Support Care Cancer (2004) 12:517–525
DOI 10.1007/s00520-004-0634-1

ORIGINAL ARTICLE

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Topical polyene antifungals in hematopoietic cell transplant patients: tolerability and efficacy

Received: 16 September 2003
Accepted: 8 March 2004
Published online: 24 April 2004

Study supported by Bristol-Myers Squibb, Co., Hopewell, NJ, USA

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Abstract *Purpose:* The effectiveness of amphotericin B oral suspension versus nystatin oral suspension for the prevention of oral colonization by *Candida* in hematopoietic cell transplant (HCT) patients was examined. *Methods:* Prior to hematopoietic cell infusion, 40 patients receiving systemic fluconazole for prophylaxis were randomized to receive either amphotericin B oral suspension or nystatin oral suspension, q.i.d. The study continued to day 21 or until the patient was discharge from the hospital or withdrawn from the study. Oral examinations were conducted twice weekly, and adverse events and compliance were recorded. Cultures were taken for quantitative counts and species identification. *Candida* isolates were assessed for resistance to the oral antifungal agents. Blood was collected for assessment of amphotericin B levels. *Results and discussion:* Ulcerative mucositis occurred in 84.6% of patients undergoing HCT, and no correlation was observed between the severity of mucositis and the presence of oral *Candida* and the severity of mucositis. Systemic and topical antifungal treatment resulted in a decrease in the number of colonized patients (54.8% before treatment; 23.1% during treatment); however, oral colonization was not eliminated. Tolerability of the oral rinse products was limited, with greater noncompliance in the amphotericin B than the nystatin group. Reports of altered taste appeared to be greater in the amphotericin B group. Minimal absorption of amphotericin B was seen following oral rinsing (serum levels 0.12–0.50 μg/ml), and no consistent changes in organism susceptibility to polyenes were seen. The results suggest that topical antifungal rinses may further control oropharyngeal colonization by *Candida* in patients on systemic antifungals receiving HCT, but the effect is limited by tolerability and reformulation and should be considered in order to increase compliance.

Introduction

There is considerable evidence that oropharyngeal flora represents an important source of systemic infection in neutropenic patients [26, 25, 9, 27, 59, 33, 40]. Systemic infection in immunosuppressed cancer patients has been attributed to oral sources in 25–50% of cases [26, 25, 9, 27, 33]. Up to one half of all oral infections in patients with acute leukemia are of fungal etiology, primarily due to *Candida* [25, 6]. Oropharyngeal candidiasis may extend regionally and result in systemic infection that is associated with high mortality rates in immunocompromised cancer patients [56, 64, 28]. Oral colonization is seen in the majority of patients who develop systemic candidiasis [22]. In patients with leukemia, disseminated fungal infections are reported in 22–56% of subjects at autopsy; however, a premorbid diagnosis is made in a maximum of 28% of cases [22, 53, 44]. Therefore, prevention of colonization of the oropharynx and prevention of clinical oropharyngeal candidiasis may be critically important in the prevention of systemic infection and in preventing mortality due to *Candida* .

Topical agents have been examined with the goal of reducing oral colonization and oropharyngeal infection. However, available topical antifungals have limitations in acceptability, efficacy, or toxicity [56, 21, 5, 43, 54, 63, 34, 4]. Amphotericin B oral suspension (Fungizone oral suspension, Bristol-Myers Squibb) is a candidate for prophylaxis of oropharyngeal candidiasis. *Candida* are rarely resistant to amphotericin B, clinically (IV use) or in vitro [11, 48, 58, 62, 37, 31, 18, 3]. However, the related topical polyene, nystatin, despite similarly rare in vitro resistance, has demonstrated poor efficacy in these situations [37, 31, 29, 2, 52, 32, 12].

While compliance with topical applications could be a limiting factor with any agent, evidence favors a superior antifungal effect of topical oral amphotericin. *Candida* generally exhibit a 2-to-10-fold lower minimal inhibitory concentration in vitro with amphotericin B than with nystatin [16, 17, 35]. Also, commercial amphotericin B suspension is prepared at a 4-fold higher concentration than that of nystatin oral suspension: nystatin 100,000 U/ml=25 mg nystatin/ml. Fungizone oral suspension contains 100 mg/ml amphotericin suspension, which has been shown to be effective in non-HIV-related candidiasis [47, 61]. In addition, cases clinically resistant to topical nystatin may respond to oral amphotericin B [1]. Use of nystatin oral suspension for prophylaxis of candidiasis in leukemia/BMT patients has been disappointing [6, 28, 21, 5, 54, 63, 29, 32, 12].

