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Oral Lapacho-Based Medication: An Easy, Safe, and Feasible Support to Prevent and/or Reduce Oral Mucositis During Radiotherapy for Head and Neck Cancer

Irene Giacomelli, Daniele Scartoni, Meacci Fiammetta, Muhammed Baki, Giacomo Zei, Cristina Muntoni, Sabrina Cappelli, Daniela Greto, Silvia Scoccianti, and Lorenzo Livi
Department of Radiation Oncology, University of Florence, Florence, Italy

The aim of our Phase II study is to demonstrate the benefits, safety, and tolerance of Orasol Plus, an easy and feasible Lapacho-based medication. Orasol Plus is a nutritional, swallowable solution, useful to support the defenses of the oropharyngeal mucosa. Between January and June 2014, 40 consecutive adult patients affected by head and neck cancer were enrolled. Orasol Plus was administered 3 times a day from the first day till the end of radiotherapy. Primary endpoint was to evaluate tolerance and safety of Orasol Plus; secondary endpoint was to evaluate the effect of Orasol Plus on the incidence of treatment discontinuation. Nearly all patients used Orasol Plus easily till the end of radiotherapy without interruptions. Only 11 (27.5%) patients developed oral mucositis (OM) Grade 2 and only 4 (10%) patients OM Grade 3, no patient developed OM Grade 4. No patient discontinued radiotherapy because of OM. Orasol Plus was well tolerated and the compliance of patients was optimal, mainly due to the fact that it can be swallowed. Data from our study are encouraging and they need to be confirmed by a Phase III study.

INTRODUCTION

Head and neck cancer (HNC) is the sixth most common type of cancer, estimated in about 650,000 new patients diagnosed worldwide each year (1). The evidence suggests that the use of radiotherapy as an integral part of primary adjuvant treatment in early stages results in high tumor control and that concurrent chemoradiation therapy determines a major advancement in the treatment of locally advanced head and neck cancer (i.e., Stage III and IV), particularly when concerning squamous cells histology, increasing survival rate, and locoregional control (1,2).

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Address correspondence to Irene Giacomelli, Department of Radiation Oncology, University of Florence, Largo G. A. Brambilla 3, 50134, Florence, Italy. Phone: +39-055-79477018. Fax; +39-055-7947263. E-mail: irenegiaco@virgilio.it

Patients treated with either radiotherapy alone (RA) or combined with chemotherapy commonly develop acute and late complications as a result of the treatment and of their disease as well; supportive care during these kind of treatments is often demanded (1). One of the most common acute side effects associated with radiation is oral mucositis (OM), almost all patients undergoing RA or concurrent chemoradiotherapy (CCR) for head and neck cancer develop OM of a sufficient severity.

Pain and ulceration associated with OM often can lead to severe difficulties in speaking, eating, drinking, and swallowing, and to taste alteration, altogether determining a worsening in the quality of life (QoL) such as to require supportive care of various levels, from analgesics administration to i.v. parenteral nutrition (TPN) or percutaneous endoscopic gastrostomy (PEG) and in worst conditions even hospitalization (3,4).

Moreover OM is an important cause of unscheduled radiation treatment breaks, which can prolong the total radiation treatment time; a higher incidence of OM is in particular noticed for those patients receiving concurrent CCR or hypofractionated radiotherapy regimens. It is demonstrated that unplanned radiation treatment breaks and prolongation of the total radiation treatment time are associated with lower survival and locoregional control rates (4–6), these findings suggest that reducing OM to the maximum is the keyword for a successful treatment and maintaining a good QoL of patients.

Currently there aren't many specific medical supplements and/or medications that may prevent OM induced by radiation therapy (7). Our purpose is to find a feasible and easy medication that can effectively help to limit as much as possible OM, determined by these kinds of treatments, which render patients to tolerate them well.

Orasol Plus is a nutritional supplement, swallowable solution, with Lapacho and other herbal ingredients (hyaluronic acid, green tea, calendula, erisimo, propolis, marigold, plantain and mauve) useful to support the defenses of the oropharyngeal mucosa. Lapacho promotes the functionality defenses

with antiinflammatory, analgesic, and antimicrobial action (8–14). Hyaluronic acid prevents tissue damage caused by pharmacological stress and promotes healing of lesions in case of mucositis (15,16). Green tea has antioxidant and antimicrobial activity (17,18). Marigold has antioxidant activity useful in case of lesions of the mucosa of mouth and pharynx (19). Erisimo has emollient activity useful against disorders of the throat (20). Propolis has antibacterial proprieties (21). Marigold, mauve, and plantain have emollient action and soothing effect on the oropharyngeal mucosa and tone of voice (22).

