EUROPEAN ACADEMY OF DERMATOLOGY & VENEREOLOGY

Information Leaflet for Patients

Skin colour changes induced by anticancer therapies

The aim of this leaflet

This leaflet is designed to inform you about changes to the colour of your skin and appendages that you may experience during your cancer therapy. We will explain what types of colour changes exist, why and how they occur, and which is the best way to manage them.

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What are anticancer treatment-related colour changes?

The cancer treament-related skin colour changes, also known as pigmentary changes, are a set of alterations of the skin, mucous membranes, hair and nails you may experience during cancer treatment. In general, these changes are different depending on the administered drug: your skin and appendages become predominantly darker when chemotherapy is used, while they become clearer or even completely depigmented when certain targeted therapies or immunotherapy are used. When the skin loses its pigmentation the term vitiligo or vitiligoid lesions may be used. Finally, radiotherapy may also induce post-inflammatory hyperpigmentation.

The onset and the persistence of these changes through time are highly variable. Irrespective of that, they may have a profound impact on quality of life and aesthetic appearance.

Which anticancer treatments can cause changes in your skin colour?

> These are the most common **chemotherapeutic agents** associated with changes to your skin colour (i.e.hyperpigmentation):

- Bleomycin
- Busulfan
- Capecitabine
- Cisplatin
- Cyclophosphamide
- Daunorubicin
- Dacarbazine
- Doxorubicin
- Hydroxyurea
- Melphalan
- Methotrexate
- Taxanes (paclitaxel, docetaxel, cabazitaxel, and nab paclitaxel)
- Topical carmustine (BCNU)
- Vinorelbine
- 5-fluorouracil (5-FU)

> These are the most common **targeted therapies** associated with skin colour changes:

- Multikinase angiogenesis inhibitors (axitinib, sunitinib, cabozantinib, pazopanib)
- BCR-ABL inhibitors (imatinib, nilotinib, dasatinib, bosutinib)
- HER inhibitors (afatinib, erlotinib, cetuximab)
- ALK inhibitors (ceritinib, alectinib)
- Alemtuzumab
- Selective proteasome inhibitors (bortezomib, carfilzomib)

> These are the most common anticancer **immunotherapy** causing colour changes (i.e. vitiligoid reactions):

- Anti-PD-1 (programmed cell death-1): cemiplimab, nivolumab, pembrolizumab, dostarlimab
- Anti-CTLA-4 (cytotoxic T-lymphocyte-associated protein-4): ipilimumab
- Anti-PD-L1 (programmed cell death ligand-1): atezolizumab, avelumab, durvalumab
- Others: aldesleukin, interferon alpha

How do colour changes appear?

> **Chemotherapy** hyperpigmentation (skin darkening) is mainly caused by the accumulation of pigment (melanin) in the skin, nails, and mucosa, either due to direct activation of skin cells (melanocytes) or due to drug-related skin inflammation, possibly with the contribution of ultraviolet (UV) radiation. Hyperpigmentation may occur all over your

skin, mimicking a tanned appearance, or more locally on contact or post-inflammatory areas. Usually, it appears 2-3 weeks after chemotherapy initiation and disappears approximately 10-12 weeks after treatment ends. However, some of these pigmentations can persist months or years after chemotherapy discontinuation.

Chemotherapeutic drugs can also cause more specific pigmentary changes. For example, **bleomycin**, causes itching and a distinctive skin change known as *flagellate hyperpigmentation*. The intravenous administration of **5-Fluorouracil**, **vinorelbine**, **daunorubicin**, **cyclophosphamide**, **nitrogen mustard**, or **taxanes** (**docetaxel**) may cause linear hyperpigmentation of the skin overlying the veins, called *serpentine supravenous hyperpigmentation*. The lesions gradually resolve spontaneously after discontinuation of the offending medication.

Chemotherapy-induced hyperpigmentation of the nails, namely **melanonychia**, is also common. For example, chemotherapy-induced **transverse melanonychia** is a benign condition in which a darkened line runs side to side along the nail plate. Also, nail depigmentation (**leukonychia**) can also occur, although with a lower incidence.

