# Mucocutaneous side effects of chemotherapy in children: a cross-sectional study in Kerman, Iran

Saeedeh Farajzadeh, MD [1]
Mahin Aflatoonian, MD [2]
Morvarid Amirmijani, MD [3]
Zahra Farahmandinia, MD [4]
Rezvan Amiri, MD [2]
Maryam Khalili, MD [2*]

1. Leishmaniasis Research Center, Kerman University of Medical Sciences, Kerman, Iran
2. Department of Dermatology, Kerman University of Medical Sciences, Kerman, Iran
3. Kerman University of Medical Sciences, Kerman, Iran
4. Department of Pediatrics, School of Medicine, Afzalipour Hospital, Kerman University of Medical Sciences, Kerman, Iran

*Corresponding author:
Maryam Khalili, MD
Department of Dermatology, Kerman University of Medical Sciences, Kerman, Iran
E-mail: m_khalili@kmu.ac.ir, Maryam_khalili36@yahoo.com

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**Background:** Complications of chemotherapy most commonly involve highly proliferative cells, including the skin and its appendages and mucosa. This study evaluated mucocutaneous complications of chemotherapy in children with cancer.

**Methods:** This descriptive cross-sectional study involved 92 children who received chemotherapy at the Pediatric Oncology Ward of Afzalipour Hospital, Kerman, Iran, between September 2018 and March 2019. Demographic and clinical features of the patients were collected by history, physical examination, and laboratory tests (biopsy, fungal and bacterial smears if necessary). Frequency and percentage were used for qualitative analysis. Mean ± standard deviation was used for quantitative analysis.

**Results:** The mean age of patients was 6.60 ± 3.70 years (range 1 to 16 years). More than half of the patients (55.4%) were males. The most common malignancy was acute lymphocytic lymphoma (ALL). More than half of the children (60%) had mucocutaneous complications due to chemotherapy; these were significantly more common in boys than girls (70.6% vs. 48.8%). The mean age of children with mucocutaneous complications (7.41 ± 3.98) was significantly higher than those without complications (5.33 ± 2.84). The most common mucocutaneous side effects were, in order, alopecia, mucositis, and skin infections.

**Conclusion:** We found that side effects of chemotherapy were significantly more common in older children, boys, and children with leukemia. Vincristine was the most common culprit.

**Keywords:** Pediatrics, chemotherapy, skin

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## INTRODUCTION

Malignant neoplasms are the second cause of death in pediatrics. The incidence of cancer in children in Iran is estimated at approximately 16.8 per 100,000 [1-3]. The side effects of chemotherapy drugs are greater on cells with a higher proliferative capacity; therefore, the skin and its appendages are more affected by these drugs [4,5]. All skin parts may be affected, especially the hair due to the high division rate of hair follicle cells. Involvement of



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the sebaceous and sweat glands is rare [6-9]. Skin complications, although not life-threatening, can impair quality of life, increase morbidity, and decrease patient adherence to treatment. Therefore, sufficient knowledge of these side effects is necessary for diagnosis and management [9-11]. This is the first study on mucocutaneous complications related to chemotherapy in children with cancer referred to a tertiary medical center in Kerman, Iran.

## METHODS

This descriptive cross-sectional study involved 92 children who received chemotherapy at the Pediatric Oncology Ward of Afzalipour Hospital, Kerman, Iran, between September 2018 and March 2019. Included were children less than 16 years with cancer referred to Afzalipour Hospital for chemotherapy. Exclusion criteria were patients with a history of dermatologic diseases before chemotherapy and with skin cancers. Data were collected through history, physical examination, and laboratory tests (biopsy, fungal and bacterial smear if necessary). Demographic and clinical features of the patients, including sex, age, type of malignancy, number and type of chemotherapy drugs, and mucocutaneous complications, were recorded.

### Ethical consideration

The study proposal was approved by the Ethics Committee of Kerman University of Medical Sciences by ettical code of IR.KMU.AH.REC.1397.041.

### Statistical analysis

Frequency and percentage were used for qualitative analysis. Mean ± standard deviation was used for quantitative analysis. SPSS 16 (software IBM, Armonk, NY, USA) was used for data analysis.

