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Quantitative Scale of Oral Mucositis Associated with Autologous Bone Marrow Transplantation

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Acute oral complications are serious and disabling secondary effects for patients undergoing cancer therapy. Therefore, the authors wanted to develop a sensitive and specific method to measure oral mucosal changes associated with autologous bone marrow transplantation. 14 patients, all volunteers, 18–56 years old, receiving conditioning regimens of cyclophosphamide and total body irradiation were included. The clinical changes of the oral mucosa and functional modifications were scored daily, over 21 days with a 16 item scale, ranging from 0 to 3. A daily index of mucositis (DIM) was established by adding the scores obtained for the 16 items and a cumulative score of oral mucositis was obtained by the addition of the 21 DIM for assessing the severity of oral mucositis throughout its duration. The internal consistency measures (Chronbach alpha) were strong (range 0.80–0.97). A scale of equivalence, pre-established in comparison with pre-existing general mucositis rating scales, permitted a day by day simple classification in a 4-grade scale, to be obtained. Support for the validity of the suggested scale is presented. This scale may help to improve the study of oral complications of cancer therapy. Copyright © 1996 Elsevier Science Ltd

Key words: autologous bone marrow transplantation, oral mucositis, quantitative scale

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INTRODUCTION

Acute oral complications are serious and disabling secondary effects for patients undergoing cancer therapy. The frequency of their appearance varies from 12% in patients receiving adjuvant chemotherapy to 100% in patients submitted to radiotherapy of the oral cavity, when the total dose exceeds 50 Gy [1]. These lesions of the oral cavity and the functional problems which they generate, grouped under the general term 'oral mucositis', are induced by the conjunction of different complementary factors, linked either to the type of therapy, or to patient susceptibilities [2]. Direct toxicity of chemotherapy or radiotherapy is the most important aetiological factor, but traumatic, local or systemic infectious complications can modify the aspect and evolution of mucositis [3]. In particular, the appearance of herpes or candidosis should systematically be examined. Mucositis can induce severe and debilitating pain which can significantly increase the morbidity of cancer therapy and be sufficiently intense to necessitate the administration of high-dose opioid analgesics. Severe mucositis can lead to modifications of treatment planning, suspension of therapy or require parenteral nutrition. It is frequently accompanied by nausea, vomiting, diarrhoea, associated with pain which considerably reduces comfort and the sensation of well-being in the patient who sleeps poorly, becomes anorexic and loses weight. The impact of oral mucositis on the cost of treatment has not been studied, but severe mucositis can certainly increase the duration of hospitalisation and the need for special care [4]. During bone marrow transplantation, mucositis is a frequent and a painful side effect [5–7]. The most notable clinical changes may occur within the first few days after the transplant and evolve for 3 weeks with a peak between days 7 and 11. They concern modifications in the colour of the mucosa (hyperkeratosis, atrophy, erythema, pseudomembranes, ulcerations), in the salivary viscosity and volume, and in the functional or subjective problems related to pain and dryness of the oral cavity. Granulocytopenia increases the risk of buccal infection, while thrombocytopenia increases the risk of oral haemorrhage. The floor of the mouth, ventral tongue, buccal and labial mucosa, and gingiva are, in decreasing order, the most frequent localisations [4, 6, 8]. The soft and hard palates are the least affected regions.

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Table 1. *Patients' characteristics*

UPN	Age	Sex	Pathology	Conditioning regimen	State of BMT	Diagnosis to BMT (months)
1	24	M	AML	CPM/TBI	RC1	3
2	18	M	ALL	CPM/TBI	RC1	5
3	29	F	ALL	CPM/TBI	RC1	5
4	18	M	AML	CPM/TBI	RC1	4
5	54	M	AML	CPM/TBI	RC1	4
6	49	F	AML	CPM/TBI	RC1	6
7	41	F	AML	CPM/TBI	RC1	5
8	18	M	ALL	CPM/TBI	RC1	5
9	34	M	ALL	CPM/TBI	RC2	10
10	48	M	AML	CPM/TBI	RC1	4
11	32	F	AML	CPM/TBI	RC1	4
12	47	M	AML	CPM/TBI	RC1	5
13	49	F	ALL	CPM/TBI	RC2	8
14	47	F	ALL	CPM/TBI	RC1	5

UPN, unique patient number, BMT, bone marrow transplant; M, male; F, female; ALL, acute lymphoblastic leukaemia; AML, acute myeloblastic leukaemia; CPM, cyclophosphamide; TBI, total body irradiation; RC1, first complete remission; RC2, second complete remission.

