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Research Article

Dermatological Side-Effects Developing in Patients Using Targeted Chemotherapy Drugs: A Review of the Literature

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Abstract

Objectives: Numerous dermatological side-effects are reported with the use of targeted therapies. These adverse events derive from common signaling pathways implicated in malignant behavior and normal homeostatic activity of both the epidermis and dermis.

Methods: Patients under follow-up at the Oncology Clinic 12 using bevacizumab, five cetuximab, four sunitinib, four sorafenib, three panitumumab, one pazopanib, one trastuzumab, and one using vemurafenib, were included in the study. Patients' cutaneous drug side-effects were assessed at dermatological examinations before starting treatment and at months 1, 3, and 6 during treatment.

Results: The most common finding was xerosis, seen in 54% (17/31) of our patients receiving targeted treatment. Papulopustular eruption was observed in 63% (12/19) of patients using epidermal growth factor receptor inhibitors. The most common finding in the nails was brittleness-tenderness. Dry mouth was prominent among the mucositis findings. The four patients with nosebleeds were using antiangiogenesis agents. Papulopustular eruptions emerged in the first month, xerosis in the second and third, dry mouth in the third, and pyogenic granuloma, nail findings, and nosebleeds in the fourth to sixth months.

Conclusion: Dermatological side-effects can impact on the patient's quality of life and cause significant morbidity. Dermatologists and oncologists should therefore collaborate closely to manage these side-effects.

Keywords: Dermatological; side effect; targeted treatment

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The aim of targeted treatments is to block specific biological transduction pathways or cancer proteins that cause tumors to grow and develop. In contrast to the injury caused to normal cells as well as to cancer cells by conventional treatments, the aim of targeted treatments is to prevent the growth and spread of cancer cells alone. The two main types of targeted treatment are monoclonal antibodies, and small molecule tyrosine kinase inhibitors.[1, 2] Monoclonal antibodies used in the treatment of cancer are large molecules that target tissue specific receptors and growth factors present in large quantities in cancer cells. Kinases are proteins that transfer phosphate groups between molecules and that can activate or inactivate another protein/molecule. Tyrosine kinase inhibitors are small molecules that intervene in cell growth and division by suppressing the efficacy of such kinases inside the cell.[1, 3] Targeted treatment currently employs epidermal growth factor receptor (EGFR) inhibitors, vascular endothelial growth factor (VEGF) inhibitors, and tyrosine kinase inhibitors.

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Different side-effects to those of conventional therapies, including dermatological findings, began being seen with the use of targeted agents. EGFR inhibitors cause dermatological side-effects such as papulopustular eruption, changes in the hair and nails, and mucosal findings.[4] Antiangiogenesis agents (VEGF inhibitors) act by inhibiting angiogenesis, and lead to mucocutaneous bleeding and impaired wound healing by impacting on skin homeostasis. Multikinase inhibitors affect several tyrosine kinase systems and lead to a wide range of cutaneous side-effects, particularly hyperkeratotic hand-foot syndrome.[5] Dermatological side-effects may necessitate dose modification or total drug discontinuation, affect the patient's quality of life, and may be long-lasting.[6, 7] The management of these side-effects must be an important focal point when using targeted treatment.

The purpose of this study was to present the frequency and time of emergence of dermatological side-effects in patients receiving targeted treatment and the treatment management applied, with a discussion of the current literature.

Methods

Thirty-one patients under follow-up at the Duzce University Medical Faculty Oncology Clinic and started on targeted treatment consisting of bevacizumab (12 patients), cetuximab (five), sunitinib (four), sorafenib (four), panitumumab (three), pazopanib (one), trastuzumab (one) or vemurafenib (one) were included in the study. Patients receiving multiple drugs due to comorbidities or drugs capable of causing papulopustular eruption or xerosis were excluded. Cutaneous drug side-effects were assessed at dermatological examinations before patients started treatment and at months 1, 3, and 6 during treatment. Papulopustular eruption, xerosis, hair changes (cicatricial/non-cicatricial alopecia, hair shaft and color changes, changes in the eyebrows/lashes, nail changes (nail tenderness, brittleness, paronychia, onycholysis, pyogenic granuloma), mucositis (oral aphthae-dry mouth-geographic tongue), photosensitivity, morbiliform rash, skin pigment changes, mucocutaneous hemorrhage, delayed wound healing, hyperkeratotic hand-foot syndrome, venous insufficiency and other findings at dermatological examinations were included in the analysis.

Ethical approval for the study was granted by the Duzce University Ethical Committee (No. 2019/280).

