Hair disorders in cancer survivors

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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 survivors; discuss the current pathogenic mechanisms underlying various treatment-related hair disorders in cancer survivors; describe the topical, systemic, cosmetic, and experimental management strategies for the management of hair disorders in cancer survivors; recognize the long-term sequelae and the impact on patients' quality of life, and develop a fundamental understanding of hair disorders in cancer survivors.

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With increasing survival rates across all cancers, survivors represent a growing population that is frequently affected by persistent or permanent hair growth disorders as a result of systemic therapies, radiotherapy, surgical procedures, and therapeutic transplants. These hair disorders include persistent chemotherapy-induced alopecia, persistent radiotherapy-induced alopecia, endocrine therapy—induced alopecia and hirsutism, postsurgery alopecia and localized hypertrichosis, and persistent stem cell transplantation and targeted therapy-induced alopecia. The information contained in this continuing medical education series should facilitate a better understanding on hair disorders in cancer survivors so that adequate support and therapies may be provided. (J Am Acad Dermatol 2019;80:1199-213.)

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Key words: alopecia; cancer survivors; cancer therapy; endocrine therapy; hirsutism; hypertrichosis; persistent alopecia; persistent chemotherapy-induced alopecia; persistent radiotherapy-induced alopecia; quality of life; therapeutic transplants.

The National Cancer Institute defines survivorship as the focus on "the health and life of a person with cancer post-treatment until the end of life."[1] It covers the physical, psychosocial, and economic issues of cancer beyond the diagnosis and treatment phases. Survivorship also includes late effects of treatment, and quality of life (QoL).[1] Cancer survivors represent a growing population with a prevalence projected to approach 18 million by 2022 in the United States[2] and >32 million people worldwide.[3] Over the past decades, advances in cancer treatment have increased the overall 5-year survival rate to approximately 70% for childhood and adult cancers.[4] Currently, around 1 in 530 young adults is a survivor of childhood cancer,[5,6] and approximately 1 in 30 adults have been diagnosed with cancer.[7] Moreover, these improvements in survival rates have resulted in increased attention to treatment sequelae, in areas including cardiac, endocrine, neurologic, cutaneous, and psychosocial domains.[8] Approximately 1 in 4 cancer survivors reports a decreased QoL related to physical conditions.[7]

Whereas the acute dermatologic adverse events (AEs) of anticancer therapies have received considerable attention, long-term dermatologic AEs, such as hair growth disorders, dyspigmentation, and scarring, remain relatively unknown in the dermatologic community, limiting care and potential therapeutic efforts in this patient population. Indeed, the incidence of persistent or permanent alopecia after cancer was reported in 14% of 14,358 childhood cancer survivors[9] and in 30% of adult breast cancer survivors.[10] The occurrence of alopecia and scarring in cancer survivors is notably associated with psychological disorders, such as depression, anxiety, and low self-esteem, eventually leading to decreased health-related QoL.[11]

The information herein will allow clinicians to better understand hair disorders in cancer survivors so that adequate support and potential therapies could be offered, thus improving their QoL and hair health.

ALOPECIA IN CANCER SURVIVORS: OVERVIEW AND CLINICAL FEATURES

Key points

- **There are an estimated 15.5 million cancer survivors in the United States, equivalent to 4.8% of the population. The majority have undergone a surgical procedure as part of their diagnosis or treatment, approximately 50% have been treated with radiotherapy, and >60% have received systemic anticancer therapies, all of which may result in persistent or permanent hair disorders**
- **Thirty percent (30%) of breast cancer survivors treated with taxanes (paclitaxel or docetaxel) will develop persistent alopecia**
- **Endocrine therapies are associated with pattern alopecia similar to androgenetic type in 15% to 25% of survivors**
- **Head and neck radiotherapy leads to persistent alopecia in 60% of survivors**
- **In survivors of childhood cancer, alopecia has been associated with anxiety and depression, and adult survivors with persistent alopecia report a negative impact on their emotions**

Persistent chemotherapy-induced alopecia

The total or incomplete hair regrowth 6 months after completion of therapy in patients who received cytotoxic chemotherapy is defined as persistent chemotherapy-induced alopecia (pCIA)[12,13] and is also described as permanent chemotherapy-induced alopecia[14-21] or chemotherapy irreversible alopecia.[22-24] Whether most cancer survivors have been evaluated and treated for this type of alopecia or if pCIA is in fact permanent or irreversible has yet to be determined. pCIA has been mostly reported in breast cancer survivors treated with taxane-based chemotherapy[12,16,20,25,26] (paclitaxel and docetaxel) and cyclophosphamide-based chemotherapy,[16,27,28] with an incidence of 30% 36 months after completion of chemotherapy.[29] In addition, pCIA has been reported in children who have undergone conditioning regimens with busulfan,[30-36] (with a cumulative incidence of 19%),[37] and with other chemotherapies used for stem cell transplantation,[38] such as thiotepa and carboplatin (Table I).

