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Effect of fluconazole antifungal prophylaxis on oral mucositis in head and neck cancer patients receiving radiotherapy

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Abstract *Goal of work:* The aim of the study is to evaluate the effect of fluconazole antifungal prophylaxis on the severity of mucositis in head and neck cancer patients receiving radiotherapy. *Patients and methods:* Sixty-three patients, with malignant head and neck tumor, eligible to receive radiotherapy, entered the study. Thirty-four patients (group A) received 100 mg/day of fluconazole prophylaxis during radiotherapy and were compared with 29 patients, who received radiotherapy alone (group B). The two groups were similar in terms of patients and radiotherapy characteristics. Smear to test for *Candida* carriage was taken before and after radiotherapy. Oral candidiasis was diagnosed using the criteria described before. Oral mucositis was recorded according to EORTC/RTOG criteria. *Main results:* A significant reduction of severe mucositis at the end of radiotherapy (14.7 vs 44.8%, p=0.018) and of interruptions (0 vs 17.2%, p=0.017) was observed in group A. Candidiasis was prevented (0 vs 34.5%, p=0.001), with a significant reduction of *Candida* carriage of 40.7% (p=0.001). *Conclusion:* Fluconazole prophylaxis showed a significant beneficial impact on the severity of mucositis and on radiotherapy interruptions in this group of patients. The current study provides data on the build of a randomized controlled trial on the effect of fluconazole prophylaxis on treatment schedule and quality of life of the patients during head and neck radiotherapy.

Keywords Antifungal prophylaxis · Fluconazole · Oral candidiasis · Oral mucositis · Radiotherapy

Introduction

Oral mucositis is an acute side effect in the case of radiation and/or chemotherapy of malignant tumors in the head and neck. It is scored in four grades; mucositis grade 1 is characterized by a diffuse erythema, mucositis grade 2 refers to the development of small foci of ulcers, whereas mucositis grades 3 and 4 are characterized by painful ulcerations extending on more than half of the oral mucosa [3, 13, 22].

About 34–43% of patients who receive conventional radiotherapy (RT), alone or in combination with chemotherapy, for head and neck malignancies may experience severe, grade 3 or 4 mucositis [24]. Severe mucositis compromises patient's quality of life, in as much as it may require feeding tube placement, hospitalization, and intensive support care.

Furthermore, severe mucositis may lead to RT interruptions, with adverse effect on treatment [9]. An overall incidence of 9–19% of radiotherapy or radiochemotherapy interruptions due to severe mucositis has been reported [24].

Five phases characterize the pathophysiologic progression that results in mucositis: initiation, upregulation and message generation, signaling and amplification, ulceration, and healing [21]. A fibrinous exudate, also referred to as a pseudomembrane, teeming with bacteria, covers the ulcers of mucositis. Oral flora colonizing the mucosa is thought to aggravate mucositis [21, 23]. Oral bacterial colonization may also lead to secondary infection.

The most common infection of the oral mucosa during radiotherapy is oral candidiasis [4, 6, 10, 14, 15, 17], whereas herpetic infection complicating mucositis has been documented in a few cases [14]. Candidiasis may be caused by different *Candida* species.

The etiologic agent for candidiasis, i.e., the different *Candida* species, resides in the oral cavities of a majority of healthy individuals as a commensal organism, with a colonization prevalence ranging between 30 and 40% [1], causing no apparent morbidity. Under several predisposing factors, including RT, candidiasis may develop in oral *Candida* carriers, with tissue penetration and inflammation of the oral mucosa [19].

Before radiotherapy, about one third or more of the patients have been reported to be *Candida* carriers, whereas, until the end of radiotherapy, half of the *Candida* negative patients will turn positive [2, 4, 11, 16–18]. A high prevalence of 62–73% of *Candida* carriage has been found after the completion of RT, whereas the incidence of candidiasis shows a wide range between 27 and 52%.

