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RESEARCH

The use of photobiomodulation therapy for the management of chemotherapy-induced alopecia: a randomized, controlled trial (HAIRLASER trial)

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Abstract

Purpose The purpose of this trial was to evaluate if photobiomodulation (PBM) can accelerate hair regrowth after chemotherapy in breast cancer patients and if this is correlated with a better quality of life (QoL).

Methods A randomized controlled trial with breast cancer patients that underwent an anthracycline and taxane-containing chemotherapy regimen was set up at the Jessa Hospital (Hasselt, Belgium). Patients were randomized into the control group (no intervention) or the PBM group (three PBM sessions each week for 12 weeks, starting the last day of their chemotherapy). Hair regrowth was evaluated based on photographic assessments. Two blinded researchers independently scored the hair regrowth using a numerical rating scale (NRS). In addition, the QoL was measured using the European Organization for Research and Treatment-QOL questionnaire and Breast Cancer-specific module (EORTC QLQ-C30 and QLQ-BR23). Data were collected on the day of their last chemotherapy session and 1, 2, and 3 months post-chemotherapy.

Results A total of 32 breast cancer patients were included in the trial between June 2020 and February 2022. Significantly higher NRS scores were observed in the PBM group at 1-month post-chemotherapy compared to baseline, whereas they remained constant in the control group. Patients allocated to the PBM group scored their global health significantly higher at all time points compared to the control.

Conclusion Based on the results of the HAIRLASER trial, PBM seems to accelerate hair regrowth after chemotherapy in breast cancer patients resulting in an improved global health status and better body image. The study was registered in July 2019 at ClinicalTrials.gov (NCT04036994).

Keywords Chemotherapy · Alopecia · Photobiomodulation · Breast cancer · Quality of life

Introduction

Hair-matrix keratinocytes have an extremely high proliferation rate, causing hair follicles to be maximally vulnerable to chemotherapy [1]. Across the literature, hair loss consistently ranks among the most distressing and traumatic aspects of chemotherapy. It negatively influences body image, sexuality, and self-esteem. As a result, 8% of patients will reject chemotherapy if there is a risk of chemotherapy-induced alopecia (CIA) [2–6]. The overall incidence of CIA is estimated at around 65%. However, it largely depends on the type of cytotoxic agent and the number of chemotherapy administrations [4]. Although the hair loss is often reversible, it requires 3–6 months; in some cases, permanent CIA is reported [7, 8].

Diverse techniques such as scalp compression and topical minoxidil have been used in an attempt to prevent CIA, with limited success [9, 10]. Only scalp cooling, based on vasoconstriction of the scalp's blood supply to reduce the uptake of the cytotoxic agents in the hair follicles, is applied at the moment. However, scalp cooling is not effective for preventing all types of CIA with a lower efficacy for anthracycline-containing chemotherapy regimens, and it causes discomfort for the patients. In addition, despite the incidence of scalp metastases after scalp cooling is low, caution must be taken [11, 12].

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Photobiomodulation (PBM) therapy is based on the application of visible and/or (near)-infrared light, produced by laser diodes or light-emitting diodes (LED), to stimulate tissue repair and proliferation. During the very first experiments of Dr. Endre Mester with PBM, better wound healing and increased hair growth were observed when PBM was administered to rats with surgically implanted malignant melanomas [13]. Since the last decade, the treatment of androgenetic alopecia with PBM has become widely acknowledged [14–18]. In addition, research shows beneficial results for the use of PBM to treat alopecia areata [19–21]. Concerning CIA, only one in vivo study could be identified. In this study, accelerated hair regrowth was observed in the PBM-treated rats compared to the control [22]. However, the use of PBM to accelerate hair regrowth in patients with CIA has never been investigated in a clinical trial.

Since hair is an important indicator of femininity, attractiveness, and personality, loss of hair could lead to body dissatisfaction and poor post-treatment adjustment [23]. Limiting the duration of this symptom could improve the quality of life (QoL). Therefore, this randomized controlled trial aimed to evaluate the use of PBM for the management of CIA. Secondarily, the patients' QoL was assessed.

