

Hair disorders in patients with cancer



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Learning objectives

After completing this learning activity, participants should be able to identify the incidence and clinical presentation of hair disorders including alopecia (transient/persistent) in cancer patients; discuss the current pathogenic mechanisms underlying various hair disorders in the oncology setting; describe the preventive, reactive, and experimental management strategies, as applicable; recognize the impact of hair disorders on patients' quality of life; and develop a fundamental understanding of hair disorders in cancer patients.

Disclosures

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Cytotoxic chemotherapies, molecularly targeted therapies, immunotherapies, radiotherapy, stem cell transplants, and endocrine therapies may lead to hair disorders, including alopecia, hirsutism, hypertrichosis, and pigmentary and textural hair changes. The mechanisms underlying these changes are varied and remain incompletely understood, hampering the development of preventive or therapeutic guidelines. The psychosocial impact of chemotherapy-induced alopecia has been well documented primarily in the oncology literature; however, the effect of other alterations, such as radiation-induced alopecia, hirsutism, and changes in hair color or texture on quality of life have not been described. This article reviews clinically significant therapy-related hair disorders in oncology patients, including the underlying pathophysiological mechanisms, severity grading scales, patient-reported quality of life questionnaires, management strategies, and future translational research opportunities. (J Am Acad Dermatol 2019;80:1179-96.)

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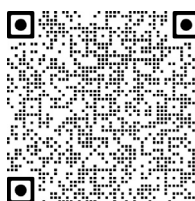
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Key words: anagen effluvium; brittleness; cancer patients; catagen effluvium; chemotherapy-induced alopecia; curling; depigmentation; eyebrow alopecia; eyelash alopecia; hair repigmentation; hirsutism; hyperpigmentation; hypertrichosis; hypopigmentation;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

Cancer is a major public health problem worldwide. In 2016, >1.6 million new cancer cases were projected in the United States and 32 million worldwide; of these, approximately 60% received systemic therapies and 50% underwent radiotherapy.¹ The most commonly encountered hair disorder is 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 $\leq 14\%$ would consider rejecting curative cancer therapies if they were associated with alopecia.¹²⁻¹⁴

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

EPIDEMIOLOGY

Key point

- Hair changes attributed to anticancer therapies are expected to occur in $\geq 65\%$ of patients receiving cytotoxic therapies, 15% with targeted therapies, $< 2\%$ on immunotherapies, and up to 100% in areas treated with radiotherapy

The widespread use of systemic anticancer therapies, their numerous combinations, and underreporting of hair disorders yield mixed incidence reports (Table I), but these events in 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.⁷² 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 both increase as the dose exceeds the threshold.^{52,73} With targeted therapies, the calculated incidence of all-grade alopecia was reported to be 15%.^{6,55} An overall incidence of all grades of alopecia were reported at 1% to 2% with immune checkpoint inhibitors, including anticytotoxic T-lymphocyte-associated protein-4, programmed cell death protein-1 receptors, and programmed cell death protein-1 ligand.^{7,59} Complete alopecia is attributed to the conditioning cytotoxic chemotherapies (ie, busulfan, melphalan, and fludarabine) developing in nearly 100% of patients who have undergone hematopoietic stem cell transplantation.⁷⁴ Endocrine therapies (ie, tamoxifen, anastrozole, letrozole, fulvestrant, and exemestane) have been related to alopecia in $\leq 25\%$ of patients.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,⁶⁷ in 30% of those receiving targeted therapies,⁵⁷ and in 2% with immunotherapies⁵⁹ (Table I).

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 because of disturbances in hair follicle cycling and functioning and hair shaft synthesis, which results in effluvium during anagen or catagen.^{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, and patient factors⁷⁶ (Table II).