Oral pseudomembranous candidiasis, presenting in the form of semi-adherent, whitish or yellowish pseudomembranes, is often superimposed on radiation-induced grade 2, 3, or 4 ulcerative mucositis. The differential diagnosis of the infection from the grades 2, 3, and 4 ulcerative/pseudomembrane mucositis, as several authors have stated [2, 6, 14, 15], is difficult or impossible.

Oral candidiasis being superimposed on the radiation-induced mucositis would be anticipated to contribute to the severity of mucositis.

The high prevalence of candidiasis during head and neck radiotherapy, combined with the difficulties in the differential diagnosis between the infection and mucositis and the potential role of candidiasis on the severity of mucositis, has led several authors to consider the need for antifungal prophylaxis [7, 12, 17, 18].

The potential role of candidiasis in the initiation, severity, and duration of oral mucositis during radiotherapy has been addressed in only two studies [7, 12]. In both studies, a beneficial effect of fluconazole antifungal prophylaxis on RT interruptions was reported.

In the first study [7], colonization by *Candida* species instead of the development of the infection was used as a determinator. In the second study [12], a historical group was used as control for the development of candidiasis. The incidence of severe (grade 3 or 4) ulcerative/pseudomembrane mucositis was not reported in either of the above studies.

Other studies, which have used topical antimycotic drug in combination with antibiotics, within a lozenge or a paste [5, 23, 25] have reported conflicting results. The incidence of pseudomembranous candidiasis, which may develop during RT, concurrently with mucositis, was not reported in any of the above three studies.

As it can be seen, either oral candidiasis or oral mucositis only is reported in each study [5, 7, 12, 23, 25], although both lesions develop in association with radiotherapy, during the same time period and on the same tissue, oral mucosa.

The aim of this open study was to evaluate the effect of fluconazole antifungal prophylaxis on the severity of oral mucositis in head and neck cancer patients receiving radiotherapy. That patient cohort received daily, from the initiation to the completion of RT, 100 mg of fluconazole to prevent the development of candidiasis and comprised the study group (group A).

That study group (group A) was compared with a patient cohort, who were irradiated without receiving daily fluconazole prophylaxis and comprised the control group (group B). That second group of patients (group B) was treated with fluconazole, 100 mg/day, for 1 week, only in case candidiasis had developed.

Both groups (all registered patients) were referred to the Dental Oncology Unit, Department of Oral Pathology and Surgery of the School of Dentistry, before the initiation of RT, from the Radiotherapy Departments of four Athens Cancer Hospitals. The decision whether each patient would receive daily fluconazole prophylaxis or not was made by the Cancer Hospitals.

The Dental Oncology Unit provided to all patients oral mucosal and dental care and followed the patients through-

out RT. Both mucosal lesions, oral mucositis and oral candidiasis, were recorded weekly.

Patients and methods

Patients and eligibility criteria

Sixty-three consecutive patients with malignant head and neck tumor, eligible to receive radiotherapy, were included in the study, within 15 months of observation.

General blood tests and liver and renal functions were within normal limits. Karnofsky performance status ranged between 80 and 100%.

All patients were thoroughly informed about their disease and the treatment they would receive. All patients agreed and gave their consent for the above.

Standard oral mucosal and dental care was introduced to all patients.

The two groups did not differ significantly in terms of sex, age, and tumor classification (Table 1).

Hypothesis and study endpoint

If the inflammation of the oral mucosa, related to the development of candidal infection during head and neck radiotherapy, is superimposed and adds to the severity of the radiation-induced mucositis, then the prevention of candidiasis should reduce the severity of radiation mucositis.

The objective of the study was to assess whether fluconazole prophylaxis would impact on the severity of oral mucositis.

A secondary endpoint was the effect of fluconazole prophylaxis on the development of candidiasis.

Radiotherapy

Sixty-two patients were irradiated with a 6-MV linear accelerator, and one patient was treated with ^{60}Co. Forty-seven patients received definitive and 16 patients received postoperative radiotherapy. The primary tumor and draining lymphatics were treated with parallel opposed fields. Supraclavicular and low neck nodes were treated with an anterior field.

