LETTER TO THE EDITOR

USE OF SODIUM HYALURONATE AND SYNTHETIC AMINO ACID PRECURSORS OF COLLAGEN FOR THE SYMPTOMATIC TREATMENT OF MUCOSITIS IN PATIENTS UNDERGOING HAEMATOPOIETIC STEM CELL TRANSPLANTS

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Oral mucositis (OM) may occur in up to 100% of patients undergoing condition regimen to hematopoietic stem cell transplant (HSCT). From the patient's perspective, OM is one of the most debilitating side effects of transplantation. It is commonly thought that oral hygiene can modify the incidence and severity of oral mucositis, therefore professional oral health care (POHC) is recommended prior to conditioning regimen for HSCT. A new strategy for the treatment of OM is sodium hyaluronate (SH) combined with amino acid precursors of collagen (Aas) (Mucosamin®). SH is a mucoaderent polymer acting as a mechanical barrier and pain reliever. Furthermore, it allows prolonged contact of the product with the mucous membrane. In this study, a total of 68 adult patients due to undergo HSCT for allogenic and autologous transplant were enrolled at the Stem Cell Transplant Unit. The patients were divided into two groups. One group was treated with POHC before HSCT and applications of Mucosamin® during the recovery after transplantation. The second group served as controls, with the usual treatment of Clorexidine 0.20% adopted by the department. After HSCT the same clinician, an expert in oral medicine trained for the clinical trial, evaluated symptoms of the patients' mucositis of both groups every day. The treated patients developed less severe OM, therefore Mucosamin® seems to have a protective role against the more severe phases of mucositis. The maximum OM pain, measured with the VAS scale, was higher in patients who did not use Mucosamin®. In the treated group OM resolved sooner than in the control group.

To the Editor,

Mucositis is a common sequel of radio- (DXR) and/or chemo-(CXR)-therapy in patients with cancer, with direct and significant impact on the quality of life and cost of care. Mucositis also affects survival, because of the risk of infection. (1) Ulcerations in the oro-esophageal and gastrointestinal mucosae resulting in pain, dysphagia, diarrhea and dysfunction, depending on the tissue affected, are typical symptoms of mucositis. In patients undergoing high-dose conditioning regimen for hematopoietic stem cell transplant (HSCT), the risk of oral and gastrointestinal mucositis is up to 100%. After HSCT, in addition to OM, therapy-induced myelosuppression causes significant risk of bacteremia and sepsis from oral microorganisms resulting in increased days of fever, antibiotic use and hospitalization (1). From the patient's

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perspective, OM is one of transplantation's most debilitating side effects (2).

The pathogenesis of OM associated to chemotherapy or radiation results from nonspecific direct effects of radiation or chemotherapy on rapidly dividing mucosal basal cells; the initial phase involves direct damage to DNA and other cellular components that occurs immediately after exposure to radiation or chemotherapy (3). The ulcerated surface can be colonized by oral bacteria, resulting in production of toxins, additional inflammatory cytokines and angiogenic factors, which may cause bacteremia and sepsis in the presence of granulocytopenia (4).

Most reports concerning dental management during HSCT recommend mouth rinses or use of antibiotic pastilles for oral decontamination (5), however, these have been found ineffective in preventing OM (6). The microorganism in the mouth contains hundreds of species of bacteria as complex, mixed, interdependent colonies in biofilms, and adheres to the teeth (7). The biofilm protects the adhering bacteria against environmental attacks. Antibiotics or oral rinses, without the mechanical removal of plaque (i.e. tooth brushing), are unable to penetrate the plaque to reach the linking film bacteria (8, 9). Almost all patients understand that regular brushing is very important for oral hygiene, but few of them brush properly. This is why professional and repeated instruction on brushing is critical for controlling plaque.

A new strategy for the treatment of OM is the sodium hyaluronate (SH) combined with amino acid precursors of collagen (Aas) (Mucosamin®). SH is a mucoaderent polymer acting as a mechanical barrier and pain reliever. As induce, the production of collagen and glycosaminoglycan by fibroblasts, a key element for the recovery of the tissue during the healing process, as demonstrate in a study by Colella (10).

The aim of the study was to evaluate the clinical efficacy of Mucosamin® in wound healing and pain management in OM after HSCT. We also evaluated the importance of professional oral hygiene by a dental hygienist to reduce the severity of OM in combination with the Mucosamin®.

MATERIALS AND METHODS

Patient characteristics

We designed a case control study. A total of 68 adult patients (average age 51, range 22-70) prepared for HSCT for allogenic and autologous transplant were recruited at the Stem Cell Transplant Unit, Città della Salute e della Scienza of Turin, and in the Oral Surgery Department, Dental School, University of Turin.

