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RESULTS OF THE DUTCH SCALP COOLING REGISTRY IN 7424 PATIENTS: ANALYSIS OF DETERMINANTS FOR SCALP COOLING EFFICACY

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ABSTRACT

Background

Chemotherapy-induced alopecia (CIA) is a common consequence of cancer treatment with a high psychological impact to patients and can be prevented by scalp cooling (SC). With this multi-center patient series, we examined the results for multiple currently used chemotherapy regimens to offer an audit into the real-world determinants of SC efficacy.

Materials and methods

The Dutch Scalp Cooling Registry collected data on 7424 scalp-cooled patients in 68 Dutch hospitals. Nurses and patients completed questionnaires on patient characteristics, chemotherapy, and SC protocol. Patient-reported primary outcomes at the start of the final SC session included head cover (HC) (e.g wig/scarf) use (yes/no) as a surrogate for patient satisfaction with SC and WHO score for alopecia (0 = no hair loss up to 3 = total alopecia) as a measure of scalp cooling success. Exhaustive logistic regression analysis stratified by chemotherapy regimen was implemented to examine characteristics and interactions associated with the SC result.

Results

Overall, over half of patients (n = 4191, 56%) did not wear a HC and 53% (n = 3784/7183) reported minimal hair loss (WHO score 0/1) at the start of their final treatment. Outcomes were drug and dose dependent. Besides chemotherapy regimen, this study did not identify any patient characteristic or lifestyle factor as a generic determinant influencing SC success. For non-gender specific cancers, gender played no statistically significant role in HC use nor WHO score.

Conclusions

Scalp cooling is effective for the majority of patients. The robust model for evaluating the drug and dose specific determinants of SC efficacy revealed no indications for changes in daily practice, suggesting factors currently being overlooked. As no correlation was identified between the determinants explaining HC use and WHO score outcomes, new methods for evaluation are warranted.

Introduction

Chemotherapy-induced alopecia (CIA) is a common yet unintended consequence of cytotoxic insult by chemotherapy agents to the mitotically-active hair matrix keratinocyte cells. CIA is considered by many patients the most distressing side effect of cancer treatment; negatively affecting body image, self-esteem, social interactions, and health-related quality of life (HRQoL) (Choi et al., 2014; Freites-Martinez et al., 2019; Ozusaglam & Can, 2021; Wils et al., 2019). Utilizing scalp cooling (SC) preceding, during and following chemotherapy infusions has shown a protective effect against CIA, with SC showing statistically significant higher hair retention rates comparable to the uncooled control groups in earlier SC trials (Betticher et al., 2013; Grevelman & Breed, 2005; Kargar et al., 2011; Lemieux et al., 2012; Nangia et al., 2017; Rugo et al., 2015; van den Hurk et al., 2013). The most documented understanding of the protective effect of SC against CIA is as a direct effect of vasoconstriction reducing blood perfusion within the hair matrix keratinocytes and decreased follicular metabolism (Grevelman & Breed, 2005; Janssen et al., 2007). However, it is becoming increasingly evident that scalp cooling protects by a variety of mechanisms which may operate in combination to prevent hair follicle cytotoxicity (Dunnill et al., 2018). Recent studies suggest that *in-vitro* cooling to 18°C provides cellular protection from drug-mediated apoptosis, reduces cellular drug uptake, upregulates the proliferative and metabolic capabilities of keratinocytes, and promotes quicker recovery (Al-Tameemi et al., 2014; Bajpai et al., 2020; Dunnill et al., 2020). Such findings lend support to the clinical observation that SC is more beneficial when the scalp skin is reduced to below 18°C (Komen, Smorenburg, et al., 2016). Additionally, SC provided superior regrowth even in patients who failed to retain their hair during treatment (Kinoshita et al., 2019; Ohsumi et al., 2021). More research is needed to allow a better, more complete understanding of the mechanisms by which SC cyto-protects to improve clinical results.

