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CME Part 1: Hair disorders in cancer patients

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Abstract

Cytotoxic chemotherapies, molecularly targeted therapies, immunotherapies, radiotherapy, stem cell transplants, and endocrine therapies may lead to hair disorders (including alopecia, hirsutism, hypertrichosis, pigmentary and textural hair changes). The mechanisms underlying these changes are varied and remain incompletely understood, hampering the development of preventive or

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Learning objectives: To prevent, diagnose and treat hair disorders developing during anticancer therapies.

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therapeutic guidelines. The psychosocial impact of chemotherapy -induced alopecia has been well-documented mainly in the oncology literature, however the effect of other alterations such as radiation-induced alopecia, hirsutism, changes in hair color or texture on quality of life have not been described. This article reviews clinically significant therapy-related hair disorders in cancer patients, underlying pathophysiological mechanisms, severity grading scales, patient reported quality of life instruments, management strategies, and future translational research opportunities.

Keywords

chemotherapy-induced alopecia; anagen effluvium; catagen effluvium; brittleness; curling; depigmentation; hirsutism; hyperpigmentation; hypertrichosis; hypopigmentation; eyelash alopecia; eyebrow alopecia; hair repigmentation; straightening; trichomegaly; cancer patients

Introduction

Cancer is a major public health problem worldwide. In 2016, more than 1.6 million new cancer cases were projected in the United States and 32 million worldwide, and of these, approximately 60% received systemic therapies, and 50% underwent radiotherapy.[1] The most commonly encountered hair disorder is cytotoxic chemotherapy-induced alopecia (CIA).[2-4] However, several other anticancer therapies may also be related to alopecia, such as radiation,[5] targeted therapies,[6] immunotherapies,[7] stem cell transplants,[8] and endocrine agents.[9] In addition, alterations in hair pigmentation, texture, and growth may also be encountered,[10] although they have not been systematically documented in this patient population. The impact of these disorders, namely alopecia, on cancer patients' quality of life (QoL) cannot be disregarded.[11] Indeed, 17% of patients with gynecologic cancers reported that alopecia was the most traumatic adverse event (AE) during their treatment, 30% were severely limited, and up to 14% would consider rejecting curative cancer therapies if they are associated with alopecia.[12-14]

The information contained in this continuing medical education article intends to contribute to greater knowledge on these untoward events in order to optimize the assessment and management of hair disorders in cancer patients.

Epidemiology

Key point

- Hair changes attributed to anticancer therapies are expected to occur in at least 65% of patients receiving cytotoxic therapies, 15% with targeted therapies, <2% on immunotherapies, and around 100% in areas of the head treated with radiotherapy

The widespread use of systemic anticancer therapies, their numerous combinations, and underreporting of hair disorders yield mixed incidence reports (Table 1), but these events at varying degrees of severity are frequent across almost all types of interventions. The estimated incidence of CIA is approximately 65% and tends to vary by the specific drugs and different regimens.[15] Alopecia is typically observed in almost every patient undergoing

radiotherapy for central nervous system malignancies treated with photon radiotherapy (traditional radiotherapy) or proton radiotherapy, and intensity and rate would increase as the dose exceeds the threshold.[16, 17] With targeted therapies, the calculated overall incidence of all-grade alopecia was reported at 15%.[6, 18] An overall incidence of all grades of alopecia were reported at 1-2% with immune checkpoint inhibitors, including cytotoxic T-lymphocyte-associated protein-4 (CTLA-4), and the programmed cell death protein-1 (PD-1) receptors and its ligand (PD-L1).[7, 19] In nearly 100% of patients status post hematopoietic stem cell transplantation, complete alopecia is attributed to the conditioning cytotoxic chemotherapies (i.e. busulfan, melphalan, fludarabine).[20] Endocrine therapies (i.e. anastrozole, letrozole, exemestane) have been related with alopecia in up to 25%.[9] Whereas alopecia receives the most attention among hair disorders in the oncology realm, changes in hair structure (becoming curly or straight) and color (hyper or hypopigmentation) have been reported in approximately 65% of patients during and after cytotoxic chemotherapies,[21] in 30% of those receiving targeted therapies,[22] and 2% with immunotherapies[19] (Table 1).

Clinical Features

Key Point

- The spectrum of hair disorders in cancer patients encompasses all hair changes including alopecia, pigmentary changes, textural changes, and cycle alterations

Hair disorders in cancer patients occur due to disturbances in hair follicle cycling and functioning, and hair shaft synthesis, which result in effluvium during anagen or telogen.[3, 4, 75] Clinical features of hair disorders induced by anticancer therapies vary depending on the anticancer therapy given, its half-life, dose, schedule, route and rate of administration, whether it is administered alone or in combination with other anticancer therapies, as well as patient factors (Table 2).[76]

Alopecia—CIA usually begins within weeks after the first dose of cytotoxic chemotherapy as a patchy or diffuse anagen effluvium with predominance on areas of increased friction, such as crown and temporo-occipital areas, that may progress to complete alopecia in 2-3 months.[77] In addition, eyelash and eyebrow alopecia, and alopecia of other body areas could be observed in association with scalp alopecia in up to 33% of patients receiving taxanes.[78] Although usually asymptomatic, CIA could also be related with trichodynia and pruritus (11%).[77] CIA is typically reversible within 2-6 months after chemotherapy is discontinued.[64, 79] Trichoscopic findings in CIA include black dots, yellow dots, exclamation mark hairs, and color and thickness changes along the hair shaft (Figure 1).[80, 81]