Criteria for inclusion were: i) age> 18 years; ii) due for HSCT; iii) informed consent and ability to complete the trial. Exclusion criteria included: i) known allergy to any of the components of the compound; ii) inability to check results; iii) patients with systemic disease, other than hematological malignancies, which impair wound healing (i.e. diabetes); iv) muco-cutaneous diseases; v) not been able/willing to give informed consent.

This study was approved by the Institutional Review Board of our Center and conducted according to the Declaration of Helsinki and all patients provided written informed consent to participate in the study.

Treatment plan

We asked each patient to complete: i) a survey regarding oral hygiene to assess the individual knowledge of the correct oral hygiene procedures and patient compliance; ii) a survey regarding radio/chemotherapy and OM to investigate the level of knowledge of the patient on interactions between drugs, radio and chemotherapy on the oral cavity, and of mucositis.

Group A included patients sent by the Haematology Departments to the Dental School to eliminate infectious foci of the oral cavity, which is mandatory in order to receive the suitability for transplantation. The patients underwent careful intra and extra oral examination, and radiological investigations to assess the need for dental treatment, compatible with the timing of transplantation. All patients in Group A had a periodontal chart analysing: i) O'Leary Index Plaque (Plaque Control Record); ii) Bleeding index; ii) Periodontal Screening and Recording Index (PSR) (11). Each of them received a complete session of professional oral hygiene, with scaling and root planing. At the end of each session, patients were educated on the correlation between oral health and OM and possible complications, and were instructed on correct home oral hygiene procedures and were motivated to maintain such

procedures during the period of hospitalization. Patients who presented periodontal problems underwent a second hygiene session for scaling and root planing of pathological sites. Patients who required further dental treatment, such as conservative treatment, endodontic or extraction, were re-motivated to maintaining a high standard of oral hygiene during the session in which they were given the suitability for transplantation. Furthermore, patients in group A were instructed by a single doctor to recognize symptoms of OM and to apply SH-AAs based spray on these lesions 3-4 times a day after a meal and oral hygiene, keeping the liquid *in situ* for at least 2 minutes and to avoid drinking, eating and rinsing the mouth for at least one hour. The same doctor controlled the patients during hospitalization in order to recognize initial and advanced signs of OM and to remind patients how to apply the compound.

Patients in Group B were recruited directly in the Haematology department, depending on availability of patients, but they were not visited in Dentistry department. They were not involved in dental hygiene sessions and did not receive Mucosamin® but they received the usual treatment of Clorexidine 0.20%. Also, we asked the patients whether they had undergone a session of dental hygiene during the 6 months prior to the transplantation.

Starting the day after HSCT, the same expert trained for the clinical trial, evaluated patients of both group every day, during hospitalization. The evaluation included three scores for OM: i) WHO mucositis scale ranging from 0= no symptoms; 1=soreness, erythema; 2=erythema, ulcers but able to eat solids (12); 3=ulcers but required liquid diet; 4=oral alimentation not possible; ii) Visual analogue scale (VAS) ranging from 0=no pain to 10=worst pain in the world (13); iii) OMAS scale (Oral Mucositis Assessment Scale): Oral cavity for Ulceration 0=No lesion; 1= Lesion <1 cm^2; 2=Lesion 1 to 3 cm^2; 3=Lesion >3 cm^2; Oral cavity for Erythema: 0= None; 1=Not severe; 2=Severe (14).

According to WHO and OMAS scales, we divided the lesions into two groups: light mucositis (WHO grade 1 and 2, OMAS grade 1) and severe mucositis (WHO grade 3 and 4, OMAS grade 2 and 3). Primary indicators of mucositis were the degrees of ulceration and redness measured in specific sites in the mouth. Secondary indicators included oral pain, difficulty swallowing and the ability to eat as assessed by the patient. A single score is not produced from this scale, rather a score for ulceration and redness based on different locations in the mouth are used.

Statistical analysis

The results included continuous and categorical variables. The former are reported as mean and standard deviation. Nonparametric tests were used: the Wilcoxon signed-rank test for comparisons of two correlated samples involving matched pairs and the Mann-Whitney test for comparisons of two independent distributions. Categorical variables, reported as count and percentage, were arranged in cross-correlation tables and compared using the χ^2 test with the Yates correction when all expected values were higher than 5 or Fisher's exact test. Statistical significance corresponded to a probability less than 0.05 that differences could be ascribed to chance.

