Oral Platelet Gel Supernatant Plus Supportive Medical Treatment Versus Supportive Medical Treatment in the Management of Radiation-induced Oral Mucositis

A Matched Explorative Active Control Trial by Propensity Analysis

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Objectives: In this active control trial, the rate of radio-induced WHO grade 3/4 oral mucositis and the change in quality of life, assessed by OMWQ-HN, were measured in subjects with head and neck cancer treated by platelet gel supernatant (PGS) and supportive medical treatment versus subjects treated by supportive medical treatment alone.

Materials and Methods: Eighty patients with nonmetastatic head and neck cancer underwent curative or adjuvant radiotherapy. All patients underwent supportive medical treatment and/or PGS at the beginning and during radiotherapy. Sixteen patients received PGS in association with supportive medical treatment. To obtain 2 groups virtually randomized for important clinical characteristics subjects were matched, by propensity analysis, with a group of subjects (64 patients) treated with supportive medical treatment alone.

Results: Subjects treated with standard supportive treatment experienced significant higher WHO grade 3/4 toxicity (55%; 35/64) than subjects treated by PGS (13%; 3/16). The reduced toxicity found in PGS group paralleled with the evidence that they developed later symptoms with respect to controls. The Cox proportional hazard model indicated that patients treated with standard supportive medical treatment experienced 2.7-fold increase (hazard ratio = 2.7; 95% confidence interval, 1.3-5.7) in the occurrence of WHO grade 3/4 toxicity. PGS group significantly experienced higher quality of life than control groups as measured by OMWQ-HN. A significant decrease in the opioid analgesics usage was found in the PGS group.

Conclusions: These preliminary data should be interpreted with caution and could serve as a framework around which to design future trials.

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ISSN: 0277-3732/17/4004-0336
DOI: 10.1097/COC.0000000000000177

Key Words: oral mucositis, platelet gel supernatant, head and neck cancer, radiotherapy, toxicity

(*Am J Clin Oncol* 2017;40:336–341)

Radiation-induced oral mucositis (OM) is an acute complication of patients with oropharynx, hypopharynx, and salivary glands malignant tumors.[1] Because of the OM severity patients often stop feeding and, as consequence, they are forced to receive nutrition through a gastrostomy tube or intravenous line with a consequent weight loss[1–3] and unplanned breaks during radiotherapy (RT).[4] To date, there are no standard medical treatments that have proven a substantial preventive action in RT-induced OM. Nutritional support, pain control, oral decontamination, palliation of dry mouth, management of oral bleeding, and therapeutic interventions based on the use of cryotherapy, growth factors, anti-inflammatory agents, antioxidants, and low-level laser therapy are currently used in OM management with unsatisfying clinical results.[5,6] Platelets, in addition to regulating homeostasis, release several factors that promote tissue repair, angiogenesis, and inflammation.[7–11] On the basis of this evidence, platelet supernatant, the supernatant obtained after the activation of coagulation of platelet concentrate, has been used for the topical therapy of various clinical conditions, including wounds and soft tissue injuries.[11–20] Recently the platelet gel supernatant (PGS) was used on a patient suffering from severe RT-induced OM that was unresponsive to conventional supportive therapies. In this patient the oral application PGS positively affected the course of radio-induced OM.[21] To the best of our knowledge, there is no scientific evidence in literature investigating the use of oral PGS in the management of chemoradio-induced OM in subjects suffering from head and neck cancer (HNC). So, this study was designed to examine the effects whether the addition of PGS to standard supportive treatment can favorably affect clinical management of radio-induced OM in subjects suffering from HNC compared with standard supportive treatment alone.

