



# The efficacy of Polyvinylpyrrolidone-Zn Gluconate and Taurine in the Prevention of Oral Mucositis in Haematological Patients

OANA OTILIA NICULITA<sup>1,2,#</sup>, CRISTINA GEORGIANA JERCAN<sup>1,2,#</sup>,  
LETITIA-ELENA RADU<sup>1,2\*</sup> (<https://orcid.org/0000-0003-1677-5479>), ZSOFIA VARADY<sup>2</sup>,  
ANCA COLITA<sup>1,2</sup>, ALINA DANIELA TANASE<sup>2,3</sup>, ANDREI COLITA<sup>1,4</sup>

<sup>1</sup>“Carol Davila” University of Medicine and Pharmacy, 8 Eroii Sanitari Blvd., 050474, Bucharest, Romania

<sup>2</sup>Fundeni Clinical Institute, Pediatric Haematology and Stem Cell Transplantation Department, 258 Fundeni Road, 022328, Bucharest, Romania

<sup>3</sup>“Titu Maiorescu” University of Medicine, 22 Dambovnicului Tineretului Str., 040441, Bucharest, Romania

<sup>4</sup>Coltea Clinical Hospital, Bucharest, Romania, Haematology Department, 1 Ion C. Bratianu Blvd., 030171, Bucharest, Romania

**Abstract:** Oral mucositis (OM) is a significant problem in patients undergoing standard or high-dose chemotherapy and/or radiotherapy for the management of haematological disorders, associated with patient morbidity and increased resource use. The OM management relies on supportive care and symptom palliation. This study evaluates the results of Polyvinylpyrrolidone-Zn gluconate and taurine (GelX® Oral Spray) in this setting. This is an observational, retrospective study, conducted on 145 paediatric and adult patients. All patients received GelX® Oral Spray as prophylaxis for OM. The research was supported by BMG Pharma S.p.A. The prevention of OM in patients treated with GelX® Oral Spray was reached in 54 patients (37.24%), 22 adults (22.22%) and 32 children (69.56%). A total number of 52 patients (35.86%) developed severe OM when GelX® was used as preventive treatment, 40 adults (40.4%) adults and 12 children (26.08%). Grade 4 OM developed in 16 patients (11.03%), 10 adults and 1 child (68.75%) had a complete remission of OM, while 3 adults and 2 children (31.25%) had partial remission. No patient had to interrupt chemo/radiotherapy due to OM. GelX® Oral Spray was considered safe, no adverse device effect or severe adverse device effect were considered related to the use of the product. This retrospective study supports prophylactic use of GelX® Oral Spray to minimize the risk of OM secondary to chemo/radiotherapy.

**Keywords:** Polyvinylpyrrolidone, Zinc gluconate, taurine, oral mucositis, chemotherapy, stem cell transplantation

## 1. Introduction

Oral mucositis (OM), defined as inflammation, with erythematous and ulcerative lesions of the oral mucosa is an important side effect observed in patients (pts) with cancer, treated with chemotherapy (CTX) and/or with radiation therapy (RTX) to fields involving the oral cavity. OM consequences are pain, dysphagia, increased risk of local and systemic infections, weight loss, increased requirement of parenteral nutrition, prolonged hospitalization time and poor quality of life [1-7]. Mucositis can also involve other areas of the alimentary tract; for example, gastrointestinal (GI) mucositis can manifest as esophagitis and diarrhoea. Thus, mucositis is a highly significant and sometimes dose-limiting complication of cancer therapy [1,2].

OM is a significant problem in pts undergoing standard or high dose CTX and/or RTX for the management of haematological disorders. In one study, it was reported that 303 of 599 pts (51%) receiving CTX for solid tumours or lymphomas developed oral and/or GI mucositis [3]. OM developed in 22% of 1236 cycles of CTX, GI mucositis in 7% of cycles, and both oral and GI mucositis in 8% of cycles. For pts receiving high-dose CTX prior to hematopoietic stem cell transplantation (SCT), OM has been reported to be the single most debilitating complication of transplantation [8].

\*email: [letitia.radu@umfcd.ro](mailto:letitia.radu@umfcd.ro)

# Equal contributions as first author

Infections associated with OM lesions can cause life-threatening sepsis during periods of profound immunosuppression [9]. Moderate to severe OM has been correlated with systemic infection and transplant-related mortality [10]. In pts with haematologic malignancies receiving allogeneic SCT, severe OM was found to be significantly associated with an increased number of days of total parenteral nutrition / narcotic therapy, with the duration of fever and life-threatening infections, with prolonged hospitalization and total overall inpatient charges [4].

