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# Investigating Dermatologic Side Effects of Anti-Cancer Chemotherapeutic Agents

✉ Melis Gönülal<sup>1</sup>, ✉ Murat Keser<sup>2</sup>, ✉ Aylin Öztürk<sup>1</sup>

<sup>1</sup>Izmir Tepecik Training and Research Hospital, Clinic of Dermatology, Izmir, Turkey

<sup>2</sup>Izmir Tepecik Training and Research Hospital, Clinic of Oncology, Izmir, Turkey

## ABSTRACT

**Background:** Various chemotherapeutic agents are used in cancer treatment. The side effects they create on skin are sometimes the same and sometimes different. We purposed to investigate skin, skin appendages and mucosa adverse effects of anti-cancer chemotherapeutic agents with literature in our study.

**Materials and Methods:** Age, gender, type of cancer, used anti-cancer chemotherapeutic agents, number of cycles of patients were noted. Skin, skin appendages and mucosa adverse effects of anti-cancer chemotherapeutic agents were recorded.

**Results:** Forty-eight patients were included in our study, 12 of them (25%) were male and 36 of them (75%) were female. We observed different skin, skin appendages and mucosa adverse effects of anti-cancer chemotherapeutic agents and presented them in tables.

**Conclusion:** Chemotherapeutics can have beneficial effects as well as damaging effects on various organs. We compared dermatologic side effects of chemotherapeutic agents in the light of literature in our study. We also mentioned dermatologic side effects that haven't been mentioned in the literature yet. We believe that our research will contribute to the literature with all these aspects.

**Keywords:** Anti-cancer chemotherapeutic agent, Skin, Skin appendage, Mucosa, Dermatologic side effects

## Introduction

Cancer is a complex disease that occurs with the uncontrolled division and proliferation of cells and consists of genetic and environmental conditions. There are various treatment methods for cancer, one of them is chemotherapy. The main purpose of chemotherapy is to kill cancer cells using chemotherapeutic agents and cytotoxic anti-neoplastic agents play the leading role in this type of therapy [1]. Conventional anticancer treatments target cells that can divide rapidly. Their side effects are observed more common in tissues containing proliferative cells, in addition, their systemic side effects are more prominent than their side effects on skin. The frequency of skin side effects of the targeted anticancer treatments is gradually increasing and their skin side effects are

more prominent than their systemic side effects [2,3]. In our study, we aimed to evaluate the skin side effects of anticancer drugs in the light of the current literature.

## Materials and Methods

This study was designed as a prospective single-center study, and it was conducted under the ethical principles reported in the Declaration of Helsinki. It was approved by the University of Health Sciences Turkey, Izmir Tepecik Training and Research Hospital Ethical Review Committee. Patients aged more than 18 who presented to the Oncology Outpatient Clinic of Izmir Tepecik Training and Research Hospital between September 2019 and March 2020 recruited into this study. Both verbal and written informed consents were



**Address for Correspondence:** Melis Gönülal MD, Izmir Tepecik Training and Research Hospital, Clinic of Dermatology, Izmir, Turkey

**Phone:** +90 506 888 95 69 **E-mail:** drmelis@gmail.com **ORCID ID:** orcid.org/0000-0002-6042-656X

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obtained from study participants. The patients included in the study were those who were currently receiving chemotherapy for their own diseases. The patients who were followed up in the oncology clinic of our hospital and had side effects on the skin, mucosa and skin appendages because of their chemotherapy, were included for the research. We noted the age, gender, cancer type, chemotherapy drug, number of cycles, examination findings about side effects of chemotherapy on skin-mucosa-skin appendages of the patients. Dermatological regions with side effects were examined under six sub-units in terms of localizations: hair, scalp, nail, oral mucosa, genital mucosa, conjunctiva, skin.

### Statistical Analysis

Statistical analyzes were performed using Statistical Package for Social Sciences (SPSS v.17.0, IBM Corporation, Armonk, NY, US) software. The results were evaluated with descriptive analysis.