Different therapies are used to reduce these side effects of cancer therapy which dramatically alter the quality of life during treatment. Even though their effects are marginal [9–12], much remains to be done for the prevention and the treatment of these complex and painful problems. One of the major limitations in the study of oral toxicity of cancer therapy resides in the difficulty to precisely classify and reproducibly measure mucosal changes and oral side effects associated with different cancer treatments. The object of this study was to describe a method to measure oral mucositis reproducibly, in order to obtain a quantitative evaluation.

MATERIALS AND METHODS

Patient selection

From June 1993 to May 1995, 14 patients receiving an autologous bone marrow transplant for diverse acute lymphoblastic leukaemia (ALL) and treated at the Paoli-Calmettes Institute (Table 1) were included in this study, which was carried out in the judicial framework of the Huriet Law (agreement on 11 February 1993). The patients, 18–56 year old volunteers who had signed a letter of agreement, were identified by number. Prior to transplant, patients were treated according to the French National Protocols (LAL 79, LALA 83, LALA 87) [13] and received induction regimens consisting of combinations of vincristine, anthracyclines and cyclophosphamide (CPM). Chemotherapy consisted of CPM 60 mg/kg/day for 2 days (days −5 and −4) given with fractionated total body irradiation (midplant dose 12 Gy over six fractions on days −3, −2 and −1; median dose rate 5 cGy/min). All patients were treated in individual rooms with HEPA filters and received a sterile diet and daily gastrointestinal decontamination (acyclovir 0.75 grs, neomycine and colimycine). Bone marrow transplants (day 0) were performed according to previously described protocols [14]. A protocol of oral care, identical for all patients, was based on daily use of dental paste containing framycetine and mouth rinses with 0.2% chlorhexidine *ad libitum*. The patients were permitted to cover their lips with vaseline to prevent dehydration. Intravenous perfusions of morphine, carefully recorded, were administered when justified by the intensity of pain.

Clinical examination of patients

Patients were examined daily over 21 days (from the day of the transplant to day 20 inclusive). All of the observations were realised by the same specialised medical staff members in illuminating conditions permitting a good clinical examination. The oral cavity was divided into four distinct anatomical zones: (1) labial, (2) gingival, (3) buccal mucosa and (4) mucosa of ventral tongue and floor of the mouth. Clinical modifications affecting each site were scored according to three clinical parameters for which changes were quantified from 0 to 3 according to the pre-established scale described on Table 2. These clinical categories were based on the different changes of the oral mucosa, classically appearing in patients submitted to conditioning regimens for bone marrow transplantation. Manifestations of hyperkeratosis, atrophy, erythema, oedema and/or ulcerations were evaluated in a purely clinical point of view and allowed 12 objective items (three for each zone) to be obtained day by day. Four subjective parameters, taking into account the patient's appreciation of his functional modifications (pain, talking, dryness of the oral cavity and swallowing), were also quantified from 0 to 3 according to the pre-established descriptive scale (Table 2). A daily index of mucositis (DIM) was established by addding up the scores obtained for the 16 items (12 objective and four subjective) to attain a global score ranging from 0 to 48 (Table 3). This daily index of mucositis can be used without the subjective signs (12 items). These two indices allowed curves of the variations of appearance, severity and evolution of observed mucositis to be plotted for each patient and all of the patients in a same group (mean daily indices of mucositis) over the period of 21 days. A scale of equivalence (Table 3), pre-established in comparison with pre-existing general mucositis rating scales [15, 16] also allowed a day by day simple classification in a 4-grade scale to be obtained, giving in a rapid and comparative manner, the number of days of mucositis as well as its severity per