With the commonly used chemotherapy regimens combining taxanes with anthracyclines in breast cancer, the risk of severe pCIA was significantly higher than the combination of doxorubicin and cyclophosphamide alone (10.5 vs 2.7%). In a questionnaire-based cross-sectional study of 265 breast cancer survivors, 7.2% reported severe pCIA (hair loss >50%).[22] A 10.1% prevalence of grade 2

Abbreviations used:

AE:	adverse event
CTCAE v5.0:	Common Terminology Criteria for Adverse Events Version 5.0
eHFSC:	epithelial hair follicle stem cell
EIA:	endocrine therapy–induced alopecia
ET:	endocrine therapy
pCIA:	persistent chemotherapy-induced alopecia
pRIA:	persistent radiotherapy-induced alopecia
QoL:	quality of life

pCIA was reported in breast cancer patients treated with docetaxel regimens with cumulative dose ≥ 400 mmg/m^2, a significantly higher prevalence than with lower docetaxel dose (0%).[39]

Multiple clinical features have been described in pCIA (Table I). The most common is a nonscarring, diffuse alopecia (53% of pCIA reported cases)[16,18,26,32] (Fig 1), and a pattern similar to androgenetic alopecia has been reported in 46.2% of cases.[17,18] pCIA may also be associated with madarosis and axillary and pubic alopecia,[19,36] although the incidence of persistent alopecia in body sites other than the scalp is unknown.

Persistent radiotherapy-induced alopecia

Hair regrowth generally occurs within 2 to 4 months after radiation to the head and neck.[40,41] Persistent radiotherapy-induced alopecia (pRIA) is the total or incomplete hair regrowth 6 months after the completion of radiotherapy and is commonly related to high-dose radiotherapy to the scalp.[42] In 26 patients with primary brain tumors, the doses reported to cause pRIA were correlated with radiotherapy dose to the hair follicles in a particular radiotherapy field, with a 50% risk of pRIA with a fractionated follicular dose of ≥43 Gy.[43] In 12 children with medulloblastoma treated with proton beam radiation in combination with high-dose vincristine-based chemotherapy, pRIA was observed in 75% and was correlated with a craniospinal radiotherapy dose ≥21 Gy.[44]

Clinical presentation of pRIA includes well defined alopecic and atrophic skin confined to the area of radiotherapy and is usually asymptomatic (Table I). Occipital, parietal, and temporal scalp are commonly focal sites of radiotherapy for brain metastases and central nervous system tumors, such as glioblastoma and astrocytoma[45] (Fig 2). Diffuse pRIA is also described with whole-brain radiotherapy for brain metastases,[45] especially when combined with chemotherapy.[46] In addition, pRIA could be also observed in any other hair-bearing area where radiotherapy is received, such as the face, neck,[47] or extremities in patients with other solid tumors.[48]

Endocrine therapy–induced alopecia and hirsutism

Endocrine therapies (ETs) are standard of care in survivors of hormone receptor–positive breast cancer (around 70% of all breast cancers).[49] ETs, including selective estrogen receptor (ER) modulators (eg, tamoxifen and toremifene), ER antagonists (fulvestrant), aromatase inhibitors (eg, anastrozole, letrozole, and exemestane), and gonadotropin-releasing hormone agonists (leuprolide) are usually administered for 5 to 10 years in the adjuvant setting to reduce the risk of recurrence.[50,51] Breast cancer survivors are known to have substantial AEs attributed to estrogen deprivation from ET,[52] and ≤8% of survivors will discontinue therapy because of alopecia related to adjuvant therapy with aromatase inhibitors.[52]

In a hospital registry–based survey study of 851 female breast cancer survivors, 22% of those who received aromatase inhibitors reported hair loss, and 32% reported hair thinning.[53] In addition, a metaanalysis of 13,415 patients in 35 clinical trials including different ETs reported an overall incidence of all-grade alopecia of 4.4%, with the highest incidence (25%) in patients who were treated with aromatase inhibitors.[54]

In a retrospective study of 112 breast cancer patients with ET-induced alopecia (EIA), causal agents included aromatase inhibitors in 67% and tamoxifen in 33% of patients. The mean time to alopecia development was 16.8 months (range 1-91 months).[55] These patients usually present with frontoparietal hairline recession (Table I), mimicking the pattern of androgenetic alopecia (Fig 3).[56] Trichoscopic features observed in patients with EIA include the concomitant presence of vellus and terminal hairs, also a hallmark of androgenetic alopecia.[55,57] Iatrogenic hirsutism has been reported in <10% of survivors receiving ET for breast cancer[58] (Fig 3).

In patients treated with cytotoxic chemotherapy followed by ET (the majority of hormone receptor–positive breast cancers), a complete medical history must be obtained to define whether alopecia is attributed to the actual ET (EIA) or to the previous chemotherapy (pCIA), or a combination of both (pCIA + EIA).

