# 15 Nail Changes with Targeted Antineoplastic Drugs

Dimitrios Rigopoulos and Ionna Triantafilopoulou

The last two decades have been extremely productive in oncology pharmacotherapy resulting in an abundance mainly of targeted drugs. Until then, broad spectrum traditional antineoplastic drugs had been used but due to their unselective mechanism of action provoked a great range of undesirable effects. The targeted drugs can be classified according to their mechanism of action. They include proteasome inhibitors, toxic chimeric proteins, and signal transduction inhibitors such as tyrosine kinase (non-receptor and receptor), serine/threonine kinase, histone deacetylase, and mammalian target of rapamycin inhibitors. Increasingly used are also targeted vascular (VEGF) and platelet-derived endothelial growth factor blockade [1]. Despite their selective and precise mechanism of action, targeted therapies do not lack adverse effects (AEs). Cutaneous toxicities are among the most frequently observed AEs [2], and their prompt and adequate management requires a close collaboration of oncologists and dermatologists. Because they are often administered in long durations, preventive and therapeutic measures are more frequently needed than with conventional chemotherapies [3]. When referring to nail changes, it is important to remember that they represent past drug effects because of their slow rate of growth. Fingernails grow at 0.1 mm per day and toenails at 0.03 per month, requiring 4–6 and 12–18 months, respectively, to regrow. Thus, prevention of nail changes has to be practiced well before the onset of the first visible sign.

As demonstrated in various studies, nail changes are quite disturbing for cancer patients [4]. Broadly used grading systems of nail toxicity fail to demonstrate the range of nail alterations provoked by antineoplastic agents in general and their correlation with patients' quality of life.

## Nail Toxicity Grading

The National Cancer Institute's Common Terminology Criteria for Adverse Events (NCICTCAE) categorizes a broad collection of AEs that are experienced by cancer patients during treatment, and each event has a structured description and rating of severity. The aim of each revision of the CTCAE is to include relevant treatment-related AEs and to update severity descriptions. The current version, v 5.0 (11/2017), divides nail AEs according to descriptive changes, namely, nail discoloration, loss, and ridging (Table 15.1). The severity of these AEs can be graded from mild to moderate given that they neither demand hospitalization nor threaten the patient's life [5].

Despite CTCAEs regular updates, another developed grading system seems to be even more

D. Rigopoulos (✉) · I. Triantafilopoulou
Department of Dermatology-Venereology, National and Kapodistrian University of Athens, Medical School, "A. Sygros" Hospital, Athens, Greece



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**Table 15.1** Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0, section on nail changes

| | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 5 |
|---|---|---|---|---|---|
| Skin and Subcutaneous Tissue Disorders (CTCAE Term) | | | | | |
| *Nail changes* | Present | | | | |
| Definition: A disorder characterized by a change in the nails | | | | | |
| *Nail discoloration* | Asymptomatic; clinical or diagnostic observations only | | | | |
| Definition: A disorder characterized by a change in the color of the nail plate | | | | | |
| *Nail loss* | Asymptomatic separation of the nail bed from the nail plate or nail loss | Symptomatic separation of the nail bed from the nail plate or nail loss; limiting instrumental ADL | | | |
| Definition: A disorder characterized by loss of all or a portion of the nail | | | | | |
| *Nail ridging* | Asymptomatic; clinical or diagnostic observations only; intervention not indicated | | | | |
| Definition: A disorder characterized by vertical or horizontal ridges on the nails | | | | | |

precise when describing skin-related adverse events. EGFRIs are one of the best examples of skin-related toxicity at concentrations necessary for antitumor effects; the coincident inhibition of the EGFR in the skin and appendages results in altered keratinocyte function.