Table 2. Guide for the evaluation of mucositis

		Grade 0	Grade 1	Grade 2	Grade 3
Lips	Aspect	Smooth, soft	Slightly wrinkled	Rough	Tumefied, cracked Ulcerated, bleeding
	Colour	Pale pink	One to several reddened zones	Red, several inflammatory zones, one zone of desquamation	Red, bleeding
	Dryness	Humid	Slightly dry	Dry	Cracked
Gingiva	Aspect	Smooth, glossy	1 to 2 inflammatory zones or 1 to 2 white plaques	Whitish coating Desquamation Inflammatory zone (10–50%)	Ulceration + edema + bleeding
	Colour	Pink	Pale	Red	Shiny red
	Dryness	Humid	Slightly dry	Dry	Bleeding
Buccal Mucosa	Aspect	Pink, smooth	1 to 2 inflammatory zones 1 to 2 white plaques (20%)	Tumefied White coating Desquamation (10 to 50%)	Bleeding, ulceration Inflammation (>50%) + edema White plaques
	Colour	Pink	Pink with some red zones	Red (>20%)	Dark red
	Dryness	Humid	Slightly dry	Dry	Ulcerated
Tongue	Aspect	Firm prominent papilla	White coating Prominent red papillae Inflammatory zones Marked median line	Heavy tumefied base Prominent red papillae	Heavy, thick, tumefied Ulcerated, streaked
	Colour	Pink	Pink with red or white zones	Entirely red with even red papillae	Extremities dark red White coating Vesicles, black ulcers
	Dryness	Humid	Dry Hardly mobile and painful	Very dry and tumefied	Very dry and rough
Swallowing		Normal Good mastication No constraint	Constraint in mastication and swallowing (conscious gesture)	Difficult Impossible to swallow solid food	Absence of swallowing and/or mastication (saliva spit)
Saliva		Fluid, light	Increased	Thick and viscous	Rare Mouth dry
Voice		Normal	Slightly changed	Raspy and deep	No longer talks
Pain		Absence	Moderate	Need for minor analgesics	Need for major analgesics

patient or group of patients over a period of 21 days. Addition of the daily indices of mucositis obtained over 21 days lead to a cumulative score of oral mucositis (CSOM), corresponding for each patient or group of patients to a total quantitative value taking into account the severity and the duration of the evaluated mucositis [12]. This cumulative score can also be expressed in the form of a daily mean, giving for each patient or group of patients, a daily cumulative index with or without subjective signs (DCI).

Statistical analysis

The construction of a scale consists of grouping all the items concerning a particular domain, so that the items considered represent a single concept under different formulations. The validation, thence, classically consists of two parts: study of the validity, on the one hand, defined as the aptitude of the scale to measure what it is supposed to measure [17], and that of its metrological qualities, on the other hand, associating a study of the sensitivity, and the

Table 3. Oral mucositis scale examination form

	Day	0	1	2	3	4	5. 17	18	19	20	Total
Lips	Aspect										
	Colour										
	Dryness										
Gingiva	Aspect										
	Colour										
	Dryness										
Mucosa	Aspect										
	Colour										
	Dryness										
Tongue	Aspect										
	Colour										
	Dryness										
Swallowing											
Saliva											
Talking											
Pain											
Mucositis	score										
Without subjective items	score										
Mucositis	Grade 0										
	Grade 1										
	Grade 2										
	Grade 3										

Scale of Equivalence: 1 to 5 Grade 0:
6 to 15 Grade 1:
16 to 30 Grade 2:
31 to 48 Grade 3.

Number of days: Grade 0:
Grade 1:
Grade 2:
Grade 3:

specificity of the method. The validation of the proposed method was carried out using: (a) a stage of internal validation, the Cronbach alpha coefficient [18] (considered satisfactory between 0.7 and 1); and (b) a stage of external validation made with the help of a study of its reproducibility measured by the test–retest correlation coefficient [19].

RESULTS

The curves obtained from the mean daily indices of mucositis (DIM) over 21 days (Figs 1 and 2) have a parallel evolution, characterised by a progressive rise from day 1, a maximal intensity between day 7 and day 10, and a rapid decrease from day 11, with a return to the normal level at day 20. The maximal values are reached on day 8 whatever the mode of calculation. The introduction of the subjective and the functional signs in the appreciation of the severity of mucositis does not modify the evolution scored by clinical changes, except for days 9 and 10 of the maximal intensity. During the 21 days of observation, no signs of herpes or candidosis were recorded for any patient.