In pts treated for solid tumours or lymphomas, the rate of infection during cycles with mucositis was more than twice compared to cycles without mucositis, and was directly proportional to the severity of mucositis [3]. Infection-related deaths were also more common during cycles with both oral and GI mucositis. In addition, the average duration of hospitalization was significantly longer during CTX cycles with mucositis. Importantly, a reduction in the next dose of CTX was twice as common after cycles with than after cycles without mucositis [3]. Thus, mucositis can be a dose-limiting toxicity of cancer treatment with direct effects on patient survival.

The mechanism for RTX/CTX induced OM is complex and much more complicated than direct damage of epithelium alone. Sonis et al. [2] proposed a five-stage model for the pathogenesis of mucositis: a) initiation of tissue injury, b) up regulation of inflammation, c) signalling and amplification, d) ulceration and inflammation, e) healing.

The prevention and treatment of CTX-induced mucositis employs a variety of methods and therapeutic agents, including basic oral care protocol (brushing, flossing, dental care and mouth-washes), anti-inflammatory agents, antimicrobial agents, cryotherapy, antiseptic agents, vitamins, cytokines, immune regulators, herbal drugs, analgesics, low level light therapy. Despite this variety of methods, there is a limited number of agents with high level of recommendation, while several of them are used in daily practice with limited evidence of efficacy and with high variability of protocols between different centres [4,11-14].

Polyvinylpyrrolidone-Zn gluconate and taurine (GelX® Oral Spray) is an oral lubricating gel used in the management of OM. GelX® Oral Spray forms an adherent barrier that covers the oral mucosa lesions, thus protecting the sensitive nerves endings and lubricating the oral tissue.

In this paper we present the results of an observational, retrospective study analysing the outcome and the impact of GelX® Oral Spray used for OM in haematological pts who received CTX and in pts who underwent SCT. All pts received GelX® Oral Spray in addition to standard OM management.

## 2. Materials and methods

### 2.1. Study population

This was a single-centre, retrospective study on oncologic pts with OM induced by RTX/CTX, or by SCT conditioning regimens. The study was performed in Fundeni Clinical Institute, Bucharest, Romania, from January 1st to December 31st 2015 on a population of OM adult and paediatric pts.

Inclusion criteria: male and female pts aged 2 years or older, who used GelX® Oral Spray at least once daily during treatment protocol, and who had their mucous membranes evaluated during treatment.

Exclusion criteria: pts who participated in a therapeutic trial on OM in the same period; pts who had active viral, bacterial or fungal infections of the mouth (i.e. stomatitis related to herpes virus or Candida); pts who were considered unable to perform oral application of GelX® Oral Spray [15].

### 2.2. Study procedures

This was a study designed to use patients' data already collected and recorded at site. No patient was enrolled and no patient visits at site were required.

The investigators reviewed medical records of pts selected according to the inclusion/ exclusion criteria and collected all available information: demographic data - age, gender, weight; number of days of hospitalization, duration of parenteral nutrition and parenteral narcotic therapy, stop of narcotic therapy and restart of eating process; adverse device effect (ADE) related to GelX® Oral Spray; data on OM (grade, start and stop date); data on received CTX/RTX; interruptions / dose reductions of received



CTX/RTX, related to OM; concomitant diseases and medications. Oral cavity examination was carried out daily and registered in medical charts. OM was measured according to the WHO scoring system [16]; this scale defines 5 grades (0-4) of severity according to the presence of erythema, ulceration and ability to eat. All pts received the following prophylactic and therapeutic measures for OM, according to internal guidelines: mouthwashes with 0.9% saline/sodium bicarbonate solution, 0.12% chlorhexidine. Oral cavity nursing with GelX® Oral Spray started on the first day of CTX and continued until recovery from neutropenic phase. All pts received systemic prophylaxis with acyclovir, fluconazole and ciprofloxacin, plus granulocyte colony stimulating factors during neutropenic phase. This retrospective study didn't involve any physical risk of harm, nor other kind of risks for the pts considered for data collection.

### 2.3. Ethical considerations

The study BMG001\_OM was notified to the National Agency for Medicines and Medical Devices, was approved by the National Bioethics Committee for Medicines and Medical devices and by the Ethics Council of the Fundeni Institute before starting data collection.

