Patient-reported Measurements of Oral Mucositis in Pediatric Patients with Cancer

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Abstract

Aims: The purpose of this study was to assess the impact of oral mucositis (OM) on oral-health related quality of life (QoL) among pediatric patients with cancer using Patient-Reported Oral Mucositis Symptom (PROMS) questionnaire. Methods: Seventy-five consequtive newly diagnosed patients undergoing chemotherapy because of different forms of cancer between the age of 8 and 18 yrs were included in the study. Children undergoing chemotherapy were required to complete the questionnaire at admission and weekly during the treatment. Results: Oral mucositis due to therapy was observed in 53/75 patients. The total PROMS score has increased gradually with a peak on day 21. A transient decrease of the total PROMS score was marked on day 28 followed by a second peak on day 35. We found significant correlations between WBC and the frequency of oral mucositis on day 7, 14 and 21. We found significant association between PROMS scores and oral mucositis scores according to the WHO protocol. Conclusions: According to our findings, oral mucositis is a common side-effect of chemotherapy which develops often in children with cancer. Based on its easy administration, PROMS questionnaire is suitable to measure self-reported changes in oral health of pediatric cancer patients.

Key Words: PROMS questionnaire, Oral mucositis, Oral-health related quality of life

Introduction

Oral mucositis (OM) is a painful and debilitating complication of cancer chemotherapy. The condition among pediatric patients is more frequent and severe compared to adults, especially in children with leukaemia [1-3]. OM is characterized by painful inflammation, ulceration and erythema of the oral mucosa; however, mucositis can occur anywhere along the gastrointestinal tract [4]. In mucositis, natural rate of mucosal cell death is accelerated by anticancer drugs. The degree of pain is usually related to the extension of tissue damage. Patients with OM may experience trouble in eating, drinking, swallowing or even speaking. OM has been shown to be associated with other adverse events caused by chemotherapy, such as loss of body weight, dehydration and fever. Moreover, OM has an adverse impact on clinical outcome of the malignant condition and on oral-health related quality of life (OHRQoL) [1]. Therefore, it is important to assess accurately OM-related symptoms of patients in order to prevent and to properly treat this side-effect. A number of clinician-rated scoring systems to detect and quantitate OM have been developed; however, there is no universally accepted self-administered OM assessment scale.

Aim

The purpose of this study was to evaluate the administration of a Patient-Reported Oral Mucositis Symptom (PROMS) scale among pediatric cancer patients, to compare PROMS-derived data with oral health measures rated by a dental clinician and to establish the adverse impact of OM on OHRQoL in children with cancer.

Methods

Patients and study design

Seventy-five consequtive newly diagnosed patients undergoing chemotherapy because of different forms of childhood cancer (29 boys and 46 girls) between the age of 8 yrs and 18 yrs (mean: 12 ± 4.3 yrs) were enrolled in the study between Jan 2, 2011 and Dec 31, 2012. The male/female ratio was 0.41. Fourty-five (60%) patients (12 boys and 33 girls, mean (±SD) age: 10 (±2.5) years) suffered from acute lymphoblastic leukemia (ALL), which is the most common type of childhood cancer. Patients with ALL were subjected to subgroup analysis in addition to the evaluation of the total patient population. Neither the age (mean ± SD = 10 ± 2.5 yrs), nor the male: female ratio 0.36 of ALL patients differed significantly from the total study population. Diagnosis and cancer treatment was performed at the Department of Pediatrics, University of Debrecen, according to the guidelines of the Hungarian Pediatric Oncology-Hematology Group. Diagnosis and treatment schedule of patients in course of antineoplastic chemotherapy are given in *Table 1*.

Inclusion criteria involved the patient's ability to complete the PROMS questionnaire without assistance and signing of the informed consent by the legal caregiver and by the patient. Exclusion criteria were the following: age < 8 and > 18 years; noncompliance with completing of the questionnaires at the scheduled sampling times (see below); patient's incapability to complete the PROMS questionnaire without assistance; patients not surviving the observation period. Informed consent was taken on first admission by a trained dental examiner (Á.J.). Before signing of the informed consent, patients and their legal caregivers were informed about the nature of the study in order to decide whether or not they

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wished to participate in the study. Altogether, 11 patients were excluded from the study.

Table 1. Diagnosis and treatment schedule of patients in course of antineoplastic chemotherapy.

