The Influence of Various Parameters on the Success of Sensor-Controlled Scalp Cooling in Preventing Chemotherapy-Induced Alopecia

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Introduction

Modern chemotherapies (CTs) achieve significant improvements in survival and prognosis in the majority of cancer entities; however, the extent of associated side effects increases accordingly.

Chemotherapy-induced alopecia (CIA) is among the most common and distressing side effects [1–3]. In the 1970s, first attempts were made to reduce cytostatic exposure of the proliferating matrix keratinocytes of the hair follicles through various methods. The use of tourniquets or ice caps provided no major success [4–7]. So far, pharmacological attempts to reduce CIA have also been rather ineffective. Topical application of minoxidil proved ineffective in suppressing CIA; however, the time to complete hair regrowth was shortened [8, 9]. Over the last years, the technique of controlled scalp cooling was developed (i.e., a constant decrease of the scalp temperature to about 7 °C during and for a certain period after CT). The aim of all the described techniques is to prevent or at least reduce CIA to the extent that the use of a head cover or wig becomes unnecessary.

Keywords

Scalp cooling · Chemotherapy-induced alopecia · Adjuvant chemotherapy · Comorbidities

Summary

Background: The influence of systemic comorbidities on the success of scalp cooling during chemotherapy (CT) is widely unexplored. Comorbidities often require additional medication which itself can occasionally cause alopecia. This study investigates the influence of selected parameters on the efficacy of scalp cooling for the prevention of CT-induced alopecia.

Patients and Methods: 226 cancer patients were treated with various CT regimens in combination with sensor-controlled scalp cooling. 136 breast cancer patients received (neo)adjuvant therapy, and 76 of these patients received epirubicine and cyclophosphamide (4x EC 3w) followed by paclitaxel (12x T w). The following parameters were prospectively investigated: chemotherapy-induced alopecia, systemic comorbidities and co-medication, nicotine abuse, hair treatment, menopausal status, and trichologic status.

Results: Scalp cooling was successful (no or not visible hair loss; common toxicity criteria 0–1) in 65% of all patients, in 65% of the 136 breast cancer patients, and in 68% of the 76 patients receiving EC/T. In this subgroup, premenopausal patients (p = 0.009) and those without systemic comorbidities (p = 0.003), without co-medication (p < 0.001) and with high hair density (p = 0.038) showed less hair loss during CT; an effect was also seen for nicotine abuse (p = 0.023). Hair length and hair treatment had no significant influence.

Conclusion: Sensor-controlled scalp cooling represents an effective addition to supportive cancer therapy. The success of scalp cooling depends on the applied CT regimen. Parameters like menopausal status, systemic comorbidities, medication, nicotine abuse, and original hair density also influence the outcome of hair loss prevention.

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According to the outcome of the latest study [10] including 101 patients with breast cancer receiving adjuvant chemotherapy, simultaneous scalp cooling (DigniCap®, Dignitana AB, Lund, Sweden) prevented hair loss in 70.3%.

Substantial scientific experience with scalp cooling has been published in the Netherlands. In the Dutch Scalp Cooling Registry, 50% of 1,411 patients treated with various CTs did not use head covers, and psychological distress was reduced [11].

Numerous cytostatics commonly used in CT cause severe hair loss (e.g. anthracyclines, taxanes, cyclophosphamide) [12]. According to the literature, the risk of complete alopecia is 94% for combined doxorubicin and cyclophosphamide [10], 98% for the combination of an anthracycline, cyclophosphamide, and a taxane within the TAC regimen (docetaxel, doxorubicin, cyclophosphamide), and 100% for the sequential use of an anthracycline and cyclophosphamide followed by paclitaxel (Pac) [13].

The influence of comorbidities on the success of scalp cooling during CT is widely unexplored. Systemic comorbidities may result in renal and hepatic dysfunction or lead to effusions which can act as reservoirs, thus altering the pharmacokinetics of the applied cytostatics. A higher degree of comorbidity usually results in the use of additional medication which itself can often be associated with alopecia [14]. Therefore, it is very likely that co-medication can influence the mode of action of substances applied as part of CT treatment, resulting in increased hair loss.

