Journal of Pakistan Association of Dermatologists. 2022;**32(3)**:557-566.

Original Article

Dermatological toxicity due to targeted anticancer drugs: A new challenge in Oncology practice

Mohammad Hussain Mir, Parvaiz Anwar Rather*, Farhana Siraj Bagdadi**

Department of Medical Oncology, Sheri Kashmir Institute of Medical Sciences, Srinagar, J&K, India.
* Department of Dermatology, Government Medical College Baramulla, J&K India.
** Department of Internal Medicine, Sheri Kashmir Institute of Medical Sciences, Srinagar, J&K, India.

Abstract

Background Although newer targeted therapeutic agents have been introduced to improve the safety profile of cancer chemotherapy, yet new adverse effects, including dermatological adverse effects, have been increasingly reported after their use.

Objective We conducted this study aimed to observe the dermatological adverse effects occurring with commonly used targeted therapeutic agents at our center.

Methods This hospital based observational descriptive study conducted over a period of more than one year, included prospective adult patients put on newer targeted therapeutic agents for different types of malignancies. Patients with prior cutaneous or other drug hypersensitivity reactions and known liver and kidney diseases were excluded from the study.

Results 24 (21.43%) of 112 patients developed dermatological adverse effects, with 45 adverse effects in all. Most common cutaneous findings were xerosis/ pruritus in 7, papulopustular eruptions in 6, Hand foot syndrome and morbilliform eruptions in 3 (10.7%) each and lichenoid eruptions in 2 (7.1) patients. alopecia in 8, paronychia in 2, oral mucositis in 4 patients were the changes seen in hair, nails and mucosae respectively.

Conclusion This study re-emphasized the need to anticipate dermatological adverse effects due to new targeted chemotherapeutic agents. Proper counseling of the patients and their family members and timely management by treating physicians, oncologists and dermatologist can guide towards rationalizing the decision regarding continuation and discontinuation of such vital therapy.

Key words
Newer targeted drugs; chemotherapeutic agents; dermatological adverse effects.

Introduction

Management of malignancies requires multidisciplinary collaboration. Newer targeted drugs have been introduced to reduce mortality and morbidity associated with the chemotherapeutic agents and preserve the functions of the organs and structures as much as possible. Targeted drugs target the specific genes, proteins, or the tissue environment that contributes to cancer growth and development.

Newer targeted therapeutic agents, developed over recent times such as epidermal growth factor receptor (EGFR) inhibitors, tyrosine kinase inhibitors, monoclonal antibodies,

Address for correspondence
Dr. Parvaiz Anwar Rather, MD
Dr. Parvaiz Anwar Rather, MD
Assistant Professor,
Department of Dermatology, Government Medical College Baramulla, J&K, India.
Ph: 9419129334
Email: parvaizanwar@gmail.com

BRAF-inhibitors, to mention a few, have fared better regarding various systemic toxicities than the conventional chemotherapeutic agents. At the same time, their use has introduced new adverse events including dermatological toxicities, which include manifestations in skin, hair, nail and mucus membranes and range from mild to more severe manifestations.[1,2]

Let us cite the example of EGFR inhibitors that target specific biochemical ligands involved in the carcinogenesis. Similar EGFR ligands are very much expressed in skin structures, hair follicles and mucosae, resulting in frequent association of EGFR inhibitors with various dermatological toxicities.[3,4]

Such adverse events not only increase the morbidity and sometimes the mortality associated with chemotherapeutic agents, at the same time, being visible to the treating physicians as well as to the patients and their family alike, force a premature discontinuation of the therapeutic cycle. Because of the same reason, there is a negative impact on the patient`s quality of life.

There is a positive aspect to the development of dermatological toxicities also, in that skin toxicity can be considered a predictive and independent survival factor for the success of response to the newer targeted therapy. It has been found that patients who develop moderate to severe cutaneous reactions have higher treatment response rate, as suggested in some meta-analysis.[5,6]

Common dermatologic toxicities related to skin include maculopapular and pustular eruptions, pruritus, xerosis, bullous eruptions, hand foot syndrome, pigmentary changes. Paronychia and other nail changes, mucositis as well as hair changes are also common.[7-10]

Anticipation of such dermatological adverse effects of newer targeted drugs, obtaining familiarity with their timely management in consultation with dermatologists, proper counseling and reassurance of the patients and family members, can go a long way in alleviating the apprehensions of the treating physicians (oncologist), the patients and their family members. This will also rationalize the decision regarding continuation and discontinuation of the therapy.