Amphotericin B oral suspension was approved by the US FDA (Food and Drug Administration) in 1970 for treatment of oral candidiasis (NDA 50–341). Since the 1960s, this suspension or similar preparations for prophylaxis and treatment of oral candidiasis has been given primarily in Europe in non-HIV-infected patients [10, 20, 30, 42, 45, 57, 23]. It also may be used as first-line therapy and prophylaxis of oral candidiasis.

Amphotericin B suspension has not been assessed in a clinical study in HCT patients to date. The purpose of this study was to access safety, tolerability, and efficacy of amphotericin B oral suspension in preventing or eliminating oropharyngeal colonization of *Candida* in patients receiving HCT.

Methods and materials

This was a randomized open-label, phase IV study comparing antifungal prophylaxis in patients receiving autologous HCT for a variety of malignancies (Table 1). There were no significant differences in the transplant conditioning regimens used in the two study groups. Patients in the amphotericin group were conditioned with the following regimens: high-dose melphalan and thiotepa with [40] or without busulfan [25], cyclophosphamide ± etoposide with either total body irradiation [9], iodine-131-radiolabled anti-CD20 antibody [25], or the following regimes: high-dose melphalan and thiotepa with [59] or without busulfan [26]; high-dose melphalan alone [26], cyclophosphamide and etoposide with either total body irradiation [25], iodine-131-radiolabled anti-CD20 antibody [9], or miscellaneous. Patients were provided with systemic fluconazole (200 mg/day) antifungal prophylaxis and acyclovir (800 mg twice a day) during the study period. In addition, patients received double-strength trimethoprim/sulfamethoxazole orally b.i.d. for approximately 1 week pretransplant and twice per week following neutrophil and platelet engraftment as antibacterial prophylaxis. When a patient developed febrile neutropenia, they were treated empirically with an antibiotic (imipenem or ceftazidime) until fever and neutropenia resolved. Flagyl was used if patients developed Clostridium difficile colitis.

Patients were adults (>16 years of age) receiving HCT with a Karnofsky performance status of $\geq$60% who were willing to comply with the study protocol and who had provided informed consent. Patients were excluded if they had an allergy to amphotericin B or nystatin or were pregnant, lactating, or breast-feeding. Potential subjects were approached by the ward staff to obtain permission for an investigator to present the study and obtain informed consent. Patients were randomized using a table of random numbers. Oral rinsing was conducted for more than 30 s q.i.d with nystatin suspension (400,000 IU) or amphotericin B suspension (500 mg).

All study patients had thorough medical evaluations within 2 weeks of administration of the study drug. Results of a patient history, physical examination (including head, neck, and intraoral examination), oral/dental disease stabilization, and standard institutional oral-care instructions were compiled. Recommended oral care included daily toothbrushing with a soft brush, flossing teeth if regular floss use prior to admission, and frequent oral rinsing with saline/bicarbonate. Effectiveness of oral hygiene was assessed by

Table 1 Medical diagnoses

Diagnosis	Amphotericin B	Nystatin
Non-Hodgkin's lymphoma	13	10
Breast cancer	5	7
Hodgkin's disease	1	2
Multiple myeloma	1	2
Testicular cancer	1	-
Total	21	21

recording a global estimate of oral hygiene. Routine clinical laboratory tests were completed including a pregnancy test for women of childbearing age. Head and neck and intraoral examination were completed on day −3 to day 0 of HCT. A presumptive clinical diagnosis consistent with oral candidiasis was based on previously described clinical findings [29], and a diagnosis of candidiasis required clinical findings and laboratory confirmation of the presence of *Candida*. Oral mucositis grade was assessed and scored using the oral mucositis index (OMI) as described by Schubert et al. [60] and the mucositis scale of the National Cancer Institute (NCI). The examiners conducted training in mucositis scoring prior to study initiation. Patients were assessed twice weekly. During each visit, taste, texture, and tolerability of the oral rinses using a visual analogue scale (VAS) and compliance with use were recorded. A diary of rinse use was completed. Results were separately recorded by the hospital staff into the patients' medical records. Concomitant medications were administered as ordered, although chlorhexidine rinse and other topical antifungal medications were prohibited. All pain-relieving medications given to the study subjects were recorded.