### Results

During the study period, 48 patients were included to our study (12 male, 25%; 36 female, 75%). The mean age of all patients was  $55.46 \pm 12.5$  (minimum: 23, maximum: 82). We determined the mean age of female patients as  $54.53 \pm 12.56$  (minimum: 37, maximum: 82) and of male patients as  $58.25 \pm 12.51$  (minimum: 23, maximum: 75). Cancer types of the patients, types of chemotherapy and the side effects of these chemotherapies are shown in the tables (Table 1, 2).

### Discussion

Various chemotherapeutic agents have been used for cancer treatment over the past 20 years. These drugs are divided into some

subgroups according to their mechanisms; signal transduction inhibitors [epidermal growth factor receptor (EBFR) antagonists, multikinase inhibitors], proteasome inhibitors, spindle inhibitors (taxanes, vinca alkaloids), antimetabolites (purine analogs, pyrimidine analogs), genotoxic agents. These chemotherapeutics may have various dermatological side effects [4].

In our study, it is thought that the papulopustular rash is mostly due to cetuximab if we compare the dual use of 5-fluorouracil (5-FU) and cetuximab with the triple use of 5-FU, oxaliplatin and cetuximab. Oxaliplatin didn't cause any additional skin findings in these two drugs combinations. Cetuximab had caused only herpes zoster in its single use. The most common side effect of cetuximab, an EBFR inhibitor, is papulopustular rash seen in 60% to 80% of patients [5]. According to the data of our study, this side effect can be brought to the fore even in combination therapies. In the work of Yazganoğlu and Baykal [6], papulopustular rash on the face of a female patient 62-year-old, had been observed in the dual use of 5-FU and cetuximab, too. Interestingly, the triple use of 5-FU, cetuximab and carboplatin caused seborrheic dermatitis and xerosis as dermatological side effects. Platins are in the cytotoxic cancer treatment category and their most common side effect is alopecia [7]. In the combination therapies using oxaliplatin and carboplatin, alopecia didn't occur. We thought that other agents in the combination could prevent the occurrence of alopecia. In the triple use of 5-FU, irinotecan, cetuximab, oral mucosa pigmentation and eczema on the hands were observed, these are rare side effects. We determined oral aphthae and desquamation on hands and feet in the triple use of 5-FU, irinotecan and aflibersept in our study, papulopustular rash didn't occur. Aflibersept has inhibitory effects on vascular endothelial growth factor (VEGF), can lead to thrombotic events [8]. We thought the cause of oral aphthae of our case was aflibersept. In addition, there were publications in the literature that aflibersept caused ulcers in the abdominal wound scar and around the stoma [8,9]. According to the data of our study, carboplatin and oxaliplatin could occur side effects more quickly. It could be observed that 5-FU, cetuximab, irinotecan and aflibersept were slow to cause dermatologic side effects.

Bevacizumab is a VEGF inhibitor and papulopustular rash because of it has been reported in a small number of cases [6]. It is known that irinotecan causes papulopustular rash. In our research, in the dual use of bevacizumab and irinotecan, the occurrence of telangiectasia contradicts the mechanism of bevacizumab, this suggests that irinotecan may be more dominant in the formation of telangiectasia. Additional studies are needed in this topic. We observed that dominant side effect was erythema on face and neck in the triple use of capecitabine, oxaliplatin, bevacizumab. Capecitabine is the prodrug of 5-FU. We thought that capecitabine was responsible for this erythema because the

**Tablo 1. Cancer types of patients**

Types of cancer	Number (gender)	Percent (%)
Lung	1 (male)	2.1
Brain	1 (male)	2.1
Kidney	1 (male)	2.1
Endometrium leiomyosarcoma	1 (female)	2.1
Liver	1 (male)	2.1
Colon	4 (3 female, 1 male)	8.3
Larynx	2 (male)	4.2
Breast	28 (female)	58.3
Stomach	1 (female)	2.1
Osteosarcoma	1 (female)	2.1
Ovary	2 (female)	4.2
Prostate	1 (male)	2.1
Rectum	2 (male)	4.2
Testis	2 (male)	4.2

dominant dermatologic side effect of oxaliplatin was alopecia and of bevacizumab was ulcer on skin. Photosensitive lichenoid skin reaction had been reported in a female patient 73-year-old because of capecitabine in the literature [10]. According to our study, side effects of paclitaxel were observed until the 12<sup>th</sup> cycle and in the

dual use of paclitaxel and carboplatin dermatologic side effects occurred earlier and less amount. Dominant side effects of taxans (dosectaxel, paclitaxel) are reversible alopecia, dorsal hand foot syndrome, edema, flexural and intertriginous rash, onycholysis, mucositis. It was reported that hand foot syndrome was caused

