CANCER
& Hair loss

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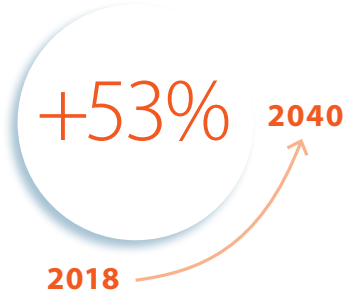
A rapidly growing concern

The increasing prevalence of cancer and use of cancer treatments

• Incidence of cancer

A growing and aging population combined with the increased risk of cancer has led to a continued rise in new cancer cases [1].

Projections indicate the number of cases will rise from **17 million in 2018 to 26 million by 2040** [2].

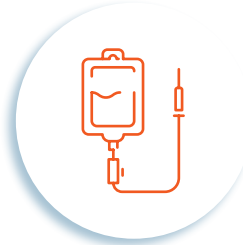


• Antimitotic chemotherapy and radiotherapy

In 2018, an estimated 10 million people were treated with chemotherapy worldwide, representing 57.7% of patients [2].

Between 2018 and 2040, the number of patients requiring chemotherapy treatment is expected to increase by 53% to 15 million patients [2].

Concurrently, the number of people treated with radiotherapy reached 7 million patients in 2012, or 1 in 2 cancer patients [3].



10 million

7 million

• Targeted therapies and immunotherapies

Over the years, a better understanding of cancer cell biology has led to research in the development of new targeted therapies. Use of these new treatments has become widespread, resulting in increased spending on targeted therapies and immunotherapies, to the detriment of «conventional chemotherapies».

Targeted therapies: 100 % of the new molecules developed in oncology in 2017

1. OMS. Communiqué de presse n° 263. 12 septembre 2018. Disponible sur: https://www.iarc.fr/wp-content/uploads/2018/09/pr263_F.pdf [consulté le 11 mars 2020]. **2.** Wilson B, Jacob S, Yap M, Ferlay J, Bray F, Barton M. Estimates of global chemotherapy demands and corresponding physician workforce requirements for 2018 and 2040: a population-based study. Lancet Oncol 2019;20:769–80. **3.** Yap M, Zubizarreta E, Bray F, Ferlay J, Barton M. Global Access to Radiotherapy Services: Have We Made Progress During the Past Decade? J Glob Oncol 2016;2(4):207-15.

Physiopathological mechanisms

Cancer treatments interfere with the hair cycle through two mechanisms: anagen effluvium (AE) and telogen effluvium (TE).

• Antimitotic chemotherapy and radiotherapy

Anagen effluvium refers to sudden, severe and widespread hair loss over a span of a few days to several weeks from the time the medication is administered. It is triggered by sudden inhibition of mitotic activity in the hair follicle matrix keratinocytes, the primary targets of cancer treatments. As a result, the growing hair shaft is only partially keratinized, leading to breakage in the hair fiber. In this case, the hair follicles in catagen or telogen phase, and thus not in active mitotic phase, are unaffected.

• Targeted therapies and immunotherapies

Targeted therapies work by blocking the oncogenic pathways required for the growth and survival of cells. Immunotherapies and stem cell transplants may also lead to alopecia (specifically alopecia areata). This side effect is likely caused by an activation of the inflammatory responses against the hair follicle antigens and an imbalance in immune tolerance in the hair follicle's environment [4].

In cases of melanomas treated with a selective BRAF-kinase inhibitor, alopecia is believed to be the result of an acute interruption of the anagen phase in the hair bulb's matrix cell, thus causing a regression in anagen follicles followed by apoptosis [5].

Focus on melanoma

- +50 % of melanomas have a BRAF mutation
- **Alopecia :** A common or very common side effect (SE) of targeted therapies targeting BRAF

• Hormone therapies and the increase in androgenetic alopecia

When the medication causing TE must be continued, this phenomenon may cause or worsen androgenetic alopecia (AGA) in patients with a genetic predisposition [6].

LH-RH agonists (goserelin, leuprolide), anti-estrogens (tamoxifen, toremifene, fulvestrant) and especially aromatase inhibitors (letrozole, anastrozole, exemestane) are likely to induce or aggravate AGA and may cause some patients to stop treatment [7].

