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ORIGINAL ARTICLE

Scalp cooling for hair loss prevention in female Japanese breast cancer patients receiving (neo)adjuvant chemotherapy

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Abstract

Purpose Scalp cooling during chemotherapy infusion has been recently reported to have moderate efficacy in the mitigation of chemotherapy-induced alopecia; however, there are few reports on Asian patients. We aimed to clarify the effects of scalp cooling in Japanese women.

Patients and methods Female Japanese breast cancer patients who planned to receive (neo)adjuvant chemotherapy participated in this prospective study on the efficacy of scalp cooling using the Paxman Scalp Cooling System for alopecia prevention. The primary outcomes were the rates of patients with Grade 3 alopecia (defined as hair loss of > 50%) and the rates of patients who used a wig or hat to conceal hair loss 1 month after the last infusion of chemotherapy. The subjects were given a brief questionnaire regarding headaches, bad mood, fatigue, and chills shortly after each cooling.

Results One hundred and forty-three patients participated in the study and used the cooling cap at least once. The mean and median ages of the subjects were 50.6 and 50, respectively (age range 28–76). One hundred and twenty-nine patients completed the planned chemotherapy of 4 to 8 cycles. Among them (7 patients were not evaluable), 74 patients (60.7%) had Grade 3 alopecia 1 month after chemotherapy. Of 80 patients who used the scalp cooling system throughout the planned chemotherapy (1 patient was not evaluable), 36 patients (45.6%) experienced Grade 3 alopecia.

Conclusion The efficacy of scalp cooling during chemotherapy infusion for hair loss mitigation in Asian women is similar to that in Caucasian women.

Keywords Scalp cooling · Hair loss prevention · Breast cancer · Asian women · Chemotherapy

Introduction

Hair loss can be considered one of the most distressing side effects for breast cancer patients who are receiving chemotherapy [1]. Chemotherapy-induced alopecia (CIA) is sometimes permanent, and almost all breast cancer patients are female; therefore, CIA should be considered a serious problem especially in breast cancer patients.

The efficacy of scalp cooling during chemotherapy infusion to mitigate CIA has been reported [2]. Recently, new types of devices to cool the scalp have been shown to be useful with moderate efficacy in prospective studies [3, 4]. However, data on scalp cooling have been mostly obtained from Caucasian patients, and data from Asian patients are few.

We performed a prospective study to examine the efficacy and safety of the use of one of these devices, the Paxman Scalp Cooling System (PAXMAN), in Japanese breast cancer patients in an adjuvant or neoadjuvant chemotherapy setting.

Patients and methods

Female Japanese breast cancer patients who planned to receive (neo)adjuvant chemotherapy participated in this prospective study on scalp cooling with PAXMAN for CIA prevention at

This study was registered to UMIN-CTR, numbered UMIN000017657, on June 1, 2015.

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the National Hospital Organization Shikoku Cancer Center. Patients who had Raynaud's disease or Raynaud's phenomena, cold agglutinin disease, cryoglobulinemia, or cryofibrinogenemia, or those who needed a wig for alopecia prior to chemotherapy, were excluded. The patients were enrolled in the study between June 2015 and March 2018.

The scalp cooling was done 30 min prior to and during and 90 min after each chemotherapy infusion. Photographs of the head of the participants were taken from 5 directions, namely, the front, back, both sides, and top, on the day (Day 1) of each chemotherapy infusion and 1 month after the last infusion, and they were asked whether they used a wig or hat to conceal the hair loss using a brief questionnaire and requested to select one of the following, not at all, sometimes, and almost always, 1 month after the last infusion of chemotherapy. Two investigators, comprising a physician (SO) and a nurse (MD), judged the grade of alopecia by looking at the photographs and using the WHO classification while blind to the level of scalp cooling. The primary outcomes were the rates of patients with Grade 3 alopecia (defined as hair loss of > 50%) and the rates of patients who used a wig or hat to conceal the hair loss 1 month after the last infusion of chemotherapy. The subjects were also asked to answer the other brief questionnaire regarding headaches, bad mood, fatigue, and chills by rating each symptom on a 4-point Likert scale as none, mild, moderate, severe, or others shortly after each scalp cooling. Although they could use the cooling cap for free on the first cycle of chemotherapy, they were required to purchase it (about US$ 1130) for the scalp cooling of the following cycles.

