RESEARCH ARTICLE

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The Role of Fluconazole Prophylaxis Regimen and the Regimes Chosen by the Patient's Risk of Fungal Infection in Reducing the Infection Rate after Bone Marrow Transplantation

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Abstract

Objective: Invasive fungal infections (IFI) in bone marrow transplant (BMT) recipients are common and lethal. Fluconazole was the choice prophylaxis previously, but recent strategy utilization antifungal drugs according to the risk of IFI in patients undergoing transplantation. In this study we aim to evaluate the efficacy of fluconazole prophylaxis regimen and the regimes chosen by the patient's risk of IFI. **Materials and Methods:** We evaluated 376 patients with BMT. Patients were divided into those treated before 2012 with fluconazole prophylaxis (group I, n=206) or those undergone transplantation after 2012 and received fluconazole, voriconazole and posaconazole prophylaxis according their risk of fungal infection (group II, n=170). **Results:** Group I was significantly younger (p=0.007), less smoker (p=0.01), received more autologus transplant (p=0.001) and mostly high risk patient for infection (p<0.001). Group I had significantly higher duration of fever (p=0.004) and increased WBC (p=0.02), longer length of stay (p=0.001), more proven and less probable fungal infections (p=0.008) and higher hepatic complications (p=0.003). There was no significant difference in fungal related and overall mortality rate between groups. **Conclusion:** The use of prophylaxis based on risk of fungal infection in patients undergoing BMT results in reduce fungal infections, duration of fever and accelerate the engraftment and patient discharge.

Keywords: Bone marrow transplantation- prophylaxis- fungal infection

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Introduction

Hematopoietic stem cell transplantation (HSCT) has been used to treat a wide variety of malignant and non-malignant hematological disorders including leukemia, lymphomas, and aplastic anemia, and indications are expanding (Busca and Pagano., 2016). Invasive fungal infections (IFI) have become the leading cause of morbidity and mortality in bone marrow transplant (BMT) recipients (Fukuda et al., 2003; Kontoyiannis et al., 2010; Neofytos et al., 2009; Pagano et al., 2007). Reported risk factors are post-transplantation immune deficiency, immune suppression, high-dose steroids, neutropenia, viral infections, and acute graft-versus-host disease (GvHD) (Busca and Pagano., 2016; SteinbachWJ., 2010; Zaoutis, 2010).

Routinely four strategies including prophylactic, empiric, preemptive, and targeted therapy are applied for the management of fungal infections (Klepser, 2011). As a common practice, high risk patients receive prophylaxis against fungal infections. As the use of antifungal prophylaxis is being increased, it becomes more important to define those patients most at risk for IFDs. For physicians faced with the challenge of selecting a systemically active oral antifungal, the principal choices are fluconazole, which lacks anti-mould activity, and the mould-active agents itraconazole, posaconazole, and voriconazole (Marks et al., 2011; Pechlivanoglou et al., 2011). However, the optimum oral agent for antifungal prophylaxis in HSCT recipients post-transplant remains uncertain.

It is shown that posaconazole, voriconazole, and micafungin, have reduced the incidence of IFI compared to fluconazole and itraconazole; posaconazole and voriconazole have also reduced transplant-related mortality significantly and the risk of proven/probable IFI compared to fluconazole and itraconazole (Bow et al., 2015; Xu et al., 2013).

In our center, all patients with BMT received fluconazole as fungal prophylaxis until 2012 and after

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2012, prophylaxis was based on the risk stratification and three anti-fungal therapies, fluconazole, voriconazole and posaconazole were administered as proper. In this study we aim to evaluate efficacy of the fungal prophylaxis protocols before and after 2012 on the incidence of IFI, mortality rate and clinical findings.

Materials and Methods

In this cross-sectional retrospective study, a total of 376 patients (220 male and 156 female between 10-68 years old) who underwent bone marrow transplantation in Taleghani Hospital, Tehran, Iran between July 2008 and July 2015 were studied. Exclusion criteria were death prior to the initiation of fungal prophylaxis or the use of an antifungal regimen other than fluconazole, voriconazole and posaconazole. Patients were also excluded if the transplant was performed at an outside institution. The study protocol was approved by ethics committee of Tehran University of Medical Sciences.

Baseline demographics, underlying disease, clinical factors, associated treatment, treatment-related adverse events, and survival and prior and concomitant medications, and concurrent medical events were collected from hospital clinical and research records on all patients. Laboratory findings including liver function tests were also recorded.

Patients were classified into three risk groups; patients were considered high risk if they had history of invasive fungal infection, being smoker or opium abuser, AML or MDS as their underlying disease. Low risk group were patients who received autologous BMT without any of above mentioned risk factors and moderate risk group were patients no included in the low or high risk group.