Material and methods

Study design

A prospective, randomized controlled pilot trial (HAIR-LASER trial) evaluated the effectiveness of PBM for the management of CIA in breast cancer patients post-chemotherapy. Patients were divided into a control group receiving no treatment, or a PBM group, receiving PBM. All patients received adjuvant or neoadjuvant chemotherapy at the Limburg Oncology Center (LOC, Jessa Hospital, Hasselt, Belgium). The ethics committees of the Jessa Hospital and the University of Hasselt both approved the study (B243201940887). The study was registered at ClinicalTrials.gov (NCT04036994).

Study population

Patients were eligible for inclusion if they were diagnosed with invasive breast adenocarcinoma, aged 18 years or above, received an anthracycline and taxane-containing chemotherapy regimen, had a skin type of I to IV on the Fitzpatrick Skin Type Scale, were diagnosed with grade 2 alopecia according to the Common Terminology Criteria for Adverse Events (CTCAE), and used a headgear (wig, cap, scarf, etc.) for at least 2 h a day. Exclusion criteria were a history of alopecia before the start of chemotherapy, usage of scalp cooling during chemotherapy, metastatic disease, and usage of stable doses of medication to treat alopecia (e.g., minoxidil). Patients were recruited at the oncology department of the Jessa Hospital (Hasselt, Belgium) 1 week before the end of chemotherapy. Written informed consent was obtained before the start of the study.

Randomization

Eligible patients were randomized (1:1) into a control group or PBM group. Patients were allocated based on a block randomization process, with a block size of four using a computer-generated random number list.

Intervention

Chemotherapy

Breast cancer patients were first treated with a combination of epirubicin (100 mg/m^2) and cyclophosphamide (600 mg/m^2) for four cycles, every 3 weeks, followed by a weekly administration of paclitaxel (80 mg/m^2), whether or not in combination with carboplatin (AUC of 5 mg/ml), for 12 weeks.

Photobiomodulation

Patients in the PBM group received a class 3R PBM device (Theradome® LH80 pro, CA, USA) and an instruction card to apply PBM at home. PBM was delivered three times a week for 3 months, starting the day of their last chemotherapy session. The number of completely administered PBM sessions was checked after 3 months. The laser helmet is made up of 80 red laser diodes with a wavelength of 678 nm, a continuous wave pulse duration, power of 5 mW, and fluence of 1.03 J/cm^2. Each PBM session took 20 min to cover 420 cm^2 of the scalp.

Outcome measures

Data were collected on the day of their last chemotherapy session (baseline) and 1, 2, and 3 months post-chemotherapy.

Patient data

Patient's personal, disease- and treatment-related characteristics were collected via patient questionnaires and the patient's medical records to rule out possible risk factors for developing CIA.

Alopecia

Hair regrowth was evaluated based on photographic assessments. Photographs of the bilateral sides of the head, the back, and the top of the head were taken using a Canon Power Shot SX70 HS camera system. Photographs were standardized for lighting, camera angle, and position of the participant's head. Two blinded researchers independently scored the hair regrowth using a numerical rating scale (NRS) in which 0 represents "total baldness" and 10 "full scalp coverage."

Quality of life

The patients' QoL was assessed by the standardized questionnaires of the European Organization for Research and Treatment-QLQ questionnaire and Breast Cancer-specific module (EORTC QLQ-C30 and QLQ-BR23). The EORTC QLQ-C30 comprises thirty questions on global health status, functional scales, and symptoms scales. The QLQ-BR23 module exists of 23 breast cancer-specific questions comprising four functional and four symptom scales. For the purposes of the current study, five subscales were considered relevant, including global health status, emotional functioning, social functioning, body image, and sexual functioning. The score for each subscale was calculated according to the guidelines ranging from 0 to 100 [24, 25]. For a functional scale or the global health status, a higher score indicates a more healthy level of functioning and better QoL, respectively. In contrast, a higher score for a symptom subscale indicates more severe symptoms.