Results

The most common finding, seen in 54% (17/31) of all patients was xerosis, which was also seen in 73% (14/19) of patients using EGFR inhibitors. Papulopustular eruption was observed in 63% (12/19) of patients using EGFR inhibitors, in all those using panitumumab, and in 80% (4/5) of those using cetuximab. No papulopustular eruption was observed in any patients using a VEGF inhibitor (bevacizumab). The most common nail finding was brittleness-tenderness, and nail findings were present in all patients using panitumumab. Paronychia was observed in two patients using cetuximab and panitumumab, and pyogenic granuloma was present in two patients using panitumumab. Dry mouth was particularly prominent among mucositis findings, and was observed in half the patients using bevacizumab. Nosebleed was observed in 33% (4/12) of patients using bevacizumab therapy, and accompanying gingival bleeding was also present in two of these. Seborrheic dermatitis was detected in two patients, hyperpigmentation in the face and palms in one, and edema in the ankle in one (Table 1). Papulopustular eruption emerged in the first month of treatment, xerosis in the second and third, dry mouth in the third, and pyogenic granuloma, nail findings, and nosebleed in the fourth to six months of treatment.

Discussion

Targeted agents exhibit their effectiveness by blocking cellular signaling pathways essential to the proliferation of malignant cells. Various agents are employed in targeted treatment. Two of the most widely used drugs from the targeted treatment family are EGFR and VEGF inhibitors, employed in the treatment of various malignancies including colorectal, head and neck, small cell lung, and breast cancer.[5, 8] EGFR inhibitors are divided into two groups – high molecular weight monoclonal antibodies that bind to the cell surface receptor, and low molecular weight drugs that inhibit intracellular tyrosine kinase. Examples include EGFR inhibitor monoclonal antibodies (such as cetuximab and panitumumab), HER 2 monoclonal antibodies (trastuzumab), EGFR-specific tyrosine kinase inhibitors (such as erlotinib, sorafenib, sunitinib, gefitinib, and pazopanib), and EGFR (ErbB1) and ErbB2 (HER2)-specific tyrosine kinase inhibitors (such as lapatinib, neratanib, and afatinib).[4, 5, 9] Other agents employed in targeted treatment are anti-VEGF monoclonal antibodies (such as bevacizumab).[5, 10]

EGFR is intensely present in the epidermis and skin patches, and is expressed in undifferentiated keratinocytes proliferating in the basal layer of the epidermis and in hair follicles. EGFR is involved in such tumor growth processes as metastasis, cell proliferation, apoptosis, angiogenesis, and cell motility.[11] In addition to their principal function performed by preventing tumor proliferation, EGFR

Table 1. Dermatological side-effects in patients receiving targeted treatment

Disease	Age	Drug used	Papulopustular eruption	Xerosis	Nail changes	Mucositis	Others findings
Rectal Ca	59	Cetuximab		In the arms and legs	Paronychia-Nail tenderness	Oral aphthae Twice monthly	
Rectal Ca	32	Cetuximab	Anterior thorax	Entire body	Nail tenderness	Oral aphthae	Eyebrow-eyelash loss, nose bleeding facial telangiectasia
Rectal Ca	70	Cetuximab	Anterior thorax		Nail tenderness		
Rectal Ca	70	Cetuximab	Anterior-posterior thorax	Entire body		Dry mouth-Oral aphthae	Seborrheic dermatitis
Colon Ca	63	Cetuximab	Anterior thorax	Entire body		Dry mouth	Photosensitivity
Colon Ca	71	Bevacizumab					
Ovarian Ca	51	Bevacizumab				Dry mouth	
Colon Ca	59	Bevacizumab			Brittle nails		Nose bleeding
Colon Ca	65	Bevacizumab			In-growing nail		Nose bleeding
Colon Ca	64	Bevacizumab		Entire body	White nail	Dry mouth-Oral aphthae	Hyperpigmentation onthe face and palm
Colon Ca	59	Bevacizumab					Nose-gingival bleeding
Colon Ca	63	Bevacizumab				Dry mouth	
Rectal Ca	47	Bevacizumab			Nail tenderness	Dry mouth	
Colon Ca	55	Bevacizumab		Entire body	Brittleness and tenderness	Oral aphthae	
GBM*	57	Bevacizumab		Arms and legs	Brittleness and tenderness	Dry mouth	
Colon Ca	48	Bevacizumab				Dry mouth	Nose-gingival bleeding
Rectal Ca	64	Bevacizumab					
Colon Ca	77	Panitumumab	Anterior-posterior thorax	Entire body	Brittleness and tenderness Onycholysis		Hair-eyebrow-eyelash loss
Colon Ca	65	Panitumumab	Chest region	Entire body	Brittleness and tenderness	Oral aphthae	Photosensitivity Hair loss
Rektum Ca	43	Panitumumab	Anterior-posterior thorax	Entire body	Brittleness and tenderness, Paronychia, Pyogenic granuloma	Dry mouth-Oral aphthae	Seborrheic dermatitis
RCC**	80	Sunitinib	Chest region	Arms and legs		Dry mouth	
RCC	43	Sunitinib	Hairy skin	Arms and legs			
RCC	66	Sunitinib					
RCC	57	Sunitinib		Arms and legs	Nail tenderness		Erythematous rash on the trunk
RCC	56	Pazopanib					
HCC***	55	Sorafenib		Entire body	Nail tenderness		Xerotic eczema on the leg
HCC	49	Sorafenib	Pustular eruption in hairy skin				Itching all over the body
HCC	63	Sorafenib		Arms and legs		Dry mouth	
HCC	72	Sorafenib				Dry mouth	Itching all over the body
Thyroid Ca	63	Sorafenib	Pustular eruption in hairy skin	Arms and legs	Nail tenderness		
Malignant melanoma	46	Vemurafenib	Chest regions	Entire body		Dry mouth-Oral aphthae (constant)	Edema in the ankle