In recent years SC has been more broadly adopted, with comprehensive research into the safety profile of SC accelerating clinical acceptance (Enzlin & Hurk, 2023). As of 2023, SC devices are available in over 40 states in the US and in over 50 other countries across the globe (DigniCap, 2022; Paxman, 2020). Despite SC showing efficacy in most cases, also in controlled trials (Nangia et al., 2017; Rugo et al., 2015; Zhou et al., 2021)), variabilities between SC protocols, infusion regimens, duration and temperature of SC and outcome evaluation hinder large scale meta-analysis review and thus the opportunity to learn from large numbers of patients how to increase SC efficiency (Breed et al., 2011). Additionally, some clinicians still underestimate the high psychological impact of transient CIA on patients HRQoL, and health care insurers ignore the cost-effectiveness of SC related to societal willingness to pay for Quality Adjusted Life Years (QALYs) (Mulders et al., 2008; van den Hurk et al., 2014). This resulted in a minimal effort toward promoting SC as a preventative measure with reimbursement of its costs remaining difficult or unavailable in many countries, but also in many hospitals in countries where SC is already used (Paxman, 2021; Singer et al., 2021). Additionally, SC is still unavailable for many eligible cancer patients, despite equipment availability. As SC is not actively offered to each patient, it introduces inequality of care (Keim et al., 2022; Komen et al., 2013). Providing a comprehensive dossier with evidence of the efficacy of SC will provide a foundation for the wider global implementation of SC. Here, we therefore provide an audit into the real-world determinants of both the decision to use a head cover (HC) (e.g wig/scarf) as a surrogate for patient satisfaction with SC (van den Hurk. et al., 2012) and hair retention (self-reported WHO score for alopecia) as a measure of success after SC in the world's largest SC database.

Materials and methods

The Dutch Scalp Cooling Registry (DSCR) commenced in January 2006 with eight community hospitals and one academic hospital (van den Hurk. et al., 2012). The data collected spans over three cohorts (2006-2009 (19%, n=1411), 2009-2013 (68%, n=5035), 2013-2019 (13%, n=978)). The introduction of electronic recording from 2013 onwards facilitated a broader scope and minimized missing data. By its completion in December 2019, the registry included data from sixty-eight clinical locations.

All patients commencing chemotherapy with SC during this time were asked to participate, regardless of whether they previously received alopecia-inducing chemotherapy treatment and whether treated in the (neo-)adjuvant or metastatic setting. Exclusion criteria included patients with prior cold sensitivity disorder, cold post-traumatic dystrophy, cold agglutinin disease, cryofibrinogenemia, and cryoglobulinemia and those under the age of 18 years. Upon inclusion in the DSCR, nurses documented the year of birth, gender, cancer type, chemotherapy regimen (sequential details available in S1), dose (in mg/m^2 or AUC) and infusion time (minutes), treatment setting ((neo-) adjuvant/curative or palliative) and liver metastases (yes/no). In the latest cohort, nurses also reported (obligation-free) baseline blood test results.

In all three cohorts, during the first SC session patients self-reported their hair characteristics: the length (shorter/longer than 5cm), density (low/moderate/high), hair type determined by ethnical background (West/East European, Asian, Afro-American, Other), and whether they had colored (yes/no), permed (yes/no), or bleached (yes/no) it within two months prior to the start of chemotherapy. They also reported previous chemotherapy (yes/no), whether they used SC (yes/no) and if they experienced earlier severe hair loss despite SC (yes/no). During all chemotherapy sessions, patients documented cap colors (cap size), pre- and post-infusion SC times and prior hair dampening with water or conditioner (yes/no) (introduced as an adapted version of the questions during 2009, so therefore excluded for the first cohort). Hair dampening with water and/or conditioner to the hair prior to scalp fitting was subsequently merged into `Dampening` (no/yes/intermittent) and dyed, bleached, and permed categories were combined into `Chemical manipulation`. Patients also reported tolerability, headaches, and use of a regular pain killer to reduce headaches. All patients wishing to prematurely stop SC were asked to provide their reasoning to do so (categories include severe hair loss/baldness, tolerability, stopping chemotherapy/disease progression and other reasons). Nurses could also report reasons for ceasing SC under the same criteria. Only the latest cohort (2013-2019) included patient-reported anthropometric characteristics (height and weight), lifestyle tendencies (smoking and drinking frequencies), pre-treatment hair greying, natural hair shedding patterns, hair color and potential technical problems with the SC machine. This cohort also included repeatedly documenting changes in growth, texture, color, and condition of the hair, barriers in access to SC, rating the expertise of SC provided by the nursing staff and progressive evaluation of satisfaction and insecurity about the result to date. For information and future reference purposes, all content included in the DSCR has been described, but not all categories will be discussed below.

