v. 4, n. 10, 2024

International Journal of Health Science

PREVENTION AND TREATMENT OF CHEMOTHERAPY-INDUCED ALOPECIA: A NARRATIVE REVIEW ON EMERGING TECHNIQUES

Ana Elisa Nunes da Rocha Dias
Faculdade IMEPAC de Itumbiara (IMEPAC ITUMBIARA)
Itumbiara - GO
https://orcid.org/0000-0001-5005-542X

Viviane Thaís Gaidarji Nesvera
Faculdade Meridional (IMED)
Passo Fundo - RS
https://orcid.org/0009-0004-6739-1576

Taís Bruna Michelon
Universidade Franciscana (UFN)
Santa Maria - RS
https://orcid.org/0009-0007-6504-3836

Bianca Azevedo Berger Amaral
Universidade Vila Velha (UVV)
Vila Velha - ES
https://orcid.org/0000-0003-3630-9635

Maria Tereza de Medeiros Leite Espínola
Centro Universitário de João Pessoa (UNIPÊ)
João Pessoa - PB
https://orcid.org/0009-0004-2990-1125

Leonardo Pizzolatti Miranda Ramos
Universidade Cidade de São Paulo (UNICID)
São Paulo - SP
https://orcid.org/0009-0007-1164-2278

Erica Domiciano Fabiano
Universidade Cidade de São Paulo (UNICID)
São Paulo - SP
https://orcid.org/0009-0006-1299-0808

Elizandra Franciele Fernandes da Silva
Universidade do Oeste Paulista (UNOESTE)
Jaú - SP
https://orcid.org/0000-0003-1214-5496

Livia Harumi Takahashi
Universidade de Marília (Unimar)
Marília - SP
https://orcid.org/0009-0007-8286-4652

João Pedro Carneiro Gallavotti
Universidade Vila Velha (UVV)
Vila Velha - ES
https://orcid.org/0000-0002-8884-4130

Marília Gabriela Tomasi Pianesso
Universidade Franciscana (UFN)
Santa Maria - RS
http://orcid.org/0009-0003-3955-983X

Amanda Carolina Zicatti da Silveira
Pontifícia Universidade Católica de São Paulo
São Paulo - SP
https://orcid.org/0000-0001-8963-9553

Abstract: Goal: To analyze emerging techniques in the prevention and treatment of chemotherapy-induced alopecia, and to evaluate how effective and safe scalp cooling and photobiomodulation techniques may be. Methods: Using the Pubmed database platform, a narrative bibliographic review was carried out, with the aim of locating relevant sources for the pre-determined research objective. The search was carried out using the search terms "Chemotherapy", "Alopecia", "Chemotherapy Induced Alopecia", "Low-Level Light Therapy", Scalp Cooling", "Prevention" and "Treatment", in association with the Boolean operators "AND" and "OR", to search for articles, resulting in 434 initial articles. Within these numbers, due to the inclusion and exclusion criteria, only 28 were selected. **Discussion:** Studies show that patients who used the hair cryotherapy technique had less hair loss. The photobiomodulation technique has been well tolerated by patients and no significant adverse effects have been reported. **Final Considerations**: Emerging treatments for alopecia, such as scalp cooling and photobiomodulation, are showing excellent results, however, they require more research in order to evaluate ideal treatment protocols, long-term patient safety and effectiveness in different types of alopecia according to different chemotherapy medications.

Keywords: Chemotherapy, Alopecia, Chemotherapy-induced alopecia, Low-level laser therapy and Scalp cooling.

INTRODUCTION

Alopecia, characterized by a reduction in hair volume, manifests itself in a variety of ways: localized, diffuse, total, sudden, gradual, acute, chronic, reversible or permanent. It is categorized into three main classes: androgenetic alopecia (AGA), cicatricial (when there is destruction of the hair follicle) and congenital. The hair cycle comprises

four phases: anagen (4 to 6 years of growth), catagen (3 weeks, period of apoptosis), telogen (3 months, followed by hair expulsion) and kenogen (2 to 12 months of latency). manifestations can be exacerbated or induced by several factors, including oncological treatments (QUESADA S. et al., 2021).

