Clinical aspects of scalp cooling in chemotherapy induced alopecia

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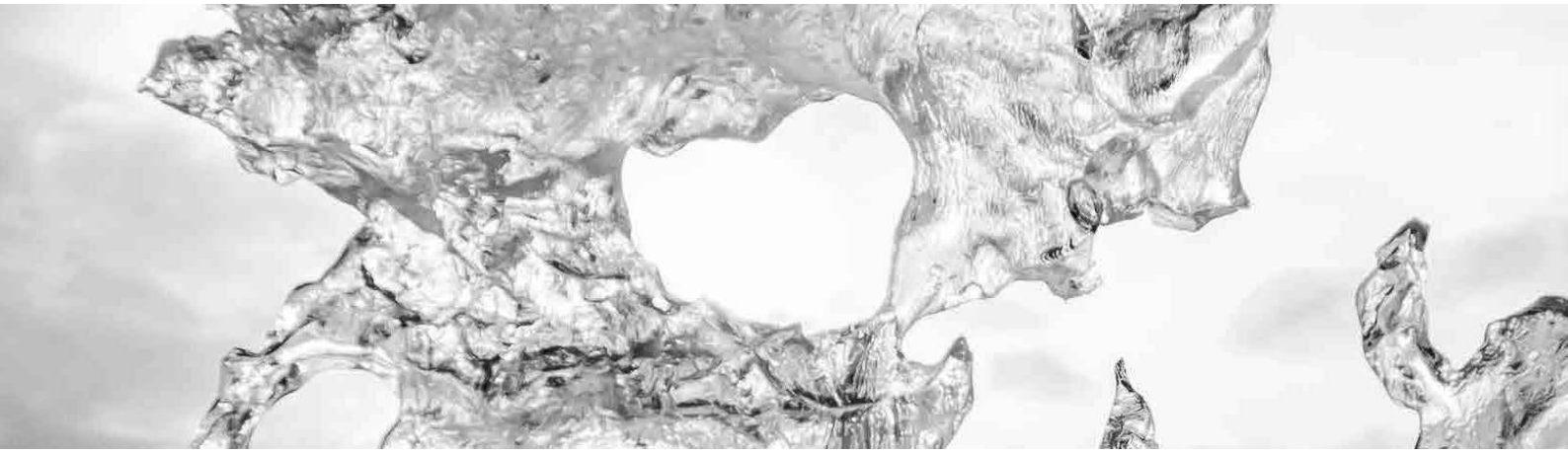
Chapter 8



General discussion and future research perspectives

GENERAL DISCUSSION

Efficacy of scalp cooling

Scalp cooling is increasingly being used in the prevention of chemotherapy-induced alopecia (CIA) in patients treated for cancer. Although a substantial number of patients does not suffer from CIA, scalp cooling is still not effective in all chemotherapy regimens and there is a subset of patients who has no beneficial effect from scalp cooling. Improvement of scalp cooling is therefore necessary as well as a better selection of patients who will likely benefit from it. To improve scalp cooling we focused on post-infusion cooling time and scalp skin temperature, two possible factors to improve outcomes. We also tried to analyse the molecular damage-response pathways in human hair follicles during and after administration of chemotherapy. Clarifying the working mechanism could help to improve scalp cooling and could be used to develop new treatment strategies for the prevention of CIA.

Adapting post-infusion cooling times

Determining the most optimal post-infusion cooling time has practical implications for scalp cooling in clinical practice. The most optimal post-infusion cooling time is unknown for many chemotherapy regimens. Is it 'the longer the better', or could it be shortened for patient comfort and for logistic reasons? The optimal cooling time for scalp cooling has not been studied extensively.(1,2)

We decided to investigate the post-infusion cooling times after treatment with low dose docetaxel (75 mg/m2 every three weeks) and after combination therapy with 5-fluorouracil, epirubicin and cyclophosphamide (FEC). In the low dose docetaxel regimen, scalp cooling is very effective (73% of patients do not require a wig)(3) and a short post-infusion cooling time (20 minutes) turned out to be just as effective as a long time (45 minutes).(2) In contrast, prolonging cooling time the FEC regimen (150 versus 90 minutes), in which scalp cooling is less effective (56%)(3), did not improve outcome significantly.(4) As the procedure of scalp cooling has to be feasible in daily practice, we decided that the small non-significant difference in effectiveness in our study with cooling times until 150 minutes did not justify further studies with even longer post-infusion cooling times.