SC was performed using the Dignitana or Paxman (PSC1, PSC2 or Orbis) systems. Infusion time protocols were hospital-specific, and some chemotherapy regimens were sequential schemes [see S1]. Pre-infusion cooling time was generally set at 30 minutes with a pre-cooled cap, (an additional 15 minutes for non-pre-cooled caps) and the infusion process started thereafter. Post-Infusion Cooling Times (PICT) were standardized at 90 minutes; however, this was subject to implementation of independent treatment specific protocols as per manufacturers advisement and at the hospital's discretion. From 2012, hospitals started to adapt the PICT for Docetaxel (D) towards 45 minutes (van den Hurk et al.,

2012) and from 2016 towards 20 minutes (Komen, Breed, et al., 2016). Jevtana (J) was introduced in cohort two and the combination therapy of 5-fluorouracil, doxorubicin, and cyclophosphamide (FAC) was no longer administered from 2014. Patients receiving docetaxel, doxorubicin, and cyclophosphamide (DAC) were recommended not to start SC from 2016, owing to earlier recognition of suboptimal responses sacrificing HRQoL (van den Hurk et al., 2010).

Patient-reported outcomes are the only feasible evaluation method in a large multi-center real-world SC cohort. SC efficacy was therefore measured by the patient's preference to wear a HC (including a wig) during their last reported scalp cooling session (yes/no). HC is commonly used as the most important outcome measure of efficacy because it represents perceived satisfaction with scalp cooling. Hair retention derived from World Health Organization (WHO) score for alopecia offers a measure of SC success (van den Hurk et al., 2013). So, in addition, patients' self-reported WHO score (0: none, 1: minimal, 2: severe and 3: total alopecia) was evaluated during the last reported session (World Health, 1979). In the last cohort, the measure on head covering was corrected against use for religious reasons and whether the patient was bald but chose not to wear a HC. Both individual's preference to wear a HC and WHO score was evaluated to establish treatment specific determinants of SC success. Final analyses included only patients who had completed at least two SC sessions or if they discontinued SC because of severe CIA after the first session. Drug categories with less than 25 patients were collated (Mixed Group) and the remaining uncategorized due to incomplete dosing schedules/small sample sizes (n<10).

Statistics

Patients within the dataset were stratified by chemotherapy regimen and dosages as chemotherapy-induced hair follicle damage and severity of CIA are understood to be drug and dosage specific and the most important determinant of SC success (Haque et al., 2020). Whether the patient, chemotherapy regimen and SC characteristics were associated with HC use or WHO score after SC was evaluated by logistic regression analyses and expressed as odds ratios (OR). Continuous variables were grouped into categories, except for the number of cooling sessions. The correlation between HC uses and binary-WHO (yes (WHO 0/1) vs. no (WHO 2/3)) was determined by Kendall's rank correlation analysis. Separate analyses were conducted for the last cohort to assess the effect of lifestyle factors on final outcomes.

Independent multivariate analysis (MVA) was completed for each of the largest treatment categories (FEC, AC, D and T; see S1) to determine the relative drug-specific relationship between the variables and identify predictors of SC efficacy. Variables used as predictors included: Clinical location, cancer type, dose, gender, treatment setting, age group, ethnic hair type, hair length, hair density, chemical manipulation, previous chemotherapy, infusion time group, PICT group, dampening, number of cooling sessions, HC use and WHO score. Outcomes were based on binary responses; HC (yes vs. no) and binary-WHO.