One hundred and fifty patients were planned to be registered due to the reason shown below. According to previous reports, the rate of Grade 3 or more hair loss or use of a wig after scalp cooling was estimated to be around 20%. Based on this assumption, 130 patients would be needed to show if it is less than 30% with a one-side *P* value of 0.05 and a power of detection of 80%. Twenty patients were expected to drop out.

Table 1 Characteristics of the patients and diseases and chemotherapeutic regimens in the evaluable patients who completed the chemotherapy ($n = 122$)

Age	Mean 49.9 (range 28–71)	Median 49
Clinical or pathological stage	Stage I	44
	Stage IIA	34
	Stage IIB	16
	Stage IIIA	13
	Stage IIIB	3
	Stage IIIC	5
	Unknown	7
Estrogen receptor status	Positive	81
	Negative	41
Progesterone receptor status	Positive	69
	Negative	53
HER2 status	Positive	26
	Negative	96
Timing of chemotherapy	Preoperative	14
	Postoperative	108
Chemotherapy regimen	TC (DTX + CPM) × 4	84
	AC or EC × 4 followed by taxane × 4	34
	EC × 4	1
	DTX × 4	1
	DTX × 6	1
	(DTX + CBDCA) × 4 followed by T-DM1 × 4	1

DTX docetaxel, *CPM* cyclophosphamide, *CBDCA* carboplatin

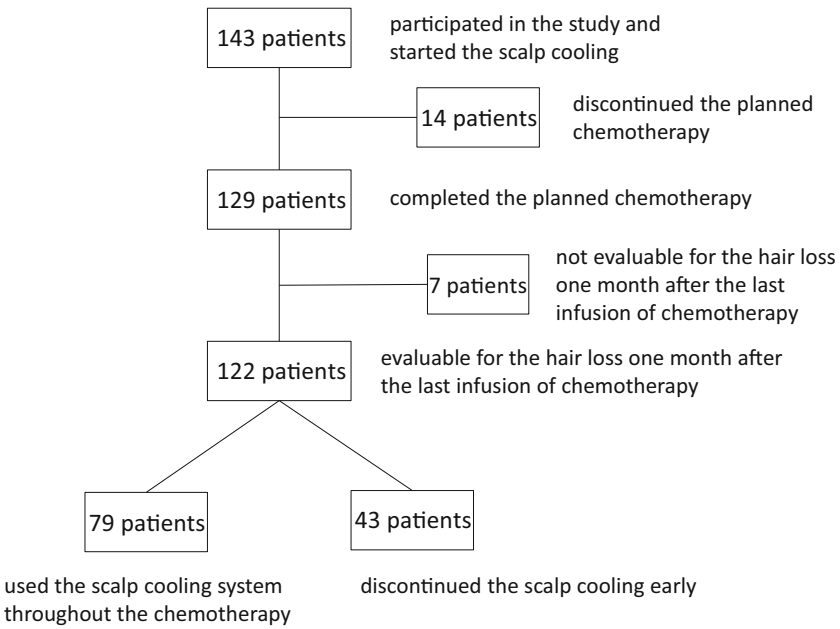

Fig. 1 Flow diagram of the patients

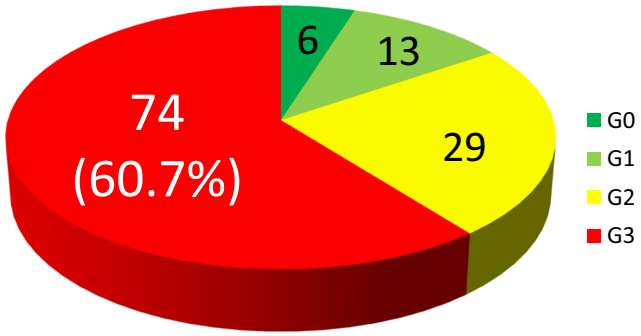

Fig. 2 Grades of hair loss 1 month after the last infusion of chemotherapy in the evaluable patients who completed the planned chemotherapy ($n = 122$)

The Chi-square test was used for the statistical analyses, and P values of < 0.05 were considered significant.