The incidence of alopecia is significantly high in individuals undergoing antineoplastic therapies, which increases the relevance of its investigation and management (QUESADA S. et al., 2021). Alopecia related to cancer and antineoplastic use (ANIA) is a complex phenomenon, associated with substantial adverse effects, deteriorating the quality of life of cancer patients. The negative perception of self-image, induced by alopecia, can precipitate anxiety, depression and other psychosocial complications, becoming an additional challenge in oncological treatment (WIKRAMANAYAKE C. T. et al., 2023).

Thus, several therapies emerge to combat this unwanted effect of chemotherapy therapy, including scalp cooling, the most effective strategy for prevention in patients with solid tumors, and treatment with topical minoxidil for hair growth after undergoing treatment. with chemotherapy. (WIKRAMANAYAKE C. T. et al., 2023; MICHEL A. et al., 2023).

This study aimed to analyze emerging techniques in the prevention and treatment of chemotherapy-induced alopecia, and evaluate how effective and safe scalp cooling and photobiomodulation techniques may be.

METHODOLOGY

This is a narrative bibliographic review developed according to the criteria of the PVO strategy, an acronym that represents: population or research problem, variables and outcome. Used to prepare the research through its guiding question: "What are the emerging techniques in the prevention and treatment of chemotherapy-induced alopecia, and how effective and safe can scalp cooling and photobiomodulation techniques be?" In this sense, according to the parameters mentioned above, the population or problem of this research refers to patients who have undergone chemotherapy who present or are at risk of developing alopecia and candidates for the use of new emerging techniques in the prevention and treatment of alopecia induced by chemotherapy, including its mechanisms of action, and thus evaluate the effectiveness of such techniques in preventing and treating alopecia in affected patients. The search was carried out using the PubMed Central (PMC) database. The search terms were used in combination with the Boolean term "AND", "OR" through the search strategy: "(Chemotherapy) AND ((Alopecia) OR (Chemotherapy Induced Alopecia)) AND ((Low-Level Light Therapy) OR (Scalp Cooling) OR (Prevention) OR (Treatment))". From this search, 434 articles were found, subsequently submitted to the selection criteria. The inclusion criteria were: articles in English and Spanish published in the period from 2018 to 2023 and which addressed the themes proposed for this research, studies of the review type, meta-analysis, observational studies and clinical trials, available in full. The exclusion criteria were: duplicate articles, available in abstract form, which did not directly address the proposal studied and that did not meet the other inclusion criteria.

A total of 28 articles were selected to compose the present study.

DISCUSSION

Chemotherapy is one of the main treatments used to fight cancer. However, this procedure generates a much-feared side effect, alopecia. That is, patients undergoing this therapeutic approach face an imbalance that interrupts the follicular growth cycle, and this disorder causes hair loss called chemotherapy-induced

alopecia (CIA). This phenomenon profoundly affects patients' quality of life, impacting their self-image. About 8% of patients refuse chemotherapy to avoid alopecia (KIM M. H. et al., 2020).

The morphological structure of the hair follicle presents distinct characteristics both laterally and longitudinally. Vertically, it is segmented into four regions: infundibulum, istimus, suprabulb and bulb. The infundibulum extends from the follicular opening to the insertion of the sebaceous gland. Just below, the istimum runs from the sebaceous gland to the arrector pili muscle, where there is a population of multipotent stem cells crucial for follicular cycling. This is followed by the suprabulbar region, characterized by thick lateral, internal and external sheaths, which surround and longitudinally delimit the follicle. Finally, the bulb contains a central and richly vascularized portion of dermal fibroblasts, called dermal papilla, surrounded by a matrix of keratinocytes with high mitotic potential, called capillary matrix. (DUNNILL C. J. et al., 2018)

Hair cycling is fundamentally dependent on the interaction between the dermal papilla and the follicular stem cell lineage, as both do not undergo mass apoptosis and remain essentially constant throughout the cycle. (DUNNILL C. J. et al., 2018)