*: Glioblastoma multiforme; **: Renal cell carcinoma; *** Hepatocellular carcinoma.

inhibitors also cause numerous cutaneous reactions by impairing keratinocyte proliferation and differentiation by blocking the EGFR pathway in the skin, and compromises normal hair follicle differentiation and development.[5, 9] EGFR prevents IL-1 related inflammation around the hair follicle, while the use of EGFR inhibitors causes papulopustular eruption by elimination that inhibition. Additionally, TNF-alpha and IL-8 can also cause papulopustular eruption in the skin through the same mechanism.[4, 5, 11] All agents targeting EGFR cause similar dermatological side-effects, such as papulopustular eruption, xerosis, changes in hair and nails, and mucosal findings.[4] A meta-analysis involving 8998 patients investigating the side-effects of EGFR inhibitors reported no mortality associated with dermatological side-effects.[6] These side-effects arise from the non-target effects of EGFR inhibitors, and can be prevented with topical menadione (vitamin K3) producing receptor dephosphorylation.[12]

Neovascularization is an important factor in meeting the oxygen requirements of rapidly multiplying neoplastic cells. Vascular endothelial growth factor (VEGF) and the VEGF tyrosine kinase receptor system function together. VEGF inhibitors prevent the proliferation of endothelial cells and reduce micropapillary formations in tumor tissue.[13] At the same time, they also impair normal tissue hemostasis and thus exhibit mucocutaneous side-effects.[14]

Multikinase inhibitors affect several tyrosine kinase systems and cause a wide variety of cutaneous side-effects, particularly hyperkeratotic hand-foot syndrome.[5]

Epidermal Growth Factor Receptor Inhibitor-Related Side-Effects

Papulopustular Eruption

Papular and pustular eruptions commence in the seborrheic regions within the first and second weeks of EGFR therapy in a dose-dependent manner and are seen in >75% of patients.[15] In contrast to acne, no comedonal-nodulocystic formation occurs, and the lesions are generally accompanied by itching. The eruptions occur in the head-neck-trunk and proximal upper extremity.[16, 17] Solar rays exacerbate eruption formation. However, studies have determined that solar protection has no effect on preventing eruption development or flare-up. Nonetheless, its use is recommended in individuals with Fitzpatrick skin types I-III.[18, 19] Treatment options vary depending on the severity of the rash. In Grade 1, rash accompanied/unaccompanied by pruritus covers less than 10% of the body, while in Grades 2-3, rash accompanied by pruritus,

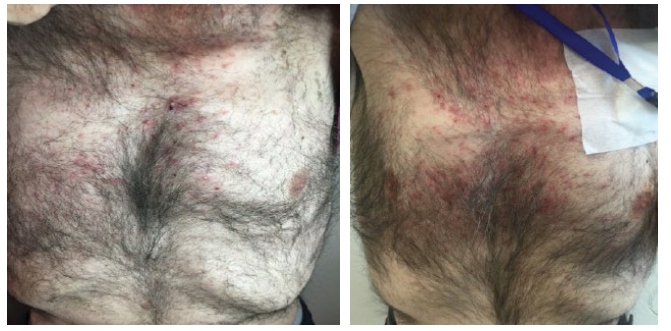

Figure 1. Clinical appearance of Grade 1 acneiform eruption on the trunk of two patients receiving epidermal growth factor receptor inhibitor therapy.