Hyperpigmentation of the buccal mucosa is an underestimated phenomenon that may be seen with the administration of certain drugs or a combination of chemotherapeutic agents (such as **capecitabine**, **cyclophosphamide**, **doxorubicin**, **docetaxel**, **hydroxyurea**, and **5-fluororacil**).

> Targeted therapies cause primarily depigmentation of the hair and, more rarely, of the skin, which is observed particularly with **multikinase angiogenesis inhibitors** (sunitinib, pazopanib, cabozantinib, axitinib) and **BCR-ABL inhibitors** (imatinib, nilotinib, dasatinib, bosutinib). These classes of drugs cause multiple patterns of progressive hypo- or depigmentation of scalp hair, body hair, eyelashes and eyebrows. Generally, they may respond to doses reduction and typically disappear after drug interruption.

> Immunotherapy may cause *vitiligo*-like depigmentation changes in up to 25% of patients, especially in patients treated for melanoma. It is more frequently observed in patients exposed to **anti-PD-1/PD-L1 therapy** (pembrolizumab, nivolumab, atezolizumab, avelumab). It may appear after several weeks of treatment, and it does not seem to be dose related. This mainly concerns the gradual development of white patches evolving into large plaques on the skin. It is sometimes combined with a depigmentation of the eyelashes/eyebrows or scalp hair. It is usually of moderate intensity and generally does not require treatment discontinuation. The lesions usually persist long after the end of immunotherapy and they do not require specific dermatologic treatment aside from photoprotective and camouflage measures to limit their psychosocial impact.

Practical advices and preventive measures

The vast majority of these pigmentary changes do not require specific management and the inducing treatment can be continued in most cases. Nevertheless, it is very important to provide reassurance to the patient and its relatives.

We present some practical advice on how to prevent or cope with colour changes during cancer treatment:

> Hair colour changes

- **Chemotherapy** – hair regrowth usually starts after ending chemotherapy. Some patients may face changes in hair colour (lighter hair colour), texture (e.g. thin, dystrophic), and curling or straightening of hair at this phase. For the first 6 months, it is recommended not to use permanent/semipermanent hair dyes or hair straightening products as hair may be fragile.
- **Targeted therapies** – some patients taking multikinase inhibitors may present hair depigmentation , which usually reverses to the original colour after the ending of targeted therapy.
- **Immunotherapy** – Patients receiving immunotherapy may experience hair bleaching that often per-sists after immunotherapy is stopped. No specific preventive measures exist.

> Skin colour changes

- Skin hyperpigmentation may be seen during and after chemotherapy, after radiotherapy or after flares of skin inflammation or skin friction. Sun exposure increases the risk of hyperpigmentation during cancer treatment. On the way to preventing or reducing the severity of hyperpigmentation, it is important to protect your skin. Take a look at the following suggestions:

  Maintain a well-hydrated skin – apply a moisturizer right after showering and during the day as many times as needed; avoid direct contact with potential skin irritants – fragrances, alcohol-based cosmetics, hot water, household cleaners; avoid rubbing the skin; be careful when going outside and look for shade; avoid direct sun exposure between 10 am to 4 pm; use sun protection (wide brimmed hat, clothes, sunglass with UV protection and sunscreen SPF ≥30, to UVA and UVB).

  After the end of treatment, hyperpigmentation is expected to fade over time.

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In patients on targeted multikinase therapies or immunotherapy with anti-CTLA-4 or anti-PD-1/PD-L1 with vitiligo-like depigmentation, it is also necessary to be attentive to sun protection measures (described above).

> nail colour changes

During cancer treatment, nails can become brown or black, dark red, brown red or orange (related to subungual haemorrages), or white. Most of these changes in colour are reversible after treatment.

There is no effective depigment product to apply on hyperpigmented nails. To hide the changes in colour you can use a dark-coloured nail polish, preferably hypoallergenic.

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