In this backdrop, we also conducted a study at our center, to observe the pattern of adverse events pertaining to skin, hair, nails and mucus membranes in patients on commonly used newer targeted chemotherapeutic agents for various types of malignancies.

Material and Methods

This descriptive hospital based observational prospective cohort study was conducted over a period of more than one year at a tertiary care center of North India. Our cohort consisted of patients with various types of malignancies put on different types of targeted chemotherapies.

Inclusion criteria: Randomly selected prospective patients of adult age groups (more than or equal to 18 years) with various types of malignancies put on targeted chemotherapeutic agents.

Exclusion criteria: Patients of pediatric age groups, those with prior cutaneous or other drug hypersensitivity reactions, those with known diseases of liver, kidney and those on concomitant radiotherapy.

All the patients, both inpatients and those visiting as outpatients, put on targeted chemotherapeutic agents, were asked about demographic details, type of malignancy, and

screened for appearance of adverse effects related to skin, hair, nails, mucosae in current visit or subsequent follow ups.

All those patients on targeted chemotherapy who developed any such adverse effect after starting targeted chemotherapy were thoroughly worked up by the same dermatologist with regards the detailed history, clinical examination, routine as well as specific diagnostic investigations, where ever needed, such as fungal scrapings for microscopy and culture, pus culture & sensitivity, Tzanck smears, skin biopsy for histopathological examination and direct immunofluorescence, along with various hematological investigations.

Approval from institutional ethics committee was obtained. Written consent was taken from the patients to participate in the study and report any adverse reaction event to targeted chemotherapy. Option of voluntary participation, patient confidentiality and human subject protection was ensured. Most of the patients were provided with free medications from the available samples for these untoward adverse events. Counseling, reassurance and awareness was simultaneously given to ally the sufferings of the patients, arising because of these dermatological adverse effects.

The data collected was compiled in Microsoft excel sheet. Calculations were done using excel formulas.

Results

This study consisted of 112 prospective patients with various malignancies put on targeted chemotherapeutic agents at our center. There were 64 males and 48 females (M:F; 1.3:1). There were 50 smokers and 62 non-smokers. The age of the patients ranged from 21-75 years, with average age of 53.38 years. There were 55 (49.1%) patients in the age group 41-60 years, followed by 32 (28.6%), 18 (16.1%) and 7 (6.2%) in the age group >61, 21-40 and ≤ 20 years respectively.

Table 1 Age and sex characteristics of the study group.

All the targeted therapy patients (n=112)				*Dermatological adverse effects (n= 24)*
Age group (Years)	*Males*	*Females*	*Total*	
≤20	4	3	7	0
21-40	11	7	18	4
41-60	31	24	55	13
>61	18	14	32	7
Total	64	48	112	24

The age and sex characteristics are summarized in **Table 1**.

The common malignancies in the study group included that of lung in 14 patients, breast in 12, colorectal in 11, non-Hodgkin`s lymphoma in 10, followed by 7 patients each with malignancies of ovaries, thyroid and Chronic Myeloid Leukemia (CML). Other types of malignancies seen in the study group are shown in **Table 2**.

The most common targeted drugs used corresponding with the types of malignancies were letrozole, anastrozole, estrogen, rituximab, followed by trastuzumab, imatinib, lenalidomide, nab paclitaxel, bortezomib. the class of drugs along with the individual drugs in each class and their usage status in various types of malignancies in the study group is summarized in the **Table 3**.

Out of 112 patients put on targeted drugs, 24 (21.43%) developed dermatological adverse events related to skin, nails, hair, visible mucosae, after a varying duration from start of therapy with an overall 45 side effects manifestations, as some patients developed adverse events related to all the four entities (skin, nails, hair, mucosae) in different

Table 2 Types of malignancies in the study group.