Statistical analysis

SAS 9.4 (NC, USA) was used to perform statistical analysis. Patient and therapy–related characteristics were analyzed by performing a Mann–Whitney *U* test, Fisher's exact test, and Pearson chi-square test, as appropriate. All primary and secondary endpoints were analyzed by an independent statistician of the Center for Statistics (CenStat) at Universiteit Hasselt by a linear mixed model when the assumption of normality and homogeneity was reached. Alternatively, generalized estimating equation models were used to compare the primary and secondary endpoints. Here, an outcome variable was re-coded to a binary variable with the value "0" if the original variable is "0" and "1" otherwise. The level of significance was set assuming a significance level of 5% ($P < 0.05$, two-tailed). The Holm-Bonferroni correction was applied for multiple comparisons.

Results

A total of 128 breast cancer patients were assessed on eligibility between June 2020 and February 2022. Seventeen patients were randomized to the control group and 15 patients to the PBM group (Fig. 1). There were no significant differences between the demographic, disease-, and treatment-related data between the two groups, except for prescribed hormonal therapy (Table 1).

Primary endpoint

The primary endpoint of this trial was a significant difference in NRS score over time in the PBM group. At 1 month post-chemotherapy, significantly higher scores in NRS were observed compared to baseline in the PBM group, whereas they remained constant in the control group (Table 2). However, at 2 and 3 months post-chemotherapy, significantly higher scores were observed compared to baseline in the PBM group, as well as in the control group.

Secondary outcome

Table 3 demonstrates the progression of the QoL of the patients during the trial. The subscale "sexual enjoyment" and "upset by hair loss" could not be analyzed since there were numerous missing values for those questions or were irrelevant. The subscales considered relevant for the purpose of the current trial are emphasized in bold. During all timepoints post-chemotherapy, significantly higher scores in global health status and body image were observed in the PBM group, whereas they remained constant in the control group. In addition, patients allocated to the PBM group scored their global health significantly higher at all time points compared to patients allocated to the control group ($Ps \leq 0.04$, data not shown). Emotional functioning significantly worsened in the control group 1 month after the end of chemotherapy whereas this was not the case in the PBM group. For social functioning, significantly higher scores were observed at 2 and 3 months post-chemotherapy in the PBM group compared to baseline, whereas the control group only showed a significantly higher score at 3 months post-chemotherapy. Sexual functioning improved significantly 2 months after the end of chemotherapy in the PBM group but remained stable in the control group.

Although less relevant for this trial, other significant differences could be observed in the EORT-QLQ C30 and BR23 questionnaires. Physical- and role functioning was significantly better in the PBM group 1 month after chemotherapy which could not be detected in the control group. In addition,

