The Effect of Posaconazole Prophylaxes on the Course of Fungal Infection in the High Risk Patients of Hematology: A Single-Center Experience in Turkey

Yüksek Riskli Hematolojik Hastalarda Profilaktik Posakanazol Kullanımının Fungal Enfeksiyon Gelişimi Üzerine Etkisi: Türkiye'de Tek Merkez Deneyimi

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ABSTRACT

Introduction: Invasive fungal infections (IFIs) are the most important cause of morbidity and mortality in the patients treated with remission-induction therapy and allogeneic stem cell transplantation (ASCT) and suffering from acute myelogenous leukemia (AML) and myelodysplastic syndrome (MDS). Difficulties and delays in diagnosis of the disease increase the mortality rate. Many clinicians and qualified international guidelines recommend the use of antifungal prophylaxis to reduce complications of the AML. Posaconazole is a new generation of broad spectrum oral azole and recent studies have shown that it is effective in curtailing risk of developing IFIs and mortality as well. In the present study, we aimed to assess the effectiveness of posaconazole prophylaxis on preventing development of IFIs, its reliability, and its tolerability in the patients treated with remission-induction therapy and ASCT and suffering from AML and MDS.

Methods: Overall, 117 patients were enrolled to the present retrospective study covering the patients followed between the years 2007 and 2020. The patients were divided into two groups as posaconazole group and control group. The posaconazole group contained 39 AML patients put on remission induction chemotherapy and 10 AML-MDS patients that received allogeneic stem cell transplantation, and all the patients in the posaconazole group were treated with posaconazole. The control group comprised 58 AML patients receiving no prophylactic antifungal treatment during the remission induction chemotherapy and 10 AML-MDS patients treated with fluconazole. Diagnoses and suspicions of fungal infections in posaconazole group and control groups were verified using the criteria set by EORTC/MSG. In addition, imaging techniques such as high-HRCT and biochemical tests, i.e., galactomannan were also utilized for diagnoses purposes.

Results: In the present study, we noted that the risk for the development of fungal infections and the need for antifungal use in the MDS and AML patients who received ASCT were markedly reduced in the patients administered with posaconazole prophylaxis in comparison to other group ($P<0.001$). The frequency of HRCT (High- Resolution Computed Tomography) findings implying potential or suspected development of fungal infections was determined to be greater in the control group (the patients treated with fluconazole prophylaxis) ($P=0.001$). In addition, there were no discernible differences between the groups for the socio-demographic characteristics such as age and gender in addition to the level of galactomannan, microbiological analysis, remission status and risk factors ($P> 0.05$). Finally, no significant difference was noticed on the development of side effects during the treatment between the groups ($P> 0.05$).

Conclusion: The results of the present study were consistent with the literature and indicated that the use of posaconazole for prophylactic purposes was more effective and reliable than fluconazole in preventing development and spread of invasive fungal infections in the patient receiving remission induction chemotherapy and ASCT.

Key words: Prophylaxes, posacanazole, fungal infection, mortality

ÖZET

Giriş: İnvaziv fungal enfeksiyonlar (IFI), remisyon-indüksiyon tedavisi alan ve allojenik kök hücre nakli yapılan akut myeloid lösemi ve myelodisplastik sendromlu hastalarda en önemli morbidite ve mortalite nedenidir. Tanı koymadaki güçlükler ve tanı koymadaki gecikmeler mortaliteyi artırmaktadır. Bu komplikasyonları azaltmak için birçok klinisyen ve uluslararası kılavuzlar tarafından antifungal profilaksi yapılması önerilmektedir. Posakanazol, yeni jenerasyon, geniş spektrumlu oral azol olup yapılan 2 randomize çalışma ile IFI gelişme riskini ve mortaliteyi de azalttığı gösterilmiştir. Bu çalışmada, posakonazol proflaksisinin, remisyon-indüksiyon tedavisi (antrasiklin bazlı tedaviler) alan akut myeloid lösemi ve myelodisplastik sendromlu ve allojenik kök hücre nakli yapılan hastalarda invaziv mantar enfeksiyonu önlemede etkinlik, güvenlilik ve tolere edilebilirliğinin değerlendirilmesi amaçlandı.