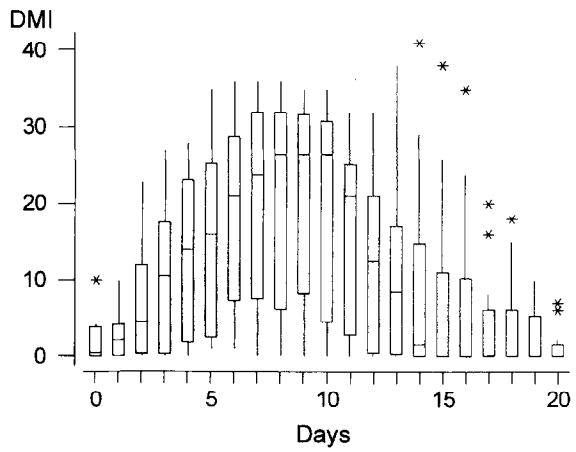

Fig. 1. Box plots of mean daily indices of mucositis including subjective and functional items over 21 days.

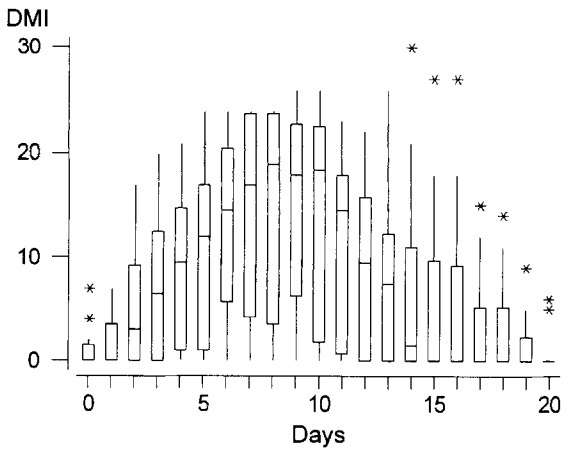

Fig. 2. Box plots of mean daily indices of mucositis without subjective and functional items over 21 days.

Table 4.

	Cumulative scores of mucositis (CSOM)	Daily cumulative indices of mucositis (DCI)
Without subjective items	158.25 (27.13)	7.53 (1.29)
With subjective items	225.75	10.75 (1.79)

Table 6. *Mean numbers of days of mucositis (SD), during* 21 *days as function of grade*

Grade 0	Grade 1	Grade 2	Grade 3
10.92 (5.43)	3.25 (2.18)	4.42 (2.68)	2.42 (2.81)

Even though all of the patients showed signs of mucositis, the means of the cumulative scores of mucositis (CSOM) and of the daily cumulative indices (DCI), with or without subjective items for the 14 patients examined (Table 4) showed, nevertheless, a large diversity, ranging from 18 to 476 with a mean of 225.75 (standard error: 37.5). This same disparity was observed using the DCI index of mucositis for which the mean over 21 days and for 14 patients was found to be 10.75 (standard error: 1.79) with extreme values ranging from 0.85 to 22.67. Comparison of the distribution of mucositis according to the maximum grade attained during the period of observation (Table 5), and as a function of the number of days (Table 6) shows that more than 70% of the patients suffered from grade 2 or grade 3 mucositis for a mean duration of 7 days. The mean consumption of morphine, varied between 0 and 56 cgs per patient and the number of days of morphine administration varied from 0 to 13 days over the observation period.

The harmony of the new scoring system was examined for its internal consistency and the test–retest reliability. The measures of internal consistency (Cronbach's coefficient alpha) were from 0.80 to 0.97, depending on the day of observation (day 0: 0.85; day 8: 0.97; day 20: 0.80) showing that the items were highly interrelated, as well as the index considered as a whole (over 21 days, $\alpha = 0.97$). Score variations of mucositis (reproducibility analysis) were evaluated by comparing the scores attributed by different medical staff members to 8 randomly selected patients with moderate or severe mucositis, on the same day. In order to obtain a linear regression analysis, the results were regrouped in pairs, composed of two successive scores. Variations between the consecutive scores were also examined. Variations in scores of mucositis given by the different examiners remained within acceptable limits, characterised by a significant correlation ($r = 0.97$, $P < 0.001$) between successive scores of mucositis.

DISCUSSION

Many scoring systems have been proposed to evaluate the action of diverse treatments on the appearance and evolution of oral mucositis. They can be divided into two groups: (a) general mucositis rating scales which score in 4 or 5 grades the general status of the oral cavity [15, 20, 21], and (b) scales with multiple variables scoring individually a certain number of parameters which are calculated to give a cumulative level of severity [8, 22–25].