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 the crown and temporo-occipital areas, that may progress to

Abbreviations used:

AE:	adverse event
CIA:	chemotherapy-induced alopecia
CTCAE v5.0:	Common Terminology Criteria for Adverse Events Version 5.0
EGFR:	epidermal growth factor receptor
MKI:	multikinase inhibitor
QoL:	quality of life
RIA:	radiotherapy-induced alopecia

complete alopecia in 2 to 3 months.⁷⁷ In addition, eyelash and eyebrow alopecia and alopecia of other body areas can be observed in association with scalp alopecia in $\leq 33\%$ of patients who are receiving taxanes.⁷⁸ Although usually asymptomatic, CIA could also be related with trichodynia and pruritus (11%).⁷⁷ CIA is typically reversible within 2 to 6 months after chemotherapy is discontinued.^{60,79} Trichoscopic findings in CIA include black dots, yellow dots, exclamation mark hairs, and color and thickness changes along the hair shaft^{80,81} (Fig 1).

Radiotherapy-induced alopecia (RIA) is characterized by an anagen effluvium caused by acute damage of the hair follicle.⁸² An alopecia patch confined to the area of radiotherapy is usually observed 1 to 3 weeks after the first irradiation,⁸³ and hair regrowth usually occurs 2 to 6 months after radiotherapy.^{53,84} Radiation dermatitis and cutaneous injury may also accompany the alopecia⁸⁵ (Fig 2). Yellow and black dots have been described as the predominant trichoscopic findings in 60% of RIA, followed by short vellus hair (50%), the peripilar sign (20%), and broken hairs (10%); trichoscopic findings are also described in patients with alopecia areata and androgenetic alopecia.^{86,87}

Whereas mild diffuse alopecia is frequent with epidermal growth factor receptor (EGFR) inhibitors (eg, erlotinib, afatinib, cetuximab, and panitumumab), scarring alopecia has been reported in 5% of patients treated with cetuximab, which may be a consequence of a secondary scalp bacterial infection (Fig 3) manifested as erosive pustular dermatosis^{65,88-90} or tufted hair folliculitis.⁹¹ Alopecia areata and universalis are considered immune-related AEs occurring in 2% of patients receiving ipilimumab.⁹²

Among patients undergoing stem cell transplantation, diffuse alopecia is reported in association with conditioning chemotherapy in nearly 100% of patients.⁶⁰ Hair changes may occur with acute graft-versus-host disease, including features of nonscarring 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 type.⁹⁵ Despite most cases of alopecia in cancer patients being transitory, 14% of childhood cancer survivors⁹⁶ and 30% of breast cancer survivors⁹⁷ 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 (Fig 4) and hyperpigmentation and are most apparent on the scalp, although the eyebrows, eyelashes, and body hair may be affected. Hair hypopigmentation has been reported with the multikinase inhibitors pazopanib, sunitinib, and regorafenib,⁹⁸⁻¹⁰⁴ whereas EGFR inhibitors result in hyperpigmentation of scalp and facial hair ($\sim 50\%$).¹⁰⁵⁻¹⁰⁷ Hair repigmentation has been described as a possible marker of tumor response in 14 patients receiving anti-programmed cell death protein-1 receptor and anti-programmed cell death protein-1 receptor ligand therapy for lung cancer.⁶⁴

In addition, straight hair may become curly or wavy in 65% of patients with cancer after treatment with cytotoxic chemotherapy.⁶⁷ With targeted therapies, hair growth on the scalp can slow down and become finer, curlier, and more brittle.^{65,108}

Hirsutism, hypertrichosis, and trichomegaly

Excessive hair growth around the periorcular area,^{109,110} hirsutism,⁶⁵ and trichomegaly (Fig 5) have been reported as an AE of EGFR inhibitors.⁶⁹⁻⁷¹ Eyelash trichomegaly also has been reported after fibroblast growth factor receptor inhibitor therapy.¹¹¹ These alterations typically resolve after discontinuation of treatment, although in some cases they can persist for several months.¹¹² Hirsutism can be seen in patients with cancer who receive endocrine therapies (antiestrogen agents), and the low incidence is likely related to underreporting.