Patients' characteristics		
Sex	**Male**	N=29
	Female	N=46
Mean age ± SD (range) (years)		12 ± 4.3 yrs
Diagnosis	**Cytostatic drugs applied**	
1. Acute lymphoblastic leukaemia	Vincristine, Prednisolon, Daunorubicin, L-Asparaginase (ALL-IC BFM 2002 protocol induction phase) [20]	N=45
2. Acute myeloid leukaemia	Daunorubicin, Cytosine arabinoside, Etoposide (AML-BFM 98 protocol) [21]	N=5
3. Hodgkin lymphoma	Doxorubicin, Prednisolon, Vincristine, Etoposide (EuroNet-PHL study) [22]	N=6
4. Non-Hodgkin lymphoma	Cyclophosphamide, Adriamycin, Vincristine, Prednisolon (NHL-BFM 95 protocol induction phase) [23]	N=4
5. Hepatoblastoma	Cisplatin, Doxorubicin (PLADO) [24]	N=3
6. Wilms tumor	Dactinomycin, Vincristine, Epirubicin (SIOP WT01) [25.]	N=3
7. Rhabdomyosarcoma	Vincristine (CW-high Risk branch) [26]	N=2
8. Serous epithelial ovarian cancer	Docetaxel, Carboplatin, [27]	N=2
9. medulloblastoma	Lomustine, Vincristine, Cisplatin (VEP) [28]	N=2
10. Ewing sarcoma	VIDE block: Vincristine, Cyclophosphamide, Doxorubicin, Etoposide (Euro-Ewing99) [29]	N=1
11. Nasopharyngeal carcinoma	Cisplatin, 5-Fluorouracil, Docetaxel + radiation therapy (total doses of 60 Gy) [30]	N=1
12. Retinoblastoma	Carboplatin, Vincristine, Etoposide [30]	N=1

The study period started on the first admission of the patients, i.e. prior to administering cancer treatment and the observation period lasted up to day 35 of cancer treatment. We established an observation period of 35 days, since induction phase of chemotherapy of patients with ALL, representing the largest subgroup of patients, took 33 days and 35 days covered the first chemotherapy treatment block and the recovery after the first treatment block in patients with other forms of cancer.

Questionnaire

The instrument of the present investigation was the original PROMS self-administered scale translated to Hungarian language by the investigators [5]. The questionnaire comprised 10 items related to most frequently occurring complaints due to chemotherapy-induced OM, i.e. (1) mouth pain, (2) difficulty of speaking because of mouth sores, (3) restriction of speech because of mouth sores, (4) difficulty of eating hard foods because of mouth sores, (5) difficulty of eating soft foods because of mouth sores, (6) restriction of eating because of mouth sores, (7) difficulty drinking because of mouth sores, (8) restriction of drinking because of mouth sores, (9) difficulty of swallowing because of mouth sores, and (10) change in taste. Participants were required to fill in the questionnaire according to the severity on a 100 mm long visual analogue scale (VAS). The maximum score was 100 for each item as well as for the total score. The higher the item scores were the more pronounced symptoms the patients experienced. The sum of the item scores characterized the respondents' oral mucosal health with higher scores representing more impaired OHRQoL. According to PROMS scale patients reaching at least 25 score (the maximum score is 100) in case of at least in four items were judged as patients affected by oral mucositis.

Patients were required to complete the questionnaire on first admission and weekly (day 7, 14, 21, 28 and 35) during the course of cancer treatment. Two trained dental surgeons (Á.J., I.J.M.) performed the investigations of patients, administered the PROMS questionnaire and registered oral mucositis scores according to the WHO protocol, collected and analyzed the data. Training was repeated as necessary.

Oral examinations

Mucositis was evaluated using the WHO scoring system [6]. WHO distinguishes four grades of oral mucositis according to severity: 0- no symptoms; 1- erythema, soreness; 2- erythema, ulceration, patient can swallow solid food; 3- erythema, ulceration, patient cannot swallow solid food; 4- ulceration,

pseudomembrane formation, alimentation is not possible [6]. Using ordinal grades of 0, 1, 2, 3 and 4 for the size of erythematous areas, the size of ulceration and the grade of restriction in swallowing patients categorized into grade 1, 2, 3 and 4 were assessed as patients affected by oral mucositis.

Periodontal condition of the participants was documented. Dental surgeons participating in this study were trained in the CPI system using calibrated WHO periodontal probe. With the CPI system a score of 0 indicated healthy periodontium; a score of 1 indicated probing up to the lowest edge of the black band, i.e. up to 3.5 mm and bleeding; a score of 2 is the same as a score of 1 except that calculus was found; a score of 3 was given when the black band partially disappeared, indicating probing up to 5.5 mm, and a score of 4 was complete disappearance of the band with probing 5.5 mm and above [7]. In case of patients who were unable to accept probing due to pain or limited opening during the severe mucositis the oral examination was repeated after healing.

White blood cell count (WBC) of patients was determined according to standard laboratory method and registered at times of the dental examinations.

Statistical methods

The mean (±SD) values of the PROMS items were calculated on first admission (baseline) and on day 7, 14, 21, 28 and 35 during the course of treatment. Using nonparametric rank correlation coefficients, we estimated the correlation between item scores and the WBC. Association between self-reported PROMS scores and clinician-rated OM scores and its components was established by one-way ANOVA test. Correlations between patients' CPI index and PROMS score components was estimated by Spearman's rho correlation. The distribution of PROMS item scores and total scores at baseline and at later time-points was represented by histograms. Statistically significant differences from the baseline were considered if $p< 0.05$.

The study was conducted in full accordance with ethical principles of the World Medical Association Declaration of Helsinki and approved by the institutional Review Board (3368-2011 DEOECRKEB/IKEB). All patients and their caregivers signed a written informed consent form.

