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ORIGINAL RESEARCH

Antifungal agent utilization evaluation in hospitalized neutropenic cancer patients at a large teaching hospital

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Abstract: To evaluate pattern of using of three antifungal drugs: fluconazole, amphotericin B and voriconazole, at the hematology–oncology and bone marrow transplant wards of one large teaching hospital. In a prospective cross-sectional study, we evaluated the appropriateness of using antifungal drugs in patients, using Infectious Disease Society of America (IDSA) and National Comprehensive Cancer Network (NCCN) guidelines. All the data were recorded daily by a pharmacist in a form designed by a clinical pharmacist and infectious diseases specialist, for antifungals usage, administration, and monitoring. During the study, 116 patients were enrolled. Indications of prescribing amphotericin B, fluconazole, and voriconazole were appropriate according to guidelines in 83.4%, 80.6%, and 76.9% respectively. The duration of treatments were appropriate according to guidelines in 75%, 64.5%, and 71.1% respectively. The dose of voriconazole was appropriate according to guidelines in 46.2% of patients. None of the patients received salt loading before administration of amphotericin B. The most considerable problems with the mentioned antifungals were about the indications and duration of treatment. In addition, prehydration for amphotericin B and dosage of voriconazole were not completely compatible with the mentioned guidelines. A suitable combination of controlling the use of antifungals and educational programs could be essential for improving the general process of using antifungal drugs at our hospital.

Keywords: utilization evaluation, fluconazole, amphotericin B, voriconazole, neutropenia

Introduction

Neutropenic patients are vulnerable to different types of vigorous bacterial and fungal infections, which can cause severe sepsis.[1] Prophylaxis or treatment with antibiotics, especially antifungal drugs, should be considered in these patients in the proper clinical setting. However, careful attention to worldwide guidelines for using these drugs is as important as giving the drugs alone. Following the practical points in these guidelines has a significant role in the prophylaxis or treatment of fungal infections in neutropenic patients.

The methods for early diagnosis of fungal infections are expensive and time consuming and also may be unavailable in all medical centers. Also, delay in diagnosis of these infections will be lethal. So in most cases of neutropenic fever, empirical antifungal treatment is used.[2–4]

Some accepted standards of using antifungal drugs are provided to achieve the best results. Drug utilization evaluation (DUE) is a method of gathering data for finding out the problems relating to the use of drugs that can evaluate the real process of prescription of drugs as well as the results of the treatment.[5]

As of now, no clinical data are available about how much our work is compatible with the approved guidelines, so we designed this study to evaluate the rate of appropriate

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use of antifungal drugs in neutropenic patients to determine the probable problems of antifungal use in our hospital.

Method

In a prospective cross-sectional study, we evaluated the appropriateness of using antifungal drugs in patients admitted in hematology–oncology and bone marrow transplant wards in Nemazee hospital, which is affiliated to Shiraz University of Medical Sciences, from September 2012 to April 2013. The patients who met the following criteria were included in this study:

1. Adulthood (≥18 years)
2. The patients who were neutropenic or developed neutropenia during the hospital course, who received one of the three drugs including fluconazole, amphotericin B, or voriconazole.

Patients who received less than three doses of antifungal drugs, who were released from treatment, or who died during the hospital course, were excluded from the study.

Neutropenia was defined as absolute neutrophil count (ANC) below 1,500 cells/μL, in adults.[6] Acute kidney injury was defined as an abrupt (within 48 hours), absolute increase in the serum creatinine concentration of ≥0.3 mg/dL (26.4 μmol/L) from baseline; a percentage increase in the serum creatinine concentration of ≥50%; or oliguria of <0.5 mL/kg per hour for more than 6 hours.[7,8]

To evaluate indicators of three types of antifungal drugs composed of deoxycholate formulation of amphotericin B, fluconazole, and voriconazole, we designed a questionnaire containing information about clinical and demographic data, indication of prescription, the type of antifungal and its dosage, route, rate, and duration of administration, and its side effects. Also, we evaluated if the essential lab data, which should be collected before and during treatment, were done routinely or not. Aspergillus or Candida polymerase chain reaction (PCR) assays or blood fungal culture are the diagnostic modalities recommended for suspicious systemic fungal infections among neutropenic patients who were included in our evaluation.