Table 5. *Distribution of mucositis as a function of the maximum grade attained during the period of observation* (21 *days*)

Grade	Score	Number of Patients
Grade 0	1–5	1
Grade 1	6–15	3
Grade 2	16–30	6
Grade 3	31–45	4

The principal advantage of general mucositis rating scales resides in their performance, patient evaluation being simple and rapid. The 5-grade WHO scale [20] combines observation of objective clinical problems (erythema and ulcerations) and subjective functional sensations (pain and feeding habits). The Western Consortium for Cancer Nursing Research Scoring System [25] is a 4-grade scale, each grade being characterised by detailed descriptions of problems tending to arise simultaneously with increasing degrees of severity. These scoring systems are, however, crude and imprecise and have progressively given way to multiple variable scales created to obtain scores giving a more precise and more detailed appreciation of the state of the oral cavity. After early scales destined to appreciate the efficacy of hygiene protocols, other scoring systems have been created for the evaluation of chemotherapy- and radiotherapy-induced mucositis [26] or preparatory regimens for bone marrow transplantation [9, 22–24, 27, 28].

Most of the recent scales privilege items linked to clinical modifications, taken as a whole [28] or on precise anatomical zones (7 for Weisdorf *et al.* [9], and 13 for Schubert *et al.* [4]). Scores are evaluated either qualitatively on scales ranging from 0 to 2 or 3 with reference to predetermined clinical descriptions, or quantitatively by measuring the surface of the lesions. Functional and subjective parameters can also be taken into consideration: modification of salivary consistency and flow, swallowing, voice quality, oral hygiene. The appreciation of these subjective parameters can be left to the examiner, or confided to the patient, thanks to the utilisation of analogical scales. Donnelly *et al.* [28] presented a scale of daily measurements in which clinical signs and most evident symptoms were evaluated in four grades, the values obtained being added up to obtain a total daily score permitting follow-up of the progression and evolution of mucositis. Evaluation from 0 to 3 (absent, slight, moderate, severe) of three clinical items: lesions, erythema, oedema and one functional item, dysphagia, allowed a daily mucositis score (DMS) ranging from 0 to 12 to be obtained. This DMS also provides a global number of days of mucositis and a mean per patient (17 days for Donnelly *et al.*) [28]. The Walsh system [24] is a multiple variable scale utilising a panel of 10 items involving: (1) the clinical aspect of five anatomical zones (lips, tongue, buccal mucosa, hard and soft palate, gingiva), (2) functional problems (voice, swallowing, saliva), and (3) oral hygiene, classified from 0 to 2 from predetermined criteria, as well as pain, classified by the patient from 0 to 3. Patients were examined 3 times a day and the daily total obtained (ranging from 0 to 21) can be plotted on a predetermined

4-stage scale of mucositis, similar to the most frequently used scales [29].

The scoring system for oral mucositis proposed in this study combines a group of 12 clinical items distributed in four distinct anatomical zones and four functional and subjective items appreciated by the examiner during 21 days (talking, salivary function, swallowing and pain). The values obtained can be used with or without subjective signs, without radial transformation of the slope of the daily curves. The 12 measured objective items may overwhelm the four symptomatic and functional scores which represent fewer variables. It could explain that the combined score parallels that of the mucositis score. However, a number of factors can influence subjective complaints and functional performance without any correlation with the status of the oral cavity. The combining of more numerous subjective assessments could provide an inappropriate rating of the tissue damage. Finally, the parallel progression of the items, described in the evaluation guide, could counterbalance the relative value granted to some clinical changes, such as ulcerations for example. The presence of these injuries comes most often with other increasing clinical symptoms, and the summation of scores could support the underlying assumption that each of the variables are equally important.

