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Cryoprophylaxis of alopecia induced by chemotherapy in cancer patients

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SUMMARY
Antitumor chemotherapy induces anagen alopecia by early apoptosis of keratinocytes in the follicle. One of the most effective methods of prevention of cytotoxic alopecia is a scalp cooling system. The essence of the method lies in the use of cooling materials at the time of administration of chemotherapeutic drugs to cause vasoconstriction in the scalp area, which in turn leads to a decrease in blood and lymph flow in the follicles and causes a decrease in the concentration of chemopreparations in the area of cooling. This review presents current data on cryoprophylaxis of chemotherapy-induced alopecia in patients with non-metastasizing breast cancer. The efficacy of the method was estimated as hair loss less than 50% and varies in the average range of 50-70%, but depends on the chemotherapy regimen, scalp cooling exposure time and individual patient characteristics. The most effective rates of anagen alopecia prophylaxis were in patients receiving taxane monotherapy. Among the adverse effects, patients reported cold sensations, dizziness, and scalp and facial soreness. The advantages and disadvantages of the method were studied.

KEY WORDS: *cytotoxic alopecia, anagen alopecia, cryoprophylaxis, chemotherapy adverse events, scalp hypothermia*

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Scalp cooling in the prevention of chemotherapy-induced alopecia of patients with cancer

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SUMMARY
Chemotherapy causes Chemotherapy-induced alopecia by early apoptosis of keratinocytes in the follicle. One of the most effective methods of combating cytotoxic alopecia is the cooling system of the scalp. The essence of the method is to use cooling materials at the time of chemotherapy to cause vasoconstriction on the scalp, which in turn leads to a decrease in blood flow and lymph flow in the follicle and causes a decrease in the concentration of the chemotherapy drug in the cooling area. The review presents current data on cryoprophylaxis of chemotherapy-induced alopecia in patients with non-metastatic breast cancer. The success rate of the method was estimated for hair loss of less than 50%. The effectiveness of the method varies between 50-70 %, but depends on the type and dose of the drug, the exposure time to scalp cooling, and the individual characteristics of the patient. The best treatment rates for anagenetic alopecia were in patients receiving taxane-based chemotherapy. Among the adverse effects, patients noted cold sensations, dizziness, and soreness of the scalp and face. The advantages and disadvantages of the method were studied.

KEYWORDS: *cytotoxic alopecia, anagen alopecia, cryoprophylaxis, adverse events of chemotherapy, scalp cooling system.*

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Introduction

Chemotherapy is one of the key elements in the successful treatment of cancer patients. However, the drugs used in this practice have a number of side effects. One of them is alopecia induced by chemotherapy. This complication occurs in 65-100% of cases and has a negative psycho-emotional character for many patients, negatively affects social activity and interpersonal relations, and in 8% of cases patients even refuse further chemotherapy treatment.

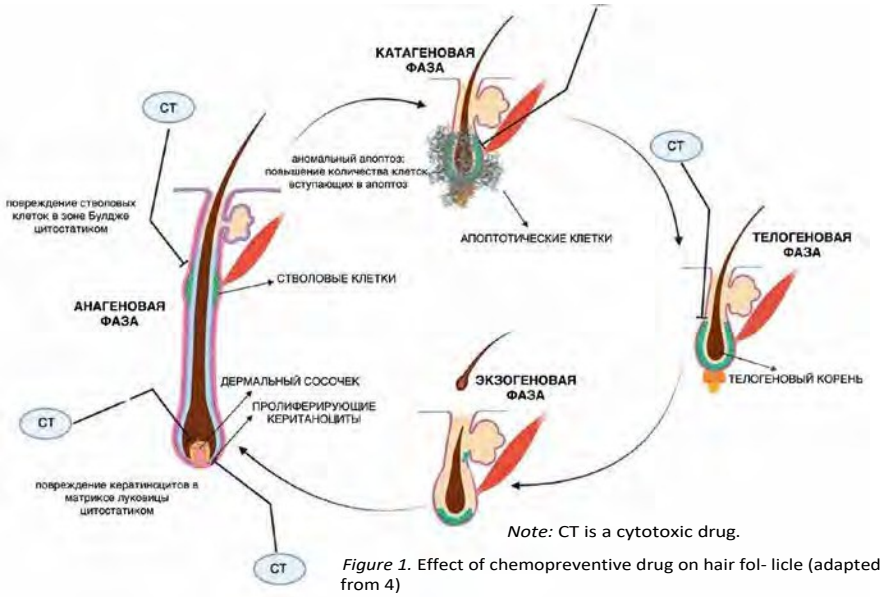
to avoid the development of alopecia areata [1-3].

