Anti-mold Prophylaxis in Patients with Superficial Fusariosis on Admission does not Prevent Invasive Fusariosis

Andrea G. Varon, Marcia Garnica, Tiyomi Akiti, Gloria Barreiros, Beatriz Moritz Trope, Simone A. Nouer, Marcio Nucci
Federal University of Rio de Janeiro, Brazil

Abstract (revised)

Objective: Since 2007 we have experienced an increase in the incidence of invasive fusariosis with a cutaneous portal of entry. We previously showed that the presence of superficial skin lesions (onychomycosis or intertrigo) growing *Fusarium* spp. on admission was associated with the subsequent development of invasive fusariosis during neutropenia. The objective of this study was to evaluate if primary prophylaxis with a mold-active azole in such patients prevents the occurrence of invasive fusariosis.
Methods: Since August 2008, all patients admitted for hematopoietic cell transplantation (HCT) or induction remission of acute leukemia were submitted to a thorough skin examination on admission, with direct exam and culture of any skin lesion. Until November 2009, no anti-mould prophylaxis was given (period 1, n=61). Starting in December 2009, all patients with baseline skin lesions growing *Fusarium* spp. received voriconazole or posaconazole prophylaxis (period 2, n=159). We compared the characteristic and outcome of these two cohorts.
Results: The two cohorts were similar regarding age, gender and underlying diseases. Multiple myeloma (35.4%) and acute myeloid leukemia (24.5%) were the most frequent underlying diseases. There were more patients undergoing allogeneic HCT in period 1 (20% vs. 1%, p<0.001). Skin lesions on admission were present in 52.5% and 30.2% in period 1 and 2, respectively (p=0.002), but the distribution of lesions was similar in the two cohorts, with ~50% of onychomycosis, ~30% of intertrigo, ~10% of a combination of the two, and ~10% other lesions. Direct exam of these lesions showed hyaline hyphae in 16 of 32 (50%) and 28 of 49 (57.1%) in periods 1 and 2, respectively (p=0.15). *Fusarium* spp. grew from 4 of the 32 cultures in period 1 and 7 of the 49 cultures in period 2 (p=0.51). Anti-mold prophylaxis was given to 1 of 4 patients with fusarial superficial infections in period 1 (voriconazole), and to 4 of 7 patients in period 2 (3 posaconazole, 1 voriconazole). Invasive fusariosis with baseline superficial fusariosis occurred in 4 of 5 patients without prophylaxis and in 1 of 6 patients receiving prophylaxis (p=0.08). Overall, invasive fusariosis was diagnosed in 6 patients in cohort 1 (10%) and 7 (5%) in cohort 2 (p=0.21).
Conclusions: The strategy of giving anti-mold prophylaxis based on positive baseline skin lesions for *Fusarium* seems to have minimal impact in reducing the overall incidence of invasive fusariosis but may prevent the occurrence of invasive fusariosis with a cutaneous portal of entry.

Introduction and Purpose

Invasive fusariosis is a mold infection with high mortality, affecting mostly patients with hematologic malignancies. Infection occurs by inhalation of spores or by direct traumatic inoculation. We have recently reported that hematologic patients with *Fusarium* onychomycosis or intertrigo were more likely to develop invasive disease during neutropenia. These patients did had not received antifungal prophylaxis with a mold active agent. This study aims to evaluate if primary prophylaxis with a mold-active azole in such patients prevents the occurrence of invasive fusariosis.

Methods

Since August 2008, all patients admitted for hematopoietic cell transplantation (HCT) or induction remission chemotherapy of acute leukemia or myelodysplasia were submitted to a thorough skin examination on admission, with direct exam and culture of any suspicious lesion. Patients admitted from August 2008 until November 2009 did not receive anti-mold prophylaxis (period 1). Starting in December 2009, all patients with baseline skin lesions growing *Fusarium* spp. received voriconazole or posaconazole prophylaxis (period 2). We compared the characteristic and outcome of these two cohorts.