Yöntemler: Retrospektif çalışmaya 2007-2020 yılları arasında takip edilen 117 hasta çalışmaya alındı. Hastalar posakanazol ve kontrol grubu olarak iki gruba ayrıldı. Posakanazol grubuna remisyon-indüksiyon tedavisi alan 39 AML ve allojenik kök hücre nakli yapılan 10 AML-MDS hasta alındı, gruptaki tüm hastalar posakanazol ile tedavi edildi. Kontrol grubuna ise remisyon-indüksiyon tedavisi esnasında profilaksi almayan 58 AML tanılı hasta ve flukanazol profilaksi alan 10 AML-MDS hasta alındı. Posakanazol kullanan ve kontrol grubundaki hastalarda fungal enfeksiyon tanısında ve şüphesinde EORTC/MSG (Avrupa Kanser Araştırma ve Tedavi Organizasyonu/ (Mikoz Çalışma Grubu) tanı kriterleri kullanıldı. Tanıya yönelik HRCT (Yüksek Rezolusyonlu Akciğer Tomografisi) gibi görüntüleme tekniklerinin yanı sıra galaktomannan gibi biyokimyasal tetkiklerde incelendi.

Bulgular: Bu çalışmada allojenik kök hücre nakli yapılan MDS ve AML hasta grubunda posakanazol profilaksisi kullanılanlarda fungal enfeksiyon gelişme riskinin ve antifungal kullanım ihtiyacının diğer gruba oranla daha düşük olduğu saptandı ($P<0,001$). Kontrol grubunda (profilakside flukanazol kullanılan hasta grubu) olası veya şüpheli fungal enfeksiyonu gösteren HRCT bulguları daha yüksek oranda tespit edildi ($P=0,001$). Yaş, cinsiyet gibi sosyodemografik özelliklerinin yanı sıra galaktomannan düzeyi, mikrobiyolojik incelemeler, remisyon durumu ve risk faktörleri açısından her iki grup arasında bir anlamlı farklılık yoktu ($P>0,05$). Tedavi esnasında yan etki gelişimi açısından iki grup arasında herhangi bir fark yoktu($P>0,05$).

Sonuç: Bu çalışmada literatür ile uyumlu olarak remisyon-indüksiyon tedavisi alan hastalarda invaziv fungal enfeksiyon gelişimini önlemede profilaktik posakanazol kullanımının etkin ve güvenli olduğu, allojenik kök hücre nakli yapılan hastalarda ise profilaktik posakanazol kullanımının flukanazol kullanımına göre daha üstün olduğu gösterilmiştir

Anahtar Kelimeler: profilaksi, posakanazol, fungal enfeksiyon, mortalite

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INTRODUCTION

Invasive fungal infections (IFIs) are important cause of morbidity and mortality in the patients with acute myelogenous leukemia (AML) and myelodysplastic syndrome (MDS) receiving remission induction chemotherapy and allogeneic stem cell transplantation(ASCT) (1-5). The frequency of IFIs has been rising over the past two decades. The central risk group for IFIs is reported to be the patients with hematological malignancies, experiencing prolonged neutropenia following myelosuppressive chemotherapy or hematopoietic stem cell transplantation (HSCT) (6). Moreover, the incidence of IFIs associated with molds and yeasts is proclaimed to reach 24% among the AML and MDS patients (7).

Earlier diagnoses of IFIs are difficult since they frequently accompany with nonspecific symptoms such as fever (8). The rate of antifungal treatment in these patients is considerable higher owing to difficulties in diagnosis and high mortality rates; consequently, the treatment of these patients becomes very costly (5, 9). Difficulties and delays in diagnoses of AML and MDS increase the mortality rates among the patients (10-12). In addition, candida infections are also frequently reported among these patients (13, 14) and studies disclose that reported mortality from candidiasis or aspergillosis might range from 40 to 50% (15, 16).