The daily and the total radiation doses are shown in Table 1. The lateral field doses were reduced after 40–43 Gy to avoid overdosage to the spinal cord. The regional nodes were irradiated to a total dose of 45–61 Gy, depending on the nodal stage. Concomitant chemotherapy, including two cycles of cisplatinum (100 mg/m^2 on days 1 and 28 of RT) and 5-fluorouracil (800 mg/m^2 on days 1–5 and on days 28–32 of RT), was administered to 25 patients.

Table 1 Patient demographics, tumor classification, type, and dose of RT

Parameter	Patients				*p* Value
	Group A (*n*=34)		Group B (*n*=29)		
	Number	Percentage (%)	Number	Percentage (%)	
Sex					
Male	21	61.8	21	72.4	0.532
Female	13	38.2	8	27.6	
Age (years)					
Median	58		59		0.654
Range	21–81		20–94		
Tumor histological diagnosis					
Oral SCca	7	20.6	9	31.0	0.740
Npca	13	38.2	9	31.0	
Supraglottic Lca	4	11.8	3	10.3	
Salivary adenoca	4	11.8	2	6.9	
Lymphomas[a] and plasmacytoma	2	5.9	4	13.8	
Other	4	11.8	2	6.9	
Tumor stage					
T1	5/31	16.1	4/24	16.7	0.415
T2	14/31	45.2	10/24	41.7	
T3	7/31	22.6	9/24	37.5	
T4	5/31	16.1	1/24	4.2	
Tx	1		1		
Node stage					
N0	11	34.4	11	44.0	0.403
N1	10	31.3	9	36.0	
N2	8	25.0	5	20.0	
N3	3	9.4	–	–	
Type of RT					
Definitive	26	76.5	21	72.4	0.938
Postoperative	8	23.5	8	27.6	
Daily dose (Gy/fraction, 5 days/week)					
1.8	14	41.2	12	41.4	0.901
2.0	18	52.9	16	55.2	
2.3	2	5.9	1	3.4	
Total dose (Gy)					
Median	63		64		0.715
Range	37–73		45–72		
Concomitant chemotherapy	16	47.1	9	31.0	0.300

SCca squamous cell carcinoma, *NPca* nasopharyngeal carcinoma
[a]Stage of lymphomas IE (*n*=1), IIE (*n*=4)

Fluconazole administration

In group A, 34 patients received fluconazole, 100 mg/day, administered per os, after lunch, from the initiation to the completion of RT.

In group B, 29 patients received fluconazole, 100 mg/day, administered per os, after lunch, upon the development of candidiasis, for 1 week. Upon recurrence of candidiasis, fluconazole was re-administered for another 1 week.

Liver and renal functions and blood were tested before and after the completion of RT in all patients.

Oral clinical evaluation

Patients were examined weekly, and oral mucosal evaluation was performed by the oral medicine specialist.

Mucosal evaluation included:

1. The scoring of oral mucositis, which was recorded according to EORTC/RTOG criteria [3].
2. The definitive diagnosis of oral pseudomembranous candidiasis. The criteria used for the diagnosis of candidiasis were the three ones published previously [14, 15], i.e., clinical presumptive diagnosis of candidiasis (criterion 1) and positive direct microscopic observation of *Candida* organisms in the smear (criterion 2) (positive *Candida* carriage). Presumptive diagnosis of candidiasis was made when easily removable, mostly painless, whitish pseudomembranes were observed. Both positive clinical and laboratory findings had to be verified by positive response to antifungal treatment (criterion 3). Thus, patients with a presumptive, clinical diagnosis of candidiasis were re-examined in 3 days for quick clinical evaluation of their antifungal response.
3. The presumptive diagnosis of herpes simplex virus-1 infection, which was evaluated according to the clinical criteria reported previously [14].

Candida carriage

Smears to test the oral *Candida* carriage were taken from the oral mucosa of all patients, before the initiation and after the completion of RT. Mycological investigation was based on positive KOH and Gram-stained microscopic examination of the mucosal scrapings and culture of the specimens plated on CHROMagar *Candida* chromogenic medium (Paris, France). Yeasts were identified using standard procedures. Susceptibility to antifungals of five different colonies from each isolate was determined by Etest (AB Biodisk, Solna, Sweden), as described before [8].

