Special Issue 2021

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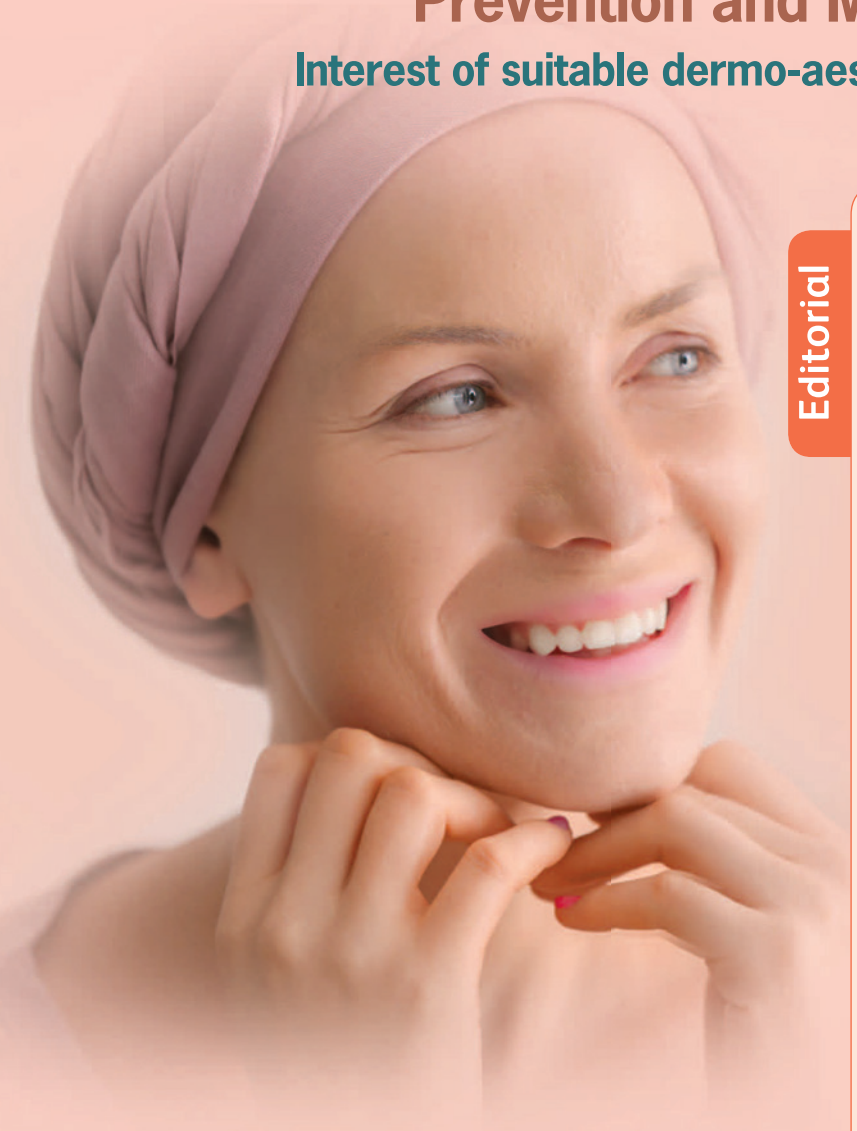
Cancer treatment-related skin toxicity

Prevention and Management

Interest of suitable dermo-aesthetic supportive care



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Editorial

There are things we can do

Skin, hair, and nail adverse effects of anticancer therapies are often underestimated or even neglected by prescribing physicians. Yet, they can have a significant impact not only on the patient's quality of life, but also on compliance with treatments. In this issue devoted to this theme, the authors discuss different disorders that can be observed during these treatments: Hand-Foot syndrome, more diffuse skin damage and nail and hair anomalies. Sometimes, these symptoms are not really adverse effects, but they can also systematically go with the action of cancer treatments and even, in certain cases, be associated with their efficacy as illustrated by the inflammatory follicular eruption associated with anti-EGFR treatments. Patients must therefore be taught that these manifestations are not signs of intolerance or allergy, but that they will have to be able to moderate their intensity and endure them over the long term.The duration of treatments is indeed another important aspect in oncology. They are very often prescribed over several months, or even years (it is besides a good sign because in general, we continue for a long time only the treatments that have demonstrated their efficacy in cancer). Dermatologic changes therefore also become chronic even if some of them tend to improve over time. The prescribing physician must therefore explain to patients from the beginning of treatment that theses adverse effects will occur and must be ready to accompany the patient for this management in parallel with that of cancer throughout the treatment. It is also important to know when to refer the patient to a specialist: dermatologist, podiatrist/pedicurist, or specialized esthetician. Cosmetic management should not be neglected. Makeup and cosmetic camouflage can help some patients, including men. It is important to release the patient from guilt about using cosmetic products and methods to help them through this difficult and sometimes very long course.