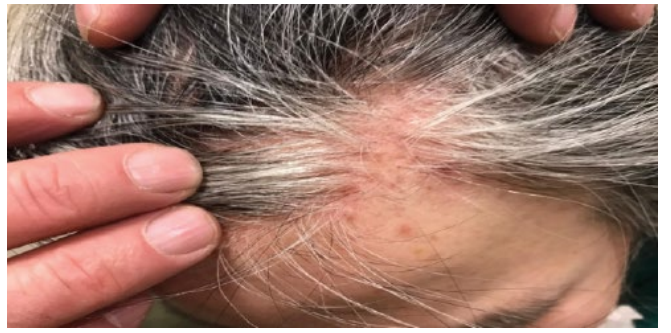

Figure 2. Papulopustular rash in hairy skin.

tenderness, and/or superinfection covers 10-30% of the body. The eruptions are aseptic pustules so long as no secondary infection occurs.[20] Topical antibiotic creams-antiseptic solutions and low-dose corticosteroids are sufficient in Grade 1 eruptions. However, systemic treatment is required in Grade 2-3 eruptions. Tetracycline is the first choice option and is probably effective due to its anti-inflammatory properties.[21] Low-dose isotretinoin is another option in unresponsive patients.[22] Antihistaminic therapy is also beneficial for pruritus.[5] In the present study, papulopustular eruption was observed in 63% (12/19) patients using EGFR inhibitors. Accompanying pruritus was present in 50% (6/12) of patients with papulopustular eruption. We learned from patients' histories that the eruptions had begun in the second week of treatment, and these were also detected at dermatological examinations at check-ups in the first month (Fig. 1). While rash was present in the thoracic region in all patients, only two had accompanying hairy skin rash (Fig. 2). Our patients' rash severity was Grade 1. In addition to topical antibacterial cream, our patients were also recommended topical steroid cream and ketoconazole shampoo. No Grade 2-3 rash was encountered in this study. We think this may be due, in addition to treatment, to patients being started on prophylactic cream in which containing vitamin K1.

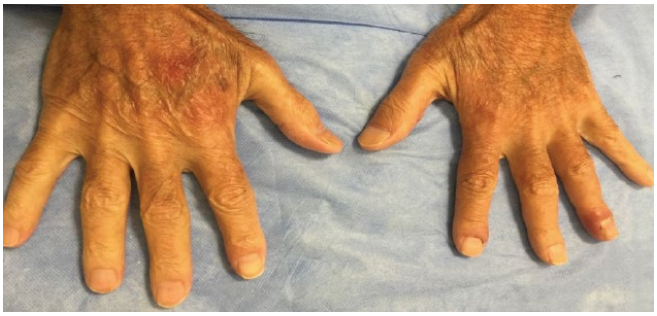

Figure 3. Secondary paronychia associated with epidermal growth factor receptor inhibitor therapy; left hand fourth finger.

Xerosis

This is frequently seen 1-3 months after EGFR use, and is the second most common side-effect. It causes dry skin fissures and cracks, and can also lead to cutaneous infections by permitting bacterial entry.[23] Xerosis is seen in 35% of patients, and has been reported at 50-100% in the few previous studies on the subjects.[23, 24] Xerosis was the most common finding in the present study, being observed in 54% (17/31) of patients, and in 73% (14/19) of patients using EGFR inhibitors. Topical moisturizers are recommended. Care must be taken to avoid moisturizer-related folliculitis.[25] Water-based moisturizers were therefore recommended to our patients.

Nail Changes

Nail changes include separation from the nail bed (onycholysis), pyogenic granuloma, and paronychia. Such changes may be seen in 17.2% of patients using EGFR inhibitors.[26, 27] Nail findings were observed in 47% (9/19) patients using EGFR inhibitors in the present study. The most common findings was nail tenderness, while paronychia was observed in two patients (Fig. 3), and pyogenic granuloma in one. Topical corticosteroids, topical-systemic antibiotics, daily washing with antiseptics, and more recently platelet-rich plasma for paronychia are recommended for treatment.[28, 29] Our patients with nail sensitivity were treated with topical corticosteroids, and patients with paronychia were treated with corticosteroid+antibacterial cream, while pyogenic granuloma was treated with cauterization.

Hair Changes

Reduced hair growth, hair shaft breakage, and thinning may be seen. Androgenic alopecia may also be observed. The eyelashes may acquire a long, thick, hard appearance (trichomegaly). Curvature of the eyelash leading to keratitis may occur.[30, 31] Trichomegaly was not observed in any of our patients, and eyebrow and eyelash loss occurred in two. Eyelash involvement in one patient consisted of more pronounced seborrheic dermatitis (Fig. 4).