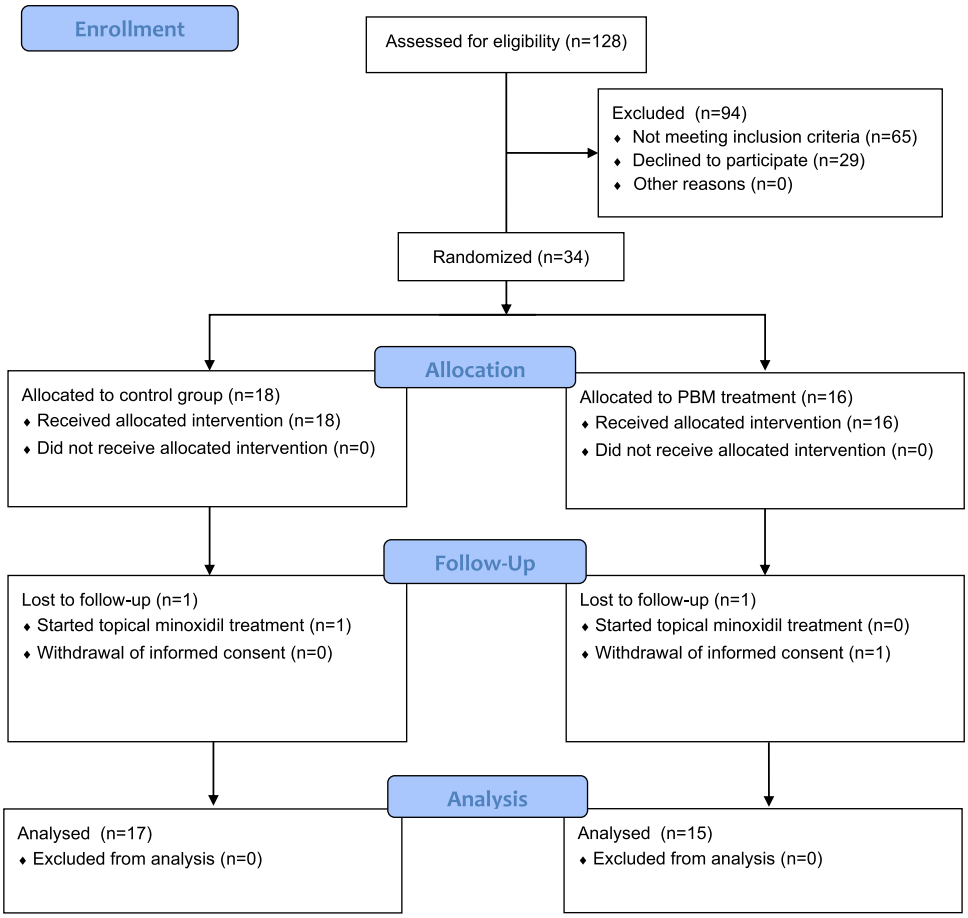

Fig. 1 Flowchart. PBM, photobiomodulation

significantly lower scores for insomnia were observed at 2 months, and significantly higher scores for future perspectives at 3 months post-chemotherapy in the PBM group. At all time points, no significant differences could be identified for those subscales in the control group. At 2 months post-chemotherapy, significant deterioration in arm symptoms was observed in the control group but remained stable in the PBM group.

The odds of developing gastrointestinal symptoms such as nausea, vomiting, and appetite loss were significantly lower in the control group at nearly all time points compared to baseline but did not change in the PBM group. In addition, dyspnea improved 3 months after the end of chemotherapy compared to baseline in the control group whereas this was not the case in the PBM group. Lastly, the odds of developing breast symptoms at 1, 2, and 3 months post-chemotherapy compared to baseline were significantly higher in the PBM group but remained constant in the control group.

Discussion

To our knowledge, this is the first prospective, randomized controlled pilot trial that demonstrates that PBM has the potential to accelerate hair regrowth after chemotherapy. Based on the photographic assessment, significantly better hair regrowth is observed in the PBM group at 1, 2, and 3 months after chemotherapy compared to baseline, whereas it took at least 2 months to observe significant hair regrowth in the control group. Since scalp hair is associated with social status, femininity, attractiveness, and personality, this accelerated hair regrowth is also reflected in the patient's QoL. Patients allocated to the PBM group had significantly better scores regarding their global health status, body image, and social-, sexual-, physical-, and role functioning at several time points compared to baseline. Insomnia and the future perspectives improved significantly in the PBM group at 2 and 3 months, respectively.

Remarkably, the risk for developing dyspnea and gastrointestinal symptoms such as nausea, vomiting, and appetite loss was significantly lower in the control group, whereas this was not the case in the PBM group. According to the literature, none of these side effects can be linked to PBM [26]. These symptoms could, therefore, be explained by the fact that significantly more patients in the PBM group received adjuvant hormonal therapy during the trial, which can cause dyspnea and gastrointestinal side effects, compared to the control group [27, 28]. Similarly, patients allocated to the PBM group had a significantly greater risk of developing