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Alopecia after certain cancer treatments

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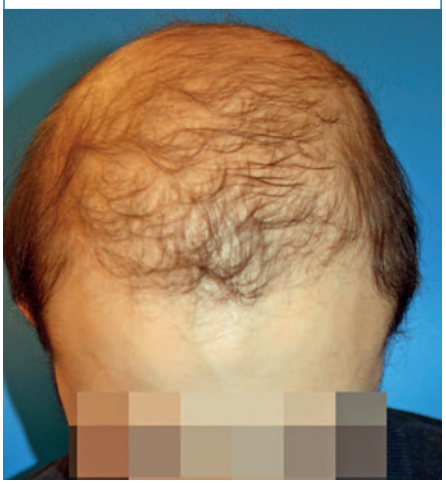
Hair changes can occur during many cancer treatments. Their frequency and clinical expression vary depending on the type of molecule used and the therapeutic protocol. Alopecia is one of the adverse effects most feared by patients and can even lead them to refuse chemotherapy[1].

Alopecia in almost two thirds of cancer patients

According to a recent analysis of the literature, around 65% of patients under treatment with cytotoxic agents will develop alopecia[1] *(case 1)*. Hair loss, which often occurs as a consequence of an acute interruption of the anagen phase (effluvium anagen), begins in general in the 2 weeks after the first chemotherapy cure[2]. It can progress to complete alopecia in 2 to 3 months[1]. The hair regrowth usually occurs 2 to 6 months after the end of the chemotherapy. Alopecia of the scalp is sometimes associated with loss of eyelashes, eyebrows, beard, and axillary and pubic hair, which regrowth is generally faster than head hair.

Alopecia induced by targeted therapies differs from that observed in chemotherapy by its frequency, with an incidence of 15% for all molecules combined, and by its more moderate severity[1].

Case 1. Definitive alopecia in an 18-year-old male after chemotherapy for sarcoma.



The hair toxicity of these treatments is most often manifested by changes in hair color (depigmentation, hyperpigmentation) and texture, with a respective incidence of around 30%[1]. These adverse effects are reversible after the end of the treatment. Immunotherapy with anti-PD1/PD-L1 agents also causes hair pigmentary anomalies in 27% of cases[1]. Of the other changes induced by certain targeted therapies, hirsutism and hypertrichosis are the most frequently described in patients treated with anti-EGFR/MEK (incidence of around 50%)[1]. Eyelash trichomegaly may also occur under EGFR inhibitors. These anomalies generally disappear after the end of the treatment, but in some cases, they can persist for several months.

A non-negligible incidence hormonal therapy-induced alopecia

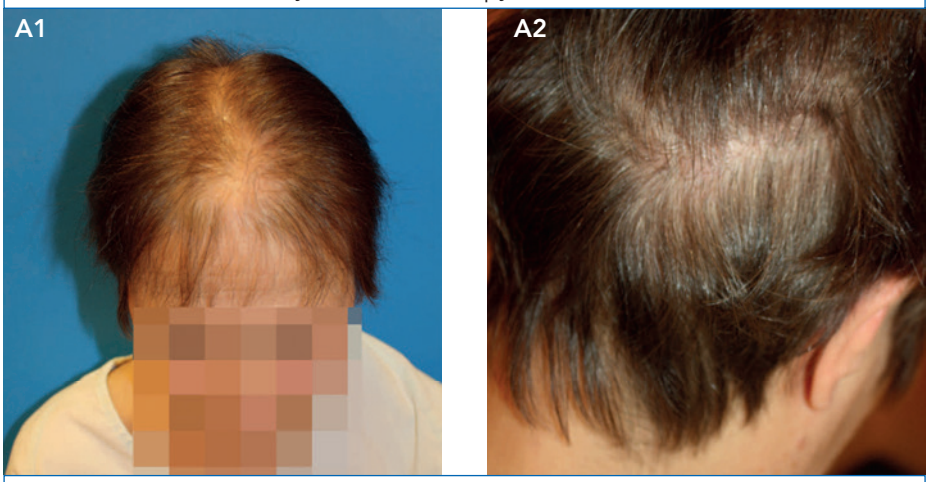
We have a lot less information about alopecia induced by anticancer hormonal therapy despite their wide use in the treatment and prevention of several solid tumors, mainly breast and prostate tumors[3]. Current data reveal a global incidence of 4.4% and, for all grades combined *(table)*, the incidence of this type of alopecia reaches 25.4% with tamoxifen[3]. Its clinical characteristics are similar to that of moderate androgenic alopecia with a decrease in the hair shaft diameter and density[4]. The reversibility of hormonal therapy-induced alopecia after discontinuation of treatment is unknown[4]. Even when moderate, progressive hair loss in

Grades of severity of alopecia induced by cancer treatments according to CTAE* and WHO*[1]