The items that were evaluated for amphotericin B included appropriate indication of administration, proper dose (appropriate according to guidelines), premedication, hydration, duration of infusion, initial dose, and further adjustment in cases who had rise in serum creatinine. Also, appropriate dilution and stability (according to guidelines) were evaluated.

We also checked if the necessary lab data for each drug were properly followed in the wards or not. For amphotericin B, serum creatinine (Cr), magnesium (Mg), potassium (K), and liver function test (LFT) should be checked before and during treatment. Checking of serum Mg, K, calcium (Ca), and amylase are necessary before and during treatment with voriconazol. Serum LFT should be checked before and during use of fluconazole.

All the mentioned data were recorded daily by a pharmacist in a form designed by a clinical pharmacist and infectious diseases specialist, for antifungal usage, administration, and monitoring. One log sheet was completed for each patient. Then, collected data were reviewed by a clinical pharmacist and an infectious diseases specialist separately. According to Infectious Disease Society of America (IDSA) guidelines printed in 2010, National Comprehensive Cancer Network (NCCN) instructions, and Lexi drug information handbook printed in 2011, we assessed the utilization of the mentioned antifungal drugs in our ward. We used SPSS version 16 for analysis of the data. Continuous variables were shown as mean ± standard deviation (SD), and categorical data were presented as percent.

Results

In our study, 126 patients met the inclusion criteria. However ten patients were excluded during the survey (Table 1). Of

Table 1 Characteristics of 116 patients included in the study at hematology–oncology and bone marrow transplant wards

	Fluconazole	Amphotericin B	Voriconazole
Age, Mean ± SD in years	39.48±14.03	36.44±10.55	49.07±11.39
Sex, male/female ratio	47/20	26/10	9/4
Underlying disease			
AML	39	28	12
ALL	13	6	1
HD	4	–	–
NHL	4	1	–
CML	3	1	–
MM	2	–	–
HCL	1	–	–
MDS	1	–	–
Indications for use of antifungals			
Febrile neutropenia	–	15	1
Prophylaxis of fungal infection	67	11	10
Lung infiltration, probably due to fungus	–	5	–
Mucormycosis	–	3	–
Aspergillosis	–	2	2

Abbreviations: AML, Acute myeloplastic leukemia; ALL, acute lymphoblastic leukemia; HD, Hodgkin's disease; NHL, non-Hodgkin lymphoma; CML, chronic myeloblastic leukemia; MM, multiple myeloma; HCL, hairy cell leukemia; MDS, myelodysplastic syndrome.

the excluded cases, five died, three transferred to other wards, and the others were released from the hospital.

Fluconazole

Fluconazole was prescribed for 67 patients, all as prophylaxis. Thirty-one patients received the drug for the total duration of the hospital course, however, in others it was changed to voriconazole or amphotericin B due to positive fungal PCR results or febrile condition. The mean duration of fluconazole treatment was 5–51 days (19±9.7 days). The patients took fluconazole 100 mg twice a day in the oncology ward and 100 mg every eight hours in the bone marrow transplant ward. The dose was given appropriately according to guidelines in 100% of patients (Table 2). During therapy, LFT was checked in 29% of patients (Table 2); none of them experienced rise in level of liver enzymes.

The most common adverse effects with fluconazole were nausea (16.1%), diarrhea (12.9%), abdominal pain (9.7%), and vomiting (6.5%).

