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Review Article

Supportive Care for Chemotherapy Induced Alopecia: Challenges and Solutions

Gulbeyaz Can[1]*, MeryemYildiz[2], and EmelEmineÖzdemir RN[3]

[1]Istanbul University Florence Nightingale Nursing Faculty, Turkey
[2]Karamanoğlu Mehmetbey University School of Health Sciences, Turkey
[3]Civilization University Faculty of Health Sciences, Turkey

*Corresponding author

Gulbeyaz Can, Istanbul University Florence Nightingale Nursing Faculty, Istanbul, Turkey, Tel: 009 0 532 6264969; Fax: 00 90 212 224 49 90; Email: gulbeyaz@istanbul.edu.tr

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Abstract

Chemotherapy induced alopecia is one of the most common side effects experienced by cancer patients. It can be an important problem, which negatively affects patients' quality of life. Showing difference in severity, depending on the type of antineoplastic agents used in treatment, alopecia occurs approximately in 65% of the patients as hair loss after 2-3 weeks of initial chemotherapy treatment and it is considered as a cause of distress and trauma to cancer patients who are taking chemotherapy. Depending on cultural and personal characteristics, the reactions of patients to chemotherapy related alopecia differ. It may cause some patients to distance themselves from social life and tend to negative thinking. Some patients may need support in coping with this problem. Educating patients about alopecia, cooling the scalp during treatment, application of tourniquet and different pharmacological approaches were used in coping with this problem. However, the results obtained from these studies are controversial and none of them put forward an effective approach to deal with this problem. Therefore, the suggestions regarding chemotherapy-induced alopecia are usually based on the experiences of health experts and based on a limited number of randomized and non-randomized study reports.

INTRODUCTION

The diagnosis of cancer and initiation of chemotherapy sometimes cause severe alopecia, which can cause feelings of stigmatization both for the patients and their close surroundings by changing the individual's identity from a healthy person to a cancer patient [1]. As hair loss becomes visible, this problem can serve as a constant visual reminder of "I have cancer", and consequently most cancer patients suffer the stigma of alopecia in their social interactions and abstain from interaction with people when they do not hide their hair loss [2]. The alopecia can affect the patients' external image, quality of life, social interaction and sexual life. It may seriously affect one's body image, which in turn has an impact on self-esteem and self-confidence. Consequently, it may cause emotional suffering, lead to personal, social and work-related problems, and may have a negative effect on quality of life [3]. It was found that most cancer patients had experienced hair loss induced by chemotherapy, which made an impact on their individuality, social relations and everyday life [2].

Some patients may need support in coping with this problem. Educating patients about alopecia, cooling the scalp during treatment, application of tourniquet and different pharmacological approaches were used in coping with this problem. However, the results obtained from these studies are controversial and none of them put forward an effective approach to deal with this problem. Therefore, the suggestions regarding chemotherapy-induced alopecia are usually based on the experiences of health experts and based on a limited number of randomized and non-randomized study reports.

CHEMOTHERAPY-INDUCED ALOPECIA

Chemotherapy-induced alopecia, which is developed 2-3 weeks after the first chemotherapy application as partial or full hair loss in approximately 65% of all cancer patients, is a common side effect of some chemotherapy regimens [1]. Frequency and severity of chemotherapy-related alopecia, differs depending on the dose, type and half-life of the chemotherapeutic agent, treatment protocol (single and combined), time of infusion and condition of hair [4]. Some antineoplastic agents don't cause any alopecia, however, others can cause partial and full hair loss [5]. The frequency of alopecia in patients being treated with anti-microtubule agents (for example: paclitaxel) is more than 80%

and it ranges between 60-100% in patients who are being treated with topoisomerase inhibitors (for example: doxorubicin). It frequency is more than 60% in patients who are being treated with alkylating agents (for example cyclophosphamide) and around 10-50% in patients who are being treated with antimetabolite agents (for example: 5-fluorouracil, leucovorin). The occurrence of alopecia is more in patients who are being treated with combined treatments compared to single agent treatments. Chemotherapy-induced alopecia is a reversible side effect; hair begins to grow back within 3-6 months after ending the chemotherapy treatment [5]. However, in some studies it has been reported that 6.3% of some female patients receiving docetaxel based chemotherapy and patients receiving busulfan chemotherapy after bone marrow transplantation may also develop irreversible diffuse alopecia [6,7]. In addition to the hair loss, some patients may experience eyebrows and eyelash loss as well, usually at their 4thtreatment cure [8] and compared to the head hair, it takes more time such as 4-6 months for eyebrows and eye-lash hair to grow back [9].