## RESULTS

In this study, 92 children undergoing chemotherapy admitted to the Pediatric Oncology Ward of Afzalipour Hospital between October 2019 and March 2020 were recruited. The mean age of patients was 6.60 ± 3.70 years (range 1 to 16 years). More than half of the patients (55.4%) were males. The most common malignancy was acute lymphocytic lymphoma (42.4%) (Table 1).

Patients received a mean number of 3.22 ± 1.96 chemotherapy drugs (range 1 to 8). Approximately 60% of the children had mucocutaneous complications due to chemotherapy; these were significantly more common in boys than girls (70.6% vs. 48.8%; $P = 0.03$). The mean age of children with mucocutaneous complications (7.41 ± 3.98) was significantly higher than those without complications (5.33 ± 2.84; $P = 0.03$). The most common mucocutaneous side effects were alopecia (34.8%), mucositis (32.6%), and skin infections (15.2%) (Table 2). The mucocutaneous complications were most commonly reported in

**Table 1.** Frequency of malignancies in children admitted to the Pediatric Oncology Ward of Afzalipour Hospital

| Malignancy | Frequency (%) |
|---|---|
| Leukemia | |
| Acute lymphoblastic leukemia | 39 (42.4) |
| Acute myeloid leukemia | 4 (4.3) |
| Nervous system tumors | |
| Peripheral primitive neuroectodermal tumor | 3 (3.3) |
| Brain glioma | 3 (3.3) |
| Astrocytoma | 3 (3.3) |
| Ependymoma | 2 (2.2) |
| Optic glioma | 1 (1.1) |
| Embryonal tumors | |
| Medulloblastoma | 3 (3.3) |
| Nephroblastoma (Wilms tumor) | 3 (3.3) |
| Neuroblastoma | 3 (3.3) |
| Retinoblastoma | 2 (2.2) |
| Embryonal rhabdomyosarcoma | 1 (1.1) |
| Lymphoma | 11 (12) |
| Bone malignancies | |
| Osteosarcoma | 8 (8.7) |
| Ewing sarcoma | 3 (3.3) |
| Nasopharyngeal carcinoma | 2 (2.2) |
| Germ cell tumor | 1 (1.1) |

**Table 2.** Frequency of mucocutaneous lesions due to chemotherapy in children

| Mucocutaneous lesion | Frequency (%) |
|---|---|
| Infectious lesions | |
| Perianal abscess | 5 (5.4) |
| Herpes simplex | 3 (3.3) |
| Cutaneous/subcutaneous abscess | 3 (3.3) |
| Candidiasis | 1 (1.1) |
| Herpes zoster | 1 (1.1) |
| Mucormycosis | 1 (1.1) |
| Alopecia | 32 (34.8) |
| Mucositis | 30 (32.6) |
| Morbilliform drug eruption | 9 (9.8) |
| Xerosis | 3 (3.3) |
| Dermatitis | 3 (3.3) |
| Urticaria | 1 (1.1) |

**Table 3.** Frequency of mucocutaneous complications due to chemotherapy in children based on the type of neoplasm, n (%)

| Variable | Alopecia | Mucositis | Infectious | Morbilliformdrug eruption | Xerosis | Dermatitis | Urticaria |
|---|---|---|---|---|---|---|---|
| Leukemia | 17 (53.1) | 17 (56.7) | 8 (57.1) | 6 (66.7) | 1 (33.1) | 3 (100) | 0 (0) |
| Lymphoma | 3 (9.4) | 3 (10) | 1 (7.1) | 1 (11.1) | 1 (33.1) | 0 (0) | 0 (0) |
| Bone malignancies | 5 (15.6) | 6 (20) | 4 (28.6) | 0 (0) | 1 (33.1) | 0 (0) | 0 (0) |
| Embryonic tumors | 3 (9.4) | 2 (6.7) | 0 (0) | 2 (22.2) | 0 (0) | 0 (0) | 0 (0) |
| Nervous system tumors | 2 (6.3) | 1 (3.3) | 1 (7.1) | 0 (0) | 0 (0) | 0 (0) | 1 (100) |
| Nasopharyngeal carcinoma | 2 (6.3) | 1 (3.3) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Germ cell tumors | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| *P*-value | 0.28 | 0.13 | 0.30 | 0.65 | 0.34 | 1 | 1 |