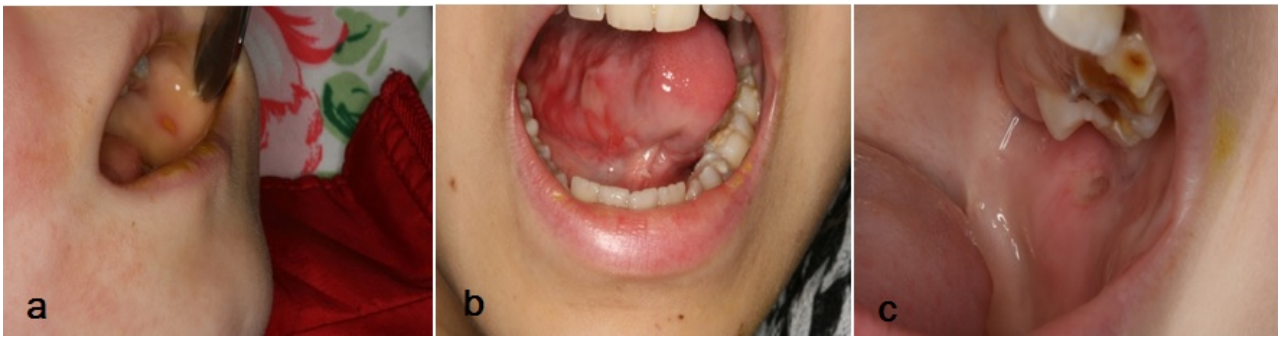

Figure 1. *a: OM in the middle third of the buccal mucosa; b: OM on the ventral surface of the tongue; c: OM in the posterior third of the buccal mucosa.*

Results

The PROMS scale was applied for a study group of 75 pediatric patients on first admission (baseline). The response rate was: 74/75 patients (98.7%) on day 7, 64/75 patients (85.3%) on day 14, 50/75 patients (66.7%) on day 21, 22/75patients (29.3%) on day 28 and 8/75patients (10.7%) on day 35.

Chemotherapy-induced OM was observed in 53/75 (70.7%) patients during the observation period according to the PROMS scores and in 58/75 patients (77.3%) according to the WHO OM tool evaluated by a dental surgeon. Representative lesions are shown in *Figures 1a, b, c*. The total PROMS score has increased significantly and gradually with a peak on day 21 of therapy (mean on first admission: 6.18; mean on day 7: 23.30; mean on day 14: 30.97; mean on day 21: 39.28).

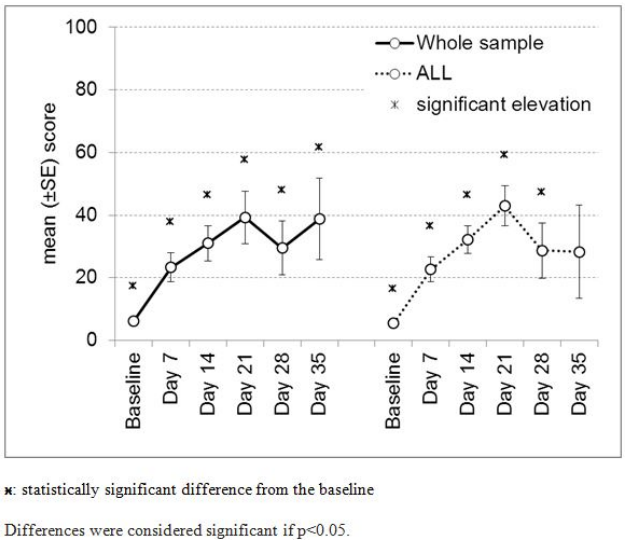

Figure 2. *Changes in total PROMS score of the total study population and patients with ALL throughout the study observation period.*

A significant transient decrease of the total PROMS score was marked on day 28 (mean: 29.47) followed by a significant second peak on day 35 (mean: 38.73) (*Figure 2*). With the exception of "change in taste" PROMS item scores showed the same significant increase up to day 21, followed by a transient decrease on day 28 and a second peak on day 35. "Change in taste" item scores increased significantly and constantly until day 35. "Difficulty of eating hard foods" was characterized by the highest (mean: 52.90) scores on day 21, the most critical period of chemotherapy (*Figure 3*). In contrast, the total PROMS scores and item scores of patients with ALL had a significant single peak on day 21 (mean: 42.92) which was followed by a constant decrease until day 35 of therapy (*Figure 2*). All ALL patients were found in complete clinical and hematological remission at day 33 of treatment. Evaluating the mean item scores of the ALL subgroup, items No 3, 4, 9 and 10 ("restriction of speech because of mouth sores, difficulty eating hard foods, difficulty swallowing because of mouth sores") peaked significantly on day 21, whereas item No 10 ("change in taste") peaked on day 28 followed by a decrease until day 35. The remaining item scores (No 1, 2, 5, 6, 7 and 8) of patients with ALL showed a similar pattern to the total study group (*Figure 4*). Patients with various forms of cancer other than ALL (N=30) exhibited a similar pattern as the total study group with respect to total PROMS score (data not shown).