The anagen phase is marked by hair growth, initiated by the secretion of growth factors by the dermal papilla, which induces the migration of stem cells from the istimum to the bulb, as well as their proliferation and differentiation. Known signaling pathways that induce anagen include: Wnt, TGF-β/BNP, Hedgehog, ECG, FGF, Notch and TNF. (DUNNILL C. J. et al., 2018)

Catagen is characterized by massive apoptosis of matrix and sheath keratinocytes, interrupting hair growth. It is induced by the presence of apoptotic factors, such as FGF-5, IFN-γ, Substance P and Caspases. Disruption of the production of dermal growth factors can also induce this phase. (DUNNILL C. J. et al., 2018)

During telogen, there is a high production of growth factor antagonists, making the follicle refractory to anagen stimuli. At this stage, the dermal papilla anatomically approaches the progenitor stem cells, and as the antagonist molecules decrease in level, the follicle prepares to enter anagen (DUNNILL C. J. et al.,2018).

At a given time, the mitotic rate of malignant cells is greater than that of healthy cells; consequently, the mechanisms of action of chemotherapy agents are mainly based on interrupting the cell cycle (DUNNILL C. J. et al., 2018) The hair follicle is particularly sensitive to such drugs, as, in the anagen phase, the keratinocytes of the matrix have high proliferative activity. In the telogen and catagen phase, due to less cell proliferation, they are less sensitive to chemotherapy drugs (RUBIO-GONZALEZ B. et al., 2018).

> The incidence of AIQ may vary with the variety of substances used in chemotherapy. Studies indicate that the degree of damage to hair follicle stem cells (HFSC) can determine the reversibility of alopecia (YANG J. et al., 2020). For example, tyrosine kinase, MEK, RAF and EGFR inhibitors block signaling pathways responsible for cell proliferation, causing diffuse alopecia (RUBIO-GONZALEZ B. et al., 2018). On the other hand, immunotherapies induce an inflammatory response against the follicles, generating a pattern of alopecia areata. Regardless of the therapy, there is generation of reactive oxygen species (ROS) and massive apoptosis of matrix keratinocytes, mediated by the p-53 protein (FREITES-MARTINEZ A. et al., 2019).

Among the approaches investigated, scalp cooling (ZHANG Y.; JIMENEZ J. J., 2023) has emerged as a non-invasive technique to preserve hair follicles during chemotherapy.

At the same time, advances in the field of pharmacology have brought to light the potential of JAK inhibitors (OCAMPO-GARZA J. et al., 2019), which have demonstrated encouraging effects in promoting hair growth. Additionally, the ECOHAIR system, with its innovative approach (ALONSO M. R. et al., 2019), and TLR7 cocrystallization agonists have been studied for their ability to activate immunological and cellular pathways to strengthen hair. The use of traditional Chinese herbs such as Xiaoaiping (Marsdeniae tenacissimae) is also a subject of investigation due to its ancient medicinal properties, while topical lotion CG428 and compounds derived from human placenta are explored for their promising bioactive activities. The "Capelli Naturali a Contacto®" (CNC®) device offers a mechanical and cosmetic approach, while photobiomodulation (PBM) or low-level laser therapy is studied for its therapeutic potential in treating alopecia (ZHANG Y.; JIMENEZ J. J., 2023). These treatment modalities reflect the diversity and potential of current research in the search for effective solutions for chemotherapy-induced alopecia.

A prospective clinical trial evaluated the compound ECOHAIR® (Coffea arabica and Larrea divaricata) in accelerating hair growth in patients with chemotherapy-induced alopecia, showing complete hair recovery in 30 days, compared to the placebo group (ALONSO M. R. et al, 2019).

Experiments with agonists in the cocrystallization of TLR7, such as Imiquimod, have shown potential to stimulate hair growth, although they require further investigation.

Other approaches include the use of Chinese herbs such as Xiaoaiping (Marsdeniae tenacissimae), the topical lotion CG428, compounds from the human placenta, and the "Capelli Naturali a Contatto®" (CNC®) device, which have shown promising results in preliminary studies, but still require more research to prove their effectiveness and safety.

Research on the induction of the P53 cell to protect hair follicles against the cytotoxic effects of chemotherapy is also a promising field, requiring further studies to evaluate in humans (ZHANG Y.; JIMENEZ J. J., 2023).