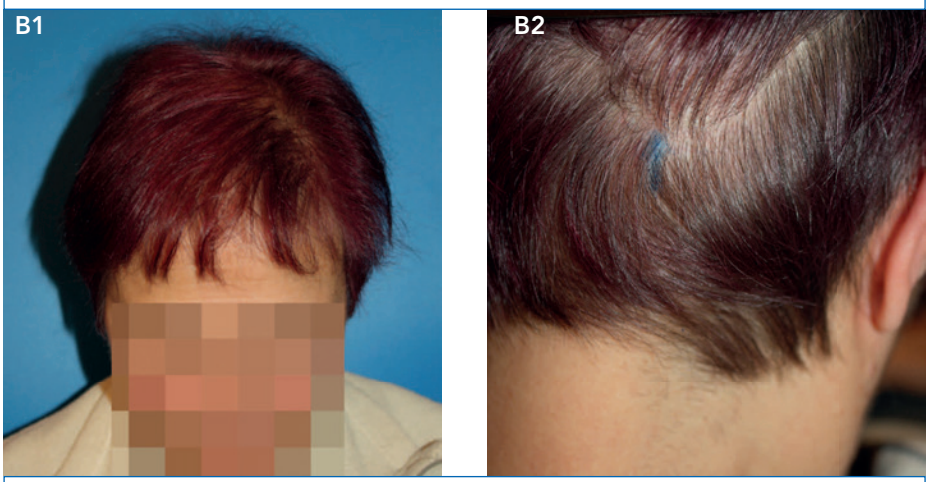
	Grade 1	Grade 2	Grade 3	Grade 4
CTAE	Hair loss < 50% of normal for that individual that is not obvious from a distance but only on close inspection; a different hairstyle may be required to cover the hair loss but it does not require a wig or hairpiece to camouflage	Hair loss ≥ 50% normal for that individual that is readily apparent to others; a wig or hair piece is necessary if the patient desires to completely camouflage the hair loss; associated with psychosocial impact	–	–
WHO	Minimal hair loss	Moderate, patchy hair loss	Complete alopecia, but reversible	Nonreversible alopecia

*CTAE: Common Terminology Criteria for Adverse Events. WHO: World Health Organisation.

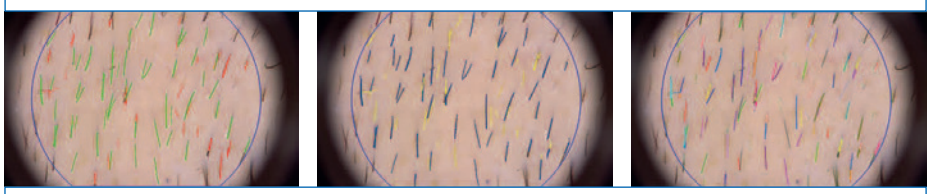
Case 2. Androgenic alopecia in a 72-year-old female patient, 9 years after breast cancer, induced by hormone therapy.



A1 and A2. Before treatment and photo of the donor area.



B1 and B2. After 1 single session of FUL hair transplant with long hair without shaving and photo of the donor area (blue arrow: linear scar).



C. Macrophotography (Trichoscale®) for an accurate assessment of quality of the donor area.

women treated with endocrine therapy for breast cancer will often have a greater impact than complete, but rapidly regressive alopecia[6].

How to manage adverse effects on hair

Due to the importance of the impact of hair, eyelash, and eyebrow loss – and most likely other hair anomalies – on the quality of life of patients, greater attention must be paid to them in order to optimize the clinical course[1,7]. There are currently, no approved treatments or preventions for chemotherapy and hormonal therapy-induced alopecia[7,4]. The studies of the efficacy of scalp cooling in chemotherapy are of low methodological quality[8]. However, these devices appear to have good performance in preventing chemotherapy-induced hair loss[8].

The efficacy and safety of hair transplantation the follicular unit long hair technique (FUL) has recently been shown in women with breast cancer and hormonal therapy-induced alopecia[4,5]. This micro-transplantation technique is considered after 6 months of spontaneous regrowth. Its advantages are the long-lasting effects (after 3-year follow-up), the low incidence and severity of adverse effects, and the fact that there are no patient compliance concerns *(case 2)*.

Finally, socio-aesthetic care, which is part of supportive care, contributes to quality of life before, during, and after cancer treatments[9]. The interest of cosmetic care in this context has been shown in women treated by chemotherapy and radiotherapy for breast cancer having been given advice including camouflage and makeup techniques[10]. If necessary, different camoufling techniques can be recommended to manage adverse effects on the hair such as wigs or hair extensions in the case of hair loss, makeup or derma pigmentation for the eyelashes and eyebrows, or waxing or hair discoloration in case of hypertrichosis[9,1].

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Hand-foot syndrome can be very debilitating

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Hand-foot syndrome is a frequent adverse effect of certain chemotherapy agents and targeted therapy. Prevention is essential, as is early management to avoid it developing into more severe lesions that can affect the quality of life.

Hand-foot syndrome (HFS) is characterized by a symmetrical lesion of the skin of the palms and/or soles such as desquamation more or less associated with an inflammatory reaction. It is characterized into three grades of severity[1]. Grade 1 corresponds to skin changes such as desquamation. In grade 2 *(figure 1)*, these manifestations are associated with pain and interference with instrumental activities of daily life (for example, doing one's shopping, preparing meals, etc.). Grade 3 *(figures 2 and 3)* involves inflammatory pains and repercussions on the elementary activities of daily life (getting dressed, make a toilet, etc.).
We distinguish two types of HFS: Diffuse HFP induced by chemotherapy, particularly capecitabine, and localized HFS observed with some targeted therapies, particularly tyrosine kinase inhibitors (sorafenib, sunitinib)[2,3] *(figure 4)*. Up to two-thirds of patients treated with capecitabine develop HFS – for all grades combined – essentially from the 3rd cure. Crevices may appear in diffuse HFS *(figures 5 and 6)*. The clinical state of the skin improves during treatment breaks. However, this improvement is usually short-lived (usually one week with capecitabine), and does not allow sufficient improvement in the more severe cases. Longer treatment breaks are therefore necessary. After stopping cancer treatments, the skin often keeps a «cardboard» aspect.

