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Algorithm for the prophylaxis and treatment of chemotherapy-induced oral mucositis in children with hemato-oncological diseases

DOCTORAL DEGREE SUMMARY

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ABBREVIATIONS AND DEFINITIONS

OM	Oral mucositis
HCS	Hematopoietic stem cells
GCS-F	Granulocyte colony stimulating factor
ATG	Anti-thymocyte globulin
VCR	Vincristine
MTX	Methotrexate
NTF	Neoadjuvant therapy
SE	Side effects
ADE	Adverse Device-Related effects
cGy	Centigray
CE	Conformité Européene
CIP	Clinical investigation plan
CV	Closing Visit
CRA	Clinical Research Associate
CRF	Case Reporting Form
CRO	Contract Research Organization
CTA	Clinical trial agreement
EC	Ethics Committee
GCP	Good Clinical Practice
FU	Follow-up
GI	Gastrointestinal
ICH	International Harmonization Committee
ICU	Intensive Care Unit
ISO	International Organization for Standardization
MV	Monitoring Visit
PI	Principal Investigator

SDAE, SAE	Serious Device-Related Adverse Events, Serious Adverse Events
ISV	Initial site visit
TMF	Trial Master File
WHO	World Health Organization
ISF	Investigator Site File
SDV	Source Data Verification

I. INTRODUCTION

Onco-Hematological pathology, although rare in pediatric age, has a major impact on the resources of the medical system, both in terms of human resources and material resources, significantly raising the costs of treatment. Malignancies require complex treatment, which combines chemotherapy, radiation therapy, cancer surgery, immunotherapy, targeted therapies and more recently, cell therapy. The most common complication secondary to chemotherapy is oral mucositis (OM), which is an inflammation of mucosa of oral cavity, with a severe impact on health. Secondary OM includes impaired nutritional status, hydro-electrolyte imbalances, debilitating pain, severe infections with a digestive starting point that can progress rapidly to sepsis in immunocompromised, onco-hematological patients. These complications delay chemotherapy regimens, with an unfavorable impact on the morbidity and mortality rate, cumulative to the primary pathology.

Oral mucositis is a significant problem in patients and for patients undergoing radio and chemotherapy for solid tumors. In one clinical study, 303 out of 599 patients (51%) who received chemotherapy for solid tumors or lymphoma reported developing oral mucositis and/ or GI [1]. Oral mucositis developed in 22% out of 1236 cycles of chemotherapy, GI mucositis in 7% of cycles, and both oral mucositis and GI mucositis in 8% of cycles. An even higher percentage (approximately 75-80%) of patients receiving high-dose chemotherapy prior to hematopoietic cell transplantation developed clinically significant oral mucositis [2].

Patients treated with radiotherapy for head and neck cancer usually receive a daily radiation dose of about 200 cGy, five days a week, for 5-7 consecutive weeks. Almost all these patients developed some degree of oral mucositis. In recent studies, oral mucositis developed in a percentage of 29-66% of all patients who have received radiation therapy for head and neck [3,4].

Most patients who receive radiation therapy for head and neck cancer cannot continue to eat orally due to pain and often receive nutrition through gastrostomy tube or intravenous line. It has been shown that patients with mucositis are significantly more likely to suffer severe pain and weight loss $\geq$ 5% [4]. In one study, approximately 16% of patients who received radiation therapy for head and neck cancer were hospitalized because of mucositis [5]. Moreover, 11% of patients who received radiation therapy for head and neck cancer had unplanned breaks in radiation therapy due to severe mucositis [5]. OM treatment is based on symptom management and supportive care.

The data suggest that oral mucositis is a common pathology, secondary to chemo and radiotherapy, with a direct impact on the association of tertiary complications that strongly influence the morbidity rates and mortality of the haemato-oncological patient.

At present, few published studies have analyzed this complication in the pediatric population with haemato-oncological diseases or / and recipients of hematopoietic stem cell transplantation.

The magnitude and difficulty of this problem associated with the care of pediatric onco-hematological patients with or without hematopoietic stem cell transplantation, with an impact on their chances of survival require innovative approaches, based on rigorous analysis, to provide evidence and represent the basis of specific recommendations and support the current chosen topic.

The motivation for choosing this topic is from the active observation of the evolution of the pediatric onco-hematological patient who performs standard chemotherapy or high-dose chemotherapy and bone marrow transplantation, an activity in which I have been involved for

the last 20 years in the Pediatrics, at Fundeni Clinical Institute, department of haemato-oncology and hematopoietic stem cell transplantation, reference center in Romania.

The lack of standardized protocols for prophylactic / therapeutic approach to oral mucositis secondary to chemotherapy / radiotherapy in children with hematological diseases and bone marrow transplantation, along with the existence of multiple choices of existing commercial products with minimal evaluations through medical studies has led to the current topic.

The Doctoral degree is a retrospective, analytical study, aimed to evaluate the results of using standardized care guidelines for OM and implement an algorithm for diagnosing and treatment OM in onco-hematological patient, especially the pediatric one, in order to reduce morbidity and mortality caused by OM and increase the compliance with chemotherapeutic treatment. This working tool, based on the experience gained in a referral center, will be useful both to the new generations of nurses and the family members involved in caring for the child with cancer and bone marrow transplantation.

The diagnostic algorithm followed the steps of classifying OM according to the VAS scale of the World Health Organization (WHO) by evaluating the clinical appearance of the jugal mucosa, gums, lips, tongue, teeth, sound appearance of the voice and pain when swallowing.

A score was calculated and a treatment algorithm adapted to the severity of OM was performed. This included the recommendation to adapt the diet, local prophylactic / curative treatment of the oral cavity with a bioactive product selected and evaluated multi parametrically and systemic adjuvant treatment of OM: antibiotic / antifungal, analgesic therapy, parenteral nutrition.

The treatment algorithm included: local care of the oral cavity, which involved combining soft / extra-soft tooth brushing with rinsing with banking soda solution or saline irrigation, with / without local disinfectant (methyl blue, chlorhexidine 1%), with / without local analgesic (lidocaine) and the local treatment itself.