Radiotherapy-induced alopecia (RIA) is characterized by an anagen effluvium due to acute damage of the hair follicle.[82] An alopecia patch confined to the area of radiotherapy is usually observed 1-3 weeks after the first irradiation,[83] and hair regrowth usually occurs 2-6 months after radiotherapy.[60, 84] Radiation dermatitis and cutaneous injury may also accompany the alopecia (Figure 2).[85] Yellow and black dots have been described as the predominant trichoscopic findings in 60% of RIA, followed by short vellus hair (50%), peripilar sign (20%), and broken hairs (10%), trichoscopic findings also described in alopecia areata and androgenetic alopecia.[86,87]

Whereas mild diffuse alopecia is frequent with EGFR inhibitors (e.g. erlotinib, afatinib, cetuximab, panitumumab), scarring alopecia have been reported in 5% of patients treated with cetuximab, which may be a consequence of a secondary scalp bacterial infection (Figure 3), manifested as erosive pustular dermatosis,[69, 88-90] or tufted hair folliculitis.[91] Alopecia areata and universalis are considered immune related AE occurring in 2% of patients receiving ipilimumab.[92]

Among patients undergoing stem cell transplantation, diffuse alopecia is reported in association with conditioning chemotherapy in around 100%.[64] Hair changes may occur with acute graft-versus-host disease, including features of nonscaring alopecia with diffuse hair thinning, patchy hair loss, and premature graying. Alopecia areata and other autoimmune skin conditions such as vitiligo have been reported in the graft-versus-host disease setting.[93, 94] Endocrine therapies have been associated with alopecia, usually mild in severity with a pattern similar to androgenetic alopecia.[95] Despite the fact that most cases of alopecia in cancer patients are transitory, 14% of childhood cancer survivors,[96] and 30% of breast cancer survivors [97] will develop persistent or even permanent alopecia.

Pigmentary and textural hair changes

Textural and pigmentary hair changes are frequent with anticancer therapies; however these are reversible upon drug discontinuation. Pigmentary hair changes include; depigmentation (Figure 4) and hyperpigmentation, most apparent on the scalp, although the eyebrows, eyelashes and body hair may be affected as well. Hair hypopigmentation has been reported with the MKIs (pazopanib, sunitinib, regorafenib), [98-104] whereas EGFR inhibitors result in hyperpigmentation of scalp and facial hair (~ 50%).[105-107] Hair repigmentation has been described as a possible marker of tumor response in 14 patients receiving anti-PD1/anti–PD-L1 therapy for lung cancer.[68]

Additionally, straight hair may become curly or wavy in 65% of cancer patients after treatment with cytotoxic chemotherapy.[21] With targeted therapies, the hair growth on scalp can slow down, become finer, curlier and brittler.[69, 108]

Hirsutism, hypertrichosis and trichomegaly—Excessive hair growth over the periocular area,[109, 110] hirsutism,[69] and trichomegaly (Figure 5) have been mostly reported as an AE of EGFR inhibitors.[72-74] Eyelash trichomegaly also has been reported after pan-FGF receptor inhibitor therapy.[111] These alterations typically resolve after discontinuation of treatment, although in some cases, they can persist for several months.[112] Hirsutism could be seen in cancer patients who receive endocrine therapies (anti-estrogen agents), and the low incidence is likely due to underreporting.

Etiology and Pathogenic Mechanisms

Key points

- The pathogenic mechanisms of anticancer therapy-induced alopecia and other hair disorders will vary depending on causal therapy

- The hair matrix keratinocytes of anagen hair follicles have a high mitotic activity, which makes them especially vulnerable to anticancer therapies
- Paradoxically, some anticancer therapies can promote hair growth, textural and hair color changes

Although the clinical manifestation of CIA from different therapies may be similar (albeit with subtle variations), accumulating evidence suggests that the molecular underpinnings are varied and share several molecular damage-response pathways.[75, 113] In particular, massive p53-dependent apoptotic cell death of hair follicle matrix keratinocytes and of hair follicle melanocytes plays a pivotal role.[114-116] In the rodent and human CIA models, rapidly proliferating anagen hair follicles and their pigmentary system, which are both very sensitive to toxins, are the main targets of cytotoxic chemotherapy-induced hair follicle damage, reducing the proliferation rate and promoting the apoptosis of matrix keratinocytes and melanogenesis in the hair bulb.[75, 116] Telogen hair follicles are less sensitive than anagen hair follicles to chemotherapy, presumably because of low-level proliferation and arrested pigmentary activity.[75] RIA is a dose-dependent treatment related acute damage to actively dividing matrix cells of anagen follicles, followed by telogen shedding due to premature catagen entry of follicles in late anagen.[82] Doses as low as 2 Gy in a single fraction have been shown to cause temporary alopecia.[117]

Targeted therapies work by blocking oncogenic pathways needed for cell growth and survival. In mice, dysregulation of the EGFR-Ras-Raf pathway can result in abnormal hair follicle morphogenesis. However, it is not known why paradoxically, EGFR inhibitors result in scalp alopecia, but result in hirsutism and eyebrow and lash trichomegaly.

Immunotherapies (anti-CTLA-4, PD-1, PDL1) and stem cell transplants may also result in alopecia, with a clinical and histologic pattern consistent with alopecia areata, likely due to the activation of inflammatory responses against hair follicle antigens, and an imbalance of the immune tolerance in the hair follicle environment. [7]. These findings are concordant with other immune-related AEs reported in immunotherapy-treated patients, in which autoimmune T and B cell-driven mechanisms underlie toxicities.[7, 94]

The mechanisms by which endocrine therapies result in alopecia is via counteracting the anagen-prolonging effects of 17-β-estradiol [118-120] and result in increased hair growth-inhibitory actions of androgens, which is probably reflected by the development of hair thinning with a predominant androgenetic pattern.[121, 122]

The pigmentary changes in regrowing hairs could be explained by an impaired transfer of melanin from hair follicle keratinocytes to the hair shaft, and the generation of an oxidative damage, [123] with induction of apoptosis of hair follicle melanocytes and melanocyte stem cells.[116] Changes in hair structure depend on multiple interacting parameters, including hair shaft keratins, and hair follicle asymmetric cell proliferation.[124, 125]