No matter how ready the patients are mentally, seeing clumps of hair on their hairbrushes and pillows cause them to experience shocks and feelings of shame. Some patients have refused treatment due to the fact that chemotherapy causes alopecia [10]. In a study 47% of the female patients who are being treated for breast cancer, stated that the alopecia is the most traumatic side effect of chemotherapy. However, 8% of the patients in that study refused treatment due to chemotherapy related alopecia [11]. Not only female but also some male patients can also be affected by chemotherapy related alopecia. In different studies, authors reported that men with alopecia had worse self-image than women with alopecia [12,13] and it was concluded that health professionals should spend more time assisting men in their adjustment to alopecia than they spent in assisting women [13]. Contrary to these assumptions, Can et al. reported that the body image of men and women, who experienced partial or full hair loss are similarly affected by alopecia [14]. In this study, the psycho-social wellness was lower in women compared to men [14]. It has been emphasized that the baldness is socially more acceptable in men [15]. Each individual has a different meaning for their disease and psychologically each are affected differently [8]. Since it is not a life threatening side effect of chemotherapy, alopecia is not taken into account very much by the health care professionals [2]. However, the psycho–social distress in patients experiencing alopecia related to cancer treatment is rather high. Health care providers should assess the effects of alopecia and must take steps in formulating and planning interventions that will strengthen the coping skills of the patients with their new looks [1,2,15,16].

MANAGEMENT OF CHEMOTHERAPY-INDUCED ALOPECIA

In management of the chemotherapy induced alopecia many interventions such as educating patients about alopecia, cooling the scalp during treatment, application of tourniquet and different pharmacological approaches were used. The number of studies is limited; the results obtained from these studies are controversial [2,9,17]. So, it not possible to decide which of these interventions is effective approach in management of this problem. Therefore, the suggestions regarding chemotherapy-induced alopecia are usually based on the experiences of health experts and based on a limited number of randomized and non-randomized study reports.

Patient and Family Education before Treatment

In literature, it has been asserted that patients have negative perception towards chemotherapy-induced alopecia, because the preparing of patient about the chemotherapy-induced alopecia is insufficient and social support is limited. So, to cope with this problem, the planning of educational programs for patients will be beneficial to change the negative perceptions of patients. The patients should be informed about hair loss before starting chemotherapy [18]. The use of some interventions should be considered for management of chemotherapy-induced alopecia during the treatment:

Before hair loss:

- Dry hair gently, keep blowdryer on low heat,
- Do not use curling irons, hair clips and hair bands,
- Do not color hair or use hair sprays or gels,
- Use wide-toothed combs and do not brush harshly,
- Use baby shampoo with neutral pH balance for hair care,
- In order to prevent cuts in skin, use electrical shaving devices to remove hair
- Purchase a wig before treatment, if needed [15].

After hair loss: Use a wig or scarf to prevent head from sun and cold air, if needed [19].

In order to minimize the negative psychological effects, patients should be encouraged to use different camouflage methods such as using a hat, wearing a weigh or having a short haircut on the day 15th of the first treatment (for treatment protocols that cause full hair loss).

In order to support patients for coping with alopecia, different education programs can be planned. In a study on preparing patients for the chemotherapy-induced alopecia, it has been reported that use of computer based imagination program is an effective method in decreasing the level of stress related to alopecia and strengthening the positive feelings [2]. In different study, the effect of the plastic surgery/beauty treatment programs was assessed. The application of these programs reduces the effect of alopecia and eases individuals' adaptation to a new physical appearance [19]. The positive effect of the plastic surgery/beauty treatment programs was supported in second study performed by Zannini et al. The researchers state that the use of wig to hide alopecia can be helpful and plastic surgery/beauty treatment programs can eliminate the negative effect of alopecia [16].

Scalp hypothermia

Scalp hypothermia is one of the widely used techniques in preventing chemotherapy-induced alopecia. In this technique, patients' scalp is cooled during the course of treatment. For cooling the scalp, different methods such as cold air, bags full

of crushed ice, frozen cryogel packages and special head gears having cryogel insulation plates or connected to cooling devices with a thermostat were used. During the cold application, the blood flow to hair follicles slows down and the cellular intakes of chemotherapeutic agents decrease, thus making the antineoplastic agents to be less harmful to hair follicles and preventing alopecia [20].

In many studies the effectiveness of scalp cooling in preventing alopecia is reported to be around 50-52% for scalp cooling apply 30 minutes prior to, during, and for 90 minutes after each chemotherapy [21,22] and the level of effectiveness has been determined as 0.38 [%95CI=0.32-0.45, I2= %73.8, p<0.001] in a meta-analysis [9]. However, it is also stated that the effectiveness of this technique was higher in the patients receiving docetaxel (D75) (%94) and paklitaxel (T70-90) (%81), rather than in the patients being treated with TAC (taxotere, adriamycin and cyclophosphamide) (8%) treatment protocol [21]. Many factors such as personal characteristics, chemotherapy regimen, and cooling method, degree of hypothermia, post-infusion application time and condition of liver functions have been reported to affect the success of cold application however the effects of those parameters have not yet been evaluated in detail [17,23].