Postsurgery-induced alopecia and localized hypertrichosis

Alopecia and scarring in cancer survivors usually appears in sites from which biopsy specimens were

Table I. Incidence, case reports, and clinical features of alopecia attributed to anticancer therapies in cancer survivors

Anticancer therapies	Predominant cancer type	Reported cases and incidence	Clinical features
Cytotoxic chemotherapy (pCIA)			
Taxane-based chemotherapy	Breast	259 (30)	Nonscarring diffuse alopecia and lightening in 53% of cases; a pattern similar to androgenetic alopecia in 46.2%; persistent changes in texture are common; scarring has been reported in 2 cases; eyelash, eyebrow, axillary, and pubic hair frequently associated
Cyclophosphamide-based chemotherapy	Leukemias, lymphomas, and solid tumors	67 (17.5)	
Busulphan-based chemotherapy	Hematologic malignancies	35 (9.2)	
Other chemotherapies (including cisplatin, methotrexate, and vincristine)	Solid tumors and hematologic malignancies	21 (5.5)	
Radiotherapy (pRIA)			
Photon radiation	Primary CNS tumors and metastasis	227 (in ~70)	Scarring and nonscarring features depending on dose; geometric alopecia and atrophic skin; diffuse alopecia in total cranial irradiation and when combined with cytotoxic chemotherapy; commonly affects the occipital, parietal, and temporal areas
Proton radiation	Medulloblastoma and ependymoma	13 (75)	
Endocrine therapies (EIA)			
Selective estrogen receptor modulators (tamoxifen, toremifene, and raloxifene)	Breast and ovarian cancers	625 (in ~15)	Nonscarring features; predominantly women with a pattern similar to androgenetic alopecia; diffuse hair thinning and lightening over the entire scalp is also reported
Aromatase inhibitors (anastrozole, letrozole, and exemestane)	Breast and ovarian cancers	223 (in ~25)	
Estrogen receptor downregulator (fulvestrant)	Breast and ovarian cancers	17 (in ~5)	
Luteinizing hormone–releasing hormone agonist (leuprolide)	Breast and prostate	28 (in ~10)	
Somatostatin analog (octreotide)	Growth hormone–producing tumor (pituitary)	3 (in ~7)	
Surgery			
Neurosurgical and scalp procedures (CNS and scalp tumor biopsy and excisions, catheter placements)	Primary CNS tumors and tumors in hair-bearing areas	Scarring/disfigurement 1143 (in ~100)	Linear scar on the scalp; hypertrophic scars may be observed; could be associated with persistent radiotherapy-induced alopecia
Flaps (eg, radial forearm flap)	Head and neck tumors		Terminal hairs in undesirable areas, such as the oral cavity or face

Immunotherapies: CTLA-4 inhibitors (eg, ipilimumab), PD-1 receptor inhibitors (eg, nivolumab and pembrolizumab), and PD-L1 inhibitors (eg, atezolizumab and avelumab)	Melanoma, lung, bladder, prostate cancer, and head and neck squamous cell carcinoma	4 (N/A)	Nonscarring alopecia with diffuse hair thinning and alopecia areata, evident 3-6 months after therapy completion; skin involvement may be present, including vitiligo or lichenoid reaction
Vismodegib	Basal cell carcinoma	4 (N/A)	Persistent diffuse severe alopecia (CTCAE v5.0 grade 2)
SCT (acute or chronic GvHD, conditioning therapy for SCT with busulfan, and total body irradiation)	Hematologic malignancies	18 (in ~20) of chronic GvHD	More likely to develop alopecia areata; skin involvement may be present (vitiligo, scleroderma, eczema, and lichenoid reaction); diffuse alopecia with scarring features could be observed
		93 (56) in conditioning therapy with busulfan	Diffuse hair loss and hair thinning

CTC, Cyclophosphamide/thiotepa/carboplatin; *CNS*, central nervous system; *CTLA-4*, cytotoxic T-lymphocyte-associated protein 4; *CTCAE v5.0*, Common Terminology Criteria for Adverse Events Version 5.0; *EGFR*, epidermal growth factor receptor; *FEC-100*, fluorouracil/epirubicin/cyclophosphamide; *GvHD*, graft versus host disease; *N/A*, not available; *pCIA*, persistent chemotherapy-induced alopecia; *PD-1*, programmed cell death protein 1; *PDGF*, platelet-derived growth factor; *PD-L1*, programmed cell death protein ligand 1; *SCT*, stem cell transplantation; *TCH*, docetaxel/carboplatin/trastuzumab.

obtained, placement of catheters, and surgeries to resect scalp and brain primary or metastatic tumors.[59-63] Frequently, combination therapy (eg, radiotherapy and cytotoxic chemotherapy) is usually required[64]; these therapies combined with surgery enhance the risk of permanent alopecia and scarring. The clinical presentation of surgery-induced alopecia includes the linear shape of the scar on the scalp. When additional radiotherapy is combined with surgery, a geometric alopecic patch confined to the area of radiotherapy is also observed (Fig 4). Hypertrophic scars may also be associated with disfigurement, pain, or pruritus.[65] Conversely, undesirable hair growth in recipient areas after reconstruction of cancer defects may be observed[66-68] (Fig 5).