Hair Disorder Severity Grading

Key point

- Adverse events in oncology clinical trials are graded using the Common Terminology Criteria for Adverse Events

The documentation of AEs is critical for patient safety and for the development of a toxicity profile for each anticancer drug/regimen. In the oncology literature, alopecia is graded by the following AE grading instruments; the World Health Organization (WHO),[126] Dean scale,[127] the Eastern Cooperative Oncology Group (ECOG),[128] Sredni et al,[129] the National Cancer Institute (NCI),[130] the EGFR inhibitors Skin Toxicity Tool (MESTT),[131] and the Common Terminology Criteria for Adverse Events, version 4.0 (CTCAE v4.0) (Table 3).[132] Of all these grading instruments, the CTCAE v4.0 [132] is the standard for the description and exchange of drug safety information in cancer treatments. Its use is mandatory in oncology trials, therefore data on alopecia incidence and severity is reported according to the CTCAE. There are some limitations in the alopecia grading (CTACE grade 1 and 2) that may not capture subtle changes in severity or the pattern, therefore more granular severity grading tools are recommended for studies investigating anticancer therapy-induced alopecia.

For eyelash and eyebrow alopecia, there are no validated grading scales, whereas hypertrichosis and trichomegaly are graded with the CTCAE v4.0. [132] The modified Ferryman–Gallwey scoring system may also be used to grade hyperthrichosis.[133]

Quality of Life In Cancer Patients With Hair Disorders

Key point

- Chemotherapy-induced scalp, eyelash, and eyebrow alopecia lead to a negative psychosocial impact. The impact of other hair disorders in oncology has not been reported, but is expected to be significant

Hair-related AEs have a profound impact on cancer patients' QoL. CIA is one of the most clinically visible and distressing AE,[2] and has been cited as the most disturbing anticipated AE by 58% of breast cancer patients prior to chemotherapy.[134] In a multicenter study, 55% of 168 breast cancer patients reported high psychological distress from CIA.[135] The impact can be so immense that coping with hair loss was felt more difficult than with loss of a breast,[136, 137] and can even lead patients to refuse treatment (8%).[136, 138] Additionally, eyelash and eyebrow alopecia resulted in psychological distress in breast cancer patients treated with taxane-based chemotherapy.[139]

The impact on QoL of changes of hair color and texture, hirsutism and hypertrichosis in cancer patients has not been reported. Treatment-related growth of unwanted facial hair can also significantly affect QoL, as shown in a previous survey-based study of several thousand women, where 62% had concerns regarding unwanted hair on the upper lip.[140, 141] Therefore, it would be important to query and measure the impact on QoL of hair disorders attributed to anticancer therapies, given the longer times patients are on therapy and the increasing number of medications with these events.

Specific Quality Of Life Instruments

Assessing the patient's own perception of their symptoms using patient reported outcome measures such as PRO-CTCAE, may complement our understanding of drug-induced hair disorders.[142] Specific instruments to assess the impact of hair disorders on cancer patients' QoL, include the Chemotherapy-induced Alopecia Distress Scale (CADS)[143] (validated in Korean patients and translated into English), which comprises 17 questions in 4 domains. In addition, the Eyelash Satisfaction Questionnaire (ESQ) was validated in a cohort of 595 cancer patients, and it includes 23 questions in 3 domains. [144, 145]

Management

Key point

- Most preventive or reactive strategies are based on uncontrolled studies, however the FDA has cleared two dynamic scalp cooling devices for the prevention of CIA in patients treated with cytotoxic therapies for solid tumors

Anticancer Therapy-Induced Alopecia

Given the varied alopecia-inducing mechanisms of action of anticancer therapies, and the individual's inherent susceptibility, no one strategy might work for alopecia induced by different therapies.[75] Management for anticancer-therapy induced alopecia can be broadly divided into preventive and reactive strategies, as summarized in Table 4.

Preventive strategies—There are no preventive pharmacologic strategies that have demonstrated satisfactory efficacy to justify their general use. For example, topical minoxidil 2% twice a day, showed no benefit to prevent CIA in a prospective trial of 10 patients.[146] However, in a randomized trial including 22 breast cancer patients who were treated with cytotoxic chemotherapy, topical minoxidil 2% solution reduced the duration of alopecia by 50 days when compared to placebo (87 vs. 137 days).[147] Trials evaluating this potential preventative strategy are needed. The topical calcitriol (BPM31543) showed benefit in a phase 1 trial of 31 patients and is currently under development.[148]

Scalp cooling has become the most widely utilized method for the prevention of CIA.[149] Scalp cooling systems include static devices (e.g. glycerin-based, Chemocoldcaps™, Penguin™),[150-153] and the recently FDA-cleared dynamic scalp cooling systems (DigniCap™, 2015; Orbis Paxman™, 2017).[154-156] The plausible mechanisms for conferring protection to the hair follicle include the reduced availability of cytotoxic drug to the hair follicle (vasoconstriction induces a decrease of 20% of scalp blood flow),[127, 156, 157] the relative reduced follicular uptake of cytotoxic therapies,[158] and decreased follicular metabolic activity.[159]

