

Permanent Alopecia in Breast Cancer Patients: Role of Taxanes and Endocrine Therapies

Christa Slaughter, MD; Michael Roman, MD; Sharona Yashar, MD; Vanessa Holland, MD; Carolyn Goh, MD

PRACTICE POINTS

- Permanent chemotherapy-induced alopecia (PCIA) is defined as hair loss that persists beyond 6 months after treatment with chemotherapy. It may be complicated by the addition of endocrine therapies.
- Patients and clinicians should be aware that PCIA can occur and appears to be a higher risk with taxane therapy.

Permanent chemotherapy-induced alopecia (PCIA) has been described following high-dose chemotherapy regimens for allogeneic bone marrow transplants; however, reports of PCIA in breast cancer patients are increasing. Many prior reports involve treatment with taxanes, but the role of endocrine therapies has not been well defined. Permanent alopecia in breast cancer patients appears to be a potential adverse effect of taxanes and endocrine therapies. Although the cytotoxic effects of taxanes may lead to permanent hair loss, the influence of endocrine therapies on the remaining follicles may affect the pattern of hair loss. Further characterization of these cases may elucidate risk factors for developing permanent alopecia, allowing for more appropriate risk stratification and counseling. We describe 3 patients with breast cancer who experienced PCIA following chemotherapy with taxanes.

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Anagen effluvium during chemotherapy is common, typically beginning within 1 month of treatment onset and resolving by 6 months after the final course.¹ Permanent chemotherapy-induced alopecia (PCIA), in which hair loss persists beyond 6 months after chemotherapy without recovery to original density, was

first reported in patients following high-dose chemotherapy regimens for allogeneic bone marrow transplantation.² There are now increasing reports of PCIA in patients with breast cancer; at least 400 such cases have been documented.³⁻¹⁶ In addition to chemotherapy, patients often receive adjuvant endocrine therapy with selective estrogen receptor modulators, aromatase inhibitors, or gonadotropin-releasing hormone agonists.⁵⁻¹⁶ Endocrine therapies also can lead to alopecia, but their role in PCIA has not been well defined.^{15,16} We describe 3 patients with breast cancer who experienced PCIA following chemotherapy with taxanes with or without endocrine therapies. We also review the literature on non-bone marrow transplantation PCIA to better characterize this entity and explore the role of endocrine therapies in PCIA.

Case Reports

Patient 1—A 62-year-old woman with a history of stage II invasive ductal carcinoma presented with persistent hair loss 5 years after completing chemotherapy. She underwent 6 cycles of docetaxel and carboplatin along with radiation therapy as well as 1 year of trastuzumab and did not receive endocrine therapy. At the current presentation, she reported patchy hair regrowth that gradually filled in but failed to return to full density. Physical examination revealed the hair was diffusely thin, especially bitemporally (Figures 1A and 1B), and she did not experience any loss of body hair. She had no family history of hair loss. Her medical history was notable for hypertension, chronic obstructive bronchitis, osteopenia, and depression. Her thyroid stimulating hormone (TSH) level was within reference range. Medications included lisinopril, metoprolol, escitalopram, and trazodone. A biopsy from the occipital scalp showed nonscarring alopecia with variation of hair follicle

Dr. Slaughter is from the Department of Dermatology, Oregon Health and Science University, Portland. Dr. Roman is from the Department of Psychiatry, University of Pennsylvania, Philadelphia. Dr. Yashar is from the Dermatology Service, Veterans Affairs Greater Los Angeles Healthcare System, California. Drs. Holland and Goh are from the Department of Medicine, Division of Dermatology, UCLA Medical Center, Los Angeles. The authors report no conflict of interest.

Correspondence: Carolyn Goh, MD, 200 Medical Plaza, Ste 450, Los Angeles, CA 90095 (cgoh@mednet.ucla.edu).

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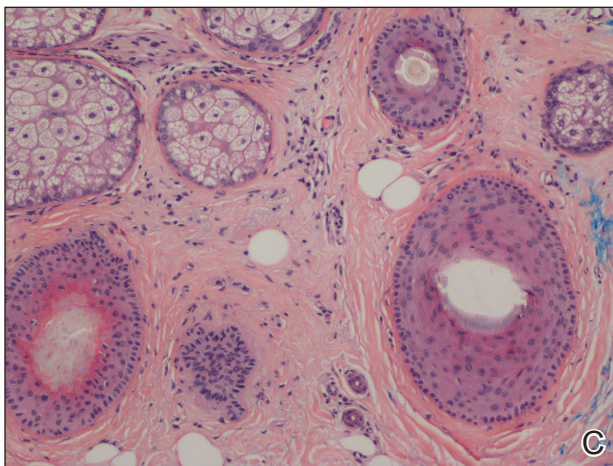


FIGURE 1. A and B, Chemotherapy-induced alopecia in patient 1. The hair was diffusely thin, especially bitemporally. C, Histopathology showed variation in hair follicle size; catagen/telogen hairs were present (H&E, original magnification $\times 100$).

size, a decreased number of hair follicles, and a decreased anagen to telogen ratio (Figure 1C). She was treated with clobetasol solution and minoxidil solution 5% for 1 year with mild improvement. She experienced no further hair loss but did not regain original hair density.

