Clinical aspects of scalp cooling in chemotherapy induced alopecia

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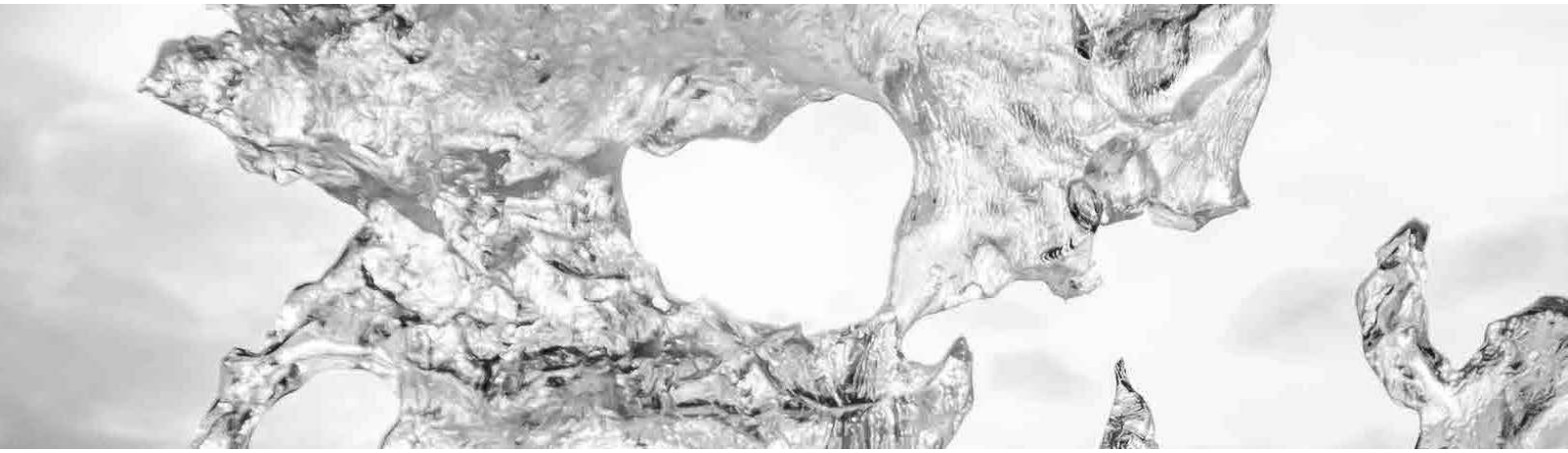
Chapter 1



Introduction

INTRODUCTION

Hair loss (alopecia) is one of the most feared side effects of chemotherapy.(1-4) About one quarter of patients with cancer is at risk for chemotherapy-induced alopecia (CIA).(5) This also applies to men, although this is often not discussed.(6) Whereas about 80% of patients considers CIA as an important side effect, (7) clinical research has shown that the impact of CIA is underestimated by both oncologists and nurses.(8-11)

Up to now, scalp cooling is the only method to prevent CIA. When using scalp cooling, a cold liquid is pumped through a cap which is placed on the head of the patient before, during and after intravenous treatment with chemotherapy. It is hypothesized that this causes subcutaneous vasoconstriction resulting in reduced perfusion of cytostatic drugs to the hair follicles and a reduction of biochemical activity. During the San Antonio Breast Cancer symposium in December 2016, the results of the randomized SCALP trial were presented. This randomized clinical trial assessed whether a scalp cooling device was effective in reducing CIA. The results showed that scalp cooling was safe and effective in 50.5% of patients.(12) Following this and another publication in JAMA(13), scalp cooling has been approved for cancer patients with solid tumors by the FDA in the United States.(12,13) A poll at the St. Gallen International Breast Cancer Conference in March 2017 showed that 83% of the participants felt that scalp cooling was a good option to prevent hair loss during (neo) adjuvant chemotherapy.

At present, scalp cooling is available in almost all hospitals in the Netherlands. It is frequently used in women with breast cancer receiving chemotherapy, but also in women with other tumor types and in men with prostate cancer receiving docetaxel. This introduction provides an overview of the main points of interest when scalp cooling is applied in clinical practice.

The hair cycle and p53 mechanism in CIA

Under normal circumstances, the growth cycle of a hair follicle consists of three main phases: the anagen, catagen and telogen phase.(14) The active growth (anagen) phase lasts for three to seven years and involves the growth of a hair from a hair follicle. During the transition (catagen) phase (2-3 weeks), the hair stops growing and releases itself from the blood supply. During the resting (telogen) phase (3-4 months), the hair stays attached to the hair follicle and does not grow. When the old hair is shed, the telogen phase ends (Figure 1).