Persistent hair changes induced by other anticancer therapies

Anticancer therapies, such as vismodegib,[69] and immunotherapies[70] have reportedly caused persistent alopecia after drug interruption or discontinuation. Chronic graft versus host disease after stem cell transplantation may induce both diffuse alopecia (15.6%)[31] and alopecia areata (20%)[71] (Table I).

HISTOPATHOLOGY AND PATHOBIOLOGY

Key point

- **Destruction of epithelial hair follicle stem cells by anticancer therapies prevents hair follicle cycling**

Histopathologic features of permanent or persistent alopecia attributed to anticancer therapies are not specific. However, a nonscarring pattern is usually described in pCIA, with an increased number of miniaturized and telogen hair follicles.[31] Other reported histopathologic features of pCIA include scarring alopecia with concentric fibrosis and a discrete perifollicular lymphoid cell infiltrate[25,31] (Fig 2). In pRIA the predominant features are compatible with a scarring alopecia[72] and it is likely that similar histopathologic features are present in permanent surgery-induced alopecia (including fibrosis along with decreased numbers or absence of hair follicles). In EIA, histopathologic features similar to androgenetic alopecia have been reported.[25]

Although the cause of permanent or persistent alopecia in cancer survivors has not been identified, irreversible damage to epithelial hair follicle stem cells (eHFSCs) in the bulge region of the hair follicle are thought to play a crucial role.[73] Compared with their differentiated progeny in the hair matrix, eHFSCs in the bulge have a low proliferation rate and are generally less sensitive to chemotherapy[74] but are

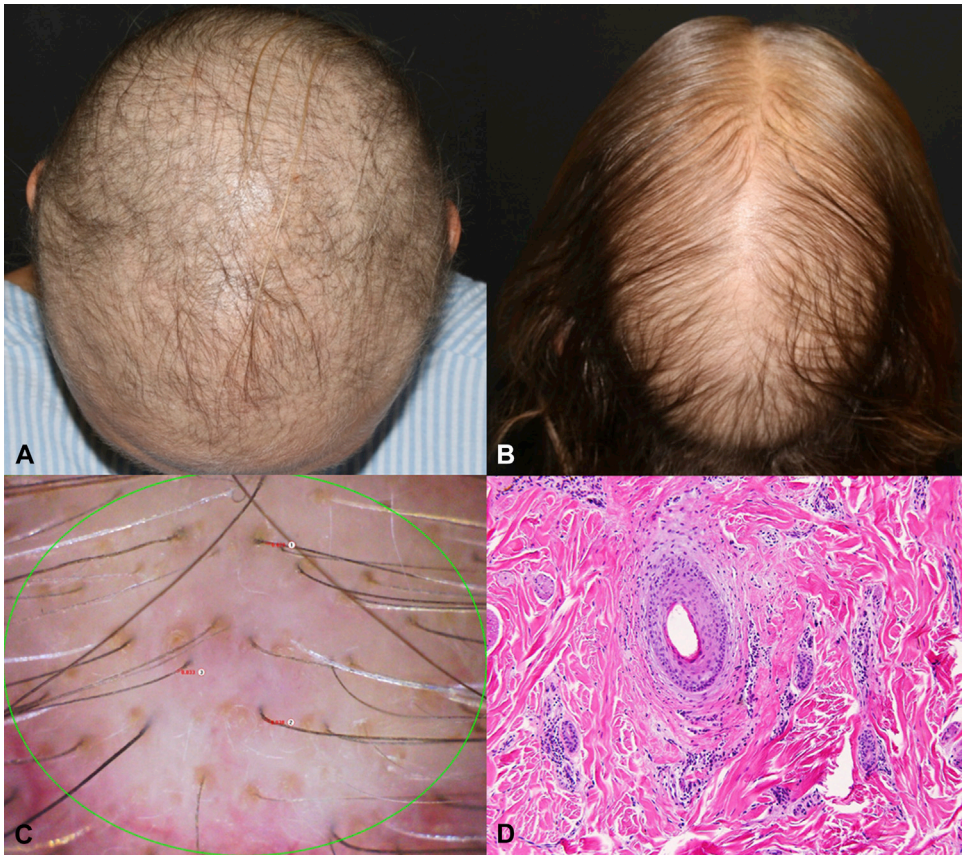

Fig 1. Persistent chemotherapy-induced alopecia (pCIA). **A**, Diffuse alopecia in a breast cancer survivor 2 years after the completion of taxane-based chemotherapy. **B**, pCIA in a breast cancer survivor, 1.6 years after the completion of taxane-based chemotherapy with a pattern similar to that of androgenetic alopecia (predominant hair thinning on the crown area). **C**, Trichoscopy of patient in (**B**), featuring hair thinning, miniaturized hairs, and yellow dots. **D**, Histology section featuring mild perifollicular inflammation and fibrosis (hematoxylin–eosin stain).

