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ORIGINAL ARTICLE

Scalp hypothermia for the prevention of chemotherapy-induced alopecia areata in breast cancer

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Abstract

Rationale. Breast cancer (BC) represents a socially significant disease in women in the world, ranking 1st in the structure of morbidity and 5th in the number of deaths. The share of polychemotherapy among the special methods of breast cancer treatment is about 80%. The main side effect significantly affecting the quality of life is alopecia, which is observed in 65% of cases on average. Objective. To evaluate the efficacy and tolerability of scalp hypothermia (SHH) for prevention of chemotherapy-induced alopecia in cancer patients.

Materials and Methods. From June 2016 to September 2023, 75 patients with stage I-IV breast cancer, median age - 44.1 years, were under observation. All patients were treated with cytotoxic therapy at different stages of treatment. Local GTCG with Orbis II device (Paxman Coolers, UK) was used for alopecia prophylaxis.

Results. Stage I of tumor process was observed in 18 (24%) patients, II - in 22 (29.3%), III - in 30 (40%), IV - in 5 (6.7%). The patients received 5 different regimens of polychemotherapy in neo- and adjuvant variants. Taxane-containing combined regimens prevailed among them. 364 sessions of GTCG of patients were performed (4-8 sessions in each patient), 48 (64%) patients received the procedure in full. Complete hair preservation was noted in 43 (57.3%) patients. Grade 1 alopecia was observed more frequently - in 19 (25.4%), and grade 2 - in 9 (12%) people. Out of 5 patients with disseminated cancer, grade 2 alopecia was observed in 1 patient, grade 3 - in 3 patients, and grade 4 - in 1 patient. Side effects were observed in 16% of treated patients. Among them the most frequently noted were cold sensation and slight headache. Due to cold helmet intolerance 3 patients refused its use. No cancer metastases to the scalp were detected during the observation period. During the procedure, almost all patients reported a high level of comfort.

Conclusion. Local GTCG is an effective method of preventing alopecia induced by cytotoxic therapy in breast cancer patients. It allows to increase psychological and social adaptation of patients.

Keywords: breast cancer, chemotherapy, alopecia, prophylaxis, hypothermia
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Introduction

Chemotherapy (CT)-induced alopecia is one of the most frequent and unpredictable adverse events (AEs) encountered by cancer patients at all stages of specialized treatment [1, 2]. Its incidence is highly variable, ranging from 65 to 100% [3].

The majority of patients (88%) who receive CT describe its presence as a severe psychological and emotional condition that significantly worsens the quality of life [1, 4, 5]. Alopecia areata is accompanied by the development of anxiety and, as a consequence, depression, negative perception of one's body image, a significant decrease in the level of self-esteem and sense of well-being. In addition, alopecia areata affects the way cancer patients are perceived by others, as well as social relationships and sexuality [1, 5-8]. As a result, patients, especially young patients, are reluctant to undergo treatment despite the fact that it could significantly prolong their lives [1, 9]. In addition, it is necessary to take into account the financial costs incurred by patients to eliminate the consequences of alopecia areata, including a variety of cosmetic drugs, wigs and other methods of hair restoration [10].

At present, the pathogenesis of alopecia induced by HT is practically studied. It is caused by the mechanism of action of cytotoxic agents that affect rapidly proliferating tumor and other tissues of the body, including hair matrix cells in the anogenic phase, bone marrow, gastrointestinal epithelium, which are unconventional targets of HT.

Hair matrix cells in the anogenic phase multiply rapidly and remain in this state for 2 to 8 years. In this phase hair follicles are very sensitive to the effects of cytotoxic drug agents, which is accompanied by their death with subsequent hair loss and the development of alopecia. Clinically, alopecia is most noticeable in the scalp, which has the highest density of hair follicles.

However, the epithelium of hair follicles controls the repair of damaged cells between HT cycles, resulting in irregular hair loss [11]. Their loss begins a few days or weeks after the 1st cycle of drug therapy (DT) [11]. Intensity,

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ORIGINAL ARTICLE

Scalp hypothermia for the prevention of of chemotherapy-induced alopecia in breast cancer

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Abstract

Background. Breast cancer (BC) is a socially significant disease in women all over the world, ranking 1st in the structure and 5th in the number of deaths. Polychemotherapy in the complex treatment of BC accounts for approximately 80%. The main side effect that significantly affects the quality of life is alopecia, which occurs on average in 65% of patients.

Aim: To evaluate the efficacy and tolerability of scalp hypothermia (SHT) for the prevention of chemotherapy-induced alopecia in patients with BC.

