash maculopapular	9	36.0
Xerosis	8	32.0
Eyelid edema	6	24.0
Pruritus	5	20.0
Hair changes	5	20.0
Nail changes	4	16.0
Infection	4	16.0
Mucosal changes	3	12.0
Other dermatoses	1	4.0
Alopecia	1	4.0

Table 6 Distribution of patients based on the class of TKI agent received

Class of TKI agent	Frequency	Percentage
EGFR inhibitor	51	48.6
BCR-ABL inhibitor	28	26.6
Multikinase inhibitor	22	21.0
ALK inhibitor	4	3.8
Total	**105**	**100.0**

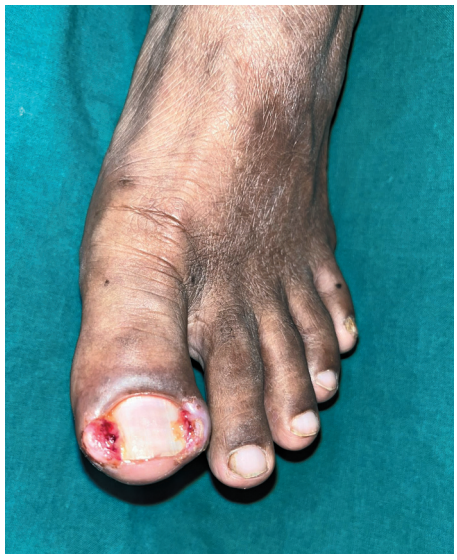

Fig. 13 Pyogenic granuloma of the lateral nail folds of the left great toe caused by gefitinib.

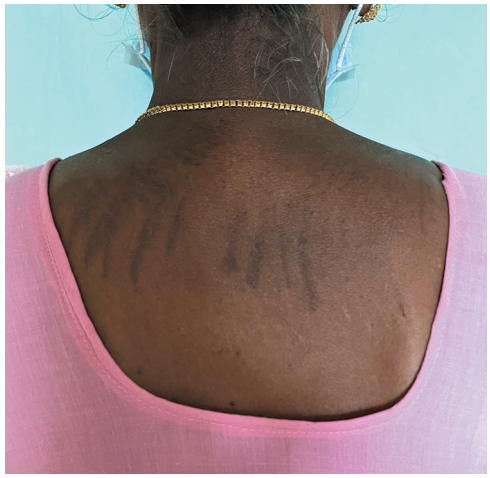

Fig. 14 Flagellate pigmentation over the upper back caused by gefitinib.

who experience nail alterations have previously experienced papulopustular rash.[18] A significant association with a *p*-value of 0.001 was noted between the occurrence of rash and the development of paronychia.

Although flagellate dermatitis is a known ADR of bleomycin, in our study one patient on gefitinib reported flagellate pigmentation (►**Fig. 14**). One patient had PRIDE complex (papulopustules and/or paronychia, regulatory abnormalities of hair growth, itching, and dryness due to EGFR inhibitors) as compared to three in the study by Saini et al.[16] ►**Table 7** shows the comparison of cutaneous adverse reactions with gefitinib in different studies.

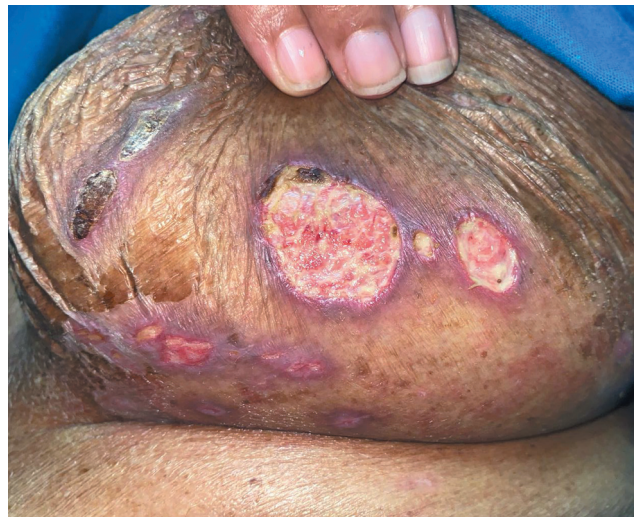

Fig. 15 Pyoderma gangrenosum involving the left mammary area caused by lenvatinib.