### 2.4. Statistical methods

No specific sample size was calculated a priori and was driven by the number of patient medical records collected, after applying the inclusion/exclusion criteria.

Descriptive analysis was performed on collected data to show the efficacy of GelX® Oral Spray on OM and its safety profile according to the study endpoints:

Primary endpoints: (1) duration of OM symptoms in pts treated with GelX® Oral Spray from its first application to remission, (2) number of pts (%) who developed severe OM when GelX® Oral Spray was used.

Secondary endpoints: a) decrease in OM grade after 1 month of treatment in transplant pts; b) number of pts (%) who developed severe OM; c) number of pts (%) who reached complete remission of OM symptoms; d) number of pts (%) able to restart chewing and swallowing food after GelX® Oral Spray use; e) number of pts (%) who had a reduction of median duration of hospitalization after GelX® Oral Spray use; f) number of pts (%) who had a reduction in duration of parenteral nutrition and parenteral narcotic therapy after GelX® Oral Spray use; g) number of pts (%) who gained weight after GelX® Oral Spray use; h) number of pts (%) who had less unplanned breaks in CTX due to OM, and after GelX® Oral Spray use, respectively; i) rate of ADE and severe ADE associated to GelX® Oral Spray application.

## 3. Results and discussions

### 3.1. Results

Data were collected retrospectively from 145 pts: 99 adults (68.27%) and 46 children (31.72%); female/male sex ratio of 1.15 in adults and 1.09 in paediatric pts; median age of entire cohort 36 years (range: 2-71), median age of adult pts 46 years (range: 22-71), median age of children 6 years (range: 2-17). At the moment of data collection, 82.75% (120 pts) were still alive, while 17.24% (25 pts) were deceased. The characteristics of pts are shown in Table 1.

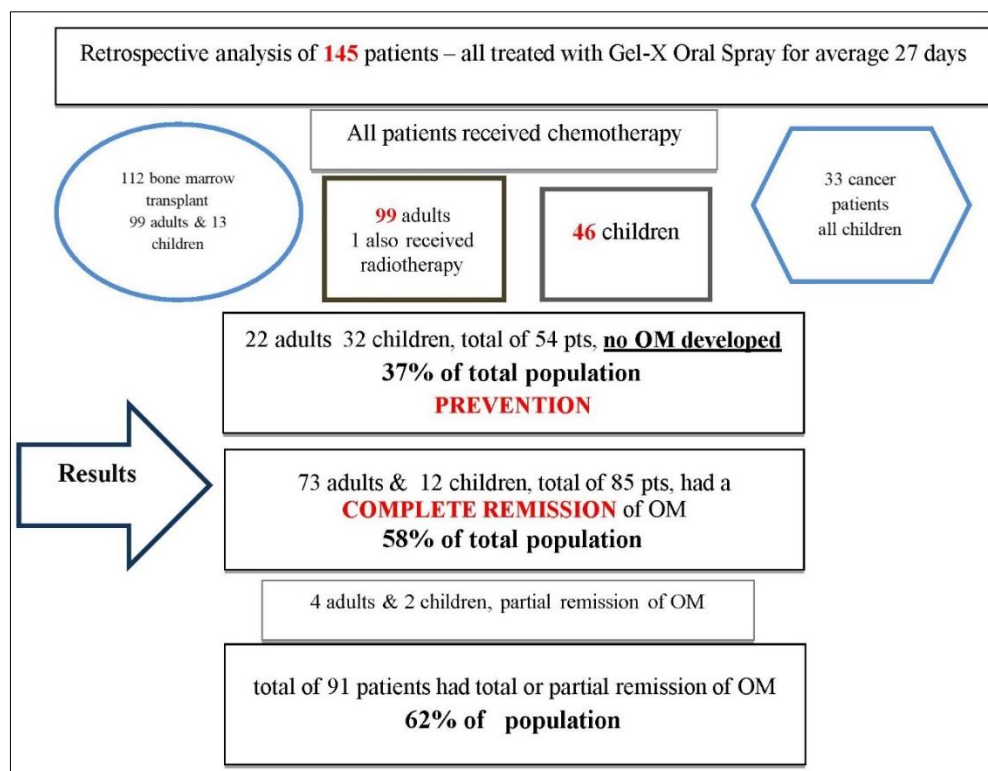
**Table 1.** Characteristics of study patients