The pathogenesis of chemotherapy-induced alopecia is now well understood and includes several links (*Fig. 1*). The cytotoxic drug causes cell death by early apoptosis, namely cells in the process of mitotic division, including keratinocytes proliferating in the hair follicle. This process leads to alopecia by two main mechanisms [2, 4].

1. Anagen hair loss: occurs at a time when keratinocyte proliferation in the hair follicle matrix is significantly inhibited and the hair loses its anatomical connection to the follicle bulb. This leads to sudden hair loss during the growth phase. A less common variant is dystrophic anagen hair loss. In this case, there is a delay in hair growth due to slow proliferation of keratinocytes [5, 6].
2. Premature telogen (premature teloposis): characterized by a shortened telogen phase, as a result of which the hair bulb separates from the follicle prematurely [2].

Chemotherapy most often results in diffuse alopecia of grade 2-3, but in some cases focal alopecia, as well as eyebrows, eyelashes and body hair lesions are observed [7,8].

The intensity of alopecia depends on the type, dosage and combination of cytotoxic drugs (*Table 1*). Topoisomerase inhibitors (irinotecan, etoposide) and anthracyclines (doxorubicin) cause alopecia in 60-100% of cases. Taxanes (docetaxel and paclitaxel) cause hair loss in more than 80% of cases, presumably due to increased toxicity to hair follicle stem cells. Alkylating agents cause alopecia in more than 60% of cases [1, 9-10]. Chemotherapy-induced alopecia areata is reversible and after completion of the main course of treatment, the hair follicle resumes its normal cycle with the participation of surviving keratinocytes and hair growth becomes visible within 3-6 months [11]. However, hair changes have been observed after completion of therapy compared to the original hair. Changes in hair color, curl and straightness are quite common (65%) due to the different effects of chemotherapy on follicular melanocytes and inner root sheath epithelium and are the result of asymmetric proliferation of keratinocytes. These changes are usually, will go away with time [11-13].



Note: CT is a cytotoxic drug.

Figure 1. Effect of chemopreventive drug on hair fol- licle (adapted from 4)

Table 1

Intensity of alopecia depending on the chemopreventive drug

Drug	Classes	Alopecia intensity
Irinotecan	Topoisomerase inhibitors	>58%
Etoposide	Topoisomerase inhibitor	>55%
Doxorubicin	Anthracyclines	80-100 %
Docetaxel	Taxanes	>80%
Paclitaxel	Taxanes	>80%
Cyclophosphamide	Alkylating agent	>60%

However, some chemotherapy drugs such as taxanes can cause persistent alopecia, which is characterized by hair loss lasting more than 6 months after the end of chemotherapy. The incidence varies from 14 to 30% [12, 14-17].

It should be emphasized that cytotoxic alopecia has a negative impact on patients' perception of their body, attractiveness and reduces their quality of life. Head and facial hair are important elements of health, beauty and youth in society. Therefore, chemotherapy-induced alopecia areata is a serious blow to patients' self-esteem, exacerbating already existing psychological problems related to the underlying diagnosis and prognosis of cancer [18-20].

A study by Saraswat et al. (2019) identified 179 patients who developed cytotoxic alopecia and showed that 56.4% of patients consider alopecia as the most unpleasant side effect of chemotherapy, 72% of patients indicate a negative impact of hair loss on their social life, and 20.6% of patients use accessories to hide hair loss [21]. In some cases, patients with cancer refuse life-saving chemotherapy because of the fear of alopecia areata. The visibility of alopecia makes it impossible to conceal the status of a cancer patient, as hair loss becomes a public sign of the disease. This leads to a change in attitudes towards patients: from sympathy to rejection [18, 22-24].

The most well-known therapies for alopecia areata (topical and systemic) have a good evidence base in the treatment of different types of alopecia. However, the use of these therapeutic approaches is effective after completion of chemotherapy [25, 26]. Due to the lack of pharmaco- logical strategies, the therapy of cytotoxic alopecia has acquired a prophylactic character in the direction of reducing the concentration of chemopreventive agents in the cells of sebaceous hair follicles. One of the methods is the use of scalp hypothermia systems (SHS) at the time of cytostatic administration [4].