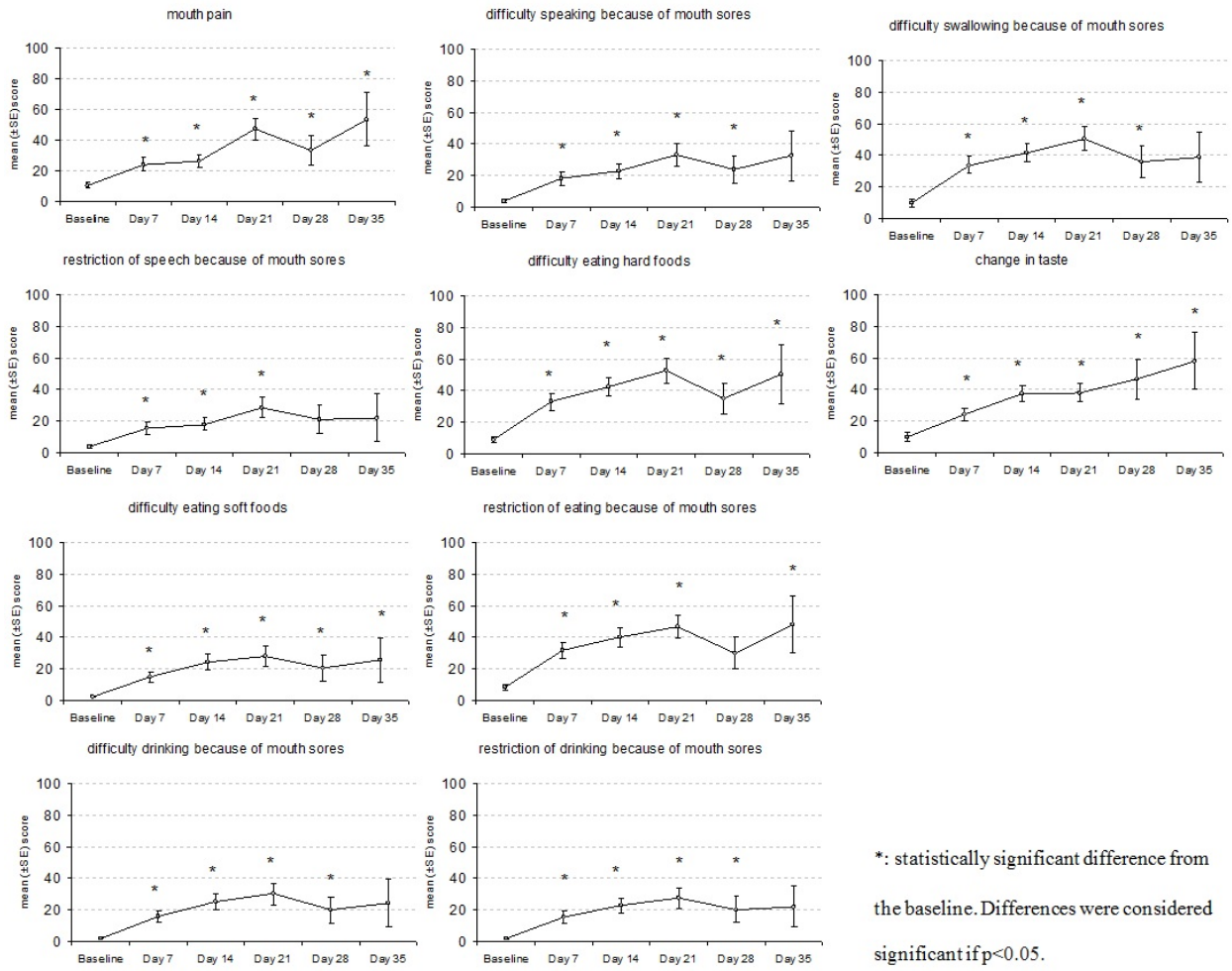

Figure 3. *Changes in PROMS item score values of the total study population throughout the study observation period (N=75).*