highly sensitive to ionizing radiation.[75,76] In addition, anticancer therapies associated with pCIA overcome the relative chemoresistance of eHFSC (for as yet not understood mechanism), and thus deplete the eHFSC pool that is vitally required for hair follicle regeneration during the next hair cycle.[73,77]

A 50% reduction in mitotic indices of hair matrix cells was found in experimentally irradiated mice, suggesting that there is a persistent or permanent decrease in the number or growth fraction of eHFSCs.[78] The effects of chemotherapy and radiotherapy on hair regrowth are related to the interval between chemotherapy sessions, dose administered, and radiotherapy exposure.[78,79] This enhancing effect may also depend on the phase of hair follicle cycle in which the activity was arrested.[46]

Estrogens and androgens act as potent hair growth modulators.[80,81] ETs modify the function and signaling of endocrine receptors, and estrogens are unable to modify the androgen metabolism in the hair follicle, increasing the amount of 5-dihydrotestosterone.[82] Indeed, androgenetic alopecia in women likely results not only from the undesired effects of androgen stimulation of androgen-sensitive hair follicles but also from a relative lack of hair follicle stimulation by estrogens,[83] which may explain the clinical similarities between EIA and androgenetic alopecia.[25] Surgery alopecia results from a hair follicle ablation during the inflammatory, proliferative, and remodeling phases of scarring, which may extend beyond the field of surgical intervention, partially by pressure atrophy of the surrounding skin appendages, and by infiltration of the fibrotic-associated tissue into neighboring skin appendages.[84,85]

QUALITY OF LIFE IN CANCER SURVIVORS WITH HAIR DISORDERS

Key point

- **Persistent or permanent alopecia after cancer therapies has been associated with depression, anxiety, and increased somatization**

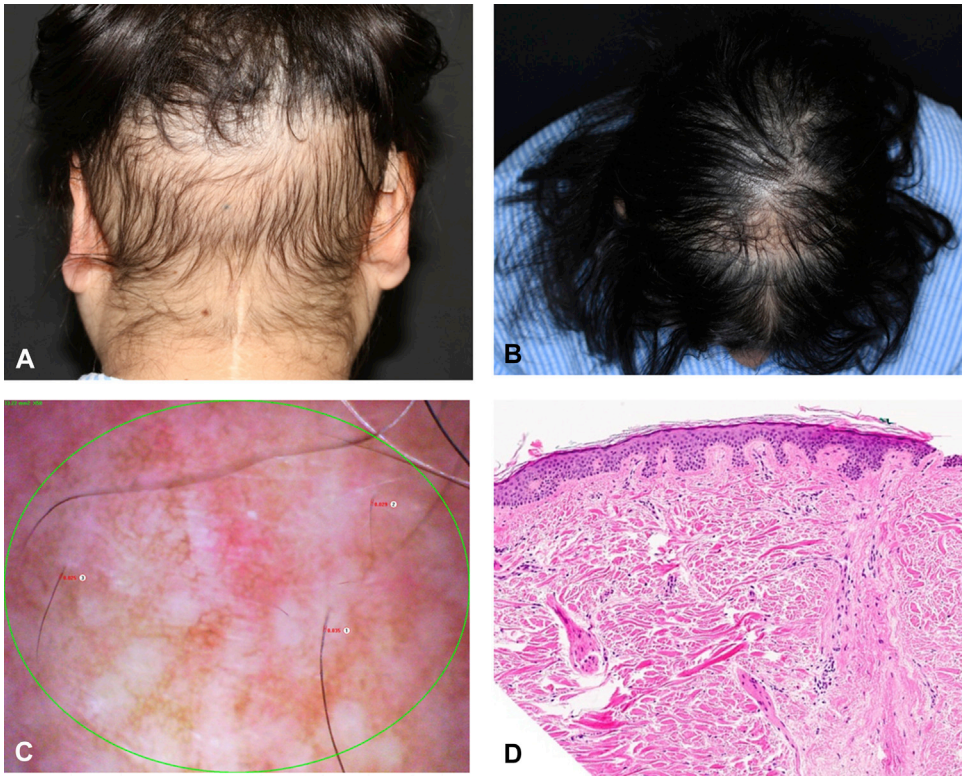

Fig 2. Persistent radiotherapy-induced alopecia (pRIA). **A**, Localized alopecia in a childhood cancer survivor with medulloblastoma treated with surgery and traditional (photon) radiotherapy. **B**, Diffuse hair loss with hair thinning on the crown area with a central scar after traditional radiotherapy and cytotoxic chemotherapy for a central nervous system tumor. **C**, Phototrichogram of patient in (**A**), featuring hair thinning, miniaturized hairs, and white dots. **D**, Histology section featuring hair follicles replaced by fibrous tracts. There is no significant inflammation (hematoxylin–eosin stain).