ETIOLOGY AND PATHOGENIC MECHANISMS

Key points

- The pathogenic mechanisms of anticancer therapy-induced alopecia and other hair disorders varies depending on causal therapy
- The hair matrix keratinocytes of anagen hair follicles have a high mitotic activity,

Table I. 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 ¹⁵⁻¹⁹	Breast cancer, leukemia, lymphoma, multiple myeloma, neuroblastoma, retinoblastoma, and ovarian cancer	25 (low dose), ~100 (high dose)
Daunorubicin ^{20,21}	AML and ALL	~100
Docetaxel ²²⁻²⁶	Breast cancer, gastric cancer, head and neck cancer, lung cancer, and prostate cancer	~100
Doxorubicin ²⁷⁻²⁹	ALL, AML, thyroid cancer, breast cancer, gastric cancer, lung cancer, bladder cancer, lymphomas, neuroblastoma, sarcomas, and Wilms tumor	80-100
Etoposide ³⁰⁻³²	Small cell lung cancer and testicular cancer	~55
Idarubicin ³³⁻³⁵	AML	~50
Irinotecan ³⁶⁻⁴⁰	Colorectal cancer	~58
Paclitaxel ⁴¹⁻⁴⁷	Breast cancer, lung cancer, gynecologic malignancies, and Kaposi sarcoma	~100
Topotecan ⁴⁸⁻⁵¹	Small cell lung cancer, ovarian cancer, and cervical cancer	20 (oral), 49 (intravenous)
Radiotherapies		
Photon radiotherapy (traditional radiotherapy) ⁵²	Primary CNS tumors, brain metastasis, and head and neck cancer	~100
Proton radiotherapy ^{53,54}	Medulloblastoma, ependymoma, other primary CNS tumors, and head and neck cancer	75-100
Targeted therapies ^{6,55}		
Vismodegib ⁵⁶	Basal cell carcinoma (locally advanced or unresectable)	62
Sorafenib ⁵⁷	Hepatocellular carcinoma, renal cell carcinoma, and thyroid cancer	26
Sunitinib ⁵⁷	Metastatic renal cell carcinoma and 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, and pazopanib) ⁵⁸	Hematologic and CNS tumors	3
Immunotherapies ^{7,59}		
CTLA-4 inhibitor	Melanoma (stage III-IV)	1-2
PD-1 and PD-L1 inhibitors	Melanoma (stage IV), lung, non-Hodgkin lymphoma, urothelial carcinoma, and advanced squamous cell carcinoma, Merkel cell cancer	2
Stem cell transplants ^{8,60}		
Conditioning chemotherapy (busulfan, fludarabine, melphalan)	Hematologic cancers	~100
Endocrine therapies ⁹		
Tamoxifen	Breast cancer, neuroendocrine tumors	2
Octreotide		6.7
Aromatase inhibitors (anastrozole, letrozole, exemestane)		~25

Continued

Table I. Cont'd

Hair disorders and cancer therapy	Tumor types indicated or under investigation	Incidence (%) or case reports
Pigmentary hair changes		
Targeted therapies (cabozantinib, pazopanib, sorafenib, sunitinib, imatinib) ⁶¹⁻⁶³	Renal cell carcinoma, thyroid cancer, hepatocellular carcinoma, desmoid tumors, gastrointestinal stromal tumor, and pancreatic neuroendocrine tumors	~30
PD-1 and PD-L1 inhibitors ⁶⁴	Melanoma (stage IV), lung, non-Hodgkin lymphoma	27
Textural hair changes		
Targeted therapies (erlotinib, cetuximab, gefitinib, lapatinib, and panitumumab) and BRAF inhibitors ^{65,66}	Tumors with EGFR or BRAF mutations	~30
Cytotoxic chemotherapies (cyclo phosphamide and taxanes) ⁶⁷	Breast cancer, AML, ALL, lymphoma, multiple myeloma, neuroblastoma, and ovarian cancer	65
Hirsutism and hypertrichosis		
EGFR/MEK inhibitors (erlotinib, cetuximab, gefitinib, afatinib, lapatinib, and panitumumab) ^{66,68}	Tumors with EGFR mutations	~50
Targeted therapies in pediatric population (EGFR/MEK inhibitors, and MKIs) ⁵⁸	CNS tumors, squamous cell carcinoma, and sarcomas	7
Eyelash trichomegaly		
Targeted therapies: EGFR inhibitors ⁶⁹⁻⁷¹	Tumors with EGFR mutations	8 (EGFR inhibitors) and case reports for BRAF and MKIs
Targeted therapies in the pediatric population (imatinib, dasatinib, erlotinib, vandetanib, sorafenib, cabozantinib, and pazopanib) ⁵⁸	Hematologic and 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; MKI, multikinase inhibitors; PD-1, programmed cell death protein 1; PD-L1, programmed cell death protein ligand 1.

