

Peer Review File

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Review Comments

Reviewer A

This is a nice review on the etiologies, clinical presentations, psychosocial effects, and various treatment and preventative options for survivors of breast cancer who develop cancer treatment-induced alopecia. The content is well-organized and the writing is easy to follow. A particular strength is the discussion of what is lacking in current knowledge, e.g., the efficacy of CIA prevention in patients with very curly/kinky hair, and the technical challenge of making well-fitting cooling caps for these patients.

There are several things that could potentially improve the review.

A general comment is that for this rather thorough review, only 34 references were cited. Frequently only one reference or only one study is cited to support a statement. This can be misleading when multiple studies report quantitative data that are quite different from each other. In this case, more than one study should be cited, and a range should be provided based on the results from different reports. Speculation on the reason for such discrepancies could also be very helpful.

Reply: Thank you for this comment, as we wholeheartedly agree. During this editing process, we added citations to reach a final citation count of 75. During this process, we also removed citations that were outdated.

(see Pages 21-32)

Another suggestion is to discuss agents and approaches being tested for the prevention of hair loss in addition to scalp cooling. Given the risk of CIA and pCIA, effective prevention is of high significance.

Reply: Thank you for this comment. We have added information regarding topical vasoconstrictors, vitamin D/calcitriol, and keratinocyte growth factor (KGF) as preventative agents and approaches against hair loss.

(see Pages 12-14, Lines 337-378)

Reviewer B

In general: please describe how you collected the literature for this review as there seems not to be a search strategy? If you randomly selected the papers, you should call it a 'narrative review'.

Reply: Thank you for this comment. We have added a methodology section that outlines the search strategy for this review. Additionally, we have renamed the article as a narrative review, as papers were selected randomly.

(see Page 4, Lines 119-128)

Especially in the first part of the paper the English language needs to be revised.

Reply: Thank you for this comment. We have edited the entire paper for grammar and spelling.

Types of alopecia

Line 67-70 these are papers that are published in 2008 and 1990: there should be a more updated studies indicating the current impact of alopecia.

Reply: Thank you for this suggestion. We have replaced the text in lines 67-70 to say:

Chemotherapy-induced alopecia is a significant side effect of breast cancer therapies (8). In one study, 55% of breast cancer patients reported high psychological stress due to CIA (9). Distress due to CIA has been found to be strongly associated with depression, lower body image, health status, and psychosocial well-being.

(See Page 4, Lines 132-135)

Line 75: it is not only taxanes, but also anthracyclines (many references to find)

Reply: Thank you for pointing this out, as we agree that both taxane and anthracycline-containing regimens are associated with CIA. We have added several sentences to reflect this:

In addition to taxane-containing chemotherapy regimens, anthracyclines are also associated with high rates of hair loss. This heightened risk of hair loss is best exemplified by studies showing that patients receiving anthracyclines are more resistant to efforts to mitigate CIA, such as scalp cooling [17-18]. One study found that longer post-chemotherapy infusion scalp cooling times were needed to prevent significant CIA [19].

(See Page 6, Lines 176-180)

Line 86 doesn't make sense without context about the types of chemotherapy

Reply: Thank you for catching this error. We have fixed this. It now reads:

In a prospective cohort study of breast cancer patients receiving paclitaxel-based chemotherapy regimens, pCIA was experienced by 39.5% and 42.3% of patients at six months and three years, respectively. A study performed in Seoul, Korea, found that 39.5% of patients receiving paclitaxel-based chemotherapy regimens had pCIA at 6 months after chemotherapy completion [16].

(See Page 6, Lines 171-175)

Line 109 'hair follicles in a pattern distribution' is unclear

Reply: Thank you for catching this error. We have re-written the sentence. It now reads:

Testosterone is known to cause hair loss by shortening the anagen phase, or growing phase, of hairs. In addition, testosterone causes miniaturization, or a decreased diameter, of hair follicles [21].

(See Page 7, Lines 202-204)

Line 113: CDK inhibitors are used very frequently, is there no more info on alopecia available than 10 patients?

Reply: Thank you for this comment. We have added the results from two clinical trials that found alopecia as an adverse effect of CDK4/6 inhibitors. It now reads:

Cyclin-dependent kinase 4 and 6 inhibitors (CDK4/6i) are novel targeted therapies increasingly used in patients with breast cancer. To date, two randomized-controlled clinical trials have reported alopecia as an adverse effect from CDK4/6 agents [22,23]. In a cohort study that included 10 patients receiving CDK4/6i, 70% of patients had alopecia on the vertex scalp, which differs from the alopecia pattern seen in women with EIA. Furthermore, CDK4/6i-alopecia (CDKIA) had a faster onset [24].