MATERIALS AND METHODS

Patient Selection

In this active control trial, patients receiving RT with or without chemotherapy for HNC and treated by PGS were

prospectively recruited and compared with a historical pool of patients selected by the propensity score analysis. This statistical strategy allowed us to obtain 2 groups of patients virtually randomized for important clinical characteristics (see the Statistical methods section). Subjects with nonmetastatic, histologically confirmed malignant neoplasm located in the oropharynx, salivary glands, and oral cavity were included in this study. Lymph node involvement was allowed. All patients received curative or adjuvant RT, both as single treatment or in association with chemotherapy. Other inclusion criteria included: age 18 years and above; life expectancy >6 months; adequate bone marrow, liver, and renal function based on laboratory assessments performed within 7 days before start of study treatment; negative serum or urine beta-HCG pregnancy test within 7 days before the first administration of study treatments for women of childbearing potential. Exclusion criteria included: previous RT for carcinoma of the head and neck; previous or concurrent cancer within 5 years before study entry; and proven bacterial or fungal infection of the oral cavity at the start of RT. The clinical characteristics of 2 groups matched by propensity analysis were shown in Table 1. This pilot study was approved by the ethical committees of the participating institution. Written informed consent was obtained from each patient.

TABLE 1. Patients' Characteristics After Propensity Matching Analysis

Characteristics	PGS Group (N = 16) (n [%])	Control Group (N = 64) (n [%])	*P*
Sex			
Male	10 (62.5)	39 (61)	0.863
Female	6 (37.5)	25 (39)	
Age (y)			
Mean ± SD	56.2 ± 8.9	57.3 ± 6.1	0.560
Site			
Oral cancer	6 (37.5)	21 (33)	0.846*
Oropharynx	5 (31.2)	25 (39)	
Salivary gland	5 (31.2)	18 (28)	
Histology			
Squamous	12 (75)	43 (67.2)	0.810*
Adenocarcinoma	2 (12.5)	9 (14)	
Mucoepidermoid carcinoma†	2 (12.5)	12 (18.8)	
Stage grouping			
I	4 (25)	20 (31.2)	0.973*
II	5 (31)	18 (28.1)	
III	4 (25)	20 (31.2)	
IV	3 (19)	6 (9.5)	
Radiotherapy			
Adjuvant (Gy) PTV1, 66‡ PTV1, 60§ PTV2, 50-54‖	12 (75)	47 (73.4)	0.849
Definitive (Gy) PTV1, 70¶ PTV2, 60# PTV3, 50-54**	4 (25)	17 (26.6)	
Chemotherapy††			
Yes	13 (81)	45 (70.3)	0.573
No	3 (19)	19 (29.7)	

*Bonferroni adjustment for more than 2 comparisons.
†Salivary glands tumors.
‡PTV1: high-risk region or postoperative bed.
§PTV1: intermediate-risk region.
‖PTV1: lower risk region.
¶PTV1: gross disease region.
#PTV1: high-risk subclinical region.
**PTV1: lower risk subclinical region.
††Platinum-based chemotherapy.

Supportive Medical Treatments

All patients were instructed to maintain the adequate hydration and nutritional status by suggesting nonirritating, nutrient dense foods and fluids accordingly with the nutritional guidelines for mucositis symptoms management.[22] Additional measures (good oral hygiene, avoidance of spicy, acidic, hard, and hot foods and beverages, use of mild-flavored toothpastes and saline-peroxide mouthwashes 3 or 4 times per day, antifungal agents) were used for minimizing OM. Patients belonging to PGS group were instructed by researchers to use PGS 3 times a day (1 hour before breakfast, lunch, and dinner), including weekends, and to refrain from any oral intake for 30 minutes after dosing. Platelet suspension gel was prepared as previously described.[21,23] Patients were monitored during the RT treatment and for the 7 weeks after the end of RT. All supportive medical treatments including PGS were administered beginning on the first day of RT or RT-chemotherapy (CHT) course and was stopped at the end of radiation course.