which makes them especially vulnerable to anticancer therapies

- **Paradoxically, some anticancer therapies can promote hair growth and 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 rodent and human CIA models, rapidly proliferating anagen hair follicles and their pigmentary system, which are both sensitive to toxins, are the primary 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 acute damage to actively dividing matrix cells of anagen follicles, followed by telogen shedding because of 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,

Table II. Clinical features of hair disorders attributed to anticancer therapies

Cancer therapy	Clinical features by predominant hair disorders
Cytotoxic chemotherapies Alkylating agents (busulfan, cyclophosphamide, and etoposide) Topoisomerase-interacting agents (teniposide, daunorubicin, doxorubicin, idarubicin, irinotecan, and topotecan) Antimicrotubule agents (paclitaxel, docetaxel, vincristine, and vinblastine)	<ol style="list-style-type: none"> 1. Alopecia: nonscarring, 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 completion. 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
Radiotherapy	<ol style="list-style-type: none"> 1. Alopecia: nonscarring, geometric shapes, or diffuse anagen effluvium is usually seen, in the irradiated area. May coexist with different grades of radiation dermatitis. Trichoscopy: yellow and black dots, short vellus hair, peripilar sign, and broken hair shafts 2. Pigmentary and textural hair changes: hair hypopigmentation and decreased shaft diameter
Targeted therapies EGFR inhibitor (cetuximab, panitumumab, gefitinib, erlotinib, afatinib, and lapatinib) VEGFR/PDGFR/KIT inhibitor (sorafenib, regorafenib, imatinib, dasatinib, sunitinib, nilotinib, ponatinib, axitinib, and pazopanib) BRAF inhibitor (vemurafenib and dabrafenib)	<ol style="list-style-type: none"> 1. Hirsutism, hypertrichosis, and trichomegaly: hirsutism and periorcular hypertrichosis could be marked. Eyelashes and eyebrows hypertrichosis are frequent, with long and curly eyelashes that may affect vision (with EGFR inhibitors) 2. Pigmentary and textural hair changes: hair discoloration, including hypopigmentation (VEGFR/PDGFR) and hyperpigmentation (EGFR inhibitors) 3. Alopecia: diffuse alopecia with nonscarring (EGFR inhibitors and VEGFR/PDGFR) and scarring features (EGFR inhibitors) after severe inflammatory follicular reactions (eg, erosive pustular dermatosis of the scalp and tufted hair folliculitis)
Immunotherapies Ipilimumab (CTLA-4) Programmed cell death protein (PD-1) receptors and its ligand (PD-L1) (eg, pembrolizumab, nivolumab, avelumab, and atezolizumab)	<ol style="list-style-type: none"> 1. Alopecia: nonscarring with diffuse hair thinning and alopecia areata. Skin involvement may coexist, including vitiligo and lichenoid reactions 2. Pigmentary hair changes: diffuse hyperpigmentation and hypopigmentation
Stem cell transplantation	<ol style="list-style-type: none"> 1. Alopecia: nonscarring, patchy, or diffuse anagen effluvium (similar as described for CIA—related to conditioning chemotherapies). Scarring alopecia and alopecia areata with acute or chronic graft versus host disease 2. Pigmentary and textural hair changes: hypopigmentation and decreased diameter of hair shafts
Vismodegib	<ol style="list-style-type: none"> 1. Alopecia: nonscarring, patchy, or diffuse anagen effluvium (similar as described for CIA)
Endocrine therapies (leuprolide, tamoxifen, raloxifene, anastrozole, exemestane, letrozole, and octreotide)	<ol style="list-style-type: none"> 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; EGFR, epidermal growth factor receptor; PDGFR, platelet-derived growth factor receptors; PD-1, programmed cell death protein 1; PD-L1, programmed cell death protein ligand 1; VEGF, vascular endothelial growth factor.