This paper focuses on the success of scalp cooling in patients with breast cancer receiving palliative and adjuvant chemotherapy. In a suitable subgroup of patients, the influence of the following parameters was investigated: hair treatment, systemic comorbidities, routine medication, nicotine abuse, menopausal status, and trichologic parameters.

Methods

Patient Cohort Characteristics

A total of 226 patients with different solid tumors received various (neo)adjuvant and palliative CT regimens simultaneously to scalp cooling at our hematology/oncology clinic. A subgroup of 136 patients with breast cancer undergoing CT regimens known for their complete or at least high rates of CIA was separately assessed. Due to the high extent of alopecia, we abstained from a control group without known for their complete or at least high rates of CIA was separately assessed. This subgroup of 136 patients was considered as very homogenous due to all known for their complete or at least high rates of CIA was separately assessed. Statistical Analysis

The subgroup of 76 patients was considered as very homogenous due to all patients receiving the same CT regimen and exhibiting a comparable health status. Therefore, this subgroup was statistically analyzed.

Ordinal and nominal scaled parameters like grouped age, menopausal status, medication, comorbidities, nicotine abuse, hair length and density, and chemical and thermal hair treatment were descriptively presented using absolute and percentage frequencies. They were compared to CIA in contingency tables and tested for association using the chi square test. Odds ratios (OR) with 95% confidence intervals (CI) were calculated to quantify the effect size. All tests were two-sided with a significance level of 5%. Alpha adjustment for multiple testing was not applied, and the results were interpreted accordingly. Calculations were carried out using SPSS Statistics 22 (IBM Corp., Armonk, NY, USA).

Results

A total of 226 patients with various solid tumors were treated with different CT regimens in the (neo)adjuvant or palliative setting simultaneously to scalp cooling. After completing (neo)adjuvant CT or after a minimum of 3 months of palliative CT.
(65%) patients showed a positive affect of scalp cooling with no or only mild alopecia (not visible, CIA grades 0 and 1). Only 28% of these 226 patients opted for a wig. The scalp cooling success rate of the 136 patients with breast cancer receiving different (neo)adjuvant CTs was 65% (88 patients) (table 1).

Regarding the subgroup of 76 patients treated with EC/Pac, scalp cooling was successful in 52 (68%) patients. A total of 5 patients developed CIA grade 2 after EC treatment, but experienced complete hair regrowth during subsequent Pac treatment and successfully finished scalp cooling after chemotherapy with CIA grade 1.

**Chemotherapy Doses**

CT regimens with different anthracycline doses (known to cause most severe alopecia) and combinations of agents showed variable outcomes with regard to hair loss (table 1). In all CT regimens with an epirubicin dose of < 100 mg/m², scalp cooling success rates varied between 50 and 75%. An epirubicin dose of 150 mg/m² (ETC regimen) was associated with no scalp cooling success, as was TAC. A dose-dense application (every 2 weeks) of an epirubicin dose of < 100 mg/m², scalp cooling was successful in 52 (68%) patients.

**Other Influencing Factors**

Referring to the subgroup of 76 breast cancer patients (EC→T2w), 29 (85%) out of 34 patients without systemic comorbidities developed no visible CIA (grade 0 and 1) compared to 23 (55%) out of 42 with systemic comorbidities (p = 0.002). Regular medication with e.g. antihypertensives, cardiovascular drugs, anti-diabetics, or analgesics is known to amplify CIA [13]. Only 17 (49%) out of 35 patients with regular co-medication showed good hair preservation compared to 35 (85%) out of 41 patients without regular co-medication (p < 0.001). However, a differentiation between direct effects of the additional medication and those of the systemic comorbidity itself was not possible (table 2).

Treatment success was seen in 40 (83%) out of 48 patients younger than 54 years compared to 12 (42%) out of 28 older than 54 years (p < 0.001).

Correspondingly, premenopausal patients developed CIA of grade 0 and 1 in 30 (81%) out of 37 cases, whereas postmenopausal women showed no alopecia in 22 (56%) out of 39 cases. Within our patient group, the impact of menopausal status on hair preservation (p = 0.006) was remarkable. Premenopausal patients had a 5.9 times higher chance of no or not visible CIA compared to patients with postmenopausal status (OR = 5.9, 95% CI = 1.1–29.7) (table 2).