Oncological Treatments

Irradiation was applied as 3D-conformal RT. For planning of the RT each patient received a computed tomographic scan in an individually adjusted precision immobilization device. In the definitive setting the gross tumor volume was defined as the tumor and any nodes that were either: 1 cm or more in short axis, necrotic, PET positive (where applicable), or biopsy proven to contain tumor. A 5 mm expansion was added to create the clinical target volume (CTV) CTV70, with a further 5 mm to create the planning target volume (PTV) PTV70 (dose of 70 Gy in 35 fractions). An optional high-risk nodal volume (CTV60) was defined for areas of uncertainty (eg, suspicious nodes not meeting the criteria above). A 5 mm margin was added to create the PTV60, (dose of 60 Gy in 30 fractions). A lower risk nodal volume (CTV50-54) was defined to include the standard lymphatic drainage sites. A 5 mm margin was added to create the PTV50-54 (dose of 50 to 54 Gy in 25 to 27 fractions). In the adjuvant setting the highest, intermediate, and the lower risk volumes were defined as for definitive setting. The only difference with respect to curative treatment was the dose delivered to the highest risk volume that was of 66 Gy. The treatments were conducted on a linear accelerator (Elekta Sinergy) of 6 to 10 MV with conventional isocentric techniques. All plans were normalized to ensure that 95% of each PTV was covered by 95% of the prescription dose for that volume. Daily cone-beam computed tomographic scans was made during treatment to verify correct positioning of patients before each RT fraction. Concurrent single-agent cisplatin was the primary choice of chemotherapeutic agent. Two regimens were used: 2 to 3 cycles (100 mg/m^2) of cisplatin on days 1, 22, and 43 or intravenous cisplatin (40 mg/m^2) administered weekly.

Assessment of Toxicity and Adverse Events

Starting with the first day of radiation treatment, 2 trained evaluation team radiation-oncologists independently assessed and documented the mucosal status grading the toxicity according to WHO. When the score of toxicity was discordant the 2 radiation-oncologists reviewed the specific case in consensus. The assessment was performed 3 times weekly (Monday, Wednesday, Friday) and intensified to daily

inspection, when first signs of mucositis were noted by the radiation-oncologists. Safety outcome measures also included monitoring of treatment-emergent adverse events on physical examination, vital signs, clinical laboratory safety tests, local tolerability, and documentation of any serious adverse events or deaths on the study.

Quality-of-Life Assessment

To assess the patients' quality of life, a mucositis-specific questionnaire already used to measure OM in subjects with HNC (OMWQ-HN) was used as a comprehensive scale.[24]

Study Endpoints

The primary endpoint was to assess the efficacy of PGS in association with standard supportive medical treatment compared with standard supportive medical treatment alone in reducing the risk for clinically significant OM (WHO grade ≥ 3) in patients receiving RT with or without chemotherapy.

The secondary endpoint was to compare the changes in the quality of life among the patients treated by standard supportive medical treatment or by standard supportive medical treatments in association with PGS. For the primary endpoint the baseline assessment was set the first day of RT. For the secondary endpoint the time frame for reference was set 1 week before RT.

Statistical Methods

The primary null hypothesis of this explorative study was that, for PGS users, WHO grade ≥ 3 OM achieved after radiation treatment should be lower than that achieved after the same treatment in subjects treated by standard medical supportive treatment. The current study was powered to determine a decrease of 35% or greater in the WHO grade ≥ 3 OM for PGS users with respect to nonusers. The literature indicates that from 34% to 57% of patients with HNC and receiving RT with or without chemotherapy experienced WHO grade 3/4 OM.[4] Thus, we set the rate of WHO grade 3/4 OM in controls at 50% (P0 = 50%). Using a 2-sided test and a 5% type I error, with the matched control to case ratio of 1:4, 16 subjects in the PGS groups and 64 in the control group would provide greater than 80% power to detect a decrease of 35% (P1 = 15%). We used an uncorrected χ^2 statistic to evaluate this null hypothesis.

To reduce treatment selection bias and determine treatment effects, a case–control-matched propensity analysis was performed. Multivariate logistic regression was used to calculate the predicted probability of the dependent variables and the propensity score for all observation in the data set. The dependent variables included in the multivariate analysis were listed in Table 1. A 1:4 matched analysis was performed where 1 case was matched to 4 controls. For the matched analysis, differences between matched pairs were evaluated using *t* test for paired data for continuous variables and the McNemar test for binary data. Continuous variables were condensed by means and SD. Differences in continuous variables were analyzed by the Student *t* test or analysis of covariance. Binary variables were condensed as absolute or relative frequencies. Differences in dichotomous variables were analyzed by χ^2 test or Fishers exact test when appropriate.

