

## Scalp Cooling for Chemotherapy-induced Alopecia Prevention: “Fantasy Turned into Reality”

Breast cancer remains the most prevalent cancer in India according to the latest GLOBOCAN statistics.<sup>[1]</sup> A majority of these patients receive either neoadjuvant or adjuvant chemotherapy as part of multimodality treatment. Chemotherapy has shown to reduce the 10-year relative risk of death from breast cancer by around 35%.<sup>[2]</sup> Over the past few decades, the toxicity of chemotherapy has been largely mitigated by various advances in supportive care such as the use of growth factors, antiemetics, and broad-spectrum antibiotics.<sup>[3]</sup> Patients are assured regarding the various side effects of chemotherapeutic agents and are motivated to undergo treatment without being fearful of overt toxicity. With patients surviving much longer than ever before,<sup>[4]</sup> there is now increased focus on the cosmetic and psychological aspects of breast cancer treatment.

One of the most distressing side effects of chemotherapy is alopecia, which has plagued women undergoing cancer treatment. Alopecia is a visible reminder to the patient as well as to other people that cancer treatment is ongoing. In a study by McGarvey *et al.*, around 50% of women considered alopecia as the most significant toxicity of chemotherapy and 8% disclosed that they would forgo chemotherapy, because of the stigma of hair loss.<sup>[5]</sup>

Scalp cooling has risen as a beacon of hope to combat alopecia. It is based on the principle of cold-induced vasoconstriction of the vessels in the scalp, resulting in reduced chemotherapy exposure to the hair follicle and a decrease in follicular metabolism, thereby resulting in reduced hair loss.<sup>[6,7]</sup> Scalp cooling was previously carried out using multiple precooled caps, which was cumbersome, required frequent changes of caps, and resulted in unpredictable variations in temperature. Scalp-cooling devices have made things simpler, with easier fitting scalp devices that circulate a coolant and regulate cooling, which maintains a steady temperature. The rate of success of scalp cooling depends on three key factors: a well-fitted cap, adequately cold temperature, and type of chemotherapy used. Ill-fitting caps can result in gaps, which may then result in hair loss in these gaps. Taxanes have shown to have better hair preservation rates when compared to anthracyclines.<sup>[8]</sup>

Recent studies have explored the role of scalp-cooling devices in preventing chemotherapy-induced alopecia in women undergoing breast cancer treatment.<sup>[8-12]</sup> To date, only two randomized trials<sup>[8,9]</sup> have reported benefit of scalp cooling in breast cancer, but they preferentially studied the use of taxanes and did not consider hair regrowth as part of their study endpoints. In addition, these trials were done largely in early-stage breast cancer patients, and the

efficacy of scalp cooling in locally advanced breast cancer was not adequately explored. Furthermore, the population included was a Western Caucasian majority. The hair characteristics, climate, and cultural practices are vastly different in Asians, and the response of hair to various forms of stress differs between the two populations.<sup>[13]</sup>

The study conducted in Tata Memorial Hospital (TMH), Mumbai,<sup>[14]</sup> was an investigator-initiated, randomized controlled trial in early and locally advanced breast cancer patients undergoing curative chemotherapy that included both taxanes and anthracyclines and looked at the efficacy of scalp cooling using the Paxman scalp-cooling system. The primary endpoint was hair preservation and secondary endpoint was hair regrowth. Hair preservation was assessed clinically as well as objectively by pictorial tool review of five photographs after four cycles or 12 weeks of chemotherapy using the Common Terminology Criteria for Adverse Events version 4.0 Scale for alopecia with failure as Grade 2 alopecia. Hair regrowth was assessed at 6 and 12 weeks defined as Grade 0 or 1 alopecia. Further validation was done by independent observers outside the study and the patients themselves to remove chances of bias. Forty percent of the study population had locally advanced breast cancer and was adequately represented. The study showed 57% hair preservation in the scalp-cooling arm and 0% in the control arm that did not receive scalp cooling ( $P = 0.00004$ ). At 6 and 12 weeks, the hair regrowth was 89% and 100% in the scalp-cooling arm, while it was 12% and 59% in the control arm, respectively ( $P < 0.0001$  and  $P = 0.0003$ ). The results also indicated that scalp cooling was more effective in women who received taxanes followed by anthracyclines, rather than the reverse order (77% vs. 33%,  $P = 0.0307$ ). The quality of life (QOL) was improved in the scalp cooled arm with regard to the question of retention of hair, while the other parameters were not significantly different. The European Organisation for Research and Treatment of Cancer QOL questionnaire does not specifically address the question of hair loss and its effects; also, the overall effect of a breast cancer diagnosis, breast surgery, and toxic chemotherapy may have impacted the QOL in both the groups resulting in a masking of the benefit of scalp cooling. Adverse events were mild, mainly consisting of headache and feeling of coldness. These findings mark a major step forward that helps in reassuring patients about to start chemotherapy for breast cancer and can improve compliance and the QOL as well. However, better QOL measures are required that encompass the effects of chemotherapy-induced alopecia on the body