[\(See Page 7, Lines 205-210\)](#)

Line 117: less responsive compared to what? You haven't discussed treatment as yet.

Reply: Thank you for this comment. We have re-written this sentence. It now reads:

In patients receiving both an endocrine therapy and a CDK 4/6i, alopecia can be less responsive to prescription hair loss treatments, such as minoxidil.

[\(See Page 7, Lines 211-212\)](#)

Line 119: CDKIA has not specified in the text above.

Reply: Thank you for catching this. We have fixed this as follows:

Furthermore, CDK4/6i-alopecia (CDKIA) had a faster onset [24].

[\(See Page 7, Lines 209-210\)](#)

Line 118-121: first it is stated that also 80% of CDKIA patients are improved, but in the second sentence it is stated that there is no improvement vor CDKIA? All in 1 study?

Reply: Thank you for catching this. We have removed the second sentence.

[\(See Page 7, Lines 211-214\)](#)

Fear: important topic but I feel the information about reference 17 is not in proportion to the other papers.

Reply: Thank you for your comment. We have summarized the information from reference 17. We have also added additional sources in this section to back up the claims presented.

[\(See Pages 9-10, Lines 256-274\)](#)

Management:

Line 212-213: abbreviations are not specified previously

Reply: Thank you for your comment. We have added the abbreviations for the treatments mentioned. It now reads:

Additionally, patients placed on the chemotherapy regimen of AC (doxorubicin hydrochloride [adriamycin] and cyclophosphamide) or AC-T doxorubicin hydrochloride, cyclophosphamide, and paclitaxel [taxol]) were less likely to pursue scalp cooling than patients on PTCH/TCHP

(docetaxel [taxotere], carboplatin, trastuzumab [herceptin] and pertuzumab [perjeta]) or TC (docetaxel and cyclophosphamide [cytoxan]) regimens [34].

(See Page 11, Lines 301-305)

Line 222 remove 'it'

Reply: Thank you for your comment. We have reworded line 222 by removing the word “it” and replacing it with the words “curly hair”. The sentence now reads:

There is a need for physicians to better understand Black kinky or curly hair, its properties, and how styling curly hair differs from styling straight hair.

(See Page 11, Lines 311-313)

Line 230: what do you mean with changes in hair due to chemicals (like chemo/immuno) that can affect effectiveness of scalp cooling? What is the rationale behind it?

Reply: Thank you for this comment. We have added in a line that specifies the types of chemicals and heat that are being discussed. It now reads:

Additionally, curly hair is often altered to a greater extent compared to straight hair when heat and chemicals are added, such as chemical straightening or topical oils, which can affect the effectiveness of scalp cooling for Black people [36].

(See Page 12, Lines 325-327)

Line 233: you mention White and Black patients, what about Asian patients?

Reply: Thank you for this suggestion. We would like to add the following:

Another area in need of further research pertains to the efficacy of scalp cooling in patients of Asian race. In one study of female Japanese breast cancer patients, it was found that 45.6% of patients who used scalp cooling therapy throughout chemotherapy infusion visits experienced Dean Score Grade 3 alopecia, comparable with scores of White women (36). We emphasize the importance of further research regarding racial differences in efficacy of scalp cooling technology in order to ensure that patients of all races can benefit from its use.

(See Page 12, Lines 330-335)

Table 1: these look like random studies that are used for each agent, that are no reviews, so highly selective information. Should be revised.

Reply: Thank you for this comment. We have updated citations to include results from systematic reviews.

(see Pages 14-15, Table 1)

Line 246: you only discuss PBM, what about other options?

Reply: Thank you for this suggestion. We have added several paragraphs that review current treatment options.

(See Pages 15-17, Lines 386-446)

Psychosocial support: I think there is more information on this than only the single ACP.

Reply: Thank you for this comment. We have added information regarding mindfulness-based stress reduction (MBSR), colocated behavioral health (CLBH) treatment, hypnotherapy, psychoimmunotherapy, and coping strategies. We have also added a few more sources to back up the claims and results mentioned in this section.

(See Page 18, Lines 475-485)

Literature

There are quite some outdated references in the literature for which more recent publications should be available.

Reply: Thank you for pointing this out. During our most recent rounds of edits, we updated several of the studies to express more recent findings.

(See Pages 21-32)

The link to ref 29 is not working

Reply: Thank you for your pointing this out. We have edited the hyperlink – it should be working now.

(See Page 29, Lines 725-728)