The odds that a patient treated with PGS in association with standard supportive medical treatments will experience WHO grade 3/4 toxicity as a function of time later than a patient treated by supportive medical treatments alone have been determined by the use of the Cox proportional hazard model.

According to propensity analysis *P*-values <0.05 were considered statistically significant. The SPSS version 13.0 software package was used for all statistical analysis and graphic presentations.

RESULTS

Between October 2012 and January 2014, 35 consecutive patients receiving RT with or without chemotherapy for HNC were screened to be included in the study. Nineteen of the 35 subjects (55%) were excluded as they refused to participate in the study (6/35; 17%), did not satisfy the inclusion criteria (3/35; 9%), and did not match with any subject included in the control group after propensity analysis (10/35; 29%). This group was compared with an historical pool of patients (110 patients) treated between August 2004 and May 2012 with RT with or without chemotherapy for HNC. Sixty-four of the 110 subjects (58%) were included in the study and were used as controls. Eighteen of the 110 cases (16.3%) were excluded as they did not match the inclusion criteria and 28 (25.5%) were excluded as their propensity scores did not match with any of the score of the subjects included in the PGS group.

All patients studied received platinum-based chemotherapy regimens and completed the treatment phase of the study. The platinum doses or regimens were comparable between the 2 treatment groups. Forty-six percent (6/13) in the PGS group and 55.6% (25/45) in the control groups received intravenous cisplatin (40 mg/m^2) administered weekly ($P = 0.753$). Subjects treated with the standard supportive medical treatment, 6% (4/64), 44% (28/64), 48% (31/64), and 6% (4/64) experienced WHO grade 1, 2, 3, and 4 OM, respectively. Subjects treated by PGS in association with the standard supportive medical treatment, 56% (9/16), 25% (4/16), 13% (2/16), and 6% (1/16) experienced grade 1, 2, 3, and 4 OM, respectively (Table 2). Interestingly, when the cutoff of clinically significant toxicity was set at WHO grade 3/4, subjects treated with standard supportive treatment experienced significantly higher toxicity (55%; 35/64) than subjects treated by PGS (13%; 3/16) ($P = 0.012$). The reduced toxicity found in the group of patients treated by PGS paralleled with the evidence that the onset of symptoms occurred at a later time than in subjects who did not use PGS. The Cox proportional hazard model indicated that patients treated with standard supportive medical treatments experienced 2.7-fold increase (hazard ratio = 2.7; 95% confidence interval, 1.3-5.7; $P = 0.0074$) in the occurrence of WHO grade 3/4 toxicity than group treated by PGS in association with standard supportive medical treatments

TABLE 2. WHO Score of Oral Mucosistis Upon Oncological Treatments

Mucositis Severity Graded as Recommended by WHO	PGS Group (N = 16) (n [%])	Control Group (N = 64) (n [%])	*P**
0	0 (0)	0 (0)	1.0
1	9 (56)	4 (6)	< 0.0001
2	4 (25)	28 (44)	0.254
3	2 (13)	31 (48)	0.012
4	1 (6)	4 (7)	1.0
Patients with WHO grade 3 and 4 toxicity	3 (19)	35 (55)	0.012

*Fisher exact test.

(Fig. 1). In addition, patients treated by standard supportive medical treatments alone experienced WHO grade 3/4 toxicity before than PGS users ($P = 0.0074$) (Fig. 1).

During RT, patients treated with PGS experienced a significant lower weight loss (Fig. 2A) and need for feeding tube (Table 3) compared with controls. Patients of both groups were weighted 1 week before RT-CHT (baseline evaluation) and then weekly during RT-CHT. The mean body weight of all patients in each group was determined and it was plotted over time to measure the changes of this parameter during RT. Figure 2A shows that the loss of body weight in PGS users was lower than controls after the sixth week of treatment and this difference increased over time reaching the highest feet apart at the end of radiation treatment (Fig. 2A). To investigate if important clinical variables affected body weight loss, the analysis of covariance test was performed. As shown in Table 4 this analysis clearly indicated that all clinical variables included in the model, except the kind of supportive treatment, did not affect body weight loss suggesting that PGS effectively impacted on body weight loss with respect to standard supportive medical treatment. In addition, there was a statistically significant difference in the opioid analgesics usage in the group treated by PGS or by standard supportive care ($P = 0.0021$) (Table 3). During RT, 19% of patients (3/16) in the PGS group and 62.5% of patients (40/64) in the control group did require narcotic medications (Table 3).