The more traditionally used stepwise (forward/backwards) approaches to linear regression modelling are cumbersome for larger numbers of predictors and mixed model approaches are often flawed by premature convergence. In the current study, the use of machine learning (ML) models trained by ML algorithms allowed the so called "brute force" exploration method for variable reduction and model refinement. This method facilitates exhaustive screening of all combinations of chemotherapy-, patient- and cooling characteristics and their interactions. Due to the limited sample sizes of many of the treatment categories (n<1000), the more conservative Akaike's Information Criteria (AIC) model selection measure was used to select the optimum generalized linear model (GLM). Where in epidemiology the (adjusted) R^2 validation is used to evaluate fitting of a model, AIC is used in statistics as an estimator of prediction error and used to determine the best of the many different models for a given dataset. Herein the lowest AIC yielding the most accurate predictive power. Using this approach, the optimum GLM ultimately explains the largest proportion of variation using the fewest possible independent variables with comparable level of precision.

Firstly, chemotherapy regimen-specific model generation was constructed using a restricted version of the dataset (complete data only, missing variable's location and quantification see S2). The remainer was retained as control data for later analyses. Secondly, optimum model selection for HC use and WHO score for each treatment was finalized by internal cross validation between the lowest AIC (+2 AIC units) models. The predictive performance of the optimum models was tested using the control data. This was assessed using confusion matrix analysis to quantify the proportion of correct predictions (see figure S3 for description of training and validation sets). Finally, the final optimum model results were recalculated using the original dataset, restricted only for missing data in the optimum model variables. Cohen's Kappa coefficient (κ) was used to measure inter-rater agreement within each model. 95% Confidence Intervals (CIs) and p-values were computed using a Wald z-distribution approximation. Statistical differences were indicated if $p<0.05$ (* $p<0.05$, ** $p<0.01$, *** $p<0.001$) and reported p-values were two-sided. Statistical analyses were performed using R software (V: 4.2.2) with the additional packages tidyverse and glmulti (Calcagno & de Mazancourt, 2010; R-Core-Team, 2022; Wickham et al., 2019)

Results

A total of 7424 patients were enrolled in the DSCR between 2006-2019. Most patients were female (87%), chemo-naïve (77%), breast cancer patients (73%), treated in the adjuvant setting (61%) (see Figure 1). The mean age was 55 years (range 18 – 98 years). The median pre-infusion cooling time was 36 minutes (Standard Deviation (SD) 10, range 15-75) and the median PICT was 90 minutes (SD 23, range 15-124). The median number of cooling sessions was 16 (SD 10, range 1 – 44). In total 52 patients (0.7%) used a Dignitana SC machine.

Overall, over half of the patients (n = 4191, 56%) chose not to wear a HC and 53% (n = 3784/7183) reported good hair retention (WHO score 0/1) during the last SC session. For those with completed data, WHO scores for alopecia (WHO 0, 1, 2, 3) for patients wearing head covering (n = 3127), were 5%, 11%, 26% and 58% (n=106 missing). For patients not wearing HC scores were (n = 4056) 39%, 42%, 19% and 0% (n=135 missing). The correlation between HC uses and binary-WHO score for the whole patient series was 0.64, z = -54.396, p=<.001).

Figure 1: Patient, treatment, scalp cooling characteristics and scalp cooling efficacy (n= 7424)

Figure 2: Scalp cooling efficacy by chemotherapy regimen and dose (n=7338)

The proportion of patients choosing not to wear a HC at the start of their final session varied dependent on chemotherapy regimen and dosage; results ranged from 10% to 98% (see Figure 2). Overall patients receiving taxanes had better results (78%) than patients receiving anthracyclines (40%) or combination therapies of anthracyclines and taxanes (45%). Patients receiving lower chemotherapy dosages had better results than patients with higher dosages of the same chemotherapy (or combination). For the sequential schemes ACT (4x AC followed by 12 x T) did better than ACD (4x AC followed by 4x D) and both did better than AC alone. FECD (FEC 3x followed by D 3x) also had better results than FEC (6x) alone. Infusion times and PICTs varied considerably within chemotherapies.

For the specified chemotherapy regimens, models were generated to predict SC outcome (see S3). Repeating the process by including interactions further improved the final model per chemotherapy regimen. The prediction accuracy of each training model was high (0.84-1.00) (Table S3). Subsequently, final models represented 90% (for AC (binary-WHO)) to 98% (for D (HC)) of the total patients receiving FEC, AC, D, T within the DSCR, (see Figure 3). See S3 for full model parameters and extended validation data.

Figure 3: Significant determinants of multivariate analyses on scalp cooling efficacy per chemotherapy regimen for head cover use and binary-WHO.