**Tablo 2. Chemotherapies and side effects on skin-mucosa-skin appendages**

Chemotherapy (type of cancer)	Number (%)	Cycle number	Side effects
5flouracil+oxaliplatin+cetuximab (colon)	1 (2.1)	5	Papulopustular rash on face, front of body and back
5flouracil+irinotecan+aflibersept (colon)	1 (2.1)	10	Oral aphthae, desquamation on hands and feet
5flouracil+setuximab (liver)	1 (2.1)	17	Papulopustular rash on scalp, neck, front of body and back
5flouracil+carboplatin+setuximab (larynx)	1 (2.1)	3	Seborrheic dermatitis on scalp, xerosis on body, arms and legs
Bevacizumab+irinotecan (brain)	1 (2.1)	4	Hair loss, telangiectasia on front of body
Bleomycin+etoposide+cisplatin (testis)	2 (4.2)	3 and 4	Hair loss, onychomadesis and onychogriphosis on thumb nail, onychogriphosis, oral aphthae, acne on shoulders, ecchymosis on front of body and back
Carboplatin+paklitaxel (ovary)	2 (4.2)	6	Hair loss, eczema on soles of feet, telangiectasia on legs
Doxorubicin+cyclophosphamide (breast cancer in 7 patients, endometrium leiomyosarcoma in 1 patient)	8 (16.8)	2-4	Hair loss, alopecia totalis, seborrheic dermatitis on scalp, oral aphthae, swelling of the palate, melanonychia striata on the nails, hyperpigmented macules on hands, seborrheic keratosis on armpits, ulcer and seborrheic dermatitis on front of body, eczema on legs
Docetaxel (prostate)	1 (2.1)	3	Hair loss, eczema on legs
Docetaxel+trastuzumab+pertuzumab (breast)	4 (8.4)	3, 7, 8	Hair loss, eyebrow loss, oral aphthae, folliculitis on genital mucosa, papulopustular rash on front of body, inflammation on thumbs, thickening of nails and melanonychia striata on nails, erythema on armpits, groins and soles of feet, xerosis
Docetaxel+cyclophosphamide (breast)	2 (4.2)	1 and 2	Hair loss, papulopustular rash on scalp, excoriation on front of body and back, desquamation on finger tips
Epirubicin+docetaxel (breast)	1 (2.1)	1	Hair loss, oral aphthae, tinea corporis on front of body
5flouracil+irinotecan+setuximab (rectum)	1 (2.1)	4	Acne on scalp and face, pigmentation on oral mucosa, eczema on hands
Capecitabin (colon)	1 (2.1)	6	Desquamation on hands and feet
Capecitabin+oxaliplatin+bevacizumab (colon)	1 (2.1)	2	Erythema on face and neck
Carboplatin+ifosfamide+etoposide (osteosarcoma)	1 (2.1)	3	Hyperpigmentation on face
Nivolumab (kidney)	1 (2.1)	4	Seborrheic dermatitis on face and scalp
Oxaliplatin+capecitabine (rectum and stomach)	2 (4.2)	4	Seborrheic dermatitis on scalp, thickening on thumb nails, papulopustular rash on neck, front of body and back
Paclitaxel (breast)	10 (21)	2-12	Hair loss, alopecia totalis, xerosis of hair, hair whitening, onychomadesis, melanonychia striata and leukonychia on nails, easy breakage in nails, oral aphthae, erythematous plaque on genital mucosa, inflammation on thumb, xerosis cutis, dorsal hand foot syndrome, geografic tongue, pruritus
Paclitaxel+trastuzumab (breast)	2 (4.2)	3 and 6	Hair and eyebrow loss, xerosis cutis
Setuximab (larynx)	1 (2.1)	11	Herpes zoster
Cisplatin+pemetrexed (lung)	1 (2.1)	1	Papulopustular rash on front of body and back
Trastuzumab (breast)	1 (2.1)	16	Melanonychia striata, herpes zoster