Of 43 patients with normal hair density (grade 1 Sinclair scale), 34 (79%) showed no visible hair loss, and of 33 patients with scarce growth (grade 2/3 Sinclair scale), 18 (55%) experienced successful scalp cooling (p = 0.038).

Statistically considered, nicotine abuse influenced the prevention of hair loss (p = 0.023). Hair length (p = 0.176), chemical hair treatment (p = 0.22), and thermal hair drying (p = 0.53) showed no significant impact on CIA.

In patients with good hair preservation, only mild toxic myelosuppression was found whereas patients with visible alopecia experienced significant neutropenia.

### Table 2. Grade of alopecia in 76 patients with breast cancer under EC→T chemotherapy in relation to selected patient characteristics

<table>
<thead>
<tr>
<th>Grade of alopecia at the end of chemotherapy, n (%)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>&lt; 45 years (p &lt; 0.001)</td>
<td>16 (100.0)</td>
</tr>
<tr>
<td>45–54 years</td>
<td>32 (100.0)</td>
</tr>
<tr>
<td>55–64 years</td>
<td>17 (100.0)</td>
</tr>
<tr>
<td>≥ 65 years</td>
<td>11 (100.0)</td>
</tr>
<tr>
<td>Menopausal status (p = 0.006)</td>
<td></td>
</tr>
<tr>
<td>pre-menopausal</td>
<td>37 (100.0)</td>
</tr>
<tr>
<td>post-menopausal</td>
<td>39 (100.0)</td>
</tr>
<tr>
<td>Medication (p &lt; 0.001)</td>
<td></td>
</tr>
<tr>
<td>present</td>
<td>41 (100.0)</td>
</tr>
<tr>
<td>Systemic co-morbidity (p = 0.002)</td>
<td></td>
</tr>
<tr>
<td>present</td>
<td>42 (100.0)</td>
</tr>
<tr>
<td>Nicotine abuse (p = 0.023)</td>
<td></td>
</tr>
<tr>
<td>present</td>
<td>12 (100.0)</td>
</tr>
<tr>
<td>Thermal distress (p = 0.538)</td>
<td></td>
</tr>
<tr>
<td>present</td>
<td>56 (100.0)</td>
</tr>
<tr>
<td>Chemical distress (p = 0.220)</td>
<td></td>
</tr>
<tr>
<td>present</td>
<td>40 (100.0)</td>
</tr>
<tr>
<td>Hair length (p = 0.176)</td>
<td></td>
</tr>
<tr>
<td>&lt; 5 cm</td>
<td>36 (100.0)</td>
</tr>
<tr>
<td>&gt; 5 cm</td>
<td>40 (100.0)</td>
</tr>
<tr>
<td>Hair density/fullness (p = 0.038)</td>
<td></td>
</tr>
<tr>
<td>thin</td>
<td>33 (100.0)</td>
</tr>
<tr>
<td>thick</td>
<td>43 (100.0)</td>
</tr>
<tr>
<td>Total</td>
<td>76 (100.0)</td>
</tr>
</tbody>
</table>

*aChi square linear trend test.*
Scalp Cooling-Related Side Effects and Dropouts

The type and frequency of side effects were similar in all investigated patient cohorts.

Overall, 58 (64%) of 90 patients with various solid tumors, 36 (60%) of 60 patients with breast cancer and various CTs, and 52 (68%) of 76 patients receiving EC/Pac CT regimens reported a slight and well tolerable sensation of cold and mild cranial pressure. Both effects occurred temporarily for a limited period during the cooling down process and disappeared after a couple of minutes.

No skin irritations were recorded. 1 patient stopped scalp cooling due to cold intolerance after 2 cycles of EC with CIA grade 1. In total, 7 patients dropped out due to cold intolerance or aversion, which led to a dropout rate due to side effects of 3.3%. Those 7 patients were not included in the analysis.

Discussion

Sensor-controlled scalp cooling offers a valuable chance to prevent CIA. The applied anthracycline dose (epirubicine) is one of the crucial factors for the success of scalp cooling. The results show that an epirubicine dose of > 150 mg/m² or the combination of an anthracycline and taxane lead to a success rate of < 50%, which does not meet our standards for successful scalp cooling.