The primary end point of our study was to test the tolerance and safety of Orasol Plus, whereas the secondary end point was to verify if it could be used as a treatment for the prevention and reduction of OM occurrence.

MATERIAL END METHODS

Orasol Plus was evaluated in an open, prospective phase II study. The study was conducted at the Radiation Oncology Center of Florence University. Eligibility criteria were male/female undergoing radiotherapy +/− chemotherapy for HNC histologically confirmed, age >18 yr, informative consensus taken. From January to June 2014, 40 patients with a median age of 64 years were enrolled in our institute: 13 of them were female and 27 were male. All patients were affected by squamous cell carcinoma of the head and neck from heterogeneous sites: 12 patients of the oral cavity, 2 patients of salivary glands, 3 patients of hypopharynx, 5 of oropharynx, 12 patients of larynx, 1 of paranasal sinuses, although 2 patients were affected by pathological lymph nodes from unknown primitive cancer and 3 patients by non-Hodgkins lymphoma localized at the level of tonsil.

The stages varied from T1 to T4, any *N* was allowed, and no patient was affected by distant metastasis. The Karnofsky Performance Status (KPS) Scale was between 80 and 100 in almost all patients, only 3 had a KPS of 70. Thirty (30) patients of the 40 analyzed were smokers and 14 of them were still smoking during treatment. Patients' characteristics are summarized in Table 1.

The treatment intent was definitive in 42.5% of patients, adjuvant in 45%, and palliative in 12.5%; patients received a total radiation dose from 30 to 40 Gy for palliative intent, from 60 to 66 Gy for the adjuvant treatment, 70 Gy for the radical intent in a number of fractions variable from 10 to 35. Volume of irradiation included always the primary site in the head and in 26 cases even the neck homo or bilaterally, depending on the stage or the site of palliation.

In 18 cases, the radiation technique used was 3D conformal radiotherapy whereas intensity modulated radiotherapy was performed in 22 cases and in 11 of them it was done by Helicoidal Tomotherapy. Chemotherapy was associated with radiation treatment in 11 patients, usually with single agent Cisplatinum or Cetuximab. Treatment characteristics are summarized in Table 2.

TABLE 1
Patient characteristics

Characteristic	No. of patients (% of total)
Sex	
Male	27 (68%)
Female	13 (32%)
Age	
<60	12 (30%)
>60	28 (70%)
KPS	
100	26 (65%)
90	9 (22%)
80	4 (10%)
70	1 (3%)
Smoking	30 (75%)
>20 pack/yr	21 (53%)
<20 pack/yr	9 (22%)
Current	14 (35%)
Primary site	
Oral cavity	12 (30%)
Oropharynx	5 (12.5%)
Salivary glands	
Tonsilla	
Larynx	12 (30%)
Hypopharynx	3 (7%)
Unknown primary	2 (5%)
Sinuses	1 (3%)
T stage	
Tx	2 (5%)
T1	11 (28%)
T2	13 (32%)
T3	7 (17.5%)
T4	7 (17.5%)
N stage	
Nx	2 (5%)
No	24 (60%)
N1	6 (15%)
N2	5 (12%)
N3	3 (8%)

KPS = Karnofsky Performance Status scale.

Orasol Plus was administrated from the first day of radiotherapy until the end daily, at the dose of 10 ml/3 times a day. Patients were weekly evaluated clinically from the first day radiation treatment, Visit 0 (V0), till the end of radiation.

At V0 we collected the following clinical data: age, sex, site of the oncological disease and stage, KPS, chemotherapy schedule if the treatment was CCR, radiotherapy technique, total dose fractionated, and number of fractions scheduled, the eventual presence of OM before the beginning of treatment, concurrent analgesic therapies or the eventual introduction of them at the time of the first radiation treatment day; then,

TABLE 2
Treatment characteristics

Treatment	*n* (%)
RT alone	29 (72.5%)
Total	
Chemoradiotherapy associated to RT	11 (27.5%)
Cisplatinum weekly administered	6 (15%)
Cisplatinum 1-21	2 (5%)
Erbitux	2 (5%)
Carboplatinum	1 (2.5%)
RT Technique	
3D CRT	18 (45%)
IMRT	22 (55%)
Intent	
Definitive	17 (42.5%)
Adjuvant	18 (45%)
Palliative	5 (12.5%)

RT = radiation therapy; 3D CRT = 3-dimensional conformal radiotherapy; IMRT = intensity-modulated radiation therapy. Total dose (range = 30 Gy-70 Gy) = average 60.2 Gy ; No fractions (range =10 fr-35 fr) = average 31 fr.

every week until the end of radiation was evaluated on the grade of OM and of xerostomia, the nutritional status, analgesic medications applied, or modified if already ongoing.