One hour after use of the rinses, oral specimens were collected for culture by oral rinsing with 5 cc of saline for one-half minute by direct swabbing of the cheeks and dorsum of the tongue. Quantitative colony counts of fungi and identification of *Candida* were completed. If fungi were isolated, fungal susceptibility testing was conducted using the broth dilution method as specified by the National Committee on Clinical Laboratory Standards [46]. Patients receiving amphotericin B oral suspension systemic absorption were assessed by determining serum levels once weekly during treatment and at the end of the study period using the agar-diffusion bioassay [39]. Laboratory tests, including hematology, liver function, and renal function, were completed at the end of the study.

Patients exited the study protocol for any of the following reasons:

1. A clinically significant adverse event (SAE) of grade 3 or higher potentially related to study medications with the exception of an SAE related to HCT (e.g., expected hematologic abnormalities related to preparative regimen and transplantation)
2. Patient required protocol-prohibited medication(s)
3. Patient refusal to continue in the study
4. Patient missed four consecutive doses of study drug

All discontinued patients remained under observation during their hospitalization, and procedures required on the last day of the study or at the time of hospital discharge were performed. Patients were prospectively stratified by the conditioning regimen (with and without radiation therapy) and by the systemic antifungal prophylaxis provided. The primary endpoint was prevention or elimination of oral colonization by *Candida*, and secondary endpoints were safety and tolerability of amphotericin B oral suspension and nystatin oral suspension. Primary efficacy was based on the intent to treat the patient populations. The presence of oral candidiasis, oral colonization by *Candida*, and quantitative colony counts were assessed. Symptoms and tolerability of rinse use were recorded using a visual analogue scale (VAS, 0=excellent/none and 100=severe/terrible).

The incidence of emergent adverse events and SAE were assessed by treatment group and compared using exact methods for chi-square analysis. Adverse events and details of their confirmation and resolution were recorded. Some *t* tests were conducted for normally distributed data, and Wilcoxon rank sum tests for non-normally distributed data.

Results

A total of 42 subjects were randomized, 21 in each rinse group. One patient was randomized to nystatin but was not eligible, and one patient withdrew consent prior to randomization. This resulted in a total of 20 subjects in both groups who received the study drug. Two subjects in the amphotericin group died, one near initial follow-up resulting in only partial initial follow-up data, and one after the first follow-up visit. Also, two subjects withdrew from the nystatin group after the initial visit but before receiving the rinse. Mean ages of patients given amphotericin were 45.6 years and nystatin 45.5 years. There were 11 men and ten women in the amphotericin group and ten men and 11 women in the nystatin group. Medical diagnoses leading to transplant are shown in Table 1. Total body irradiation (TBI) was included in the transplant protocol in five patients in the amphotericin group and six in the nystatin group. All patients were provided systemic fluconazole prophylaxis except three in the nystatin group who received systemic amphotericin B (0.3–0.5 mg/kg IV) prophylaxis. No statistically significant differences were seen at baseline between the two treatment groups in vital signs and in clinical laboratory test results, including hematologic and biochemistry studies and urinalysis. One patient in the amphotericin B group and two in the nystatin group were diabetic.

Examination of the head, neck, and oral soft tissues at study enrollment revealed no differences between the groups. Four patients in the amphotericin group had dentures: one did not use the prosthesis while in the hospital, and three wore the prostheses occasionally. In the nystatin group, eight patients had dentures. Six wore the prosthesis regularly during the day and two wore the appliance occasionally. No differences were seen throughout the study in global assessment of oral hygiene (Table 2), and no differences in the oral mucositis grade (OMI and NCI) were seen at the initial visit or over the follow-up period

Table 2 Global estimate of oral hygiene. *HCT* hematopoietic cell transplant

Study group	Pretreatment				Worst oral hygiene during HCT*	
	Excellent	Good	Fair	Poor	Good	Fair
Amphotericin B	1	15	2	1	14	6
Nystatin	2	15	3	0	10	9
	Exact p=>0.99 chi-square				Exact p=.33 chi-square	

* N=39; data missing for one subject at follow-up

Table 3 Most severe mucositis score during in-patient hematopoietic cell transplant (HCT)

Study group	Oral mucositis index (OMI)			
	OMI score			
	0	≤0.40	≤0.60	≤1.0
Amphotericin	1	7	6	6
Nystatin	2	5	5	7
	Exact p=0.90 chi-square			
	National Cancer Institute grade			
	0	1	2	3
Amphotericin	1	0	4	15
Nystatin	2	3	1	13
	Exact p=0.17 chi-square			