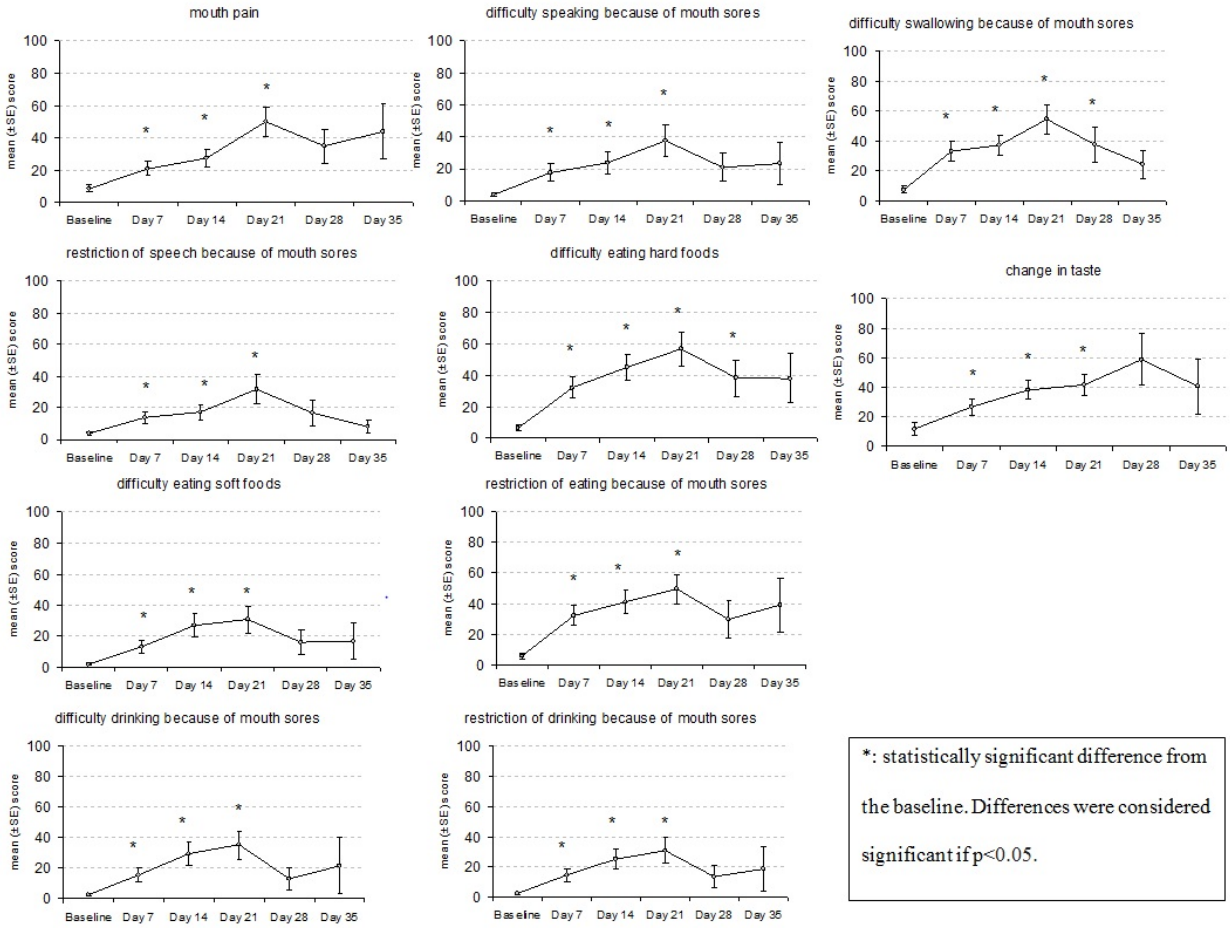

Figure 4. *Changes in PROMS item score values of patients with ALL throughout the study observation period (N=45).*

We found significant associations between PROMS item scores (representing patients' subjective assessment of OM) and the WHO OM score and its components (representing the objective assessment of OM) using one-way ANOVA test (*Table 2*). The grade of erythema, plaque accumulation on the oral mucosa, ulceration and alimentation difficulties evaluated by a dental surgeon correlated significantly and meaningfully with the total PROMS score and item scores during hospitalization.

Table 2. *Associations between WHO OM score components and PROMS score components. Probability (p values) of correlations estimated by one-way ANOVA test. p< 0.05 were considered significant (bold boxes).*

PROMS score componentsWHO OM score components		Day 7	Day 14	Day 21	Day 28	Day 35
Mouth pain	erythema	0,123	**<0,001**	**<0,001**	**0,003**	**0,008**
	plaque	**<0,001**	**<0,001**	**<0,001**	**0,002**	**0,008**
	ulceration	nc	**<0,001**	**<0,001**	**0,005**	nc
	feeding	nc	**<0,001**	**0,001**	**<0,001**	nc
Difficulty speaking because of mouth sores	erythema	0,471	**<0,001**	**<0,001**	**0,005**	**0,018**
	plaque	**<0,001**	**<0,001**	**<0,001**	**0,003**	**0,018**
	ulceration	nc	**<0,001**	**<0,001**	**<0,001**	nc
	feeding	nc	**<0,001**	nc	nc	nc
Restriction of speech because of mouth sores	erythema	0,763	**<0,001**	**<0,001**	**0,001**	**0,001**
	plaque	**<0,001**	**<0,001**	**<0,001**	**<0,001**	**0,001**
	ulceration	nc	**<0,001**	**<0,001**	**<0,001**	nc

