

## ORIGINAL RESEARCH



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## Assessment of oral mucositis degree due to cytostatic treatment in patients with malignant lymphomas.

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### Abstract

**Introduction:** Oral mucositis characterized by inflammation of the oral mucosa, ulcers, angular cheilitis, accompanied by pain in the maxillary facial area are symptoms of patients who have undergone cytostatic treatment, affecting over 75% of high-risk patients.

**Material and methods:** From the total of 182 patients with hematological malignancies, we selected 59 patients, diagnosed with malignant lymphomas and treated at the Hematology Department of the Medical Clinic 1 in Tîrgu Mureș, between July 2013 and June 2016, analyzing the data in the data observation sheets. The study is a retrospective one.

**Results:** In the group of patients studied, who were treated based on the aforementioned cytostatic plans, we found that the CVP + Rituximab plan frequently causes 1st and 2nd class stomatitis, with no patients with 3rd and 4th class stomatitis. The CHOP + Rituximab therapy plan in a total of 80 applications had complications of 1st and 2nd class stomatitis, much more frequent 1st class without stomatitis of 2nd and 4th degree. Grade III stomatitis occurs in two cases in the CHOP-Bleo belts. Introducing dental medicine in the context of medical multidisciplinary in oncology hematology is a real necessity because the oral complications of chemotherapy treatments by their severity can lead to compromise of the treatment protocol by reducing the doses or even stopping the treatment

**Conclusions:** Malignant hemopathies represent a significant percentage in dental disorders, and among them, the maximum severity belongs to the non-Hodgkin and Hodgkin malignant lymphomas. Stomatitis, also called gingivotoxic stomatitis caused by medication, is an acute oral complication, with erythema and edema of the entire oral cavity. The role of the dentist in the diagnosis, prevention and treatment of oral lesions, following the cytostatic therapy, is extremely important.

**Keywords:** mucositis, chemotherapy, cytostatic oral manifestation.

### Introduction

Oral mucositis characterized by inflammation of the oral mucosa, ulcers, angular cheilitis, accompanied by pain in the maxillary facial area are symptoms of patients who have undergone cytostatic treatment, affecting over 75% of high-risk patients [1].

Symptoms of these conditions vary depending on the type of cytostatics, the number of treatments administered and the general condition of the patient, taking different forms from the most mild ones such as inflammation, dryness of the mouth, gingival bleeding, to the most serious ones such as pain, impossibility to swallow food, infections of the oral mucosa that can lead to altered general condition. [2,3].

Research into the prevention and treatment of mucositis in this setting remains limited,

with an overwhelming amount of small, single-center studies that fail to achieve a sufficient level of evidence [4].

The management of oral mucositis is a challenge, due to its complex biological nature. Over the last 10 years, different strategies have been developed for the management of oral mucositis caused by chemotherapy [5].

Generally, cytostatics have a more pronounced selective toxicity for malignant cells, being unable to act strictly selectively, to differentiate a tumor cell from a normal cell. The toxic effect of these drugs is manifested especially on tissues with a high degree of multiplication, such as the epithelium of the digestive tract, especially the oral cavity, the epidermis and the bone marrow.

Objectives

In this study, we propose the assessment of the degree of detectable stomatitis in the oral cavity following the administration of cytostatics used in the treatment of malignant lymphomas.

### Material and methods

From the total of 182 patients with hematological malignancies, we selected 59 patients, diagnosed with malignant lymphomas and treated at the Hematology Department of the Medical Clinic 1 in Țirgu Mureș, between July 2013 and June 2016, analyzing the data in the data observation sheets. The study is a retrospective one, and it is based on the findings in the patients' observation sheets. The study protocol has been approved by the institutional ethical committee and from the head of the Medical Clinic 1 in Țirgu Mureș. We quantified the following parameters:

- The type of lymphomas established by histopathological immunohistochemical and cytogenetic examination.
- The staging of the disease, according to the criteria of Ann Arbor plan and the degree of malignancy appreciated according to WHO and REAL classifications.