To provide effectiveness of this technique, it is necessary to keep scalp temperature under the 22^0C and the depth of cooling should be reached at least 1-2 mm under the scalp skin [20]. It is also stated that the blood flow slows down 20% when the cooling temperature reaches 20^0C. Ekwall et al. (2013) reported that it is necessary to cool the head gear at least by 3°C in order to get this effect and examined two different computer controlled cooling temperatures (3°C and 8°C) to assess the effect of cooling in management of chemotherapy induced alopecia. In this study they determined that there is no difference between two groups in terms of preventing alopecia. However, the headaches and felt cold was higher in the group receiving 3°C cooling temperature [23]. On the other hand keeping the temperature constant is very hard. Therefore, gel headgears or ice packs must be renewed in every 20-40 minutes to keep scalp cold [17]. The effects of the cooler connected headgears are better. In prevention of alopecia, the use of cooler connected headgears and ice packages were compared in a study conducted with the participation of 62 patients who are being treated with Doxorubicin, and as a result, it was determined that 63% of the patients who were treated with cooler connected headgear and 56% of the patients who were treated with ice packages didn't require a wig [22].

Betticher et al., (2013) compared the effectiveness and tolerance of two different cooling systems in prevention of alopecia related with docetaxel treatment. The patients attended to this study are divided into 3 groups: the group receiving cold application with PSC -2 machine (PAX), the group using the cooling cap (CC) and the group with no cold treatments. Cold application started 15 minutes before the chemotherapy and ended 90 minutes after chemotherapy. The cap used in cold cap treatment was replaced with a new one at the 25^{th} and 45^{th} minute of treatment., Alopecia incidence in PAX group, CC group, and group without cold application was 23%, 27%, and 74% for 3 weeks and 7%, 8%, ve 17% for weekly docetaxel treatment, respectively. It has been determined that the general effectiveness of the cold application (PAX and CC combined) is 78% (hazard ratio 0.22; 95%CI 0.12 -0.41). The CC and PAX effectiveness were similar, thus it has been reported that both cold application methods can be used in prevention of docetaxel related alopecia [24].

Depending on the concern of cooling reliability the USA Food and Drug Administration prohibited the use of cooling techniques because there is no adequate evidences to show their effectiveness [17]. However, in a prospective study initiated and planned by Rugo et al. (2013), the effect of DigniCap method in preventing chemotherapy-induced alopecia on patients with breast cancer undergoing adjuvant chemotherapy was evaluated. DigniCap system consists of a soft snug-fitting silicone cooling cap (Dignicap), an outer cap made of neprene (DigniTherm) and a coolant (DigniCool) connected to a control unit (Digni C3) digitalized to cool the head skin. The efficacy of this system was tested through a self-evaluating method of head's condition with five photographs of head by using Dean's scale for hair loss quantification. The success score of the treatment was determined as 0-2 (≤% 50 hair loss). As a result, the application of DigniCap system was recorded to prevent hair loss when compared to control group. Whereas 94% of the patients in the control group experienced 75% hair loss, DigniCap method prevented hair loss in 70.3% of the patients in independent group. The treatment was well tolerated and there was no evidence of metastasis observed on scalp. The status of the patients will be followed for long term reliability of this system. The use of DigniCap system is clinically proven to effectively reduce chemotherapy-induced alopecia. This system has been approved by Food and Drug Administration (FDA) on December 8, 2015 [25].

Although the cold application is well tolerated by patients in general, it is contraindicate for use in people with cold sensitivity, cold agglutinin disease, crioglobulinemia and criofibrinogenemia. Headache, dizziness, nausea and vomiting, sense of coldness on scalp and the whole body, sense of heaviness on the head, scalp metastasis and not feeling the head temporarily after the cap is off are among the side effects of these applications [21, 24]. For this reason, cold application is not recommended in curative chemotherapy practices such as leukemia, lymphoma, and hematologic malignancy [26]. In addition, there is also proof reporting the development of scalp metastasis after cold application process. Due to these reasons, patients experience anxiety and refuse cold application treatment. However, in a retrospective cohort study conducted for determining scalp metastasis development frequency in neoadjuvant and adjuvant chemotherapy receiving breast cancer patients, the metastasis incident is found to be 1.2% for women (6 incident in 553 patients) who had cold application treatment and 1.1% for women (1 incident in 87 patients) who didn't have cold application treatment [27]. On the other hand, in a meta-analysis done in 2012 by Hsieh, 6 cohort studies were analyzed and this analysis revealed 0.56% (12 in 2129 patients) scalp metastasis incident in patients who had cold application and further revealed 0.65% (12 in 1833 breast cancer patients). Researchers stated that 12 patients developing scalp metastasis were all breast cancer patients. In addition, researchers further stated that median monitoring time was different in all of the studies and indicated the need to have planned studies analyzing longer

monitoring periods and higher number of patients in order to determine the risk [28].