Moreover, many clinicians have used empirical treatment approaches for the treatment of fungal infections until recently (17-24). Even though their use has significantly increased the cost of treatments, antifungal prophylaxes have been increasingly used since incidence of IFI and IFI-associated mortalities have increased markedly. Fluconazole, voriconazole, itraconazole, posaconazole, and amphotericin B are among the most commonly used agents in the antifungal prophylaxes (25). While fluconazole is shown to be effective against candida spp, it is not efficient against aspergillus spp; on the other hand, itraconazole is effective against aspergillus spp but tolerability of its oral form is poor (26-28). Posaconazole, a new generation triazole antifungal agent with wide spectrum, is effective against aspergillus spp and other fungi spp (29-31). Two randomized studies about posaconazole were carried out and showed that antifungal prophylaxis established with posaconazole reduced incidence of IFI and IFI-associated mortalities (2, 32).

Several studies that have been carried out up to today proclaim diverse opinions on the type and significance of prophylaxis. In the present study, we aimed to assess the effect of posaconazole prophylaxes on the prevention of development of invasive fungal infections in the AML patients receiving remission induction chemotherapy (anthracycline based therapy) and the patients with MDS and AML receiving allogeneic stem cell transplantation.

METHODS

Overall, 117 patients who were followed between the years 2007 and 2020 at the Department of Internal Medicine-Division of Hematology were enrolled to the present study. The patients were divided into two groups as posaconazole and control groups. The posaconazole group contained 39 AML patients put on remission induction chemotherapy and 10 AML-MDS patients received allogeneic stem cell transplantation, and all the patients in the posaconazole group were treated with posaconazole. The control group comprised 58 AML patients receiving no prophylactic antifungal treatment during the remission induction chemotherapy and 10 AML-MDS patients treated with fluconazole. The sociodemographic features such as age and gender, type of diagnose, and state of remission of the patients in addition to the antibiotics were used during hospitalization and potential risk factors for them were investigated in detail. The

patients in the posaconazole group initially received posaconazole at 3x1 doses simultaneously with the remission induction chemotherapy. The posaconazole treatment of the patients were continued till they were recovered from the neutropenia. However, posaconazole treatment was continued until 100th day after allogeneic stem cell transplantation. The posaconazole treatment was terminated in the patients with uncontrollable fever, firm or potential fungal infections and an appropriate antifungal treatment for the patient was chosen. The side effects observed during the treatment were recorded.

We used the criteria set by EORTC/MSG (European Organization for Research and Treatment of Cancer (EORTC)/The Mycoses Study Group (MSG) in suspicion and diagnoses of the fungal infections in both the posaconazole and control groups (33). The diagnoses were further checked using the HRCT (High Resolution Computed Tomography) and galactomannan tests.

In the present study, the data obtained were analyzed using IBM SPSS 20. While Shapiro- Wilk test was applied to continuous variables to test their normality, Mann Whitney-U test was used for analyses of discontinues variables. Median (Quartiles) values were provided for the descriptive statistics. In addition, Continuity Correction and Fisher's Exact Chi-Square tests were applied for categorical variables.

Ethical approval was obtained from Eskişehir Osmangazi University Non-Interventional Clinical Research Ethics Committee.

RESULTS

Our observations showed that the amount of antifungals needed and the risk for the development of the fungal infections in the MDS and AML patients who received allogeneic stem cell transplantation were significantly lower in the posaconazole group than the control group (P<0.001). The rates of HRCT findings indicating presence of potential or suspicious fungal infections were higher among the patients treated with fluconazole in the control group (P=0.001). However, we detected no statistically meaningful difference between the groups with respect to the age, gender, the levels of galactomannan, microbiological investigations, state of remission, and risk factors (P>0.05) (Table 1).

Table 1. Patient characteristics of ASCT group

	Posaconasole n=10	**Control n=10**	**P**
Age (median/year)	42	41	>0.05
Sex **Male** **Female**	 4 6	 2 8	>0.05
Use of systemic Antibiotic Agents (n)	3	1	>0.05
Use of Central Venous Catheter (n)	9	9	>0.05
Duration of Neutropenia (days)	25	24	>0.05
Length of stay (days)	38	60	0.02
Galactomannan (n) **Positive** **Negative**	 0 10	 0 10	>0.05
HRCT (Probable invasive fungal disease) (n) **Positive** **Negative**	 0 0	 8 2	0.001
Use of Ampirical Systemic Antifungal Agents (n)	0	9	<0.001

Likewise, there was also no significant difference in the percentage of developing side effects between the groups (P>0.05) (Table 2).