The success of scalp cooling appears to depend on the type of the chemotherapy regimen. In a prospective study in 124 women with breast cancer receiving taxane-based chemotherapy, Dignicap scalp cooling conferred protection against hair loss (Dean score of 0-2) in 66% compared to 0% in the uncooled group.[160] In a multicenter, randomized study using the Orbis Paxman scalp cooling system,[161] hair preservation was observed in 50% (cooling

group) vs. 0% (controls) after the 4th chemotherapy cycle (taxane/ anthracycline/ or both). Another prospective randomized study of 79 patients (41 receiving Dignicap scalp cooling) reported lower hair preservation rates (39%) among patients undergoing scalp cooling versus 0% in the no scalp cooling arm.[162, 163] Differences between devices are likely related to operator experience and types of chemotherapy regimens of patients enrolled, with patients on taxane-based regimens showing a higher benefit from scalp cooling. Regarding safety, the most common adverse device events include headache (11%), nausea (4%), and dizziness (3%).[161] A meta-analysis of 10 trials that included 1,959 patients demonstrated no differences in the incidence of scalp metastases between cooled (0.61%) vs non-cooled patients (0.41%).[164] Scalp cooling has been reported effective in 3 breast cancer patients treated with taxane-based chemotherapy and with CIA grade 2 (CTCAE) in order to prevent alopecia in future chemotherapy sessions, and consequently allow sooner reestablishment of scalp hair density, however, the risk of frostbite should be considered.[165] In general, pre-cooled caps remain very popular because of their widespread availability. Although four cases of thermal injury has been reported due to improper caps applications.[166]

Although the 30% incidence of persistent CIA [97] augments the interest in preventing CIA, there is no data on the efficacy of scalp cooling devices on persistent alopecia, hence their use cannot be recommended for this purpose. Despite the relative success of the scalp cooling system in preventing CIA, this system has been reported as not effective to prevent RIA.[167] Additionally, scalp cooling system use is not reimbursable by insurance companies, and costs may be elevated. Financial assistance may be obtained through hairtostay.org and coldcapitalfund.org.

There is no data on preventive strategies for non-cytotoxic agent-induced alopecia. Therefore, we recommend pre-therapy counseling and on-therapy evaluations by the oncology team for atypical patterns or severity of alopecia, so that any comorbidities or exacerbating factors may be addressed and patient is referred to a dermatologist if indicated

Reactive strategies—The reactive strategies are mostly based on case series, case reports, and expert opinion. Immunotherapies and stem cell transplant have been related with alopecia areata.[7, 93] Therefore, topical and intralesional therapy with corticosteroids have shown efficacy in anecdotal reports of 2 patients.[7] Cancer patients may have hormone-sensitive tumors that could react with systemic therapies used for androgenetic alopecia (e.g. spironolactone, finasteride, cyproterone acetate); we have therefore held with caution these strategies for cases of persistent alopecia in cancer survivors. Camouflage and supportive care should be provided to patients with CIA (Table 4).

Eyelash and Eyebrow Alopecia

Relatively inexpensive cosmetics and camouflage products could be used as long as eyelashes are still present. The effect of bimatoprost solution 0.03% on chemotherapy-induced eyelash hypotrichosis was examined in a controlled study of 130 breast cancer patients receiving cytotoxic chemotherapy showing that treatment with bimatoprost resulted in increased length and thickness compared to the vehicle control group (eyelash length 38% vs 16%; eyelash thickness 245% vs 33%).[168]

Pigmentary and Textural Hair Changes

Hair repigmentation and textural hair shaft changes have been reported with targeted and immunotherapies.[68] Initially, most patients are satisfied with their new hair characteristics. Nevertheless, if management is requested, options such as hair dyeing and changes in hairstyle (i.e. straightening or curling) should be recommended as they pose no additional risk in cancer patients. The use of hair dyes and their association with cancer development is conflicting with non-Hodgkin lymphoma, none to insignificant for leukemias, and non-existent for breast cancer.[169]

Hirsutism, Hipertrichosis And Trichomegaly

Topical or cosmetic interventions are recommended (e.g. waxing or bleaching).[170] Laser and photoepilation treatments are the most effective, especially in patients with lighter skin and dark-colored hairs.[171] For eyelash and eyebrow trichomegaly related with targeted therapies, eyelash clipping and referral to an ophthalmologist is indicated for patients with ocular symptoms.[172]

Experimental Therapies

Several pre-clinical approaches have been tried for CIA and RIA, although only a few have shown some clinical benefit. Moreover, there are no public trials for the prevention or management of other anticancer therapy-induced hair disorders.

AS101 (ammonium trichloro (dioxoethylene-O,O-) tellurate) is an immunomodulatory tellurium compound based on a derivative of cisplatin. The drug has been shown to protect against CIA by reducing the severity but it does not prevent hair loss.[129] A topical botanical blend solution for the treatment of androgenetic alopecia [173] is currently being investigated for the prevention of permanent CIA in a double-blind, randomized controlled trial in breast cancer survivors.[174] It is hypothesized that this herbal medication may normalize apoptotic process in the hair follicle cells, and reduces chemotherapy-induced inflammation in the scalp.

Tempol is a nitric oxide radioprotector and its topical formulation has been found to be protective against RIA in both animal models and humans.[175] In a phase Ib study, the application of tempol gel 15 minutes before radiotherapy followed by wash-off, led to full scalp retention in 3/5 evaluable patients.[176]

Challenges and Future Perspectives

Despite the prevalence and psychosocial impact of the anticancer therapy-induced hair disorders, research into their clinical presentation, pathophysiology, and management strategies has not received the attention it justifies. A comprehensive knowledge of the impact of hair disorders on QoL would be critical in order to optimize the shared decision-making process between doctors and patients regarding cancer therapies. As patients live longer on cancer therapies, there is a need to identify risk factors of clinically significant events and to develop improved and widely available preventive strategies, all of which would contribute to the optimal and comprehensive care of cancer patients.