In view of all the emerging techniques discussed, due to their prevalence, access and clinical effectiveness, the following will focus on detailing the use of scalp cooling techniques and photobiomodulation.

SCALP COOLING OR HAIR CRYOTHERAPY

Hair cryotherapy, also known as scalp cooling technique, is one of the most used techniques to prevent chemotherapy-induced alopecia today. This technique is based on the premise that reducing local temperature can induce vasoconstriction, thus limiting blood flow to the hair follicles. With less chemotherapy reaching the scalp, the follicles are less affected by the toxicity of the treatment. Furthermore, cooling decreases the metabolic rate of the follicles, reducing their activity and, consequently, their susceptibility to chemotherapy damage (AMARILLO D. et al., 2021). The effectiveness of this method may vary depending on the genetic predisposition of each patient and the chemotherapy agent used, since different medications affect the hair follicle in different ways (MARTÍN M. et al., 2023).

The administration of chemotherapy drugs must be started just 30 minutes after the scalp begins to cool, to ensure an ideal temperature in the follicular unit when the medication reaches the area. After completion of the session, cooling must be maintained for a period, which varies according to the dosage and medication regimen, sometimes up to 90 minutes later to maximize the

effectiveness of the method. This technique is not recommended for individuals with sensitivity to cold, cryoglobulinemia and patients with hematological tumors (SILVA G. B. et al., 2020).

In general, patients found the cooling to be very tolerable and with minimal discomfort. However, some reported headache, scalp pain, dizziness, and a feeling of heaviness and cold in the head, leading some individuals to discontinue treatment (ORLANDO L. et al., 2019). The technique is most effective with certain types of chemotherapy and may not be appropriate for all patients, especially those with hematological cancers where there is a concern that malignant cells may remain in hair follicles that are cold and therefore beyond the reach of chemotherapy. There is also concern about possible metastases to the scalp, due to the reduced concentration of drugs in the region. However, some studies have indicated that there is no association between cooling and the incidence of metastasis (MUNZONE E. et al., 2019).

Patients who underwent scalp cooling had less hair loss compared to the control group. Proving to be an effective and safe approach to preventing alopecia (BAJPAI J. et al., 2020; BRUNNER C. et al., 2022).

PHOTOBIOMODULATION OR LOW INTENSITY LASER THERAPY

Photobiomodulation (PBM), also known as low-level laser therapy (LLLT), is a therapeutic technique that uses low-power light emissions to stimulate biological processes in the body. In the context of treating chemotherapy-induced alopecia, PBM has gained attention due to its ability to promote tissue regeneration and repair, including damaged hair follicles. There are a variety of PBM devices available on the market, designed to stimulate hair growth in individuals affected by alopecia, including that induced by medications (HAMBLIN. M. R., 2022).

Chemotherapy affects keratinocytes located in the bulb region in the anagen phase, which is responsible for hair production. As a consequence, the hair follicle transitions to a dystrophic catagen stage, resulting in hair loss (HAMBLIN. M. R., 2022). This therapy works by emitting specific wavelengths of light that are absorbed by cells. This absorption energizes the mitochondria, which are the energy centers of cells, thus increasing the production of adenosine triphosphate (ATP), which can accelerate cell repair and growth. Furthermore, PBM can reduce inflammation and stimulate blood microcirculation, providing a conducive environment for hair growth. In vivo studies have also shown that PBM can inhibit cell apoptosis by promoting increased expression of antiapoptotic proteins. This technique involves the application of low-power light sources in the visible and infrared spectrum (GOBBO M. et al., 2023; HAMBLIN. M. R., 2022).

The procedure is non-invasive and generally well tolerated, with no associated pain or significant side effects reported. The treatment involves direct exposure of the scalp to laser light for a specified period, which may vary according to the specific protocol used. Furthermore, clinical trials have also demonstrated the effectiveness of PBM in preventing and managing severe radiodermatitis, providing pain relief and improving patients' quality of life. This improvement is attributed to the regenerative action of PBM on injured tissues, reduction of the inflammatory response and attenuation of painful sensation (ROBIJNS J. et al, 2019).