The purpose of this review is **to** analyze the current data on cryoprophylaxis of cytotoxic alopecia, its efficacy and safety.

This review is based on the analysis of published scientific papers on cryoprophylaxis of chemotherapy-induced alopecia areata. The literature search was performed in PubMed, Google Scholar, UpToDate and eLIBRARY databases, covering the period from 2014 to 2024. *Inclusion criteria* were: randomized controlled clinical trials involving patients with cancer undergoing cytotoxic therapy. The search was performed using specialized keywords and terms.

Results and Discussion

History of scalp hypothermia The first development of scalp hypothermia began in the 1970s. The essence of the method was the use of cooling materials at the time of chemotherapy to induce vasoconstriction on the scalp, which in turn leads to a decrease in blood and lymph flow to the follicle and causes a decrease in the concentration of chemotherapy in the area of cooling or impairment of its delivery to the skin cells. Initially, ice or cooling air was used. Over time, techniques with cryogel became available. Special helmets were filled with gel and frozen to -50$^{(o)C}$, then used during chemotherapy, changing several times. Examples of this method are ChemoCap (Canada), Elasto-GelTM Cold Caps (Southwest Technologies, Akromed Inc.) and Penguin Cold Caps (Medical Specialities Of California). Current scalp hypothermia technology is focused on the development of automated cooling machines that deliver refrigerant continuously to the helmet without the need to change the helmet. Paxman (PCS-1 and 2, Orbis. UK), Dignitana (DigniCapTM. Sweden), Capelli (Brazil), and Amit Technology (SCSIITM) are engaged in this development [2, 3].

Currently, the US Food and Drug Administration (FDA) has recognized the use of automated scalp cooling systems (DigniCap) as the only method to control cytotoxic alopecia [18, 27]. The Brazilian Health Regulatory Agency (ANVISA) has certified three scalp cooling systems for clinical use: Elasto-gel, Paxman, and Capelli [2]. In the Russian Federation, the Ministry of Health has registered Paxman equipment (Orbis device) for the prevention of alopecia during chemotherapy.

Methods of using scalp cooling systems

Scalp cooling is started 30 minutes before cytostatic infusion. The temperature is lowered to 18-22ºC and maintained during and after chemotherapy administration. Scalp hypothermia exposure depends on the chemotherapy regimen and dosage and should take into account the pharmacokinetics of the cytotoxic drug and its metabolites [28-30]. For drugs with a long half-life, the refrigerant can be administered for several hours after the end of infusion [28, 31]. For some other drugs, such as docetaxel, an effective exposure of 20 minutes after the end of cytostatic infusion has been proven [7, 32, 33]. The study by Komen et al. compared the use of refrigerant for 90 and 150 minutes after the end of infusion of fluorouracil, epirubicin and cyclophosphamide, where the time of 90 minutes showed the best results [34].

Criteria for the effectiveness of cryoprophylaxis of cytoo toxic alopecia areata

There are several options for evaluating the efficacy of hypothermia of the HFH skin. One of the criteria is the modified Dean scale, where grade 0 is considered as no alopecia, grade 1 - hair loss ≤25%, grade 2 - >25% and up to ≤50%, grade 3 - >50% and up to ≤75%, grade 4 - >75%. Another indicator characterizing the degree of alopecia is the CTCAE classification (Criteria for the Evaluation of the Severity of Adverse Events), which is widely used in oncological practice to systematize side effects in oncology treatment. According to this classification, grade 1 alopecia corresponds to less than 50% hair loss that does not require the use of a wig or head covering; grade 2 - hair loss is more than 50% and a wig or scarf is necessary [2, 35, 36].

In most scientific studies, the criterion for successful cytotoxic alopecia prophylaxis is <50% hair loss (STSAE grade 1 or Dean grade 1-2) [37].

Effectiveness of HFH skin hypothermia depending on the type of chemotherapy (Table 2).

Several prospective multicenter studies by JAMA (2017) proved the effectiveness of DigniCap and Paxman cooling helmets in breast cancer patients in the early stages of chemotherapy with taxanes without anthracyclines: alopecia less than 50% was observed in 66.3% and 50.5% of respondents, respectively. Patients showed improvement of psycho-emotional state, reduction of anxiety and feeling of phi-

Table 2

Effectiveness of cryporophylaxis depending on the chemotherapy regimen.