Table 1 Patient characteristics

	Control group ($n=17$)		PBM group ($n=15$)		
	Median ± IQR				P^a
Demographics					
Age	50.81 (32.50)		50.00 (11.00)		0.69
BMI	24.39 (5.87)		24.17 (4.51)		0.51
	n	%	*n*	%	P^b
Skin type					0.51
II	1	5.88	2	13.33	
III	7	41.18	6	40.00	
IV	7	41.18	7	46.67	
Unknown	2	11.76	0	0.00	
Menopause before cancer diagnosis					0.24
Yes	7	41.18	9	60.00	
No	10	58.82	6	40.00	
Smoking					0.364
Current	4	23.53	1	6.67	
Former	3	17.65	5	33.34	
Never	9	52.94	9	60.00	
Unknown	1	5.88	0	0.00	
Disease-related					
Tumor location					0.72
Left	6	35.29	7	46.67	
Right	11	64.71	8	53.33	
Tumor type					1.00
Invasive lobular adenocarcinoma	1	5.88	1	6.67	
Invasive ductal adenocarcinoma	16	94.12	14	93.33	
T-stage					0.44
1	3	17.65	2	13.33	
2	11	64.71	8	53.33	
3	1	5.88	4	26.67	
4	2	11.76	1	6.67	
N-stage					0.43
0	12	70.59	8	44.44	
1	4	23.53	4	26.67	
2	0	0.00	0	0.00	
3	1	5.88	3	20.00	
Prognostic factors†					
Estrogen positive	6	35.29	10	66.67	0.08
Progesterone positive	5	29.41	7	46.67	0.26
Excess HER2 protein	5	29.41	7	46.67	0.26
Triple-negative	9	52.94	3	20.00	0.06
Start hair loss					0.63
< 1 week after initiation CT	0	0.00	1	6.67	
1–2 weeks after initiation CT	9	52.94	6	40.00	
2–3 weeks after initiation CT	6	35.29	7	46.67	
3–4 weeks after initiation CT	1	5.88	1	6.67	
Unknown	1	5.88	0	0.00	
Therapy-related					
Type of chemotherapy					0.18

Table 1 (continued)

	Control group ($n=17$)		PBM group ($n=15$)		
		Median ± IQR		P^a	
Epirubicin and cyclophosphamide + paclitaxel	10	58.82	12	80.00	
Epirubicin and cyclophosphamide + paclitaxel and carboplatin	7	41.18	3	20.00	
Timing chemotherapy					0.44
Adjuvant	2	11.76	3	20.00	
Neoadjuvant	15	88.24	12	80.00	
Surgery					0.24
Lumpectomy	10	58.82	6	40.00	
Mastectomy	7	41.18	9	60.00	
Hormonal therapy					0.03*
Tamoxifen	1	5.88	6	40.00	
Aromatase inhibitor	5	29.41	5	33.33	
None	11	64.71	4	26.67	
Targeted therapy (trastuzumab)					0.27
Yes	4	23.53	6	40.00	
No	13	76.47	9	60.00	
Radiotherapy					0.25
Yes	16	94.12	12	80.00	
No	1	5.88	3	20.00	

BMI, body mass index; *PBM*, photobiomodulation; *IQR*, interquartile range; *CT*, chemotherapy. †The percentages may not add up to 100% due to combinations of prognostic factors. [a]Mann-Whitney *U* test (two-tailed), [b]chi-square tests (two-tailed), or Fisher's exact tests, as appropriate (two-tailed), *statistically significant

breast symptoms such as swollen or oversensitive breasts, while this was not the case in the control group. Although not significant, a higher proportion of patients allocated to the PBM group received a mastectomy (60%) compared to the control group (41.18%), which could explain these results.

A meta-analysis of 2021 investigating the use of PBM for the treatment of androgenetic alopecia observed a significant increase in hair density (hairs/cm^2) in patients treated with laser diodes or LEDs compared to control ($P<0.00001$). In addition, this meta-analysis identified no significant difference between the two device types, comb-style versus helmet/hat style ($P=0.08$) [18]. Unlike androgenetic alopecia, there is limited data regarding PBM for alopecia areata. An in vivo study from 2012 demonstrated increased anagen hair follicles based on histologic assessment in laser-treated mice, which was not the case in the sham-treated mice [21]. Additionally, one study successfully elicited hair regrowth in 7 out of 15 patients suffering from alopecia areata when using PBM ($P=0.003$) [19]. Regarding the use of PBM for the management of CIA, only one in vivo study could be identified. In this trial, a rat model for the CIA was used. The rats were randomized to receive only chemotherapy (control group, $n=10$), chemotherapy, and PBM (1 min daily for 10 days with a wavelength of 655 nm and beam diameter < 5 mm, $n=10$), or chemotherapy and sham ($n=10$). It was demonstrated that rats receiving PBM regrew hair 5 days earlier than rats receiving chemotherapy alone or a

Table 2 Numerical rating scale (NRS) for hair regrowth

	Control group				PBM group			
	Estimate	95% CI	SE	P^a	Estimate	95% CI	SE	P^a
1 month	0.56	−0.15, 1.27	0.36	0.12	1.15	0.40, 1.90	0.38	0.0036*
2 months	3.59	2.78, 4.40	0.36	<0.0001*	4.37	3.51, 5.23	0.38	<0.0001*
3 months	6.49	5.61, 7.37	0.37	<0.0001*	6.78	5.87, 7.70	0.38	<0.0001*