	feeding	nc	**<0,001**	nc	**<0,001**	nc
Difficulty eating hard foods	erythema	**<0,001**	**<0,001**	**<0,001**	**<0,001**	nc
	plaque	nc	**<0,001**	**<0,001**	**<0,001**	nc
	ulceration	nc	**<0,001**	**<0,001**	**0,001**	nc
	feeding	nc	nc	**<0,001**	nc	nc
Difficulty eating soft foods	erythema	0,107	**<0,001**	**<0,001**	**0,001**	**0,001**
	plaque	**<0,001**	**<0,001**	**0,001**	**<0,001**	**0,001**
	ulceration	nc	**<0,001**	**<0,001**	**0,001**	nc
	feeding	nc	**<0,001**	nc	nc	nc
	erythema	**0,004**	**<0,001**	**<0,001**	**0,001**	**0,002**
Restriction of eating because of mouth sores	plaque	**<0,001**	**<0,001**	**<0,001**	**<0,001**	**0,002**
	ulceration	nc	**<0,001**	**<0,001**	**<0,001**	nc
	feeding	nc	**<0,001**	nc	nc	nc
Difficulty drinking because of mouth sores	erythema	0,415	**<0,001**	**0,003**	**0,001**	**0,014**
	plaque	0,058	**<0,001**	**0,014**	**0,001**	**0,014**
	ulceration	nc	**<0,001**	**0,002**	**<0,001**	nc
	feeding	nc	**<0,001**	nc	nc	nc
Restriction of drinking because of mouth sores	erythema	0,169	**<0,001**	**0,005**	**0,001**	**0,005**
	plaque	0,268	**<0,001**	**0,015**	**<0,001**	**0,005**
	ulceration	nc	**<0,001**	**0,014**	**<0,001**	nc
	feeding	nc	nc	nc	nc	nc
Difficulty swallowing because of mouth sores	erythema	**<0,001**	**<0,001**	**<0,001**	**0,007**	nc
	plaque	nc	**<0,001**	**<0,001**	**0,004**	nc
	ulceration	nc	nc	**<0,001**	**0,002**	nc
	feeding	nc	**<0,001**	**<0,001**	nc	nc
change in taste	erythema	**0,007**	**<0,001**	**<0,001**	**0,033**	**0,009**
	plaque	**<0,001**	**<0,001**	**<0,001**	**0,019**	**0,009**
	ulceration	nc	**<0,001**	**<0,001**	**0,012**	nc
	feeding	nc	nc	nc	**<0,001**	0,564
Total PROMS score	erythema	0,180	**<0,001**	nc	**0,006**	nc
	plaque	nc	**<0,001**	nc	nc	nc
	ulceration	nc	nc	nc	nc	nc
	feeding	nc	nc	nc	nc	nc
nc= Non-conclusive: one-way ANOVA test was not successful and had no result						

According to the registered pathologic pocket depths, supra- or subgingival calculus and gingival bleeding 47/75 (63%) patients had gingivitis without clinical attachment loss and 28/75 (37%) patients had healthy periodontium. We did not observe severe or moderate forms of periodontitis. Spearman's rho correlation test did not show any significant association between patients' CPI index observed before hospitalization and total PROMS score and item scores (data not shown).

Significant correlations were found between patients' total PROMS score and item scores and WBC according to the nonparametric rank correlation test (*Table 3*). WBC count of the respondents correlated significantly and meaningfully with total PROMS score on day 7, 14 and 21 (r= -0.645 on day 7;

r= -0.585 on day 14; r=-0.709 on day 21). Correlation coefficients (r) were considered significant if p<0.001.

Table 3. Correlation between PROMS item scores and WBC observed on days 7, 14, 21, 28 and 35 of the follow-up period.

	Day 7	Day 14	Day 21	Day 28	Day 35
mouth pain	**-0.522**	-0.422	**-0.694**	-0.41	-0.862
	(<0.001)	-0.009	**(<0.001)**	-0.164	-0.006
difficulty speaking because of mouth sores	**-0.531**	-0.528	**-0.619**	-0.462	-0.719
	(<0.001)	-0.001	**(<0.001)**	-0.112	-0.045
restriction of speech because of mouth sores	**-0.476**	**-0.547**	-0.55	-0.593	-0.368
	(<0.001)	**(<0.001)**	-0.002	-0.033	-0.37
difficulty eating hard foods	**-0.503**	**-0.551**	**-0.716**	-0.598	-0.886
	(<0.001)	**(<0.001)**	**(<0.001)**	-0.031	-0.003
difficulty eating soft foods	-0.423	**-0.603**	-0.506	-0.686	-0.59
	-0.002	**(<0.001)**	-0.005	-0.01	-0.124
restriction of eating because of mouth sores	**-0.613**	-0.493	**-0.735**	-0.601	-0.778
	(<0.001)	-0.002	**(<0.001)**	-0.03	-0.023
difficulty drinking because of mouth sores	**-0.494**	**-0.59**	-0.588	-0.701	-0.473
	(<0.001)	**(<0.001)**	-0.001	-0.008	-0.237
restriction of drinking because of mouth sores	**-0.498**	**-0.566**	-0.507	-0.748	-0.42
	(<0.001)	**(<0.001)**	-0.005	-0.003	-0.3
difficulty swallowing because of mouth sores	**-0.56**	-0.37	**-0.643**	-0.575	-0.814
	(<0.001)	-0.024	**(<0.001)**	-0.04	-0.014
change in taste	**-0.555**	-0.254	-0.471	-0.034	-0.886
	(<0.001)	-0.129	-0.01	-0.911	-0.003
Total PROMS score	**-0.645**	**-0.585**	**-0.709**	-0.399	**-0.898**
	(<0.001)	**(<0.001)**	**(<0.001)**	-0.177	**-0.002**

Correlations were estimated by Spearman's test. Rho (r) values and p values (in parentheses) were given. Taking into account the multiple hypothesis testing, correlations were considered significant if p<0.001 for PROMS components and p<0.01 for PROMS scores (bold boxes).