**Table 4.** Percentage of mucocutaneous complications due to chemotherapy in children based on the type of prescribed drug

| Variable | Alopecia | Mucositis | Infectious lesions | Morbilliformdrug eruption | Xerosis | Dermatitis | Urticaria |
|---|---|---|---|---|---|---|---|
| Vincristine | 21.3 | 17.9 | 15.4 | 0 | 25 | 14.3 | 50 |
| Doxorubicin | 13.8 | 14.1 | 12.9 | 0 | 12.5 | 0 | 0 |
| Daunorubicin | 6.3 | 7.7 | 7.7 | 18.2 | 0 | 28.5 | 0 |
| Idarubicin | 0 | 1.3 | 2.4 | 0 | 0 | 0 | 0 |
| Methotrexate | 8.8 | 16.7 | 15.4 | 9.1 | 25 | 14.3 | 0 |
| Cytarabine | 7.5 | 6.4 | 7.7 | 9.1 | 12.5 | 14.3 | 0 |
| Tioguanine | 3.8 | 1.3 | 2.6 | 0 | 0 | 0 | 0 |
| Mercaptopurine | 1.2 | 1.3 | 5.1 | 0 | 0 | 0 | 0 |
| Cyclophosphamide | 11.3 | 8.9 | 7.7 | 0 | 0 | 0 | 0 |
| Ifosfamide | 1.2 | 0 | 2.6 | 0 | 0 | 0 | 0 |
| Lomustine | 1.2 | 1.3 | 0 | 0 | 0 | 0 | 0 |
| Cisplatin | 5 | 5.1 | 5.1 | 0 | 12.5 | 0 | 0 |
| Carboplatin | 1.2 | 0 | 2.6 | 9.1 | 0 | 0 | 50 |
| Thiotepa | 2.4 | 2.6 | 0 | 0 | 0 | 0 | 0 |
| Etoposide | 7.5 | 7.7 | 7.7 | 18.2 | 0 | 14.3 | 0 |
| Dactinomycin | 0 | 1.3 | 0 | 0 | 0 | 0 | 0 |
| L-asparaginase | 7.5 | 6.4 | 5.1 | 36.4 | 12.5 | 14.3 | 0 |

patients with leukemia (Table 3). Vincristine was the most common culprit drug (Table 4). Alopecia was reported more frequently in hematologic than non-hematologic malignancies (37% vs. 31.6%). Skin infections were mainly bacterial (57.1%) or viral (28.6%). Morbiliform drug reactions were reported in 9.8% of cases, primarily with L-asparaginase (36.4%), followed by daunorubicin and etoposide.

## DISCUSSION

This study investigated the mucocutaneous side effects of chemotherapy in 92 children admitted to the Pediatric Oncology Ward of Afzalipour Hospital. Hematologic malignancies (54.4%) were the most common malignancies, including acute lymphocytic leukemia (42.2%) and lymphoma (12%), aligning with the Shedeed *et al.* study in Egypt (51.76%) [12]. In the present study, the side effects of chemotherapy were predominantly observed in the hair, skin, and mucosa (34.8%, 33.8%, and 32.6%, respectively), agreeing with Rajashekar *et al.* (68.3%, 19%, and 14.28%, respectively) [13].

We found alopecia (34.8%) to be the most common complication related to chemotherapy, and the most common culprit drugs were vincristine (21.3%), doxorubicin (13.8%), and cyclophosphamide (11.3%). Günaydın *et al.* in Turkey demonstrated that alopecia (50%) was the most commonly reported complication in children undergoing chemotherapy, and the main causative drugs were cyclophosphamide (32.3%), daunorubicin (25.8%) and vincristine (22.6%) [6]. Rajashekar *et al.* cited alopecia as the most common complication (68.3%), caused by cyclophosphamide, etoposide, and docetaxel. More than half the cases (55%) had anagen effluvium between 3 and 6 weeks after beginning chemotherapy [13]. All cases of alopecia in the present study were anagen effluvium, which started 2 to 3 weeks after chemotherapy.

