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RESEARCH ARTICLE

Comparison of fluconazole and posaconazole for fungal prophylaxis in high-risk patients with hematological malignity

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ABSTRACT

Objective: To compare the frequency of fungal infection and mortality rates in patients with hematological malignity and receiving either flucanazole (FLU) or posaconazole (POS) prophylaxis.

Methods: This retrospective, observational study investigated fungal prophylaxis in patients with a high risk of invasive fungal infections (IFIs) and diagnosed with hematological malignity at our hospital hematology clinic between 01.01.2011 and 01.01.2013. FLU (n=70) was the prophylactic regimen between 2011 and 2012 which was replaced by POS (n=35) in the following period. The incidence and mortality rates of IFIs developing in the two periods were compared.

Results: The incidence of IFI in patients administered FLU prophylaxis was 22/70 (31%), compared to 13/35 (37%) in the patients receiving POS. Incidence of invasive pulmonary aspergillosis (IPA) in the FLU group was 21/70 (31%), compared to 9/35 (26%) in the POS group. The mortality rate in the group receiving FLU prophylaxis was 17 (24%), compared to 4 (11%) in the POS group. The difference was attributed to causes other than fungal infection. Results of subgroup analysis performed for AML were similar to the general findings in terms of both incidences of fungal infection and of mortality levels. In multivariate analysis, mean duration of neutropenia was correlated with prophylaxis failure.

Conclusion: We conclude that both agents can be successfully used in fungal infection prophylaxis for patients at high risk for IFI. *J Microbiol Infect Dis 2014;4(1): 1-6*

Key words: Fungal prophylaxis, invasive fungal infections, mortality

Hematojlojik malignitesi olan yüksek riskli hastalarda flukonazol ve posakonazol proflaksisinin karşılaştırılması

ÖZET

Amaç: Bu çalışmada hematolojik malignitesi olan ve flukonazol (FLU) veya posakonazol (POS) proflaksisi uygulanan hastalarda görülen fungal enfeksiyon sıklığı ve mortalite oranları karşılaşıldı.

Yöntemler: Bu retrospektif, gözlemsel çalışmada 01 Ocak 2011-01 Ocak 2013 tarihleri arasında hastanemiz hematoloji kliniğinde hematolojik malignite tanısıyla izlenmekte olan hastalara verilen antifungal profilaksiler değerlendirildi. Birer yıllık 2 dönemin ilkinde, hastalara proflaktik olarak FLU, 2.dönemde ise POS uygulandı.

Bulgular: FLU proflaksisi alan hastalarda görülen fungal enfeksiyon sıklığı 22/70 (31%) iken, POS alan hastalarda 13/35 (37%) olduğu görüldü. İnvaziv pulmoner aspergilloz (İPA) görülme sıklığı FLU kolunda 21/70 (31%) bulunurken, POS kolunda bu oran 9/35 (%26) bulundu. FLU proflaksisi alan gruptan 17 hasta öldü (%24), POS alan gruptan ise 4 (%11) hasta öldü. Bu farkın fungal enfeksiyon dışı nedenlerden kaynaklandığı düşünüldü. AML için yapılan subgrup analizinde fungal enfeksiyon sıklığı ve mortalite oranları bakımından sonuçlar, genel sonuçlarla benzerdi. Çoklu varyasyon analizinde hastalardaki ortalama nötropeni süresinin uzunluğuyla fungal proflaksi başarısızlığı arasında ilişki bulundu.

Sonuç: Her iki ajanın da yüksek riskli hastalardaki fungal enfeksiyon proflaksisinde başarıyla kullanılabileceği sonucuna varıldı.

Anahtar kelimeler: Fungal proflaksi, invaziv fungal enfeksiyonlar, mortalite.

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INTRODUCTION

Patients receiving intense/high-dose chemotherapy for acute leukemia and with deep neutropenia lasting more than one week are at greater risk of developing invasive fungal infections (IFIs).[1,2] The prophylactic approach is therefore important, particularly for patients identified as being at high-risk.

Antifungal drugs are now available for prophylaxis, which was a controversial issue until recently. However, there is as yet no consensus on which agent should be preferred in prophylaxis.[3-6] This study investigated the effectiveness of flucanazole (FLU) and posaconazole (POS) applied as prophylactic agents in high-risk patients with hematological malignity.

METHODS

This retrospective, observational study investigated fungal prophylaxis in patients at high risk of IFI and diagnosed with hematological malignity at our hospital hematology clinic between 01.01.2011 and 01.01.2013. Patients who had undergone bone marrow or solid organ transplantation were excluded from the study.