Whereas shortening of the post-infusion scalp cooling time did not show differences in scalp cooling effectiveness in patients treated with low dose docetaxel, better results of scalp cooling were observed with the lower weekly docetaxel dose in comparison with the higher three weekly docetaxel dose. These findings are in line with the findings of Al Tameemi et al. who showed dose-dependent cytotoxicity in their in vitro model.(5) Apparently, the peak concentration of a cytostatic agent is more

important in determining toxicity than the exposure over time to chemotherapy. It is likely that individual variation in the efficacy of scalp cooling is due to interpatient variability in chemotherapy pharmacokinetics and peak drug concentrations.

It would be interesting to investigate short (20-minute) post-infusion cooling times in other chemotherapy regimens in which scalp cooling is used successfully (for example, all regimens with >70% effectiveness in preventing CIA). The so-called standard of 90-minute post-infusion cooling time has been chosen arbitrarily with the introduction of scalp cooling in the Netherlands. A possible explanation for protecting hair follicles even with shorter cooling times could be that the drug is flushed away from the hair follicles more rapidly during scalp cooling. Considering this, one might even question whether it is possible to omit the post-infusion cooling time.

Scalp skin temperature

In addition to the differences between individual patients with respect to pharmacokinetics of chemotherapy, the optimum scalp skin temperature during scalp cooling could also contribute to a better scalp cooling effect. When one wants to investigate this, an easy accurate temperature measurement of the scalp skin during scalp cooling is necessary. We used temperature probes to record scalp skin temperatures during cooling.(6) These measurements were accurate, but they were very time consuming and not useful in daily practice. It has been suggested that a scalp skin temperature $\leq$18°C is necessary for optimal scalp cooling results.(6) It would be interesting to investigate whether it is possible to decrease the scalp skin temperature below this level in those patients who do not reach this temperature.

Failing to reach a temperature $\leq$18°C did not explain all differences in efficacy in our patients. We observed patients with a scalp skin temperature of 13-14°C, without a beneficial effect from scalp cooling. Apparently, not all patients will benefit from adapting the temperature, but it will obviously be worthwhile to try this in some of them as a next step to improve scalp cooling results.

Individualizing scalp cooling

To improve scalp cooling, it is important to understand the exact mechanism by which cooling reduces the risk of chemotherapy induced alopecia. It has been suggested that vasoconstriction and reduced cell metabolism are important factors. In addition, the process of hair loss during and after chemotherapy might be mediated by specific molecular pathways. Understanding these mechanisms enables evaluation of the influence of various factors and might be of value to predict the outcome of scalp cooling. Van den Hurk et al. concluded in 2012 that type and dose of chemotherapy, infusion time, age, gender and type of hair significantly influenced the proportion of head cover

use.(3) Schaffrin et al. concluded in 2015 that menopausal status, systemic comorbidities, medication, nicotin abuse and hair density could also influence the outcome of hair loss prevention.(7) However, determinants of scalp cooling results vary considerably.(3,7-9)

Predicting the outcome of scalp cooling with these or other factors could be meaningful in counseling patients in the future. However, at present a prediction can only be made based on the type, dose and schedule of chemotherapy. Patients should be properly informed on the risk of alopecia and other possible side-effects to decide with their oncologist which treatment they will receive, ideally in the process of shared decision making. It has been shown that patients who lose their hair despite scalp cooling experience additional stress.(10) Therefore, it is important to select patients who will likely benefit from scalp cooling and provide them with reliable information about what to expect in their specific situation.

Limitations and confounding factors

The many publications reporting scalp cooling contain conflicting data. The influence of various factors such as menopausal status or liver function is unknown(7,11), but could have influenced the results. This also applies for the chosen method to measure CIA. In research focusing on scalp cooling, it is difficult to put the results in a broader perspective, because of the lack of a standardized method to measure the amount of hair loss. Scalp cooling studies in The Netherlands generally measure CIA by reporting the need to wear a wig or other head covering to mask visible hair loss. In other trials the use of the World Health Organization (WHO) classification of chemotherapy-induced alopecia(12), the Common Terminology Criteria for Adverse Events (CTC-AE)(13) or Visual Analogue Scale (VAS) is reported.(14) We concluded that the patient's opinion of hair loss should be considered as the best subjective method to assess the efficacy of scalp cooling. It is recommended to register both the patient's opinion and the VAS or WHO classification to facilitate the comparison of the efficacy of scalp cooling in the various scalp cooling publications.(15)

An important limitation in our research was the small sample size in our studies. Therefore, the studies might have been underpowered. This particularly applies to our study investigating a longer post-infusion cooling time in the FEC-regimen. It was difficult to motivate patients to randomize between 90 and 150 minutes, because patients thought 150 minutes post-infusion cooling time would not be tolerated. Although we could not exclude a clinical meaningful difference between the two post-infusion cooling times, we are inclined to state that it would be more interesting to investigate a shorter post-infusion cooling time in regimens with good scalp cooling results (>70%) than to repeat studies with longer post-infusion cooling times in a larger sample size.