	Adult cohort	Paediatric cohort	Total population
<b>Number of patients (percentage)</b>	99 (68.27)	46 (31.72)	145
<b>Age (years)</b>			
<b>Median</b>	46	6	36
<b>Range</b>	22-71	2-17	2-71
<b>Sex</b>			
<b>Male</b>	46 (46.5)	22 (47.9)	68 (46.9)
<b>Female</b>	53 (53.5)	24 (52.1)	77 (53.1)

<b>Transplant patients</b>	99 (100%)	13 (28.26%)	112 (77.24)
<b>Days of chemotherapy</b>			
<b>Median</b>	1	5	
<b>Range</b>	1-5	1-45	

The patient’s primary diagnosis was: leukaemia - 62 pts, multiple myeloma - 40 pts, lymphoma - 37 pts, severe aplastic anaemia -2 pts, myelodysplastic syndrome - 1 patient, sarcoma - 1 patient, neuroblastoma- 1 patient, primary systemic amyloidosis - 1 patient. All 145 pts underwent CTX, while only 1 adult patient received also RTX. An average of 11.4 concomitant medications/patient were administered for different comorbidities reported as medical and surgical history, as well as for the several adverse events.

All 145-pts received GelX® Oral Spray for preventing OM. The median duration of applications was 24 days (range: 5-65) in the total population, 23 days (range: 15-64) in the adult population, and 26.5 days (range: 5-65) in the paediatric population, respectively. GelX® Oral Spray was applied 3, 4 or 6 times a day with 1 spray/application of GelX® Oral Spray in adults, while all paediatric patients applied 2 sprays/application. Study design and results are shown in Figure 1 and Table 2.



**Figure 1.** Study design and results

**Table 2.** Results of OM management with GelX® Oral Spray

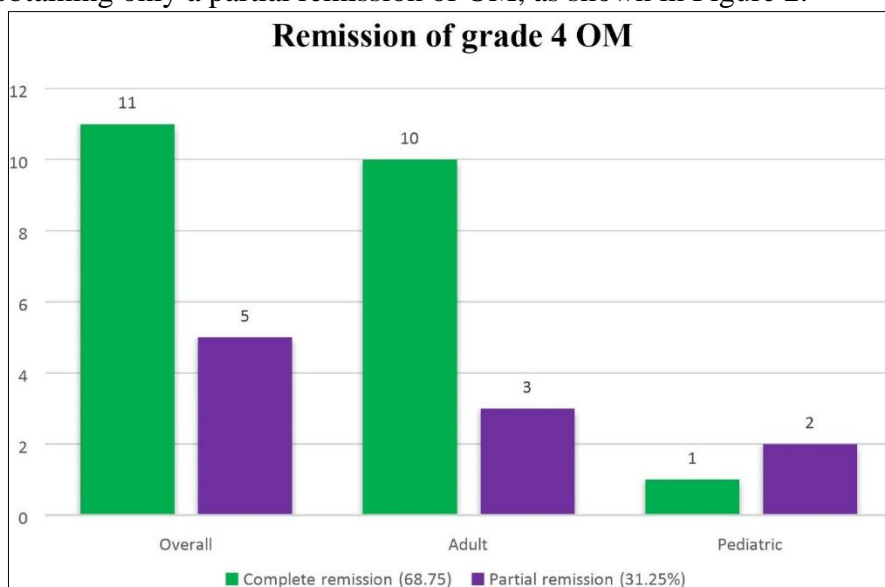
	Adults (%)	Children (%)	Total (%)
Number of patients	99	46	145
<b>OM Grade 0</b> (prophylaxis efficacy)	22 (22.22)	32 (69.56)	54 (37.24)
<b>OM total</b>	77 (77.7)	14 (30.43)	91 (62.75)
OM grade 1	15 (15.18)	0 (0)	15 (10.34)
OM grade 2	22 (22.2)	2 (4.34)	24 (16.55)
OM grade 3	27 (27.27)	9 (19.56)	36 (24.82)
OM grade 4	13 (13.13)	3 (6.52)	16 (11.03)
Severe OM (grade 3+4)	40 (40.4)	12 (26.08)	52 (35.86)
<b>OM at follow-up</b>	99	46	145
No OM	22 (22.22)	32 (69.56)	54 (37.24)
OM grade 0	73 (73.7)	12 (26.08)	85 (58.62)