EGFR inhibitors result in scalp alopecia but also cause hirsutism and eyebrow and eyelash trichomegaly.

Immunotherapies (anti-cytotoxic T-lymphocyte-associated protein-4 and programmed cell death

protein-1 receptor and its ligand) and stem cell transplants may also result in alopecia, with a clinical and histologic pattern consistent with alopecia areata, likely caused by the activation of inflammatory responses against hair follicle antigens and an

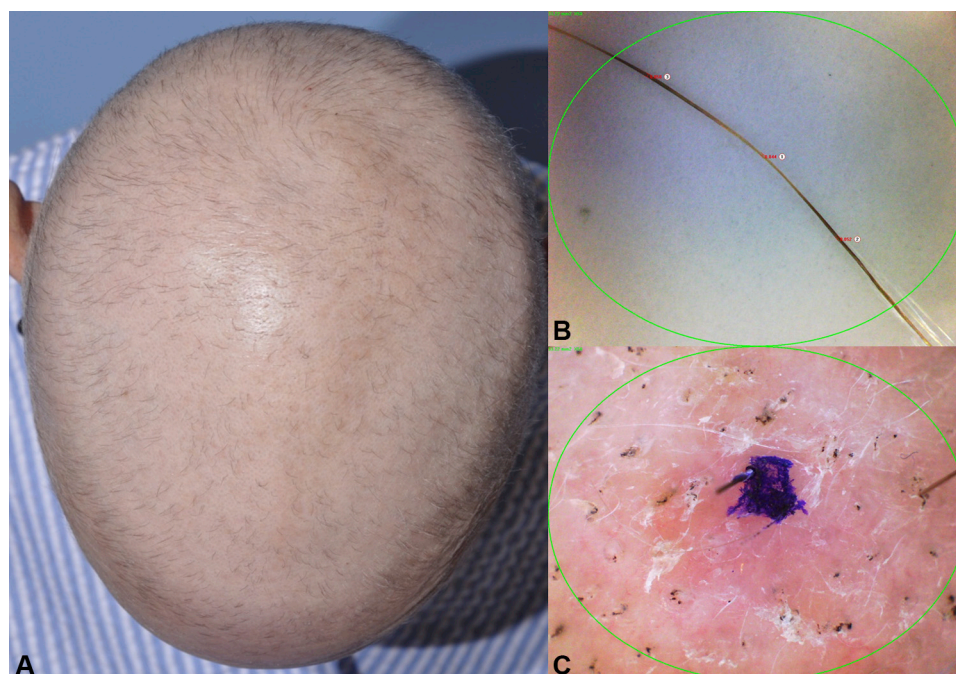


Fig 1. Chemotherapy-induced alopecia. **A**, Clinical image of scalp alopecia 1 month after the first taxane-based chemotherapy cycle. **B**, Pohl–Pinkus constrictions observed in monilethrix-like hairs after weekly cyclophosphamide-based chemotherapy. **C**, Trichoscopy of chemotherapy-induced alopecia reveals black dots, fractured hair shafts, and vellus hairs.