RESULTS

Patient characteristics

Table I shows the demographic details of the patients and other baseline information. The sample is homogeneous for age and sex. All patients were candidates for HSTC for hematological malignancies. Thirty-two patients were in group A and 28 in group B. Eight patients previously enrolled in the study did not proceed with the transplant because of their poor general health condition, death or lack of available donor. In both groups, the predominant pathology was acute myeloid leukemia. Two patients in group A and 4 patients in group B were treated with Total Body Irradiation (TBI) and chemotherapy while the other patients underwent a conditioning regimen of only high-dose chemotherapy. Three patients in group A and 6 in group B did not develop OM. Patients who did not developed mucositis, were excluded from the results.

Treatment administration

There was no indication of any intolerance to the product. Based on the interview we conducted during the study, all patients except one, liked the consistency of the product in the mouth and they were able to use it during the day based on the instructions of the dentist. There were no differences in OM location among patients receiving Mucosamin® (group A) and in those who did not (group B).

Patients in group A who used Mucosamin® on initial lesions developed less severe OM, while

Table I. *Patients' baseline characteristics.*

		Group A	Group B
	no.	32	28
Sex	M	14 (49%)	14 (50%)
	F	18 (51%)	14 (50%)
Age	< 30 y.	3 (9%)	2 (6%)
	31 - 40 y.	5 (16%)	1 (16%)
	41-50 y.	9 (28%)	6 (23%)
	51 - 60 y.	10 (31%)	9 (32%)
	> 60 y.	5 (16%)	10 (33%)
Transplant	Autologous	5 (16%)	6 (26%)
	Allogenic	27 (84 %)	22 (74%)
Conditioning Regimen	TBI	2 (6 %)	4 (14%)
	Non TBI	30 (94 %)	24 (86%)
Pathology	Acute Myeloid Leukaemia	8 (25 %)	9 (34%)
	Chronic Myeloid leukaemia	4 (13%)	1 (3%)
	Hodgkin's Lymphoma	3 (9%)	1 (3%)
	Non Hodgkin's Lymphoma	8 (25%)	7 (26%)
	Myelofibrosis	1 (3%)	0 (0%)
	Multiple Myeloma	2 (6%)	6 (23%)
	Myelodysplastic Syndrome	6 (19%)	4 (10%)

M: Male; F: Female; TBI: Total Body Irradiation

Table II. *Evaluation of gravity of oral mucositis related to use of Mucosamin and a session of POHC.*

	Light Mucositis	Severe Mucositis	
Group A	20	9	**P=0.02 * RR=0.49 ***
Group B	8	14	
Group A1	19	7	**P=0.006 * RR=0.38 ***
Group CTRL	5	12	

*Group A= Mucosamin group; Group B=No Mucosamin group. Group A1 (Mucosamin and oral hygiene within 6 months from HSTC) Group CTRL (No Mucosamin and oral hygiene more than 6 months from HSTC). P<0.05 *statistically significant.*

patients who did not use the compound developed more severe and painful lesions; this result is statistically significant (P=0.02*). Mucosamin® seems to have a protective role against the more severe phases of mucositis (Table II).

The maximum OM pain, measured with the VAS scale, was higher in patients who did not use Mucosamin®: maximum VAS average in Group A 4.42 (DS ±2.61) and in Group B 4.77 (DS ±3.33). In group A, OM resolved sooner than group B, although the difference was not statistically significant: the average duration in Group A was 9 days (DS ±7), and in Group B 11 days (DS ±16).

Role of professional oral health care (POHC)

To evaluate whether there is a strengthening of the results with the association between Mucosamin® and POHC, patients of group A who had POHC in the 6 months prior to HSTC (Group A1) were compared to patients who neither used Mucosamin® nor had POHC within the 6 month before HSTC (Group CTRL) (Table II).

Patients who had a more recent session of POHC in association with Mucosamin® developed significantly lighter OM. Use of Mucosamin® associated to oral hygiene seems to have a synergy that protects the oral cavity from the highest grades of OM.

DISCUSSION

The present study showed that patients who used Mucosamin® on initial lesions during hospitalization had a lower risk of developing the highest grades of mucositis. Mucosamin® appears to play a role in reducing the severity and the duration of OM, as most of the patients treated had a less severe and less painful type of lesion (grade 1-2) while the control group who has not used the compound, had a predominance of more painful lesions (grade 3-4), statistically confirmed.