The local treatment targeted a selected product containing: a bioactive combination of Zinc, Taurine and polyvinylpyrrolidone (PVP), a commercial product that is also accessible in Romania, CE marked with mechanical action indication for management MO, pain relief, treatment of lesions by adherence to the surface oral mucosa, soothing of lesions caused by chemotherapy and/ or radiation therapy. The spray product is manufactured according to the rules of asepsis and antisepsis, easy to use, with a standardized chemical formula / vial.
This study was conducted in accordance with established ethical principles.

The analysis of the data of the 149 haemato-oncological patients included in the doctoral degree led to results with positive statistical significance and to the achievement of the proposed goal, the implementation of a standardized protocol for the care of oral mucositis with direct impact on haemato-oncological pathology in Romania, Fundeni Clinical Institute being the center of reference in our country.

This paper contains 181 pages and consists of two parts. The first part, the general one, divided into eight chapters, is an update of the general notions related to the etiopathogenesis, epidemiological aspects, the clinical diagnosis, the classification in degrees of severity and the topical therapeutic aspects of the oral mucositis. The special part, essential for personal contributions, sets out: the working hypothesis, the methodology, the results, the discussions and the conclusions of the doctoral study.

The personal contributions brought by this paper are evident by demonstrating the working hypothesis, with the achievement of all the objectives highlighted by the final results presented.

Working hypothesis: I assume that the implementation of a standardized prophylactic / therapeutic guide for OM care will increase patient compliance with treatment, reduce resource consumption, and decrease secondary morbidity and mortality. I support the hypothesis through a retrospective study of the impact of the use of some agents in the prophylaxis of oral mucositis.

There is no standard OM treatment protocol in Romania.

To evaluate the impact of local treatment used for the care of OM in patients with malignancies and / or hematopoietic stem cell transplants who received radio- or chemo-therapy, we analyzed data from a group of patients from 1st of January 2015 to December 2015. The subjects were hospitalized in the Hematology Center, Fundeni Clinical Institute. Data was collected from patients' medical records available in the clinic's archives. The database was designed during the doctoral study and included 149 patients; multiple parameters were evaluated to assess the impact of prophylaxis / treatment of OM. The intention to implement a standardized protocol for the care and treatment of OM also evaluated a product, a selected bioactive combination, available in Romania, which would meet patient safety criteria.

This was a one-center retrospective study for pre-specified target in patients receiving radiation or chemotherapy as a treatment for malignancies and in patients with hematopoietic stem cell transplantation.

The specific sample size was not calculated for data collection, as the available sample size was not known with a priori accuracy and was determined by the number of medical records of patients collected from 1st of January 2017 to 31st of December 2020 - the period of the doctoral study - which complied with the inclusion / exclusion criteria. The subjects were hospitalized in Fundeni Clinical Institute.

Finally, data were collected from 149 patients, including 99 adults and 50 children. Data collection was completed in December 2020. Data analysis and thorough design of this paper were between January 2021 and January 2022.

The objectives of the study were as follows:

Main objectives

- Duration of OM symptoms in patients treated with oral gel from the first application;
- Number of patients (in percentage) who developed severe OM when the oral gel was used as a preventive treatment.

Secondary objectives

- Decreased severity of OM after 1 month of treatment in transplant patients;
- Number of patients (in percentage) who have developed severe OM since its first application;
- Number of patients (in percent) who achieved complete remission of OM symptoms;
- Number of patients (in percentage) able to resume chewing and swallowing food after using the oral gel;
- Number of patients (in percentage) who reduced the average number of hospitalization days after using the oral gel;
- Number of patients (in percentage) who reduced the number of days requiring parenteral nutrition and parenteral narcotic therapy after use of the oral gel;
- Number of patients (in percentage) who gained weight after using the oral gel;
- Number of patients (as a percentage) who discontinued morphine for OM-associated pain;

- Number of patients (in percentage) who continued the planned chemotherapy after using the oral gel;
- ADE rate associated with oral gel application
- SDAE rate associated with oral gel application;

Data management and statistical evaluation fully ensure compliance with applicable laws and regulations on the protection of data confidentiality.

Given the retrospective aspect of data collection, not all data were available to all patients, standard descriptive statistics were used to calculate all study variables. For continuous variables, statistics include means with min-max limits, average values, standard deviations.

Descriptive analysis was provided for demographic characteristics; concomitant diseases and concomitant treatment have been described by statistical features.

The statistical analysis was performed in the IBM SPSS version 20 program. In order to obtain the statistical results, multiple tests were used depending on the characteristics of the variables.

The results of the present study are eloquent and have led to the implementation of a standardized care algorithm based on the analysis of the risk of developing OM and the evaluation of specific symptoms. Local treatment of OM has a great contribution to achieving better therapeutic results in the treatment of cancer.

DISCUSSIONS

In this analytical, retrospective study, data was collected from 149 patients considered suitable for enrollment.

In the current study, the adult population predominated 66.4% (99 patients), and the pediatric population only 33.6% (50 patients) with an average age of 7.2 (min-max: 2-17) years and age median of 6 years. The sample of interest in the current study was the pediatric population. In 2021 the incidence of cancer in the pediatric population estimated by the American Cancer Registry is 15.500 new cases per year and 400.000 new cases / year according to the WHO, increasing compared to previous years which supports the importance and timeliness of the chosen topic [6-8].

Cancer treatment involves chemotherapy according to current standardized protocols, OM being a common complication of this treatment. OM to varying degrees, secondary to chemotherapy or radiation therapy is the pathology targeted by the doctoral study [9].

The patient population from which the data were collected in this study consisted of patients of both sexes, with a prevalence of women, 52.3% (78 patients) in the total population and 47.7% men (71 patients), and in adult patients with 53.5% (53 patients) women and 46.5% (46 patients) men, while in children and adolescents the patients were distributed equally by sex. The sex of cancer patients is an important parameter that influences the incidence, prognosis and mortality of the disease [10]. Males associate an increased incidence of up to 20% of cancer, with a high mortality, but with minor side effects associated with chemotherapy compared to females [11-12].