PBM, photobiomodulation; *CI*, confidence interval; *SE*, standard error. [a]Linear mixed model; *statistically significant using the Holm-Bonferroni correction

Table 3 Quality of life. Comparison of quality of life using the European Organization for Research and Treatment-QLQ questionnaire and Breast Cancer-specific module (EORTC QLQ-C30 and QLQ-BR23) questionnaire between baseline and 1, 2, and 3 months post-chemotherapy for the control group ($n=17$) and PBM group ($n=15$). Changes from baseline in the EORTC QLQ-C30 and QLQ-BR23 were determined using linear mixed models or generalized estimating equation models as appropriate. A positive estimated intercept indicates a higher score for the respective assessment time point compared to the baseline. An odds ratio greater than one indicates an increased risk for a higher score for the respective assessment time point compared to the baseline. For a functional scale or the global health status, a higher score indicates a more healthy level of functioning and better QoL, respectively. In contrast, a higher score for a symptom subscale indicates more severe symptoms

			Control group				PBM group			
			Estimate	95% CI	SE	P^a	Estimate	95% CI	SE	P^a
EORTC-QLQ30	Global health status[c]	1 month	1.83	−6.21, 9.87	4.10	0.66	8.44	0.56, 16.33	4.02	0.04*
		2 months	7.48	−1.35, 16.31	3.94	0.06	18.10	8.65, 27.55	4.22	<0.0001*
		3 months	9.68	0.17, 19.19	3.98	0.02	18.75	8.67, 28.83	4.22	<0.0001*
	Physical functioning[c]	1 month	7.37	−2.15, 16.89	4.86	0.13	10.99	1.67, 20.31	4.76	0.02*
		2 months	14.28	3.83, 24.73	4.66	<0.01*	17.25	6.07, 28.43	4.99	0.001*
		3 months	22.91	11.67, 34.15	4.70	<0.0001*	21.11	9.18, 33.04	4.99	<0.0001*
	Role functioning[c]	1 month	13.47	−0.84, 27.79	7.30	0.07	14.76	0.74, 28.78	7.16	0.04*
		2 months	25.82	10.11, 41.54	7.02	<0.001*	26.84	10.03, 43.66	7.51	<0.001*
		3 months	32.68	15.77, 49.60	7.08	<0.0001*	32.08	14.14, 50.02	7.51	<0.0001*
	Emotional functioning[c]	1 month	−10.92	−20.06, −1.79	3.82	<0.01*	3.19	−4.13, 10.51	3.73	0.40
		2 months	0.079	−7.11, 7.27	3.67	0.98	3.87	−4.92, 12.66	3.93	0.33
		3 months	−1.65	−9.92, 6.63	3.69	0.66	6.17	−3.21, 15.55	3.93	0.12
	Cognitive functioning[c]	1 month	2.25	−5.99, 10.50	4.21	0.59	1.61	−6.44, 9.66	4.11	0.70
		2 months	4.93	−4.11, 13.96	4.03	0.23	6.63	−3.04, 16.30	4.32	0.13
		3 months	5.92	−3.80, 15.63	4.07	0.15	8.87	−1.45, 19.19	4.32	0.04
	Social functioning[c]	1 month	7.85	−6.36, 22.06	7.25	0.28	6.84	−7.10, 20.78	7.11	0.34
		2 months	14.80	−1.11, 30.72	7.10	0.04	20.40	2.61, 38.20	7.45	0.01*
		3 months	18.98	2.18, 35.78	7.03	<0.01*	17.02	0.33, 33.70	7.45	0.03*
	Fatigue[d]	1 month	−25.00	−36.47, −13.54	5.85	<0.0001*	−21.04	−32.25, −9.84	5.72	<0.001*
		2 months	−31.21	−44.05, −18.38	5.73	<0.0001*	−23.73	−37.17, −10.29	6.00	<0.001*
		3 months	−32.28	−45.80, −18.76	5.66	<0.0001*	−26.48	−40.82, −12.14	6.00	<0.0001*
	Insomnia[d]	1 month	13.57	−4.47, 31.62	7.55	0.08	−13.88	−28.40, 0.65	7.41	0.06
		2 months	0.15	−14.36, 14.65	7.40	0.98	−21.70	−40.24, −3.16	7.76	0.01*
		3 months	−4.62	−21.02, 11.79	7.32	0.53	−17.32	−34.70, 0.05	7.76	0.03