Characteristics of patients and outcomes

Characteristics	Period 1 N=61	Period 2 N=159	P value
Age (years), median (range)	44 (14 – 66)	50 (13 – 72)	0.13
Gender (male/female)	37/24	101/58	0.69
Underlying disease, n (%)			
Multiple myeloma	20 (32.8)	58 (36.5)	0.97
Acute myeloid leukemia	14 (22.9)	40 (25.2)	0.73
Acute lymphoid leukemia	11 (18.0)	18 (11.3)	0.25
Myelodysplasia	4 (6.6)	2 (1.3)	0.06
Non-Hodgkin's lymphoma	4 (6.6)	12 (7.5)	0.94
Hodgkin's lymphoma	4 (6.6)	22 (13.8)	0.29
Aplastic anemia	3 (4.9)	3 (1.9)	0.22
Other	1 (1.6)	4 (2.5)	0.69
Type of treatment, n (%)			
Autologous hematopoietic cell transplantation	26 (42.6)	92 (57.9)	0.04
Allogeneic hematopoietic cell transplantation	12 (20.0)	1 (0.6)	<0.001
Induction remission chemotherapy	22 (56.1)	60 (37.7)	0.43
Other chemotherapy	1 (1.6)	6 (3.8)	0.63
Graft versus host disease, n (%)	4 (6.6)	0	<0.001
Receipt of corticosteroids, n (%)	38 (62.3)	82 (51.6)	0.15
Duration (days) of neutropenia), median (range)	8 (0 – 40)	8 (1 – 73)	0.86
Superficial skin lesion, n (%)	32 (52.5)	49 (30.2)	0.002
Onichomycosis	16/32 (50.0)	28/49 (57.1)	0.15
Intertrigus	8/32 (25.0)	13/49 (26.5)	0.89
Onichomycosis + intertrigus	5/32 (15.6)	7/49 (14.3)	0.73
Other	3/32 (9.4)	1/49 (2.0)	0.16
Fusarium spp. growth in superficial skin lesion, n (%)	4/32 (12.5)	7/49 (14.3)	0.51
Anti-mold azole prophylaxis, n (%)	2 (3.3)	18 (11.3)	0.06
Death, n (%)	11 (18.0)	16 (10.1)	0.10

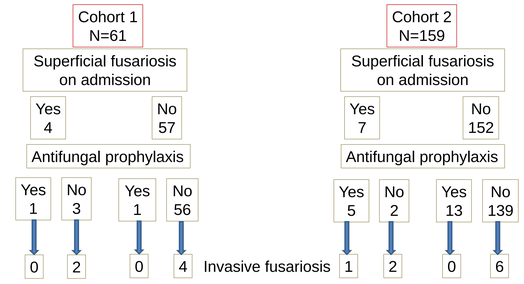
Characteristics of patients with baseline skin lesions growing *Fusarium* spp.

Patient	Underlying disease	Treatment	Type of skin lesion	Anti-mold prophylaxis	Duration (days) of neutropenia	Days from prophylaxis to neutropenia	Invasive fusariosis	Days from neutropenia to fusariosis	Days from prophylaxis to fusariosis
1	MM	Autologous HCT	Onychomycosis	-	3	-	Yes	-1	-
2	HL	Autologous HCT	Intertrigus	-	7	-	Yes	4	-
3	MM	Autologous HCT	Onychomycosis + intertrigo	-	7	-	No	-	-
4	AML	Allogeneic HCT	Intertrigus	-	20	-	Yes	13	-
5	ALL	Chemotherapy	Intertrigus		17	-	Yes	-10	-
6	ALL	Chemotherapy	Intertrigus	Voriconazole	35	3	No	-	-
7	MM	Autologous HCT	Onychomycosis + intertrigo	Voriconazole	4	7	No	-	-
8	LNH	Chemotherapy	Intertrigus	Posaconazole	10	-9	No	-	-
9	MM	Autologous HCT	Intertrigus	Posaconazole	8	6	No	-	-
10	MM	Autologous HCT	Intertrigus	Posaconazole	6	-5	No	-	-
11	MDS	Chemotherapy	Intertrigus	Posaconazole	65	-39	Yes	43	4

MM = multiple myeloma; HL = Hodgkin's lymphoma; AML = acute myeloid leukemia; ALL = acute lymphoid leukemia; MDS = myelodysplasia; HCT = hematopoietic cell transplantation

Superficial Fusariosis, Antifungal Prophylaxis and Invasive Fusariosis

	Period 1 N=61	Period 2 N=159	P value
With superficial fusariosis on admission			
No. receiving anti-mould azole	1 / 4 (25%)	5 / 7 (71%)	0.24
No. with invasive fusariosis	2 / 4 (50%)	3 / 7 (43%)	1.00
Fusariosis in recipients of anti-mould azole	0 / 1	1 / 5 (20%)	1.00
Without superficial fusariosis on admission			
No. receiving anti-mould azole	1 / 57 (1.7%)	13 / 152 (8.5%)	0.12
No. with invasive fusariosis	4 / 57 (7%)	6 / 152 (4%)	0.47
Fusariosis in recipients of anti-mould azole	0 / 1	0 / 13	-
All patients			
No. receiving anti-mould azole	2 / 61 (3%)	18 / 159 (11%)	0.07
No. with invasive fusariosis	6 / 61 (10%)	9 / 159 (6%)	0.37
Fusariosis in recipients of anti-mould azole	0 / 2	2 / 18 (11%)	1.0



Conclusions

- High incidence of invasive fusariosis in both periods (10% and 6%)
- Higher incidence of fusariosis in patients with superficial fusariosis on admission (5 cases in 11 [45%] vs. 10 cases in 209 [5%], p<0.001)
- Prophylaxis with anti-mould azoles was associated with a non-significant reduction in the incidence of invasive fusariosis (3% vs. 11%, p=0.07)
- However, because in the majority of cases of invasive fusariosis superficial fusariosis was not present on admission, relying on superficial fusariosis to initiate anti-mold prophylaxis did not result in a significant reduction in the incidence of invasive fusariosis
- A strategy of primary prophylaxis with mold active azole may prevent the occurrence of invasive fusariosis, and should be explored in prospective studies