Tests such as blood cultures, pulmonary high resolution computerized tomography (HRCT), serum galactomannan (GM) levels and histopathological analysis were used in diagnosing IFI, in addition to clinical evaluation. GM was investigated regularly, twice a week, in these patients, and the result was regarded as positive when >0.5 in two consecutive specimens and >0.7 in a single serum specimen.[7] Under the European Organization for the Treatment of Cancer/Mycoses Study Group (EORTC/MSG) guideline, cases are evaluated as possible, probable or proven.[8] Possible pulmonary fungal disease (PFD) was defined as radiological findings concordant with PFD without microbiological evidence and probable invasive pulmonary aspergillosis (IPA) was diagnosed based on radiological evidence and GM positivity. Bronchoscopy could only be performed in three of these patients. No aspergillus growth was seen in any specimen, and no results histopathologically compatible with aspergillosis were obtained.

Our hospital's hematology and infectious diseases departments meet every six months to assess hematological patients' current data and to determine the protocols to be applied in monitoring, prophylaxis and treatment. Under this approach, considering one-year patient data between January 1st 2011 and January 1st 2012 and in the light of the current literature, we decided that POS should be used as of January 1st 2012 in the prophylaxis of patients at high risk for IFI. Therefore, in this study, patients at high risk for IFI and monitored between January 1st 2011 and January 1st 2012 were given 400 mg/d FLU (400 mg/d) by the oral route (Period 1), while between January 1st 2012 and January 1st 2013, similar patients were administered POS (3x200 mg/d) prophylaxis by the oral route (Period 2). Seventy patients were given FLU prophylaxis in the first period, and 35 patients were given POS prophylaxis in the second. Patients given prophylaxis had no fungal infection prior to prophylaxis. On the basis of up-to-date guideline recommendations, high risk for IFI was defined as deep neutropenia (<100/mm^3) lasting more than 1 week. Fungal prophylaxis was initiated for patients expected to remain in deep neutropenia for more than 1 week and due to receipt of induction chemotherapy, at the stage when chemotherapy initiated. Prophylaxis was maintained until patients left the high risk group. Fungal prophylaxis was given to all patients during hospitalization, and these cases were monitored up to the end of prophylaxis. Approval was received from the Ministry of Health for off-label use of POS prophylaxis in patients with disorders other than acute myelocytic leukemia (AML) and myelodysplastic syndrome (MDS). The incidence and mortality rates of IFIs developing in patients in both periods were then compared. Since the prophylactic efficacy of POS for malignities other than AML is not well known, our AML patient group was also assessed using subgroup analysis.

During the first period there was a construction in stem cell transplantation ward which is close to the hematology ward where patients receive high dose chemotherapy for several hematologic malignancies. In the second period when POS is used there was no construction. Apart from POS prophylaxis, no change was made in the second period compared to the first in terms of preventing fungal infections.

Failure of antifungal prophylaxis was interpreted as the development of IPA and microbiologically documented fungal infection in cases despite prophylaxis and/or the commencement of empiric antifungal therapy while prophylaxis was continuing.

Statistical analysis

The study data were transferred to SPSS 13.0 and analyzed using the chi-square test. Significance was set at $p<0.05$. Variables thought of as a risk factor for failure of antifungal prophylaxis was analyzed with multivariate logistic regression analysis.

These variables were mean duration of neutropenia, status of underlying disease, type of antifungal prophylaxis, nausea and vomiting at antifungal prophylaxis.

RESULTS

One hundred and five patients who received antifungal prophylaxis were evaluated, 67 (64%) male and 38 (36%) female. Mean age was 44.5±8 years (between 17 and 65 years). In terms of underlying diseases, 50 (48%) consisted of acute myeloid leukemia (AML), 35 (33%) acute lymphocytic leukemia (ALL), 11 (10%) Hodgkin and non-Hodgkin lymphoma, and 9 (9%) multiple myeloma. All the patients given antifungal prophylaxis had received remission-induction chemotherapy. Mean duration of neutropenia in both groups was above 2 weeks, and the duration of neutropenia were similar (18.4±3.0 and 19.5±2.0 days, respectively, p=0.463).