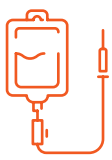
4. Freites-Martinez A, Shapiro J, Goldfarb S, Nangia J, Jimenez JJ, Paus R, et al. Hair disorders in patients with cancer. Journal of the American Academy of Dermatology 2019;80(5):1179–1196. **5.** Piraccini B, Starace M, Alessandrini A. Hair Changes due to Drugs. In: Alopecia. Elsevier Health Sciences; 2018. p. 245 58. **6.** Tosti A, Misciali C, Piraccini BM, Peluso AM, Bardazzi F. Drug-Induced Hair Loss and Hair Growth. Drug-Safety 1994;10(4):310 7. **7.** Matard B, Reygagne P. Alopécies. In: Dubertret P. Thérapeutique Dermatologique [Internet]. Fondation René Touraine; 2016. Disponible sur: https://www.therapeutique-dermatologique.org/spip.php?article1023&var_recherche=Alop%C3%A9cies [consulté le 11 mars 2020].

Primary causes of alopecia in cancer patients

Chemo-induced alopecia depends on the percentage of follicles in anagen phase. It therefore affects mainly the scalp, where 90% of hair follicles are normally in anagen phase.

Other hair regions, such as the beard, eyelashes, eyebrows, underarms and pubic area, are affected at varying degrees [5,8].

The duration of alopecia varies depending on the chemotherapies used [9]. In the vast majority of cases, the condition is reversible and the hair grows back several weeks after the treatment is stopped. In general, body hair grows back faster than the hair on the head. Regrowth occurs at a speed of approximately 1 cm per month, meaning patients must wait several months for their hair to return [5,6,8].



• Chemotherapy: alopecia affects 65% of patients

Alopecia usually begins 1 to 3 weeks into chemotherapy treatment, with total hair loss occurring after 1 or 2 months.

The risks and severity of hair loss vary depending on the anti-cancer agent prescribed, its route of administration, dose and administration schedule, and the patient's individual response to the treatment [8]. According to some researchers, the incidence of alopecia reported with antimicrotubule agents is 80%, 60% to 100% with topoisomerase inhibitors, over 60% with alkylating agents, and 10% to 50% with antimetabolites [5].

When cancer drugs are used in combination, the incidence and severity of alopecia increase accordingly [5].

Main chemotherapies that induce alopecia

Activities	Molecules		
CHEMOTHERAPIES that frequently induce alopecia (more than 60% patients)	Adriamycin Cyclophosphamide Daunorubicin Docetaxel	Doxorubicin Epirubicin Etoposide Ifosfamide	Irinotecan Paclitaxel Topotecan
CHEMOTHERAPIES with possible alopecia	Bleomycin Busulfan Cytarabine Fluorouracil Gemcitabine	Hydroxycarbamide Melphalan Methotrexate Pemetrexed Thiotepa	Vinblastine Vincristine Vinorelbine
CHEMOTHERAPIES that very rarely induce alopecia	Capecitabine Carboplatin	Cisplatin Fludarabine	Mitomycin C Procarbazine

8. Patel M, Harrison S, Sinclair R. Drugs and Hair Loss. Dermatologic Clinics [Internet]. 2013 ;31(1):67 73. **9.** Piérard-Franchimont P, Piérard G. Comment j'explore... une perte de cheveux chez un patient cancéreux. Rev Med Liège 2004;59(9):525 9.

• Radiotherapy: alopecia affects up to 100% of patients

Nearly all patients undergoing radiotherapy treatment for malignant tumors in the central nervous system will develop alopecia.

With conventional radiotherapy or proton therapy, the onset of alopecia depends on the field and dose of radiation delivered.

The significance of this often-permanent hair loss varies depending on the indications of the radiotherapy.

When palliative radiotherapy is used to treat brain metastases, for example, alopecia is hardly a primary concern. This is not the case, however, when radiotherapy is used to treat the early stages of skin or brain neoplasms for which recovery is possible [4,9].

Risk factors

Other risk factors also contribute to the prevalence of alopecia. The clinical hair pattern prior to starting chemotherapy, for example, is a very important factor.

The presence of AGA, particularly in the crown region and on the sides of the head above the ears, the first area affected by chemotherapy, **predisposes patients to hair loss** [5].

• Targeted therapies and immunotherapies: alopecia affects 15% of patients

Alopecia is a common side effect of the new targeted cancer treatment therapies. An increasing number of patients are turning to these new therapies, and, in order to treat them properly, dermatologists need to be aware of the drugs involved.

The five therapies with the highest rates of alopecia are presented in the table below [10].