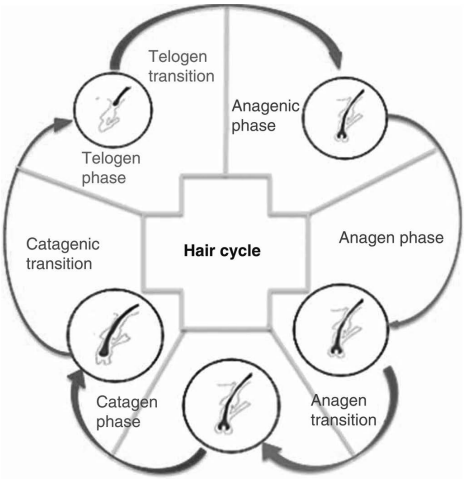


Figure 1: Hair cycle. Adapted from: Drug discovery for alopecia: gone today, hair tomorrow. Santos et al. Expert Opin Drug Discov. 2015;10(3):269-292.(15)

Since 90% of all hair is in anagen phase and rapidly proliferates, hair follicles are highly at risk to be affected by chemotherapy, resulting in CIA.(16,17) Hair shaft shedding begins days to weeks after the initiation of chemotherapy. The exact mechanism is not completely understood, but it is known that regression of the hair follicle activates a variety of signaling pathways, which induce apoptosis.(18) Although the role of many molecular factors in the DNA-damage response remain to be explained, P53, a key mediator of cellular mechanism of stress response, has a crucial role in the occurrence of apoptosis.(16) (Figure 2) In a mouse model for CIA, Botchkarev demonstrated that p53 is essential in this process. Administration of cyclophosphamide was associated with rapid increase of p53 concentrations in hair-matrix keratinocytes, followed by apoptosis. By contrast, genetic p53 ablation in mice rendered hair follicles completely resistant to cyclophosphamide.(16)

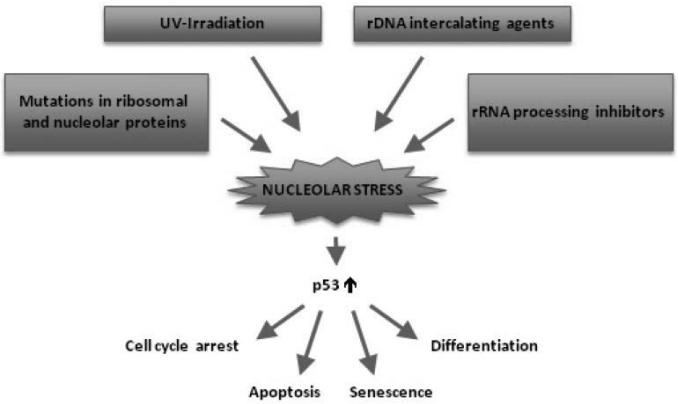


Figure 2: Apoptosis depends on p53. Adapted from p53 -Dependent and -Independent Nucleolar Stress Responses. Olausson et al. Cells. 2012 Dec; 1(4): 774–798.(19)

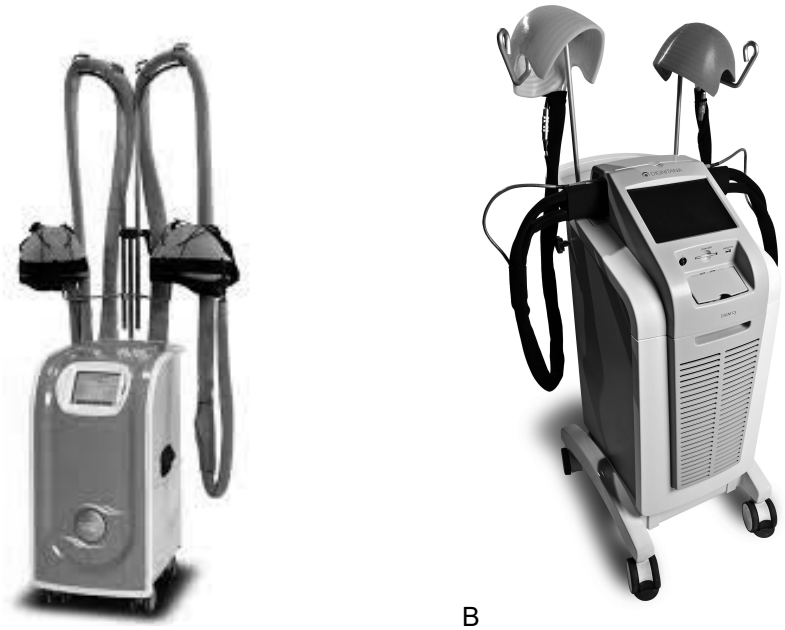
Prevention of chemotherapy induced alopecia