The effectiveness of PBM in preventing chemotherapy-induced alopecia is still under investigation, but preliminary research

suggests it may be a promising option.

With the added benefit of being a non-pharmacological therapy, PBM represents an attractive alternative or complement to conventional alopecia treatment methods. Clinical studies are ongoing to evaluate optimal treatment protocols, long-term safety, and efficacy of PBM in different types of alopecia. (HAMBLIN. M. R., 2022).

FINAL CONSIDERATIONS

This study addressed chemotherapy-induced alopecia, a side effect with a significant impact on patients' quality of life. The negative perception of self-image, associated with anxiety, depression and even refusal of treatment, highlights the importance of emerging techniques for the treatment of alopecia, such as scalp cooling and photobiomodulation. Hair cryotherapy is the technique most used today to prevent chemotherapy-induced alopecia, being effective and safe. It works by local cooling, inducing vasoconstriction and limiting blood flow to the hair follicles. This results in less chemotherapy reaching these areas and a reduction in the metabolic rate of the follicles, thus reducing their susceptibility to damage. However, the effectiveness of this treatment varies depending on the patient's genetic predisposition and the chemotherapy medication used. The technique is not recommended for patients with sensitivity to cold, cryoglobulinemia and hematological tumors. Among the adverse effects reported are headache, scalp pain, dizziness and a feeling of cold in the head. There are also concerns about possible metastases to the scalp, although other research downplays this possibility. On the other hand, photobiomodulation, also a non-invasive procedure, has demonstrated the ability to promote the regeneration of damaged hair follicles. This method uses specific wavelengths of light that, when absorbed by cells, increase the production of adenosine triphosphate, accelerating cell repair and growth. Furthermore, it reduces inflammation, stimulates blood microcirculation, inhibits cell apoptosis and increases the expression of antiapoptotic proteins. It is a well-tolerated procedure, with no associated pain or significant adverse effects. Although the evidence on these techniques is promising, they are still under investigation. It is crucial to expand research to determine ideal treatment protocols, evaluate long-term safety and effectiveness in different types of alopecia, considering different chemotherapy medications.

REFERENCES

ALONSO, Maria del Rosario; ANESINI, Claudia Alejandra. A natural product that accelerates hair growth in women with chemotherapy-induced alopecia. **Journal of Biomedical Science**, v.4, n.3, OAJBS, 2021.

AMARILLO, D. et al. Alopecia, quimioterapia y gorras de frío o «scalp cooling system. **Actas Dermo-Sifiliográficas**, v. 113, n. 3, p. 278-283, 2022.

BAJPAI, J. et al. Randomised controlled trial of scalp cooling for the prevention of chemotherapy induced alopecia. **The Breast**, v. 49, p. 187-193, 2020.

BOLAND, VANESSA et al. The physical, psychological and social experiences of alopecia among women receiving chemotherapy: An integrative literature review. **European Journal of Oncology Nursing**, v. 49, p. 101840, 2020.

BRUNNER, C. et al. Hair safe study: Effects of scalp cooling on hair preservation and hair regrowth in breast cancer patients receiving chemotherapy-A prospective interventional study. **The Breast**, v. 64, p. 50-55, 2022.

DUNNILL, C.J et al. A Clinical and Biological Guide for Understanding Chemotherapy- Induced Alopecia and Its Prevention. **The Oncologist**, v. 23, n. 1, pág. 84-96, 2018."

FREITES-MARTINEZ, Azael et al. CME Part 1: Hair disorders in cancer patients. **Journal of the American Academy of Dermatology**, v. 80, n. 5, p. 1179, 2019.

GOBBO, M. et al. Photobiomodulation therapy for the prevention of acute radiation dermatitis: a systematic review and meta-analysis. **Supportive Care in Cancer**, v. 31, n. 4, p. 1-14, 2023.

HAMBLIN, M.R. Photobiomodulation for the management of alopecia: mechanisms of action, patient selection and perspectives. **Clinical, Cosmetic and Investigational Dermatology**, v.12, p. 669-678, 2022.