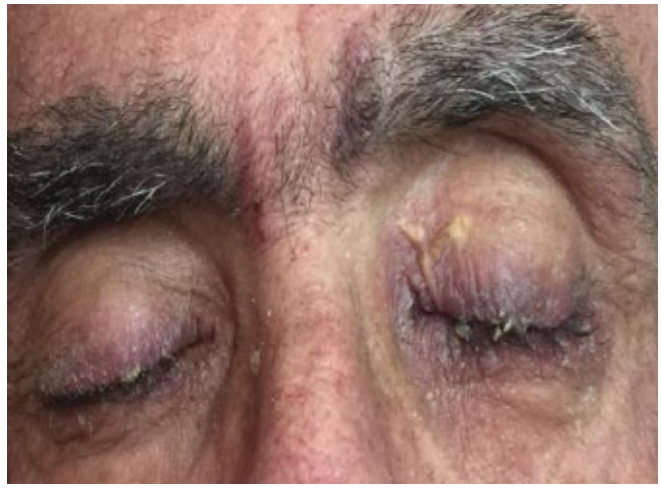

Figure 4. Seborrheic dermatitis exhibiting more pronounced involvement at the base of the eyelashes.

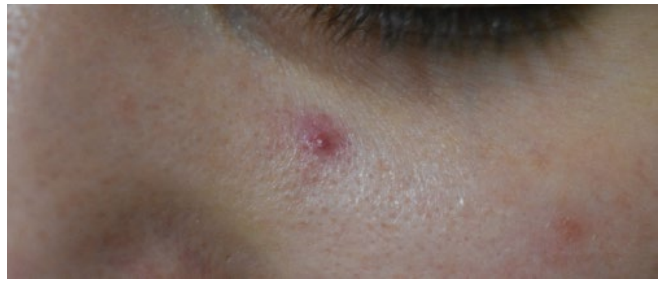

Figure 5. Facial telangiectasia.

Mucositis

Oral aphtha, dry mouth or geographic language can be observed in targeted chemotherapy.[32] Geographic tongue generally develops in association with bevacizumab and multikinase angiogenesis inhibitors.[33] Genital involvement may be seen in the form of vulvovaginitis, balanitis, or genital aphthae. Oral aphthae are treated as idiopathic oral aphthae.[5]

In this study, dry mouth was observed in 37% (7/19) patients using EGFR inhibitors, and oral aphthae in 32% (6/19).

Photosensitivity

Telangiectasia, hyperpigmentation,[34] photosensitive rash,[35, 36] and phototoxic reaction[37] in areas exposed to sunlight have been reported in patients using EGFR inhibitors. Photosensitivity was determined in two of our patients, and facial telangiectasia (Fig. 5) in one. Increasing palmar hyperpigmentation was present in one patient. Hyperpigmentation and telangiectasia may resolve after discontinuation of treatment. Laser is recommended if telangiectasia does not improve. Due to these side-effects, use of solar protection must be recommended in patients using EGFR.[5]

Antiangiogenesis Agent-Related Side-Effects

The inhibition of angiogenesis also affects normal skin hemostasis. Mucocutaneous hemorrhages or delayed wound healing may be observed in association with this.

Mucocutaneous Hemorrhage

In the same way that VEGF inhibitors affect vascular proliferation, they also increase vascular permeability. Findings manifest as mild mucosal bleeding, and epistaxis is frequently seen.[36] Mucocutaneous hemorrhage may be seen in 20-40% of patients using bevacizumab.[32, 33] In the present study, nosebleed was determined in 33% (4/12) of patients using VEGF inhibitors, and accompanying gingival bleeding was also present in two of the patients with nosebleed. Due to their effects on vascular proliferation and permeability, VEGF inhibitors should be employed approximately one month after elective surgery because of cutaneous and/or mucosal bleeding, thromboembolism, or delayed wound healing.[38, 39] The use of bevacizumab has also recently become promising in patients with hereditary hemorrhagic telangiectasia.[40] Osteonecrosis of the jaw and geographic tongue may develop in association with bevacizumab use.[32, 33]

Impaired Wound Healing

Dose-dependent worsened wound healing occurs and must be considered in patients scheduled to undergo surgical treatment.[5] Worsened wound healing during treatment was determined in 33% (3/12) of our patients using bevacizumab.