Patients educated and motivated on the importance of oral hygiene had reduced mucositis severity and duration, therefore a session of POHC before HSTC, as well as information on the correlation between oral hygiene and mucositis, was effective in maintaining good oral hygiene by patients. These observations are in agreement with several studies that emphasize the importance of effective control of plaque, because oral health conditions are among the most important risk factors for the development of mucositis (15). Our results also corroborate the importance of the role of the dental hygienist and confirm the necessity of creating a team hematologist-dentist-hygienist for management of complications of the oral cavity in patients undergoing bone marrow transplant. Furthermore, when Mucosamin® and POHC are associated, the risk of developing higher grades of mucositis is strongly reduced.

According to our study, the use of Mucosamin® can influence the type and severity of oral mucositis, allowing patients to have a better quality of life. The efficacy of Mucosamin® in decreasing pain and accelerating wound healing relies on its ability in tissue repair, activation and modulation of inflammatory responses, promoting the proliferation and cell migration, angiogenesis, increased re-epithelialization, born of basal keratinocytes and collagen deposition, thus acting on ulcerative mucositis by forming a protective layer.

The analysis of our data showed that the combination of a recent POHC, appropriate oral hygiene during hospitalization and use of Mucosamin® exponentially reduces the severity/ duration of mucositis, as well as the discomfort of the patient. Finally, we can say that using Mucosamin® also determines a reduction in the extent of the lesions induced by chemotherapies. This spray based on hyaluronic acid and amino acids can be a valid therapeutic aid in the treatment of mucositis.

REFERENCES

1. Scully C, Sonis S, Diz PD. Oral mucositis. Oral Dis 2006; 12 (3):229-41.
2. Rubenstein EB, Peterson DE, Schubert M, et al. Clinical practice guidelines for the prevention and treatment of cancer therapy-induced oral and gastrointestinal mucositis. Cancer 2004; 100(9 S):2026-46.
3. Sonis ST. Oral mucositis in cancer therapy. J Support Oncol 2004; 6(S 3):3-8.
4. Kashiwazaki H, Matsushita T, Sugita J, et al.

Professional oral health care reduces oral mucositis and febrile neutropenia in patients treated with allogeneic bone marrow transplantation. Support Care Cancer Off J Multinatl Assoc Support Care Cancer 2012; 20(2):367-73.

5. Weisdorf DJ, Bostrom B, Raether D, Mattingly M, Walker P, Pihlstrom B, et al. Oropharyngeal mucositis complicating bone marrow transplantation: prognostic factors and the effect of chlorhexidine mouth rinse. Bone Marrow Transplant 1989; 4(1):89-95.
6. Bondi E, Baroni C, Prete A, et al. Local antimicrobial therapy of oral mucositis in paediatric patients undergoing bone marrow transplantation. Oral Oncol 1997; 33(5):322-26.
7. Pihlstrom BL, Michalowicz BS, Johnson NW. Periodontal diseases. Lancet 2005; 366(9499):1809-20.
8. Landa AS, van der Mei HC, Busscher HJ. Detachment of linking film bacteria from enamel surfaces by oral rinses and penetration of sodium lauryl sulphate through an artificial oral biofilm. Adv Dent Res 1997; 11(4):528-38.
9. Hellström MK, Ramberg P, Krok L, Lindhe J. The effect of supragingival plaque control on the subgingival microflora in human periodontitis. J Clin Periodontol 1996; 23(10):934-40.
10. Colella G, Cannavale R, Vicidomini A, Rinaldi G, Compilato D, Campisi G. Efficacy of a spray compound containing a pool of collagen precursor synthetic aminoacids (l-proline, l-leucine, l-lysine and glycine) combined with sodium hyaluronate to manage chemo/radiotherapy-induced oral mucositis: preliminary data of an open trial. Int J Immunopathol Pharmacol 2010; 23(1):143-51.
11. Landry RG, Jean M. Periodontal Screening and Recording (PSR) Index: precursors, utility and limitations in a clinical setting. Int Dent J 2002; 52(1):35-40.
12. López-Castaño F, Oñate-Sánchez RE, Roldán-Chicano R, Cabrerizo-Merino MC. Measurement of secondary mucositis to oncohematologic treatment by means of different scale. Review. Med Oral Patol Oral Cir Bucal 2005; 10(5):412-21.
13. Price DD, McGrath PA, Rafii A, Buckingham B. The validation of visual analogue scales as ratio scale measures for chronic and experimental pain. Pain 1983; 17(1):45-56.
14. Sonis ST, Oster G, Fuchs H, et al. Oral mucositis and the clinical and economic outcomes of hematopoietic stem-cell transplantation. J Clin Oncol Off J Am Soc Clin Oncol 2001; 19(8):2201-5.