Alopecia is often considered by health care professionals as a "temporary" and "cosmetic" condition in cancer survivors, even though the actual distress associated with hair loss is complex and can be overwhelming.[86] Moreover, permanent or persistent alopecia is rarely included as an AE during clinical trials and usually underrecognized by health care providers.[87] Some patients also accept alopecia as a trade-off for a cure and therefore do not present with hair-related QoL issues.[88] However, permanent alopecia related to anticancer therapies has been associated with depression, anxiety, and increased somatization.[9] In addition, head and neck scarring and permanent or persistent alopecia (after chemotherapy, surgery, or cranial radiotherapy) has been reported as the strongest predictors of distress, suggesting that outward physical appearance played a prominent role in emotional adjustment of survivors.[9,89]

Distressing psychological consequences were common and severe among breast cancer survivors with pCIA, as reflected by wearing hairpieces or scarves in 14 of 20 patients.[27] In addition, in 18 breast cancer survivors with pCIA, 33% were worried about their alopecia, and it interfered with functioning in 28%.[90] The satisfaction score regarding the state of their hair in breast cancer survivors with pCIA was significantly lower when compared to breast cancer patients without pCIA.[22]

The clinical severity of alopecia may not correlate with the negative impact on a patient's QoL.[27,91] In 112 patients diagnosed with EIA, 93% had mild alopecia (grade 1, <50% of hair loss) based on the Common Terminology Criteria for Adverse Events Version 5.0 (CTCAE v5.0). However, these patients reported a negative emotional impact when compared to the other psychological domains.[55] Therefore, it is important to consider the distress that any grade of alopecia may have on cancer survivors' QoL. Focus group interviews including 25 breast cancer patients treated with taxane-based chemotherapy revealed that madarosis has a

Fig 3. Endocrine therapy-induced alopecia (EIA). **A**, EIA with a pattern similar to androgenetic type, predominantly on the frontoparietal hairline. **B**, EIA with a pattern similar to androgenetic type, predominantly on the crown area. **C**, Trichoscopy featuring vellus hairs and intermediate and thick terminal hairs. **D**, Hirsutism in a patient receiving endocrine therapy.

significant emotional impact.[92] Conversely, the impact of hirsutism attributed to anticancer therapies on QoL has not been defined.

MANAGEMENT

Key point

- **Management of hair disorders in cancer survivors is supported by anecdotal reports and case series that fail to meet strict evidence-based medicine standards**

Management of permanent or persistent alopecia in cancer survivors is mostly based on case series, case reports, and expert opinion (level of evidence IV). Despite these limitations, we have reviewed the available information (Table II). Therefore, the prevention of persistent or permanent hair growth disorders is key to mitigate this untoward consequence in cancer survivors. Scalp cooling has become the most widely used standard for the prevention of chemotherapy-induced alopecia, showing prevention of grade 2 (>50% alopecia) in 51% to 67% of patients.[93,94] Additionally, in a prospective study of 120 patients undergoing docetaxel therapy and scalp cooling, all-grade pCIA was reported in 1 patient (<1%). These findings suggest that scalp cooling may be an effective method to prevent pCIA in the docetaxel-treated population. Randomized studies to confirm these findings with docetaxel and other agents are needed.[39]

The main objectives of reactive alopecia therapy in cancer survivors are to stop or reduce the hair loss and stimulate growth. Duration of therapy should be guided by clinical response, and a laboratory analysis may help to exclude other causes of alopecia, such as thyroid disease and vitamin or mineral deficiency.

Topical therapy with minoxidil 2% or 5% has been shown to stabilize or improve alopecia in case reports and in a retrospective multicenter cohort study of pCIA.[25,27,95] However, in 14 of 20 breast cancer survivors it was unsuccessful after >3 months of therapy.[28] On the other hand, treatment with

Fig 4. A, Linear scar on the scalp after surgery of a skull base tumor. **B**, Postsurgery and persistent radiotherapy-induced alopecia.

Fig 5. Postsurgery hair disorders. Terminal hairs on the tongue after reconstruction using a hairy donor site.

topical minoxidil 5% daily in 46 breast cancer survivors with EIA, moderate or significant improvement was observed in 80%.[55] A case report showed that oral minoxidil improved pCIA in a breast cancer survivor.[14] In contrast, pCIA treated with spironolactone (150 mg/day for 3 months) in 1 breast cancer survivor showed no efficacy.[27] However, in our experience with breast cancer survivors using spironolactone alone or in combination with minoxidil 5% for pCIA and EIA, 60% of patients had a moderate or significant clinical improvement as confirmed with baseline clinical and trichoscopy standardized photographs (Fig 6). These positive clinical outcomes have been mostly observed in patients with alopecia grade 1 (CTCAE v5.0). Other options should be discussed in patients with alopecia grade 2 (CTCAE v5.0), so that the expectations of alopecia improvement are realistic. There is a putative risk of hormonal stimulation of endocrine receptor–positive tumors with the use of systemic therapies for androgenetic alopecia (eg, spironolactone and finasteride), so these agents must be used with caution.[96] Support groups may be helpful, and patients with pCIA can be directed to http://aheadofourtime.org/.