Table 2 Evaluation of antifungal use prescribed for 116 patients during 7 months in the hematology–oncology and bone marrow transplant wards

	Amphotericin B (n=36)	Fluconazole (n=67)	Voriconazole (n=13)
Appropriate antifungal usage, n (%)			
Proper indication[a]	30 (83.4%)	54 (80.6%)	10 (76.9%)
Proper dose[a]	26 (72.3%)	67 (100%)	6 (46.2%)
Proper duration[a]	27 (75%)	43 (64.5%)	9 (71.1%)
Lab data monitoring before antifungal initiation, n (%)			
Potassium	36 (100%)	NI	13 (100%)
Calcium	NI	NI	13 (100%)
Magnesium	0	NI	0
Calculating creatinine clearance[b]	36 (100%)	0	NI
Liver function test	36 (100%)	52 (77.6%)	13 (100%)
Amylase	NI	NI	0
Lab data monitoring after antifungal initiation, n (%)			
Potassium	36 (100%)	NI	13 (100%)
Calcium	NI	NI	2 (15.4%)
Magnesium	0	NI	0
Calculating creatinine clearance[b]	36 (100%)	0	0
Liver function test	36 (100%)	19 (29%)	3 (23.1%)
Amylase	NI	NI	4 (30.8%)

Notes: [a]Compared with IDSA 2010 and NCCN guidelines; [b]renal function calculation based on Cockroft–Gault equation.

Abbreviations: NI, not indicated; IDSA, Infectious Disease Society of America; NCCN, National Comprehensive Cancer Network.

Amphotericin B

Amphotericin B was prescribed for 36 patients, as prophylaxis for 26 of the patients and as treatment for fungal infection for the rest of the patients. The duration of infusion was not proper according to guidelines in 25% of patients; ie, the duration of infusion was less than 4 hours (Table 2). The mean time of taking the drug was 3–46 days (13± 8.9 days). The appropriate dose according to guidelines of the drug was measured by calculating the total body weight (Table 2). Ten patients took a dose of the drug that was inappropriate according to guidelines, including more than recommended dose in six patients and low dose in four patients (Table 2). Twenty-five percent (n=9) of patients developed acute kidney injury, and in 44% of those patients amphotericin B was discontinued; in 22% the dose was given every other day, and for the rest no changes were made.

The method of performing initial reconstitution was not suitable for any patients. Final dilution was done appropriately according to guidelines in 66.7% of patients.

Infusion-related reaction preventive interventions, like hydrocortisone, were administered for all patients. None of the patients received salt loading for ameliorating the amphotericin B-induced nephrotoxicity. PCR was checked in 25% of patients for Candida and in 80.6% of patients for aspergillosis. The result for aspergillosis was positive in 5.6%. The result was negative for Candida in all patients.

Some patients experienced side effects as follows: hypokalemia (69.4%), fever and chills (55.6%), headache (27.7%), and pruritus (5.5%).

Voriconazole

Voriconazole was prescribed for 13 patients; for eleven patients as prophylaxis and for the rest of them as treatment for fungal infections. It was administered orally between 4 and 32 days (21.1±7.9 days). The dose was appropriate according to guidelines in 46.2% of patients (Table 2). The indication of voriconazole was proper in 76.9% (Table 2). Calcium and potassium were checked prior to therapy initiation; calcium was checked during therapy in only two patients, and neither of these two patients developed hypocalcemia. Twenty-three percent of patients developed hypokalemia. None of the patients in whom LFT and amylase were checked during therapy (Table 2) developed rise in liver enzymes or serum amylase. Side effects like visual disturbance (15.4%) were observed in patients who received the drug for more than 28 days. PCR was positive for aspergillosis in two patients who were treated with voriconazole.

Discussion

Invasive fungal infections are common in high-risk, immune-deficient cancer patients despite the introduction of new antifungals.[4] It has been shown that the rate of these infections increases with the severity and duration of neutropenia, number of cycles of chemotherapy, and duration of antibiotic therapy.[9,10] Antifungal prophylaxis in patients with neutropenia should not be used commonly, however the use of prophylaxis can be rationalized in a special group of high-risk patients, for example those with chronic severe neutropenia or with graft-versus-host disease after allogenic hematopoietic stem cell transplantation.