Determinants per chemotherapy differed tremendously and trends were not analogous between primary outcomes (see Figure 3; for full breakdowns see S4). The most common predictor of both HC and binary-WHO outcomes was the number of SC sessions. In most cases, HC was a predictor of binary-WHO outcome and vice versa. Additional factors including age group, gender, dose, cancer type, treatment setting, previous chemotherapy, chemical manipulation, dampening, hair type, and PICT group were only selectively associated with the primary outcomes. Clinical location, hair length and hair density failed to be included as predictor factors in any model. Intercept significance for AC and D refers to an unaccounted baseline effect which is not explained by the independent variables in the model. This is an indication that important working mechanisms have been overlooked.

For non-gender-specific cancer types, 81% (n=693/856) of the patients received comparable treatment regimens. Gender played no statistically significant role in the preference to wear a HC (p=0.912), nor the WHO score (p=0.393), nor an individual's decision to prematurely cease SC (p=0.329) (see Figure 4).

Figure 4: Non-gender specific cancer results of scalp cooling (n=693)

Of the 961 individuals in cohort 3 reporting lifestyle tendencies (Smoking: Yes, current (n=116), Yes, ex-smoker (n=360), No (n=485); Drinking: Regularly (n=224), Occasionally/Socially (n=404), No, never (n=333)), neither smoking nor drinking habits showed significant impact on HC use, or WHO score when corrected for gender, age, cancer type, or chemotherapy regimen.

Discussion

To our knowledge this is the largest prospective multi-center patient series on SC. The DSCR data showed that SC results of individuals not wearing a HC at the start of their final treatment varied per chemotherapy regimen, as reported in the global SC literature (Martín et al., 2018; Nangia et al., 2017; Vasconcelos et al., 2018). Despite the substantial number of patients, our robust models did not show any patient, nor cancer or treatment characteristic as generic determinant influencing SC success. This is parallel to earlier smaller studies (Pedersini et al., 2021). In contrast with another study where nicotine abuse was linked to suboptimal hair retention rates (Schaffrin-Nabe et al., 2015), our results did not link lifestyle characteristics with SC efficacy. The lack of significance indicates that there will be other -yet unknown- factors primarily differentiating patients with good and suboptimal outcomes. Also dampening the hair did not show convincingly improved results.

For the whole patient series better responses for FECD than FEC shows that the switch to a taxane (D) is less cytotoxic to the follicles than continuing with an anthracycline. Also, ACT and ACD perform better than AC with SC in terms of hair retention derived from the WHO score, although dosages were comparable. There might be a twofold explanation; first, it might be attributed to information bias, i.e., nurses might have registered patients on the sequential scheme in the AC group because that was the chemotherapy at SC initiation. Secondly, it is known that hair grows during taxane treatment with SC (Bajpai et al., 2020; de Barros Silva et al., 2017; Fushimi et al., 2019; Kinoshita et al., 2019; Sahadevan et al., 2016), so the added three months before final review may account for the improved outcome; camouflaging incomplete hair loss within AC treatments. Therefore, patients should be encouraged to continue SC, also if the result is not satisfactory during AC.

The correlation between HC uses and WHO score was moderate, however, both were each other's predictors. Head covering is a logical consequence of hair loss severity, however this holds true for many but not all patients, as described in earlier studies (Komen et al., 2018; van den Hurk et al., 2013). In addition, determinants influencing SC success differed between both primary outcomes, indicating that these are really two different measures. It endorses that outcome measures for SC, irrelevant of logical psychological assumptions, should not be combined in meta-analyses. In addition, as both HC and binary-WHO outcomes are fitted to different data, models cannot be directly compared. Here, the HC use training models had lower AIC scores and incorporated fewer variables where binary-WHO models with more variables were more accurate predictors of outcome, with almost perfect to perfect inter-rater agreement. Because the preference for providing scores is different for many patients, a combination of methodologies could be a solution. An example is to allow patients to rate hair loss based on pre-defined images in combination with a numerical and a categorical score like used in the HAIR-QoL measure for alopecia (van den Hurk et al., 2023; Winstanley et al., 2023). Other aspects of evaluation are the pattern and the course of hair loss over time.