Patient 2—A 35-year-old woman with a history of stage II invasive ductal carcinoma presented with persistent hair loss 10 months after chemotherapy. She underwent 4 cycles of doxorubicin and cyclophosphamide followed by 4 cycles of paclitaxel and was started on trastuzumab. Tamoxifen was initiated 1 month after completing chemotherapy. She received radiation therapy the following month and continued trastuzumab for 1 year. At the current presentation, the patient noted that hair regrowth had started 1 month after the last course of chemotherapy but had progressed slowly. She denied body hair loss. Physical examination revealed diffuse thinning, especially over the crown, with scattered broken hairs throughout the scalp and several miniaturized hairs over the crown. She was evaluated as grade 3 on the Sinclair clinical grading scale used to evaluate female pattern hair loss (FPHL).¹⁷ Her family history was remarkable for FPHL in her maternal grandmother. She had no notable medical history, her TSH was normal, and she was taking tamoxifen and trastuzumab. Biopsy was not performed. The patient was started on minoxidil solution 2% and had mild improvement with no further broken-off hairs after 10 months. At that point, she was evaluated as grade 2 to 3 on the Sinclair scale.¹⁷

Patient 3—A 51-year-old woman with a history of papillary carcinoma and extensive ductal carcinoma in situ presented with persistent hair loss for 3.5 years following chemotherapy for recurrent breast cancer. After her initial diagnosis in the left breast, she received cyclophosphamide, methotrexate, and 5-fluorouracil but did not receive endocrine therapy. Her hair thinned during chemotherapy but returned to normal density within 1 year. She had a recurrence of the cancer in the right breast 14 years later and received 6 cycles of chemotherapy with cyclophosphamide and docetaxel followed by radiation therapy. After this course, her hair loss incompletely recovered. One year after chemotherapy, she underwent bilateral salpingo-oophorectomy and started anastrozole. Three months later, she noticed increased shedding and progressive thinning of the hair. Physical examination revealed diffuse thinning that was most pronounced over the crown. She also experienced lateral thinning of the eyebrows, decreased eyelashes, and dystrophic fingernails. Fluocinonide solution was discontinued by the patient due to scalp burning. She had a brother with bitemporal recession. Her medical history was notable for Hashimoto thyroiditis, vitamin D deficiency, and peripheral neuropathy. Her TSH occasionally was elevated, and she was intermittently on levothyroxine; however, her free T4 was maintained within reference range on all records. Her medications at the time of evaluation were anastrozole and gabapentin. Biopsies taken

from the right and left temporal scalp revealed decreased follicle density with a majority of follicles in anagen, scattered miniaturized follicles, and a mild perivascular and perifollicular lymphoid infiltrate. Mild dermal fibrosis was present without evidence of frank scarring (Figure 2). She declined treatment, and there was no change in her condition over 3 years of follow-up.

Comment

Classification of Chemotherapy-Induced Hair Loss—Chemotherapy-induced alopecia is typically an anagen effluvium that is reversed within 6 months following the final course of chemotherapy. When incomplete regrowth persists, the patient is considered to have PCIA.¹ The pathophysiology of PCIA is unclear.

Traditional grading for chemotherapy-induced alopecia does not account for the patterns of loss seen in PCIA, of which the most common appears to be a female pattern with accentuated hair loss in androgen-dependent regions of the scalp.¹⁸ Other patterns include a diffuse type with body hair loss, patchy alopecia, and complete alopecia with or without body hair loss (Table).^{3–8} Whether these patterns all can be attributed to chemotherapy remains to be explored.