Chemotherapy regimen	Hair loss≤ 50% (Dean's scale 0-2) Multicenter studies				
	Gurk 2012	Rugo 2015	JAMA 2017	Munson 2019	Giarratano 2020
Taxanes (monotherapy)	81-94 %	66,3 %	50,5-66,3 %	-	71%
Taxanes+anthracyclines (combination)	39 %	-	16 %	43 %	54 %

The authors identified mild headache and cold sensation among the side effects. The authors identified mild headache and cold sensation as side effects. However, 3 patients (0.02%) in the group using DigniCap helmets refused to use the device at all because of the discom- fort of the cold sensation [35, 36, 38].

In an additional study in the group using anthracyclines, the efficacy of cryoprophylaxis for cytostatic alopecia was lower (16%) [35]. However, in 2019, Munzon et al. published the results of the use of hypothermia of HFH skin in patients diagnosed with breast cancer using anthracycline-based chemotherapy. The efficacy was 43% [39]. Giarratano et al. (2020) presented their study comparing the efficacy of cryoprophylaxis in patients with different treatment regimens. A higher efficacy of the technique was observed when using taxane chemotherapy without anthracycline (71%) compared to anthracycline-containing regimens (54%) [40].

A Dutch registry study including 1411 patients showed that scalp cooling with Paxman devices was more effective with low-dose docetaxel (75 mg/m^2) and paclitaxel (70-90 mg/m^2) (94% and 81% success rates, respectively), compared to chemotherapy with a combination of anthracyclines (doxorubicin) and alkylating agents (cyclophosphamide) (39%) [41].

Rugo et al. investigated hypothermia of the skin of HFH using Dignitana cooling systems and proved the efficacy of cooling in 66.3% of patients receiving taxane monotherapy [35,42].

Side effects and contraindications of cryoprophylaxis.

The most common side effects of HFH skin hypothermia include headaches, cold sensation, and increased scalp sensitivity *(*Table *3*), as a result of which patients may discontinue (from 3 to 14%) the cryoprophylaxis procedure due to individual intolerance [42-44]. Additional side effects include itching; soreness in the head, neck, and shoulders; toothache; chills; and vertigo [45, 46]. It is also worth noting the need to have completely dried hair, as wet or damp hair can increase the scalp cold sensation and cause intolerance to the procedure [47].

Cryoprophylaxis is not combined with a number of drugs used during chemotherapy. For example, patients receiving platinum derivatives are at risk of developing severe peripheral neuropathy, which limits their tolerance to cold. Patients with hematologic tumors should also avoid scalp cooling because of the increased risk of scalp metastasis [48-50].

Effect of cryoprophylaxis on post-treatment hair regrowth

The efficacy of HFG hypothermia in the pro- phylaxis of persistent alopecia is worth noting. In a study by Kinoshita et al. (2019) evaluated the rate of hair growth after complete completion of chemotherapy. The authors noted that 12 weeks after the end of chemotherapy, the number of patients with grade 2 alopecia in the scalp cooling group was 3.5 times lower than in the control group (14.3%and 50%, respectively) [53].

Table 3

Side effects of scalp hypothermia

Most common adverse events	Number of patients (%)	Number of patients who discontinued the procedure due to intolerance (%)
Headache	68	9
Scalp and neck pain	47	1
Cold sensation	14	14
Dizziness	8	-
Frostbite	1	-

Conclusion

The effectiveness of cryoprophylaxis of chemotherapy-induced alopecia varies between 50-70%. In addition to hair preservation of more than 50%, patients report improved psycho-emotional state, reduced anxiety and improved quality of life.

The result of cryoprophylaxis will depend on the chemotherapy regimen, properly selected time of helmet exposure after infusion, depending on the half-life of the administered cytostatic and individual characteristics of the organism. The high efficiency of HFG hypothermia in the prevention of persistent alopecia and rapid restoration of hair volume at the end of the course of chemotherapy is of no small importance.

Taking into account the negative psycho-emotional impact of alopecia on the patient, the search and development of methods to prevent hair loss during chemotherapy is an actual direction of research. Cryoprophylaxis of cytostatic alopecia improves the quality of life of oncologic patients, which allows them to follow the therapy regimen and, ultimately, undoubtedly has a positive effect on the results of antitumor treatment.

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Author contribution: *E.A.S - designed the study; A.N.P and L.A.P - analyzed data. L.A.P -. wrote the manuscript with input from all authors; E.A.S - oversaw the project. All authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work.*

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