Multikinase Inhibitor-Related Side-Effects

Multikinase inhibitors affect several tyrosine kinase systems and cause various dermatological side-effects. Possible cutaneous side-effects include hyperkeratotic hand-foot syndrome, morbiliform rash, depigmentation in the hair and skin, and localized psoriasiform or lichenoid-like eruption involving the scrotum or vulva.[41–43]

Hyperkeratotic Hand-Foot Syndrome

Hyperkeratotic hand-foot syndrome is a dose-dependent side-effect emerging in the first weeks of sorafenib, sunitinib, pazopanib, and cabozantinib use.[44–46] Papulopustular eruptions in hairy skin were present in two of our patients using sorafenib.

Hyperkeratotic hand-foot syndrome emerges in the form of bilateral painful, hyperkeratotic plaques hindering daily activities. Soft, orthopedic shoes are recommended as treatment. Topical steroids, moisturizers, topical keratolitics, and sometimes systemic retinoids in Grade 3 patients may be used, depending on the severity of medical treatment.[5]

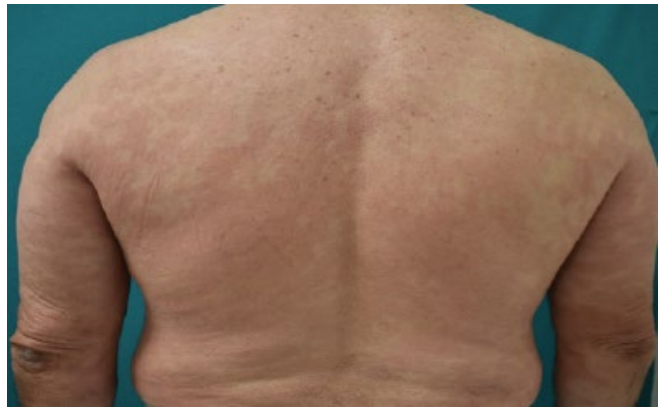

Figure 6. Erythematous patch lesion blanching with pressure on the trunk.

Other Side-Effects

Morbiliform rash begins in the face, exhibits centripetal spread, and is seen in the first weeks of treatment.[8] Diffuse erythematous patch lesions were observed on the trunk in the third week of treatment in our patient using sunitinib (Fig. 6). Cutaneous depigmentation is particularly observed in patients using pazopanib,[47] while hair depigmentation is seen in patients using sunitinib[48] and pazopanib.[49] Facial edema associated with sunitinib, and cases of eruptive nevi formations associated with sunitinib and sorafenib have also been reported.[50, 51]

Conclusion

Cutaneous side-effects are the most common findings of several targeted treatments. Dose modification or drug discontinuation may be required when cutaneous side-effects are severe or prolonged. Early diagnosis and treatment of skin-related toxicities are important. With the constant expansion of the targeted treatment family, cutaneous side-effects will occupy an important place in the multidisciplinary approach to oncological care.

Disclosures

Ethics Committee Approval: Ethical approval for the study was granted by the Duzce University Ethical Committee (No. 2019/280).

Informed Consent: Written consent to the use of photographs was obtained from patients and their relatives.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – E.K; Design – E.K., O.E.; Supervision – E.K.; Materials – E.K., O.E.; Data collection and/or processing – E.K., O.E; Analysis and/or interpretation – E.K; Literature search – E.K., O.E; Writing – E.K., O.E; Critical review – E.K., O.E.