As the use of EGFRIs has been expanding in several solid tumors, the necessity of developing a better scale to fully characterize their toxicities in order to improve clinical research reporting, dosing adjustments during treatment, and management of treatment side effects was obvious. Thus, in 2010 the MASCC (Multinational Association of Supportive Care in Cancer) skin toxicity study group presented a new scale to detect and report EGFRI-related toxicities with greater sensitivity, specificity, and range than the scales currently used (MASCC EGFR Inhibitor Skin Toxicity Tool – MESTT) (Table 15.2). The severity grading (0–5) used was the same as in the CTCAE scale (Table 15.3). Concerning nail changes, this time they were divided according to the anatomical site of the nail apparatus affected, namely, changes of the nail fold, nail plate, and nail tip. Moreover, the severity grading reached grade 3 in all cases, and this is important because supportive care interventions and dose modifications usually take place in grades 3 and 4. This new scale could serve as an example for the future more adequate development of grading systems that could encompass the totality of skin-related adverse events due to targeted therapies [6].

Concerning the instrumental activities of daily living (iADL) where both scales rely on, there are typically eight areas of focus to assess how cancer therapy affects patients' activities: ability to use the telephone, laundry and dressing, shopping and running errands, transportation, meal preparation, medication management, housekeeping activities, and ability to manage finances. On the other hand, self-care ADL refers to bathing, dressing and undressing, feeding self,

**Table 15.2** MASCC Study Group EGFRI-dermatologic AE grading scale, section on nail changes

| Adverse event | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| Nail changes - nail plate | Onycholysis or ridging without pain | Onycholysis with mild/moderate pain; any nail plate lesion interfering with instrumental ADL | Nail plate changes interfering with self-care ADL | – |
| Nail changes - nail fold | Disruption or absence of cuticle; OR erythema | Erythematous/tender/painful; OR pyogenic granuloma; OR crusted lesions OR any fold lesion interfering on instrumental ADL | Periungual abscess: OR fold changes interfering with self-care ADL | – |
| Nail changes - digit tip | Xerosis and/or erythema without pain | Xerosis and/or erythema with mild/moderate pain or stinging; OR fingertip fissures; OR any digit tip lesion interfering with instrumental ADL | Digit tip lesions interfering with self-care ADL | – |

**Table 15.3** Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 – Grading

| Grades | |
|---|---|
| Grade 1 | Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated |
| Grade 2 | Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL[a] |
| Grade 3 | Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[b] |
| Grade 4 | Life-threatening consequences; urgent intervention indicated |
| Grade 5 | Death related to AE |

*Activities of daily living (ADL)*

[a]Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b]Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden

using the toilet, taking medications, and not confined to bed; that is why it is linked to a significantly deteriorated quality of life and a higher grading (grade 3) compared to iADL (grade 2) [7]. In the last years, a few attempts have been made to alter, improve, or completely change the current grading systems. A recently published article proposed the use of a novel scoring system for paronychia related to oncologic treatments (SPOT) and showed a good correlation of paronychia severity with DLQI and pain index. It may thus prove useful in clinical practice [8].

## Nail Changes with Targeted Therapies

Table 15.4 illustrates the nail changes that result from targeted antineoplastic drugs.

Paronychia is the most frequent AE appearing on the nails of patients receiving targeted treatments. It is characterized by acute inflammation of the nail fold of one or more nails and presents as erythema, edema, and tenderness and may progress to painful pyogenic granuloma-like lesions, mimicking an ingrown nail. Pyogenic granuloma-like lesions result from the piercing of perionychium from the nail pate followed by an aberrant healing process and often appear at the proximal nail folds of the great toes. While initially sterile, superinfection of these lesions with bacteria, mainly *Staph. aureus* or fungi, may occur. If paronychia is painful, it may cause significant debilitation and result in substantial functional impairment thus leading to a reduction or cessation of treatment with the targeted therapy. Paronychia develops in 10–20% of patients treated with a first- or second-generation EGFR TKIs and occurs 20 days to 6 months after the start of treatment. It may also appear after treatment with mTOR, MEK, and BRAF inhibitors [3, 12, 32].