Table 3 (continued)

			Control group				PBM group			
BR-23	Body image[c]	1 month	1.63	−9.70, 12.97	5.78	0.78	18.73	5.22, 32.23	5.65	<0.001*
		2 months	10.98	−1.44, 23.41	5.55	0.05	13.76	0.46, 27.06	5.94	0.02*
		3 months	11.18	−2.18, 24.55	5.59	0.05	13.62	1.98, 25.26	5.94	0.02*
	Sexual functioning[c]	1 month	3.04	−5.03, 11.12	4.12	0.46	8.66	−0.68, 18.00	4.17	0.04
		2 months	6.71	−2.16, 15.57	3.96	0.09	12.30	1.66, 22.95	4.45	0.01*
		3 months	8.24	−1.31, 17.79	3.99	0.04	4.55	−4.18, 13.28	4.45	0.31
	Future perspective[c]	1 month	−2.24	−14.10, 9.62	6.05	0.71	8.12	−3.50, 19.73	5.93	0.17
		2 months	3.95	−9.06, 16.97	5.81	0.50	9.12	−4.81, 23.05	6.22	0.15
		3 months	7.91	−6.10, 21.92	5.86	0.18	16.47	1.61, 31.34	6.22	0.01*
	Systemic therapy side effects[d]	1 month	−14.40	−21.30, −7.51	3.52	0.0001*	−13.85	−21.58, −6.13	3.45	0.0001*
		2 months	−19.18	−26.75, −11.61	3.38	<0.0001*	−13.91	−21.11, −6.72	3.67	<0.001*
		3 months	−21.83	−29.98, −13.69	3.41	<0.0001*	−15.94	−24.59, −7.30	3.62	<0.0001*
	Arm symptoms[d]	1 month	4.75	−7.82, 17.32	5.61	0.40	4.89	−5.87, 15.66	5.49	0.38
		2 months	14.12	1.24, 27.00	5.39	0.01*	8.65	−4.27, 21.57	5.77	0.14
		3 months	4.51	−6.14, 15.16	5.43	0.41	8.99	−4.79, 22.77	5.77	0.12
			OR	95% CI		P^b	OR	95% CI		P^b

Table 3 (continued)

			Control group			PBM group		
EORTC-QLQ30	Nausea/vomiting[d]	1 month	0.29	0.09, 0.88	0.03*	0.13	0.01, 1.41	0.04
		2 months	0.10	0.02, 0.52	<0.01*	0.30	0.06, 1.41	0.08
		3 months	0.13	0.03, 0.62	0.002*	0.78	0.27, 2.26	0.65
	Pain[d]	1 month	2.36	0.40, 13.77	0.28	0.83	0.19, 3.60	0.80
		2 months	2.70	0.51, 14.45	0.16	1.55	0.44, 5.45	0.40
		3 months	0.98	0.42, 2.30	0.97	0.80	0.19, 3.34	0.73
	Dyspnea[d]	1 month	0.49	0.18, 1.29	0.15	0.96	0.30, 3.03	0.94
		2 months	0.39	0.13, 1.16	0.05	0.65	0.21, 2.04	0.37
		3 months	0.19	0.04, 0.87	<0.01*	0.65	0.15, 2.87	0.51
	Appetite loss[d]	1 month	0.38	0.10, 1.42	0.15	0.51	0.11, 2.25	0.28
		2 months	0.27	0.07, 0.98	0.02*	0.76	0.26, 2.21	0.62
		3 months	0.11	0.02, 0.65	0.003*	0.56	0.10, 3.17	0.46
	Constipation[d]	1 month	1.00	0.35, 2.85	0.99	1.14	0.26, 4.98	0.86
		2 months	1.02	0.26, 3.92	0.98	0.49	0.10, 2.37	0.31
		3 months	1.81	0.51, 6.40	0.26	0.23	0.01, 3.61	0.20
	Diarrhea[d]	1 month	0.36	0.11, 1.20	0.06	0.39	0.05, 2.83	0.29
		2 months	0.48	0.19, 1.17	0.11	0.71	0.09, 5.79	0.75
		3 months	0.31	0.10, 1.02	0.02	0.44	0.10, 2.00	0.20
	Financial difficulties[d]	1 month	1.35	0.84, 2.15	0.13	1.44	0.60, 3.42	0.35
		2 months	1.53	0.49, 4.76	0.41	1.42	0.65, 3.12	0.38
		3 months	0.75	0.36, 1.56	0.44	2.20	0.67, 7.23	0.11
BR-23	Breast symptoms[d]	1 month	1.65	0.45, 6.11	0.39	4.80	1.04, 22.20	0.04*
		2 months	3.33	0.59, 18.67	0.10	7.92	1.51, 41.69	<0.01*
		3 months	1.71	0.46, 6.34	0.42	8.48	1.06, 67.64	0.02*