N=39; data missing for one subject in each group pre-treatment

Table 5 Adverse effects of oral rinses

Adverse event	Severity				
	None	Mild	Moderate	Severe	P value*
Nausea					
Amphotericin	4	6	7	3	–
Nystatin	3	8	6	2	1.00
Vomiting					
Amphotericin	7	8	3	2	–
Nystatin	8	6	4	1	0.75
Diarrhea					
Amphotericin	14	5	1	0	–
Nystatin	14	5	0	0	1.00

* Exact p-value, chi-square, comparing none versus mild to severe

between the treatment groups (Table 3). Similarly, Bearman toxicity was identified as 0 in one amphotericin patient and four nystatin patients and scored as 2 in 16 amphotericin patients and 15 nystatin patients. Three patients completed treatment without developing mucositis, and in those who developed mucositis, the severity was similar between the groups. Also, no differences in oral bleeding, oral hygiene, self-report of dry mouth, oral or throat discomfort with eating, or use of topical anesthetic agents were seen between study groups. No patient smoked during the transplant period.

Compliance with use of oral rinses was carefully assessed. Patient, and medical records of use, were assessed. Patients were observed for duration of oral rinsing weekly. At the termination visit, 15 refused rinsing with amphotericin, results were missing for two subjects, and only four patients used the rinse for more than 1 minute. In the nystatin group, eight refused rinsing at follow-up, data were missing for six, six rinsed more than 1 minute, and one rinsed less than one-half minute. The volume of rinse used per day was less in the amphotericin B group (median=6.9, range=2.0–10.0) than the nystatin group (median=12.7, range=4.0 to −14.8, p=0.0001 Wilcoxon) due to different volumes required for dosing. Similarly, the total volume of rinse used over the study period was less in the amphotericin B group (median=24, range=2–170) than in the nystatin group (median=112, range=4–250, p=0.0067, Wilcoxon). The number of doses used per day was similar between the two groups (amphotericin, median=2.5, range=1.0–3.7; nystatin, median=2.7, range=1.0–3.4, p=0.6, Wilcoxon), but the total number of times the rinse was used was less in the amphotericin B group (median=9.5, range=1–62) than the nystatin group (median=19.0, range=1–51, p=0.06 Wilcoxon). There was no difference between the total number of times the rinse was swallowed following rinsing (Table 4). Similar reports of rinse use per day were reported by the study patients and in compliance records. The adverse effects associated with the use of the oral rinses were similar between groups (Table 5). There were fewer subjects in the amphotericin B group (n=3) than in the nystatin group (n=10) completing the study (exact p=0.043, chi-square). Early study termination of the study rinse was due primarily to patient compliance (Table 6).

The median number of days in hospital was 8.5 (range 3–19) for amphotericin and 11 (range 6–23) for nystatin. The median number of days following transplant at termination of rinsing was 5 (range=0–18) for amphotericin B and 8 (range=0–20) for nystatin (p=0.018 Wilcoxon). Reasons recorded for termination of the rinse are shown in Table 7. No significant differences were seen at the termination visit in vital signs and in clinical laboratory testing other than creatinine (milligrams per deciliter), amphotericin median=0.7 (range=0.5–1.3), nystatin median=0.6 (range=0.2–1.1, p=0.026 Wilcoxon).

No differences in risk factors for candidiasis were seen between patient groups, including diabetes, denture use, tobacco use, subjective dry mouth, and oral hygiene. Nine patients in the amphotericin group were provided topical anesthetics during the trial, and two used oral mucosa coating agents. Five in the nystatin group used topical anesthetic agents and two used coating agents. Systemic opioid analgesics for oropharyngeal pain were provided to

Table 4 Compliance with oral antifungal rinse use: median (range)

	Study group		
	Amphotericin B	Nystatin	P value (Wilcoxon)
Number of times rinse used	9.5 (1–62)	19.0 (1–51)	0.06
Number of days rinse used	4.0 (0–18)	6.0 (0–18)	0.18
Number of times rinse swallowed	6.0 (0–61)	6.0 (0–51)	0.36
Number of times rinse spit out	2.0 (0–27)	4.0 (0–44)	0.46

Table 6 Reason for study termination

Study group	Investigator termination	Patient termination	Missing	Completed study
Amphotericin	2	14	1	3
Nystatin	1	7	2	10
			Exact p=0.04 chi-square*	