Most of the mild complaints improved by using Corsodyl (0.12% chlorhexidine digluconate containing mouth rinse). Thirty of patients (40%) developed oral thrush throughout the study follow-up period and required local and systemic anti-fungal treatment.

Discussion

Early and late side-effects of childhood cancer therapy often involve various anatomical structures of the oral cavity. Oral mucositis is one of the most frequent and debilitating condition [1-3,8-10]. Stomatotoxicity is due to the inhibitory effects of cytotoxic drugs and irradiation on stem cell self-renewal within the basal layer of the oral mucous membrane. Bone marrow suppression may have an additive effect. Symptoms start usually one week after of the administration of the cytostatic agent and may last up to 2-3 weeks. Non-keratinized surfaces, such as buccal and labial mucosa, floor of the mouth, ventral surface of the tongue, and soft-palate are more severely affected [11]. OM scoring systems can be divided into two major categories: i) assessment of symptoms may rely on measurable changes within the oral cavity determined by a dental expert; and ii) scoring can be based on patient-reported questionnaires. The former ones are lesser biased by subjective complaints, the latter ones represent OHRQoL more reliably. Among adults with head and neck cancer receiving irradiation therapy, Etiz et al. compared and validated five different mucositis scoring systems. Objective mucositis scores demonstrated a strong correlation with patient-reported symptoms [12].

Despite of the frequency of OM in children treated for cancer, this particular side-effect has rarely been addressed by accurate investigations. Moreover, there have been no uniformly used scoring systems developed for the pediatric age group to evaluate the severity of this complication; therefore, preventive and treatment measures cannot be based on generally accepted guidelines. Valera et al. and Soares et al. investigated children with ALL in different phases of antineoplastic treatment. OM was characterized by general appearance in these studies [13,14]. Cheng et al. and Wogelius et al. used two different self-reported scoring systems, the

Mouth and Throat Soarness-related questions of the Oral Mucositis Daily Questionnaire (OMDQ) and the validated Danish version of the Child Perceptiones Questionnaire involving a larger (No=140) and a smaller (No=18) group of children with hematological malignancies and solid tumors, respectively [1,15]. Jacobs et al. evaluated the reliability and validity of the self-reported Children's International Mucositis Evaluation Scale (ChIMES) by comparing data with that of two patient-reported tools, the OMDQ, and the mucositis Visual Analogue Scale; and with two clinician-based, objective tools, the WHO OM scoring system, and the National Cancer Institute Common Terminology Criteria v3.0 functional/symptomatic mucositis scale. Investigating 87 children and adolescents undergoing either myeloablative hematopoetic stem cell transplantation (HSCT) or receiving high-dose doxorubicine ($\geq$60 mg/m^2/course) or methotrexate ($\geq$12 g/m^2), they suggested to incorporate ChIMES into clinical trials aimed at OM prevention and treatment in children with cancer [16].

In this study we used the self-reported PROMS scale to evaluate severity, onset and clinical course for the first time in children with cancer. The measuring tool has originally been developed in 38 adults undergoing myeloablative HSCT. In the hands of the investigators of the Princess Margaret Hospital, Toronto (ON, Canada), the PROMS scale had high internal reliability and good convergent and discriminant validity. Changes in PROMS scores strongly correlated with changes in clinical assessment of OM [5]. Since the original report, PROMS has been reported as useful and reliable indicator of OM by Bezinelli et al. investigating adult HSCT patients and by Gussard et al. investigating adults with head and neck cancer [17,18]. In a more recent study, Gussard et al. suggested that the association between PROMS and WHO OM scores was nonlinear and that PROMS represented the OM-related condition of patients more reliably than the clinician-rated tools [19]. *Table 1* can be referred for Diagnosis and treatment schedule of patients in course of antineoplastic chemotherapy [20-30].