Several researchers have investigated pharmacological as well as nonpharmacological measures to prevent CIA. Little information is available in terms of medications. At present, there are no approved drug treatments for preventing CIA. Minoxidil is well recognized to promote hair growth, but topical administration of minoxidil, as well as other hair growth cycle modifiers, does not prevent CIA.(14,20) Other agents with different action mechanisms like cytokines, growth factors, antioxidants, proliferation modifiers and inhibitors of apoptosis showed some effect, but only in animal CIA models.(14) Reliable preventive pharmacological therapy to prevent CIA in human is still sought. Nonpharmacological measures such as scalp tourniquets were designed to reduce the blood flow to scalp hair follicles during chemotherapy infusion.(2,20) However, most studies investigating the effect of tourniquets used inconsistent techniques and involved small numbers of patients. Therefore, it was difficult to determine the exact effect.(20) Tourniquets are no longer recommended due to patient discomfort. Currently, most research on preventing CIA focuses on scalp cooling.

Scalp cooling

Methods

In the Netherlands cooling machines both from Paxman (England) and from Dignitana (Sweden) are used. These are the two largest suppliers on the market and although both types of coolers differ slightly from each other, no differences in results are seen in practice.



A B

Figure 3: Cooling machines from Paxman (A) and Dignitana (B)

Liquid circulates through the devices at a constant temperature of -10°C. For the best possible result, the cooling cap, which is connected to the device, must be optimally connected to the head. Scalp cooling is applied during the infusion of chemotherapy, with a pre-cooling time of 30 minutes to ensure the scalp is at the required temperature, and a follow-up time of usually 90 minutes.

Results

Within the literature, efficacy results for scalp cooling vary because of variability in study design, such as population, chemotherapy regimen, outcome measure, type of cooling system/device, and cooling duration.(21) In most trials, scalp cooling has shown a positive effect in reducing CIA following a number of different chemotherapy regimens.(2,12,13,22) A meta-analysis of Shin et al. in 2015 showed that the risk of hair loss became three times smaller due to the use of scalp cooling.(23) These results were confirmed in 2017 with a meta-analysis of randomized scalp cooling studies,(24,25) and a review of controlled clinical trials(25), which added additional support to the finding of statistically significant higher rates of hair preservation with scalp cooling compared to chemotherapy administered without cooling.

In the Netherlands, scalp cooling has been used since 1970. A Dutch open patient registration study was started in 2006, in which more than 7000 patients have now been included. Scalp cooling results in this registry were positive for most chemotherapy regimens.(22) Successful scalp cooling was the patient's self-determined need to wear a wig or other head covering. It was concluded that results were best for monotherapy with low dose taxanes (95% effect) and poor in the TAC regimen, a combination chemotherapy with docetaxel, adriamycin and cyclophosphamide (8% effect). These findings are confirmed in other studies.(12,13)

Factors that influence the result of scalp cooling

The type of chemotherapy, the number of cycles, the dose, administration route and the speed of administration can strongly influence the result of scalp cooling.(22,26) The influence of all other patient-related factors (age, gender and hair type) is less convincing or lacking.(2,22,23,27) Factors such as liver function and menopausal status might influence the efficacy, but there is no convincing evidence yet.(2,22,23,27) The influence of the scalp skin temperature is probably the most important factor influencing the result of scalp cooling.(28) However, the scalp skin temperature in patients using scalp cooling does not always decrease to optimal temperature levels.(28,29) Both a better connection between the cap and the head and individual temperature adjustment could overcome this problem. Temperature has also been proven to be critical in in vitro research. Laboratory studies provided biological evidence for a positive correlation between the

degree of cooling and the survival of hair follicles. Al Tameemi et al. reported a study in which they found that lowering the temperature from 22 °C to 18 °C and even further to 14 °C, resulted incrementally in a better degree of rescue from drug cytotoxicity. Cytoprotection was detectable even for the maximal drug doses tested, which had previously resulted in complete loss of cells.(30) Despite the increased knowledge about the effect of temperature on cell survival, there still is a lack of knowledge about the optimal temperature of scalp cooling and how to reach this. This lack of knowledge also applies for the post-infusion cooling time, another factor which could influence the effect of scalp cooling. Shortening the post-infusion cooling time from the usual 90 minutes to 20 minutes is justified for docetaxel, but for other regimens this time is unknown and should be studied.(6)

Tolerance

Scalp cooling is usually well tolerated.(23,31,32) Several publications report a visual analogue scale (VAS) score of 6.9-8.3 (0 'not tolerable' to 10 'very well tolerated').(2,6,33,34) Side effects include chills, dizziness, headache, nausea and a sensation of cold.(12,21) However, these side effects are mild (mostly grade 1) and are for less than 5% of patients a reason to stop scalp cooling.(2,21-23)