For hypertrichosis and hirsutism in cancer survivors, ruling out common causes of hyperandrogenism is important.[97] In our experience, hirsutism attributed to anticancer therapies is predominantly mild (grade 1, CTCAE v5.0) in cancer survivors, especially in postmenopausal women once they

Table II. Hair disorders in cancer survivors: Management and recommendations

Hair disorder	Intervention	Level of evidence
pCIA	CTCAEv5.0 grade 0: Alopecia prevention with scalp cooling	IV
	CTCAEv5.0 grade 1: Topical minoxidil foam 5% twice daily	
	CTCAE v5.0 grade 2: Spironolactone (escalating dose ≤200 mg/d) in addition to therapy recommended in alopecia grade 1 (caution because of the theoretical risk of hormonal stimulation of ER-positive tumors)	
	Oral minoxidil (potential adverse events should be considered)	
pRIA	CTCAE v5.0 grade 1: Topical minoxidil foam 5% twice daily, botulinum toxin type A: 5 U per 0.1 mL every 3 months for 12 months	
	CTCAE v5.0 grade 2: Scalp reconstruction (eg, simple excision or flaps, tissue expansion)	
	Hair transplant (if no fibrosis)	
EIA	CTCAE v5.0 grade 1: Topical minoxidil foam 5% twice daily	III
	CTCAE v5.0 grade 2: Spironolactone (escalating dose ≤200 mg daily) in addition to therapy recommended in alopecia grade 1 (caution because of the theoretical risk of hormonal stimulation of ER-positive tumors)	
Hirsutism and hypertrichosis	CTCAE v5.0 grade 1 (mild hair growth): Local therapy, such as threading, electrolysis, lasers	III
	CTCAE v5.0 grade 2 (prominent thick hairs, associated with psychosocial impact): Laser or intense pulsed light	
	Spironolactone appeared to be as effective as flutamide and finasteride (avoid in hormonal-sensitive tumors)	
	Other physiologic causes of hirsutism may be ruled out; laser (Nd:YAG) for hair in unwanted areas (eg, oral cavity)	
Postsurgery alopecia	First line: Management of scar symptoms if present (topical or intralesional steroid, laser and light-based treatment)	IV
	Second line: Hair transplants	
	Scalp reconstruction (eg, simple excision or flaps, tissue expansion)	IB
Eyebrow and eyelash alopecia	Topical bimatoprost solution 0.03%, hair transplants, microblading (medical tattoo)	
SCT (chronic GvHD, conditioning therapy for SCT with chemotherapy, or total body irradiation)	In GvHD depends upon the organs involved and severity of symptoms; topical and intralesional steroid for alopecia areata (level II-III), and in steroid-resistant JAK inhibitors (level IV)	II-IV
	Conditioning chemotherapy or total body irradiation; follow the interventions of pCIA and pRIA, respectively	IV
Immunotherapies: CTLA-4 inhibitors (eg, ipilimumab), PD-1 receptor inhibitors (eg, nivolumab and pembrolizumab), PD-L1 inhibitors (eg, atezolizumab and avelumab)	Potent topical steroids	IV
Vismodegib	Not reported	No evidence

Continued

Table II. Cont'd

Hair disorder	Intervention	Level of evidence
General recommendations	Therapy should be discussed to have realistic expectations of therapy outcome; follow-up at least 3 months after alopecia therapy started; laboratory analysis including, ferritin, vitamin D, zinc levels, and thyroid function may be requested if other causes of alopecia (eg, androgenetic, telogen effluvium, or thyroid-related) are suspected; camouflage techniques should be provided (eg, crayons, powder, volumizers, hair weaves/hair extension, scalp micropigmentation/tattoo, and hairpieces); if emotionally affected, psychological counseling is recommended; involve nurses and other health care providers in the cancer survivor's care	IV

CTCAE v5.0 grade 1 for alopecia: 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 hair piece to camouflage. CTCAE v5.0 grade 2 for alopecia: hair loss of ≥50% of normal for that individual that is readily apparent to others; a wig or hairpiece is necessary if the patient desires to completely camouflage the hair loss; associated with psychosocial impact.
CTCAE v5.0, Common Terminology Criteria for Adverse Events Version 5.0; *CTLA-4*, cytotoxic T lymphocyte–associated protein 4; *ER*, endocrine receptor; *GvHD*, graft versus host disease; *JAK*, Janus kinase; *EIA*, endocrine therapy–induced alopecia; *Nd:YAG*, neodymium-doped yttrium aluminium garnet; *pCIA*, persistent chemotherapy-induced alopecia; *PD-1*, programmed cell death protein 1; *PD-L1*, programmed cell death protein ligand 1; *pRIA*, persistent radiotherapy-induced alopecia; *SCT*, stem cell transplantation.