Of 11 (44%) patients showing pigmentary changes after imatinib, diffuse hypopigmentation was seen in 6 (54.5%) patients and melasma-like pigmentation in 5 (45.5%) patients.

In addition to inhibiting *BCR–ABL*, imatinib additionally blocks ligands from attaching to c-KIT receptors on melanocytes, which lowers melanocyte activity and causes hypopigmentation. Rarely, it can sporadically induce paradoxical hyperpigmentation. Although melasma-like is a rare adverse effect, the higher prevalence in our study could be due to ethnically pigmented skin. Five patients with melasma-like pigmentation after imatinib therapy were described by Ghunawat et al.[22]

Periorbital edema was noted in 6 (24%) patients on imatinib in the current study, as opposed to 81 (18.5%) in the study by Vinay et al.[23] This is due to inhibition of PDGFR, which plays a crucial role in the regulation of interstitial fluid balance. ►**Table 8** shows the comparison of cutaneous ADRs with imatinib in different studies.

Table 7 Comparison of cutaneous ADRs with gefitinib in different studies

Adverse reactions	Yoshida et al[19]	Chularojanamontri et al[20]	Chanprapaph et al[14]	Lee et al[21]	Our study
Papulopustular rash	67 (62.6%)	46 (79.3%)	5 (20.8%)	25 (39%)	23 (50%)
Xerosis	–	48 (82.8%)	10 (41.7%)	23 (36%)	18 (39.1%)
Nail changes	17 (15.9%)	27 (46.6%)	1 (4.2%)	4 (6%)	12 (26.1%)
Mucosal changes	4 (3.7%)	–	1 (4.2%)	3 (6%)	6 (13%)
Maculopapular rash	–	–	5 (20.8%)	–	4 (8.7%)
HFSR	4 (3.7%)	–	–	–	–
Desquamation	–	36 (62.1%)	–	–	5 (10.8%)

Table 8 Comparison of cutaneous ADRs with imatinib in different studies

Adverse reactions	Vinay et al[23]	Khokar et al[24]	Arora et al[25]	Valeyrie et al[5]	Our study
Eczematous changes	–	–	–	–	13 (52%)
Pigmentary changes	260 (59.4%)	101 (76.5%)	44.5%	–	11 (44%)
Maculopapular rash	–	–	12.7%	36 (66.7%)	9 (36%)
Xerosis	16 (3.7%)	22 (16.7%)	–	–	8 (32%)
Eyelid oedema	81 (18.5%)	64 (48.5%)	48%	35 (64.8%)	6 (24%)
Mucosal changes	77 (17.6%)	–	–	–	3 (12%)
Pruritus	12 (2.7%)	9 (6.8%)	–	22 (40.7%)	5 (20%)

Of 8 (7.6%) patients on lenvatinib, HFSR was noted in 5 (62.5%) patients and xerosis and nail changes in 4 (50%) patients each. Pyoderma gangrenosum was noted in one patient, which led to a subsequent dose reduction (►**Fig. 15**). Cha et al.[26] reported a case of lenvatinib-induced skin ulceration in a 60-year-old HCC patient.

Of 9 (8.6%) patients on sunitinib, the most common ADRs noted were eczematous changes in 6 (66.7%) patients, followed by xerosis in 5 (55.6%) and alopecia and facial edema in 4 (44.4%) patients each. Mucosal changes and HFSR were seen in 3 (33.3%) patients each. In a study by Lee et al,[27] of 119 patients on sunitinib, the most frequent ADR was HFSR in 43 (36%) patients, which was similar to the current study.

Of 14 (13.3%) patients with HFSR, 8(57.1%) had grade 1, and 6(42.9%) had grade 2 reactions, while grade 3 HFSR was not observed. In the study by Autier et al,[28,29] of 26 patients on sorafenib with HFSR, 16 (61.5%) had grade 1, which correlated with our study.

Most patients experience HFSR during the first 2 to 4 weeks after starting MKI treatment.[30] It starts as yellow hyperkeratotic lesions that develop into calluses and, in certain instances, there is superficial blistering on the palms and soles, and often features a distinctive peripheral erythematous halo.[9]

In the current study, of 14 patients with HFSR, 11 (78.6%) patients underwent dose reduction as opposed to the study by Autier et al,[28] where HFSR led to dose reduction in only 2 (7.7%) patients.