Treatment	% of patients with alopecia	Indications
ERIVEDGE (Vismodegib)	**56.9 (5.6 - 63.1)**	**Basal-cell carcinoma,** metastatic or locally advanced
NEVAXAR (Sorafenib)	**29 (23.9 - 34.7)**	Advanced **hepatocellular, thyroid or kidney carcinoma**
ZELBORAF (Vemurafenib)	**23.7 (9.6 - 47.5)**	**Melanoma** unresectable or metastatic with a BRAF V600 mutation
STIVARGA (Regorafenib)	**23.5 (9.7 - 46.7)**	**Colorectal cancer, gastrointestinal stromal tumors, hepatocellular carcinoma**
TAFINLAR (Dabrafenib)	**18.9 (10.5 - 31.5)**	**Bronchial cancer and melanoma,** non-small-cell with a BRAF V600 mutation

10. Mir-Bonafé JF, Saceda-Corralo D, Vañó-Galván S. Adverse Hair Reactions to New Targeted Therapies for Cancer. Actas Dermo-Sifiliográficas (English Edition). 2019.

Consequences and repercussions

• Psychological trauma

Fear of alopecia post chemotherapy can be such that nearly 8% of patients may refuse life-saving chemotherapy treatment as a result [11].

Most often temporary, alopecia is the adverse effect that patients dread the most and is even the primary burden of the disease. Hair loss is easily visible and may be stigmatizing, acting as a constant reminder of the person's illness, both for the patient and for the people around them.

The distress caused by hair loss is the same for all types of cancer and throughout all cultures, even those where women customarily cover their hair with a traditional scarf. The negative body image associated with hair loss affects patients of all ages, both young and old [11].

Chemo-induced alopecia changes how the patient socializes with family members and coworkers and diminishes quality of life [12].

• Trichodynia [13]

Trichodynia refers to a collection of symptoms including pain, discomfort and/or paresthesia of the scalp.

Trichodynia had previously been reported mainly in association with telogen hair loss, at an incidence of 29% in patients with AGA or TE and at 50.7% in patients with AGA and TE simultaneously.

Today, we know that hair loss resulting from chemo-induced alopecia is mostly anagen but with a portion in anagen-telogen conversion.

According to a recent observational study conducted on a cohort of breast cancer patients undergoing chemotherapy or hormone therapy treatment:

- 100 % of patients treated with conventional chemotherapy experienced trichodynia (of which 87% was associated with pruritus) appearing on average 11 days after the start of treatment.
- 19 % of patients treated with tamoxifen experienced trichodynia (of which 12% was associated with pruritus).

11. Boyle FM, Shaw J, Young A, van den Hurk C, Rugo HS, Fogarty GB, et al. Management of Alopecia Due to Cancer Therapies. In: Olver I, éditeur. The MASCC Textbook of Cancer Supportive Care and Survivorship. Cham: Springer International Publishing; 2018. p. 621 31. **12.** Battu C. Alopécie et traitements anticancéreux. Actual Pharm. 2018;57(579):59–61. **13.** Kanti V, Nuwayhid R, Lindner J, Hillmann K, Bangemann N, Kleine-Tebbe A, Blume-Peytavi U, Garcia Bartels N. Evaluation of trichodynia (hair pain) during chemotherapy or tamoxifen treatment in breast cancer patients. JEADV 2016, 30, 112–118.

Preventive and reactive strategies

Today, the preventive and reactive strategies for treating chemo-induced alopecia are limited [4,11].

• Preventive strategies:

No medication has been approved so far for the prevention of hair loss, but some agents and treatments have been studied.

Results on the preventive use of topical 2% minoxidil are contradictory and based on studies involving very few patients.

Calcitriol has shown promising results in terms of prevention in a phase I study including 31 patients. It is currently under development.

Cooling the scalp with a cold cap has become the most widely used approach to prevent chemo-induced alopecia. This solution is currently recommended by the FDA for the prevention of chemo-induced alopecia in patients undergoing cytotoxic chemotherapies for solid tumors [4].

It is important to note that wearing a cold cap does not prevent radiation-induced alopecia.

• Reactive strategies:

Reactive strategies are based solely on case series, case reports and expert opinions.

Topical and intralesional therapies using corticosteroids have proven effective in anecdotal cases. AGA treatments have shown to be beneficial in the case of hormone-sensitive tumors. Any recommendations must be considered with a great deal of caution.

However, camouflage and make-up solutions may be recommended freely [4].

Advice to give to patients

- **Get informed** about the disease, its treatment and the negative consequences of following the treatment, including alopecia. Patients prefer to have the ability to prepare for how they will manage the side effect rather than simply being subjected to it [12].
- **Cut hair relatively short** to prevent it from falling out in clumps and avoid using hair dye or other harsh products.
- **Wash hair and scalp with a gentle,** detergent-free and high-tolerance **shampoo** during treatment and the regrowth stage.
- **Style hair** using your hands rather than with a hair brush.

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