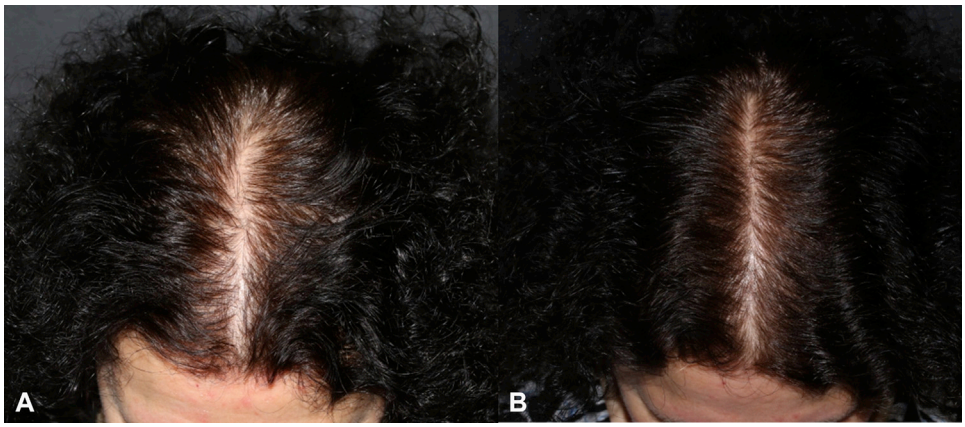

Fig 6. Endocrine therapy-induced alopecia (EIA), (**A**) baseline and (**B**) 6 months after therapy with topical minoxidil foam 5% twice a day.

have completed cytotoxic chemotherapy or in those receiving ET, and requires only reassurance and local therapies, such as epilation, laser therapies, or bleaching if needed (Table II). Neodymium-doped yttrium aluminium garnet laser therapy appears to have a hair clearance of >90% after 1 to 4 sessions in 5 of 9 patients suffering from growth of terminal hair in the oral cavity after reconstruction using a hairy donor site.[98]

Multiple scalp reconstructive options have been described to improve the appearance of the localized pRIA, including tissue expansion and hair transplant.[42] However, the success of these techniques relies on the skin viability and severity of hair follicle damaged.[99] There is no reported experience using platelet-rich plasma to treat alopecia in cancer survivors, and costs may be elevated. Hair follicle neogenesis with autologous cell populations may become a future therapeutic option for pCIA and pRIA.[100,101]

A randomized controlled trial including 20 patients treated with bimatoprost 0.03% gel for chemotherapy-induced eyelash alopecia, improvement in length (1.50 vs 0.46 mm), and thickness (3 vs 2, in a scale of 1-5) of treated eyelashes was observed, with an increase of patient satisfaction (16 vs 26) after 3 months of therapy[102] (Fig 7).

Interventions with skin camouflage (including powders, scalp micropigmentation/tattoo, and hair color and hairstyle changes) can modify the concerning body image to mask skin discoloration

Fig 7. Topical bimatoprost 0.03% solution for persistent chemotherapy-induced alopecia (pCIA) of the eyelashes (**A**) baseline and (**B**) 6 months after therapy.

and alopecia. This effect acts to improve the visible impact of deformity.[103,104] When camouflage may be indicated, patients should be informed. Initially, most patients are reluctant to use any camouflage, but they can enhance self-confidence and QoL.[105] The market for home use cosmetic devices is rapidly expanding; however, there are no reports measuring their efficacy for hair growth disorders in cancer survivors.

CHALLENGES AND FUTURE PERSPECTIVES

The ongoing Chemotherapy-Induced Hair Changes and Alopecia, Skin Aging and Nail Changes in Women With Non-Metastatic Breast Cancer trial (NCT02530177) examining the incidence, risk factors, psychosocial impact, and clinical features of pCIA and EIA in 500 breast cancer patients will yield additional information that will be critical to identifying preventive and treatment strategies. Similar studies in other patient populations are needed.

Additional efforts should be made to understand the mechanism of hair follicle alteration and to identify effective strategies for the prevention and treatment of permanent or persistent alopecia in cancer survivors. Patient counseling regarding the possibility of developing persistent or permanent hair disorders with anticancer therapies will also be important so that anticipatory coping can take place. Prospective studies evaluating patients during and after their treatments are needed to identify the real incidence and severity of these conditions. Therapeutic options remain limited in number and efficacy, and additional research is needed to determine optimal preventive and therapeutic approaches for the various hair disorders observed in the growing population of cancer survivors.

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Answers to CME examination

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