Statistical analysis

Chi-squared test was employed to compare the two groups of interest with respect to baseline characteristics, incidence of mucositis, candidiasis, and *Candida* carriage. Loss of weight, age, and daily and total doses of RT were assessed by Mann–Whitney *U*-test. Differences of mucositis free distribution curves between groups A and B were investigated by log-rank statistic. The incidence of *Candida* carriage before and after RT in paired observations was assessed by McNemarr's chi-squared test. All tests were two-sided, and the level of statistical significance was set at 5%.

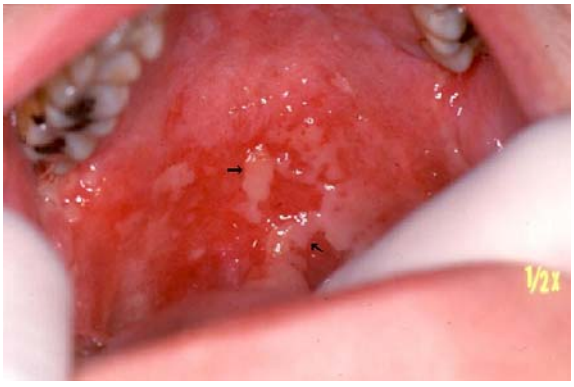

Fig. 1 Grade 3 radiation mucositis on the palate of a 35-year-old female (third week of RT for nasopharyngeal carcinoma, T2N1M0, daily RT dose 2.3 Gy, concomitant chemotherapy). Smear for *Candida* carriage was negative. Whitish-yellowish pseudomembranes (*arrows*) cover the superficially ulcerated mucosa

Results

Radiotherapy

From group A, 32 of 34 patients completed radiotherapy within the preplanned time. Two patients interrupted RT, for 2 weeks, due to weakness.

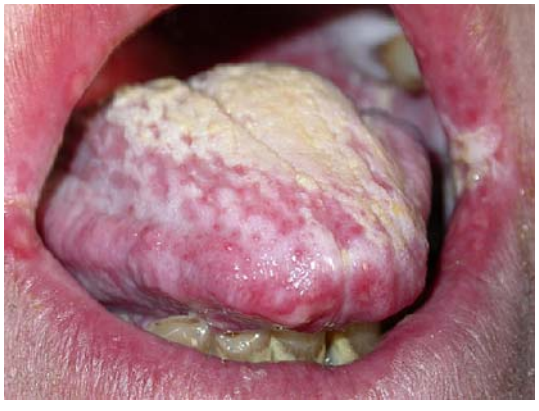

Fig. 2 Oral pseudomembranous candidiasis on the dorsum of the tongue of a 59-year-old male (third week of RT for a squamous cell carcinoma of the floor of the mouth, T3N0M0, daily dose 1.8 Gy)

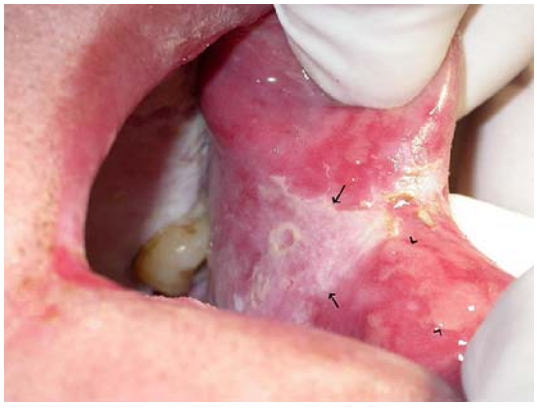

Fig. 3 The same patient of Fig. 2, on the same day. Pseudomembranous candidiasis is also seen on the buccal mucosa (*arrows*), next to lesions of ulcerative/pseudomembrane grade 3 mucositis (*arrowheads*)

From group B, 21 of 29 patients completed RT within the preplanned time. Three patients interrupted RT, for 2 weeks, due to weakness, a cold, and a reduction of white blood cells.