HAQUE, Emaan et al. Management of chemotherapy-induced alopecia (CIA): A comprehensive review and future directions. **Critical Reviews in Oncology/Hematology**, v. 156, p. 103093, 2020.

KANG, DANBEE et al. Impact of a topical lotion, CG428, on permanent chemotherapy-induced alopecia in breast cancer survivors: a pilot randomized double-blind controlled clinical trial (VOLUME RCT). **Supportive Care in Cancer**, v. 28, p. 1829-1837, 2020.

KIM, M.H. et al. Human placenta induces hair regrowth in chemotherapy-induced alopecia via inhibition of apoptotic factors and proliferation of hair follicles. **BMC Complementary Medicine and Therapies**, v. 20, p. 1-7, 2020.

MARTÍN, M. et al. Enfriamiento del cuero cabelludo para la prevención de la alopecia secundaria a quimioterapia: revisión sistemática y metanálisis. **Revista española de salud pública**, n. 97, p. 31, 2023.

MICHEL, Alissa et al. Improving Quality of Life During Chemotherapy: Cannabinoids, Cryotherapy, and Scalp Cooling. **American Society of Clinical Oncology Educational Book**, v. 43, p. e390428, 2023.

MUNZONE, E. et al. Preventing chemotherapy-induced alopecia: a prospective clinical trial on the efficacy and safety of a scalp-cooling system in early breast cancer patients treated with anthracyclines. **British journal of cancer**, v. 121, n. 4, p. 325-331, 2019.

OCAMPO-GARZA, J. et al. New drugs under investigation for the treatment of alopecias. **Expert opinion on investigational drugs**, v. 28, n. 3, p. 275-284, 2019.

ORLANDO, LAURA et al. Final results of a prospective study of scalp cooling in preventing chemotherapy-induced alopecia. **Future Oncology,** v. 15, n. 29, p. 3337-3344, 2019.

PETRUZZI, A et al. Evaluation of the CNC® prosthetic system in recurrent breast cancer patients with chemotherapy-induced alopecia: a pilot study. **BMC Women's Health**, v. 22, n. 1, p. 1-8, 2022.

QUESADA, S. et al. Cancer-related alopecia: from etiologies to global management. **Cancers**, v. 13, n. 21, p. 5556, 2021.

ROBIJNS, J. et al. Photobiomodulation therapy for the prevention of acute radiation dermatitis in head and neck cancer patients (DERMISHEAD trial). **Radiotherapy and Oncology**, v. 158, p. 268-275, 2021.

ROBIJNS, Jolien et al. Photobiomodulation therapy for acute radiodermatitis. **Current Opinion in Oncology**, v. 31, n. 4, p. 291-298, 2019.

RUBIO-GONZALEZ, B. et al. Pathogenesis and treatment options for chemotherapy-induced alopecia: a systematic review. **International journal of dermatology**, v. 57, n. 12, p. 1417-1424, 2018.

RUBIO-GONZALEZ, Belen et al. Pathogenesis and treatment options for chemotherapy-induced alopecia: a systematic review. **International Journal of Dermatology**, v. 57, n. 12, p. 1417-1424, 2018.

SILVA, Giselle de Barros et al. Scalp cooling to prevent chemotherapy-induced alopecia. **Anais Brasileiros de Dermatologia**, v. 95, p. 631-637, 2020.

WIKRAMANAYAKE, Tongyu C. et al. Prevention and Treatment of Chemotherapy-Induced Alopecia: What Is Available and What Is Coming?. **Current Oncology**, v. 30, n. 4, p. 3609-3626, 2023.

YANG, J et al. Design, synthesis, and biological activity of TLR7-based compounds for chemotherapy-induced alopecia. **Investigational New Drugs**, v. 38, p. 79-91, 2020.

YU, F. et al. The Chinese herb Xiaoaiping protects against breast cancer chemotherapy-induced alopecia and other side effects: a randomized controlled trial. **Journal of International Medical Research**, v. 47, n. 6, p. 2607-2614, 2019.

ZHANG, Yusheng; JIMENEZ, Joaquin J. Mild oxidative stress protects against chemotherapy-induced hair loss. **Frontiers in Oncology**, v. 12, p. 1078916, 2023.