- Therapeutic plan followed
- The assessment of cytostatic toxicity on the oral mucosa was made based on information gathered from the patient's observation sheets and the assessment and recording of the stomatitis degree was done according to the oral toxicity scale approved by the WHO:

- Class 0 - without objective and subjective symptoms
- Class 1 – pain + erythema
- Class 2 – erythema, ulcers; patients can swallow food
- Class 3 – extended erythema, ulcers, patients cannot swallow solid foods
- Class 4 – enlarged mucositis, feeding is impossible.

### Results

Of the total of 59 patients diagnosed with malignant lymphoma, 18 patients suffered of Hodgkin's Malignant Lymphoma (HL) and 41 patients of Non-Hodgkin's Malignant Lymphoma (NHL). (Table 1)

Table 1. Number of patients depending on the type of malignant lymphomas

Srt. no.	Diagnosis	Patients	
		Number	Percentage %
1	Non-Hodgkin malignant lymphoma (NHL)	41	69,49%
2	Malign Hodgkin lymphoma(HL)	18	30,50%
3	<b>Total</b>	<b>59</b>	<b>100%</b>

Both patients with Hodgkin's Lymphoma and those with non-Hodgkin's Lymphomas belonging to the studied group were in different stages of clinical evolution at the time of starting the cytostatic treatment.

Of the 18 patients with HL, 3 patients were in clinical stage II with no risk factors, 10 patients in clinical stage III, of which 5 with risk factors and 5 patients in clinical stage IV, of which 3 with risk factors. Cytostatic administrations applied to patients with malignant lymphomas are listed in table no. 2.

The main therapy plans used in the Hematology Service in the patients in the studied group were the following:

- ABVD (Anthracycline, Bleomycin, Vinblastin, Dacarbazin).
- CVP (Cyclophosphamide, Vincristin, Prednisone) + Rituximab
- CFA (Cyclophosphamide) + Rituximab
- CFA (Cyclophosphamide) + Fludarabine combinations

- CHOP (Cyclophosphamide, Doxorubicin, Vincristin, Prednisone) + Rituximab most commonly used.
- CHOP-Bleo (Cyclophosphamide, Doxorubicin, Vincristin, Prednisone, Bleomycin)
- CHOP-ETOP (Cyclophosphamide, Doxorubicin, Vincristin, Prednisone, Etoposide)
- DHAP (Cytosin Arabinoside Pharmacorubicin Prednisone)
- CASC (Cyclophosphamide, Cytosine-Arabinoside, Soludecortin Cisplatin)  
The last 4 treatments are used in increasingly rare cases, especially in cases of relapse or refraction.

Table II Type of medication given depending on the disease

Malignant lymphoma	Type of cytostatic treatment	No. of applications
NHL	CVP+Rituximab	44
	Fludarabină	31
	CFA+Rituximab	26
	CHOP-ETOP	14
	CHOP+Rituximab	80
	CHOP-Bleo	19
NHL refractory or relapsed	DAHP	14
	CASC	13
HL	ABVD	127

Of the 41 patients with NHL, 10 patients suffered of indolent lymphoma and 31 patients suffered of aggressive lymphoma. (Table 3)

The severity of stomatitis according to the type of cytostatics and the number of treatments administered in patients with Malignant Lymphomas is shown in table no. 4.

In the group of patients studied, who were treated based on the aforementioned cytostatic plans, we found that the CVP + Rituximab plan frequently causes 1st and 2nd class stomatitis, with no patients with 3rd and 4th

class stomatitis. The CHOP + Rituximab therapy plan in a total of 80 applications had complications of 1st and 2nd class stomatitis, much more frequent 1st class without stomatitis of 2nd and 4th degree. Grade III stomatitis occurs in two cases in the CHOP-Bleo belts.

The Chi square test, with the value 0.1138, so  $p > 0.05$ , shows that there is no statistically significant association between the degree of stomatitis and the type of cytostatic / number of treatment plans administered.