This study was approved by the ethical committee of the National Hospital Organization Shikoku Cancer Center in May 2015 and registered to UMIN-CTR, numbered UMIN000017657, on June 1, 2015.

Results

One hundred and forty-three patients participated in the study, and all used the cooling cap at least once. Written informed consent was obtained from all the participants. The mean and median ages were 50.6 and 50, respectively (age range 28–76). One hundred and twenty-nine patients completed the planned chemotherapy of 4 to 8 cycles, and 122 patients (94.6%) were evaluable for hair loss (Fig. 1). The following data are those of the 122 evaluable patients. Table 1 shows characteristics of the patients and diseases and chemotherapeutic regimens. Of these patients, 74 patients (60.7%) had Grade 3 alopecia 1 month after chemotherapy (Fig. 2).

Of the 79 patients who used the scalp cooling system throughout the planned chemotherapy, 36 patients (45.6%) experienced Grade 3 alopecia. On the other hand, of the 43 patients who discontinued the cooling mostly after the 1st cycle, 38 (88.3%) had Grade 3 alopecia (Fig. 3). Restricting the data to the 28 patients who decided to discontinue the cooling by Day 10 of the first cycle of chemotherapy to exclude the patients who discontinued it because of a lower effect on alopecia prevention than they expected, 25 (89.3%) experienced Grade 3 alopecia (Fig. 4). Comparing the results of those who completed the cooling and patients who decided to discontinue it by Day 10 of the first cycle, the rates of Grade 3 alopecia (45.6% vs. 89.3%) were significantly lower in the former ($P < 0.001$).

Most patients received one of two regimens, namely, 4 cycles of docetaxel and cyclophosphamide (TC) (84 patients, 68.9%) and 4 cycles of anthracycline and cyclophosphamide (AC or EC) followed by 4 cycles of taxane (34 patients, 27.9%). When the results of hair loss mitigation between the two regimens were compared, the rate of Grade 3 hair loss after TC × 4 was significantly higher than that after AC or EC × 4 followed by taxane × 4 (67.9% vs. 44.1%, $P = 0.017$) (Fig. 5). We compared the rates of patients who completed the scalp cooling between the two regimen groups, but there was no significant difference (66.7% vs. 61.8%, $P = 0.40$) (Fig. 6). Among the patients who completed the scalp cooling throughout the chemotherapy, distributions of the patients in each grade are shown in TC × 4 and AC or EC × 4 followed by taxane × 4 groups separately in Fig. 7.

All the participants but one answered the question regarding the use of a wig or hat 1 month after the last infusion. Their answers were "not at all" in three, "sometimes" in 13, and "almost always" in 105, respectively (Fig. 8).

Most patients complained of some headaches, bad mood, fatigue, and chills (Fig. 9), but these symptoms were relatively mild, except for chills, and self-limited. Fifty-four patients had pain of the jaw, mainly due to the strap around the jaw which was used to make the cooling cap fit the scalp more tightly.

Discussion

Adjuvant or neoadjuvant chemotherapy has been one of standard primary treatments for patients with operable breast cancer, especially high-risk patients, because it has been shown to