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Abbreviations

AE	Adverse event
CIA	Chemotherapy-induced alopecia
CTCAEv4.0	Common Terminology Criteria for Adverse Events Version 4.0
EGFR	Epidermal growth factor receptor
MKIs	Multikinase inhibitor
QoL	Quality of Life
RIA	Radiotherapy-induced alopecia

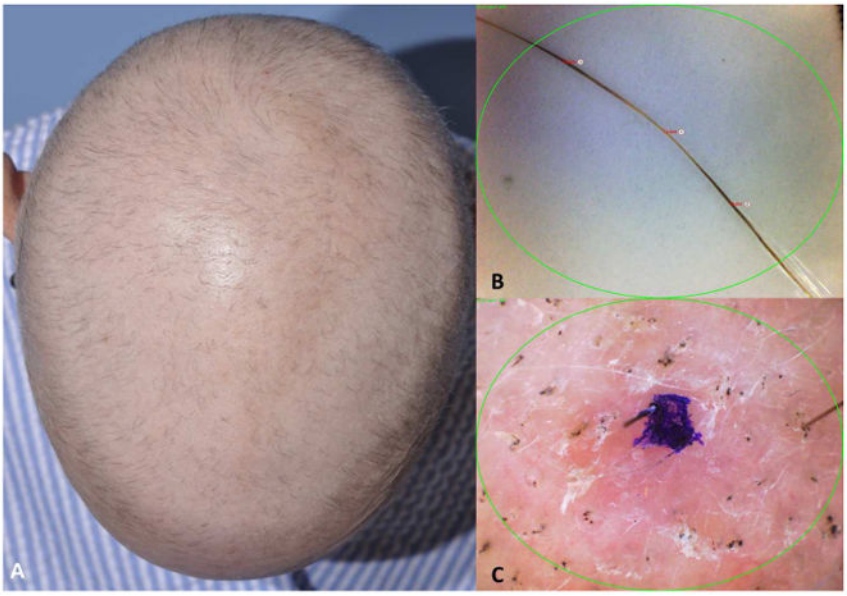

Figure 1.

Chemotherapy-induced alopecia (CIA). A. Clinical image of scalp alopecia one month after first taxane-based chemotherapy cycle. B. Pohl-Pinkus constrictions observed in monilethrix-like hairs following weekly cyclophosphamide-based chemotherapy. C. Trichoscopy of CIA shows black dots, fractured hair shafts and vellus hairs.

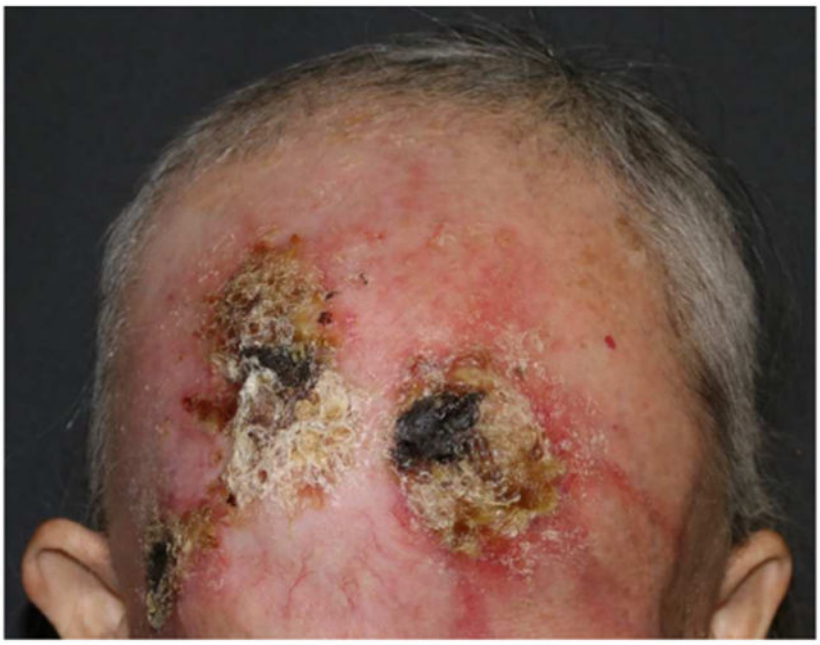

Figure 2.
Radiotherapy-induced alopecia (RIA). Alopecia, erythema and ulceration related to photon radiotherapy used for treating scalp metastasis. Ulceration resulted in permanent/cicatricial alopecia.

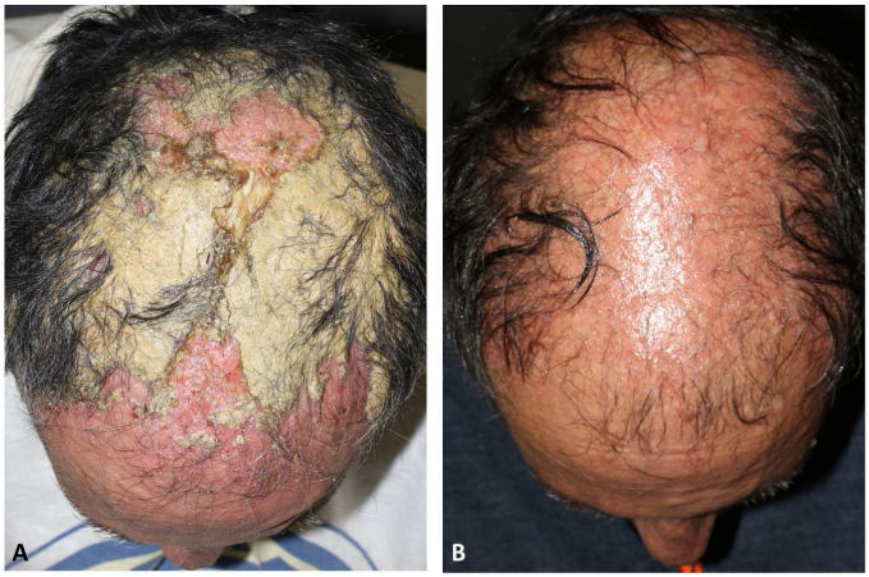

Figure 3.
Scalp folliculitis (Skin infection grade 3 (CTCAEv4)) in a patient receiving cetuximab. A. Before therapy with oral doxycycline and topical high potency corticosteroids. B. Two weeks after dermatologic therapy.