Safety

The lack of safety research has limited the use of scalp cooling for years. In particular, it was feared that scalp cooling would protect possible occult metastases in the scalp from chemotherapy, with the danger of scalp metastasis. Therefore, scalp cooling is not recommended in patients with hematological malignancies. In one patient with leukemia and another patient with mycosis fungoides, who both chose to use scalp cooling, cutaneous disease recurred on the scalp after several years, with no other evidence of disease.(35,36) However, in solid tumors, there has never been evidence for the occurrence of scalp metastases due to scalp cooling.(2,5,23,37) Scalp metastases rarely appear in patients with breast cancer (0.003-3%).(5,24) This risk is not increased in patients who use scalp cooling (0.04-1%).(5,24) A retrospective study with 6-8 years follow up found no difference in the occurrence of scalp metastases between patients with and without scalp cooling.(38) A large study by Van den Hurk et al. with a follow-up of 5 years also showed no increased risk of developing scalp metastases.(22) These results were confirmed by a meta-analysis, performed by Rugo(24) and Shah(25) in 2017. When scalp metastases occurred during scalp cooling in the metastasized setting, they always appeared simultaneously or after occurrence of metastases elsewhere.(37) During many years of application of scalp cooling, there has never been an adverse effect of scalp cooling on the disease.

The risk of possible metastases in the skull or even in the brain is very unlikely. Research has shown that there is no or only a minimal decrease in temperature both in the skull and in the brain.(39)
Scalp cooling is contraindicated in patients who suffer from cold sensitivity, cold agglutinin disease, cryoglobulinaemia, cryofibrinogenaemia or cold posttraumatic dystrophy.

Developments and recommendations

The use of scalp cooling in oncology patients treated with chemotherapy in the Netherlands is still low (29%).(7) There are large differences in the supply of scalp cooling between hospitals and sometimes scalp cooling is not used in (neo)adjuvant chemotherapy regimens. This limited application lies both in the limited supply and the limited demand. Only 30% of potential candidates for scalp cooling is aware of the existence of scalp cooling. (Multiscope, personal communication, 2016-2017)

Offering the possibility of scalp cooling largely depends on the opinion of doctors and nurses on the efficacy of scalp cooling to prevent CIA.(40) As a result, there are large differences in the availability of scalp cooling for men and women, for different age groups and for different types of chemotherapy. In addition, the administration of scalp cooling is often limited because of staff shortages or logistical problems.

Given their role in the use of scalp cooling, nurses are perhaps best equipped to inform patients about scalp cooling. Together with oncologists and managers, preconditions such as training and extra time could be created, so that every patient with a desire to try scalp cooling can be informed and given the opportunity to use it.
It appears that the knowledge on CIA and scalp cooling is evolving slowly, but it is expected that this will change due to the breakthrough of scalp cooling in the USA. Further research should focus on improving the results of scalp cooling and on personalizing scalp cooling. In addition, implementation of scalp cooling should be included in (international) oncology guidelines.

OBJECTIVES AND OUTLINE OF THIS THESIS

The aim of this thesis was to study the mechanism of scalp cooling in patients treated with chemotherapy and to refine and personalize the technique.

In **chapter 2** we examine various factors influencing the effectiveness of scalp cooling in the prevention of chemotherapy-induced alopecia and provide a critical appraisal of clinical studies.

In **chapter 3** we discuss the relation between scalp skin temperature and the efficacy of scalp cooling. Apart from the type or dose of chemotherapy, as described in chapter 2, the scalp skin temperature during scalp cooling is a very important factor to prevent hair loss. To obtain optimal results, we analysed which threshold should be reached below which hair loss can be prevented.

In **chapters 4 and 5** we compared different post-infusion scalp cooling times to investigate its effect on the outcome of scalp cooling. The duration of post-infusion cooling implies a prolonged stay on the chemotherapy ward, which is potentially a disadvantage both for patients and for the logistics of the clinic. **Chapter 4** describes a shorter post-infusion time in the low dose docetaxel chemotherapy regimen, in which cooling is very effective. On the other hand, scalp cooling is also offered in regimens with a more limited effect. Therefore, a prolonging of the post-infusion cooling time was investigated in an anthracycline containing chemotherapy regimen. **Chapter 5** presents the results of a randomized study, investigating a longer post-infusion scalp cooling time.

In **chapter 6** the various methods used to evaluate the outcome of scalp cooling are assessed. In this study the common subjective methods to evaluate hair loss were compared with a new objective method in order to standardize the measurement of hair loss in clinical trials. Standardization of measurement would simplify the evaluation and comparison of potential therapies to prevent CIA.

In **chapter 7** we explored molecular damage-response pathways in hair follicles from patients treated with chemotherapy, to provide a better understanding of the scalp cooling working mechanism. Investigating hair follicles of patients treated with chemotherapy, is the only way to demonstrate the working mechanism of scalp cooling and to explain why scalp cooling works in one patient, but not in the other.

This thesis ends with concluding remarks and future prospects in **chapter 8**.

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