At the time of data entry, overall cohort survival was 83.2% (124 patients in the total population were still alive, 80 adults and 44 children, 88%), while overall mortality was 16.8%. (25 were dead, respectively 19 adults and 6 children, 12%). The pediatric patients in the study had a higher survival rate similar to the current literature [13].

There is no statistical difference in the analysis of the mortality rate in the two categories of subjects, adults vs. children.

Weight was initially measured in all patients. The results of the current study reveal an average weight of the adult population of 76.1 (min-max: 44.4-143), with the average weight being 26.3 (min-max: 13-81) in the pediatric population. The importance of the parameter is eloquent because the medication administered to the subjects either chemotherapy or adjuvant treatment with possible impact on the oral mucosa will be evaluated according to the dose related to 1Kg/body weight, but also the parameter for monitoring the nutritional status in relation to the OM degree. Severe OM, grade 4, is associated with severe local pain with loss of appetite and inability to administer oral food and medication, secondary weight loss, and involvement of intravenous hydration and parenteral nutrition with increased secondary morbidity. Some studies report low weight of pediatric subjects prior to administration of chemotherapy as an increased risk parameter for the development of OM, in children with cancer [14].

Regarding the medical history of the subjects, the predominant hematological pathology revealed the following results: within the cohort the most frequent diagnosis was Leukemia. In the sample of adult subjects in descending order of frequency of the main diagnosis were identified: Leukemia, Multiple Myeloma, Lymphoma, and in the cohort of pediatric subjects: Acute Leukemia, predominantly lymphoblastic followed by myeloblastic. The literature cites a 7 times higher frequency of ALL in the pediatric population compared to adults [15].

Secondary pathologies were also considered for the rest of the pediatric patients with the following distribution: gastrointestinal area 5 pediatric patients, pulmonary area 5 pediatric patients, renal / urinary tract 4 pediatric patients, neurological area 1 pediatric patient, metabolic / endocrine pathology 1 pediatric patient, apparently reproductive 1 pediatric patient. It predominated, in equal proportions, the associated pathologies represented by the diseases of the gastrointestinal tract, respectively those of the urinary tract. The most common infections found in the present study were gastrointestinal infections. Comorbid conditions generated by digestive pathology in the pediatric cohort are consistent with the presence and evolution of OM [16].

All patients included in the current study have hematological pathologies. Treatment regimens included: chemotherapy according to standardized protocols (VCR, Doxorubicin, MTX, L-asparaginase) or in the pre-transplant conditioning course of HSCT (Melphalan, Fludarabine, Busulfan, etc.), associated immunosuppressive therapy (cortisone, cyclosporine, ATG) and treatment adjuvant (antibiotics, antifungals, granulocyte growth factor, hepato-protectants, etc.), so that subjects were registered with at least one concomitant drug, and most had more than one concomitant drug. In the pediatric population, the average number of concomitant medications per patient was approximately 4-fold, 23 (min-max: 10-72) compared to the adult population where the average number of concomitant medications per patient was only 5.5 (min-max. max: 1-14). The results of the study revealed the predominance of adjuvant medication in children. This included antibiotics (Meropenem, Amikacin, Gentamicin, Cefuroxime, Ceftriaxone, Amoxicillin-clavulanic acid, Ciprofloxacin, Sulfamethoxazole-Trimethoprim, etc.), antifungals (fluconazole, Posaconazole), antiparasitic (metronidazole), electrolytes (Glucose, Sodium, Calcium, Potassium, Chlorine), parenteral nutrition, hepatotropic (amino acids, ursodeoxycholic acid), anticonvulsants (diazepam, levetiracetam), sedatives (tramadol, morphine), antihypertensives (metoprolol, amlodipine), symptomatic (diosmectite, drotaverine, dicarbocalm and others). The results show an adjuvant, supportive treatment more intense in children compared to adults because the cooperation of pediatric subjects is minor, and intensive and careful care with combined local and intravenous treatment prevents in such pathologies the tremendous complications associated with OM and the

underlying disease [17]. The survival rate of children with hematological disorders is higher than in adults [18].

The existence of few effective local therapies and standardized guidelines for the prevention and treatment of OM constantly decreases the quality of life and the prognosis of the cancer patient [53].

According to the data, many drugs have been administered to all subjects because patients with malignancies and those after transplantation receive a complex medication: chemotherapy according to standard therapy under current treatment protocols, to which supportive medication (NTF) is added, so that the amount of data to be entered was very large, making it difficult to analyze the data by limiting the ADE evaluation generated only by the application of the selected local product. The existence of drug interactions generated by basic therapy with secondary drug SE independent of the locally applied product for OM prophylaxis has been difficult to quantify and limit.

The following drugs have been specified in NTFs:

- children: ciprofloxacin, metronidazole, fluconazole, Posaconazole, granisetron, hydrating fluids (NTF 3 attachment)
- adults: ciprofloxacin, metronidazole, acyclovir, fluconazole, pantoprazole, granisetron (NTF 4 attachment)

Chemotherapeutics agents (details in Table 1), reported as administered to patients selected for data collection:

Table 1. Distribution of subjects in relation to the chemotherapeutic drug

CHEMOTHERAPEUTIC AGENT						
	Total		AGE			
			Adults		Children	
	N	%	N	%	N	%
MELPHALAN	43	28.9	43	43.4	-	-
BUSULFAN	22	14.8	17	17.2	5	10
CARMUSTINE	20	13.4	15	15.2	5	10
FLUDARABINE	15	10.1	13	13, 1	2	4
CITARABINUM	13	8,7	-	-	13	26
VINCRISTINE	13	8,7	-	-	13	26
LOMUSTINE	10	6,7	10	10,1	-	-
METOTREXATE	9	6	-	-	9	18
CYCLOPHOSPHAMIDE	3	2	1	1	2	4
TREOSULPHAN	1	0, 7	-	-	1	2
TOTAL	149	100	99	100	50	100

Chemotherapy treatment was administered in 100% of cases, only one subject received additional treatment with radiotherapy. Chemotherapy with Melphalan, a cytotoxic agent included in the conditioning therapy of subjects with hematological disorders following HCST, predominated. One of the many very common side effects of this chemotherapeutic is ulceration of the oral mucosa, OM. According to current studies, over 88% of children treated with chemotherapy develop OM [19].