The success of scalp cooling is influenced by multiple factors. Higher cytostatic dosages, particularly in combination with additional drugs, have a negative impact. Individual responses such as distinct vasoreactivity, which impede a certain scalp temperature decrease, deteriorate the efficacy of scalp cooling. To explore the effects of some of the above parameters, a group of 76 patients with comparable health status was separately investigated. To our knowledge, these patients, all of whom received EC→Tw, represent the largest such collective reported in the literature.

Several authors mentioned that systemic diseases (e.g. high blood pressure, metabolic syndrome, coronary heart disease) can cause androgenic alopecia [18–21]. It is likely that comorbidities and related additional medication cause a (sometimes invisible) weakening of the hair follicles and therefore enhance the negative effect of CT treatment on the success of scalp cooling.

This thesis was confirmed by the findings of our study (table 2) as well as by the formerly reported experience that the pattern of initial CIA is very comparable to the hair loss pattern of androgenic alopecia [22]. On the other hand, it has to be considered that the fronto-parietal scalp is covered with a comparatively high amount of hair follicles in the anagen phase extremely sensible to toxic effects of cytostatics [23].

The frequency of cardiovascular risk factors with related implications and medication is generally higher in elderly patients. Age-related pharmacokinetic and pharmacodynamic changes can lead to increased organ toxicity and therefore enhanced defluvium capillorum[24]. For doxorubicin and weekly application of taxane, an age-related lower renal clearance was found [24].

Robbins et al. [25] found that the hair of postmenopausal women has a smaller diameter. If the proliferation of ceratinocytes in hair follicles in the anagen phase is hampered by cytostatics, hair with reduced diameter is produced. Moreover, less secretion of sebum into the hair canal causes increased adhesion between hair root sheath and hair shaft, which can finally result in hair breakage. Age-related degeneration of sebaceous glands caused by menopausal changes [25, 26] can be enhanced by CT and might be the reason for the significant difference in the success of scalp cooling in elderly menopausal women found in this study [26, 27].

Aging skin has reduced cold-induced vasoconstriction. This probably causes concentrations of cytostatics that exceed the threshold for successful scalp cooling [28].

Unprotected exposure to sunlight can cause alopecia during CT in the exposed scalp areas. Especially anthracyclines are known to damage sebaceous glands and therefore also the skin barrier [26, 29]. Additionally, increased sensitivity of the skin to ultraviolet radiation can lead to a phototoxic effect on the ceratinocytes finally resulting in their apoptosis with subsequent alopecia [30].

The extent of scalp cooling-related side effects was small. Reported side effects were generally temporary and mild, and a side effect-triggered dropout rate of 3.3% shows the good tolerability of sensor-controlled scalp cooling.

The often discussed and dreaded topic of increased scalp metastases triggered by scalp cooling was not observed in this patient cohort, which is in accordance with international databases. The risk for breast cancer patients to develop scalp metastases during CT without scalp cooling is about 0.03–3%. This rate increases to 0.04–4% with simultaneous scalp cooling [31].

Summary and Conclusion

The analysis of scalp cooling data of 226 patients with various solid tumors and undergoing different CTs revealed that 65% showed no visible hair loss (CTC grades 0–1), which means 2/3 of patients needed no head cover. This directly corresponds to the results of Rugo et al. [10] presented at the ASCO Meeting 2015.

The type of substance, dose, and combination of the cytostatics used, the patient’s age, menopausal status, and systemic comorbidities with related regular co-medication, as well as hair density significantly influence the success of scalp cooling; a statistical influence was also seen for nicotine abuse.

In the future, histomorphologic analysis of a patient’s hair follicles prior to CT may provide more detailed information about existing follicular damage and hence allow better prediction of the chances for successful scalp cooling during CT.

The presented data show the important influence of formerly unexplored parameters on the success of scalp cooling. Sensor-controlled scalp cooling is an effective supportive method to prevent CIA during CT. It is well tolerated, and in the majority of cases it generates considerable benefit for the patients. We suggest the introduction of a scalp cooling data base on an international level as a foundation for further investigations, and we can recommend the use of scalp cooling as a valuable supportive therapy.
Disclosure Statement

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