At the end of the treatment patients received another clinical evaluation in which the physician assessed the grade of treatment related toxicities (OM, xerostomia), the eventual suspension of Orasol Plus, the eventual radiotherapy interruptions in the scheduled treatment due to OM toxicities and, if there were any, how many days. The physician also assessed whether the patient's nutritional status had worsened, and evaluated the eventual increase or reduction of medical therapy for pain due to mucositis if already present in the medical history of the patient, or the eventual introduction of a new medical therapy for the same reason.

Primary endpoint was to evaluate safety and tolerance of Orasol Plus and secondary endpoints were to evaluate incidence and severity of OM with eventual requirement of drugs to reduce/solve it and the effect of Orasol Plus on the incidence of treatment discontinuation.

OM and Xerostomia were evaluated according to the Common Terminology Criteria for the Adverse Events (CTCAE) Version 4.0. Dose constraints used in different settings were oral mucosa mean dose of 30 Gy if it was not involved in the PTV and of 40 Gy if it was involved in the PTV, these constraints were obtained from numerous Radiation Therapy Oncology Group (RTOG) protocols and clinical trials (23,24).

RESULTS

Nearly all patients completed the study protocol. The study product was generally well tolerated and the compliance of patients was optimal. Concerning toxicities, during the treatment period 19 (47.5%) patients developed OM Grade 1 (G1) at a mean dose of 63 Gy, 11 (27.5%) patients developed OM Grade 2 (G2) at a mean dose of 31 Gy, whereas 4 (10%) patients developed OM of Grade 3 (G3) at a mean dose of 52 Gy and no patient developed OM Grade 4 (G4). Characteristics of patients who developed OM G1, G2 and G3 are summarized in Table 3.

TABLE 3
Toxicity characteristics: mucosite

Mucosite	MUCOSITE G1	MUCOSITE G2	MUCOSITE G3
Total 34 pt (85%)	19 pt (47.5%)	11 pt (27.5%)	4 pt (10%)
Primary tumor site			
Oral cavity	5 (12.5%)	5 (12.5%)	2 (5%)
Oropharynx	0	3 (7.5%)	2 (5%)
Larynx	5 (12.5%)	2 (5%)	0
Sinuses	3 (7.5%)	1 (2.5%)	0
Salivary Glands	2 (5%)	0	0
Tonsilla	1 (2.5%)	0	0
Hypopharynx	2 (5%)	0	0
Unknown primary	1 (2.5%)	0	0
Technique			
Tomotherapy	5 (12.5%)	3 (7.5%)	1 (2.5%)
IMRT	10 (25%)	5 (12.5%)	1 (2.5%)
3DCRT	4 (10%)	3 (7.5%)	2 (5%)
Mean doses of mucosite development	63 Gy	31 Gy	52 Gy
Chemotherapy	8 (20%)	2 (5%)	1 (2.5%)
Median doses to the oral mucosa	29 Gy	42 Gy	30 Gy

Six (6) patients did not develop OM, but all of them had performed radiation treatment alone. All patients continued to maintain feeding all treatment long with a maximum weight loss of 4 kg; no patient needed parenteral nutrition. We also collected data about xerostomia, all patients in this study did not develop any grade of xerostomia as an acute side effect during the treatment.

OM did not affect the progress of the treatment. In fact no patient discontinued radiotherapy due to that; only one patient interrupted radiotherapy because of desquamation of the neck. Patients included in the study were smokers in 22 cases whereas 18 patients have never smoked or were ex-smokers from at least 10 years. Eight of the smokers declared to have quit smoking before the beginning of treatment, so only 14 patients were still smoking during the radiation treatment.

G0 mucositis was found in 14% of smokers vs. 15% of nonsmokers, G1 in 29% of smokers vs. 58% in nonsmokers, G2 mucositis in 36% of smokers vs. 23% of nonsmokers, and finally mucositis G3 in 21% of smokers vs. 4% in nonsmokers.

In addition, there was a statistically significant difference between nonsmokers and smokers who developed OM > G2 in favor of nonsmokers ($P < 0.021$), statistical analysis was performed with χ^2 test, significant for $P < 0.05$, using the SEM V3.5 software (Sivex, Mirefleus, France).

From a dosimetric point of view we evaluated the possible correlation between median dose at the oral cavity and the development of OM: patients with OM G1 received a median dose at oral cavity of 29 Gy (range 2 Gy–60 Gy), patients with OM G2 received a median dose of 42 Gy (range 2 Gy–66 Gy), whereas G3 mucositis received a median dose of 30 Gy (range 3 Gy–52 Gy).