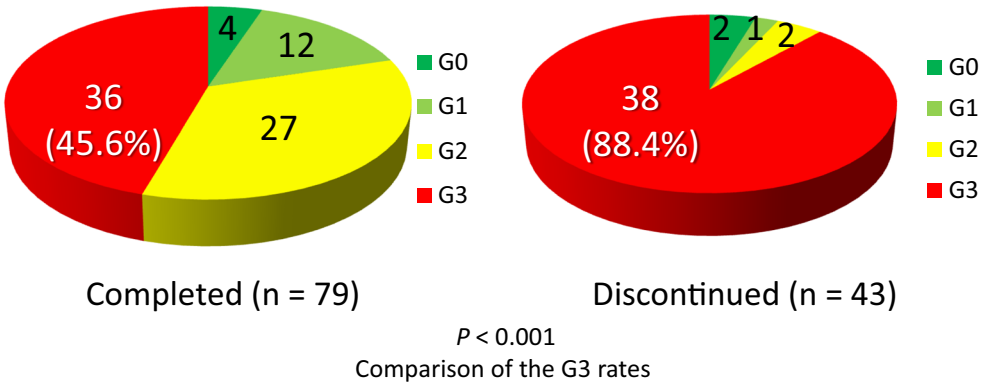

Fig. 3 Grades of hair loss 1 month after the last infusion of chemotherapy in the evaluable patients who completed the planned chemotherapy. Comparison between the patients who completed the scalp cooling for the entire cycles ($n = 79$) and those who discontinued it ($n = 43$)

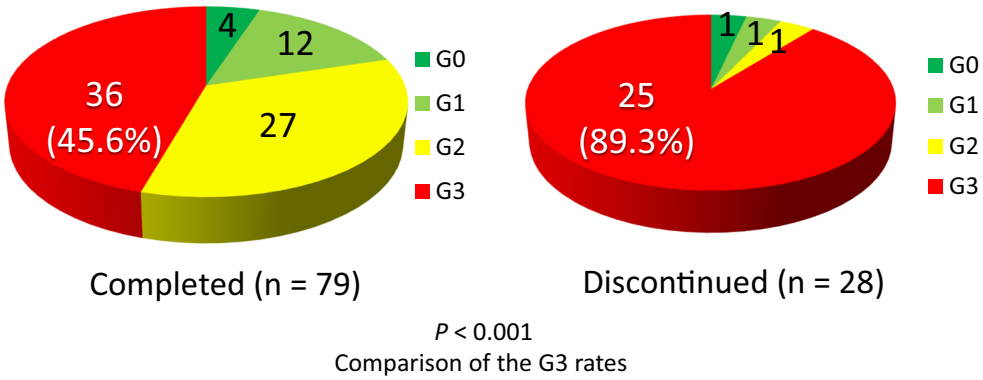

Fig. 4 Grades of hair loss 1 month after the last infusion of chemotherapy in the evaluable patients who completed the planned chemotherapy. Comparison between the patients who completed the scalp cooling for the entire cycles ($n = 79$) and those who discontinued it by Day 10 of the first cycle ($n = 28$)

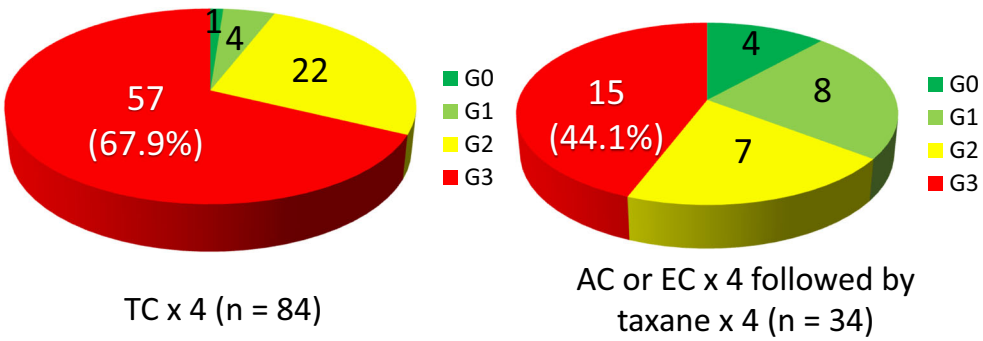

Fig. 5 Grades of hair loss 1 month after the last infusion of chemotherapy in the evaluable patients who completed the planned chemotherapy. Comparison between patients who received TC × 4 ($n = 84$) and those who received AC or EC × 4 followed by taxane × 4 ($n = 34$)