Table 2. Summary of adverse events of ASCT group

Adverse Events	**Posaconazole n=10**	**Control n=10**	**p**
Diarrhea	5	5	>0.05
Jaundice	1	6	>0.05
Headache	2	0	>0.05
Biluribinemia	1	0	>0.05
Increased aminotransferases	4	6	>0.05
Hypopotassemia	5	5	>0.05
Hemorragia	0	0	>0.05

The patients well tolerated posaconazole treatment. Two patients only developed oral intolerance to posaconazole treatment and their treatment was continued with amphotericin. Overall, hospitalization time for the patients in the posaconazole group was lower than the control group (P=0.001).

Moreover, the need for antifungal use and the risk for developing fungal infections were significantly lower in the AML patients put on posaconazole prophylaxis compared with the control group (P<0.001). The ratios of HRCT findings implying existence of possible or suspicious fungal infections were higher among the patients in the control group (P=0.001). Nonetheless, we determined no statistically important discrepancy between the groups with respect to the age, gender, the levels of galactomannan, microbiological investigations, state of remission, and risk factors (P>0.05) (Table 3).

Table 3. Patient characteristics who received remission induction chemotherapy

	Posaconazole n=39	Control n=58	P
Age (median) (year)	51	48	>0.05
Sex (n)			
Male	16	29	>0.05
Female	23	29	
Use of systemic Antibiotic Agents (n)	5	6	>0.05
Use of Central Venous Catheter (n)	1	2	>0.05
Duration of Neutropenia (days)	23	20	0.042
Length of stay (days)	32	34	0.045
Galactomannan (n)			
Positive	3	3	>0.05
Negative	36	55	
HRCT (Probable invasive fungal disease) (n)			
Positive	11	51	0.001
Negative	28	7	
Use of Ampirical Systemic Antifungal Agents (n)	18	54	0.024

In addition, no significant differences were observed in the percentage of developing side effects between the groups (P>0.05) (Table 4).

Table 4. Summary of adverse events who received remission induction chemotherapy

Adverse Events	Posaconazole N=39	Control N=58	p
Diarrhea	12	15	>0.05
Jaundice	3	2	>0.05
Headache	4	1	>0.05
Biluribinemia	3	2	>0.05
Increased aminotransferases	9	24	>0.05
Hypopotassemia	13	19	>0.05
Hemorragia	0	0	>0.05

The patients well tolerated posaconazole treatment and mean time for the use of posaconazole was 23 days but neutropenia time was longer (P=0.042). The most common reason for the termination of the treatment in the posaconazole group was the uncontrollable fewer but not the presence of potential or suspicious fungal infections. In general, hospitalization time for the patients in the posaconazole group was lower than the control group but the difference was not statistically important (P=0.084).The results of the present study were consistent with the literature; the need for antifungal use and the risk for developing suspected or potential invasive fungal infections were reduced in the patients receiving allogeneic stem cell transplantation and treated with posaconazole.

Our study was designed in accordance with the principles of the Helsinki Declaration and regulation of patient rights and approved by the clinical research ethics committee of Eskişehir Osmangazi University with the date of 29.09.2020 and the number of 48.

DISCUSSION

Invasive fungal infections have shown to be responsible for markedly increased fungi-associated mortality and

morbidity rates in particularly immunosuppressed neutropenic patients (1-5). Difficulties and delays in proper diagnoses in addition to long hospital stays are major factors for increased risk factors for fungal infections (10-12). Nonetheless, antifungal prophylaxes established during the cancer treatment are shown to be effective in reducing the risk factor for developing fungal infections and increasing survival rates among the patients (2, 32,34-36).