Identifying the contributing factors

There are many factors favoring the occurrence of HSF, including unsuitable socks and shoes, and the poor initial state of the skin (xerosis, points of hyper pressure). Cotton or bamboo socks must be prefered to synthetic socks in order to limit excessive sweating. Wearing shoes adapted to the morphology of the patient's foot is essential. Patients will be recommended to wear shoes with a good insole, and a fairly high upper (front of the shoe). Trainers are the most suitable shoes. For elderly

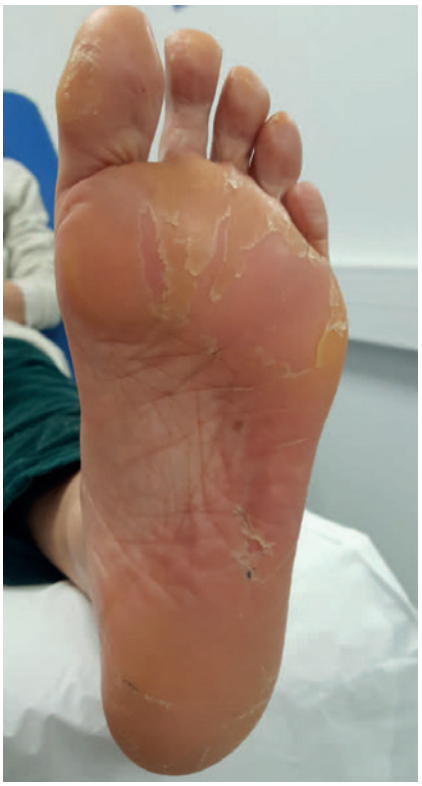
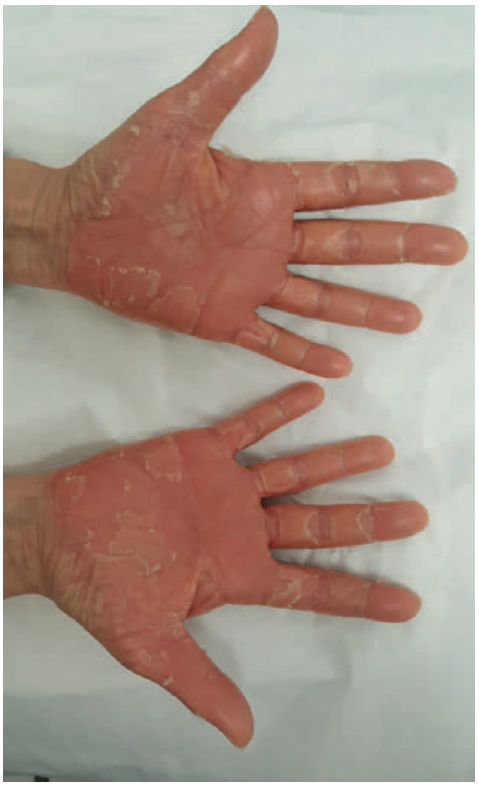
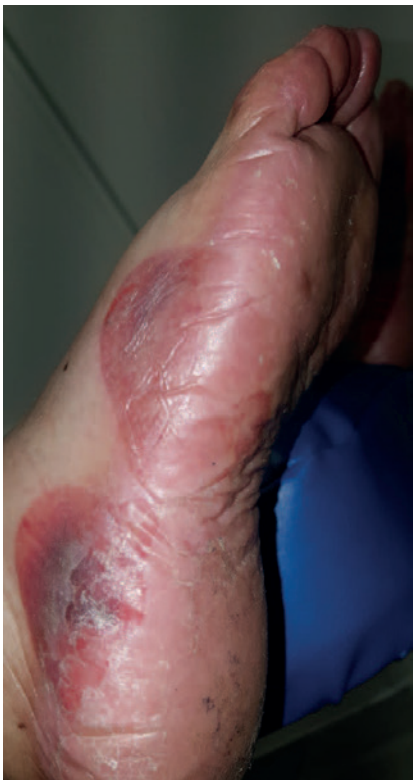


Figure 1. Grade 2 hand-foot syndrome under capecitabine.





Figures 2 and 3. Grade 3 hand-foot syndrome under capecitabine.

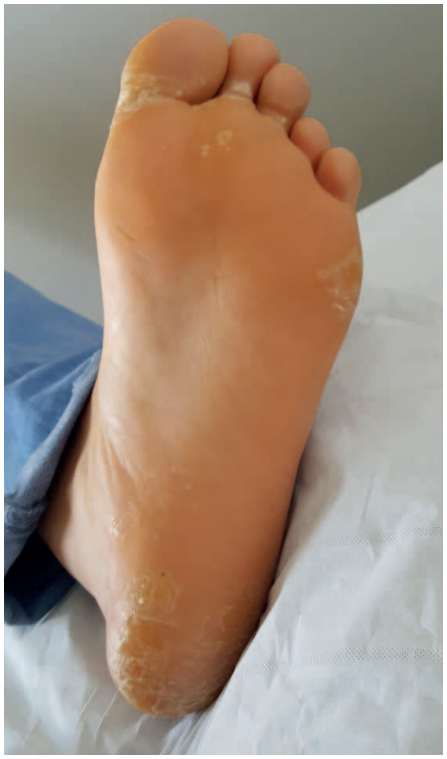


Figure 4. Grade 2 localised hand-foot syndrome under sorafenib.