improve their prognosis in many randomized controlled trials and meta-analyses of them [5–7]. The essential chemotherapeutic agents used in an adjuvant or neoadjuvant setting in breast cancer are anthracyclines and/or taxanes. Both agents cause severe hair loss at almost 100%, and thus, one of the most distressing side effects of chemotherapy. Although some genetic assays, such as OncotypeDX®, are usable to identify hormone receptor positive breast cancer patients who do not need adjuvant chemotherapy [8], many patients are still recommended to have adjuvant or neoadjuvant chemotherapy. If CIA can be mitigated, breast cancer patients who are candidates for chemotherapy may more readily accept this treatment.

The idea of using scalp cooling to prevent CIA is relatively old. Possible mechanisms are as follows: scalp cooling constricts the blood vessels in the scalp, then the blood flow in the scalp decreases, and scalp cooling lowers the metabolism of cells in the hair follicles. Both decreased blood flow and lowered metabolism reduce uptake of chemotherapeutic agents by the hair follicle cells [9, 10]. As a result, CIA may be prevented.

So-called "cold caps" without any mechanical devices, such as the "Penguin Cold Cap," have long been used for

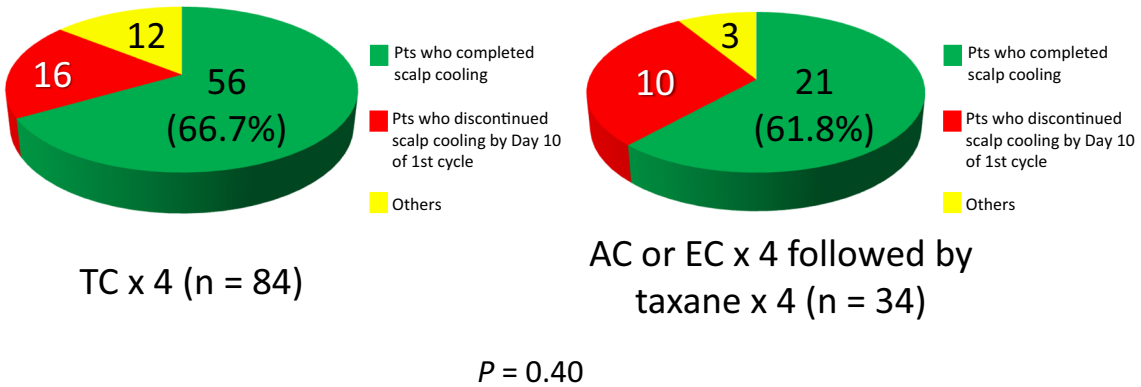

Fig. 6 Rates of patients who completed the scalp cooling and those who discontinued it by Day 10 of the first cycle. Comparison between patients who received TC × 4 ($n = 84$) and those who received AC or EC × 4 followed by taxane × 4 ($n = 34$)

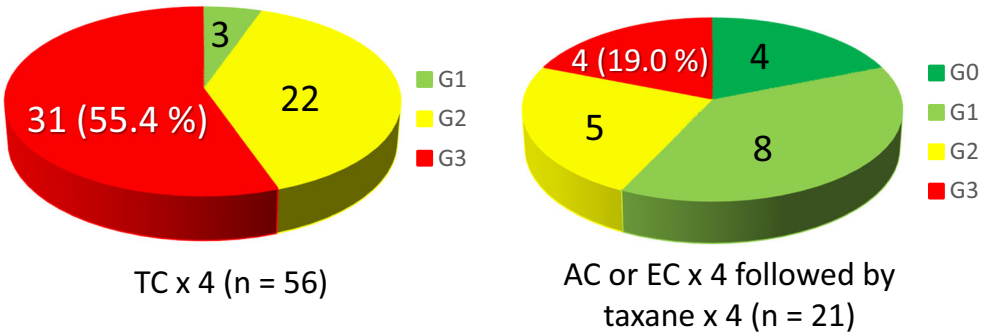

Fig. 7 Grades of hair loss 1 month after the last infusion of chemotherapy in the evaluable patients who completed both the planned chemotherapy and the scalp cooling throughout the chemotherapy in TC × 4 ($n = 56$) and AC or EC × 4 followed by taxane × 4 ($n = 21$) groups