Materials and methods. From June 2016 to September 2023, 75 patients with a median age of 44.1 years with stage I-IV BC were observed. All patients received cytotoxic therapy at various stages of treatment. To prevent alopecia, local SHT was used using an Orbis II device (Paxman Coolers, United Kingdom).

Results. Stage I of the disease was observed in 18 (24%) patients, stage II in 22 (29.3%), stage III in 30 (40%), and stage IV in 5 (6.7%). Patients received 5 different neo- and adjuvant regimens of polychemotherapy. Taxane-containing combined regimens prevailed. 364 SHT sessions (4-8 sessions per patient) were performed; 48 (64%) patients received the procedure in full. Complete hair preservation was achieved in 43 (57.3%) patients. Grade 1 alopecia was observed in 19 (25.4%) patients and grade 2 in 9 (12%) patients. Of the 5 patients with advanced BC, grade 2 alopecia was reported in 1 patient, grade 3 in 3, and grade 4 in 1. Side effects were reported in 16% of cases; the most common were a feeling of cold and a slight headache. Due to the intolerance of the cold helmet, 3 patients refused to use it. No scalp metastases were observed during the follow-up. During the procedure, almost all patients noted a high level of comfort.

Conclusion. Local SHT is an effective method of preventing cytotoxic therapy-induced alopecia in patients with BC. It improves the psychological and social adaptation of patients.

Keywords: breast cancer, chemotherapy, alopecia, prevention, hypothermia.

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as well as the degree of alopecia depends on the type of cytotoxic agent. Thus, when topoisomerase inhibitors (irinotecan, etoposide) and anthracyclines (doxorubicin) are used, the frequency of alopecia varies from 60 to 100%, and when taxanes (docetaxel and paclitaxel) are used - over 80%; the latter, apparently, are more toxic for hair follicle stem cells. Alkylating chemotherapeutics cause alopecia in more than 60% of cases. The lowest risk of its development is observed with the use of antimetabolites [12, 13].

In addition, other risk factors include drug dose, pharmacokinetics, treatment regimens, including the combination of cytotoxic agents, age, comorbidities, nutritional status, and hormonal background [12].

Cytotoxic therapy (CT) usually temporarily suppresses hair growth. At the end of treatment, the hair starts to grow again because the stem cells of the hair follicle are protected from toxic effects due to their slow growth and enhanced repair mechanisms [11]. Moreover, hair growth resumes within 1-3 months after the last chemoprevention [11, 12].

In 65% of cases there are changes in growth pattern (curly, straight), texture and color. This is the result of asymmetric proliferation during hair follicle regrowth and melanocyte response to drugs [11, 14, 15]. These changes are well traced at different stages of trichoscopy [16].

In some cases after polychemotherapy (PCT), alopecia may be persistent (so-called persistent alopecia). It is defined as the absence or suboptimal hair growth that persists for more than 6 months after stopping the treatment [15]. Its incidence ranges from 14% in children to 30% in patients treated for breast cancer (BC) [17].

This variant occurs more frequently after high-dose CT before stem cell and bone marrow transplantation and radiation therapy with taxanes [18]. In addition, cases of ethnic influence on the frequency of persistent alopecia areata have been described in the literature. Thus, D. Kang et al. (2019) found its presence in 42% of Asian patients with breast cancer after 3 years since the completion of CT with the use of taxanes [12]. For a long time, the strategy of effective methods for the prevention of LT-induced alopecia has been an integral part of the progress in the therapy of oncologic oncologic diseases.

Drugs have been proposed which, when applied locally, promote local enhancement of hair growth, but they do not prevent alopecia areata - minoxy dil, calcitriol, ligands of parathyroid hormone receptors [19, 20].

Hypothermia of the scalp (HTKG) against the background of CT is now an effective method of alopecia prophylaxis according to the data of a number of well-planned clinical randomized trials [21-24]. However, since 2011, when these devices were officially authorized for medical use, there are few reports devoted to this problem in the Russian literature. That is why any experience in real clinical practice is of certain professional interest.

The aim of the study was to evaluate the efficacy and tolerability of GTCG for the prophylaxis of alopecia induced by CT in breast cancer patients.

Materials and Methods

From June 2016 to September 2023, local GTCG using Orbis II cooling system (Paxman Coolers, Great Britain) was applied in Oktyabrskaya 23, LLC to prevent alopecia during HT in 75 patients with breast cancer of different stages.

The GTCG procedure consisted of three consecutive stages: pre-cooling before cytotoxic agent infusion, cooling during drug infusion and cooling at the end of the CT session. The duration of cooling regimes was used according to ESMO Clinical Practice Guidelines (2021) [25].

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The number of GTCG sessions was determined not only by the number of courses, but also by the development of NSAIDs and patients' adherence to treatment.