Finally, across the study period, PGS group significantly experienced higher quality of life, as measured by OMWQ-HN (Fig. 2B) ($P < 0.001$), and lower mouth and throat soreness (Fig. 2C) ($P < 0.001$) with respect to controls. Interestingly, the incidence of WHO grade 3/4 toxicity peaked just before the worsening of quality of life measured by OMWQ-HN. In the group treated by PGS, WHO grade 3/4 mucositis appeared 28 days (mean, 31 ± 2.6 d) after beginning of radiation course. In the control group the same toxicity appeared 21 days (25.8 ± 3 d) after beginning of radiation course with a significant difference ($P = 0.016$) with respect to PGS group. The higher toxicity found in the control group paralleled with longer duration of radiation course with respect to PGS groups (52.3 ± 4.5 vs. 49.5 ± 5.1 d) ($P = 0.03$). In this regard, a total of 2 patients (12.5%) and 18 patients (28.1%) temporarily discontinued radiation treatment for 5 or more consecutive fractions in the PGS and control groups, respectively. Four patients

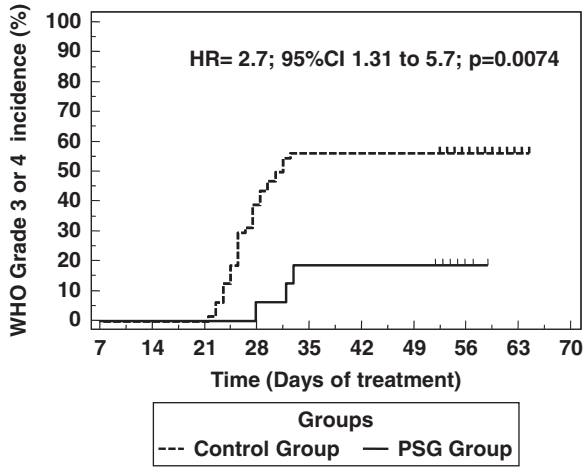

FIGURE 1. Kaplan-Meier plot of time to onset of severe oral mucositis (WHO grade 3/4) by treatment group.