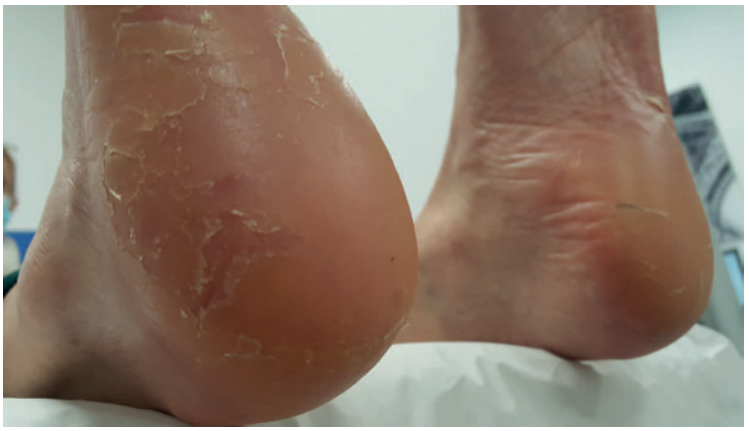


Figure 5. Crevices associated with grade 3 hand-foot syndrome.

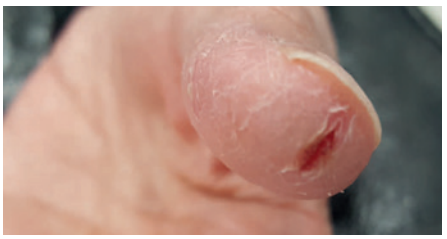


Figure 6. Crevices under cetuximab.

patients, the prescription of temporary or permanent shoes is useful.
The presence of areas of hyperkeratosis (such as calluses) is a risk factor for localized HFS. A pedicure-podiatry consultation at the initiation of treatments is recommended[2]. Suitable topical treatments should be prescribed. Urea-based topical treatments can also be prescribed to limit hyperkeratosis. During the current pandemic, the hands are being damaged by the intense use of hand sanitazer. Washing hands with soap and water is preferable when possible.

Management of hand-foot syndrome

Management varies depending on the degree of severity of this adverse effect HFS. Local treatment is sufficient for grade 1 HFS. Pedicure care are recommended, but it should preferably be carried out during the weeks of treatment break. In the case of localized HFS, orthopedic insoles can help to limit calluses[4]. In grades 2 and 3, topical corticosteroids should be applied without hesitation until disappearance of inflammation. The use of dermo-cosmetic products suitable for the patient helps maintain adequate skin hydration *(box)*. Adjusting doses or even temporary discontinuation of the cancer treatment may be necessary in very severe cases of HFS. ▮

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Protecting the skin and nails

Regular application of moisturizer on the hand and feet skin before, during, and after treatment has a protective effect. It must be suitable for the patient's skin type. Sticks (for example, lip balm sticks) can be used in addition to the management of cracks and crevices.
Nail care must begin before taxane treatment and continued for several months after the end of the chemotherapy. Silicon nail polishes are used to strengthen nails. It is advisable to remove the nail polish regularly in order to spot warning signs such as a change in the nail color. Nail polish removers, even acetone-free ones, can cause damage. The aggressive effect of nail removers can be counteracted by the double action, nourishing and stripping, of dissolving oils. Nail hardeners, which are formalin based, should be avoided.
Oils, creams, and butters may also be applied on the cuticles to improve the state of the nail. For all advised means of protection, both in hand-foot syndrome and in nail and periungual lesions, it is essential to ensure the good patient's compliance and, most of all, to regularly monitor their palmoplantar skin in order to allow early diagnosis of adverse effects.

Do not neglect nail and periungual toxicities

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Given their aesthetic, functional and psychological impact, the nail and periungual toxicities associated with cancer treatments require close attention[1,2].

Nail changes, such as onycholysis, are essentially induced by chemotherapy, in particular taxanes, and periungual lesions (paronychia) by targeted therapies, especially anti-EGFR[1,2]. About two of three patients on taxanes will have nails weakened by their treatment. In the feet, the hallux nails are the most affected. This toxicity is manifested by the formation of subungual hematomas during cure, which causes nail pressure pain, and can lead to the progressive partial detachment of the nail plate. The nail loss, which is painless and most often occurs a posteriori, 2 to 3 weeks after the end of the chemotherapy. Grade 1 nail changes are characterized by asymptomatic separation of the nail bed from the nail plate or nail loss *(figures 1 and 2)*. The nail lesions are classed as grade 2 *(figure 3)* anti-when these manifestations are symptomatic and limit activities of daily life[3]. The self-esteem disturbance caused by nail loss can be as important as that of alopecia. This harmful effect should not be neglected.