The average number of days of chemotherapy was 4 times lower, 2 (min-max: 1-45) in the total patient population, compared to the population of children and adolescents, 10.6 (min-max: 1- 45) with a statistically significant difference between the number of cycles of chemotherapy administered to children vs. adults. Children required significantly more cycles than adults, $p < 0.001$. OM is a secondary complication of chemotherapy more common in children compared to adults [20].

There is a statistically significant, negative correlation between the number of cycles of chemotherapy and the doses administered, thus, a higher number of cycles is associated with lower doses of chemotherapy, $p < 0.001$, $r = -0.386$, moderate binding power. These parameters are important to evaluate because the literature claims that the frequency of administration of chemotherapy cycles has a stronger influence on the risk of severe OM in relation to the type of chemotherapy, especially in the case of solid tumors [21].

The literature closely mentions the association between the type, duration and number of cycles of chemotherapy and the development of OM, so it is necessary to standardize a protocol for the prophylaxis and treatment of OM applied rigorously [19,23].

OM is a debilitating complication secondary to chemotherapy [9].

The implementation of a standardized protocol for the prophylaxis and treatment of OM was one of the objectives of the current study and involved the application of local gel by all patients to relieve symptoms of OM, according to the instructions for use and regular daily practice, for an average of 26.9 (min-max: 5-65) days in the total population, with a higher average number of days in the pediatric population of 28.5 (min-max: 5-65) than in adults for whom the average number of days was 26.1 (min-max: 15-64). OM being more common in the adult cohort compared to children. The current literature exposes the need for standardized therapies for OM care [25].

1. OM EVALUATION

All patients received topical gel treatment. The bioactive combination of Zinc, Taurine and Polyvinylpyrrolidone (PVP) was used to prevent or cure oral mucositis, the commercial product available in Romania (selected oral gel). The basic substance used is being evaluated by current international studies [26,27].

Most patients develop OM as a side effect of chemotherapy or radiation therapy.
The oral gel was given as both a prophylactic and a curative treatment.
OM intensity gradation followed the VAS scale, so grade 4 defines severe OM, and grade 1 minimum OM, grade 0- being assigned to subjects without OM. Within the studied cohort, the distribution of subjects according to the degree of OM was as follows: the majority was represented by patients without OM 36.2%, the majority being children and only 10.7% presented severe OM lesions, of the highest degree, grade 4.

In the pediatric cohort, 64% did not have OM, only 6% of pediatric subjects had severe OM. This aspect highlights the importance of rigorous local sanitation and the administration of local gel treatment, both prophylactic and curative, especially with regard to pediatric cases that have evolved more favorably compared to adults [28].

The first patient data were entered in January 2017, while the last patient was introduced in December 2020, and all 149 patients were treated with selected devices, oral spray, bioactive combination of: zinc, taurine and PVP for approx. 4 weeks, especially for an average number of 26.9 days in the total population, 26.1 average number of days in the adult population and an average number of days slightly higher than 28.5 in the pediatric population.

The degree of oral mucositis varies with age, so in the adult population the frequency of more severe degrees increases, the milder forms being more common in the pediatric population, $p < 0.001$, without a statistically significant difference between the number of days required to apply treatment for those two established age categories, $p = 0.159$, but with a statistically significant difference between the need for applications of local treatment per day in children and adults, for children a more frequent application is required, $p < 0.001$.

In the study sample, it was observed that the pediatric population has milder forms of OM compared to adults because the daily applications of the oral gel were higher in number, over a longer period of time. The literature records a higher incidence of OM with a higher frequency of severe forms in the pediatric population [29].

The period of oral gel treatment for OM was very similar to that of hospitalization, which suggests that improvements in OM symptoms, such as complete or partial remission of OM, help reduce the length of hospitalization of patients after transplantation or for the treatment of various malignancies.

2. DISCUSSIONS ON THE PERFORMANCE AND SAFETY PROFILE OF THE SELECTED GEL

The results were analyzed to show the performance of a local treatment on symptoms of OM (primary endpoint) such as: decrease in OM after 1 month of treatment in transplant patients, number patients (in percentage) who developed severe OM from the first application, number of patients (in percentage) who achieved complete remission of OM symptoms, number of patients (in percentage) able to resume chewing and swallowing food after using the oral gel, number of patients (in percent) who reduced the average number of days of hospitalization after use of the oral gel, number of patients (in percentage) who reduced the number of days requiring parenteral nutrition and parenteral narcotic therapy after use of the oral gel, number of patients (in percent) who gained weight after using the oral gel, the number of patients (percentages) who have discontinued morphine due to pain associated with OM, the number of patients (in percentage) who reduced unplanned breaks in cancer therapies due to OM after using oral gel. The analysis of these parameters are predictive factors for the evaluation of local methods of OM care for standardization [30].

OM is the most common complication secondary to chemo-radiotherapy. Rigorous prophylaxis and intensive local treatment can prevent severe complications caused by OM.

i. <u>Performance of oral gel on symptoms of OM (main objective)</u>

Prevention of OM in patients treated with oral gel was achieved in 36.24% (n = 54) of patients, while in 57.04% a complete remission was obtained, curative treatment and a reduction in OM grade or partial remission was achieved at 6.04%, only 0.67% no remission was observed and no worsening of OM was reported [117]. Such results show that 36.24% achieved OM prevention, that 63.08% of patients generally had an improvement, which means a remission of the degree of OM, of which 90.42% had a complete remission = healing of OM lesions (57.04% complete remission of the total population included). No patient had a worsening of the degree of OM. These results support the excellent performance of the oral gel. Significant reduction in OM symptoms in the treatment of patients, adults, children and adolescents with this selected gel under severe oncological conditions, after chemotherapy or radiotherapy or after transplantation for malignant tumors is the positive response in the evaluation of the gel.
Conclusion: The primary endpoint was achieved.

ii. <u>Decreased severity of OM after 1 month of treatment in transplant patients</u>

In the total population, 85 patients with an initial degree of OM> 0, had a complete remission of OM after the period of local gel treatment, of which 73 adults and 12 children, regardless of the initial degree of OM (4, 3, 2 or 1). This suggests the beneficial effect of applying local treatment, with patients having a favorable response even those with high OM degree, 4 [31].