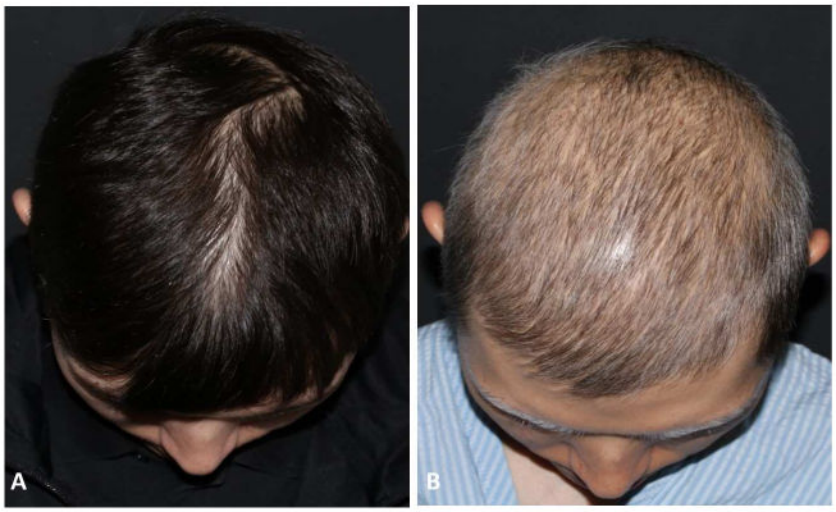

Figure 4.

Depigmentation and hair thinning in a patient receiving tremelimumab. A. Before therapy. B. 3 months after first dose of treatment.

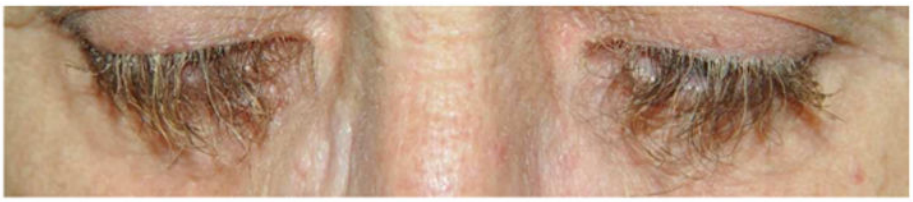

Figure 5.
Trichomegaly in a patient on erlotinib during a year.

Table 1
Selected anticancer therapies (representative) commonly causing hair changes

Hair disorders and cancer therapy	Tumor types indicated or under investigation	Incidence (%) or case reports
Alopecia/hair loss		
Chemotherapies		
Cyclophosphamide[23-27]	Breast cancer, leukemia, lymphoma, multiple myeloma, neuroblastoma, retinoblastoma, ovarian cancer	25 (low dose) ~ 100 (high dose)
Daunorubicin [28, 29]	AML, ALL	~ 100
Docetaxel[30-34]	Breast cancer, gastric cancer, head and neck cancer, lung cancer, prostate cancer	~ 100
Doxorubicin[35-37]	ALL, AML, thyroid cancer, breast cancer, gastric cancer, lung cancer, bladder cancer, lymphomas, neuroblastoma, sarcomas, Wilms tumor	80 - 100
Etoposide[38-40]	Small cell lung cancer, testicular cancer	~ 55
Idarubicin[41-43]	AML	~ 50
Irinotecan[44-48]	Colorectal cancer	~ 58
Paclitaxel[49-55]	Breast cancer, lung cancer, gynecologic malignancies, Kaposi's sarcoma	~ 100
Topotecan[56-59]	Small cell lung cancer, ovarian cancer, cervical cancer	20 (oral); 49 (i.v)
Radiotherapies		
Photon radiotherapy (traditional radiotherapy)[16]	Primary CNS tumors, brain metastasis, head and neck cancer	~ 100
Proton radiotherapy[60, 61]	Medulloblastoma, ependymoma, other primary CNS	75 - 100
Targeted therapies[6, 18]		
Vismodegib[62]	Basal cell carcinoma (locally advanced or unresectable)	62
Sorafenib[22]	Hepatocellular carcinoma, renal cell carcinoma, thyroid cancer	26
Sunitinib[22]	Metastatic renal cell carcinoma, gastrointestinal stromal tumor	6
Regorafenib	Colorectal cancer	4
Vemurafenib	Melanoma (stage IV)	24
Dabrafenib	Melanoma (stage IV)	19
Targeted therapies in pediatric population (including imatinib, dasatinib, erlotinib, vandetanib, sorafenib, cabozantinib, pazopanib)[63]	Hematologic and CNS tumors	3
Immunotherapies[7, 19]		
CTLA-4	Melanoma (stage III-IV)	1-2
PD-1 and PD-L1	Melanoma (stage IV), lung, Hodgkin lymphoma, urothelial carcinoma	2
Stem cell transplants[8, 64]		
Conditioning chemotherapy (busulfan, topotecan, thiotepa, tacrolimus, melphalan, methotrexate, etoposide, cyclophosphamide)	Leukemia	~ 100
Acute graft vs host disease		20
Neoadjuvant endocrine therapies[9]		
Leuprolide	Breast cancer, hepatocellular carcinoma, neuroendocrine	2