To assess the severity of alopecia induced by HT, a modified Dean hair loss scale was used [26], according to which a distinction is made:

0 degree - no hair loss; 1st degree - from 0 to 25% hair loss; 2nd degree - hair loss >25% to ≤50%; 3rd degree - hair loss >50% to ≤75%; 4th degree - >75% hair loss.

According to the literature, scalp cooling is considered effective if the alopecia frequency is less than 50% (grade 1 or 2 of the modified Dean scale) [21, 26].

Results

During the analyzed period, 75 patients received GTCG for alopecia prophylaxis. The average age of the patients was 44.1 years, and the age range was 35-52 years. Stage I of the tumor process was observed in 18 (24%) patients, II - in 22 (29,3%), III - in 30 (40%), IV - in 5 (6,7%) patients.

All patients underwent CT with different drug regimens depending on the molecular and biological variant of the tumor.

Neoadjuvant PCT was given to 7 (9,3%) patients. In the vast majority of cases - 63 (84%) patients - it was performed in adjuvant mode; 5 (6,7%) patients with disseminated tumor process received therapeutic CT. CT regimens were combined, 4 of them contained taxanes: docetaxel (3) and paclitaxel (1), and 3 - anthracyclines (Table 1).

The range of PCT cycles varied from 4 to 8. A total of 364 sessions of GTCG on the background of CT were performed. The range of GTCG sessions per 1 patient was from 4 to 8, with an average of 5 sessions. 48/64% of patients received the full GTCG procedure (see Table 1). The effectiveness of GTCG was evaluated by the severity of alopecia according to the Din alopecia severity according to the Dean's scale (Table 2).

After GTCG application alopecia was absent in 43/57,3% of patients, while its various degrees were found in 42,7% of patients with breast cancer. In the majority of cases (25.4%) alopecia was considered to be of the 1st degree; its 2nd degree was observed twice less, amounting to 12%. In 3 patients with disseminated tumor process there was alopecia of the 3rd degree, in 1 patient it was represented by alopecia of the 2nd degree, and in 1 patient - by alopecia of the 4th degree. In the vast majority of cases, alopecia of the 1st degree was observed against the background of combined treatment: taxanes + anthracyclines.

The patients evaluated the comfort of the procedure by means of questionnaires on a 10-point scale. The average score was 8.2 points.

Side effects were observed in 12 (16%) patients. Cold sensation in the scalp was noted in 5 (6.7%) patients, mild headache was noted in 4 (5.3%) patients, 3 subjects refused to use the cold helmet due to intolerance (Table 3).

Discussion

According to the World Health Organization, in 2018, 57.7% of newly diagnosed patients with malignant neoplasms required treatment [27]. One of the most serious complications of PCT is alopecia areata. This is a passing and, as a rule, reversible consequence of systemic therapy of malignant tumors [2]. The reversibility of alopecia is related to the degree of damage to stem cells of hair follicles [11]. It is considered to be one of the most negative consequences for the quality of life of cancer patients [28]. The psychological and emotional trauma suffered by patients can be quite severe. This leads them to refuse treatment or postpone treatment

Table 1. Chemotherapy regimens and number of GTCG sessions in breast cancer patients, abs. (%), n=75 Table 1. Chemotherapy regimens and number of scalp hypothermia (SHT) sessions in patients with breast cancer (BC), abs. (%), n=75

Regimens	Number	
	patients	hypothermia sessions
4 docetaxel+ cyclophosphane	35 (46,7)	140
4 AC+4 paclitaxel	25 (33,3)	130
4 AC+4 docetaxel	8 (10,7)	64
4 AC	5 (6,7)	20
Docetaxel+ carboplatin AUC6	2 (2,7)	10
Total	75	364

Table 2. Frequency of alopecia in breast cancer patients after CT using Orbis II GTCG, n=75
Table 2. Incidence of alopecia in patients with AF after chemotherapy with SHT using the Orbis II device, n=75

Degree of alopecia (according to Dean)	Number of patients	
	abs.	%
0 - no hair loss	43	57,3
1	19	25,4
2	9	12
3	3	4,0
4	1	1,3
Total	32	42,7

Table 3. Side effects of SHT with Orbis II in patients with BC, n=75 Table 3. Side effects of SHT with Orbis II in patients with BC, n=75

SIDE EFFECTS	Number of patients	
	abs.	%
Refusal to use cold helmet	3	4
Feeling cold	5	6,7
Mild headache	4	5,3
Total	12	16

The alopecia induced by HT is most pronounced on the scalp, with a predominance of alopecia on the top of the head and frontal areas, where recovery is slowest [15].