Onycholysis refers to the detachment of the nail plate from the nail bed and when caused by antineoplastic drugs is usually painful. Apart from the well-known taxane-induced phenomenon, it seems that, to a lesser extent, targeted therapies

**Table 15.4** Nail changes with targeted antineoplastic drugs

| Nail changes | Class of targeted antineoplastic drugs | References |
|---|---|---|
| Nail fold | | |
| Paronychia/pyogenic granuloma-like lesions | EGFRi | [3, 9–15] |
| | MEKi | [16, 17] |
| | mTORi | [18, 19] |
| | BRAFi | [16, 20, 21] |
| Nail plate | | |
| Onycholysis | EGFRi | [3, 22, 23] |
| | MEKi | [3, 16] |
| | mTORi | [19, 24] |
| Ridging/brittle nails | EGFRi | [3] |
| | MEKi | [16] |
| | mTORi | [19] |
| | Bruton TKI | [25] |
| Melanonychia | Imatinib | [26, 27] |
| Xanthonychia | mTORi | [28] |
| Nail bed | | |
| Splinter subungual hemorrhages | VEGFR/VEGF | [3, 29] |
| | Cabozantinib | [30, 31] |
| Apparent leukonychia | TKI | [3] |

such as EGFR, MEK, and mTOR inhibitors may also lead to onycholysis [3, 16, 19, 22–24].

Thinning of the nail plate, nail ridging, and brittle nails are all changes stemming from nail matrix affection by targeted drugs. EGFR, MEK, mTOR, and Bruton TK inhibitors may provoke such changes to the nail plate [3, 16, 19, 25].

Imatinib, a TKI, is known to induce transverse melanonychia, a rather rare AE of targeted therapies, whereas mTOR inhibitors may be responsible for another rare event, xanthonychia, i.e., yellow nail discoloration [26, 27].

Splinter subungual hemorrhages occur during the first weeks of treatment with VEGFRi and disappear spontaneously, growing out progressively with the nail. It seems that VEGFR inhibition restricts the physiological repair processes of the nail bed capillaries and might account for development of these lesions [3, 29–31].

Apparent leukonychia presents as parallel, white bands that disappear with pressure. It is probably caused by affected nail bed vessels and resolves after cessation of treatment [3].

## Why Is It Important to Address Nail AEs?

Nail changes caused by antineoplastic drugs have to be properly addressed for multiple reasons. First of all they may significantly affect the quality of life of patients, including their physical, emotional, and psychological well-being, especially if they interfere with instrumental or self-care ADL. Additionally, paronychia when accompanied by bacterial or fungal infections in neutropenic patients, as they frequently are following antineoplastic treatments, may put their life at risk [32]. Furthermore, if the AEs are not timely addressed or prevented, they seem to augment significantly the cost of the patient's treatment. In a 2018 study, it was demonstrated that grade 1 dermatological toxicity does not require additional costs; however, the cost of treatment for grade 2 or 3 in the outpatient setting was about 185$/event, and hospitalization resulted in substantially higher costs (approximately $4500/event) [9]. Finally, nail AEs can

affect medication adherence and cancer therapy dosing, as adverse events of grade 3 or greater justify dose modifications [2].

## Preemptive or Reactive Treatment?

In 2010 Lacouture et al. demonstrated the importance of preemptive treatment for skin toxicity in patients with metastatic colorectal cancer through the STEPP, phase II, open-label randomized trial. Patients receiving panitumumab-containing therapy were randomly assigned 1:1 to preemptive or reactive treatment. Preemptive treatment included use of skin moisturizers, sunscreen, topical steroid, and doxycycline. The incidence of specific > or = grade 2 skin toxicities during the 6-week skin treatment period was reduced by more than 50% in the preemptive group compared with the reactive group [33]. Patients in the preemptive group reported less QOL impairment than patients in the reactive group. In 2015 the J-STEPP phase III trial on the skin toxicity of panitumumab in Japanese patients with colorectal cancer yielded similar results. In the panitumumab-alone group, the cumulative incidence of ≥ grade 2 skin toxicities in 6 weeks was 28.1% in the preemptive group compared with 69.0% in the reactive group [34]. Preemptive treatment is currently recommended by most for all patients initiating treatment with anti-EGFR therapy and usually consists of oral antibiotics (doxycycline, minocycline) and topical corticosteroids, alone or in combination with daily nonpharmacological prophylactic measures, including moisturizers, sunscreen, and oatmeal baths. Preemptive daily treatment with corticosteroids has been shown to reduce the incidence of paronychia in both the J-STEPP and STEPP studies [9].