Hair disorders and cancer therapy	Tumor types indicated or under investigation	Incidence (%) or case reports
Octreotide	tumors	6.7
Aromatase inhibitors (anastrozole, letrozole, exemestane)	Metastatic estrogen–receptor-positive (ER+) breast cancer	~ 25
Pigmentary hair changes		
Targeted therapies (cabozantinib, pazopanib, sorafenib, sunitinib, imatinib)[65-67]	Renal cell carcinoma, thyroid cancer, hepatocarcinoma, desmoid tumors, gastrointestinal stromal tumor, pancreatic neuroendocrine tumors	~ 30
PD-1 and PD-L1[68]	Melanoma (stage IV), lung, Hodgkin lymphoma, urothelial carcinoma, head and neck squamous cell carcinoma	27
Textural hair changes		
Targeted therapies (erlotinib, cetuximab, gefitinib, lapatinib, panitumumab), BRAF inhibitors[69, 70]	Tumors with EGFR mutation, including non-small-cell lung cancer, squamous cell carcinoma of the head and neck	~ 30
Cytotoxic chemotherapies (cyclophosphamide, taxanes)[21]	Breast cancer, AML, ALL, lymphoma, multiple myeloma, neuroblastoma, ovarian cancer	65
Hirsutism and hypertrichosis		
EGFR/MEK inhibitors (erlotinib, cetuximab, gefitinib, afatinib, lapatinib, panitumumab)[70, 71]	Tumors with EGFR mutation, including non-small-cell lung cancer, squamous cell carcinoma of the head and neck	~ 50
Targeted therapies in pediatric population (EGFR/MEK inhibitors, and MKIs) [63]	CNS tumors, squamous cell carcinoma, sarcomas	7
Eyelash trichomegaly		
Targeted therapies: EGFR inhibitors [72-74]	Tumors with EGFR mutations, including non-small-cell lung cancer, squamous cell carcinoma of the head and neck	8 (EGFR inhibitors) and case reports for BRAF and MKIs
Targeted therapies in pediatric population (including imatinib, dasatinib, erlotinib, vandetanib, sorafenib, cabozantinib, pazopanib) [63]	Leukemia, CNS tumors	17

AML, acute myelogenous leukemia; ALL, acute lymphocytic leukemia; BRAF, proto-oncogene B-Raf; CNS, central nervous system; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; EGFR, epidermal growth factor receptor inhibitor; MKIs, Multikinase inhibitors; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; ~, approximately.

Table 2
Clinical features of hair disorders attributed to anticancer therapies

Cancer therapy	Clinical features by predominant hair disorders
Cytotoxic chemotherapies	**1. Alopecia:** non-scarring, patchy or diffuse dystrophic anagen or catagen effluvium with predominance on areas of increased friction (crown and temporo-occipital areas). Usually recover in 2-6 months after chemotherapy cessation. Eyelash, eyebrow, axillary and pubic hair could be involved (recovery is generally more rapid than scalp alopecia). Trichoscopy: black dots, yellow dots, exclamation mark hairs, and color and thickness changes along the hair may exist **2. Pigmentary and textural hair changes:** Slight changes from dark to graying, and from graying to dark. Upon regrowth, straight hair may become curly or wavy, and finer **3. Hirsutism:** hirsutism may appear
Alkylating agents (e.g. busulfan, cyclophosphamide, etoposide)	
Topoisomerase-interacting agents (e.g. teniposide, daunorubicin, doxorubicin, idarubicin, irinotecan, topotecan)	
Antimicrotubule agents (e.g. paclitaxel, docetaxel, vincristine, vinblastine)	
Radiotherapy	**1. Alopecia:** non-scaring, geometric shapes or diffuse anagen effluvium is usually seen,in relation with the irradiated area. May coexist with different grades of radiationdermatitis. Trichoscopy: yellow and black dots, short vellus hair, peripilar sign andbroken hair **2. Pigmentary and textural hair changes:** hair hypopigmentation and decreased shaftdiameter may be seen
Targeted therapies	**1. Hirsutism, hypertrichosis and trichomegaly:** hirsutism and periocular hypertrichosis could be marked. Eyelashes and eyebrows hypertrichosis are frequent, with long and curly eyelashes that may affect vision (predominantly with EGFR inhibitors) **2. Pigmentary and textural hair changes:** hair discoloration, includinghypopigmentation (VEGFR/PDGFR) and hyperpigmentation (EGFR inhibitors) **3. Alopecia:** diffuse alopecia with non-scarring (EGFR inhibitors, VEGFR/PDGFR)and scarring features (EGFR inhibitors) after severe inflammatory follicular reactions (e.g. erosive pustular dermatosis of the scalp, and tufted hair folliculitis)
EGFR inhibitor (e.g. cetuximab, panitumumab,gefitinib, erlotinib, afatinib, lapatinib)	
VEGFR/PDGFR inhibitor (e.g. sorafenib, regorafenib, imatinib, dasatinib, sunitinib, nilotinib, ponatinib,axitinib, pazopanib)	
BRAF inhibitor (e.g. vemurafenib, dabrafenib)	
Immunotherapies	**1. Alopecia:** non-scaring with diffuse hair thinning and alopecia areata. Skininvolvement may coexist, including vitiligo and lichenoid reactions **2. Pigmentary hair changes:** diffuse hyperpigmentation and hypopigmentation
Ipilimumab (CTLA-4)	
Programmed cell death protein (PD-1) receptors and its ligand (PD-L1) (e.g. pembrolizumab, nivolumab, avelumab, atezolizumab)	
Stem cell transplantation	**1. Alopecia:** non-scarring, patchy or diffuse anagen effluvium (similar as described forCIA –related to conditioning chemotherapies-). Scarring alopecia, and alopecia areatawith acute or chronic graft versus host disease **2. Pigmentary and textural hair changes:** hypopigmentation and decreased diameterof hair shafts
Vismodegib	**1. Alopecia:** non-scarring, patchy or diffuse anagen effluvium (similar as described for CIA)
Endocrine therapies (e.g. leuprolide, tamoxifen, raloxifene, anastrozole, exemestane, letrozole, octreotide)	**1. Alopecia:** pattern alopecia, similar to androgenetic type **2. Pigmentary and textural hair changes:** finer hairs **3. Hirsutism:** hirsutism may be observed

CIA, chemotherapy-induced alopecia; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; EGFRI, epidermal growth factor inhibitor; PDGFR, platelet-derived growth factor receptors; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; VEGF, vascular endothelial growth factor.