In 98.94% (n = 94) of patients treated with oral gel, the degree of OM was reduced, to a complete remission in 89.47% (n = 85) of patients treated. The effectiveness of the local treatment being evaluated, with similar results by the current literature [32].

iii. Number of patients (in percentage) who developed severe OM from its first application

Only two pediatric patients developed severe OM from the first application of oral gel; of these, one patient (50%) had a complete remission of OM symptoms, and the second patient (50%) had a partial remission of OM severity.

These results support oral gel performance even in severe OM [33].

iv. Number of patients (in percentage) who achieved complete remission of OM symptoms

Out of a total of 149 patients treated, 85 (57%) achieved complete remission of OM, of which 73 adults (73.7%) and 12 children (24%).

It should be noted that prevention of OM in 54 patients (36.2%) was achieved, of which 22 were adults (22.2%) and 32 were children (64%), which is in favor of the high oral gel performance profile. Local oral treatment of OM leads to positive results, which is why it is necessary to standardize a care guide [34].

v. Number of patients (in percentage) who were able to resume chewing and swallowing food after using the oral gel

Data for 146 patients (99 adults and 47 children) were reported on parenteral nutrition, while for 3 patients, children and adolescents, did not have data available.

In patients treated with local gel, several patients received parenteral nutrition on a different number of days. Of these patients, 9 patients who also had a partial remission of OM received parenteral nutrition for up to 48 days, during a period of local gel treatment for up to 8 weeks, while 85 patients who had had a complete remission of OM, received parenteral nutrition for up to 13 days, during a period of local gel treatment for up to 8 weeks.

A maximum of 12 days of parenteral nutrition have been reported in 51 patients who have been prevented from developing OM, therefore parenteral nutrition most likely refers to a parenteral administration of various parenteral solutions according to the complex oncology regimen [35].

Data for a total of 146 patients (99 adults and 47 children and adolescents) were reported on parenteral nutrition, while no data were available for 3 patients in the children and adolescents' group.

The results show that the average parenteral nutrition period of 3.9 days is much shorter than the oral gel treatment period (overall average 26.9 days), which supports the idea that patients can resume chewing and swallowing after a short period of time if are under treatment with oral spray gel for OM, resulting in statistical significance $p < 0.001$.

vi. Number of patients (in percentage) who reduced the average number of days of hospitalization after using gel spray

The results show that the period of hospitalization (on average 28.9 days) was very similar to the period of oral gel treatment (an overall average of 26.9 days), which supports the idea that oral gel treatment for OM could help patients reduce the length of hospital stay. Results consistent with current studies [36].

vii. Number of patients (as a percentage) who reduced the number of days requiring parenteral nutrition and parenteral narcotic therapy after use of oral gel

As in patients treated for OM with oral gel (mean 26.9 days), the period of parenteral nutrition and narcotic therapy is very low, averaging 3.9 and 3.2, respectively, is a very short period, such results confirm that in patients treated with spray gel the need for parenteral nutrition and narcotic therapy is very short.

viii. Number of patients (in percentage) who gained weight after using oral gel

Most of the 102 patients who gained weight also had a complete remission of OM: 11 adult patients (10.74%), and while 4 patients (3.92%) with weight gain had a partial remission of OM and 6 patients (5.88%) had a weight gain when the preventive effect of oral gel was obtained.

Given the severe pathological conditions of the patients included in this study, 20.58% of patients who gained weight after the oral spray gel treatment period support the positive effect in treating oral OM with spray gel.

ix. Number of patients (as a percentage) who discontinued morphine due to OM-associated pain

Neither of the 2 patients receiving morphine discontinued its use due to symptoms associated with OM, such as pain.

x. Number of patients (as a percentage) who missed unplanned breaks in oral cancer therapy after oral gel

None of the 149 patients in this study had discontinuation of OM cancer therapy after oral gel use, which would support the therapeutic results. better in the treatment of cancer when using the selected gel applied orally for the treatment of OM, because no interruptions in the treatments for cancer are necessary.

xi. Safety analysis of the selected product

Several SEs were reported in the study population, all related to the therapies used to treat the main pathology, while no ADE was reported during the treatment period, for any of the 149 patients.

Given that all patients received local gel, even if they did not initially have OM, with the intention of preventing the development of OM or, if it occurs, reducing its intensity (degree of OM) and its duration, the fact that no ADE reports a high safety profile of the gel and supports its prescription for both preventive and curative purposes.

3. RISK AND BENEFIT ASSESSMENT

The aim of this study was to analyze the results and impact of oral gel used on OM in patients who have received radiotherapy or chemotherapy to treat malignant tumors and in transplant patients.

As a retrospective collection of data, this study did not involve any physical risk of injury or any other type of risk, while all information and data relating to the subjects or their participation in this process will be considered and will remain confidential.

OM management is based on sustained care and symptom relief. However, OM is a common problem associated with significant patient morbidity and increased resource use. The scale of the issue requires innovative approaches based on expert judgment, as evidence is gathered to support specific recommendations.

The results show that oral gel OM treatment has a great contribution to achieving better therapeutic results in the treatment of cancer without interruption, in reducing periods of parenteral nutrition and narcotic therapy, in helping patients to resume chewing and swallowing food earlier and therefore for to gain weight as well as to reduce the period of hospitalization.

Oral gel treatment has a high safety profile and is well tolerated by both adult and pediatric patients.

Given the high negative impact on the development of patients receiving chemo- and radiotherapy, which may affect nutritional intake, oral care, and quality of life, and also taking into account the high-performance results and safety profile of oral gel obtained in this retrospective study, it appears that GelX® Oral Spray could be a good alternative to effectively prevent the development of OM in patients receiving radiation or chemotherapy, as a consequence of malignancies and transplant patients, and if OM cure when present until complete remission within an average of 1 month of treatment.