## Preventive Measures

In order to minimize nail changes, patients are advised to follow preventive measures as long as they start treatment with a targeted antineoplastic agent. Careful nail inspection of the hands and feet should be repeated in every clinic visit. Patients are encouraged to keep their feet and hands as dry as possible and always use gloves when soaking their hands for a prolonged period of time. Their feet should be dried well before putting on shoes. Their nails should be regularly filed and clipped conservatively, and they should avoid frequent use of nail polish and nail polish removers. They also have to frequently moisturize their hands and feet using thick moisturizers or zinc oxide cream. Their shoes should be comfortable and flat so as to avoid friction and pressure of the toes. Finally they are advised to perform bleach soaks to prevent infection and take a supplement of biotin to strengthen their nails [14].

## Treatments

In a retrospective study published in 2016, Goto et al. [35] evaluated all possible methods of treating cancer pharmacotherapy-induced paronychia in their clinic. The first-line treatment was strong corticosteroid ointment which in general was sufficient except for severe cases. Minocycline was another option for its anti-inflammatory and antibacterial properties but in their clinic did not result in significant improvement. Cryotherapy used for pyogenic granuloma-like lesions was not significantly effective as well; in some cases it even deteriorated pain and swelling. Adapalene [36] had been reported as effective due to its anti-inflammatory properties, but according to this study, it should be considered as a prophylactic or a combination treatment. Taping, i.e., separating the nail plate from the perionychium with a stretchable bandage, could be effective but is user-dependent and could be wrongly applied in cases of affected ADL. Chemical matricectomy with phenol 90% under local anesthesia appeared to be highly effective, providing additionally disinfecting and anesthetic effects. However, it

should be reserved for severe cases, when anticancer treatment is at risk because it is an invasive treatment, resulting to permanent partial nail loss. Apart from that, as long as anticancer therapy is not interrupted, paronychia and pyogenic granuloma-like lesions may recur. Other suggested treatments for paronychia are the use of gentamycin ointment for 4 to 5 weeks, use of topical calcineurin inhibitors, bathing the hands and/or feet in diluted chloramine bath daily in order to avoid superinfection, cushioning inserts within shoes to pad the affected nails, pain control, and daily application of platelet-rich plasma for paronychia [2]. Finally for the pyogenic granuloma-like lesions, agents with a drying effect such as topical silver nitrate and trichloroacetic acid may be beneficial [37] as well as the novel approach of topical b-blockers use. A recently published case series and review of the use of topical timolol 0,5% gel twice daily under occlusion for 30 days demonstrated at least partial benefit in the majority of treated patients and suggested this approach to fragile cancer patients unwilling to receive a more invasive treatment [38]. Other suggested treatment regimens were that of propranolol 1% cream once daily under occlusion and betaxolol 0.25% eye drops once daily under occlusion for 1 month accompanied by an excellent safety profile.

In case of onycholysis, the detached nail should be removed, the nail bed should be kept dry, and topical application of a steroid lotion for a few weeks is advisable. For brittle and fragile nails, nail lacquers that produce a barrier to the nail plate, such as hydroxypropyl chitosan or polyureaurethane 16%, seem to be useful [16, 39].

For the rest of the nail changes, there seem to be no effective treatments but the changes usually resolve after cessation of the responsible drug.

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