Oral mucositis

From group A, 24 of 34 patients developed grade 2 or 3 ulcerative/pseudomembrane mucositis (Fig. 1) at different times throughout RT, with a median onset at the fourth week.

From group B, 23 of 29 patients developed grade 2, 3, or 4 ulcerative/pseudomembrane mucositis during RT, with a median onset at 3 weeks.

The incidence of ulcerative mucositis (grades 2, 3, and 4), during RT and the week of the onset of mucositis between the two groups did not differ significantly.

At the end of RT, five patients from group A as opposed to 13 patients from group B completed RT with severe, grade 3 mucositis. The difference in the incidence of severe mucositis at the end of RT between the two groups was found significant (p=0.018). The likelihood of severe mucositis at the end of RT in group B is 4.7 times higher as compared to group A [95% CI of OR=(1.4–15.6)].

No patient from group A interrupted RT due to severe mucositis as opposed to five patients from group B; two of those five dropped out and never completed RT.

The difference of RT interruptions due to severe mucositis between the two groups was found significant (p=0.017).

Oral candidiasis

No case of candidiasis was documented in group A as opposed to ten cases of candidiasis (Figs. 2, 3) in group B; three of those ten cases recurred during RT, after 1 week of antimycotic treatment.

The prevention of candidiasis in group A, after fluconazole prophylaxis, was significant (p=0.001).

Side effects, attributed to fluconazole, were not observed, except for one case of transient nausea. Patients' liver and renal functions remained within normal limits at the end of RT.

Table 2 Week of onset of ulcerative mucositis, severe mucositis at the end of RT, RT interruptions due to mucositis, candidiasis, *Candida* carriage, antiviral treatment, and loss of weight

	Patients				*p* Value
	Group A (n=34)		Group B (n=29)		
	Number	Percentage (%)	Number	Percentage (%)	
Week of RT					
Second	5	14.7	8	27.6	0.216
Third	10	29.4	12	41.4	
Fourth	2	5.9	–	–	
Fifth	4	11.8	2	6.9	
Sixth	2	5.9	1	3.4	
Seventh	1	2.9	–	–	
Total	24		23		
Patients with severe mucositis	5	14.7	13	44.8	0.018
RT interruptions due to severe mucositis	–	–	5	17.2	0.017
Candida carriage before RT	24	70.6	18	62.1	0.655
Candidiasis during RT	–	–	10	34.5	0.001
Candida carriage after RT	7/27	25.9	13/25	52.0	0.100
Patients who received antiviral treatment	15	44.1	13	44.8	0.746
Loss of weight (kg)					
Median	5		8		0.061
Range	−1–35		0–16		

Table 3 Overall prevalence of yeast species isolated before and after RT

	Patients							
	Group A (n=34)				Group B (n=29)			
	Before RT		After RT		Before RT		After RT	
	Number	Percentage (%)	Number	Percentage (%)	Number	Percentage (%)	Number	Percentage (%)
Yeast species								
Candida albicans	22	70.97	6	50	13	52	7	50
Candida glabrata	3	9.68	3	25	4	16	3	21.43
Candida tropicalis	1	3.22	1	8.33	5	20	3	21.43
Candida krusei	1	3.22	1	8.33	–	–	1	7.14
Candida dubliniensis	2	6.46	–	–	–	–	–	–
Candida kefyr	–	–	–	–	1	4	–	–
Candida globosa	–	–	–	–	1	4	–	–
Candida parapsilosis	1	3.22	1	8.33	–	–	–	–
Cryptococcus humicolus	1	3.23	–	–	–	–	–	–
Saccharomyces kluverii	–	–	–	–	1	4	–	–
Total	31	100	12	100	25	100	14	100

Antiviral treatment

A similar percentage of patients from both groups received empirical antiviral treatment, after a presumptive diagnosis for herpetic infection.