Patients were divided in to two groups; group one, were those who underwent transplantation between 2008 and 2012 and received fluconazole as antifungal prophylaxis and second group were those patients with transplantation between 2012 and 2015 and received antifungal prophylaxis (fluconazole, voriconazole and posaconazole) according their risk of fungal infection. This group was administered voriconazole, posaconazole and amphotericin B prophylaxis (high risk), voriconazole and amphotericin b prophylaxis (moderate risk) and fluconazole prophylaxis (low risk). The doses of anti-fungal drugs were as follows: cap fluconazole 100 mg twice daily, tab voriconazole 200 mg twice daily, syrup posaconazole 200 mg three times a day and amphotericin b 25 mg intravenously daily.

Invasive fungal infection (IFI) has been redefined as invasive fungal disease (IFD) by the EORTC/MSG Consensus Group (2008). IFI is defined into three different categories; possible, probable and proven based on a combination of host factors, clinical criteria and mycological criteria (De Pauw et al., 2008). Patients were considered non-probable infection if it did not met criteria of above mentioned categories.

Statistical analysis

All data were analyzed using SPSS20 (version 20; SPSS Inc., Chicago, IL). Results are expressed as Mean ± standard deviation or percentage. The chi-squared and fisher exact tests were used to compare categorical variables and the Mann–Whitney U-test and independent t-test to compare continuous variables. p values of less than 0.05 were considered statistically significant.

Results

Pre-transplant hematological diseases of the patients included multiple myeloma in 137 cases (36.5%), Hodgkin lymphoma in 106 cases (28.2%), non-Hodgkin lymphoma in 54 (14.2%), AML in 39 (10.4%), ALL in 23 (6.1%) and solid tumors including PNET, germ cell tumor in 17 cases (4.6%). Autologous and alogen transplant was performed in 310 (82.4%) and 66 (17.6%), respectively.

Of 376 patients, 206 (54.8%) were in group one and 170 (45.2%) were in group two. Patients' baseline findings are shown in Table 1. Group I was significantly younger, less smoker, received more autologus transplant and mostly high risk patient for infection.

Probable/proven IFI occurred in 27 (7.18%) of all BMT cases; possible infection was observed in 128 (34%) of cases. Table 2 demonstrates the fungal infection findings between groups. Group I had significantly higher duration of fever and increased WBC, longer length of stay, more proven and probable fungal infections and higher hepatic complications. There was two deaths related to fungal infection, both occurred in group I. Three deaths in group I and 4 deaths in group II occurred due to non-fungal causes. In allogenic transplant patients acute GVHD and sepsis due to non-fungal infections and

Table 1. Patients' Baseline Findings

	Group I	Group II	P value
Age (years)	37.18±14.1	41.07±13.5	0.007
Gender, male/female	123/83	97/73	0.6
Smoking	7 (3.4%)	17 (10%)	0.01
Opium use	1 (0.5%)	5 (2.9%)	0.09
Pulmonary disease	10 (4.9%)	4 (2.4%)	0.28
Transplant type			
Autologous	184 (89.3%)	129 (75.9%)	0.001
Allogeneic	22 (10.7%)	41 (24.1%)	
Underlying disease			<0.001
Lymphoma	115 (55.8%)	48 (28.2%)	
Multiple myeloma	63 (30.6%)	75 (44.1%)	
Acute Myeloid Leukemia	14 (6.8%)	25 (14.7%)	
Acute Lymphoblastic Leukemia	7 (3.4%)	16 (9.4%)	
Solid Tumors	7 (3.4%)	7 (3.5%)	
Prophylaxis			-----
Fluconazole	206 (100%)	89 (52.4%)	
Voriconazole	---	30 (17.6%)	
Posaconazole	---	27 (15.9%)	
Amphotericin	---	6 (3.5%)	
Combination therapy	---	18 (10.6%)	
Infection risk			
Low risk	24 (11.7%)	92 (54.1%)	<0.001
Moderate risk	19 (9.2%)	30 (17.6%)	
High risk	163 (79.1%)	48 (28.2%)	

Table 2. The Fungal Infection Findings between Groups

	Group I	Group II	P value
Fever duration (days)	4.7±0.26	3.2±0.66	0.004
Increased white blood cell duration (days)	13.47±6.3	12.12±4.9	0.02
Length of stay (days)	31.72±10.75	27.94±10.12	0.001
Empirical amphotericin use	29 (14.1%)	23 (13.5%)	0.88
Duration of empirical amphotericin use (days)	10.35±9.05	8.68±7.71	0.45
Galactomannan antigen	15 (7.3%)	8 (4.7%)	0.39
Imaging indicative of fungal infection	10 (4.9%)	6 (3.5%)	0.52
Invasive fungal infection			
Non-probable	130 (63.1%)	131 (77.1%)	0.008
Possible	61 (29.6%)	27 (15.9%)	
Probable	12 (5.8%)	11 (6.5%)	
Proven	3 (1.5%)	1 (0.5%)	
Hepatic complication grade			
0	116 (56.3%)	95 (55.9%)	0.003
1	61 (29.6%)	67 (39.4%)	
≥2	29 (14.1%)	8 (4.7%)	
Death due to fungal infection	2 (1%)	0	---
Death with no fungal infection	3 (1.5%)	4 (2.4%)	0.7

in autologous patients, also non fungal sepsis was the most common cause of death.