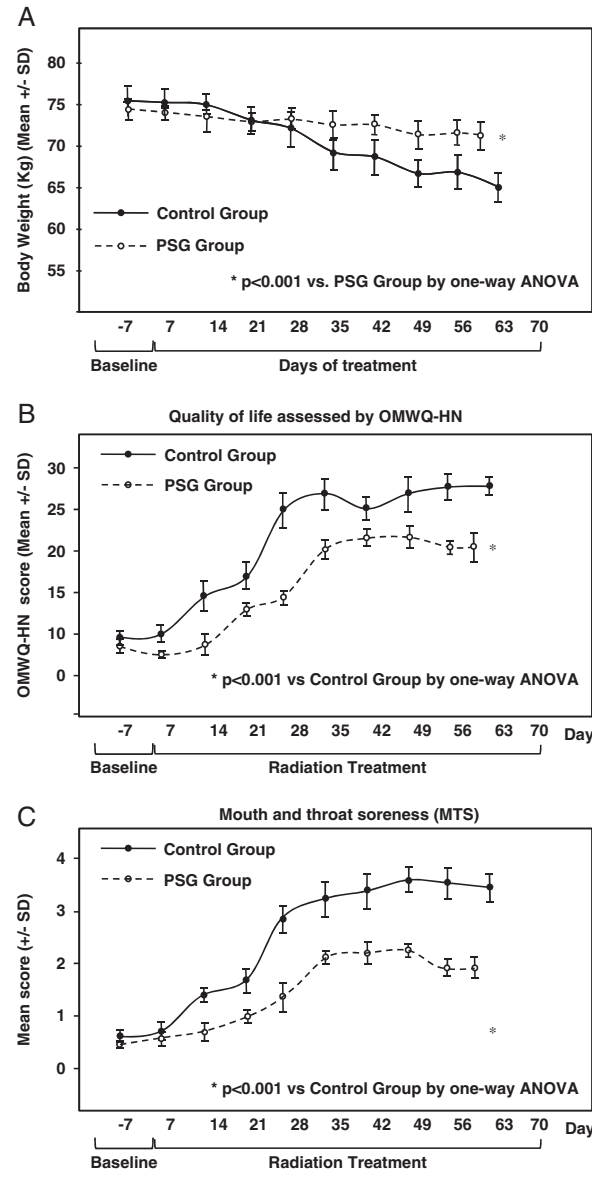

FIGURE 2. Body weight loss of patients treated (PGS) or not (control) with PGS during the radiation course (A). OMWQ-HN mean scores (B) and mouth and throat soreness (MTS) assessment (C) during radiation treatment.

TABLE 3. Narcotic Analgesic and Tube Feeding Use in Patients Treated or Untreated with PGS

	PGS Group (N = 16) (n [%])	Control Group (N = 64) (n [%])	*P**
Opioid analgesics use			
Requiring	3 (19)	40 (62.5)	0.0021
None	13 (81)	24 (37.5)	
Feeding tube			
Requiring	2 (12)	13 (20.3)	0.72
None	14 (88)	51 (79.7)	

*Fisher exact test.

TABLE 4. Impact of Clinical Variables on Body Weight Loss Determined by Analysis of Covariance

Confounding Factors	Sum of Squares	*df*	Mean Square	*F*	*P*
Chemotherapy use	2.210	1	2.210	0.374	0.543
RT dose	3.220	1	3.220	0.545	0.463
Stage grouping	0.0395	1	0.0395	0.00669	0.935
Age	2.123	1	2.123	0.326	0.521
Sex	0.0123	1	0.0123	0.00233	0.821
Site	0.0231	1	0.0231	0.00345	0.844
Treatments	520.726	1	520.726	88.120	<0.001
Coefficient of determination R^2	0.5698				
R^2-adjusted	0.5444				

Pairwise Comparisons						
Variables			Mean Difference	SE	*P**	95% CI*
PGS groups	vs.	Control groups	6.6272	0.7060	<0.0001	5.2208-8.0336

*Bonferroni corrected.
ANCOVA indicates analysis of covariance; CI, confidence interval; df, degrees of freedom; PGS, platelet gel supernatant; RT, radiotherapy.

(6.2%) in the control group and none in the PGS group discontinued radiation treatment for a total of 10 or greater radiation doses.

The safety profile of PGS administered concomitantly with standard supportive medical treatment was comparable with that of standard supportive medical treatment alone. PGS oral administration was generally well tolerated. A number of subjects reported 1 or more treatment-emergent adverse event related to chemotherapy. Adverse events included: (i) nephrotoxicity (6.2%, 5/80) (elevations in BUN and creatinine), (ii) ototoxicity (1.2%, 1/80) (tinnitus), (iii) mild to moderate myelosuppression (19%, 15/80), (iv) nausea and vomiting (51.2%, 41/80). The events were resolved spontaneously without sequelae or by specific supportive medical treatment. There was no local tolerance issue, deaths, or serious adverse events in the study.