CIA prevention [9–12], and they have been shown to be effective. However, it is necessary to change the caps almost every 30 min, and they are extremely cold. On the other hand, new types of scalp cooling systems with cooling devices like PAXMAN are easy to use and not too cold. Data for new cooling systems have been reported recently [3, 4], and the effects of mitigation of CIA are similar between the old and new cooling methods [13].

Rugo et al. performed a prospective multicenter study in which DIGNICAP, another new scalp cooling system, was used to examine the hair loss mitigation effect in 106 women with stage I or II breast cancer and compare the results to the control group in which 16 patients did not use DIGNICAP and were matched in terms of age and chemotherapy regimen [4]. The rate of hair loss less than 50%, 4 weeks after the end of chemotherapy, which was the primary endpoint, was 66.3% in the study group and 0% in the control group ($P < 0.001$).

On the other hand, Nangia et al. conducted a multicenter prospective randomized study to investigate the effect of hair loss prevention by PAXMAN in breast cancer patients in an adjuvant or neoadjuvant setting [3]. Forty-eight (50.5%) of 95 patients in the cooling cap group showed hair loss less than 50% after 4 cycles of chemotherapy, whereas no patient (0%) of 47 patients in the control group kept more than 50% of their hair ($P < 0.001$).

Rugo et al. reported the results of a meta-analysis of 5 randomized trials including 295 patients, which were conducted to examine the effect of scalp cooling for hair loss

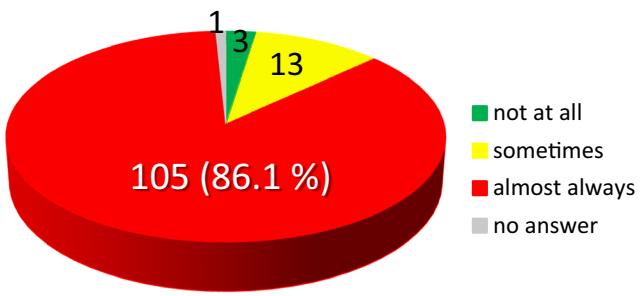

Fig. 8 Patients' answers to the question regarding use of a wig or hat 1 month after the last infusion of chemotherapy in the evaluable patients who completed the planned chemotherapy ($n = 122$)

prevention in chemotherapy [2]. They showed a 46% reduction in the risk of significant alopecia by scalp cooling.

Scalp metastases had long been suspected to increase due to scalp cooling during chemotherapy infusion in the USA. However, it was found not to be true in breast cancer patients. Rugo et al. reported no increase in scalp metastases in breast cancer patients after scalp cooling during (neo)adjuvant chemotherapy infusion compared to those without scalp cooling in a review of 10 studies [14].

Although we expected that the rate of more than 50% (Grade 3) hair loss using PAXMAN would be approximately 20%, we found that it was 60.7%. However, the participants of our study were required to purchase the cooling cap for about US$ 1100 to continue the scalp cooling in the second or later lines of chemotherapy. Thirty-five percent of the evaluable patients ($n = 122$) discontinued, and 28 of them decided to discontinue it by Day 10 of the first cycle of chemotherapy. Since CIA starts after Day 10 of the first cycle, the reasons for stopping scalp cooling were not the poor effect of PAXMAN. Therefore, we compared the effects between the patients who had their scalp cooled throughout the planned chemotherapy ($n = 79$) and the patients who had decided to discontinue it by Day 10 ($n = 28$). The rates of Grade 3 hair loss were 45.6% and 89.3%, respectively. The former rate is comparable to that of Nangia's report [3].