4. DISCUSSION OF CLINICAL RELEVANCE AND IMPORTANCE OF RESULTS

Oral mucositis (OM) refers to erythematous and ulcerative lesions of the oral mucosa observed in cancer patients treated with chemotherapy and / or radiotherapy in the fields involving the oral cavity. Oral mucositis lesions are often very painful and compromise nutrition and oral hygiene, and also increase the risk of local and systemic infection.

Oral mucositis is a significant problem in patients undergoing radiotherapy and chemotherapy for solid tumors, and a high percentage of patients receiving chemotherapy for solid tumors or lymphoma may develop oral mucositis and / or GI, while an even higher percentage of patients receiving high-dose chemotherapy before hematopoietic cell transplantation develop clinically significant oral mucositis; Almost all patients treated with radiation therapy for head and neck cancers may develop some degree of oral mucositis, even severe oral mucositis.

For patients receiving high-dose chemotherapy prior to hematopoietic cell transplantation, oral mucositis has been reported as the single most debilitating complication of transplantation, and infections associated with oral mucositis lesions may cause life-threatening systemic sepsis during periods of immunosuppression.

Oral mucositis can be very painful and can have a significant negative impact on the progress of patients receiving chemotherapy and radiation therapy: it can affect nutritional intake, oral care and quality of life; moderate to severe oral mucositis has been associated with systemic infection and transplant-related mortality; in patients with hematological malignancies who have received allogeneic hematopoietic cell transplantation, it has been found that increased severity of oral mucositis is significantly associated with an increased number of days, requiring total parenteral nutrition and parenteral narcotic therapy, increased number of days with fever, significant infection, increased hospital time and increased total hospitalization fees; patients receiving radiation therapy for head and neck cancer cannot continue to eat orally due to mucosal pain and often receive nutrition through a gastrostomy tube or intravenous line; patients with oral mucositis are significantly more likely to have severe pain and weight loss $\geq$ 5%. Patients receiving radiation therapy for head and neck cancer have unplanned breaks in

radiation therapy due to severe mucositis. Thus, mucositis may be a dose-limiting toxicity in the treatment of cancer with direct effects on the patient's survival.

The results obtained after the oral gel treatment showed an excellent performance in the prevention of OM and no adverse effects of the device in any of the patients studied from the point of view of safety. The results are consistent in supporting the high safety profile and performance when used for different periods, averaging 1 month, in both adult and pediatric patients.

5. SPECIFIC BENEFITS OR SPECIAL PRECAUTIONS REQUIRED FOR INDIVIDUAL SUBJECTS OR GROUPS CONSIDERED EXPOSED TO THE RISK

The results of the study reveal a high performance and safety profile of the oral gel spray on patients who have received radio-chemotherapy as a consequence of malignancies and transplant patients.

Given that the investigators prescribed oral gel to all patients, even if they did not initially have OM, with the intention of preventing the development of OM or, if it occurs, to reduce the intensity and duration of OM, the fact that they were not reported ADE shows a high safety profile of oral spray gel and supports its prescription for both preventive and curative purposes in adult and pediatric patients.

No ADE or device deficiencies have been reported, no special precautions are required for subjects treated with oral spray gel, which supports a high safety profile.

6. LIMITATIONS OF THE CLINICAL STUDY AND IMPLICATIONS FOR FUTURE CLINICAL INVESTIGATIONS

As we look back over the study and examine exposures to risk factors or protective factors in relation to a result established at the beginning of the study, their value in clarifying the safety profile is clear. However, a prospective investigation could be useful in obtaining more accurate estimates of long-term performance in oral spray gel treatment in preventing the development of severe OM in patients receiving radiotherapy or chemotherapy as a result of malignancies and transplant patients.

The analysis of the data of this doctoral study led to the results presented with the implementation of an algorithm for the prophylaxis and treatment of OM. The implemented protocol is in line with current OM care recommendations [37-49].

The current literature supports the urgency of such OM care protocols. [50 - 52]

CONCLUSIONS:

Retrospective study performed in a reference center of Hematology and Hematopoietic stem cell transplantation, Fundeni Clinical Institute, Bucharest, Romania.

The personal study did not involve any commercial or financial marketing involvement.

The study was performed in accordance with current rules of ethics.

The most common hematological pathology identified in the current study was Acute Leukemia, on the sample of interest, the pediatric population, representing 33.5% of the total subjects included.

The proposed objectives have been achieved.

Standardized chemotherapeutic treatment involves blocks of chemotherapy with a direct impact on the production of OM. Prophylactic and curative treatment is part of the current adjuvant therapy mentioned in chemotherapy protocols, but without standardization.

All subjects enrolled in the study received prophylactic and curative treatment with the same bioactive combination selected and proposed for evaluation.

The selected product met the following criteria: product accessible in Romania, spray that facilitates local application to the mucosa, especially in the pediatric population, complies with the rules of asepsis and contains the patented bioactive combination with beneficial effects on oral mucosal lesions.

The degree of OM varies according to age.

The primary goal has been achieved:

Rigorous prophylaxis and long-term local treatment in the pediatric population have resulted in positive results for local administration of the selected gel. The children showed milder forms of OM. Only 6% of pediatric subjects had severe grade 4 OM, although they had a higher number of cycles of chemotherapy compared to adults, but received the average number of days of oral gel.

Secondary objectives were achieved:

Complete remission of OM was achieved in over 90% of cases by administration of the selected gel.

Only one patient presented with OM from the first application

The increased number of patients who were able to resume chewing is directly proportional to:

- the low number of subjects who lost weight
- the low number of days of parenteral nutrition
- the low number of days of narcotic therapy
- low number of patients with unplanned breaks in cancer therapy

The period of oral gel treatment for OM was very similar to that of hospitalization

No adverse events associated with local therapy were identified.

The implementation of an algorithm for the diagnosis and treatment of OM that targets the onco-hematological patient, especially the pediatric one, in order to decrease the morbidity and mortality generated by OM has led to increased compliance with chemotherapeutic treatment.