Fluconazole

In our study, in 19.4% of cases who received fluconazole, the drug was not prescribed appropriately according to guidelines because patients were in low-risk group (autologous hematopoietic stem cell transplantation recipients who receive growth factor and who do not have significant mucositis). In 53.7% of patients, fluconazole was changed to voriconazole or amphotericin B due to positive PCR results or developing fever while receiving fluconazole. In these groups, 25% of patients had history of prolonged or recurrent neutropenia, and, therefore, covering mold species should be considered.

In a prospective study, fluconazole was only prescribed for high-risk patients.[11] These results showed that in our center there is a trend to cover organisms like sensitive Candida, whereas in AML patients with prolonged neutropenia covering mold is crucial.

In our study, the duration of treatment was not appropriate according to guidelines in 35.5% of the patients treated with fluconazole, however, in a study performed by Ananda-Rajah et al[9] from 1998 to 2010, all the patients completed the duration of treatment, ie, till absolute neutrophil count (ANC) became more than 500 cells/μL. Also, in another study performed in 89 centers, 234 patients with neutropenia received the necessary duration of fluconazole.[12] The results of our study were not compatible with other studies because of shortage of beds in our center for neutropenic patients and because of consideration of the total count of white blood cells, not ANC, as the reference of treatment by physicians in our center. In a prospective study performed in Canada[13] and in Russia,[6] the patients took the necessary dose of fluconazole, ie, 200–400 mg per day, as in our center.

Amphotericin B

Studies recommend to administer amphotericin B over a period of 4–6 hours to reduce the incidence of probable side effects,[1] and the duration of treatment should be continued until improvement of clinical and paraclinical symptoms.[14] Unfortunately, the duration of infusion and also duration of therapy were less than optimal in 25% of our patients. In a study performed in some oncology centers in America, amphotericin B was discontinued when the patient's clinical symptoms improved and ANC rose to more than 1,000 cells/μL. Also, shortage of beds in our oncology ward considering the number of patients, and probably inattention of our physicians to ANC, are the causes of therapy duration in our ward not being appropriate according to guidelines.

The appropriate dose according to guidelines of amphotericin B should be adjusted according to the reason for the prescription, ie, the prophylactic dose differs from the therapeutic dose to treat aspergillosis or mucormycosis.[15]

In a study performed in one of the oncology wards in Tehran, 28.57% of patients received a dose of the drug that was not appropriate according to guidelines (14.28% of patients received more than the maximum dose and 14.28% of patients received less than minimum dose). However, in another study by Cagnoni,[14] appropriate dose according to guidelines of amphotericin B was prescribed in all neutropenic fever patients. In our center, dose of the drug was not calculated according to ideal body weight in any of the patients, and 27.7% of patients received a dose that was not appropriate according to guidelines (less or more than the sufficient dose). The nephrotoxicity of amphotericin B is increased with higher daily dose and inadequate dose of this drug would not provide enough protection against fungal infections.

In 16% of our patients, combination of amphotericin B and voriconazole was used; this is not consistent with the guidelines, as previous articles reported that simultaneous use of amphotericin B and voriconazole would decrease the antifungal effect of amphotericin B.[15]

Renal functional impairment is the most clinically important complication of conventional amphotericin B. In the two largest reviews, a 50% or greater increase in serum creatinine was observed in 138 of 494 (28%) and 174 of 643 (27%) patients, respectively.[16,17] This problem was seen in 25% of our patients (nine patients of 36). In 16.6% of patients cyclosporine and vancomycin were simultaneously used with amphotericin B, and in 8.4% of patients vancomycin was simultaneously used. So, we cannot correlate the rise of creatinine directly to the use of amphotericin B. However, with concurrent administration of the other nephrotoxins (such as an aminoglycoside, cyclosporine, nephrotoxic cancer chemotherapy) the risks of nephrotoxicity of amphotericin B increase.[18] Prehydration was not followed in

any of our patients; it seems necessary to develop a protocol for volume expansion with intravenous sodium chloride in our wards to ameliorate the rate of acute kidney injury. The nephrotoxicity associated with amphotericin B is usually reversible with discontinuation of therapy.[19] In 16.6% of the patients (six out of 36), alternate day therapy of twice the daily dose was given or it was discontinued; however, in 8.4% of the patients nothing was done. In a study by Hayatshahi et al,[20] in 27.7% of the patients (15 out of 54 patients) rise of creatinine was observed, and in 3.7% of the patients dose adjustment was done.