DISCUSSION

Despite multimodal prophylaxis and therapy, radioinduced OM often takes a therapeutically refractory turn necessitating the use of topical and systemic analgesics.[5,6] So, it is essential to identify new strategies that quickly counteract the mucositis progression improving patients' quality of life and treatment compliance. In this study, we demonstrate that PGS when administered in association with standard supportive medical treatment topically to the oral mucosa as a prophylactic treatment decreased the incidence and severity of clinically significant OM in a cohort of subjects suffering from HNC and treated by RT with or without chemotherapy. Topical PGS treatment substantially reduced the development of severe OM (WHO grade ≥ 3) of the study cohort in a manner consistent. The incidence of WHO grade 4 OM was comparable between 2 study groups suggesting that PGS effectively decreased WHO grade 3 OM. The evidence that PGS results in a preferential decrease of WHO grade 3 OM may not have an univocal interpretation. Surely the low number of subjects within each subgroup stratified according to WHO toxicity score may explain the lack of statistical significance with respect to grade 4 toxicity. The onset of clinically significant severe OM (WHO grade ≥ 3) in PGS users was moved forward in time with respect to subjects treated by standard medical supportive treatment. The Cox proportional hazard model indicated that PGS users in association with standard medical supportive treatment experienced WHO grade ≥ 3 later than subjects treated by standard medical supportive treatment alone. In addition, PGS users experienced 2.7-fold decrease (95% confidence interval, 1.31-5.7; $P = 0.0074$) in the risk for severe OM during radiation course with respect to nonuser. The impact of PGS on OM onset was probably due to the effect that this treatment may exert an epithelial cell proliferation of the oral mucosa. It is well known that PGS regulates tissue homeostasis and favors the release of biological factors able to promote tissue repair and angiogenesis.[7,8] The observed reduction in the maximum severity of OM between PGS users and nonusers had an evident impact on the need for opioid use. These data paralleled with the findings that the higher toxicity found in the control group paralleled with longer duration of radiation course with respect to PGS users. In addition, a lower body weight loss in the group treated with PGS was found with respect to controls. The severity of mucositis adversely impacted on the quality of life of patients treated with the only standard supportive medical treatment. The use of PGS in association with standard supportive care treatment resulted in a significant improvement in quality of life as attested by the use of specific standardized measures. From a methodological point of view, the most interesting strength point of our explorative study was the use of propensity score analysis. The propensity score is the probability of treatment assignment conditional on observed baseline characteristics. This statistical analysis allows one to design and analyze an observational (nonrandomized) study so that it mimics some of the particular characteristics of a randomized controlled trial. In particular, the propensity score is a balancing score: conditional on the propensity score, the distribution of observed baseline covariates will be similar between treated and untreated subjects. So, the use of this powerful methodological approach allowed us to improve the soundness of obtained evidence.

With respect to toxicity ascribable to PGS, the literature does not report specific data in this regard. In our study the oral toxicity found among PGS users was judged as not being caused by PGS as the kind of local toxicity seemed clearly related to chemotherapy or RT. Concerning the possible effect of PGS on the incidence of systemic adverse events our data seem to confirm that PGS administration is associated with a good toxicity profile as no difference in the rate systemic toxicity between the 2 groups was found. Although we cannot definitively exclude that PGS may adversely affect oral function or have systemic effects this treatment seems to positively

affect the clinical course of subjects with radio-induced OM with respect to non-PGS users.

Several limitations affect our study. The main ones are the small sample size and the use of a nonrandomized study design. To date, large randomized controlled trials have provided the strongest evidence for the efficacy of therapeutic procedures or treatments in the clinical setting. However, this bias has been mitigated by the use of a strategy based on propensity score analysis, which helped us to obtain 2 groups of patients virtually randomized for important clinical characteristics. Thus, comparative analysis by propensity-matched pairs contributed to the results being less prone to methodological biases than other usual statistical methods. With respect to the small sample size, the main influence of this parameter on the quality of a clinical study concerns the statistical power. If the sample size declines, the power also declines. Thus, if the sample size of a study is too small, the power of a study may be low to the point of unreliably showing the traits that are sought by the researcher.

Another limit concerns the study protocol used. Radiation toxicity may further get worse after RT and a treatment strategy based on the use of PGS both during and after RT instead of a strategy based on an administration during RT could configure as more effective in reducing radio-induced OM. So our study may have underestimated the beneficial effects of PGS on the radio-induced OM.

Finally, all radiation treatments were performed by a 3D-conformal approach which, although is considered a standard of treatment in HNC, toxicity may be higher than with IMRT. In this regard, the use of PGS during IMRT may have a lesser clinical impact than with other radiation approaches.

Although the observational nature of our study means that our results have to be interpreted with caution, we found that PGS used in association with supportive medical treatments is a new, potentially beneficial, medical device in the management of OM induced by chemo-RT. These preliminary data should be interpreted with caution and could serve as a framework around which to design future trials.

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