Paronychia can also affect the fingernails as well as the toenails *(figure 4)*. It is characterized by inflammation of the periungual tissue and, in the most severe forms, by the formation of a fleshy bump (pyogenic granuloma). For this lesion, the NCI-CTCAE* classification defines three severity grades: Discontinuity or even disappearance of the cuticle (grade 1), damage associated with pain with or without impact on daily life activities (grades 2 and 3). When treatment is stopped, there is usually complete regrowth of the nails and the spontaneous healing of periungual lesions.

*National Cancer Institute - Common Terminology Criteria for Adverse Events.

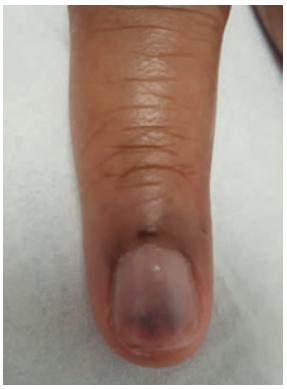

Figure 1. Grade 1 onycholysis under taxanes.

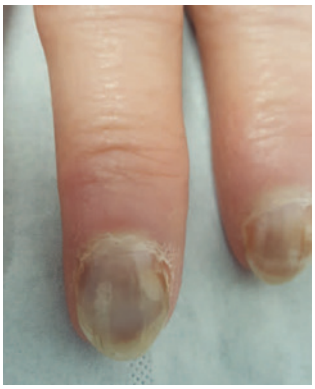

Figure 2. Grade 1 onycholysis.

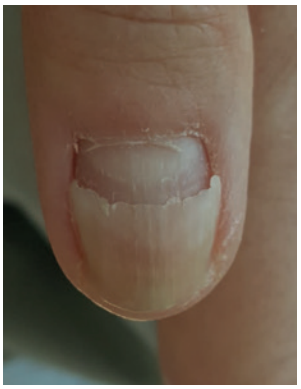

Figure 3. Grade 2 onycholysis under taxanes.

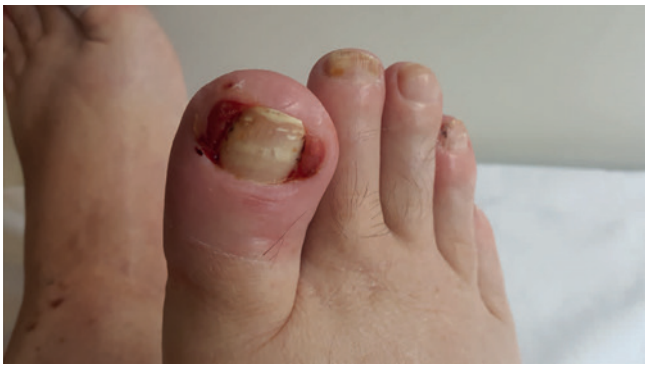

Figure 4. Grade 3 paronychia under anti-EGFR.

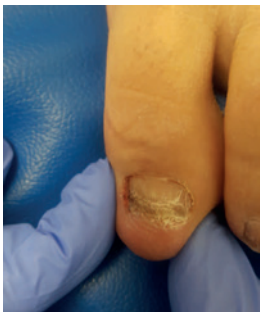

Figure 5. Onychoptosis under taxanes.

How to manage

The management of these toxicities must be adapted to the degree of severity and the impact on daily life activities. It includes local treatment, is based on eviction of contributing factors (for example, poor initial state of the nails, not wearing protective gloves when doing household chores, unsuitable shoes), but also on the use of protective measures for the nails and the skin of the hands and feet *(box, page 5)*. In the case of grade 2 onycholysis, local care is essentially based on drying the lesions (drying lotion) in order to limit the risks of maceration and bacterial superinfection. Severe onycholysis can lead to complete nail loss or onychoptosis *(figure 5)*. In paronychia, there is no indication for first-line surgery or routine antibiotic therapy. Local care is most often sufficient but can be very painful. Contact anesthetics may be necessary to perform these procedures. Topical corticosteroids are useful for grades 2 and 3. In more complex cases, a temporary suspension of anticancer treatment is necessary. Treatment of the pyogenic granuloma using phenolisation can give good results. Footwear advise are the same as for hand-foot syndrome. Finally, closed-toe compression stockings can maintain this adverse effect. Preference should be given to open toe compression stockings.

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Hygiene and pharmacy care advices

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Dermatologic adverse effects associated with anticancer therapies are common. The hygiene and care advices in pharmacies are very important to allow patients to continue their treatment in the best possible conditions.

Radiation dermatitis

Skin lesions will appear in the days or weeks following the radiotherapy session, depending on the dose and the type of radiation. They can manifest as acute erythema with or without edema and moist desquamation (acute radiation dermatitis). Sometimes, these lesions can appear several months or years after radiation (chronic radiation dermatitis).