Organ System	*Type of Malignancy*	*Male*	*Female*	*Number of patients n=112)*	*Total (n=112)*
Lung		5	2	7	14
	Adenocarcinoma	6	1	7	
Breast		0	12	12	12
GIT	Colon	4	2	6	23
	Rectum	4	1	5	
	Hepatocellular	4	1	5	
	Pancreas	2	2	4	
	GIST	2	1	3	
NHL		4	2	6	10
	T Cell NHL	3	1	4	
Ovary		0	7	7	7
Head & Neck	SCC	2	2	4	11
	Thyroid	3	4	7	
Hematological	CML	5	2	7	15
	MM	3	2	5	
	Ph +ve ALL	3	0	3	
Hodgkin`s lymphoma		4	2	6	6
Prostate		5	0	5	5
Renal		3	2	5	5
Soft tissue	Sarcoma	2	2	4	4
Total		64	48	112	112

proportions, in the same patient.

Among the 24 patients who developed dermatological adverse effects, 13 (54.1%) were in the age group 41-60, followed by 7 (29.2%) and 4 (16.7%) in age group > 61 and 21-40 years respectively. No patient ≤20 years developed dermatological adverse effects, as summarized in **Table 1**.

The most common dermatological adverse effects were cutaneous, comprising 28 out of 45 (62.2%) adverse effects, followed by 9 (20%) hair changes and 4 (8.9%) each in nails and mucosa.

Most notable among the cutaneous findings were xerosis/ pruritus in 7 (25%), papulopustular (acneiform) eruptions 6 (21.4%) **(Figure 1)**, Hand foot syndrome 3 (10.7%) **(Figure 2)**, maculopapular (morbilliform) eruptions 3 (10.7%) **(Figure 3)**, lichenoid eruptions 2 (7.1) **(Figure 4)**, followed by 1 (3.6%) each of hyperpigmentation, depigmentation, erythema

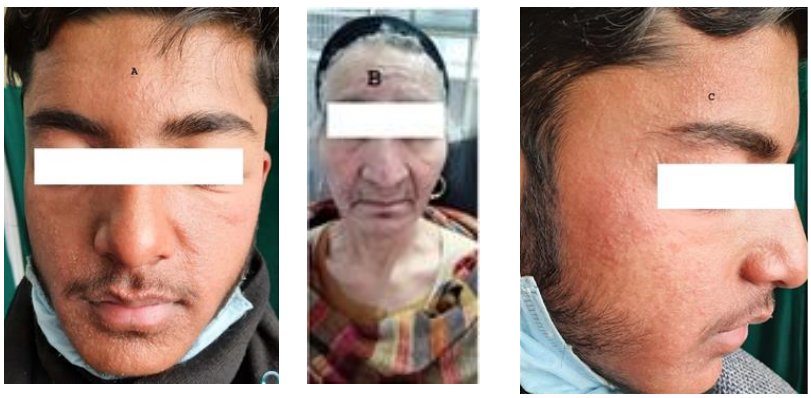

Figure 1 Papulopustular (Acneiform) eruptions.

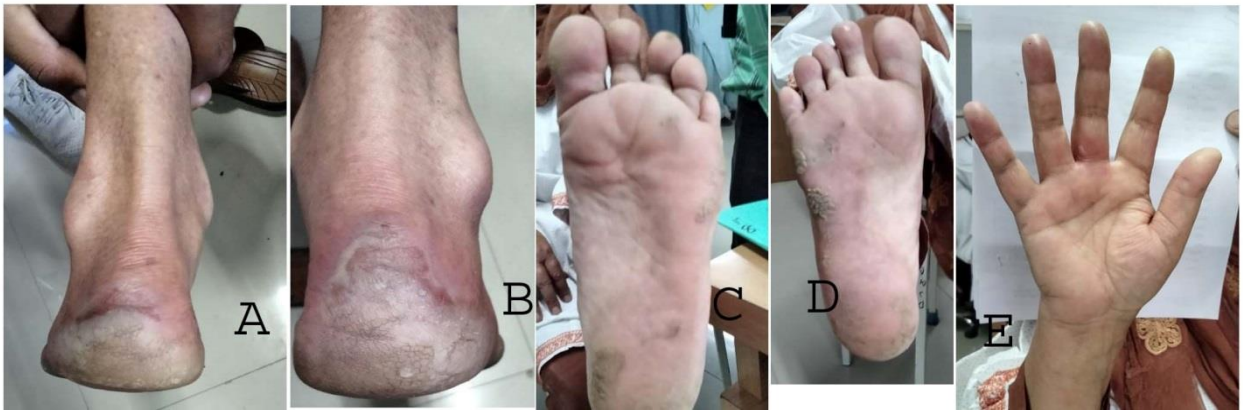

Figure 2 Hand Foot syndrome.