Biographical references:

1. Sherman RG, Prusinski L, Ravenel MC, et al., Oral Ravened Int. 2002; 33:521-532.
2. Lockhart PB, Sonis ST., Relationship of oral complications to peripheral blood leukocyte and platelet counts in patients receiving cancer chemotherapy. Oral Surg Oral Med Oral Pathos. 1979 Jul;48(1):21-8
3. Imanguli MM, Alevizos I, Brown R, et al Oral graft-versus-host disease. Oral Dis. 2008 Jul;14(5):396-412.
4. Horwitz ME, Sullivan KMJBr, et al., Chronic graft-versus-host disease. 2006; 20:15-27.
5. Sonis ST. Mucositis: The impact, biology and therapeutic opportunities of oral mucositis. Oral Oncol. 2009 Dec;45(12):1015-20.
6. http://www.empr.com/gelx/drug/22863/
7. www.cancer. gov
8. Steliarova-Foucher E, Colombet M, Ries LAG, et al; IICC-3 contributors. International incidence of childhood cancer, 2001-10: a population-based registry study. Lancet Oncol. 2017 Jun;18(6):719-731.
9. World Health Organization. "CureAll framework: WHO global initiative for childhood cancer: increasing access, advancing quality, saving lives." (2021).
10. Bardellini E, Majorana A. Oral Complications in Children Undergoing Chemotherapy: The COMEDY (Clenching, Oral Mucositis, Eyes, DYsphagia) Pattern. J Pediatr Hematol Oncol. 2019 Apr;41(3):249.
11. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin. 2016 Jan-Feb;66(1):7-30.
12. Kim HI, Lim H, Moon A. Sex Differences in Cancer: Epidemiology, Genetics and Therapy. Biomol Ther (Seoul). 2018 Jul 1;26(4):335-342.
13. Attinà G, Romano A, Maurizi P, D'Amuri S et al. Management of Oral Mucositis in Children with Malignant Solid Tumors. Front Oncol. 2021 Mar 30; 11:599243.
14. Ward ZJ, Yeh JM, Bhakta N, et al. Global childhood cancer survival estimates and priority-setting: a simulation-based analysis. Lancet Oncol. 2019 Jul;20(7):972-983.
15. Cheng KK, Goggins WB, Lee VW, et al. Risk factors for oral mucositis in children undergoing chemotherapy: a matched case-control study. Oral Oncol. 2008 Nov;44(11):1019-25.
16. A. Coliţă, A. Coliţă, et al. Leucemia acuta limfoblastica la copii, Editura “Carol Davila”, Bucureşti, 2016(2), 21
17. Pulito C, Cristaudo A, Porta C, et al. Oral mucositis: the hidden side of cancer therapy. J Exp Clin Cancer Res. 2020 Oct 7;39(1):210.
18. McGuire DB, Fulton JS, Park J, et al; Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO). Systematic review of basic oral care for the management of oral mucositis in cancer patients. Support Care Cancer. 2013 Nov;21(11):3165-77.
19. Roberts, KG (2018). Genetics and prognosis of ALL in children vs adults. Hematology 2014, the American Society of Hematology Education Program Book, 2018(1), 137-145.
20. Carreón-Burciaga RG, Castañeda-Castaneira E, González-González R, et al. Severity of Oral Mucositis in Children following Chemotherapy and Radiotherapy and Its Implications at a Single Oncology Centre in Durango State, Mexico. Int J Pediatr. 2018 May 10;2018:3252765.
21. Attinà G, Romano A, Maurizi P, et al. Management of Oral Mucositis in Children With Malignant Solid Tumors. Front Oncol. 2021 Mar 30; 11:599243.

22. Ribeiro ILA, Melo ACR, Limão NP, et al. Oral Mucositis in Pediatric Oncology Patients: A Nested Case-Control to a Prospective Cohort. Braz Dent J. 2020 Jan-Feb;31(1):78-88.
23. Hendrawati, S., Nurhidayah, I., Mediani, HS, et al. (2019). Incident of Mucositis and The Factors that Influence it on Children with Cancer Who Received Chemotherapy. Jurnal Keperawatan, 10(2), 139-150.
24. Damascena LCL, de Lucena NNN, Ribeiro ILA, et al. Factors Contributing to the Duration of Chemotherapy-Induced Severe Oral Mucositis in Oncopediatric Patients. Int J Environ Res Public Health. 2018 Jun 1;15(6):1153.
25. Kusiak A, Jereczek-Fossa BA, Cichońska D, et al. Oncological-Therapy Related Oral Mucositis as an Interdisciplinary Problem-Literature Review. Int J Environ Res Public Health. 2020 Apr 3;17(7):2464.
26. Al-Taie A, Al-Shohani AD, Albasry Z et al. Current topical trends and novel therapeutic approaches and delivery systems for oral mucositis management. J Pharm Bioallied Sci. 2020 Apr-Jun;12(2):94-101.
27. Kanagalingam J, Chopra A, Hong MH, et al. Povidone-iodine for the management of oral mucositis during cancer therapy. Oncol Rev. 2017 Sep 15;11(2):341.
28. Murshid, EZ, Azizalrahman, TA, & AlJohar, AJ (2017). Oral mucositis in leukemic Saudi children following chemotherapy. The Saudi Journal for Dental Research, 8(1-2), 79-85.
29. Nemes J, Jenei Á, Márton I. A gyermekkori malignus kórképek kemoterápiájának leggyakoribb mellékhatása, az oralis mucositis. Irodalmi áttekintés [Oral mucositis as the most common complication of childhood cancer therapy. Review of the literature]. Orv Hetil. 2018 Apr;159(13):495-502. Hungarian.
30. Damascena LCL, de Lucena NNN, Ribeiro ILA, et al. Factors Contributing to the Duration of Chemotherapy-Induced Severe Oral Mucositis in Oncopediatric Patients. Int J Environ Res Public Health. 2018 Jun 1;15(6):1153.
31. Maria OM, Eliopoulos N, Muanza T. Radiation-Induced Oral Mucositis. Front Oncol. 2017 May 22;7:89.
32. Al-Ansari S, Zecha JA, Barasch A, et al. Oral Mucositis Induced By Anticancer Therapies. Curr Oral Health Rep. 2015;2(4):202-211.
33. Al-Taie A, Al-Shohani AD, Albasry Z, et al. Current topical trends and novel therapeutic approaches and delivery systems for oral mucositis management. J Pharm Bioallied Sci. 2020 Apr-Jun;12(2):94-101.
34. Kusiak A, Jereczek-Fossa BA, Cichońska D, et al. Oncological-Therapy Related Oral Mucositis as an Interdisciplinary Problem-Literature Review. Int J Environ Res Public Health. 2020 Apr 3;17(7):2464.
35. Zheng Z, Zhao X, Zhao Q, et al. The Effects of Early Nutritional Intervention on Oral Mucositis and Nutritional Status of Patients With Head and Neck Cancer Treated With Radiotherapy. Front Oncol. 2021 Feb 1;10:595632.
36. Damascena LCL, de Lucena NNN, Ribeiro ILA, et al. Factors Contributing to the Duration of Chemotherapy-Induced Severe Oral Mucositis in Oncopediatric Patients. Int J Environ Res Public Health. 2018 Jun 1;15(6):1153.
37. American Academy on Pediatric Dentistry Clinical Affairs Committee; American Academy on Pediatric Dentistry Council on Clinical Affairs. Guideline on dental management of pediatric patients receving chemotherapy, hematopoietic cell transplantation, and/or radiation. Pediatr Dent. 2008-2009;30(7 Suppl):219-25. PMID: 19216425.
38. Institute NC. Cancer Information. 2010 [cited 5 October 2010]; Available from: http://www.cancer.gov/cancertopics/youngpeople/page7#G7