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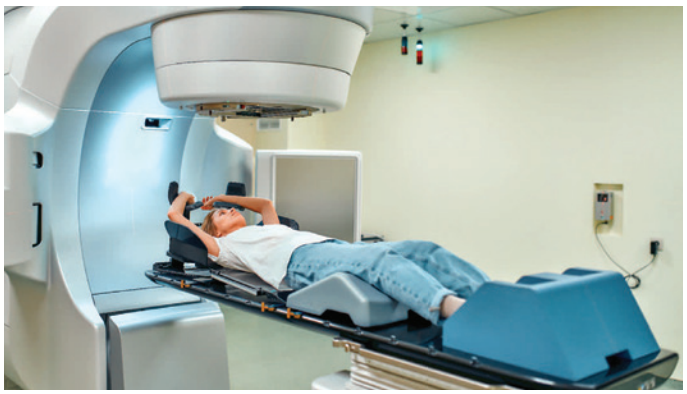

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How to manage

• **Prevention:** Do not apply any product to the treated area before the radiotherapy session in order to avoid a bolus effect. On irradiated areas, do not apply perfumes, alcohols, adhesive dressing, and exfoliating products, and avoid tight clothes and underwired bras. Sun exposure of these areas is not recommended for up to one year after the end of the radiotherapy.

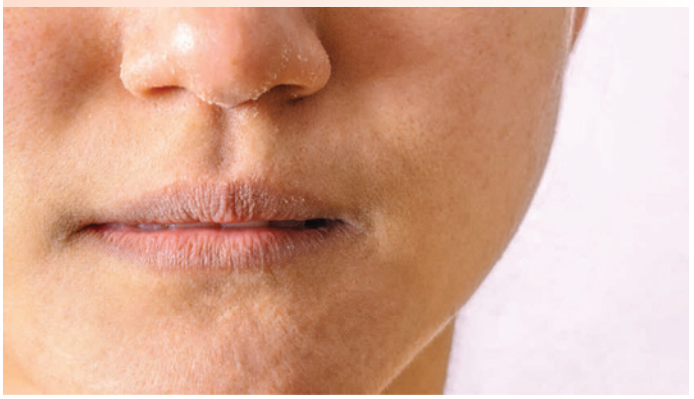
• **Hygiene and care:** Prefer lukewarm showers and use a gentle shower gel such as a syndet, dry the skin delicately. At the erythema stage, apply a moisturizer for dry or atopic skin in order to alleviate skin dryness and relieve itching.

Xerosis or xeroderma

Xerosis is a very common condition under targeted therapy (bevacizumab, cetuximab, panitumumab, erlotinib, sorafenib). It appears after 2 to 4 months of treatment. The face and body skin is dry, sometimes scaly. The oral and vaginal mucous membranes, the lips and the conjunctiva may be affected.

How to manage

Chose products for sensitive or atopic skin with a minimum of components. Recommend the use of liquid soap or dermatological bars of soap with a pH of around 5 for the body. For the face, advise the use of micellar water and moisturizer, and the application of moisturizing one to three times a week.



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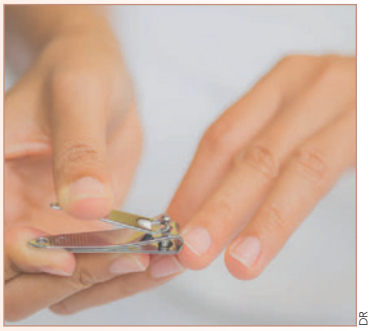
Nail damages

We can observe inflammation around the nail (with targeted therapies), soft, brittle, and detaching nails (with taxanes and anthracyclines) and the appearance of ridges, spots, or even hemorrhages (with sorafenib).

How to manage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- **Prevention:** Keep the nails short to avoid them breaking, avoid cutting the cuticles. In order to limit injuries and infections, wear comfortable shoes and wear gloves for household chores or gardening. Limit prolonged immersion in water. Avoid the use of false nails, acetone remover, or overly damaging nail hardeners.

Specific care: Thoroughly moisturize the cuticles and the sides of the lateral edges of the nails with emollient product or with fortifying vegetable oil. Apply an opaque silicon nail polish or nail polish with UVA and UVB filters for the whole duration of the treatment and until the complete regrowth of a normal nail.

Hand-foot syndrome

This is an adverse effect of certain chemotherapy agents (capecitabine, doxorubicin, 5-FU, taxanes, methotrexate, etc.) and several targeted therapies. The lesions (inflammatory erythema progressing to cracking and desquamation) appear after 2 to 3 months of treatment in pressure and/or friction areas, on the soles of the feet and/or the palms of the hands, preceded by a tingling or a burning sensation.

How to manage

- **Prevention:** Manicure and/or pedicure can be recommended to remove calluses, wearing cooling gloves and slippers during the chemotherapy infusion. Recommend syndet bar for the body and apply an emollient cream for severe skin dryness on the hands and feet.

- **Avoid** adhesive dressing and exposure to heat (sun, hot water, saunas), wear comfortable and flexible shoes, and wear gloves for household chores.


DR

- **Specific care** such as repairing and healing creams based on copper, zinc or sucralfate, and, in some cases, urea or salicylic acid-based treatments can be useful.

Acneiform folliculitis

This dermatological condition is common with targeted therapies and anti-HER2 therapies. It appears 1 to 3 weeks after the beginning of treatment in the face, upper trunk, and scalp. The rash is inflammatory with no comedones or microcysts, with a possible burning or itching sensation.