Probable/proven IFI was seen in 23 (7.8%) of patients with fluconazole prophylaxis, 2 (6.7%) of voriconazole prophylaxis and 1 (3.7%) of posaconazole prophylaxis. There was no significant difference between fluconazole and other two groups in infection rate.

Discussion

In this study, we evaluated the rate of IFI in patients receiving fluconazole regardless of their risk category with patients receiving the regimes based on the patient's risk of IFI. We observed probable/proven IFI in 7.18% and possible infection in 34% of all BMT patients. This is higher than reported prevalence in other studies. In a study of United States tertiary care centers, overall incidence of proven/probable IFD was 3.4% (range, .9% to 13.2%) (Kontoyiannis et al., 2010). This is also reported by other large and small studies (Kurosawa et al., 2012; Pagano et al., 2007).

However, similar to our findings, in a large study in China, the overall incidence of proven or probable IFD was 7.7% (Sun et al., 2015). They indicated that insufficient use of prophylaxis in these patients, especially high risk patients, was associated with an increased incidence of IFD. Furthermore, fluconazole was mostly used and for a shorter duration than recommended which has suboptimal efficacy compared with newer agents. All our patients received antifungal prophylaxis regardless of their risk category. Fluconazole was also used as the most common prophylaxis.

Varieties of antifungal agents are now used for prophylaxis in different centers. Martino et al., (2002) reported that 73% of patients received fluconazole, 17% itraconazole and 4% amphotericin B for prophylaxis and 6% did not receive any antifungal agent for this purpose. Similarly, in our study, most patients received fluconazole, then voriconazole and posaconazole.

Fluconazole is the most used and accepted antifungal treatment with more cost-benefit and cost-effectiveness. Previous studies have shown the significant efficacy of fluconazole prophylaxis. Ziakas et al., (2014) in their meta-analysis reported that patients receiving fluconazole compared to placebo accompanies with reduced risk of IFI, systemic candidiasis and the need for empiric antifungal treatment.

Nowadays, the antifungal agent of choice for the prophylaxis of invasive fungal infection is a triazole (voriconazole or posaconazole) (Fleming et al., 2014; Marks et al., 2011; Soysal., 2015; Ullmann et al., 2007). Different studies have tried to compare the efficacy of these new agents with fluconazole. Wingard et al., (2010) compared voriconazole with fluconazole in allogeneic HSCT recipients. There was no difference in the incidence of proven-probable or presumptive IFI between two treatments; but the incidence of aspergillosis was marginally reduced in patients who received voriconazole.

Posaconazole was also compared with fluconazole for prophylaxis of IFI (Ullmann et al., 2007). Although the incidence of IFI was higher in fluconazole, but the difference was not significant between groups, but deaths due to IFI was higher in fluconazole group.

In our study, we observed no significant difference between fluconazole with voriconazole and posaconazole groups regarding probable/possible IFI rate. Fluconazole group compared to risk-base treatment received more autologus transplant and were mostly high risk patient for IFI. They also had longer duration of fever, longer length of stay, more proven and less probable fungal infections and higher hepatic complications. But the difference between treatments in cumulative sum of proven/probable cases was not significant. There was no significant difference in fungal related and overall mortality rate between groups.

In order to choose proper antifungal drugs with better treatment efficacy, we need to understand the exact pharmacokinetics of each drug including the interaction of a drug with the host, measurements of absorption, distribution, metabolism and elimination which will help in choosing most efficacious and safe dose and interval of administration for a particular pathogen and infection site. Amphotericin B is eliminated by bile and kidney and is contraindicated in reversible renal impairment but could be used with no dose adjustment in hepatic impairment. Dose adjustment should be considered for fluconazole in renal impairment and for voriconazole in hepatic impairment while posaconazole needs no dose adjustment in renal or hepatic impairment. We should also consider the drug-drug interactions of these antifungal drugs; both fluconazole and voriconazole are strong inhibitors of CYP3A4 and 2C9. These drugs can decrease the availability of some drugs and so increase their efficacy and possible side effects (Bellmann and Smuszkiewicz, 2017).

Considering the high costs of new agents and low tolerance rate, voriconazole and posaconazole, it is better

to use these agents in high risk patients. Fluconazole is well-tolerated and less expensive and could be used for prophylaxis in most centers. As there was no significant difference among our patients with three different prophylaxis (fluconazole, voriconazole and posaconazole), it seems rationale to use fluconazole as the first choice of prophylaxis. However, that risk stratification may improve the proper use of antifungal prophylactic agents and reduce the possible costs.

In conclusion, the use of prophylaxis based on risk of fungal infection in patients undergoing BMT results in reduced duration of fever and accelerates the engraftment and patient discharge. We found no significant difference regarding IFI rate between prophylaxis groups.

Acknowledgments

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