For non-gender-specific cancer types, gender played no statistically significant role in the outcomes of SC success nor prematurely ceasing it. This is in contrast with previous notions that higher success rates in the small proportion of men undertaking SC (overall no HC average of 86% versus 52% for females – see Figure 1) are attributed to a combination of factors including short hair, hormone levels, lower dose regimens (e.g. D for prostate cancer vs breast cancer) and societal acceptance of male baldness as fashionable (van den Hurk. et al., 2012).

For many chemotherapies, the extent of hair loss without SC is unknown, with data mostly being drawn from pharmaceutical trials and practice-based information from medical personnel. Randomized control trials (RCT) are now scarcely performed owing to earlier recognition of the benefits of SC against CIA (Nangia et al., 2017; Rugo et al., 2015; Zhou et al., 2021). Consequently, the extent of the added value of SC for chemotherapies with less pronounced hair loss is unknown. Moreover, it is less clear how effective the use of a HC is as a surrogate for patient satisfaction with SC for these chemotherapy treatments. Furthermore, with the increasing research into SC preventing persistent-CIA, previous assumptions of ineligibility based on chemotherapy regimen need to be revisited (van den Hurk et al., 2010).

A strength of this study is the extent of the database with high completeness of data, especially for patient-reported data from multiple centers. The increased completeness in the second and third cohort (see S5) reflects the benefits of forced response electronic data collection. However, despite this being a relatively large study, and advancements were made to standardize SC procedures (PICT, outcomes etc.), hospital-specific variabilities between SC protocols, dosages, infusion regimens, and pre- and post-infusion cooling times still makes interpretation of significant determinants for outcomes challenging (see S6). This would argue for even more detailed guidelines, preferably specified for each drug regime. A disadvantage for this and many other SC studies is the primary endpoint. For large multicenter studies, reliable clinical evaluation of hair loss is not feasible. Furthermore, physical hair checks are possible for trials but are labour intensive and not practical for real world cohorts (Komen et al., 2018). Patient-reported outcome data collection is challenging to implement; however, its recurrent application limits recall bias and it bypasses medical personnel interrater variability (Komen et al., 2018). The currently used end-point evaluation may not be optimal for SC efficacy review, and it should preferably be measured some weeks after treatment completion instead of during chemotherapy. Another limitation is that for ML preferably larger patient samples are used to enable methodologies that further improve model sensitivity, e.g. Bayesian Information Criterion (BIC) or least absolute shrinkage and selection operator (LASSO). Besides, ML methods are generally not built with p-values to check statistical thresholds, but assess predictive ability through self-learning. As such, further evaluation using the more commonly used Shapley value may improve understanding of ML model predictions (Rodríguez-Pérez & Bajorath, 2020).

The most important clinical implication is that medical personnel involved in patient care need to be aware that males are also eligible for and benefit from scalp cooling. In addition, comprehensive standardized registration with more extensive outcome evaluation of hair loss and recovery is essential for long-term international protocol optimization and revealing the true determinants of SC efficacy to accelerate advances for individual patient care. Adding biomarkers, for example scalp skin temperatures, to clinical studies will contribute to better predictions of who will experience hair loss and why (van de Poll-Franse et al., 2022).

Conclusion

In conclusion, we have described and validated a robust model for evaluating the chemotherapy specific determinants of SC efficacy. This study implies that apart from chemotherapy regimen, no specific characteristics were universal determinants of SC efficacy. Whilst currently unknown determinants may be exerting a baseline influence on efficacy outcomes, gender plays no significant role. SC is effective for the majority of patients, and it offers patients the opportunity for privacy, identity, and control in their cancer treatment journey.

Implications for practice

The most important clinical implication is that medical personnel involved in patient care need to be aware that males are also eligible for and benefit from scalp cooling. In addition, comprehensive standardized registration with more extensive outcome evaluation of hair loss and recovery is essential for long-term international protocol optimization and revealing the true determinants of SC efficacy to accelerate advances for individual patient care. Adding biomarkers, for example scalp skin temperatures, to clinical studies will contribute to better predictions of who will experience hair loss and why.

Conflicts of interest

The authors declare no conflicts of interest.

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