PBM, photobiomodulation; *CI*, confidence interval; *SE*, standard error; *OR*, odds ratio. [a]Linear mixed model, [b]generalized estimating equation models (with the value "0" if the original variable is "0" and "1" otherwise), *statistically significant using the Holm-Bonferroni correction, [c]higher score is better, [d]lower score is better

sham treatment, without compromising the efficacy of chemotherapy ($P < 0.01$) [22].

Although increasing evidence suggests PBM could be used to manage hair loss, the molecular mechanism behind these results remains unclear. According to an in vivo study by Jin et al., PBM triggers a new hair cycle by upregulating β-CATENIN expression in hair follicle stem cells. However, to explore the effect of PBM on the hair cycle, old mice were used during this trial to mimic hair loss instead of a model with CIA [29].

During the current HAIRLASER trial, a home-based device was used to improve the comfort of the patients. Furthermore, by using a PBM helmet instead of a labor-intensive hair comb, the discomfort is diminished as much as possible. A few limitations of the present study need to be addressed. Patients allocated to the PBM group needed to wear the device three times a week. Although the total amount of completed PBM sessions was registered and checked at the last study visit, there was no control over who used the helmet and when. In future studies, this could be improved by registering the number of PBM sessions at each study visit. Next, during this trial, we had no information regarding the patients' premorbid hair density, which could be masked by the chemotherapy treatment. Furthermore, the EORTC questionnaire, as well as the NRS, lack objectivity. A more objective method to access CIA includes trichoscopy. During trichoscopy, a dermoscopic image of the scalp and hair is made and analyzed with a manual dermoscope. However, for this procedure, the hair must be clipped even throughout the image [30, 31]. Another important limitation might be the small sample size. Of all eligible patients, almost half of them (46%) declined to participate in the trial. The main reason for the low adherence rates is the additional demand that study protocol puts on the patient during an already burdensome period. In addition, other factors such as transport problems and the COVID pandemic played a role in the study participation. Lastly, significantly more patients allocated to the PBM group received tamoxifen compared to the control group. Reduced estrogenic effects due to tamoxifen enable the hair follicle to go into the resting phase, inducing hair loss and hair thinning [32]. According to a study by Saggar et al., alopecia occurs in 9.3% of patients receiving tamoxifen [33]. This unfortunate disbalance could mask the effect of PBM. We, therefore, recommend stratifying the patients on their prescribed hormonal therapy in future follow-up trials.

Conclusion

Despite the small sample size, the HAIRLASER trial reported promising results concerning the management of CIA with PBM in breast cancer patients. Hair regrowth was accelerated in the PBM group by 1 month compared to control. This resulted in significantly higher scores regarding their global health and body image, whereas they remained stable in the control group. However, larger randomized controlled trials with emphasis on endocrine therapy, other types of cancer patients, and a wider variety of chemotherapy regimens are necessary to support these findings.

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Data availability Not applicable.

Code availability Not applicable.

Declarations

Ethics approval This research is approved by the ethics committees of the Jessa Hospital and the University of Hasselt (B243201940887).

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Consent to participate Informed consent was obtained from all individual participants included in the study.

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