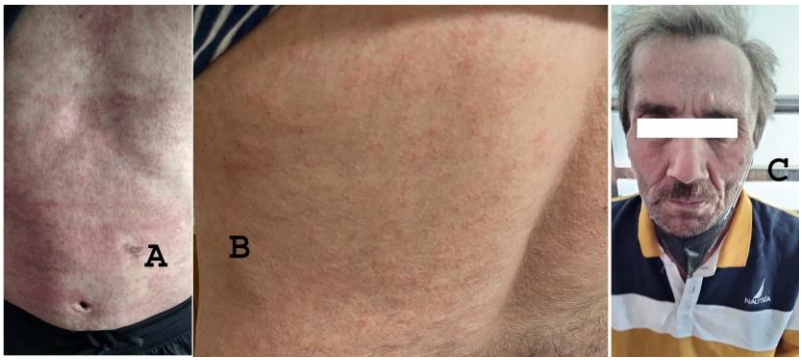

Figure 3 Maculopapular eruption (A, B) and Seborrheic dermatitis like facial erythema (C).

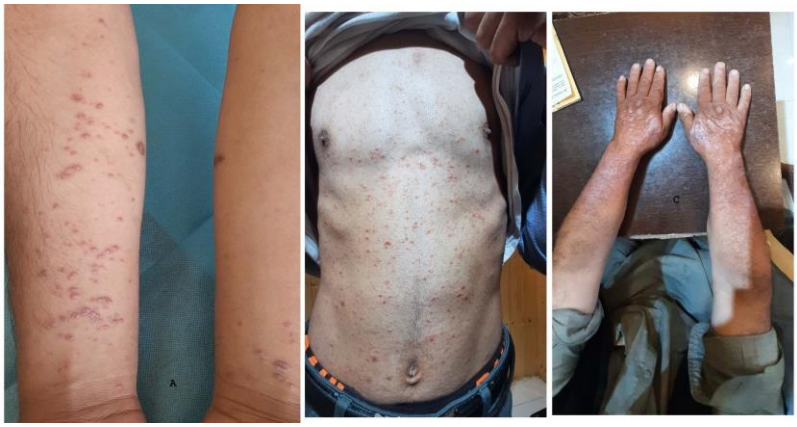

Figure 4 Lichenoid eruption.

trastuzumab, erlotinib, lenvatinib, sunitinib, letrozole, anastrozole, nab paclitaxel, liposomal doxorubicin, as outlined in **Tables 3 & 4**. The dermatological adverse effects seen with cetuximab included xerosis/ pruritus, papulopustular (acneiform) eruption, alopecia, hair thinning and brittleness, paronychia, oral mucositis. These side effects developed after 2-3 weeks of starting cetuximab.

Rituximab use resulted in papulopustular (acneiform) eruption, maculopapular (morbilliform) eruption, erythema multiforme, seborrheic dermatitis like facial erythema, alopecia after 2-4 weeks of starting.

multiforme, erythema nodosum, psoriasiform eruption, cutaneous, small cell vasculitis, seborrheic dermatitis like facial erythema, as detailed in **Table 4**.

Hair changes included alopecia in 8 patients and brittle hair in 1.

Nail changes included paronychia in 2 and 1 nail change each of hyperpigmentation and onycholysis. Mucosal change noticed was oral mucositis/ stomatitis in 4 patients. Among all the targeted therapeutic agents that we used, the drugs that resulted in development of dermatological adverse effects in our study were cetuximab, nivolumab, pembrolizumab, imatinib, lenalidomide, rituximab,

Table 3 Targeted drugs with indications, used in the study group.