Candida carriage

Before the initiation of RT, the prevalence of *Candida* carriage was similar in both groups. Twenty-four smears in group A and 18 in group B were found *Candida* positive. Multiple yeast species were isolated in four of 24 smears from group A and in six of 18 smears from group B.

After the completion of RT, a significant reduction of 40.7% (p=0.001, 95% CI 16.7–64.8) of the prevalence of *Candida* carriage was observed in group A as a result of antifungal prophylaxis. The reduction of *Candida* carriage observed in group B, attributed to fluconazole therapy of patients who developed candidiasis, was not statistically significant.

Multiple yeast species were isolated in four smears from group A and in six smears from group B. *Candida dubliniensis* was found as a colonizer in two smears from group A.

Fluconazole-resistant isolates were not recorded in either group.

Table 2 shows the onset, in weeks, of ulcerative mucositis and the number of patients in both groups, the incidence of severe mucositis (grade 3 or 4) at the end of RT, the incidence of interruptions of RT due to severe mucositis, the incidence of candidiasis, the *Candida* carriage before and after RT, the number of patients who received empirical antiviral treatment, and the weight loss. The p value is also shown in each parameter. As it is shown in Table 2, the patients of group B have a higher weight loss (p=0.061), indicating their increased difficulty in food intake.

Table 3 shows the cumulative, overall yeast species isolated before and after RT.

Discussion

Oral mucositis is one of the most significant toxicities associated with head and neck radiotherapy. Radiation-related mucosal barrier injury allows for microbial colonization and infection, leading, in turn, to amplification of tissue injury [21].

Oral candidiasis, after mucosal colonization by *Candida* species, is the most common infection in head and neck cancer radiotherapy. One out of three patients is anticipated to develop oral pseudomembranous candidiasis during the course of RT [4, 6, 10, 14, 15, 17], with penetration and inflammation of the oral mucosa [19].

Candidiasis-related mucosal inflammation, being superimposed on mucositis, should add to the severity of radiation-related mucosal injury.

In the present study, the severity of oral mucositis was evaluated after the prevention of candidiasis, using daily fluconazole antifungal prophylaxis throughout RT as opposed to fluconazole therapy, when the infection had developed. A significant reduction in the incidence of severe, grade 3 or 4 mucositis at the end of RT in group A, which received fluconazole prophylaxis, was observed (p=0.018), pointing to a beneficial effect of fluconazole on the severity of mucositis.

The 44.8% incidence of severe mucositis observed in the present study, in the patient group B, without fluconazole prophylaxis, is in agreement with the mean in-

cidence of severe mucositis reported in the review of 33 studies by Trotti et al. [24] during radiotherapy (34%) and radiochemotherapy (43%).

A similar overall 43 and 50% incidence of severe mucositis has also been reported by Wijers et al. [25] and by El-Sayed et al. [5], respectively. Those authors used topical antimicrobial prophylaxis, including an antifungal, during RT. In the first study [25], the counts of *Candida* species were not affected, and in the second study [5], yeast counts were assumed to have been suppressed. In both studies, the incidence of the development of candidiasis or the prevention of candidiasis was not reported.

In addition to the beneficial effect on the incidence of severe mucositis, in the present study, fluconazole prophylaxis resulted in a significant beneficial impact on RT interruptions due to severe mucositis (p=0.017).

No patient from group A, with fluconazole prophylaxis, interrupted RT because of severe mucositis as opposed to 17.2% of patients from group B, without fluconazole prophylaxis. Similar to group B of the present study, 9–19% of patients had also RT regimens interrupted or modified because of mucositis, in five studies, in the review by Trotti et al. [24].

As in the present study, a significant beneficial effect of fluconazole prophylaxis on RT interruptions was also reported by Mucke et al. [12]. A significant prevention of the development of "*Candida* stomatitis" was also observed. *Candida* stomatitis was evaluated as the cause of RT interruptions.

The beneficial impact of fluconazole prophylaxis on RT interruptions was also shown by Koc and Aktas [7]. "Clinical candidiasis" was reported as the cause of RT interruptions.

