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. 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. Targeted treatment currently employs epidermal growth factor receptor (EGFR) inhibitors, vascular endothelial growth factor (VEGF) inhibitors, and tyrosine kinase inhibitors.
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, morbilliform 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 (ErB1) and ErB2 (HER2)-specific tyrosine kinase inhibitors (such as lapatinib, neratinib, 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

<table>
<thead>
<tr>
<th>Disease</th>
<th>Age</th>
<th>Drug used</th>
<th>Papulopustular eruption</th>
<th>Xerosis</th>
<th>Nail changes</th>
<th>Mucositis</th>
<th>Others findings</th>
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</thead>
<tbody>
<tr>
<td>Rectal Ca</td>
<td>59</td>
<td>Cetuximab</td>
<td>Anterior thorax</td>
<td>Entire body</td>
<td>Nail tenderness</td>
<td>Oral aphthae</td>
<td>Eyebrow-eyelash loss, nose bleeding, facial telangiectasia</td>
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<td>Entire body</td>
<td>Nail tenderness</td>
<td>Dry mouth-Oral aphthae</td>
<td>Seborrheic dermatitis</td>
</tr>
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<td>Dry mouth</td>
<td>Photosensitivity</td>
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<td>Brittle nails</td>
<td>Dry mouth</td>
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<td>Nose bleeding</td>
<td></td>
</tr>
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<td>Anterior thorax</td>
<td>Entire body</td>
<td>Brittle nails</td>
<td>Nose bleeding</td>
<td></td>
</tr>
<tr>
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<td>64</td>
<td>Bevacizumab</td>
<td>Anterior thorax</td>
<td>Entire body</td>
<td>Brittle nails</td>
<td>Dry mouth-Oral aphthae</td>
<td>Hyperpigmentation on the face and palm</td>
</tr>
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<td>Anterior thorax</td>
<td>Entire body</td>
<td>Brittle nails</td>
<td>Dry mouth</td>
<td>Nose-gingival bleeding</td>
</tr>
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<td>Anterior thorax</td>
<td>Entire body</td>
<td>Brittle nails</td>
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<td>Brittle nails</td>
<td>Dry mouth</td>
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<td>Brittle nails</td>
<td>Dry mouth</td>
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<tr>
<td>GBM*</td>
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<td>Entire body</td>
<td>Brittle nails</td>
<td>Dry mouth</td>
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<td>Dry mouth</td>
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<td>Bevacizumab</td>
<td>Anterior thorax</td>
<td>Entire body</td>
<td>Brittle nails</td>
<td>Dry mouth</td>
<td></td>
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<td>Panitumumab</td>
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<td>Brittle nails</td>
<td>Oral aphthae</td>
<td>Hair-eyebrow-eyelash loss</td>
</tr>
<tr>
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<td>Panitumumab</td>
<td>Anterior-posterior thorax</td>
<td>Entire body</td>
<td>Brittle nails</td>
<td>Dry mouth-Oral aphthae</td>
<td>Hair loss</td>
</tr>
<tr>
<td>Rektum Ca</td>
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<td>Anterior-posterior thorax</td>
<td>Entire body</td>
<td>Brittle nails</td>
<td>Dry mouth-Oral aphthae</td>
<td>Seborrheic dermatitis</td>
</tr>
<tr>
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<td>Entire body</td>
<td>Brittle nails</td>
<td>Dry mouth-Oral aphthae</td>
<td></td>
</tr>
<tr>
<td>RCC</td>
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<td>Entire body</td>
<td>Brittle nails</td>
<td>Dry mouth-Oral aphthae</td>
<td></td>
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<tr>
<td>RCC</td>
<td>66</td>
<td>Sunitinib</td>
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<td>Entire body</td>
<td>Brittle nails</td>
<td>Dry mouth-Oral aphthae</td>
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<tr>
<td>RCC</td>
<td>57</td>
<td>Sunitinib</td>
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<td>Entire body</td>
<td>Brittle nails</td>
<td>Dry mouth-Oral aphthae</td>
<td></td>
</tr>
<tr>
<td>RCC</td>
<td>56</td>
<td>Pazopanib</td>
<td>Anterior-posterior thorax</td>
<td>Entire body</td>
<td>Brittle nails</td>
<td>Dry mouth-Oral aphthae</td>
<td></td>
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<tr>
<td>HCC***</td>
<td>55</td>
<td>Sutafenib</td>
<td>Anterior-posterior thorax</td>
<td>Entire body</td>
<td>Brittle nails</td>
<td>Dry mouth-Oral aphthae</td>
<td></td>
</tr>
<tr>
<td>HCC</td>
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<td>Sutafenib</td>
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<td>Entire body</td>
<td>Brittle nails</td>
<td>Dry mouth-Oral aphthae</td>
<td></td>
</tr>
<tr>
<td>HCC</td>
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<td>Sutafenib</td>
<td>Anterior-posterior thorax</td>
<td>Entire body</td>
<td>Brittle nails</td>
<td>Dry mouth-Oral aphthae</td>
<td></td>
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<tr>
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<td>Brittle nails</td>
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<tr>
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<td>Dry mouth-Oral aphthae</td>
<td></td>
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<td>Vemurafenib</td>
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<td>Entire body</td>
<td>Brittle nails</td>
<td>Dry mouth-Oral aphthae</td>
<td>Itching all over the body</td>
</tr>
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</table>

*: 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 seborrhoeic 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, 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.\[^30\]\ 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.
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 cautery.

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).

Mucositis
Oral aphthae, 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 homeostasis. 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. Mucocutaneous hemorrhage may be seen in 20-40% of patients using bevacizumab. 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. The use of bevacizumab has also recently become promising in patients with hereditary hemorrhagic telangiectasia. Osteonecrosis of the jaw and geographic tongue may develop in association with bevacizumab use.

**Impaired Wound Healing**
Dose-dependent worsened wound healing occurs and must be considered in patients scheduled to undergo surgical treatment. 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, morbilliform rash, depigmentation in the hair and skin, and localized psoriasiform or lichenoid-like eruption involving the scrotum or vulva.

**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. 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.

**Other Side-Effects**
Morbilliform rash begins in the face, exhibits centripetal spread, and is seen in the first weeks of treatment. 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, while hair depigmentation is seen in patients using sunitinib and pazopanib. Facial edema associated with sunitinib, and cases of eruptive nevi formations associated with sunitinib and sorafenib have also been reported.

**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.

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