The mean peaks are situated on both curves on day 8 corresponding to most of the reported results. For Schubert *et al.* [4], using his Oral Mucositis Rating Scale to evaluate autologous or allogeneic transplant patients, the maximum clinical symptoms occur between days 7 and 11. This maximum value was found on days 7 and 8 for Donnelly *et al.* [28], on day 11 for Kolbinson *et al.* [6], on day 12 for Seto *et al.* [15]. A more precise examination of the daily results obtained in this study shows that, although all of the individual curves of evolution have a comparable profile between days 0 and 20, their maximum value can be situated between day 4 and day 14. Utilisation of cumulative scores of mucositis (CSOM) combining the addition of 21 daily indices permits a better appreciation of the severity of the mucositis supported by the patient, by combining intensity and duration. Although all of the patients showed signs of mucositis, the scores show a large diversity, ranging from 18 to 476 with a mean of 225.75 (S.E.: 37.50), confirming that, with the same treatment, patient variations play a very important role. The same disparity is observed using the daily cumulative index of mucositis, for which the mean over 21 days for 14 patients is 10.75 (7.53 without consideration of subjective items) with extreme values ranging from 0.85 to 22.67.

The possibility of transcribing the daily indices (DIM) obtained in the grade of mucositis thanks to the predetermined analogical scale, can permit comparison with experiments utilising general mucositis rating scales. It can also be ascertained that over 21 days, in the experimental conditions of this study, patients have no mucositis (grade 0) during a mean of 10 days, grade 1 mucositis for 3 days without great clinical incidence, grade 2 for 5 days, and grade 3 for 3 days, thus life-threatening mucositis during a mean of 8 days, requiring set-up of secondary palliative measures. Although pain and functional problems have important clinical implications, their quantitative analysis is difficult. Pain, in particular, is a complex experience for which the patient's subjective expression is not directly linked to verified clinical alterations. Some patients express feelings of intense oral pain in spite of the presence of modest buccal changes. Others, presenting severe and extensive lesions, complain only of minimum pain and functional problems. In this study, whereas the mean consumption of morphine over 21 days was 14.71 ± 17.00 cgs, the values ranged from 0 to 56 cgs. The absence of apparent concordance between the cumulative scores of certain patients and their consumption of morphine translates this subjectivity. This is the reason why some recent scales [26, 27] minimise or eliminate these variables from the composition of their score.

It is evident that none of the scales presently available for measuring mucositis can be considered ideal in all possible situations. Each scale having its advantages and disadvantages, the final selection resides in the nature of the information to be obtained. A general mucositis rating scale can satisfy the need for a general clinical appreciation. For the research of direct clinical improvement, a more or less complex scale including an appraisal of eventual functional improvements can thus be selected. Specific research, more closely centred on the secondary toxicity of a product or therapy, could justify the utilisation of a more complex scale, devoted to the measurement of clinical changes.

The scoring system presented here confirms that mucositis changes its character every day, justifying the need for daily surveillance in the study of morbidity linked to regimens conditioning bone marrow transplantation. The daily index of mucositis (DIM) offers a simple and efficient means to study the epidemiology and the impact of prophylactic and therapeutic measures on its appearance and evolution. The proposed scale has been constructed from a selection of clinical descriptions of oral mucosal changes known to appear in patients receiving an autologous bone marrow transplantation. These descriptions have been distributed on a 4-grade scale (0 to 3) permitting a realistic and consistent appreciation of mucosal changes. These grades do not consist of a subjective appreciation of the same phenomenon (for example: 1 = slight reaction or 3 = severe reaction), but correspond to a precise clinical and objective description of the severity of the phenomenon, appreciated through a daily index of mucositis (DIM). The incorporation or the withdrawal of subjective signs can permit the plotting of two curves from which the correlation brings an adequate support for the validity of an index which could be affected by patient-linked variables, such as mental health or drug absorption. As the patients were all being examined over the same number of days, daily indices can also be added up for each patient, giving rise to cumulative scores of oral mucositis (CSOM) with or without subjective signs. The use of the means of these cumulative scores permits total inter-group statistical comparisons.

The scoring method proposed here for oral mucositis seems to offer the following advantages: (1) division of the oral mucosa into several zones for clinical measurements using predetermined descriptive criteria for pathological changes; (2) the possibility to include subjective measurements of functional problems and pain, (3) daily examinations to better circumscribe individual and systemic variations, (4) cumulative scores over 21 days to account for duration of mucositis and permit quantification of the real intensity of the side effect (intensity and duration), and (5)

possibility of a simplified comparison with 4-grade scales by a predetermined analogical equivalence. After having reviewed the different available methods of appreciation of oral conditions, this new instrument seems to correspond to the three principal objectives: clearness of expression, good reproducibility, efficacy in accomplishment. The scale proposed here should allow a simple adaptation for different reasons, needs or goals necessitating the appraisal of mucositis.

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