* Comparing completed study versus not completed study

Table 7 Symptoms reported with oral rinsing*

Symptom	Amphotericin	Nystatin	P value
	Mean (SD)	Mean (SD)	(t test)
Taste	61.9 (20.4)	47.4 (26.2)	0.06
Texture	68.7 (26.3)	48.8 (27.3)	0.03
Nausea	46.6 (36.9)	50.7(33.1)	0.72
Oral discomfort	40.4 (32.8)	39.4 (34.7)	0.93
Oral burning	22.9 (26.4)	21.7 (29.3)	0.90
Overall tolerability	65.9 (25.6)	51.5 (32.2)	0.13

*Mean VAS score 0=excellent, 100=terrible

Table 8 Clinical signs of oropharyngeal candidiasis*

Study group	Pretreatment		During treatment	
	Yes	No	Yes	No
Amphotericin	1	20	4	16
Nystatin	3	18	8	11
	Exact p=0.61**		Exact p=0.18**	
Oral colonization by candida species using oral rinse				
Amphotericin	13	8	4	16
Nystatin	10	11	5	14
	Exact p=0.54**		Exact p=0.72**	

* White adherent patches that wipe off, erythema; later confirmed with *Candida* isolation
** Chi-square

12 of the amphotericin patients and 13 of the nystatin subjects. Antibiotics were provided to ten patients in the amphotericin B group and 13 in the nystatin group.

The presence of clinical oral candidiasis and oral colonization by *Candida* are shown in Table 8. Prior to the initiation of study rinses, 13 (65%) patients in the amphotericin group were colonized with *Candida* species and ten (50%) in the nystatin group. In the amphotericin group, the median cfu was 0 (range=0–1,500), and in the nystatin group 0 (range=0–4000, p=0.73 Wilcoxon). *Candida* were identified in four patients while on the study rinse using amphotericin B and in five patients using nystatin (exact p=0.72 chi-square). The most common organism was *C. albicans*. *C. glabrata* was detected at the initial visit in three patients in the amphotericin B group and none in the nystatin group (exact p=0.098 chi-square). In one patient colonized with *C. glabrata*, colonization continued while on fluconazole and while using the oral amphotericin B rinse. Median colony forming units of *Candida* species while using the oral rinse in the amphotericin group was 0 (range=0–40) and in the nystatin group 0 (range=0–220, p=0.52 Wilcoxon). One patient in the amphotericin group had a marked increase in *Candida* counts from 30 to 8,000 cfu following discontinuation of amphotericin B rinse. In the nystatin group, four had colony counts decrease while on nystatin rinse, one had an increase, and two had an increase on discontinuing the rinse. Minimal blood levels of amphotericin B were detected in the patients provided amphotericin B suspension (median=0.24, range=0.12–0.50). No trends were seen in the sensitivity of *Candida* isolates to the polyenes.

Discussion

Amphotericin B is the "gold standard" for systemic antifungal therapy. The potential for topical application of amphotericin B in prevention of oropharyngeal colonization and infection is of continuing interest. This study evaluated the effect of amphotericin B suspension versus nystatin suspension for the prevention of colonization and infection by *Candida* in the oral cavity of patients receiving HCT in addition to the systemic prophylaxis. Topical amphotericin was compared to the institutional protocol of use of topical nystatin in addition to systemic prophylaxis.

Amphotericin B is classified as a Category B risk to the developing fetus because the drug crosses the placenta, although there are no reports of subsequent fetal abnormalities [14}. Teratogenicity has been assessed in animal studies [47, 14]. However, teratogenicity is of no concern in studies of HCT patients, as transplant patients are virtually all sterile due to their medical treatment and they are told not to conceive because of the teratogenic effects of the conditioning chemotherapy and irradiation.

A retrospective analysis of neutropenic patients provided intravenous, oral, and nebulized amphotericin B, as prophylaxis for fungal infection was compared to historical controls. The use of amphotericin B provided effective prophylaxis [19]. Amphotericin B oral suspension has been reported to be well tolerated at a wide range of doses, although side effects include gastrointestinal discomfort, nausea, vomiting, or diarrhea, especially at $\geq$2,000 mg/day [47], and subjects rarely experience irritation of the oral mucous membranes [47]. However, extemporaneous preparations of amphotericin have poor palatability. Commercial amphotericin B oral suspension contains flavorings designed to overcome this problem, although it is reported that some patients find the taste disagreeable.