References

1. Gerber D.E. Targeted Therapies: A New Generation of Cancer Treatments. Am Fam Physician 2008;77:311–19.
2. Cemre ACAR, Tunca Gül ALTUNTAŞ. Hedefe Yönelik Kanser Tedavisinde Kullanılan Akıllı İlaçlar: EGFR İnhibitörleri. J. Pharm. Sci 2019;44:47–63.
3. Baykara O. Kanser Tedavisinde Güncel Yaklaşımlar. Balıkesir Health Scıences Journal 2016;5:154–65.
4. Saraswat N, Sood A, Kumar D, Verma R, Sushil K. Clinical Profile of Cutaneous Adverse Effects of Epidermal Growth Factor Receptor Inhibitors: A Prospective Observational Study of 76 Cases. Indian Dermatol Online J 2019;10:251–55.
5. 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;72:203–18.
6. Jatoi A, Nguyen PL. Do patients die from rashes from epidermal growth factor receptor inhibitors? A systematic review to help counsel patients about holding therapy. Oncologist 2008;13:1201–4.
7. Dy GK, Adjei AA. Understanding, recognizing, and managing toxicities of targeted anticancer therapies. CA Cancer J Clin 2013;63249–79.
8. Johnston JB, Navaratnam S, Pitz MW, Maniate JM, Wiechec E, Baust H, et al. Targeting the EGFR pathway for cancer therapy. Curr Med Chem 2006;13:3483–92.
9. Lacouture ME, Anadkat M, Jatoi A, Garawin T, Bohac C, Mitchell E. Dermatologic Toxicity Occurring During Anti-EGFR Monoclonal Inhibitor Therapy in Patients With Metastatic Colorectal Cancer: A Systematic Review. Clin Colorectal Cancer 2018;17:85–96.
10. Robert C, Sibaud V, Mateus C, Cherpelis BS. Advances in the management of cutaneous toxicities of targeted therapies. Semin Oncol 2012;39:227–40.
11. Kurtuluş Didem Yazganoğlu, Can Baykal. Hedefe Yönelik Kemoterapi İlaçlarına Bağlı Akneiform Döküntü ve Eşlik Eden Diğer Dermatolojik Yan Etkiler: Retrospektif Bir Değerlendirme Türkderm 2012;46:84–9.
12. R. Perez-Soler, Y. Zou, T. Li, C. Tornos, Y. Ling . Topical vitamin K3 (Vit K3, Menadione) prevents erlotinib and cetuximab-induced EGFR inhibition in the skin. Journal of Clinical Oncology 2006:18;3036.
13. Roskoski R Jr. Vascular endothelial growth factor (VEGF) signaling in tumor progression. Crit Rev Oncol Hematol 2007;62:179–213.
14. Roskoski R Jr. VEGF receptor protein-tyrosine kinases: structure and regulation. Biochem Biophys Res Commun 2008;375:287–91.
15. Madke B, Gole P, Kumar P, Khopkar U. Dermatological Side Effects of Epidermal Growth Factor Receptor Inhibitors: 'PRIDE' Complex. Indian J Dermatol 2014;59:271–74.
16. Segaert S, Chiritescu G, Lemmens L, Dumon K, Van Cutsem E, Tejpar S. Skin toxicities of targeted therapies. Eur J Cancer 2009;45:295–308.
17. Yalici-Armagan B, Ayanoglu BT, Demirdag HG. Targeted tumour therapy induced papulopustular rash and other dermatologic side effects: a retrospective study. Cutan Ocul Toxicol 2019;38:261–66.
18. Luu M, Lai SE, Patel J, Guitart J, Lacouture ME. Photosensitive rash due to the epidermal growth factor receptor inhibitor erlotinib. Photodermatol Photoimmunol Photomed 2007;23:42–5.
19. Jatoi A, Thrower A, Sloan JA, Flynn PJ, Wentworth-Hartung NL, Dakhil SR, et al. Does sunscreen prevent epidermal growth factor receptor (EGFR) inhibitor-induced rash? Results of a placebo-controlled trial from the North Central Cancer Treatment Group (N05C4). Oncologist 2010;15:1016–22.
20. Chen AP, Setser A, Anadkat MJ, Cotliar J, Olsen EA, Garden BC, et al. Grading dermatologic adverse events of cancer treatments: the Common Terminology Criteria for Adverse Events Version 4.0. J Am Acad Dermatol 2012;67:1025–39.
21. Robert C, Sibaud V, Mateus C, Cherpelis BS. Advances in the management of cutaneous toxicities of targeted therapies. Semin Oncol 2012;39:227–40.
22. Bidoli P, Cortinovis DL, Colombo I, et al. Isotretinoin plus clindamycin seem highly effective against severe erlotinib-induced skin rash in advanced non-small cell lung cancer. J Thorac Oncol 2010;5:1662–3.
23. Owczarek W, Słowińska M, Lesiak A, Ciążyńska M, Maciąg A, Paluchowska E, et al. The incidence and management of cutaneous adverse events of the epidermal growth factor receptor inhibitors. Postepy Dermatol Alergol 2017;34:418–28.
24. Chanprapaph K, Vachiramon V, Rattanakaemakorn P. Epidermal growth factor receptor inhibitors: a review of cutaneous adverse events and management. Dermatol Res Pract 2014;2014:734249.
25. Busam KJ, Capodieci P, Motzer R, Kiehn T, Phelan D, Halpern AC. Cutaneous side-effects in cancer patients treated with the antiepidermal growth factor receptor antibody C225. Br J Dermatol 2001;144:1169–76.
26. Garden BC, Wu S, Lacouture ME. The risk of nail changes with epidermal growth factor receptor inhibitors: a systematic review of the literature and meta-analysis. J Am Acad Dermatol 2012;67:400–8.
27. Lacouture M, Sibaud V. Toxic Side Effects of Targeted Therapies and Immunotherapies Affecting the Skin, Oral Mucosa, Hair, and Nails. Am J Clin Dermatol 2018;19:31–9.
28. Robert C, Sibaud V, Mateus C, Verschoore M, Charles C, Lanoy E, et al. Nail toxicities induced by systemic anticancer treatments. Lancet Oncol 2015;16:181–9.
29. Kwon SH, Choi JW, Hong JS, Byun SY, Park KC, Youn SW, et al.