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

imbalance of the immune tolerance in the hair follicle environment.⁷ These findings are concordant with other immune-related AEs reported in patients who are treated with immunotherapy, 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 -estradiol¹¹⁸⁻¹²⁰ 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 oxidative damage¹²³ with the 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,¹²⁶ Dean scale,¹²⁷ the Eastern Cooperative Oncology Group,¹²⁸ Sredni et al,¹²⁹ the National Cancer Institute,¹³⁰ the EGFR Inhibitors Skin Toxicity Tool,¹³¹ and the Common Terminology Criteria for Adverse Events Version 5.0 (CTCAE v5.0 Table III).¹³² Of these grading

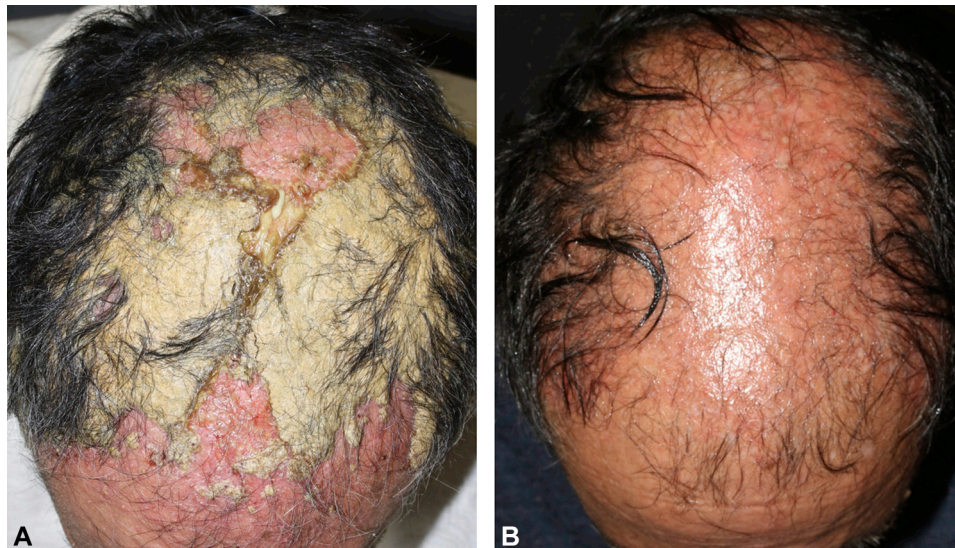


Fig 3. Scalp folliculitis (skin infection grade 3 [CTCAE v5.0]) in a patient receiving cetuximab. **A**, Before therapy with oral doxycycline and topical high-potency corticosteroids. **B**, Two weeks after dermatologic therapy.

instruments, the CTCAE v5.0¹³² 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 are reported according to the CTCAE. There are some limitations in alopecia grading (CTCAE grades 1 and 2) that may not capture subtle changes in severity or pattern, and 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 v5.0.¹³² The modified Ferryman–Gallwey scoring system may also be used to grade hypertrichosis.¹³³

QUALITY OF LIFE IN PATIENTS WITH CANCER WITH HAIR DISORDERS

Key points

- 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 likely significant

Hair-related AEs have a profound impact on cancer patient QoL. CIA is one of the most clinically visible and distressing AEs,² and has been cited as the most disturbing anticipated AE by 58% of breast

cancer patients before 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 to be more difficult than the loss of a breast,^{134,136} and can even lead patients to refuse treatment (8%).^{134,137} In addition, eyelash and eyebrow alopecia resulted in psychological distress in breast cancer patients who were treated with taxane-based chemotherapy.¹³⁸

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 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.^{139,140} Therefore, it is important to query and measure the impact on QoL of hair disorders attributed to anticancer therapies, given the longer survival times and the increasing number of medications leading to 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.¹⁴¹ Specific instruments to assess the impact of hair disorders on cancer patients' QoL include the Chemotherapy-induced Alopecia Distress Scale¹⁴² (validated in Korean patients and translated into



Fig 4. Depigmentation and hair thinning in a patient receiving tremelimumab. **A**, Before therapy. **B**, Three months after the first dose.



Fig 5. Trichomegaly in a patient taking erlotinib for 1 year.