Class of drug	*Individual drugs*	*Therapeutic uses*
Hormonal (Aromatase inhibitor)	Letrozole*; Anastrozole*	Ca Breast
Hormonal (Estrogen receptor modulator)	Estrogen*	Ca Breast
Monoclonal Antibody (Anti CD20)	Rituximab*	NHL
Proteosome inhibitor	Bortezomib* (MC); Carfilzomib** (LC)	Multiple myeloma
Monoclonal Antibody (Anti Her2)	Trastuzumab*	Ca Breast
Monoclonal Antibody (Anti Her2 and Her3)	Pertuzumab***	Ca Breast
Monoclonal antibody (Anti VEGF)	Bevacizumab**	Ca Colon, Ca Rectum, Ca Ovary
Monoclonal Antibody (Anti EGFR)	Cetuximab**	SCCHN, Ca Colon, Ca Rectum
Monoclonal antibody drug conjugate (anti CD30)	Brentuximab*** Vedotin***	HL, T Cell NHL
TKI	Sunitinib**	Renal Cell Ca
TKI	Sorafenib***	Renal Cell Ca, Hepatocellular Ca, Soft tissue Sarcoma
TKI	Imatinib*	CML, GIST, Ph +ve ALL
TKI	Axitinib***	Adenocarcinoma Lung
TKI	Dasatinib** (LC); Nilotinib** (LC); Bosutinib*** (VR)	CML, Ph +ve ALL
TKI	Lenvatinib**	Renal cell Ca, Thyroid Ca
TKI	Pazopanib**	Renal Cell Ca, Soft tissue Sarcoma
Hormonal (selective estrogen deregulator)	Fulvestrant**	Ca Breast
CDK4/CDK6 inhibitor	Palbociclib***; Ribociclib***	Ca Breast
Immunomodulator	Lenalidomide*	Multiple myeloma, NHL
Immunomodulator	Pomalidomide**(LC); Thalidomide*** (VR)	Multiple myeloma
Immunomodulator	Nivolumab***	Ca Lung, HL, Melanoma
Immune checkpoint inhibitor (Anti PD1 INHIBITOR)	Pembrolizumab***	Ca Lung
EGFR inhibitor	Gefitinib** (LC); Erlotinib** (LC)	Adenocarcinoma Lung
TKI ALK inhibitor	Crizotinib*** (R); Ceritinib*** (R)	Adenocarcinoma Lung
Taxane with albumin bound nanoparticle drug	Nab Paclitaxel*	Ca Breast, Ca Lung, Ca Pancreas
Nano particle technology formulation Taxane	Doceaqualip**	Ca Prostate, Ca Breast
Albumin bound Anthracycline	Liposomal Doxorubicin**	Ca Ovary

* More commonly used; ** Less commonly used; *** Rarely use
TKI: Tyrosine Kinase Inhibitors; Ca: Carcinoma;
Ph +ve ALL: Philadelphia Positive Acute Lymphocytic Leukemia; NHL: Non-Hodgkin`s Lymphoma; HL: Hodgkin`s Lymphoma; SCCHN: Squamous Cell Carcinoma Head & Neck; GIST: Gastrointestinal Stromal Tumor; CML: Chronic Myeloid Leukemia

Sunitinib, imatinib, lenvatinib use showed xerosis and pruritus, Hand Foot syndrome, lichenoid eruption, hyperpigmentation, erythema nodosum, psoriasiform eruption, alopecia, oral mucositis after 3-6 weeks of initiation. Lenalidomide, nivolumab presented with xerosis and pruritus, papulopustular (acneiform) eruption, maculopapular (morbilliform) eruption, alopecia, lichenoid eruption after about 1-4 weeks of starting the therapy. Patient on erlotinib developed papulopustular (acneiform) eruption, oral mucositis after 1-3 weeks of initiation.

Table 4 Dermatological adverse effects in relation to therapeutic agents, and types of malignancies