Safety information

For a long time, there was no reliable information on the safety of scalp cooling in clinical practice. This prohibited broad scale implementation of scalp cooling, in particular in the United States. Besides, clinicians and nurses doubted the effect of scalp cooling, because information from well-organized, properly performed randomized scalp cooling studies was lacking.

Since 2009 important safety data have become available.(16-19) A major concerns with scalp cooling was that its use would increase the risk of scalp skin metastases. Several reports and multiple reviews (16-19) provided evidence to refute any potential risk of worse cancer outcome associated with scalp cooling.

In 2017 Nangia et al. provided evidence for the positive effect of scalp cooling in a randomized clinical trial.(20) Women with stage I to II breast cancer receiving chemotherapy with either a taxane an anthracycline or both, were randomized between the use of scalp cooling or not. The patients who received chemotherapy with scalp cooling experienced significantly more often $\leq$50% hair loss after the fourth chemotherapy cycle compared with those patients who were randomized to chemotherapy without scalp cooling. The trial was stopped early after advice from the safety monitoring board because of superiority of hair retention in the participants who received scalp cooling. Another publication in 2017 of Rugo et al. also provided evidence for less hair loss due to the use of scalp cooling in a prospective cohort study among women undergoing non-anthracycline-based adjuvant chemotherapy for early stage breast cancer. The results of both studies, lead in 2017 to FDA approval for scalp cooling in The United States.(20,21) Since then the use of scalp cooling worldwide has increased and the need for improvement of the efficacy of scalp cooling with better selection of patients has been emphasized.

FUTURE RESEARCH PERSPECTIVES

We have shown that shortening the post-infusion cooling time after the administration of docetaxel does not negatively influence the outcome of scalp cooling. This is advantageous for the patient who can leave the hospital earlier and for the logistics of the nursing staff in planning patients for chemotherapy in the outpatient unit. Shortening the post-infusion cooling time in other chemotherapy regimens with reasonable scalp cooling results would be worthwhile to investigate in future studies. If the outcome is positive, it will overcome the disadvantage of a longer stay in the outpatient clinic, since we know that this is one of the reasons why not all oncological outpatient clinics offer their patients scalp cooling.

Adapting the cooling temperature could possibly improve outcomes in a subgroup of patients using scalp cooling. This should be one of the areas to explore further in the future.

Another interesting area is the use of topicals in combination with scalp cooling. Anagen protective agents like ciclosporin or tacrolimus might reduce visible hair loss.(22) However, administration of anagen protecting agents is complicated because the effect must be limited to the hair-follicle epithelium to avoid favoring intracutaneous micro metastasis.(22) Despite this limitation, this is an unexplored area which is interesting to investigate.

Improving cap fitting or adapting the scalp cooling technique will probably not lead to major improvements of the efficacy of scalp cooling. To move the technology forward and improve efficacy, the biological mechanism behind scalp cooling needs to be better understood.(23) From rodent and ex-vivo models we know that hair follicle apoptosis largely depends on p53, a key mediator of cellular damage caused by a stress response.(22) Development of hair follicle research enables direct testing of the damaging effects of cytostatic agents in human hair follicles and allows real-time assessment of the efficacy of potential preventive treatments.(23) Results of such studies could guide our thoughts for larger studies in which for example the addition of topicals to scalp cooling can be investigated in a randomized study. To explore molecular damage-response pathways in plucked human hair, it is important to select the most suitable method. We used the method of Randall et al.(24) Unfortunately, hair follicle research is a very delicate process and depends too much on the availability of dedicated people. We failed in making a robust model for large scale analysis of hair bulbs. The procedure was too time consuming and despite all effort, too much tissue was not evaluable. For a better understanding of the working mechanism of CIA, the method as described by Randall et al. may not be the best option. Solid methods which consistently and reliably can demonstrate molecular damage response pathways are needed. Microscopy with Ultraviolet Surface Excitation (MUSE), which produces high-resolution images of tissue samples within minutes, could be helpful. 3-D scanning, to visualize the entire hair, is another important development which is promising. Hopefully, research in this area will expand and lead to a better understanding of scalp cooling and ways to improve.

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