English), which comprises 17 questions in 4 domains. In addition, the Eyelash Satisfaction Questionnaire was validated in a cohort of 595 patients with cancer; it includes 23 questions in 3 domains.^{143,144}

MANAGEMENT

Key point

- **Most preventive or reactive strategies are based on uncontrolled studies; however, the US Food and Drug Administration has cleared 2 dynamic scalp cooling devices for the prevention of CIA in patients treated with cytotoxic chemotherapies for solid tumors**

Anticancer therapy—induced alopecia

Given the varied alopecia-inducing pathogenic mechanisms and an individual's inherent susceptibility, no single strategy may be effective for alopecia induced by different therapies.⁷⁵ Management for anticancer therapy—induced alopecia can be divided into preventive and reactive strategies (Table IV).

Preventive strategies. There are no preventive pharmacologic strategies that have demonstrated satisfactory efficacy to justify their general use. For example, topical minoxidil 2% twice daily showed no benefit to prevent CIA in a prospective trial of 10 patients.¹⁴⁵ However, in a randomized trial including

22 patients with breast cancer who were treated with cytotoxic chemotherapy, topical minoxidil 2% solution reduced the duration of complete alopecia by 50 days when compared to placebo (87 vs 137 days).¹⁴⁶ Trials evaluating this potential preventative strategy are needed. The topical calcitriol (BPM31543) showed benefit in a phase I trial of 31 patients and is currently under development.¹⁴⁷

Scalp cooling has become the most widely used method for the prevention of CIA.¹⁴⁸ Scalp cooling systems include static devices (eg, glycerin-based, Chemocoldcaps [Chemotherapy Cold Caps, Inc, Dallas, TX], and Penguin [Penguin Cold Caps, London, United Kingdom])^{149,150} and dynamic scalp cooling systems that were recently cleared by the US Food and Drug Administration (DigniCap [Dignitana, Lund, Sweden], in 2015, and Orbis [Paxman Coolers Ltd, Huddersfield, United Kingdom], in 2017).^{151,152} 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),^{127,153,154} the relative reduced follicular uptake of cytotoxic therapies,¹⁵⁵ and decreased follicular metabolic activity.¹⁵⁶

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 who were receiving taxane-based chemotherapy, Dignicap scalp cooling conferred protection against hair loss (Dean scale score of 0-2) in 66% compared to 0% in the uncooled group.¹⁵¹ In a multicenter, randomized study using the Paxman Orbis scalp cooling system,¹⁵² hair preservation was observed in 50% (cooling group) versus 0% (controls) after the

Table III. Grading scales used for anticancer therapy—induced hair changes

Alopecia grading			
CTCAE v5.0			
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	50-75% hair loss	75-100% hair loss
WHO handbook for reporting results of cancer treatment			
Minimal hair loss	Moderate, patchy hair loss	Complete alopecia, but reversible	Nonreversible 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 v5.0			
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 v5.0			
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 IV. 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 Contraindications to scalp cooling include hematological malignancies, and the following: cold sensitivity and cold triggered 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	IB IB
Radiotherapy-induced alopecia (RIA)	Reactive strategies: Topical minoxidil 5% daily (radiation dermatitis should be managed first with topical corticosteroid, if present)	IV
Alopecia attributed to targeted therapies (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	IV IV
Alopecia attributed to Immunotherapies (CTLA-4, PD1, PDL-1)	High potency topical corticosteroid if alopecia areata; rule out thyroid dysfunction (immune related adverse event)	IV
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	IV
Alopecia attributed to vismodegib	CTCAE v5.0 grades 1 and 2: topical minoxidil 5% daily continued until 6 months post-therapy	IV
Endocrine therapy-induced alopecia (EIA)	CTCAE v5.0 grades 1 and 2: topical minoxidil 5% daily	III
Eyebrow and eyelashes alopecia	Chemotherapy-induced alopecia: topical bimatoprost solution 0.03%	IB
Pigmentary and textural hair changes	If needed, options such as hair coloring and changes in hairstyle should be recommended (eg, hair straightener, hair permanent)	IB
Hirsutism and hypertrichosis	Reactive strategies: CTCAE v5.0 grade 1 (mild hair growth)—local therapy, such as epilation, depilation, shaving, eflornithine, or laser treatment; CTCAE v5.0 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	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 (eg, crayons, powder, volumizers, hair weaves/hair extension, scalp micropigmentation/tattoo and hairpieces) could be recommended If the patient is emotionally affected, psychological counseling is recommended Involve nurses and other health care providers in the cancer patients hair care	