Side effects	*No of patients (n=24)*	*Causative drug*	*Type of malignancy*
Cutaneous			
Xerosis and Pruritus	7	Cetuximab	Ca Colon, Ca Rectum
		Nivolumab	HL
		Imatinib	Ph +ve ALL
		Lenalidomide	MM
Papulopustular (Acneiform) eruption)	6	Rituximab	NHL
		Lenalidomide	HL
		Cetuximab (60-80%)	SCCHN
		Trastuzumab (60-90%)	Ca Breast
		Erlotinib	Adeno Ca lung
Hand Foot syndrome	3	Lenvatinib (32-75)	Ca Thyroid; Renal cell Ca
		Sunitinib	Renal Cell Ca
Maculopapular (Morbilliform) eruption	3	Lenalidomide	MM
		Rituximab	NHL
		Anastrozole	Ca Breast
Lichenoid eruption	2	Nivolumab	Ca Lung
		Imatinib	GIST
Hyperpigmentation	1	Imatinib	CML
Depigmentation	1	Pembrolizumab	Ca Lung
Erythema Multiforme	1	Rituximab	NHL
Erythema nodosum	1	Imatinib	CML
Psoriasiform eruption	1	Imatinib	Ph +ve ALL
Small vessel Vasculitis	1	Letrozole	Ca Breast
Seborrheic dermatitis like facial erythema	1	Rituximab	NHL
Total	28		
Hair			
Alopecia	8	Rituximab	NHL
		Cetuximab	Ca Colon; Ca Rectum
		Trastuzumab	Ca Breast
		Lenalidomide	NHL
		Sunitinib	Renal Cell Ca
		Letrozole	Ca Breast
Hair thinning, brittleness	1	Cetuximab	Ca Colon
Total	9		
Nails			
Paronychia	2	Cetuximab	Ca Colon; Ca Rectum
Nail Hyperpigmentation	1	Nab Paclitaxel	Ca Breast
Onycholysis	1	Liposomal Doxorubicin	Ca Ovary
Total	4		
Mucosa			
Oral Mucositis	4	Erlotinib	Adeno Ca lung
		Cetuximab	Ca Colon
		Lenvatinib (20-35)	Renal Cell Ca
		Sunitinib	Renal Cell Ca
Total	4		
Total	45		

Ph +ve ALL: Philadelphia Positive Acute Lymphocytic Leukemia; MM: Multiple Myeloma; NHL: Non-Hodgkin`s Lymphoma; HL: Hodgkin`s Lymphoma; SCCHN: Squamous Cell Carcinoma Head & Neck; Ca: Carcinoma; GIST: Gastrointestinal Stromal Tumor; CML: Chronic Myeloid Leukemia

letrozole, anastrozole showed maculopapular (morbilliform) eruption, cutaneous small vessel vasculitis, Alopecia after 2-4 weeks of initiation.

trastuzumab use resulted in papulopustular (acneiform) eruption; alopecia after 2-3 weeks of start of the therapy.

pembrolizumab, nab paclitaxel and liposomal doxorubicin presented with depigmentation, nail hyperpigmentation and onycholysis respectively as dermatological adverse effects.

All the patients who developed dermatological adverse effects were managed simultaneously and effectively, without the need to change or stop the therapy.

Discussion

Newer therapeutic drugs which target a specific biochemical pathway responsible for carcinogenesis are preferred these days in order to obviate various systemic toxicities of conventional nonspecific chemotherapeutic drugs. At the same time, dermatological adverse effects due to targeted agents have been increasingly reported, because of common target molecules found in malignant cells and those in skin, hair, nails and mucosae.

Our study consisted of male: female ratio of 1.3:1, with slight male preponderance, in accordance with most of the studies in the literature,[1,11] but differing slightly from the results of some other studies.[8]

The common malignancies in the study group included that of lung in 14 patients, breast in 12, colorectal in 11, non-Hodgkin`s lymphoma in 10, followed by 7 patients each with malignancies of ovaries, thyroid and Chronic Myeloid Leukemia (CML).

Reporting of similarly occurring common malignancies with slight variations have been reported in various studies across the literature.[1,4,8,10]

24 (21.43%) of patients started on targeted chemotherapeutic agents during the study period developed various dermatological adverse effects related to skin, hair, nails and mucosae. Similar frequency of dermatological side effect patterns was also found in some previous studies.[1,8,11]

Most of the patients who developed dermatological adverse effects were in the age group 41-60 years, because the same age group presented with higher number of malignancies.

Most common cutaneous adverse effects seen in this study were xerosis with subsequent pruritus (25%), acneiform papulopustular eruptions (21.4%), hand foot syndrome (10.7%), morbilliform maculopapular eruption (10.7%), lichenoid eruptions (7.1%). Almost similar patterns of cutaneous side effects due to targeted chemotherapy drugs were reported as common occurrence in most of the previous studies available in the literature.[1,4,8,11-15]

Less common cutaneous adverse effects were diffuse hyperpigmentation, vitiligo like depigmentation, erythema multiforme, erythema nodosum, psoriasis like eruption, seborrheic dermatitis like eruption on face and cutaneous small vessel vasculitis.