In different review of 2005, scalp skin metastases were found in nine patients out of a total of approximately 2500 patients in 56 scalp cooling studies. In all these cases, it was very unlikely that scalp metastases were a result of scalp cooling. Scalp metastases were never the first single site of recurrence, but were diagnosed at the same time, or after previous diagnosis of metastases at other sites [17].

TOURNIQUET APPLICATION TO SCALP

Tourniquet application to scalp is one of the simplest and oldest method used in preventing the chemotherapy-induced alopecia. It can be simply described as a method of keeping the head under pressure with a bandage (cuff) wrapped around the head. The cuff is blown up 10 mmHg over patient's systolic blood pressure during tourniquet application. It is applied during chemotherapy for 10 minutes when drug plasma concentration peaks and it is repeated after a break. It is continuously repeated for 10 minute periods during the infusion time. The blood flow in superficial veins slows down when pressure is applied which means less blood flow to hair follicles and less harm by the drug administered. For this reason, it is contraindicated in leukemia and lymphoma due to metastasis risk. The most common side effect is numbness of scalp. It can be applied alone or together with cooling method. There are studies on the reliability of tourniquet application to scalp. In a randomized controlled study, tourniquet application to scalp was found ineffective for preventing chemotherapy-induced alopecia. This method is not being used for the last 30 years and instead of scalp tourniquet, cold application is being preferred [29].

BIOLOGICAL METHODS

Effects of different biological agents such as Minoxidil, AS101, Cyclosporine A (CSA) have been analyzed in management of chemotherapy-induced alopecia and different results that are not used in routine applications with regard to effectiveness of these approaches were obtained. The effect of Minoxidil, which is effective on baldness in men, was evaluated, however, usually revealed negative results. In a study with the participation of 6 female patients state that treating the scalp with 2% tropical minoxidil twice a day developed extensive hair loss in 5 out of 6 patients [30]. Rodriguez et al., (1994), carried out a study with participation of 48 female patients analyzing the effects of using 2% minoxidil solution in prevention of doxorubicin induced alopecia. In this study, patients were recommended to use 5 ml of 2% minoxidil twice a day. As a result of this study, the use of this approach was reported as being ineffective due to the intensive alopecia seen 88% in experiment group and 92% in controlled group [31]. Duvic et al., (1996), applied 1 ml of 2% minoxidil twice a day to female patients who are receiving adjuvant chemotherapy after breast surgery and assessed the effects of the method. They found significant difference between the times of full hair loss and regrowth (86.7 *vs.* 136.9 p=0.03) [32]. Even though Minoxidil is reported as an effective medication in management of alopecia in female patients, there is need for conducting many more randomized controlled studies analyzing the effectiveness of this medication to decide whether it can be used in management of chemotherapy-induced alopecia or not.

Furthermore, the effect of AS101 was assessed in an open-label prospective randomized controlled study conducted with the participation of 44 patients. AS101 was given in 300 mg/m^2 IV doses 3 times a week before the start of chemotherapy and was continuously being given for 30 minutes before each chemotherapy for at least 8 weeks. As a result of the study, it was reported that AS101 was a more effective medication in preventing chemotherapy-induced alopecia in the experiment group compared to control group [33]. The effect of calcitriol, which has a type of Vitamin D3 analogue, was also assessed. In this study, calcitriol in cream form was applied in 3 different doses twice a day: 1) 500 grams 7 days before chemotherapy, 2) 1000 grams 7 days after chemotherapy and 3) 2000 grams 5 days before and after chemotherapy. In the study, all patients developed grade 2 alopecia and some patients developed dermatitis in the application areas [34].

There are no biological agents proven to be effective to prevent chemotherapy-induced alopecia today. There is a need for more well planned studies to be conducted to prove the effectiveness of biological agents.

CONCLUSION

According to numerous studies, chemotherapy-induced alopecia is a side effect of chemotherapy causing the most distress and refusal of the treatment in some patients. Today, there is no method proven to be effective to cope with this problem and patients try to hide alopecia by using scarfs, hats and wigs. In fact, some patients require psychological support due to hair loss. Nevertheless, there is insufficient evidence for when, how long and what kind of social support should be given to the patients with regard to psychological effects of alopecia.

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