CTCAE v5.0, Common Terminology Criteria for Adverse Events Version 5.0; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; EGFR, epidermal growth factor receptor; PDGFR, Platelet-derived growth factor receptors; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; VEGF, vascular endothelial growth factor.

fourth 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.^{157,158} Differences between devices are likely related to operator experience and types of chemotherapy regimens of patients enrolled, with patients undergoing taxane-based regimens showing a higher benefit from scalp cooling. Regarding safety, the most common AEs include headache (11%), nausea (4%), and dizziness (3%).¹⁵² A metaanalysis of 10 trials that included 1959 patients demonstrated no differences in the incidence of scalp metastases between cooled (0.61%) versus noncooled patients (0.41%).¹⁵⁹ Scalp cooling has been reported to be effective in 3 patients with breast cancer who were treated with taxane-based chemotherapy and with CIA grade 2 (CTCAE) in order to prevent alopecia in future chemotherapy sessions, and consequently allow earlier reestablishment of scalp hair density; however, the risk of frostbite should be considered.¹⁶⁰ In general, precooled caps remain popular because of their widespread availability; however, 4 cases of thermal injury have been reported because of improper cap applications.¹⁶¹

Despite the relative success of the scalp cooling system in preventing CIA, this system has been reported as not effective to prevent RIA.¹⁶² In addition, 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 are no data on preventive strategies for noncytotoxic agent–induced alopecia. Therefore, we recommend pretherapy 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 the patient can be referred to a dermatologist if indicated.

Reactive strategies. Reactive strategies are primarily based on case series, case reports, and expert opinion. Immunotherapies and stem cell transplants have been related to 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 (eg, spironolactone, finasteride, or cyproterone acetate);

we have therefore held with caution these strategies for cases of persistent alopecia in cancer survivors.¹⁶³ Camouflage and supportive care should be provided to patients with CIA (Table IV).

Eyelash and eyebrow alopecia

Relatively inexpensive cosmetics and camouflage products can 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 patients with breast cancer who were 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%).¹⁶⁴

Pigmentary and textural hair changes

Hair repigmentation and textural hair shaft changes have been reported with targeted and immunotherapies.⁶⁴ Initially, most patients are satisfied with their new hair characteristics. Nevertheless, if management is requested, options such as hair dyeing and changes in hairstyle (ie, straightening or curling) should be recommended because they pose no additional risk in patients with cancer. The use of hair dyes and their association with cancer development is conflicting with non-Hodgkin lymphoma, none to insignificant for leukemias, and nonexistent for breast cancer.¹⁶⁵

Hirsutism, hypertrichosis, and trichomegaly

Topical or cosmetic interventions are recommended (eg, waxing or bleaching).¹⁶⁶ Laser and photoepilation treatments are the most effective, especially in patients with lighter skin and dark-colored hairs.¹⁶⁷ For eyelash and eyebrow trichomegaly related to targeted therapies, eyelash clipping and referral to an ophthalmologist is indicated for patients with ocular symptoms.¹⁶⁸

Experimental therapies

Several preclinical 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 alopecia¹⁶⁹ is currently being investigated for the prevention of permanent CIA in a double-blind, randomized controlled trial in breast cancer survivors.¹⁷⁰ It is hypothesized that this herbal medication may normalize apoptotic processes in hair follicle cells and reduce 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.¹⁷¹ 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 of 5 evaluable patients.¹⁷²

CHALLENGES AND FUTURE PERSPECTIVES

Despite the prevalence and psychosocial impact of 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 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 patients with cancer.

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