In this study, initial reconstitution was not done appropriately according to guidelines in any patients, and, also, final dilution was not performed appropriately according to guidelines in 33.3% of patients. We think that providing lectures for our nurses would help to get them familiar with the detailed instructions on the use of these drugs.

It is recommended to use premedications such as acetaminophen, antihistamines, or hydrocortisone to prevent amphotericin B infusion-related reactions.[21] Prophylactic use of hydrocortisone was done in all of our patients. Hypokalemia, fever, and headache were the most common side effects of amphotericin B in our patients, as other studies declared.[20,21]

Voriconazole

Voriconazole is usually used as a prophylactic antifungal drug in cases with history of previous infection with aspergillosis, or refractory hematologic disease, or in cases with recurrence of disease. So, according to these criteria, in 23.1% of our cases use of voriconazole was not indicated, because they were new cases. In a study performed from 2003 to 2010, the authors concluded that fluconazole as a prophylactic drug was more cost-effective and efficient than voriconazole in new cases.[22] However, previous studies showed that in high risk group (relapse of leukemia or patients with allogenic bone marrow transplant), use of prophylactic voriconazole caused a decrease in the rate of invasive fungal infections.[9,23] So it seems that the type of prophylactic antifungal should be chosen carefully according to patient history and clinical data to achieve maximum protection along with imposing less expense on patients.

In a study performed from 1998 to 2010 on 82 patients receiving voriconazole, all the patients received the drug until ANC rose to more than 500 cells/μL;[9] however, in 28.9% of our patients this procedure was not followed.

Voriconazole as prophylaxis should be used at 200 mg twice a day, as previous studies reported.[24] However, 53.8% of our patients took a dosage of this drug that was not appropriate according to guidelines (200 mg once a day).

Hypokalemia (23%) and visual disturbance (15.4%) were the most common side effects with voriconazole in our patients. Voriconazole is associated with several adverse reactions; including transient vision changes, which are seen mostly in those on long-term voriconazole therapy.[25] Clinical trials suggest that visual abnormalities may be associated with higher dosing or serum concentrations.[26] These effects generally subside with continued therapy over several weeks.[25] However, in other studies the rates of side effects were different. In a study on 415 patients who were on voriconazole in 73 different centers, the most common side effects were: hypomagnesemia (78.6%), visual disturbance (21.9%), hypokalemia (18.8%), and nausea (9.4%).[23] The reasons for this difference might be due to the different genetic backgrounds of our patients causing different reactions to this drug.

Overall in our study, possible causes of the high level of deviation from the standard could be due to not following standard treatment guidelines, absence of clinical pharmacist in the wards, untrained nursing staff, high voriconazole treatment related cost, and shortage of beds in our oncology–hematology wards. Providing standard treatment guidelines for the rational and cost-effective use of antifungal drugs, especially voriconazole, optimal education about antifungal drugs to oncology nurses, and attendance of clinical pharmacist in the hematology–oncology wards, can be effective policies to improve rational antifungal usage.

Conclusion

In summary, the most considerable problems with use of amphotericin B, fluconazole, and voriconazole in these hematology–oncology and transplant wards, are indications, duration of treatments, and amphotericin B prehydration. Besides assessment of the relative level of immunosuppression and comorbidities of the patients and pattern of antifungal sensitivity, considering guidelines can help us to use antifungals rationally. We hope that collecting different data concerning the use of antifungal drugs could turn into a strong motivation in the near future for implementation of policies for prevention and treatment of cancer-related fungal infections.

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Disclosure

The authors report no conflicts of interest in this work.

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