Table 3. Number of patients with malignant lymphomas depending on the diagnosis and clinical stage

Srt. No.	Diagnosis	Clinical stage	No. of patients
1	Non-Hodgkin malignant lymphoma	Indolent	10
2	Non-Hodgkin malignant lymphoma	Aggressive	31
3	Hodgkin malignant lymphoma	II	3
4	Hodgkin malignant lymphoma	III	10
5	Hodgkin malignant lymphoma	IV	5
6	Total	-	59

Table 4. Correlation of stomatitis degrees with cytostatic type

Treatment type	CVP+	CHOP+	CHOP-	DAHP	CASC	ABVD
	Rituximab	Rituximab	Bleo			
	N=44	N=80	N=19	N=14	N=14	N=127
Stomatitis GR I	15 34,09%	19 23,75%	8 42,1%	2 14,28%	2 15,38%	15 11,81%
Stomatitis GR II	3 6,81%	8 10%	5 26,31%	4 28,57%	3 23,07%	7 5,5%
Stomatitis GR III	0	0	2 10,52%	2 14,28%	6 46,15%	8 6,2%
Stomatitis GR IV	0	0	0	5 35,71%	3 23,075%	0
Total	18 40,90%	27 33,75%	15 78,93%	13 92,85%	14 100%	30 23,62%

The most commonly used ABVD treatment plans caused frequent lesions in stages I, II and III, but did not reach stage IV.

The most common oral cavity lesions encompassing all four stages of stomatitis were found in the case of DAHP and CASC treatments where 35% and 23%, respectively, of class IV stomatitis were reported with severe injuries and inability to feed. Also, 46% of the treatments with CASC caused class III

stomatitis with extensive injuries and the impossibility of solid nutrition.

### Discussions

Authors, like Roşianu R. Roşu A, state that mucositis can occur in patients treated with cytostatics even after the chewing process because the loss of immunity leads to dry mucous membranes and any irritation is followed by painful ulcerative lesions [6].

Introducing dental medicine in the context of medical multidisciplinary in oncology hematology is a real necessity because the oral complications of chemotherapy treatments by their severity can lead to compromise of the treatment protocol by reducing the doses or even stopping the treatment [7].

Administration of honey, zinc, and glutamine reduce the risk of developing oral mucositis during chemotherapy or radiotherapy [8].

Studies on mice at the University of Tokyo Japan have shown that stomatitis occurs in 40% of cases of cytostatic administration and in 100% of cases when cytostatic administration has been combined with radiotherapy [9].

The cytostatic toxicity of the oral mucosa is influenced by the dose of the medicine and the immunosuppressive status of the body which leads to the occurrence of infections and oral bleeding. These complications aggravate the patient's condition by prolonging the healing time, the need for parenteral nutrition, the need for antibiotic, antimycotic and analgic treatment, sometimes of the opiate type, and the pain in the oral mucosa becomes violent and dragging [10].

Most authors consider that maintaining thorough hygiene, applying mouthwashes to the oral mucosa (anesthetic and anti-inflammatory), as well as draining the oral cavity are factors that manage the risk of mucositis in patients with lymphomas and cytostatic therapy. Patients benefited from initial dental treatments, before the administration of cytostatics, as well as during the oncological treatment, recommending the maintenance of rigorous oral hygiene, oral showers, avoiding acid foods, and applying topical solutions with anesthesia and hydrocortisone on the oral mucosa [11].

Data from the literature indicate that stomatitis accompanies about 30% of the cases treated with cytostatics. Stomatitis is commonly associated with alopecia urticaria and local reactions at the site of the administration being part of the skin-bone disorders group. Besides, early complications of cytostatic treatment may be represented by gastrointestinal disorders of which vomiting

and anorexia occur in 20% of cases and hepatotoxicity in 23% [12].