Fluconazole prophylaxis is shown to significantly reduce the incidence of mortality owing to invasive fungal infections or any other causes in only the patients undergoing hematopoietic stem cell transplantation (37). Fluconazole prophylaxis has become care standard in this clinical ground (38) and although its advantage in reducing morbidity or mortality has not been proven and no consensus exists on its use in these high-risk patients among the clinicians, fluconazole prophylaxis has been used in the patients undergoing remission induction for acute leukemia (39). The European Conference on Infections in Leukaemia (ECIL) suggested that posaconazole remains the drug of choice when the incidence of invasive mould diseases exceeds 8%. Similarly, aerosolized liposomal amphotericin B combined with fluconazole can be considered forpatients at high risk of invasive mould diseases but other formulations of the polyene are discouraged. Fluconazole is stil recommended as primary prophylaxis for patients at low risk of invasive mould diseases during the pre-engraftment phase of allogeneic HSCT whereasonly a moderatere commendation could be made for itraconazole, posaconazole and voriconazole for patients at high risk. Posaconazole is strongly recommended for preventing invasive mould disease post-engraftment but only when graft-versus-hostdisease (GvHD) was accompanied by other risk factor ssuch as its severity, use of an alternative donor or when unresponsive to standard corticosteroid therapy (40).

Although the use of itraconazole is proven to be decreased the incidence of invasive fungal infections, large scaled studies indicate that it does not provide a better significant survival benefit in comparison to fluconazole and itraconazole also shown to be associated with a higher toxicity (41, 42). Until the use of posaconazole, fluconazole and itraconazole had been shown to be more effective than placebo; therefore, these agents had been routinely used as care standards. However, neither superiority of an azole to other azole was clearly identified (42, 43) nor there was novel data regarding the features of the one of the azures (36). At their study on the 602 neutropenic patients received remission-induction therapy, Cornely et al. introduced posaconazole prophylaxis to the 304 patients and the remaining patients received fluconazole and itraconazole prophylaxes. They reported that the risk of developing invasive fungal and aspergillus infections was lower and total mortality was reduced among the patients received posaconazole prophylaxis with respect to the group treated with fluconazole and itraconazole prophylaxes (44).

Furthermore, the time for free survival was shown to be longer than that of invasive fungal infections (2). In the current study, we noted no marked difference in terms of side effects between fluconazole and posaconazole. Present evaluation of 100-day mortality indicated that the use of posaconazole in the patients slightly increased survival time with respect to the control group ($p>0.05$). Similarly, fluconazole and posaconazole triggered comparable side effects in allogeneic stem cell transplantation (ASCT) patients. The use of posaconazole prophylaxis in the AML and MDS patients receiving remission-induction therapy has started appearing in international guides soon after the completion of the present study. In the present study,

the need for the antifungal use to control development of suspected or potential invasive fungal infections was lower in posaconazole group.

At their study performed on 600 patients treated with allogeneic stem cell transplant, Ulmann et al. compared efficiency of posaconazole prophylaxis and fluconazole prophylaxis. They determined that the incidence of developing invasive aspergillosis or invasive fungal infections was curtailed in the group treated with posaconazole prophylaxis. Another study reported that total mortality was similar in both groups but mortality associated with invasive fungal infections was noted to be dropped in posaconazole group (32). A recent study indicated that this real-world evidence supports the use of posaconazole over itraconazole in AML or MDS patients under going intensive chemotherapy (45).Correspondingly, the results of the present study were consistent with the literature; the need for antifungal use and the risk for developing suspected or potential invasive fungal infections were reduced in the patients receiving allogeneic stem cell transplantation and treated with posaconazole. Additionally, we noticed that occurrence of potential or suspected invasive fungal infection all through the first consolidation treatment in 18 of 21 patients who received posaconazole prophylaxis during remission induction cure and did not develop invasive fungal infections. This observation suggests that the use of posaconazole prophylaxis not only during the treatment of remission induction but also consolidation is efficient in preventing development of invasive fungal infections. Larger randomized trials are needed for clarifying present observation regarding posaconazole prophylaxis.

CONCLUSION

The results of the present study were consistent with the literature and indicated that the use of posaconazole for prophylactic purposes was effective and reliable in preventing development and spread of invasive fungal infections in the patient receiving remission induction chemotherapy. The use of posaconazole was more effective and dependable than fluconazole in controlling development of invasive fungal infections in the patients receiving allogeneic stem cell transplantation. In addition, the present results also suggested that the use of posaconazole during consolidation therapy was useful.

Conflict of Interest: The authors declare that they have no conflict of interest

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