ADRs were dose-dependent for lenvatinib, gefitinib, sunitinib, sorafenib, cabozantinib, and lapatinib. The specific dose-dependent ADRs associated with each TKI agent were HFSR and pyoderma gangrenosum for lenvatinib, papulopustular rash with paronychia for gefitinib, HFSR, and eczematous changes for sunitinib, cabozantinib, and lapatinib, and HFSR for sunitinib. In our study, the relation between HFSR and a subsequent dose reduction was analyzed in detail and showed a statistically significant association.

Limitations: A relatively small sample size pertaining to individual TKI agents, individual patients were not followed up in the long run, and only a few widely used TKI agents were analyzed.

Grey areas: Many newer and less frequently used TKIs may have distinct cutaneous ADR profiles that remain uncharacterized. Limited data are available on chronic sequelae after discontinuation of TKIs. Future research is encouraged to include a larger number of participants and newer TKI agents.

Strength: A pooled study of regularly used TKI agents is quite uncommon, despite the fact that individual TKI agents have been reviewed in the literature.

Conclusion

Although deemed safer when compared to the conventional chemotherapeutic agents, the newer targeted therapies do exhibit cutaneous toxicities, affecting skin, hair, nails, and mucosa. Certain ADRs exhibit a dose-dependent relationship, wherein increased drug concentrations are associated with heightened toxicity. Recognizing this correlation underscores the need for vigilant monitoring and emphasizes the importance of interdisciplinary cooperation between oncologists and dermatologists to facilitate accurate diagnosis and prompt management of various cutaneous toxicities. This will substantially reduce patient morbidity, boost adherence, and facilitate the treating oncologist to make necessary decisions regarding whether to stop, reduce, or continue the drug.

Patients' Consent

Photographs of the cutaneous lesions of patients who consented to it were taken, and the patients' identities were kept confidential.

Funding

None.

Conflict of Interest

None declared.

References

1 Macdonald JB, Macdonald B, Golitz LE, LoRusso P, Sekulic A. Cutaneous adverse effects of targeted therapies: Part I: Inhibitors of the cellular membrane. J Am Acad Dermatol 2015;72(02): 203–218, quiz 219–220

2 Heidary N, Naik H, Burgin S. Chemotherapeutic agents and the skin: an update. J Am Acad Dermatol 2008;58(04):545–570

3 Dervis E, Ayer M, Akin Belli A, Barut SG. Cutaneous adverse reactions of imatinib therapy in patients with chronic myeloid leukemia: a six-year follow up. Eur J Dermatol 2016;26(02): 133–137