Alopecia induced by HT is most pronounced on the scalp, with predominance on the scalp and frontal areas, where recovery is the slowest [15]. The degree of its manifestation depends on a number of factors, including the type of drug, dose regimen, pharmacokinetics, age and presence of concomitant pathology. At the same time, patients of different ages consider alopecia areata to be the most significant side effect [29].

alopecia areata [29].

According to the data of the literature, alopecia areata most often develops with doxorubicin (80-100%), cyclophosphane (25-100%), and taxanes (approximately 70%). Currently, the use of targeted and immunotherapy may also be accompanied by the development of alopecia [30]. A weekly regimen of CT usually results in slower and incomplete alopecia. With prolonged treatment, hair regrowth may resume. At the same time, high-dose CT prior to hematopoietic cell transplantation leads to rapid and incomplete alopecia.

leads to rapid and complete alopecia [31].

Docetaxel and, somewhat less frequently, paclitaxel can cause long-term or permanent alopecia [32, 33].

Along with DT, alopecia areata as an NI occurs in hormone therapy with estrogen (25%) and aromatase inhibitors (up to 34%), and it increases in combination with cyclin kinase 4/6 inhibitors [34, 35].

One way to prevent alopecia is GTCG in patients with various solid malignancies.

in patients with various solid malignant tumors undergoing CT. The evidence of benefit in the literature is primarily in patients with breast cancer (36). In addition, patients with disseminated tumor process receiving palliative CT may be offered the option of GTCG when alopecia develops [36].

We performed GTCG i n 5 patients with disseminated cancer. Alopecia of the 2nd degree was obtained in 1 patient, in 3 patients - in the 3rd degree. Alopecia of the 4th degree was found in 1 patient. Nevertheless, despite this result, we support the necessity and possibility of using GTCG in patients with advanced cancer.

It is proved that the use of local hardware GTCG is well tolerated [36, 37]. Side effects are mild, including discomfort from the sensation of cold, headache (28%), nausea, dryness of the scalp, and claustrophobia; thermal damage to the scalp is possible [21, 38].

Nevertheless, there are other opinions. For example, K. Smetanay et al. (2019) described 163 NIs after GTCG, among which are oznob (81.6%), headache (76.3%), a feeling of heaviness in the head (68.4%), scalp pain (63, 2%) and neck pain (52.6%). Moreover, they most frequently described chills and headache [39].

We observed side effects in 12 (16%) RRM patients who underwent GTCG. Among them, the most frequently reported were mild headache and a cold sensation in the skin area during the procedure, as well as refusal to use a helmet for cooling.

There are indications in the literature that there may be an increased risk of metastasis to the scalp. However, most authors deny the existence of such a possibility. For example, J. Bajpai et al. (2020) never observed the development of metastases to the scalp during a median follow-up of 17.1 months [40].

We have never observed any metastatic scalp lesions during long-term observation of patients who underwent GTCG.

Patients do not experience any discomfort during the procedure. Thus, J. Nangia et al. (2017) indicate that almost all patients felt comfortable during the GTCG sessions [22].

According to the data obtained, all patients reported a high level of comfort, which amounted to 8.2 points.

Scalp cooling with the use of various aparates as an option for the prevention of alopecia in DTC is a proven fact in a number of randomized clinical trials.

In 2023, M. TrujilloMartin et al. published the results of a systematic review and meta-analysis of the literature up to November 2021 on the prevention of alopecia induced by PCT. The study included 832 participants, of whom 97.7% were women. The main drugs used for treatment were anthracyclines or a combination of anthracyclines and taxanes. According to the results, GTCG reduced alopecia areata by 43% compared to the control group. The authors conclude the efficacy and safety of local GTCG based on the results obtained in 13 randomized clinical trials [23].

Currently, this method is included in the clinical practice guidelines of the NCCN and the European Society of Medical Oncology ESMO [41, 25].

According to the data obtained, we observed alopecia of various degrees in 42.7% of patients using scalp cooling. It should be noted that alopecia of the 3rd and 4th degree was registered in 3 and 1 cases, respectively, in patients with disseminated cancer. Absence of alopecia and aesthetic satisfaction amounted to 57.3%.

Conclusion

GTCG is an alternative option for alopecia prophylaxis in patients with solid tumors receiving HT treatment in different regimens. The evidence of its u s e f u l n e s s is most convincing in patients with cancer, especially when treated with taxanes. The use of this method allows preserving all or most of the hair.

According to the data obtained, the use of local GTCG prevented alopecia and preserved esthetic satisfaction in 57.3% of patients with cancer with a minimal (16%) frequency of side effects. In addition, a variant of GTCG for alopecia prophylaxis can be offered to patients with disseminated tumor process during palliative CT.

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