Our results demonstrated that PROMS could be used among pediatric cancer patients older than 7 years and that it proved to be a reliable indicator of OM. There was a strong correlation between PROMS items scores and components of the WHO OM score, but not between PROMS scores and CPI characterizing periodontal health. OM was a frequent finding during the observation period, i.e. induction treatment of ALL and first course of cytotoxic treatment applied because of other forms of childhood cancer. More than 70% of patients were diagnozed with OM based on the results obtained by the PROMS questionnaire and over 77% of patients exhibited OM according to the WHO OM tool. A mild gingivitis was present in 63% of patients. The incidence of OM was higher in our study than in two other pediatric studies which reported OM incidence figures. Cheng et al. observed a 41% OM frequency during induction or consolidation phases of chemotherapy in children with ALL and solid tumors. However, the observation period in that study was 14 days and we found increasing PROMS scores up to 21 days and a second peak in the total patient group at day 35 [1]. In the study reported by Soares et al. the frequency of OM was 20% among patients with ALL receiving induction treatment. However, patients received prophylactic treatment with 0.12% chlorhexidine gluconate solution whereas patients in our study received only interventional management for OM [14]. Of the pediatric studies investigating OM in children with cancer, only Valera et al. [12] described the clinical course of oral complications, including OM, as judged by clinical appearance. According to their results, the frequency of oral manifestations started to rise in the first week after the application of cytostatic agents and lesions became more frequent and severe for another 14-21 days when the neutrophil leukocyte counts were low [13]. In our study PROMS scores showed a steady increase until day 21 followed by a decrease in PROMS scores at day 28. After this evaluation time, PROMS scores of the total study polpulation, including children with non-ALL malignancies, exhibited a second peak at day 35, and remained at the same level as day 28 in case of children with ALL. Similar to Valera et al. [12] we found a strong correlation between WBC and PROMS scores. Our results suggest, that onset and severity of OM in children with cancer is related to the application of cytotoxic treatment as described by others, i.e. the first patient-reported complaints and clinical symptoms start about 7 days after the first application of the cytotoxic agents and signs and symptoms deteriorate during the next 2-3 weeks, as indicated by the increasing PROMS scores in our study. Healing starts after 4 weeks of the beginning of antineoplastic therapy. Patients with ALL entered clinical and hematological remission by that time and maintained their oral condition. The majority of children with cancer different from ALL; however, will have received their second antineoplastic treatment block between day 21 and day 28; therefore they experienced a second decline in oral health and, in parallel, a second increase in PROMS scores by day 35 [5,11,17]. The observation period limited to 35 days can be regarded as one of the limitations of our study. However, studies investigating treatment-related OM of cancer patients were similar or shorter in duration with the exception of Gussard et al. who had followed adult patients irradiated because of head and neck cancer during the 6-7 weeks of radiotherapy and at a single occasion 4-6 weeks after completing treatment [1,5,16-18]. Moreover, we experienced a considerably decreasing response rate in course of the investigation preventing any meaningful interpretation of the results after day 35. The significant dropout rate of our study from day 7 to day 35 can be explained by the severe general health condition of patients due to chemotherapy. However, in case of patients who were unable to accept oral examination and probing due to pain or limited opening because of severe mucositis, oral examination was repeated after the healing, but we lost major proportion of the questionnaires until day 35. These challenges necessarily require multivariate, multilevel analyses of a larger sample size. The risk of potential bias introduced has been acknowledged. Elimination of the above mentioned difficulties would enhance the significance of the study.

The second limitation of our study was that the number of patients with various forms of cancer other than ALL was too small to allow statistically relevant analysis of the individual subgroups. Separate prospective multi-center studies are required to establish the exact role of PROMS questionnaire in groups of patients with different types of childhood cancer.

In conclusion, the present investigation represents the first experience with the administration of PROMS scale among pediatric cancer patients. Since both clinician-rated and self-reported evaluations of oral condition in children with cancer is underreported, the comparison of self-reported PROMS data with the evaluation of a dental surgeon based on the WHO OM assessment tool provided significant and novel pieces of information in the field. Clinician-rated evaluation of oral conditions in children with cancer has not been frequently investigated and compared with clinician-rated data. One of the novelties of the present investigation was the comparison of self-reported data with the evaluation of a dental surgeon. Our observations demonstrated the importance of accurate and clinically meaningful evaluation of OM-related symptoms of patients in order to prevent and to properly treat this often neglected side-effect. OM scoring systems can be divided into two major categories: i) assessment of symptoms may rely on measurable changes within the oral cavity determined by a dental expert; and ii) scoring can be based on patient-reported questionnaires. The former ones are lesser biased by subjective complaints, the latter ones represent OHRQoL more reliably. We found significant associations between PROMS item scores (representing patients' subjective assessment of OM) and the WHO OM score and its components (representing the objective assessment of OM). Despite of the frequency of OM in children treated for cancer, this particular side-effect has rarely been addressed by accurate investigations. Moreover, there have been no uniformly used scoring systems developed for the pediatric age group to evaluate the severity of this complication; therefore, preventive and treatment measures cannot be based on generally accepted guidelines. According to a recent study, Gussard et al. [18] suggested that the association between PROMS and WHO OM scores was nonlinear and that PROMS represented the OM-related condition of patients more reliably than the clinician-rated tools as we pointed it out. Our results demonstrated that PROMS could be used among pediatric cancer patients older than 7 years and that it proved to be a reliable indicator of OM. Since both clinician-rated and self-reported evaluations of oral condition in children with cancer is underreported, the comparison of self-reported PROMS data with the evaluation of a dental surgeon based on the WHO OM assessment tool provided significant and novel pieces of information in the field. PROMS is a promising tool to evaluate OM-dependent OHRQoL in children with cancer. Results obtained with the use of PROMS questionnaire in this age group may contribute to the development of clinical guidelines to prevent and treat antineoplastic therapy-related OM.

Further multicentric studies involving a larger number of patients and applying a longer observation period may establish the proper place of the PROMS scale in the supportive treatment strategy of children with cancer.

Acknowledgements

The study is supported by the TÁMOP 4.2.1./B-09/1/ KONV-2010-0007 project and by the OTKA 105034 project.

Conflicts of interest

The authors declare that they have no competing interests.

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