39. Group CsCaL. Brush up on the best type of mouth care. 2010; Available from: http://www.cclg.org.uk/contact/article.php?art=272&2id=10&issue=35
40. McWhirter WR, Dobson C, Ring I. Childhood cancer incidence in Australia, 1982-1991. Int J Cancer. 1996 Jan 3;65(1):34-8.
41. Baade PD, Youlden DR, Valery PC, et al. Trends in incidence of childhood cancer in Australia, 1983-2006. Br J Cancer. 2010 Feb 2;102(3):620-6.
42. Smith MA, Ries LAG., et al., Childhood cancer; incidence, survival, and mortality. In: Pizzo PA, Poplack DG, eds. Principles and Practice of Pediatric Oncology. 4th ed. Philadelphia: Lippincott Williams & Wilkins 2002:1-12.
43. Marques AP, Walker PO. Intraoral etiology of a life-threatening infection in an immunocompromised patient: report of case. ASDC J Dent Child. 1991 Nov-Dec;58(6):492-5. PMID: 1783702.
44. Hong CH, daFonseca M. Considerations in the pediatric population with cancer. Dent Clin North Am. 2008 Jan;52(1):155-81, ix.
45. da Fonseca MA. Dental care of the pediatric cancer patient. Pediatr Dent. 2004 Jan-Feb;26(1):53-7. PMID: 15080359.
46. Barbería E, Hernandez C, Miralles V, et al. Paediatric patients receiving oncology therapy: review of the literature and oral management guidelines. Eur J Paediatr Dent. 2008 Dec;9(4):188-94. PMID: 19072007.
47. Ferretti GA, Raybould TP, Brown AT et al. Chlorhexidine prophylaxis for chemotherapy- and radiotherapy-induced stomatitis: a randomized double-blind trial. Oral Surg Oral Med Oral Pathol. 1990 Mar;69(3):331-8.
48. Ried H, Zietz H, Jaffe N. Late effects of cancer treatment in children. Pediatr Dent. 1995 Jul-Aug;17(4):273-84. PMID: 7567631.
49. Group U-PMC. Mouth Care for Children and Young People with Cancer: Evidence-based Guidelines. 2006 [cited 19 October 2010]; Version 1:[Available from: http://www.rcn.org.uk/__data/assets/pdf_file/0017/11276/mouth_care_cyp_cancer_guideline.pdf
50. Devi KS, Allenidekania A. The Relationship of Oral Care Practice at Home with Mucositis Incidence in Children with Acute Lymphoblastic Leukemia. Compr Child Adolesc Nurs. 2019;42(sup1):56-64.
51. Ribeiro ILA, de Castro RD, Costa RC, et al. Integrated oral care contributes positively to the course of treatment of oncopediatric patients. Eur J Pediatr. 2021 Sep;180(9):2757-2764.
52. Bezerra PMM, Sampaio MEA, Dos Santos FG, et al. The effectiveness of an oral health education and prevention program on the incidence and severity of oral mucositis in pediatric cancer patients: a non-randomized controlled study. Support Care Cancer. 2021 Dec;29(12):7877-7885.
53. Brown TJ, Gupta A. Management of Cancer Therapy-Associated Oral Mucositis. JCO Oncol Pract. 2020 Mar;16(3):103-109.

List of scientific research:

1. Niculiță OO, Jercan, CG, Radu, L., Varady, Z., Coliță, A., Tanase, AD, Coliță, A. (2020). 'The efficacy of Polyvynilpyrrolidone-Zn Gluconate and Taurine in the Prevention of Oral Mucositis in Haematological Patients',*Revista de Chimie,*71(8), pp. 195-205. https://revistadechimie.ro/Articles.asp?ID=8280
2. Niculiță, OO, Marcu, AD, Bică, AM, Doncu, RE, Coliță, A., & Jercan, CG (2021). ORAL MUCOSITIS–SIGNIFICANT COMPLICATION OF PEDIATRIC PATIENTS UNDERGOING HEMATOPOIETIC STEM CELL TRANSPLANTATION.*Romanian Journal of Pediatrics*,*70*(2). https://rjp.com.ro/rjp-vol-lxx-nr-2-an-2021/
3. Niculiță OO, Jercan, CG, Coliță, A, Mucozita orală postchimioterapie – implicații clinico-terapeutice – Poster
4. Niculiță OO, Jercan, CG, Coliță, A, Oral mucositis in autologous stem cell transplantation for solid tumors in children: comparison between single and tandem procedures - Poster