image, sexuality, and mental well-being of our patients. Application of these newer tools can then actually demonstrate the convincing benefit of scalp cooling.

Scalp cooling in the TMH study led to hair preservation in only 33% of patients who received anthracyclines first. However, even after significant hair loss, the regrowth rate was fast during the paclitaxel phase and patients went back to normal hair density quicker. Successful hair preservation was defined as WHO Grade 0 (no loss of hair) and 1 (<50% loss of hairs) alopecia. Hence, some loss of hair, which can easily be camouflaged by the remaining hair, can be expected with scalp cooling. There was a slight imbalance in age and prevalence of hypothyroidism in the two groups. However, after adjusting for imbalance, scalp cooling and chemotherapy sequence continued to have significant impact on hair preservation.<sup>[15]</sup>

A similar Asian study was recently reported from Japan,<sup>[16]</sup> which looked at the efficacy of scalp cooling along with hair regrowth at 12 weeks. Among 48 patients, 34 patients received scalp cooling using the Paxman system. No alopecia was seen in 26.7% of the patients in the scalp-cooling group versus 0% in the control group. Faster recovery of hair volume was seen in the scalp-cooling group as well. The main drawback of the study when compared to the TMH study was that it was nonrandomized. Other trials from the Western world, including those by Nangia *et al.* and Rugo *et al.*, mirrored the results obtained in the TMH study.<sup>[8,9,17,18]</sup>

The risk of scalp metastasis has been addressed by various studies. A systematic review of three studies involving more than 50,000 patients followed for 2.2–9 years found about a 1% rate of scalp metastases with or without scalp cooling.<sup>[19]</sup> A meta-analysis of data on 1959 patients who used scalp cooling and 1238 who did not<sup>[20]</sup> found the incidence of scalp metastases to be under the 1% mark, with the *P* value not statistically significant.

Another issue is the increased risk of systemic metastasis as circulating tumor cells may lodge in the scalp and be shielded from chemotherapy owing to the cold-induced vasoconstriction.<sup>[21]</sup> These cells may then spread out later resulting in widespread metastatic disease. However, a retrospective review among patients who used scalp cooling or not, showed comparable number of metastatic events with comparable hazard ratios.<sup>[22]</sup> However, more prospective data are required to fully answer this question.

The main hurdle to the use of these scalp-cooling devices in low- and middle-income countries is the increased total duration of chemotherapy.<sup>[18]</sup> A typical patient who opts for scalp cooling will require an additional 30 min before the start of chemotherapy and another 90 min of postcooling time after the end of chemotherapy. Most hospitals are already overburdened<sup>[17]</sup> and use of scalp cooling may

result in delay of starting chemotherapy in subsequent patients. However, with improvements in the health-care infrastructure, this concern may be corrected. An option is to have a separate scalp cooling area near the daycare where the patient can be shifted to, once chemotherapy is over. Furthermore, if biologicals such as trastuzumab are required, they can be started during the postcooling time. Furthermore, training of nurses for ensuring adequate cap fit is a must and must be ensured even in busy centers.

Another issue is the question of reimbursement, as temporary hair loss could be perceived as cosmetic and may not be covered by government insurances. This is a concern that may need to be addressed to reduce out-of-pocket expenditures of our patients.

We now have adequate evidence, for the widespread adoption of scalp cooling in controlling alopecia, a visual stigma that labels someone as a cancer patient. However, we need to develop better QOL tools to investigate impact of this intervention in QOL. This method offers hope to many who would consider omitting chemotherapy, fearing social discrimination, and loss of body image. The variation in hair preservation according to the sequence of chemotherapy can also help in deciding the chemotherapy regimen causing the least alopecia. Accessibility and implementation remains a concern, but with the latest approach of “patient centric care,” the physical as well as the mental health of our patients take center stage in the treatment decisions of tomorrow and scalp cooling definitely features high up on that list.

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There are no conflicts of interest.

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