by especially docetaxel [11]. In our research, we observed that this syndrome could be caused by paclitaxel although rare. These dominant side effects were in line with the results of our study. The side effects of trastuzumab are mild on the skin. In the study of Adachi et al. [12], skin side effects in 25 patients, nail side effects in 14 patients and both skin and nail side effects in 12 patients were observed. Eruptions on face and body, thinning of skin of hands and feet, pruritus, xerosis cutis, softening and thinning of nails, paronychia, discoloration were determined. In our study, in the single use of trastuzumab, melanonychia striata and herpes zoster occurred. To sum up, we thought that carboplatin and trastuzumab could decrease the side effects of paclitaxel in the combination treatments.

The most side effects of capecitabine are edema on hands and feet, feeling of tightness and pain [13]. In our study we observed desquamation on hands and feet, probably, we thought that there was edema firstly and desquamation developed as the skin healed.

In the research of Prussick et al. [14], in the triple use of carboplatin, ifosfamide and etoposide, periorbital erythema, mucositis, erythema on face and groin occurred in eight patients. In addition there are publications that reported hyperpigmentation because of ifosfamide in the literature [15]. These results were consistent with our study.

In the study of Swain et al. [16], alopecia, rash on body, pruritus and xerosis cutis occurred in the triple use of pertuzumab, trastuzumab and docetaxel. Baselga et al. [17] determined alopecia, rash on body, peripheral edema, xerosis cutis in their research. In the research of Nakatsukasa et al. [18], peripheral edema and rash on body occurred in the dual use of cyclophosphamide and docetaxel in 48 female patients. Nitz et al. [19] determined hand and foot syndrome and mucositis/stomatitis in 198 patients. These all results were consistent with our research.

In the study of Petrioli et al. [20] stomatitis was observed in 10 patients of those using epirubicin only, in five patients of those using docetaxel only. Hand and foot syndrome was determined in six cases of those using epirubicin only and in three cases of those using docetaxel only. According to these results, epirubicin has a higher potential to cause side effects on skin and its appendages than docetaxel. We observed in our study that hair loss, oral aphthae, tinea corporis on front of body could occur in the dual use of epirubicin and docetaxel.

Nivolumab is a chemotherapeutic agent from the programmed cell death inhibitor 1 group. It causes lichenoid reactions, eczema, vitiligo and pruritus especially [21]. Incompatible with this study we observed that nivolumab could cause seborrheic dermatitis on face and scalp.

### Study Limitations

Our study has some limitations which need to be considered while evaluating its findings. First, it is a single-center study. Second, although oncologist was always working in the same part of hospital, dermatologists were working in the three different parts of the hospital during the process of research, therefore patients who had skin damage because of anticancer drugs, couldn't be sometimes examined by dermatologists. If dermatologists and oncologist always worked in the same part of hospital, the number of patients would be higher.

### Conclusion

In conclusion, chemotherapeutics can have beneficial effects as well as damaging effects on various organs. We compared dermatologic side effects of chemotherapeutic agents in the light of literature in our study. We also mentioned dermatologic side effects that haven't been mentioned in the literature yet. We believe that our research will contribute to the literature with all these aspects.

### Ethics

**Ethics Committee Approval:** It was approved by the University of Health Sciences Turkey, Izmir Tepecik Training and Research Hospital Ethical Review Committee (protocol number: 2019/13-30, date: 11/09/2019).

**Informed Consent:** Both verbal and written informed consents were obtained from study participants.

**Peer-review:** Externally and internally peer-reviewed.

### Authorship Contributions

Surgical and Medical Practices: M.G., M.K., A.Ö., Concept: M.G., M.K., A.Ö., Design: M.G., M.K., A.Ö., Data Collection or Processing: M.G., M.K., A.Ö., Analysis or Interpretation: M.G., M.K., A.Ö., Literature Search: M.G., M.K., A.Ö., Writing: M.G., M.K., A.Ö.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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