OM grade 1	1 (1.01)	1 (2.17)	2 (1.34)
OM grade 2	1 (1.01)	1 (2.17)	2 (1.34)
OM grade 3	2 (2.02)	0 (0)	2 (1.34)
OM grade 4	0 (0)	0 (0)	0 (0)
<b>Median duration of GelX® Oral Spray treatment according to response (days)</b>			
Complete remission	28	26.5	
Partial remission	31	28	
No response	0	42	
<b>Days of parenteral nutrition</b>			
Average	3.6	4.6	3.9
Range	0-48	0-35	0-48
<b>Hospitalization days</b>			
Median	23	29.5	25
Range	15-71	5-78	5-78
<b>Days of parenteral narcotic therapy</b>			
Average	3.7	2.1	3.2
Range	0-36	0-22	0-36
<b>Weight gain</b>	21	1	22
<b>Interruptions of chemo/radiotherapy due to OM</b>	0	0	0

### 3.1.1. Primary endpoints

The median duration of OM symptoms in pts treated with GelX® Oral Spray, from its first application to remission, was 12 days (range 4-45).

The prevention of OM in pts treated with GelX® Oral Spray was reached in 37.24% (54 pts), 22 adults (22.22%) and 32 children (69.56%). A total number of 52 pts (35.86%), 40 adults (40.4%) and 12 children (26.08%), developed severe OM (grade 3 and 4). Grade 4 OM developed in 16 pts (11.03%), 11 of them (68.75%) achieving a complete remission (10 adults and 1 child), while 31.25% (3 adults and 2 children) obtaining only a partial remission of OM, as shown in Figure 2.

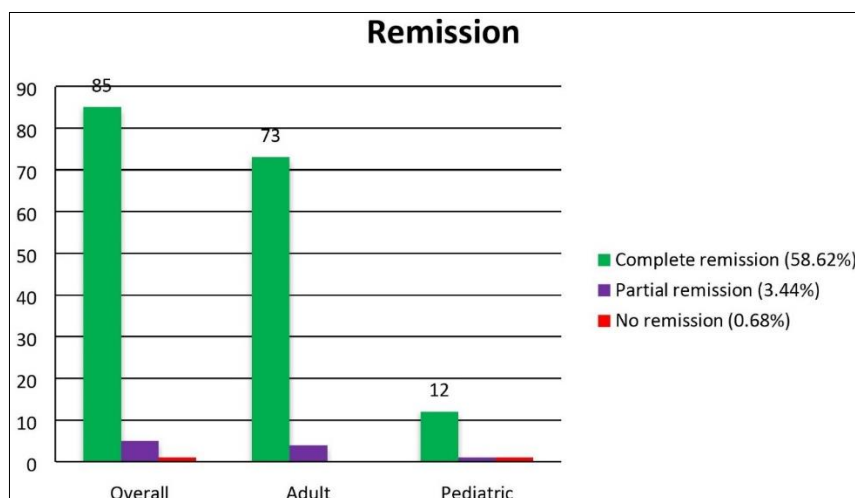


**Figure 2.** GelX® Oral Spray induced a significant improvement of OM symptoms in patients developing Grade 4 OM

### 3.1.2. Secondary endpoints

In the cohort of pts experiencing OM, after one month of treatment, 85 pts (58.62%) had a complete remission. A reduction of OM grade (partial remission) was reached in 3.44% (5 pts), only in 1 patient (0.68%) no remission was noticed. No worsening of OM was reported. This shows that OM grade was reduced in 98.90% (91 pts) treated with GelX® Oral Spray, of which 85 pts (93.47%) achieved complete remission of symptoms, 73 were adults (73.7%) and 12 were children (26.08%),