In the present study, severe mucositis was evaluated as the cause of RT interruptions instead of *Candida* stomatitis or clinical candidiasis.

Differences in definition, differentiation, and diagnostic criteria of severe mucositis and pseudomembranous candidiasis are possibly the cause for the above discussed discrepancies, as to whether clinical candidiasis or *Candida* stomatitis or severe mucositis may cause RT interruptions. Nevertheless, all three studies agree on the beneficial effect of fluconazole prophylaxis on RT interruptions.

The delay in the onset of ulcerative mucositis observed in our study, median fourth week in group A as opposed to third week in group B, was not found significant. The delay in the onset of "mycotic mucositis" observed by Koc and Aktas [7] was not reported as significant either. That finding could be in accordance with the concept that the role of bacteria in mucositis occurs late in the pathobiology of mucositis, after ulceration has occurred [21].

Candida carriage before RT was similar in both groups of our patients and was in agreement with the incidence of *Candida* carriage reported by others [2, 4, 11, 12, 14–18], in head and neck cancer patients during and after RT.

In the patient cohort studied, *Candida albicans* was the most common isolate, before and after RT, as noted before [4, 7, 11, 12, 14–17].

C. dubliniensis was identified, in our head and neck cancer patients, as a colonizer of the oral mucosa, before RT, with an overall prevalence of 2.94% of all yeast species isolated before and after RT. A similar 2% prevalence of the above *Candida* species was also found by Sebti et al. [20] at a cancer center. *C. dubliniensis*, first described in 1995 in HIV-seropositive patients, seems to show an expanding clinical and geographic distribution.

In conclusion, fluconazole antifungal prophylaxis showed a significant beneficial impact on the incidence of severe, grade 3 or 4, mucositis and mucositis-related RT interruptions in our group of patients and supported the hypothesis that candidiasis plays a significant role on the severity of radiation mucositis.

Oral candidiasis was prevented, but mycological cure was not achieved.

Resistant yeast isolates were not identified, whereas side effects as a result of the prophylactic administration of fluconazole were not observed.

As a limitation of the study, the relatively small size of each treatment arm might be considered. Post hoc power analysis though, based on the incidence of severe mucositis in the two groups, revealed that the power for declaring current results as significant at 5% level is 75%. Acknowledging this fact, we believe that the current study provides data on the build of a randomized controlled trial on the effect of fluconazole prophylaxis on treatment schedule and the quality of life of the patients during head and neck radiotherapy.

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References

1. Arendorf TM, Walker DM (1980) The prevalence and intra-oral distribution of *Candida albicans* in man. Arch Oral Biol 25:1–10
2. Chen TY, Webster JH (1974) Oral Monilia study on patients with head and neck cancer during radiotherapy. Cancer 34:246–249
3. Cox JD, Stetz J, Pajak TF (1995) Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). Int J Radiat Oncol Biol Phys 31:1341–1346
4. Dahiya MC, Redding SW, Dahiya RS et al (2003) Oropharyngeal candidiasis caused by non-albicans yeast in patients receiving external beam radiotherapy for head–neck cancer. Int J Radiat Oncol Biol Phys 57:79–83