Alopecia was the main hair changes reported, in accordance with that of other studies.[8,16]

Paronychia, nail hyperpigmentation and onycholysis were the nail changes noticed in this study, similar to other studies in the literature.[8]

Mucosal change was limited to oral mucosa and

included oral mucositis/ stomatitis, in accordance with the findings in other previous studies.[8,17]

In this study, the main class and individual drugs which resulted in most of the dermatological adverse effects were Anti EGFR Monoclonal Antibody (Cetuximab), EGFR inhibitor (Erlotinib), Anti CD20 Monoclonal Antibody (Rituximab), Tyrosine Kinase Inhibitors (Sunitinib, Imatinib, Lenvatinib), Immunomodulator (Lenalidomide, Nivolumab), Aromatase inhibitor hormonal agents (Letrozole, Anastrozole), Anti Her2 Monoclonal Antibody (Trastuzumab).

Gene amplification and aberrant cellular proliferation, because of epidermal growth factor receptor (EGFR) overexpression, is one of the main mechanisms for carcinogenesis, making EGFR an effective potential anticancer target.[18,19] Epidermal keratinocytes and pilosebaceous units also contain sufficient EGFR ligands,[19,20] as a result of which inhibition of EGFRs by EGFR inhibitors and anti-EGFR antibodies can expectedly exert inflammatory and toxic effects on the skin and its appendages.[4,19,21,22]

Small molecule tyrosine kinase inhibitors stop angiogenesis and tumor proliferation by blocking the vascular endothelial growth factor receptor (VEGFR) and platelet derived growth factor receptor (PDGFR). This dual inhibition disrupts the normal repair process that involves capillaries and fibroblasts, and leads to inflammation of friction and trauma prone areas such as hands and feet.[1,11,23,24]

Almost all side effects due to signal transduction inhibitors in this study were because of Imatinib, with no side effect noted with dasatinib and nilotinib, on expected lines as reported in the literature.[12]

Infrequent occurrence of adverse effects occurred with Immune checkpoint inhibitor (Anti PD1 inhibitor) (pembrolizumab), taxane with albumin bound nanoparticle drug (nab paclitaxel), albumin bound anthracycline (liposomal doxorubicin).

Conclusion

It has now been established as a fact, through evidence-based research studies, that newer targeted drugs in use for various types of solid and hematological malignancies are associated with various adverse effects related to skin, hair, nails and mucosae, because of common or identical biochemical ligand found at these sites and those in cancer cells.

Most common dermatological adverse effects reported in our study and across the literature are xerosis and pruritus, papulopustular eruptions, hand foot syndrome, maculopapular eruption, lichenoid eruptions, alopecia, paronychia and melanonychia.

Anticipation of such dermatological adverse effects as well as preparedness in advance, with multidisciplinary approach involving dermatologists along with the treating physician and oncologist can help in far better and timely management of such patients. This will also alleviate the apprehensions of the patients and their family members and also help treating oncologist to take appropriate and timely decision regarding continuation or discontinuation of the therapy, whether temporarily or on permanent basis. In most of such situations, treatment may be continued after proper management of the dermatological condition and counseling of the patients and their family members.