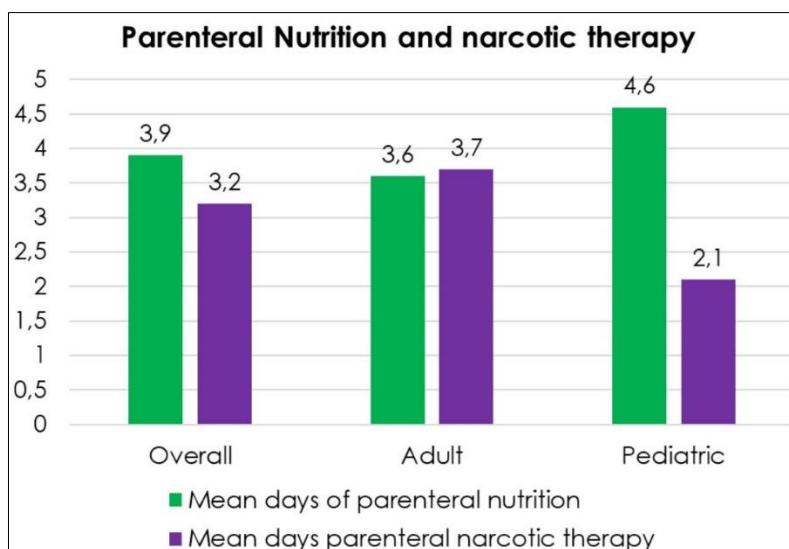
as depicted in Figure 3.



**Figure 3.** GelX® Oral Spray induced a significant remission on OM symptoms

Data regarding parenteral nutrition was reported from 145 pts (99 adults and 46 paediatric). The results show that the period of average overall parenteral nutrition period was 3.9 days, significantly lower than the treatment period without GelX® Oral Spray (26.9 days), which supports the idea that pts can restart chewing and swallowing in a shorter period of time when treated with GelX® Oral Spray.

The period of narcotic therapy in pts receiving GelX® Oral Spray is very short (average 3.2 days). These results are shown in Figure 4.



**Figure 4.** GelX® Oral Spray improve parenteral nutrition dependence in OM patients

The period of hospitalization (average of 28.9 days) was similar to treatment duration with GelX® Oral Spray (average overall of 26.9 days).

Weight gain has been observed in 21 pts, 11 (10.8%) with complete remission of OM, 4 pts (3.9%) with partial remission of OM and 6 pts (5.9%) had a weight gain when the preventive effect of GelX® Oral Spray was obtained. Considering the complex pathological conditions of the pts analysed, these results suggest the positive effect in treating OM.

None of the 145 pts of this study had interruptions of cancer therapy for OM while using GelX® Oral Spray. Several adverse events were reported in the study population, all related to the therapies used for treating the main pathology. A total of 27 severe adverse events were reported, all linked to treatment for primary disease, and none of them to the treatment with GelX® Oral Spray, therefore no action had to be taken in regard to GelX® Oral Spray.

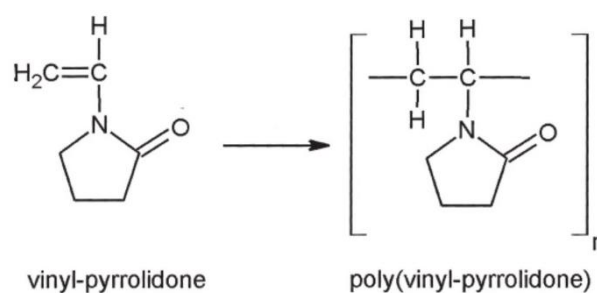
### 3.2. Discussions

OM is a common problem associated with significant patient morbidity and increased resource use. Current management of OM relies on supportive care and symptom palliation. However, the magnitude of the problem demands innovative approaches based on expert judgment as evidence accumulates to support specific recommendations. According to current clinical practice guidelines (MASCC/ISOO, ESMO, EBMT), there are few recommendations and suggestions in the favour of prophylactic/therapeutic interventions for OM in haematological/SCT pts [14,17]:

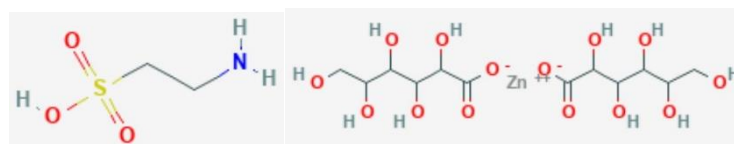
1) Recommendations: human keratinocyte growth factor/palifermin to prevent OM in autologous SCT; low-level laser therapy to prevent OM in SCT; patient controlled analgesia with morphine to treat OM related pain in SCT.

2) Suggestions: oral care protocols to prevent OM in all age groups and in all cancer treatment modalities; oral cryotherapy to prevent OM in pts receiving high-dose melphalan in SCT; transdermal fentanyl to treat pain in pts receiving standard or high-dose CTX; 0.5% doxepin mouth wash to treat pain due to OM.