Breast Cancer Therapies Causing PCIA—The main agents thought to be responsible for PCIA in breast cancer patients are taxanes. The role of endocrine therapies has not been well explored. Trastuzumab lacks several of the common side effects of chemotherapy due to its specificity for the HER2/neu receptor and has not been found to increase the rate of hair loss when combined with standard chemotherapy.^{19,20} Although radiation therapy has the potential to damage hair follicles, and a dose-dependent relationship has been described for temporary and permanent alopecia at irradiated sites, permanent alopecia predominantly has been reported with cranial radiation used in the treatment of intracranial

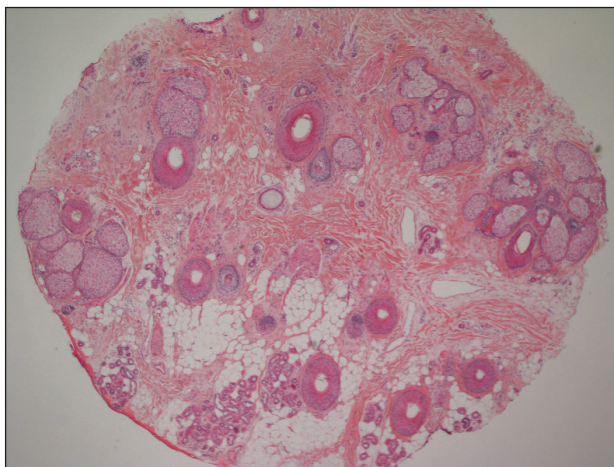


FIGURE 2. Histopathology of patient 3 showed decreased follicle density with scattered miniaturized follicles and a background of mild dermal fibrosis (H&E, original magnification $\times 200$).

malignancies.²¹ The role of radiation therapy of the breasts in PCIA is unclear, as its inclusion in therapy has not been consistently reported in the literature.

Docetaxel is known to cause chemotherapy-induced alopecia, with an 83.4% incidence in phase 2 trials; however, it also appears to be related to PCIA.²⁰ A PubMed search of articles indexed for MEDLINE was performed using the terms *permanent chemotherapy induced alopecia, chemotherapy, docetaxel, endocrine therapies, hair loss, alopecia, and breast cancer*. More than 400 cases of PCIA related to chemotherapy in breast cancer patients have been reported in the literature from a combination of case reports/series, retrospective surveys, and at least one prospective study. Data from some of the more detailed reports ($n=52$) are summarized in the Table. In the single-center, 3-year prospective study of women given adjuvant taxane-based or non-taxane-based chemotherapy, those who received taxane therapy were more likely to develop PCIA (odds ratio, 8.01).⁹

All 3 of our patients received taxanes. Interestingly, patient 3 underwent 2 rounds of chemotherapy 14 years apart and experienced full regrowth of the hair after the first course of taxane-free chemotherapy but experienced persistent hair loss following docetaxel treatment.

Adjuvant endocrine therapies also may contribute to PCIA. A review of the side effects of endocrine therapies revealed an incidence of alopecia that was higher than expected; tamoxifen was the greatest offender. Additionally, using endocrine treatments in combination was found to have a synergistic effect on alopecia.¹⁸ Adjuvant endocrine therapy was used in patients 2 and 3. Although endocrine therapies appear to have a milder effect on hair loss compared to chemotherapy, these medications are continued for a longer duration, potentially contributing to the severity of hair loss and prolonging the time to regrowth.

Furthermore, endocrine therapies used in breast cancer treatment decrease estrogen levels or antagonize estrogen receptors, creating an environment of relative hyperandrogenism that may contribute to FPHL in genetically susceptible women.¹⁸ Although taxanes may cause irreversible hair loss in these patients, the action of endocrine therapies on the remaining hair follicles may affect the typical female pattern seen clinically. Patients 2 and 3 who presented with FPHL received adjuvant endocrine therapies and had positive family history, while patient 1 did not. Of note, patient 3 experienced worsening hair loss following the addition of anastrozole, which suggests a contribution of endocrine therapy to her PCIA. Our limited cases do not allow for evaluation of a worsened outcome with the combination of taxanes and endocrine therapies; however, we suggest further evaluation for a synergistic effect that may be contributing to PCIA.

Conclusion

Permanent alopecia in breast cancer patients appears to be a true potential adverse effect of taxanes and endocrine