References

1. Lupu I, Voiculescu N, Bacalbasa N, *et al*. Cutaneous complications of molecular targeted therapy used in oncology. *J Med Life*. 2016;**9(1)**:19-25.
2. Shi VJ, Levy LL, Choi JN. Cutaneous manifestations of nontargeted and targeted chemotherapies. *Semin Oncol*. 2016; **43(3)**:419-25.
3. Crisci S, Amitrano F, Saggese M, *et al*. Overview of Current Targeted Anti-Cancer Drugs for Therapy in Onco-Hematology. *Medicina (Kaunas)*. 2019;**55(8)**:414.
4. Fabbrocini G, Panariello L, Caro G, *et al*. Acneiform Rash Induced by EGFR Inhibitors: Review of the Literature and New Insights. *Skin Appendage Disord* 2015;**1(1)**:31-7.
5. Petrelli F, Borgonovo K, Barni S. The predictive role of skin rash with cetuximab and panitumumab in colorectal cancer patients: a systematic review and meta-analysis of published trials. *Target Oncol*. 2013;**8(3)**:173-81.
6. Petrelli F, Borgonovo K, Cabiddu M, *et al*. Relationship between skin rash and outcome in non-small-cell lung cancer patients treated with anti-EGFR tyrosine kinase inhibitors: a literature-based meta-analysis of 24 trials. *Lung Cancer*. 2012;**78(1)**:8-15.
7. Balagula Y, Lacouture ME, Cotliar JA. Dermatologic toxicities of targeted anticancer therapies. *J Support Oncol*. 2010;**8(4)**:149-61.
8. Pavey RA, Kambil SM, Bhat RM. Dermatological adverse reactions to cancer chemotherapy. *Indian J Dermatol Venereol Leprol*. 2015;**81**:434.
9. Macdonald JB, Macdonald B, Golitz LE, *et al*. Cutaneous adverse effects of targeted therapies: Part I: Inhibitors of the cellular membrane. *J Am Acad Dermatol*. 2015;**72(2)**:203-18.
10. Stanculeanu DL, Zob D, Toma OC, *et al*. Cutaneous toxicities of molecular targeted therapies. *Maedica (Buchar)*. 2017;**12(1)**:48–54.
11. Reyes-Habito CM, Roh EK. Cutaneous reactions to chemotherapeutic drugs and targeted therapy for cancer: Part II. Targeted therapy. *J Am Acad Dermatol*. 2014;**71(2)**:217.
12. Amitay-Laish I, Stemmer SM, Lacouture ME. Adverse cutaneous reactions secondary to tyrosine kinase inhibitors including imatinib mesylate, nilotinib, and dasatinib. *Dermatol Ther*. 2011;**24(4)**:386-95.
13. 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(2)**:201-6.
14. 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(5)**:1045-51.
15. Lipworth AD, Robert C, Zhu AX. Hand-foot syndrome (hand-foot skin reaction, palmar-plantar erythrodysesthesia): focus on sorafenib and sunitinib. *Oncology*. 2009;**77(5)**:257-71.
16. Belum VR, Marulanda K, Ensslin C, *et al*. Alopecia in patients treated with molecularly targeted anticancer therapies. *Ann Oncol*. 2015;**26(12)**:2496-502.
17. Vigarios E, Epstein JB, Sibaud V. Oral mucosal changes induced by anticancer targeted therapies and immune checkpoint inhibitors. *Support Care Cancer*. 2017; **25(5)**:1713-39.
18. Pinto C, Barone CA, Girolomoni G, *et al*. Management of Skin Reactions During Cetuximab Treatment in Association With Chemotherapy or Radiotherapy: Update of the Italian Expert Recommendations. *Am J Clin Oncol*. 2016;**39(4)**:407-15.
19. Cho YT, Chen KL, Chu CY. Treatment strategies of epidermal growth factor receptor inhibitor-induced skin toxicities: pre-emptive or reactive? *Ann Transl Med*. 2016;**4(16)**:318.
20. Pastore S, Mascia F, Mariani V, *et al*. The epidermal growth factor receptor system in skin repair and inflammation. *J Invest Dermatol*. 2008;**128**:1365-74.
21. Owczarek W, Słowińska M, Lesiak A, *et al*. The incidence and management of cutaneous adverse events of the epidermal growth factor receptor inhibitors. *Postepy Dermatol Alergol*. 2017;**34(5)**:418-28.
22. Osio A, Mateus C, Soria JC, *et al*. Cutaneous side-effects in patients on long-term treatment with epidermal growth factor receptor inhibitors. *Br J Dermatol*. 2009;**161(3)**:515-21.
23. Zimmerman EI, Gibson AA, Hu S, *et al*. Multikinase Inhibitors Induce Cutaneous Toxicity through OAT6-Mediated Uptake and MAP3K7-Driven Cell Death. *Cancer Res*. 2016;**76(1)**:117-26.
24. Kozuki T. Skin problems and EGFR-tyrosine kinase inhibitor. *Jpn J Clin Oncol*. 2016; **46(4)**:291-8.