FLU prophylaxis was given to 70 patients in 2011. *Rhinocerebral mucormycosis* was determined in one of these and invasive pulmonary aspergillosis in 13 cases as probable infection. POS prophylaxis was given to 35 patients in 2012. *Candida krusei*, *Candida norvegensis* and *Trichosporon beigelii* strain were detected in blood cultures of three cases. Probable IPA developed in eight patients. The prevalence of fungal infection in all patients receiving FLU prophylaxis was 22/70 (31%), compared to 13/35 (37%) in patients receiving POS (p=0.827). A similar situation applies in terms of IPA. The incidence of IPA in the FLU group was 21/70 (31%), compared to 9/35 (26%) in the POS group (p=0.705). The difference was not statistically significant. In terms of levels of commencement of empiric antifungal treatment, these were 15 (21%) in the FLU group and 7 (20%) in the POS group (p=0.932). Antifungal prophylaxis failed in 37 (53%) cases in the FLU group and 20 (57%) in the POS group (p=0.845). When subgroup analysis was performed for AML, IFIs were seen in 12/33 (36%) of patients in the FLU group and 6/17 (35%) in the POS group (p=0.650). Incidence of IPA in the FLU group was 12/33 (36%), and 5/17 (29%) in the POS group (p=0.813). Antifungal prophylaxis failed in 20 (60%) cases in the FLU group and in 10 (59%) in the POS group (p=0.854). Demographic characteristics, fungal infections and prognoses of the patients receiving FLU and POS prophylaxis are shown in Tables 1 and 2.

Table 1. Patients' demographic characteristics, fungal infections and prognoses.

Variables	FLU prophylaxis, (n=70)	POS prophylaxis (n=35)	P value
Age, Mean±SD (min-max)	44.6±8.5 (17-65)	44.4±7.5 (18-60)	0.452
Sex (M)	45 (64%)	22 (63%)	0.942
Underlying diseases			
Acute myeloid leukemia (AML)	33 (47%)	17 (48.5%)	0.944
Acute lymphocytic leukemia (ALL)	23 (33%)	12 (34%)	0.941
Hodgkin/non-Hodgkin lymphoma	8 (11%)	3 (9%)	0.916
Multiple myeloma (MM)	6 (9%)	3 (8.5%)	0.646
Status of underlying diseases			
New diagnosis	10 (14%)	3 (8.5%)	0.944
Relapse	35 (50%)	17 (48.5%)	0.944
Refractory	25 (36%)	15(43%)	0.618
Mean duration of neutropenia (day)±SD	18.4±3.0	19.5±2.0	0.463
Fungal infection agents			
Candida albicans	0	1 (8%)	
Non-albicans Candida	0	2 (17%)	
Rhinocerebral mucormycosis	1 (7%)	0	
Trichosporon beigelii	0	1 (8%)	0.705
Possible pulmonary fungal disease+IPA	21 (31%)	9 (26%)	0.827
Total	22 (31%)	13 (37%)	
Antifungal treatment starting empirically	15 (%21)	7 (20%)	0.932
Failure of antifungal prophylaxis	37 (53%)	20 (57%)	0.835
Ex	17 (24%)	4 (8%)	0.195

FLU= Flucanazole, POS= Posaconazole, IFI= Invasive fungal infection, IPA= Invasive pulmonary aspergillosis, SD= Standart deviation.

Table 2. AML patients' demographic characteristics fungal infections and prognoses

Variables	FLU prophylaxis (n=33)	POS prophylaxis (n=17)	P value
Age, Mean±SD (min-max.)	43±7.0 (17-65)	43±8.0 (18-60)	0.552
Sex (Male)	23 (70%)	11 (65%)	0.937
Status of underlying diseases			
New diagnosis	3 (9%)	2 (11%)	0.944
Relapse	18 (55%)	9 (53%)	0.812
Refractory	12 (36%)	7(36%)	0.928
Chemotherapy protocol			
Remission-induction	33 (100%)	17 (100%)	0.944
Fungal infection agents			
Non-albicans Candida	0	1 (14%)	0.813
IPA	12 (36%)	5 (29%)	0.650
Total	12 (36%)	6 (35%)	
Empiric antifungal treatment	8 (24%)	4 (23.5%)	0.621
Failure of antifungal prophylaxis	20 (60%)	10 (59%)	0.854
Ex	8 (24%)	2 (12%)	0.461

FLU= Flucanazole, POS= Posaconazole, IFI= Invasive fungal infection, IPA= Invasive pulmonary aspergillosis, SD= Standart deviation.