Reports of PCIA in Breast Cancer Patients

Patient characteristic	Reference						
	Tallon et al ³	Miteva et al ⁴ (N=6)	Prevezas et al ⁵	Prevezas et al ⁶	Masidonski and Mahon ⁶ (N=13)	Kluger et al ⁷ (N=20)	Fonia et al ⁸ (N=10)
Age, y	72	Unknown	58	55	28-78	38-69	46-72
Gender	F	F	F	F	F	F	F
Ethnicity/race	White	White, Asian, and Black	White	White	White, Black	Black	White, Afro-Caribbean
Cancer type and stage	Stage IIA, ER/PR+, HER2/neu+ breast cancer	Recurrent breast cancer (unknown type)	Recurrent breast cancer (unknown type)	Recurrent breast cancer (unknown type)	Various ductal breast carcinomas, ER/PR variable, HER2/neu+ variable	Invasive ductal and lobular breast carcinoma	Invasive ductal and lobular breast carcinoma
Chemotherapeutic agents	Docetaxel, carboplatin (later removed), trastuzumab	Docetaxel	Docetaxel	Paclitaxel	Anthracycline, cyclophosphamide, taxane (n=11); anthracycline and cyclophosphamide (n=2)	Fluorouracil, epirubicin, cyclophosphamide, docetaxel (n=20)	Fluorouracil, epirubicin, cyclophosphamide, docetaxel (n=10); 1 patient received paclitaxel once in addition to docetaxel 3 times
Trastuzumab	Yes	No	No	No	No	Yes (n=3)	Yes (n=5)
Radiation therapy	Yes	None	None	Yes	None	Yes	Yes
Antihormonal therapy	None	None	Letrozole	None	Various aromatase inhibitors (n=6)	14/20 patients total: exemestane (n=3), tamoxifen (n=8), anastrozole (n=3), letrozole (n=6)	4/10 patients: tamoxifen only (n=2), tamoxifen and letrozole (n=1), anastrozole (n=1)

continued

TABLE (continued)

Reference

Patient characteristic	Tallon et al ³	Miteva et al ⁴ (N=6)	Prevezas et al ⁵	Prevezas et al ⁵	Masidonski and Mahon ⁶ (N=13)	Kluger et al ⁷ (N=20)	Fonia et al ⁸ (N=10)
Clinical pattern of hair loss	Severe diffuse hair loss most prominent over the crown	Hair loss ranged from severe to very severe, including severe diffuse hair loss accentuated on the androgen-dependent area of the vertex	Diffuse alopecia with androgenetic hair loss and absence of scalp fibrosis	Severe and diffuse hair shedding of the scalp, eyebrows, eyelashes, and axillary and pubic regions	White women: female pattern alopecia on the top of the head; Black women: generalized baldness	Diffuse loss and thinning predominating over the crown and frontal scalp with thinning and widening of the central parting of the scalp in an oval form	Diffuse (n=4), diffuse with accentuation on the vertex (n=5), diffuse and patchy (n=1)
Dermatopathology	Marked reduction in anagen hair follicles; multiple linear aggregates of basaloid epithelium in the reticular dermis and subcutis; no perifollicular inflammation; mild perifollicular fibrosis	Nonscarring; reduced hair density but preserved number of follicular units; decreased anagen to telogen ratio; no fibrosis; increased vellus hairs; increased number of fibrous streamers	Reduced hair follicle density; increased vellus hairs; low number of terminal anagen follicles; mild dermal lymphocytic infiltrate; no peribulbar inflammation; no fibrosis	Discrete peribulbar lymphocytic infiltrate; diminished number of hair follicles; no fibrosis	Unknown	Normal (n=3); reduced terminal hairs (n=8); increased miniaturized follicles (n=1); mild interstitial and perifollicular lymphocytic infiltrate (n=11); mild perifollicular deposition of mucin (n=1)	Nonscarring with preservation of sebaceous glands (n=10); increased miniaturized follicles (n=10); pigment cases in telogen hair follicles (n=6); dysmorphic telogen germinal units (n=9); trichomalacia (n=3); peribulbar lymphoid cell infiltrate (n=2); avascular fibrous tracts (n=10)
Alopecia therapy	Topical minoxidil 2%	Unknown	Topical minoxidil 5%	Topical minoxidil 5%	Unknown	Long-term minoxidil (n=1)	Long-term minoxidil 5% (n=1)
Response to therapy	No improvement	Unknown	Discrete amelioration	Discrete amelioration	Unknown	No improvement	Slow, complete regrowth

Abbreviations: PCIA, permanent chemotherapy-induced alopecia; F, female; ER, estrogen receptor; PR, progesterone receptor.

therapies, and it is important to characterize it appropriately so that its mechanism can be understood and appropriate treatment and counseling can take place. Although it may not influence clinical decision-making, patients should be informed that hair loss with chemotherapy can be permanent. Treatment with scalp cooling can reduce the risk for severe chemotherapy-induced alopecia, but it is unclear if it reduces risk for PCIA.^{12,15} Topical or oral minoxidil may be helpful in the treatment of PCIA once it has developed.^{7,8,15,22} Better characterization of these cases may elucidate risk factors for developing permanent alopecia, allowing for more appropriate risk stratification, counseling, and treatment.

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