Systemic absorption of orally administered amphotericin is reported to be minimal except after antineoplastic chemotherapy [47, 42, 15], and systemic absorption was assessed in the current study. The minimal blood levels of amphotericin B seen in the current trial suggest minimal though measurable uptake of amphotericin B despite limited compliance with use of the rinse. This finding may have implications for the total dose of systemic amphotericin B that may be available for treatment in these patients. Systemic toxicities from systemic administration, such as renal insufficiency, anemia, hypokalemia, or hypomagnesemia, were not identified in our study. In another trial, no laboratory abnormalities were associated with the suspension in patient studies using up to 2,000 mg/day [47]. In our study, no significant differences were seen at the termination visit in vital signs or in clinical laboratory tests. In other studies, amphotericin B oral suspension was well tolerated [61, 1, 41]. Alban and Groel found no toxicities in 63 patients treated with 100 mg q.i.d. for 14 days [1]. In a more recent study of antifungal prophylaxis in neutropenic leukemia patients, 400 subjects received amphotericin B oral suspension 500 mg q.i.d. for a mean of 25 days [41]. Side effects consisted of gastrointestinal disturbances such as nausea or vomiting in 28 patients (7%), and treatment-limiting side effects occurred in 13 patients (3%) [41].

We found considerable difficulty with patient compliance due to texture and taste of the oral suspension used, although nystatin may be better tolerated. The topical preparations used in this study may be more poorly tolerated in HCT patients who frequently experience altered taste, nausea, and vomiting during transplant. Therefore, study of formulations of topical medications should be subjected to clinical trials in the patient populations for whom the product is intended.

Results of the present study document that more than 50% of patients admitted for HCT were colonized by *Candida*, with *C. albicans* being the most common species while a small percentage were colonized with *C. glabrata*. During treatment, oropharyngeal colonization was identified in patients despite systemic antifungal prophylaxis (fluconazole) and topical use of antifungals. CFUs and frequency of colonization were decreased during treatment with the use of the topical antifungals and increased following discontinuing the topical agent, which suggests that use of topical antifungal agents have an additional impact on oropharyngeal colonization in HCT despite the use of systemic fluconazole prophylaxis. A study of 115 consecutive HCT patients reported continuing oral colonization by *Candida* in one third of patients despite systemic antifungal prophylaxis [28]. The use of topical antimicrobials was assessed, and in patients provided chlorhexidine and nystatin suspension, *Candida* colonization was significantly greater than in those using chlorhexidine alone suggesting that in combination the agent-agent interaction blocks the effect on *Candida* [28].

No differences were seen in mucositis scores between patient groups in the current trial, as previously reported [28, 29], confirming that *Candida* species do not contribute to oral mucositis in HCT. Also, no difference in opioid use (most commonly due to mucositis) during HCT was seen, with approximately two thirds of patients requiring opioids during HCT.

While our study showed that topical antifungal prophylaxis may promote control of oropharyngeal colonization in patients on systemic antifungals receiving transplant, the tolerability of the oral-rinse products was limited. The principal difficulty related to tolerability was texture (viscosity) of the suspension, with greater noncompliance in the amphotericin B than the nystatin group. In addition, reports of altered taste appeared to be greater in the amphotericin B than the nystatin group. Difficulty with the use of the rinses due to texture or taste developed during the course of HCT, likely due to the conditioning regimen. However, there were no differences between the total number of times the rinse was swallowed following use, and no statistically significant difference in overall tolerability of the rinses was seen. Consistent with previous literature [11, 48, 58, 62, 37, 31, 18, 3], there was no evidence of polyene resistance occurring in *Candida* recovered during the study However, it must be noted that the mean number of days and doses of topical therapy was limited.

Almost all recent investigations of oral suspensions, including those in HIV-infected patients, employed a higher volume and/or greater milligram strength of amphotericin B recommended for either therapy or prophylaxis [45, 57, 23, 41, 13, 49]. In current use in France, amphotericin B oral suspension is generally prescribed at 5 ml (500 mg) three-to-four times a day, and studies in patients with an HIV infection demonstrate the adequacy of a 2-week course for most patients [47]. No data are available on the use of alternative topical protocols of amphotericin B in a patient with an HIV infection on maintenance therapy.

