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COMMENTARY

Chemotherapy drug concentrations in hair follicles: a potential biomarker to monitor the effectiveness of scalp cooling for chemotherapy-induced alopecia

Jung-Woo Chae[1,2,3] · Raymond Ng[4,5] · Alexandre Chan[1,2,5,6]

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Chemotherapy-induced alopecia (CIA) is commonly described as one of the most distressing adverse events of breast cancer treatment, with patients experiencing negative body image and poor self-esteem [1]. Breast cancer patients have described CIA as being more devastating than losing a breast, as hair loss often signifies as a visible sign of cancer as well as a loss of femininity [2]. Women even refuse chemotherapy due to this fear [1]. Two trials were recently published and had reported the effectiveness of scalp cooling to prevent CIA. In one study ($n = 182$), scalp cooling prevented hair loss in 50% of patients randomized to the scalp cooling, compared to those in the control arm in which all patients experienced hair loss [3]. Another multicenter prospective cohort study, which enrolled 106 women treated taxane-based chemotherapy, reported that scalp cooling prevented hair loss in 66.4% of all participated patients, whereas all patients without receiving scalp cooling experienced hair loss [4]. These data have also led to FDA clearance to market for two scalp cooling systems (Dignicap® and Paxman®) that reduce hair loss in breast cancer patients undergoing anthracycline- or taxane-based chemotherapy.

Scalp cooling is speculated to induce vasoconstriction in the scalp, resulting in a reduction of chemotherapy delivery to the hair follicles, consequently decreasing cellular drug uptake and increasing cytoprotection of keratinocytes [5, 6]. Interestingly, none of the aforementioned clinical trials that utilized scalp cooling devices had evaluated the association between chemotherapeutic concentrations in the hair follicles and the success of hair preservation, while studies have focused mainly on the clinical efficacy of scalp cooling [1, 3, 4]. The success of alopecia prevention has been known to be associated with several factors, including proper fitting of the cooling cap and the biochemical properties of chemotherapy [7, 8]. Yet, a number of questions are still remained to be answered: (1) How can we further increase the success rate of scalp cooling? (2) If safety is not a concern, can we further reduce the scalp temperature to intensify cooling to improve the scalp cooling efficacy further? (3) What is the maximum concentration threshold of chemotherapy in the hair follicle beyond which clinically significant alopecia is inevitable? The optimization of scalp cooling for alopecia prevention will continue to remain as a challenge, in the absence of a comprehensive understanding of the mechanisms underlying the efficacy of scalp cooling.

We have recently presented the effect of scalp cooling on the reduction of chemotherapeutic concentration in hair follicles at the Multinational Association of Supportive Care in Cancer (MASCC) 2017 conference [9]. In this pilot study, we have recruited two groups of early-stage breast cancer patients who received anthracycline-based or taxane-based chemotherapy (7 CarbonCool™ scalp cooling and 3 without scalp cooling). In the scalp cooling arm, patients were provided scalp cooling for 30 min prior to chemotherapy infusion

✉ Alexandre Chan
phaac@nus.edu.sg

1 Department of Pharmacy, National University of Singapore, Singapore, Singapore

2 Department of Pharmacy, National Cancer Centre Singapore, Singapore, Singapore

3 College of Pharmacy, Chungnam National University, Daejeon, South Korea

4 Division of Medical Oncology, National Cancer Centre Singapore, Singapore, Singapore

5 Duke-NUS Graduate Medical School Singapore, Singapore, Singapore

6 Department of Pharmacy, Faculty of Science, National University of Singapore, 18 Science Drive 4, Block S4A, Singapore 117543, Singapore

and continued until 1-h post treatment. The CarbonCool™ utilizes carbon, which possesses excellent thermal conductivity (CarbonCool™ system – 35 W/mK, ice – 2.3 W/mK), to deliver consistent cryotherapy to the scalp [10]. The scalp surface temperature was monitored using a LCD thermometer probe and maintained ≤ 19 °C to ensure consistent cooling [8]. CIA was assessed using Dean's score by photographic documentations. Hair follicles were taken 5 days after the first cycle of chemotherapy, and samples were analyzed using liquid chromatography-tandem mass spectrometry. Patients treated with scalp cooling had lower mean (±SD) concentrations of cyclophosphamide (2100 ± 1059 vs. 2816 ± 2207 pg/5 cm) and doxorubicin (1123 ± 617 vs. 3147 ± 2017 pg/5 cm) in the hair follicles, comparing to those without scalp cooling. Lower cyclophosphamide concentrations were also associated with the success of hair preservation among those treated with scalp cooling ($P = 0.045$ for trend).

One of the limitations of this study is the usage of CarbonCool™ which is not a cooling system cleared by the FDA. Further validation studies using cooling system cleared for marketing are required to confirm the findings. In addition, we did not consider the drug regimens/doses for comparison of chemotherapy drug concentration in the hair follicles. To clarify the effects of drug regimens/doses on hair loss, future studies should evaluate how drug regimens/doses may contribute to the differentiation of chemotherapy drug concentration in the hair follicles.

Unveiling the influence of diminished quantities of chemotherapy on hair follicles can potentially allow us to understand how to improve the current status of scalp cooling delivery. In our study, we have observed a correlation between hair preservation and concentration of chemotherapy in the hair follicle. Hence, chemotherapy drug concentrations in hair follicles can serve as an objective biomarker to monitor the effectiveness of scalp cooling, allowing clinicians and patients to decide whether scalp cooling should be continued in future cycles of chemotherapy. It is also important to note that current obtaining FDA clearance of scalp cooling devices focuses on the safety and efficacy, and not requiring the manufacturer to demonstrate that reduced follicular drug uptake is associated with prevention of alopecia [11]. Hence, device approval agencies may want to demand incorporating routine monitoring of chemotherapeutic hair concentrations in future clinical trials that involve the approval of scalp cooling devices. A clear understanding of the underlying mechanism would be necessary to ensure that these expensive technologies are backed by rigorous scientific evidence.

Compliance with ethical standards

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