It should be noted that in the cases that benefited from treatment with CASC and DAHP stomatitis occurred in about 100% of the cases the most frequent forms being the most serious respectively class III and class IV. In the treatments with ABVD, the most frequently used, we found stomatitis in 23% of the treatments. The most frequent form being stomatitis of class I.

Comparing the CVP + Rituximab versus CASC, DAHP treatment plans, we have found significant differences in toxicity, with more aggressive treatments leading to more serious complications.

Another category of early complications of cytostatic treatment are neurological disorders like peripheral neuropathy present in 10% and hematological disorders like hemorrhagic syndromes that occur between 7 and 17 days after the onset of the treatment in a percentage of about 11-12% especially after the treatments with AHP and CASC, as Welbury and Murray point out in their studies. In some cases, severe neutropenia and thrombocytopenia require an increase in the interval between treatments, antiviral and antimicrobial prophylaxis, and a decrease of cytostatic doses by 20%.

In our study, the patients did not have neurological disorders, and the antimicrobial treatment for lesions in the oral cavity was performed according to the antibiogram. Severe thrombocytopenia required thrombocyte mass administration [13].

Authors from Australia in their studies concluded that Palifermin has activity as a mucosal protectant in patients receiving intensive chemotherapy [14].

Oral cryotherapy is effective for the prevention of oral mucositis in adults receiving fluorouracil-based chemotherapy for solid cancers, and for the prevention of severe oral mucositis in adults receiving high-dose melphalan-based chemotherapy [15,16]

Other studies: Welbury R and Murray J. show that oral lesions occur mainly in patients with poor oral hygiene and periodontal disorders [17].

In the studies conducted by Spielberger R. in California USA, the authors found that the severity of oral mucositis following cytostatic

treatment and radiotherapy is lower when Palifermin is administered. The study was carried out on a batch of 212 patients diagnosed with hematological cancers, 106 patients receiving Palifermin treatment and 106 receiving placebo treatment. The incidence of oral mucositis class 3 and 4, according to the WHO was 63% in the group of patients receiving Palifermin and 98% in the patients receiving placebo. This study confirms that the administration of adjuvant medication in cytostatic treatments and radiation therapy decreases the severity of oral mucositis [18].

A single dose of palifermin before each cycle reduced the incidence and severity of mucositis. The drug was generally well tolerated, but most patients experienced thickening of oral mucosa [19].

Recently, various natural agents in plants have been noticed in mucositis, which may improve the symptoms through different interventions [20].

### Conclusions

1. Malignant hemopathies represent a significant percentage in dental disorders, and among them, the maximum severity belongs to the non-Hodgkin and Hodgkin malignant lymphomas, which also cause the most severe complications in the oral cavity.
2. The cytostatic toxicity on the oral mucosa is influenced by the type and dose of the medication, but also by the immunosuppressive status of the body, which leads to the occurrence of infections, ulcerations and oral bleeding.
3. Stomatitis, also called gingivo-toxic stomatitis caused by medication, is an acute oral complication, with erythema and edema of the entire oral cavity, following the cytostatic therapy, which evolves from class I to class IV extremely quickly, causing additional suffering to patients.
4. The most common lesions of the oral cavity covering all four stages of mucositis were found in the case of DAHP and CASC treatments, where stomatitis was reported 100% and 23%, respectively, stomatitis of class IV with severe lesions and impossibility to feed.
5. There is no significant difference in toxicity between CVP+Rituximab and CHOP+Rituximab, CHOP-Bleo treatments, comparing the occurrence of stomatitis and its severity.
6. The role of the dentist in the diagnosis, prevention and treatment of oral lesions, following the cytostatic therapy, is extremely important, contributing to reducing discomfort and improving the quality of life.
7. Maintaining a rigorous hygiene, the application of mouthwashes to the oral mucosa (anesthetic and anti-inflammatory), as well as the drainage of the oral cavity are factors of risk management of mucositis in patients with lymphomas and cytostatic therapy.

**Conflict of interest:** None to declare.

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