5. El-Sayed S, Nabid A, Shelley W et al (2002) Prophylaxis of radiation-associated mucositis in conventionally treated patients with head and neck cancer: a double-blind, phase III, randomized, controlled trial evaluating the clinical efficacy of an antimicrobial lozenge using a validated mucositis scoring system. J Clin Oncol 20: 3956–3963
6. Epstein JB, Freilich MM, Nhu DL (1993) Risk factors for oropharyngeal candidiasis in patients who receive radiation therapy for malignant conditions of the head and neck. Oral Surg Oral Med Oral Pathol 76:169–174
7. Koc M, Aktas E (2003) Prophylactic treatment of mycotic mucositis in radiotherapy of patients with head and neck tumors. Jpn J Clin Oncol 33:57–60
8. Kollia K, Arabatzis M, Kostoula O et al (2003) *Clavispora (Candida) lusitaniae* susceptibility profiles and genetic diversity in three tertiary hospitals (1998–2001). Int J Antimicrob Agents 22:455–457
9. Kwong DLW, Sham JST, Chua DTT, Choy DTK, Au GKU, Wu PM (1997) The effect of interruptions and prolonged treatment time in radiotherapy for nasopharyngeal carcinoma. Int J Radiat Oncol Biol Phys 39:703–710
10. Makkonen TA, Minn H, Jekunen A, Vilja P, Tuominen J, Joensuu H (2000) Granulocyte-macrophage colony-stimulating factor (GM-CSF) and sucralfate in prevention of radiation-induced mucositis: a prospective randomized study. Int J Radiat Oncol Biol Phys 46:525–534
11. Martin MV, Al-Tikriti U, Bramley PA (1981) Yeast flora of the mouth and skin during and after irradiation for oral and laryngeal cancer. J Med Microbiol 14:457–467
12. Mucke R, Kaben U, Libera T et al (1998) Fluconazole prophylaxis in patients with head and neck tumours undergoing radiation and radiochemotherapy. Mycoses 41:421–423
13. Nicolatou O, Sotiropoulou-Lontou A, Skarlatos J, Kyprianou K, Kolitsi G, Dardoufas K (1998) A pilot study of the effect of granulocyte-macrophage colony-stimulating factor on oral mucositis in head and neck cancer patients during X-radiation therapy : a preliminary report. Int J Radiat Oncol Biol Phys 42:551–556
14. Nicolatou-Galitis O, Dardoufas K, Markoulatos P et al (2001) Oral pseudomembranous candidiasis, herpes simplex virus-1 infection, and oral mucositis in head and neck cancer patients receiving radiotherapy and granulocyte-macrophage colony-stimulating factor (GM-CSF) mouthwash. J Oral Pathol Med 30:471–480
15. Nicolatou-Galitis O, Sotiropoulou-Lontou A, Velegraki A et al (2003) Oral candidiasis in head and neck cancer patients receiving radiotherapy, with amifostine cytoprotection. Oral Oncol 39:397–401
16. Paula CR, Sampaio MCC, Birman EG, Siqueira AM (1990) Oral yeasts in patients with cancer of the mouth, before and during radiotherapy. Mycopathologia 112:119–124
17. Redding SW, Zellars RC, Kirkpatrick WR et al (1999) Epidemiology of oropharyngeal *Candida* colonization and infection in patients receiving radiation for head and neck cancer. J Clin Microbiol 37:3896–3900
18. Rossie KM, Taylor J, Beck FM, Hodson SE, Blozis GG (1987) Influence of radiation therapy on oral *Candida albicans* colonization: a quantitative assessment. Oral Surg Oral Med Oral Pathol 64:698–701
19. Samaranayake LP, MacFarlane TW (1990) Oral candidosis. Wright, London, p 7
20. Sebti A, Kiehn TE, Perlin D et al (2001) *Candida dubliniensis* at a Cancer Center. CID 32:1034–1038
21. Sonis ST (2004) A biological approach to mucositis. J Support Oncol 2:21–36
22. Spijkervet FKL, van Saene HKF, Panders AK, Vermey A, Mehta DM (1989) Scoring irradiation mucositis in head and neck cancer patients. J Oral Pathol Med 18:167–171
23. Spijkervet FKL, van Saene HKF, van Saene JJM et al (1991) Effect of selective elimination of the oral flora on mucositis in irradiated head and neck cancer patients. J Surg Oncol 46:167–173
24. Trotti A, Bellm LA, Epstein JB et al (2003) Mucositis incidence, severity and associated outcomes in patients with head and neck cancer receiving radiotherapy with or without chemotherapy : a systematic literature review. Radiother Oncol 66:253–262
25. Wijers OB, Levendag PC, Harms ERE et al (2001) Mucositis reduction by selective elimination of oral flora in irradiated cancers of the head and neck: a placebo-controlled double-blind randomized study. Int J Radiat Oncol Biol Phys 50:343–352