Table 3
Grading scales used for anticancer therapy-induced hair changes

Alopecia grading			
CTCAE V4.0			
Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hair loss of <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 of >=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	-	-
Dean's grading scale of hair loss protection from anticancer therapies			
>0 to 25% hair loss	25 to 50% hair loss	50 to 75% hair loss	75 to 100% hair loss
WHO handbook for reporting results of cancer treatment			
Minimal hair loss	Moderate, patchy hair loss	Complete alopecia, but reversible	Non-reversible alopecia
EGFR Inhibitor Skin Toxicity Tool (MESTT)			
Hair loss <50% of normal for that individual that may or may not be noticeable to others but is associated with increased shedding and overall feeling of less volume. May require different hairstyle to cover but does not require hairpiece to camouflage	2A. Hair loss associated with marked increase shedding and 50-74% loss compared to normal for that individual Hair loss is apparent to others, may be difficult to camouflage with change in hairstyle and may require a hairpiece 2B. Marked loss of at least 75% hair compared to normal for that individual with inability to camouflage except with a full wig OR new cicatricial hair loss documented by biopsy that covers at least 5%scalp surface area. May impact on functioning in social, personal or professional situations	-	-
Hypertrichosis grading			
CTCAE V4.0			
Increase in length, thickness or density of hair that the patient is either able to camouflage by periodic shaving or removal of hairs or is not concerned enough about the overgrowth to use any form of hair removal	Increase in length, thickness or density of hair at least on the usual exposed areas of the body [face (not limited to beard/moustache area) plus/minus arms] that requires frequent shaving or use of destructive means of hair removal to camouflage; associated with psychosocial impact	-	-
Hirsutism grading			
CTCAE V4.0			
In women, increase in length, thickness or density of hair in a male distribution that the patient is able to camouflage by periodic shaving, bleaching, or removal of hair	In women, increase in length, thickness or density of hair in a male distribution that requires daily shaving or consistent destructive means of hair removal to camouflage; associated with psychosocial impact	-	-

Table 4
Management of hair disorders in patients receiving anticancer therapies

Hair disorder	Interventions	Level of evidence
Chemotherapy-induced alopecia (CIA)	**Preventive strategies:** Scalp cooling: caps or cooling systems, only for cancer patients with solid tumors	Level IB
	Contraindications to scalp cooling include hematological malignancies, and the following: cold sensitivity and cold trigged diseases, central nervous system malignancies, small cell carcinoma of the lung, cancers of the head and neck, skin cancer, and in pediatric patients Topical minoxidil 2% daily, over the entire scalp throughout chemotherapy and up to 4 months post-chemotherapy	Level IB
Radiotherapy-induced alopecia (RIA)	**Reactive strategies:** Topical minoxidil 5% daily (radiation dermatitis should be managed first with topical corticosteroid, if present)	Level IV
Alopecia attributed to targeted therapies (e.g. EGFR inhibitors, VEGFR/PDGFR/ BRAF inhibitors)	**Reactive strategies:** Non-inflammatory alopecia (VEGFR/PDGFR): topical minoxidil 5% daily continued until 6 months after therapy ends If scalp inflammation (EGFR inhibitors): topical corticosteroids; if secondary infection present treat with culture/sensitivity-driven oral antibiotics	
Alopecia attributed to Immunotherapies (e.g. CTCLA-4, PD1, PDL-1)	High potency topical corticosteroid if alopecia areata; rule out thyroid dysfunction (immune related adverse event)	
Alopecia attributed to stem cell transplant	If alopecia areata, topical corticosteroids or Janus kinase inhibitors If diffuse or pattern alopecia (similar pattern to CIA); topical minoxidil 5% daily	
Alopecia attributed to vismodegib	**CTCAEv4.0 grade 1 and grade 2:** Topical minoxidil 5% daily continued until 6 months post-therapy	
Endocrine therapy-induced alopecia (EIA)	**CTCAEv4.0 grade 1 and grade 2:** Topical minoxidil 5% daily	
Eyebrow and eyelashes alopecia	Chemotherapy-induced alopecia: topical bimatoprost solution 0.03%	Level IB
Pigmentary and textural hair changes	If needed, options such as hair coloring and changes in hairstyle should be recommended (e.g. hair straightener, hair permanent)	Level IB
Hirsutism and hypertrichosis	**Reactive strategies:** **TCAEv4.0 grade 1 (mild hair growth):** Local therapy such as epilation, depilation, shaving, eflornithine, laser treatment **CTCAEv4.0 grade 2 (prominent thick hairs, associated with psychosocial impact):** Laser or intense pulsed light Trimming for eyelash trichomegaly, referral to an ophthalmologist when irritation or discomfort is present Patients can be reassured that these hair changes are temporary; normal growth should begin within 1 month after cessation of medication	Level III
General recommendations	As a prevention of patient distress, we recommend patient education and support Most of the hair changes are temporary. However, if therapy is requested, this should be discussed to have realistic expectations of therapy outcome Camouflaging techniques (e.g. crayons, powder, volumizers, hair weaves/hair extension, scalp micropigmentation/tattoo and hairpieces) could be recommended If emotionally affected; psychological counseling is recommended Involve nurses and other health care providers in the cancer patients hair care	

CTCAEv4.0, Common Terminology Criteria for Adverse Events Version 4.0; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; EGFRI, epidermal growth factor inhibitor; Nd:YAG, neodymium-doped yttrium aluminium garnet; PDGF-R, Platelet-derived growth factor receptors; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; VEGF, vascular endothelial growth factor.