Gefitinib-induced paronychia: response to autologous platelet-rich plasma. Arch Dermatol 2012;148:1399–1402.
30. Fraunfelder FT, Fraunfelder FW. Trichomegaly and other external eye side effects associated with epidermal growth factor. Cutan Ocul Toxicol 2012;31:195–7.
31. Zheng H, Zhang H, Zhang T, Wang Q, Hu F, Li B. Trichomegaly and scalp hair changes following treatment with erlotinib in pulmonary adenocarcinoma patients: A case report and literature review. Exp Ther Med 2016;12:1287–92.
32. Vigarios E, Epstein JB, Sibaud V. Oral mucosal changes induced by anticancer targeted therapies and immune checkpoint inhibitors. Support Care Cancer 2017;25:1713–39.
33. Hubiche T, Valenza B, Chevreau C, Fricain JC, Del Giudice P, Sibaud V. Geographic tongue induced by angiogenesis inhibitors. Oncologist 2013;18:16–7.
34. Kong HH, Fine HA, Stern JB, Turner ML. Cutaneous pigmentation after photosensitivity induced by vandetanib therapy. Arch Dermatol 2009;145:923–5.
35. Fukai T, Hasegawa T, Nagata A, Matsumura M, Kudo Y, Shiraishi E, et al. Case of erlotinib-induced photosensitivity. J Dermatol 2014;41:445–6.
36. Tokimasa Y, Fujiwara K, Higo H, Kameyama N, Kayatani H, Sato K, et al. Photosensitivity reaction induced by erlotinib. International Cancer Conference Journal 2012;1:173–5.
37. Yin Y, Qiu XY, Zhang YH, Zhang B. A rare cutaneous phototoxic rash after vandetanib therapy in a patient with thyroid cancer: A case report. Medicine (Baltimore) 2019;98:16392.
38. Chen HX, Cleck JN. Adverse effects of anticancer agents that target the VEGF pathway. Nat Rev Clin Oncol 2009;6:465–77.
39. Wozel G, Sticherling M, Schön MP. Cutaneous side effects of inhibition of VEGF signal transduction. J Dtsch Dermatol Ges 2010;8:243–9.
40. Kanellopoulou T, Alexopoulou A. Bevacizumab in the treatment of hereditary hemorrhagic telangiectasia. Expert Opin Biol Ther 2013;13:1315–23.
41. 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;144:886–92.
42. Lipworth AD, Rober C, Zhu AX. Hand-foot syndrome (hand-foot skin reaction, palmar-plantar erythrodysesthesia): focus on sorafenib and sunitinib. Oncology 2009;77:257–71.
43. 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;72:203–18.
44. Sil A, Das NK. Sorafenib-induced hand-foot syndrome in a patient of renal cell carcinoma. Indian J Pharmacol 2014;46:334–36.
45. Belum VR, Serna-Tamayo C, Wu S, Lacouture ME. Incidence and risk of hand-foot skin reaction with cabozantinib, a novel multikinase inhibitor: a meta-analysis. Clin Exp Dermatol 2016;41:8–15.
46. Lai JS, Beaumont JL, Diaz J, Khan S, Cella D. Validation of a short questionnaire to measure symptoms and functional limitations associated with hand-foot syndrome and mucositis in patients with metastatic renal cell carcinoma. Cancer 2016;122:287–95.
47. Robert C, Sibaud V, Mateus C, Cherpelis BS. Advances in the management of cutaneous toxicities of targeted therapies. Semin Oncol 2012;39:227–40.
48. Bansal S, Sardana K, Singh K, Garg VK. Concurrent hand-foot skin reaction and hair depigmentation with sunitinib: report of a case and literature review of kinase inhibitors and blocking antibodies. Indian J Dermatol 2014;59:588–91.
49. Šeparović R, Pavlović M, Silovski T, Tečić Vuger A. Rapid hair depigmentation in patient treated with pazopanib. BMJ Case Rep 2018.
50. Jiménez-Gallo D, Albarrán-Planelles C, Linares-Barrios M, Martínez-Rodríguez A, Báez-Perea JM. Eruptive melanocytic nevi in a patient undergoing treatment with sunitinib. JAMA Dermatol 2013;149:624–26.
51. Uhlenhake EE, Watson AC, Aronson P. Sorafenib induced eruptive melanocytic lesions. Dermatol Online J 2013;19:18184.