How to manage

Wash the face and body with liquid soaps or dermatological bars without fragrances, alcohols, nor fruit and plant extracts. Apply a copper and zinc-based cream to spots. Recommend a sun protection product (SPF 30+, UVA/UBA protection).


DR

To find out more:

- https://www.afsos.org/wp-content/uploads/2016/09/2014-12-12-_J2R_tox_cutanee_radioinduite_VF.pdf
- https://www.chuv.ch/fileadmin/sites/dso/documents/MDS_Radiodermite_DSO-FT_-Adultes-007_1.0_.pdf
- https://www.oncopaca.org/sites/default/files/2013-12_ref_soins_support_fiches_bonnes_pratiques_socio-esthetique_afsos.pdf
- https://www.larevuedupraticien.fr/article/cancerologie
- https://oncologypro.esmo.org/fr/ oncology-in-practice/palliative-and-supportive-care/effets-indesirables-dermatologiques-lies-aux-egfri/professionnels-de-la-sante/symptomes-et-classification/modifications-de-la-peau/rash-acneiforme
- https://www.has-sante.fr/upload/ docs/application/pdf/2020-12/pied_de_la_personne_agee_-_fiche_outil_n4_effets_secondaires_traitements_anti-cancereux

Pharmaceutic Interviews in Oncology

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DR

Over the last few years, the development of oral chemotherapy and targeted therapies has revolutionized cancer treatments. The management, which was carried out exclusively in the hospital, is currently provided partly in town for many patients.

According to the French National Cancer Institute (Institut National du Cancer – INCa), in 2019, spending related to cancer treatments in community pharmacies reached 2.78 billion, two-thirds of which are for targeted therapies. It is a shift to ambulatory care and the proportion of patients treated out the hospital will increase over the next few years.
The development of home treatments has some advantages (more comfort, less fatigue), but also leads to the emergence of new difficulties for the patient. First of all, depending on the degree of understanding of the treatment modalities, drug adherence may be problematic: Dosage errors, difficulties adjusting the setting times, non-compliance with recommendations in case of a missed dose. Additionally, most of these recent molecules can cause potentially serious adverse effects.

System and Objectives

For the last few years, community pharmacists have been encouraged to develop dedicate time to dispensing oral cancer treatments. Since September 2020, amendment no. 21 to the pharmaceutical agreement has allowed community pharmacists to conduct interviews with patients treated by oral cancer drugs. The system provides for an initial interview and two more thematic interviews. The objectives are to improve compliance, detect adverse effects early, and make the patient a stakeholder in their health.
Eligible patients are aged 18 or older and must be treated with oral cancer drug (initiation of treatment or treatment that has been in place for some time). The medications concerned belong to the ATC L01 class (chemotherapy and targeted therapy protein kinase inhibitor) and the L02 class (hormone therapy) administered by oral route. This classification is recognized by World Health Organization (WHO) and these medications can be found on the Vidal website (vidal.fr). According to the latest statistics, 500,000 people could be affected in France, giving an average of 20 patients per community pharmacy.
Prior pharmacist training is not necessary, but is recommended to reinforce their knowledge and to better control the course of the interview.

In Practice

Interviews are proposed to eligible patients as specific and personalized support. The inclusion of patients in the system is confirmed by signing a form downloadable from National Health Insurance website (ameli.fr). Preparation for the initial interview is important. The pharmacist must inform himself about drug (s)-based cancer treatments and, more particularly, about their adverse effects. A synthesis of the chronic treatments and the complementary therapies must also be made in order to anticipate drug interactions. The National Health Insurance provides support documents (interview guide, patient follow-up sheet) that must be used. Meeting a cancer patient can be an emotional moment and highlight our own fears in some cases. It is important to prepare for it. The appearance of cancer is a personal and unique experience in the patient's life. There are no "minor cancers" and each patient experience this upheaval in their own way.
The first interview is a privileged moment during which the patient can speak freely about his treatment, their difficulties and their doubts, sometimes for the first time. The patient must feel that this time is devoted to him. That's why the interview must be conducted in a confidential area, out of sight, without being disturbed. The attitude towards the patient is important: Avoid face-to-face, each position at 90°. It is also necessary to make sure that you are clearly understood by the patient. Non-verbal communication is sometimes more important than words. There is no limit to the length of the interview, but this one must respect the fatigue of the patient. The interview guide recommends addressing several points: A reminder of objectives, assessment of the patient's experience and knowledge, and of his adherence to treatment, screening of adverse effects. The content of the interview can however be adapted to the context according to the difficulties detected. On this occasion, it is possible to take stock of the potential adverse effects and to verify that the patient has the resources required to manage them. The following two interviews, conducted at 1 month and 6 months, are shorter and thematic. They focus on adverse effects and compliance.

Conclusion

These pharmaceutic interviews are therefore complementary to the initial hospital management and boost the patient's adherence to his treatment. They also reinforce the role of the pharmacist as a full and active member of the patient's healthcare team.

To find out more:

• INCa : Overview of cancers in France 2021.
• https://www.ameli.fr/pharmacien/exercice-professionnel/services-patients/accompagnement-patients-chroniques
• https://www.sfpo.com/wp-content/uploads/2021/02/Recommandations-SFPO-sur-la-realisation-des-entretiens-Pharmaceutiques-a-lofficine.pdf

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