Table 3. Multivariate regression analysis of failure of antifungal prophylaxis in patients

Risk factors	Odds ratio (OR)	95% Confidence Interval	P value
Mean duration of neutropenia	5.5	3.0-9.5	0.01
Status of underlying disease	1.2	0.8-2.9	0.06
Type of antifungal prophylaxis	1.0	0.7-1.4	0.08
Nausea and vomiting on antifungal prophylaxis	1.1	0.7-1.6	0.07

Table 4. Multivariate regression analysis of failure of antifungal prophylaxis in AML subgroup

Risk factors	Odds ratio (OR)	95% Confidence Interval	P value
Mean duration of neutropenia	5.7	3.0-9.8	0.01
Status of underlying disease	1.1	1.4-20	0.08
Type of antifungal prophylaxis	1.0	0.8-1.2	0.09
Nausea and vomiting on antifungal prophylaxis	1.2	0.9-2.6	0.07

Multivariate logistic regression analysis was used to investigate the factors related to antifungal prophylaxis failure. Mean duration of neutropenia, status of underlying disease, type of antifungal prophylaxis, nausea and vomiting and antifungal prophylaxis were included in two separate analyses. The first evaluation was done for all patients receiving antifungal prophylaxis, and then AML subgroup of patients (Table 3 and 4). Only mean duration of neutropenia was determined to be correlated with breakthrough IFIs (OR 5.5, 95%CI 3.0-9.5, p=0.01, OR 5.7, 95%CI 3.0-9.8, p=0.01, respectively).

The most frequent side effects associated with both antifungals were those involving the gastrointestinal system, mainly taking the form of nausea-vomiting. Rate of nausea and vomiting were higher in the POS patients compared to those receiving FLU, in 5% and 15% of patients, respectively (p=0.267).

Crude mortality (death due to any reason until resolution of neutropenia) in the FLU prophylaxis group was 17 (24%), compared to 4 (8%) in the group receiving POS (p=0.195). For AML patients, these levels were 8 (24%) in the FLU group and 2 (12%) in the POS group (p=0.207).

DISCUSSION

Since IFI causes high mortality, patients at high risk of these developing infections should be administered prophylaxis. Additionally, IFIs lead to a delay in the chemotherapy procedure to be applied to such patients and complicate the treatment of the underlying disease.[3] Patients developing IFI have longer terms of hospitalization, and higher mortality rates and hospital costs compared to patients without IFI.[3] However, broad, controlled studies are needed in order to be able to recommend routine antifungal prophylaxis in these patients.

Opinions differ regarding which prophylactic agent should be given, although the ideal agent should have a broad spectrum, be well tolerated and come in oral and parenteral forms. In that context, amphotericin B, FLU, voriconazole, itraconazole (ITZ), POS, caspofungin and micafungin are antifungals with differing mechanisms that can be employed in prophylaxis.[9-14]

One large study involving 603 MDS and AML patients with remission induction compared the effectiveness of POS and FLU/ITZ in these long-term neutropenic subjects. Proven/probable IFI was significantly lower in the POS group. Survival was also significantly higher in the POS group. Side-effects involving the gastrointestinal system were the most common effects in both groups.[15] In one study performed in China, the prophylactic efficacy of FLU and POS was compared in AML and MDS patients.[16] One hundred twenty-three patients received FLU in that study, and 129 POS. Clinical failure and incidence of IPA were significantly lower in the POS group compared to the FLU group, and time of commencement of antifungal therapy was significantly longer. The drug side-effects were at similar levels in the two groups, and the study concluded by emphasizing that POS was a good prophylactic option in patients at high risk for IFIs. In another study, Bertz et al.[17] compared FLU and POS in prophylaxis in patients at high risk for IFI.[7] No mortality was seen in that study, and no significant difference was determined between the groups in terms of commencement of antifungal therapy.

In our retrospective analysis, the prevalence of fungal infection and rates of commencement of empiric antifungal therapy were lower in the FLU group compared to the POS group. This might be partially related to poor absorption of POS from gastrointestinal system in case of nausea-vomiting. In addition, however, no significant relation was seen at multivariate logistic regression analysis between gastrointestinal complaints caused by antifungal drugs and failure seen in fungal prophylaxis. Of the parameters investigated in this analysis, only mean duration of neutropenia was correlated with prophylaxis failure. The incidence of IPA in the FLU group in our study was higher than that in the POS group, though the difference was not significant. We thought that construction work carried out in the first period might have been a factor in IPA developing in the study period. Although there was no statistically significant difference between mortality rates in the two prophylaxis groups in our study, it was higher in the FLU group. Since there were a large number of treatment-refractory patients in the FLU group, we thought that the poor prognostic course associated with the primary disease might be attributed to this. Results of subgroup analysis performed for AML were similar to the general findings in terms of both incidences of fungal infection and mortality levels. Mean duration of neutropenia was found to be correlated with prophylaxis failure also in this group.

In summary, IFI and crude morality rates were similar in the two groups. We conclude that both of FLU and POS can be successfully used in fungal infection prophylaxis for patients at high risk for IFIs. We believe that our study will shed light on a prospective study we are planning for the next stage involving a wider patient series under more standardized conditions.

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