As for the chemotherapy regimen, Nangia et al. reported that 65% (41/63) of the patients who received taxane-based chemotherapy and 22% (7/32) of those who had anthracycline-based chemotherapy showed less than 50% hair loss after scalp cooling with PAXMAN [3]. We mainly used either TC, docetaxel and cyclophosphamide, or AC or EC followed by taxane. We observed that 32.1% of the former and 55.9% of the latter had less than 50% hair loss after scalp cooling. We cannot explain the difference between Nangia's results and ours.

We collected the data of use of a wig or hat by the patients as one of the primary outcomes. Unfortunately, almost all the patients used a wig or hat 1 month after the last infusion of chemotherapy. But this result was not unexpected, because Japanese women are extremely sensitive to how they look in general. It is thought that they tend to conceal even a little hair loss.

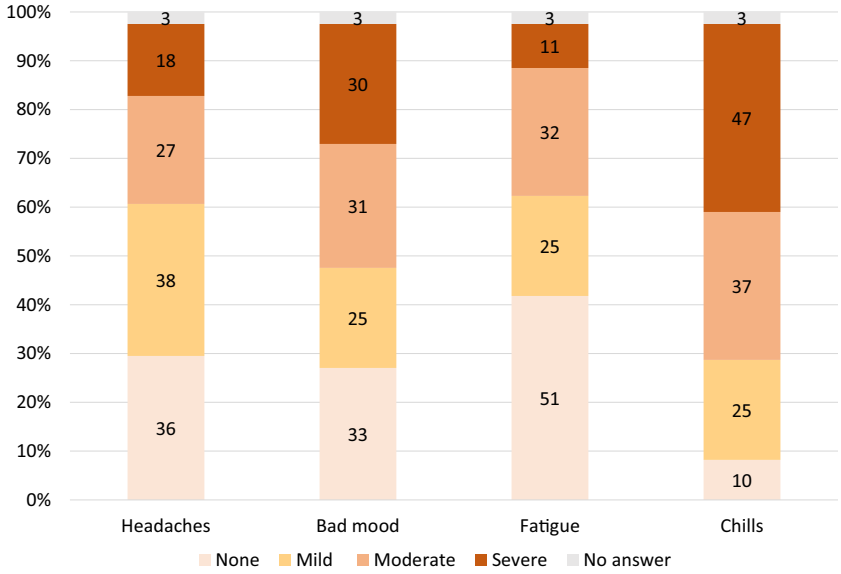

Fig. 9 Patients' complaints regarding headaches, bad mood, fatigue, and chills during the scalp cooling ($n = 122$). The worst grades during the cooling procedures are shown

The strength of our study is a relatively large size and prospective design. But there are several limitations. First, this is a single-arm study. We did not have a control arm. However, a relatively large proportion of the participants discontinued the use of PAXMAN probably due to the high cost of the cooling cap. We used the patients who discontinued it as a control group. Although there may have been some biases, we found significantly better preservation of hair by PAXMAN. Second, 14 patients did not complete the planned chemotherapy and evaluable data were not obtained from 7 of the patients who completed the chemotherapy because of our failure, or their refusal. They were excluded from the analyses.

Scalp cooling for CIA prevention is usually done 30 min prior to and during and 90 min after each chemotherapy infusion, and we used this time schedule in our study. However, trials to reduce the cooling duration after chemotherapy infusion have been done. Van den Hurk compared 90 and 45 min of post-infusion cooling time for patients receiving docetaxel chemotherapy in a randomized fashion [15]. They showed a slightly better result in the 45-min group than that in 90-min one. Komen et al. investigated the CIA prevention effect of 20-min post-infusion scalp cooling compared to 45-min cooling for patients receiving docetaxel chemotherapy in a randomized trial [16]. There was no significant difference in CIA mitigation between the two groups. Post-infusion cooling duration was beyond the scope of our study. But 90 min of scalp cooling after infusion is quite a long time. Therefore, this is an important area for future studies.

We conclude PAXMAN is effective in CIA-mitigation in (neo)adjuvant chemotherapy for Japanese breast cancer patients, and its effect is comparable to that in Caucasian patients.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Written informed consent was obtained from all individual participants included in the study.

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