4 Scheinfeld N. Imatinib mesylate and dermatology part 2: a review of the cutaneous side effects of imatinib mesylate. J Drugs Dermatol 2006;5(03):228–231
5 Valeyrie L, Bastuji-Garin S, Revuz J, et al. Adverse cutaneous reactions to imatinib (STI571) in Philadelphia chromosome-positive leukemias: a prospective study of 54 patients. J Am Acad Dermatol 2003;48(02):201–206
6 Zubair T, Bandyopadhyay D. Small molecule EGFR inhibitors as anti-cancer agents: discovery, mechanisms of action, and opportunities. Int J Mol Sci 2023;24(03):2651
7 Medina PJ, Goodin S. Lapatinib: a dual inhibitor of human epidermal growth factor receptor tyrosine kinases. Clin Ther 2008;30(08):1426–1447
8 Ara M, Pastushenko E. Antiangiogenic agents and the skin: cutaneous adverse effects of sorafenib, sunitinib, and bevacizumab. Actas Dermosifiliogr 2014;105(10):900–912
9 Arora A, Scholar EM. Role of tyrosine kinase inhibitors in cancer therapy. J Pharmacol Exp Ther 2005;315(03):971–979
10 Suyama K, Iwase H. Lenvatinib: a promising molecular targeted agent for multiple cancers. Cancer Control 2018;25(01):1073274818789361
11 Naveed S, Thappa DM, Dubashi B, Pandjatcharam J, Munisamy M, Singh N. Mucocutaneous adverse reactions of cancer chemotherapy and chemoradiation. Indian J Dermatol 2019;64(02):122–128
12 Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 [Internet]. U.S. Department of Health and Human Services. November 2017. Accessed October 10, 2025 at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf
13 WHO-UMC. The use of the WHO-UMC system for standardised case causality assessment [Internet]. Accessed October 10, 2025 at: https://www.who.int/docs/default-source/medicines/pharmacovigilance/whocausality-assessment.pdf
14 Chanprapaph K, Pongcharoen P, Vachiramon V. Cutaneous adverse events of epidermal growth factor receptor inhibitors: a retrospective review of 99 cases. Indian J Dermatol Venereol Leprol 2015;81(05):547
15 Madke B, Gole P, Kumar P, Khopkar U. Dermatological side effects of epidermal growth factor receptor inhibitors: 'PRIDE' complex. Indian J Dermatol 2014;59(03):271–274
16 Saini K, Sutaria A, Shah B, Brahmbhatt V, Parmar K. Cutaneous adverse drug reactions to targeted chemotherapeutic drugs: a clinico-epidemiological study. Indian J Dermatol 2019;64(06):471–475
17 Fabbrocini G, Panariello L, Caro G, Cacciapuoti S. Acneiform rash induced by EGFR inhibitors: review of the literature and new insights. Skin Appendage Disord 2015;1(01):31–37
18 Fakih M, Vincent M. Adverse events associated with anti-EGFR therapies for the treatment of metastatic colorectal cancer. Curr Oncol 2010;17(Suppl 1, Suppl 1):S18–S30
19 Yoshida T, Yamada K, Azuma K, et al. Comparison of adverse events and efficacy between gefitinib and erlotinib in patients with non-small-cell lung cancer: a retrospective analysis. Med Oncol 2013;30(01):349
20 Chularojanamontri L, Tuchinda P, Likitwattananurak C, et al. Cutaneous toxicities of epidermal growth factor receptor inhibitors: a prospective study in 60 Asian patients. Asian Pac J Allergy Immunol 2019;37(01):12–18
21 Lee MW, Seo CW, Kim SW, et al. Cutaneous side effects in non-small cell lung cancer patients treated with Iressa (ZD1839), an inhibitor of epidermal growth factor. Acta Derm Venereol 2004;84(01):23–26
22 Ghunawat S, Sarkar R, Garg VK. Imatinib induced melasma-like pigmentation: report of five cases and review of literature. Indian J Dermatol Venereol Leprol 2016;82(04):409–412
23 Vinay K, Yanamandra U, Dogra S, et al. Long-term mucocutaneous adverse effects of imatinib in Indian chronic myeloid leukemia patients. Int J Dermatol 2018;57(03):332–338
24 Khokar A, Malik U, Butt G, Naumeri F. Cutaneous manifestations in chronic myeloid leukemia in chronic phase treated with imatinib. Int J Dermatol 2019;58(09):1098–1101
25 Arora B, Kumar L, Sharma A, Wadhwa J, Kochupillai V. Pigmentary changes in chronic myeloid leukemia patients treated with imatinib mesylate. Ann Oncol 2004;15(02):358–359
26 Cha S, Kim DW, Choe JW, et al. A case report of a patient presented with skin ulcer after treatment of lenvatinib. J Liver Cancer 2021;21(02):194–198
27 Lee WJ, Lee JL, Chang SE, et al. Cutaneous adverse effects in patients treated with the multitargeted kinase inhibitors sorafenib and sunitinib. Br J Dermatol 2009;161(05):1045–1051
28 Autier J, Escudier B, Wechsler J, Spatz A, Robert C. Prospective study of the cutaneous adverse effects of sorafenib, a novel multikinase inhibitor. Arch Dermatol 2008;144(07):886–892
29 Porta C, Paglino C, Imarisio I, Bonomi L. Uncovering Pandora's vase: the growing problem of new toxicities from novel anticancer agents. The case of sorafenib and sunitinib. Clin Exp Med 2007;7(04):127–134
30 McLellan B, Kerr H. Cutaneous toxicities of the multikinase inhibitors sorafenib and sunitinib. Dermatol Ther 2011;24(04):396–400