In the current study, the rate of alopecia in hematologic malignancies was higher than in non-hematologic malignancies (37% vs. 31.6%). In the Shedeed *et al.* study, alopecia was reported in 91.92% of hematologic malignancies and 45.35% of non-hematologic malignancies [12]. In a study in Turkey in 2015, the highest rate of alopecia was reported in central nervous system (CNS) tumors (55.6%), followed by hematologic malignancies (51.6%) [6]. The mechanism of hair loss in chemotherapy is a severe decrease in the mitotic activity of hair follicle matrix cells due to the cytotoxic effects of chemotherapy drugs. Hair loss can have immense psychological effects, making it an important issue. The incidence of this complication varies depending on the drug type and the drug concentration in the hair follicle [14,15].

The second side effect in the current study was mucositis (32.6%). The most common causative drugs were vincristine (17.9%), methotrexate (16.7%), and doxorubicin (14.1%). In Rajashekar *et al.*'s study, mucositis was observed in (14.28%); the most common causative drugs were cyclophosphamide, daunorubicin, and doxorubicin [13]. In other studies, the rate of this side effect varied between 15.79% and 55.6% [6,12,15,16]. The difference in the frequency of this side effect may be due to the different definitions of mucositis. In some studies, aphthous and infectious lesions were classified separately, while others classified them as mucositis. Previous studies have reported the highest incidence of mucositis in patients with leukemia and with methotrexate-based chemotherapy regimens, consistent with our study [6]. In the present study, 56.7% of patients with leukemia had mucosal lesions. Also, the most common drugs causing mucosal lesions were vincristine and methotrexate. Underlying disease and chemotherapy regimen are the two main risk factors for mucositis in treated patients. Since there is no standard treatment for mucositis, oral hygiene is the most important preventive measure and should be recommended to patients undergoing chemotherapy [6].

The third most common mucocutaneous complication in the current study was skin infections (15.2%), most commonly seen in patients treated with vincristine or methotrexate (each 15.4%). Nearly more than half of infections (57.1%) were bacterial, consistent with the Shedeed *et al.* (56.52%) and Bailey *et al.* (60%) studies [12,16]. Cutaneous abscesses and perianal abscesses were the most common infectious complications in the present study, in line with Garg *et al.* [14]. Viral infection was the second cause of infection in the present study (28.6%). Rajashekar *et al.* and Cardoza-Torres *et al.*, in contrast to our study, reported viral infections as the most common cause of infectious diseases (42.85% and 19.6%, respectively) [13,15].

Drug reactions were seen in 9.8% of cases in the present study, and the most causative drugs were L-asparaginase (36.4%), danarubicin, and etoposide, respectively. In the Shedeed study, this rate was 21.05% [12].

Xerosis accounted for only 3.3% of the mucocutaneous complications in this study, most commonly observed with vincristine and methotrexate (25% each). In the Cardoza-Torres *et al.* study, xerosis was reported in almost half of the cases (56.4%), most frequently with daunorubicin (28.5%). Accumulation of cytotoxic drugs in the epidermis (especially the basal layer), immunosuppression, malnutrition, and anemia have been suggested as possible causes of xerosis [15].

## CONCLUSION

In this study, mucocutaneous side effects were recorded in nearly 60% of children with cancer who underwent chemotherapy. Side effects were observed more frequently in older children and boys. The most common mucocutaneous side effects were alopecia, mucositis, and skin infections. More than half of all infections were caused by bacterial agents. Side effects were most common in children with leukemia; vincristine was the most common culprit.

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### Authors contribiutions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Saeedeh Farajzadeh, Morvarid Amirmijani, Zahra Farahmandinia , Maryam Khalili, Rezvan Amiri, and Mahin Aflatoonian. The first draft of the manuscript was written by Mahin Aflatoonian and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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