Polyvinylpyrrolidone (PVP) is a lubricating agent, a synthetic polymer (shown in Figure 5), that under high temperature or pressure, radiation or chemicals, is transformed into PVP hydrogel [18, 19]. This compound has been used in different studies on OM management [20-23]. Taurine (2-aminoethanesulfonic acid) is an organic acid with osmoregulatory, antioxidative, antiapoptotic, anti-inflammatory and antilipid activity [24, 25]. Zinc gluconate is the zinc salt form of gluconic acid and acts as an antioxidant and immunostimulant. Both structures are depicted in Figure 6 [26, 27]. The combination of taurine and zinc gluconate conveys a bacteriostatic action to GelX® Oral Spray, that in addition to PVP demonstrated an anticorrosive effect [28]. PVP-Zn gluconate and other Zn containing products have been used in the management of CTX-associated OM in adults, but also in other aetiologies of aphthous lesions [29].



**Figure 5.** The structure of polyvinylpyrrolidone [18]



**Figure 6.** The structures of taurine and zinc gluconate [26, 27]

Vokurka et al. [30] conducted a study on 22 pts showing decreased oral microbial colonization and better pain control in cases with OM after allogeneic SCT receiving PVP-sodium hyaluronate. Watanabe et al. [31] showed lower incidence and severity of RTX/CTX-induced OM, pain, xerostomia and taste disturbance in pts with head and neck cancer treated with polaprezinc, a chelated form of zinc and L-



carnosine. Several other studies demonstrated the efficacy of PVP containing agents in the management of CTX-induced mucositis, showing superior results in pain control, food intake and mucositis severity [32, 33].

The results of this study showed that in 37.24% of pts the prevention of OM was reached. Out of the 59.34% of pts who had improvement, 93.4% had a complete remission (57.04% complete remission in total population). No patient had a worsening in OM grade. These findings sustain the performance of GelX® Oral Spray on reducing OM symptoms when treating both adult and paediatric pts with severe oncological conditions, after CTX/RTX/SCT for their malignancies. Only 16 pts (11.03%) developed grade 4 OM.

Children under the age of 12 have a higher risk of developing OM, with 90% of cases reported, and severe forms in 34-43% of pts [34]. In the paediatric cohort analysed, 33 pts received standard CTX, while 13 pts received high dose CTX and SCT. We observed a very high efficacy of GelX® Oral Spray, only 1 child in the CTX setting developed grade 4 OM. No patient in the CTX setting needed parenteral narcotic therapy for the treatment of OM-induced pain. Regarding the 13 paediatric transplant pts, all developed severe OM, but only 2 had grade 4 OM. Morphine therapy was administered in 2 pts and parenteral narcotic therapy was given to 10 pts for a median of 6.5 days (range 5-22).

In the adult setting, a higher percentage (approximately 75–80%) of pts who received high-dose CTX prior to hematopoietic SCT developed clinically significant OM [4], depending on the type of transplant and intensity of conditioning (35-75% in autologous SCT and 75-100% in allogeneic SCT) [4,9,12,35]. In our study, in the adult cohort, all 99 pts were transplanted for haematological diseases. The prophylactic purpose has been reached in 22 pts (22.22%) and severe OM developed in 40 pts (40.4%).

The majority of patients with OM are unable to continue eating due to severe pain and often receive parenteral nutrition. It has been demonstrated that pts with OM are significantly more likely to have severe pain and a weight loss of  $\geq 5\%$ . [6]. In our study, the 85 pts who achieved complete OM remission received parenteral nutrition for maximum of 13 days, while the 5 pts that achieved partial OM remission received parenteral nutrition for a maximum of 48 days. Pts were exposed to an average period of 3.9 days of parenteral nutrition (much lower than the average duration of treatment of 26.9 days).

Hospitalization period for pts analysed was, on average, 27 days, comparable to the duration of hospitalization in haematological/SCT pts of 29 days (range: 1-12 weeks) and similar to engraftment period after SCT.

#### 4. Conclusions

GelX® Oral Spray actively prevented OM and induced a significant remission of OM in pts that already showed OM symptoms. The percentage of pts that showed prevention or remission of OM after receiving GelX® Oral Spray was 99.3% of the total cohort. No patient had to interrupt CTX/RTX due to OM. GelX® Oral Spray was considered safe, and no adverse event was considered related to the use of the product. This retrospective study suggests prophylactic use of GelX® to minimize the risk of OM secondary to CTX/RTX.

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