Concerning the tolerance of Orasol Plus, it was interrupted only in 1 case because of itching at the second week of treatment. Another patient developed glossitis at the beginning of treatment with Orasol Plus but without interrupting it; the glossitis was solved without any medication.

In 10 (25%) cases, patients needed an intensification of dose or the introduction of additional antalgic therapy during treatment consisting in Opioid or FANS.

DISCUSSION

OM is a very common side effect during head and neck cancer radiotherapy treatment; it is disabling and may be the most important acute toxicity that can seriously affect the QoL of patients, causing pain, difficulty in feeding and weight loss, and an unavoidable psychological impact reflecting on social aspect and aggravation dealing with an already severe disease.

Finding supplements to improve the tolerance to this kind of treatment is basic. There is no standardized treatment protocol for preventing OM caused by the lack of consensus therapy, class of drug, kind of administration, pharmaceutical forms (25). The goal of our study was to provide a way to prevent OM using an easy medication, feasible even in patients with strong oral pain and discomfort limitation in oral movements.

Our Phase II study has clearly demonstrated the benefits, safety, and good tolerance of Orasol Plus for the prevention and/or reduction of both the incidence and severity of OM radiation induced. During the study period, Orasol Plus was well tolerated by patients. Indeed only 2 patients have complained difficulties or disturbs using this nutritional supplement.

The excellent tolerance is a very important aspect to be considered especially in those patients who have olfactory and taste problems during or after chemotherapy and radiotherapy; often these disorders may limit their use.

Several trials analyze the possible preventive strategies and treatment approaches for patients with established OM. The several solutions, drugs, and methods used and studied in the prophylaxis and therapy of chemoradiotherapy induced OM reflects the need of new, more efficient tools in the management of this complication (26–28).

A recent review published by Quinn (28) reported encouraging results regarding a calcium phosphate oral rinse for preventing OM. Nine of the 12 studies analyzed reported a prevention in the development of OM or reduced the severity of this. Moreover all the comparative and the observational studies relieved a reduced OM associated pain with a reduced requirement of analgesia (28).

In our study, we used Orasol Plus, a blend of natural substances, to prevent OM and all the consequences directly connected; data emerged are very good in fact we found only 11 (27.5%) patients who developed OM G2 and only 4 (10%) patient with OM G3 whereas no patient developed OM G4–G5.

Our results seem better than data showed in current literature about acute OM radiation or chemoradiation therapy related; for example, Patrick et al. reported in their trial a G3 OM of 38% (29), whereas Saigal et al. found in their study a G3–G5 OM in the 44% of patients in some cases with the necessity of PEG positioning (30).

This benefit could be related to the hypothetical role of Orasol Plus in the prevention of OM, in fact not one of the patients included in our study needed hospitalization during the treatment and no one patient needed auxiliary feeding systems like TPN or PEG and could feed fairly regularly with a minimum weight loss. A high rate of patients experience unplanned radiation treatment breaks due to toxicity, Tarnawski et al. found a rate of 90% in their group of study (31).

Because Robertson et al. (32) demonstrated, in a sample of 2225 patients who underwent radiotherapy of various schedules from retrospective studies of 4 institutions, that a break or prolongation by 1 day was associated with a lower 2-yr local control rate by 0.68% per day, and Fowler et al. (33) detected, in a literature review that analyzed 3834 patients from 12 reports, that overall treatment time was correlated with local control and that a median loss of local control was 14% per week (range = 3–25%), it is important to underline that no one of the patients in our study experienced unscheduled

radiation treatment breaks due to OM and it may be related with the use of Orasol Plus all treatment long.

Moreover we can add another favorable data: Only 10 patients of the 40 included in our study needed to introduce or increase analgesic therapy, including steroid support.

Considering the extreme heterogeneity of mean doses to the oral mucosa and that there is no correlation between them and the development of mucositis of any grade, we cannot evaluate the benefit role of Orasol Plus in patients with unfavorable dosimetric parameters.

It's important to highlight that patients with G0 OM didn't perform associated chemoradiotherapy treatment but radiotherapy alone, suggesting that chemotherapy could be an important co-factor in the onset of OM.

We collected even data about xerostomia but the results during treatment were always G0 for all patients; it may be due to the fact that xerostomia is more frequently as a late side effect and it doesn't occur very often in acute toxicities.

CONCLUSIONS

The use of a medication to prevent the development of acute OM and its related complications should be taken in consideration as a good practice. Orasol Plus is an easy, safe and feasible approach to prevent OM in head and neck cancer patients treated with RA or CCR.

Data from our study to prevent OM and all consequences directly connected, using Orasol Plus, are encouraging and they need to be confirmed by a phase III study.

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