The choice of a topical antifungal includes azoles or polyenes. Topical azoles may be more effective than nystatin in management of oral candidiasis [2, 52, 50], although use must be tempered with the evidence of fungal resistance or colonization by resistant strains to azoles, which is rarely seen with the polyenes [18, 3, 51]. The combination of an azole and amphotericin B suspension was suggested as a means of decreasing colonization and development of resistant species [51]. The effectiveness of topical amphotericin B was compared to fluconazole suspension in 305 elderly patients with oropharyngeal candidiasis and clinical response in more than 80% of cases [61]. Symptoms improved more rapidly in the fluconazole-treated patients, although mycologic cure was seen in 35% of patients treated with fluconazole and 46% treated with amphotericin B (NS) [61]. There is little published data regarding oral amphotericin in the treat-

ment of fluconazole-resistant candidiasis. Despite using amphotericin concentrations 100-to-500-fold lower than previously shown as optimal in the treatment of pseudomembranous candidiasis [47], two small studies have demonstrated some success [23, 49]. Dewsnup and Stevens reported four cases successfully treated with an extemporaneous preparation of amphotericin, 1 mg in 5 ml of diluent q.i.d. [23]. Both patients were infected with *C. glabrata*, and both isolates were fluconazole resistant in vitro. The first patient remained relapse free for 3 months on once per day maintenance therapy. In the second report [49], five patients received 5 ml five times a day of a 0.2–1.0 mg/ml amphotericin solution, and all were reported to have initial, although incomplete, response, with relapse in 1–3 months. The greatest experience with oral amphotericin B in fluconazole-resistant thrush may be in France, where the suspension is available. Although data are preliminary, one investigator reported that amphotericin B oral suspension was clinically effective in 60–70% of treated patients (personal communication, Bertrand Dupont).

Fungal resistance in patients treated with topical amphotericin B is poorly defined. In vitro polyene resistance is rare but has been reported occasionally in exposed patient populations and its significance remains uncertain [18, 3, 24, 38, 55]. There are no reports of resistance developing in patients receiving amphotericin B oral suspension. In our present study, we isolated *C. glabrata* in 10% of patients, and colonization was eliminated in three of four of these patients who were in the amphotericin-B-treated group. We found no evidence of a pattern of fungal resistance, although duration of rinsing in this study was limited.

There is a continuing need for the study of prophylaxis and treatment of oropharyngeal candidiasis in neutropenic cancer patients. A multicenter study compared 144 patients given itraconazole oral solution (100 mg b.i.d.) and 133 patients given amphotericin B (500 mg t.i.d.) plus nystatin 2 MU daily [12]. A total of 65% of the itraconazole patients were effectively prophylaxed versus 53% of the polyene group, and while proven deep-fungal infection was present in 5% of both groups, fewer in the itraconazole group had superficial infections (3 versus 8%) [12].

A metaanalysis assessed 13 trials comparing fluconazole to amphotericin B in neutropenic patients and found that fluconazole and amphotericin B (mostly given orally) had similar effects, whereas nystatin (three trials) was equal to the placebo [36]. A Cochrane analysis reviewed studies of nystatin prophylaxis of the fungal infection and found nystatin prophylaxis similar to the placebo in impact on fungal colonization. Fluconazole was more effective in preventing invasive fungal infection and colonization. This lead to a recommendation against the use of nystatin for prophylaxis or treatment of fungal infection in immunosuppressed patients [32].

Our current study carefully assessed compliance with the use of topical antifungal rinses, which was found to be very limited. The findings of this study suggest that topical antifungal drugs have the potential to reduce colonization of oral and pharyngeal mucosa in HCT-caused immune suppression even with concurrent use of systemic fluconazole prophylaxis. But current formulations are poorly tolerated thus limiting their clinical utility. Nausea was a frequent complaint in patients discontinuing the oral rinses in our trial and has been reported previously [12].

New formulations that allow improved compliance are needed. Current research suggests that nonviscous liquid preparations for oral rinsing are necessary in patients where oral dryness, oral mucositis, nausea, and vomiting are common complaints [7, 8]. The evidence suggests that topical application of antifungal agents to the oropharynx may provide an advantage in HCT even in conjunction with the use of systemic broad-spectrum antifungal agents. Previous trials of oral-care products have not provided details of compliance with the use of the study agent or other oral-care products. In future trials of topical oral-rinse products, careful assessment of compliance and concurrent use of other oral-care products and patient oral hygiene is essential, as these factors may greatly affect the outcome of the study.

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