

Comparing Antifungal Prophylaxis Efficacy Between Fluconazole and Amphotericin B Lipid Complex in Adult Acute Lymphocytic Leukaemia and Acute Lymphoblastic Lymphoma (ALL) Patients Receiving Hyper-CVAD Based Chemotherapy

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1. ABSTRACT

1.1. Background: Fungal infection is common in Acute Lymphocytic Leukaemia (ALL), which can lead to significant mortality and morbidity. Our aim is to compare the efficacy of antifungal prophylaxis using fluconazole 400 mg once daily *versus* Amphotericin B lipid complex 2.5 mg/kg three times per week in adult ALL patients during the neutropenic nadir who received Hyper-CVAD as part of their chemotherapy regimen.

1.2. Methods: It was a retrospective, cohort chart review study conducted on eligible ALL patients who received Hyper-CVAD based chemotherapy regimen between January 1, 2007, and December 31, 2016, at KAMC, Jeddah. We included ALL patients who completed at least one course of Hyper-CVAD and received antifungal prophylaxis with age >14 years. We excluded patients who received BFM regimen. Data have been collected using hospital information system. The primary endpoint was the incidence of fungal infection, which was assessed using microbiology data and imaging studies for radiological evidence of fungal infections. The secondary endpoints were to assess QTc prolongation in Ph+ve ALL that is associated with fluconazole use in combination with TKI and lastly cost impact based on the type of antifungal prophylaxis used.

1.3. Results: A total of 105 cycles of Hyper-CVAD were reviewed. In 70 cycles, fluconazole was used as antifungal prophylaxis (n = 70) and in 35 cycles amphotericin B lipid complex was used (n = 35) as antifungal prophylaxis. Microbiologically documented fungal infection have been found in 2 out of 70 cycles in fluconazole arm and radiologically documented fungal infections was found in one patient in the fluconazole group. QTc prolongation was observed in 12 cycles. In 9 out of 12 cycles, events of QTc prolongation observed during the study, fluconazole was used as antifungal prophylaxis and patients were on TKI. In 3 out of 12 cycles, events of QTc prolongation were observed during the study, amphotericin B Lipid Complex was used as antifungal prophylaxis and patients were on TKI.

1.4. Conclusion: Fluconazole is considered a standard antifungal prophylaxis in ALL patients with acceptable safety profiles. Fluconazole had comparable efficacy to Amphotericin lipid complex. Fluconazole may cause QTc prolongation when used in combination with TKIs and need to monitor the patients more closely when this combination is used in Ph+Ve ALL patients.

2. INTRODUCTION

The annual incidence of acute lymphocytic leukaemia and Acute Lymphoblastic Lymphoma (ALL) in the United State is 6000 (0.4% cases of all new cancer cases) (3400 male and 2600 female). In 2013 the prevalence of people who are living with acute lymphocytic leukaemia was 77,855 [1].

Acute Lymphoblastic Leukaemia (ALL) is a type of haematological malignancy that affects the white blood cell (lymphocytes) in the bone. If more than 20% of the bone marrow replaced with the cancerous blast cells, then the disease is considered acute leukaemia [2]. Acute Lymphoblastic Leukaemia (ALL) usually affects children, adolescents, and young adults, or those 15 to 39 years of age. Most cases of ALL occur in children. In 2016, the estimated number of patients who will die from acute lymphocytic leukaemia in the United States is 1,430 (around 4 out of 5 ALL patients will die) [2].

Around 20% to 30% of ALL patients have Philadelphia chromosome (abnormality of chromosome 22) [3], which is translocation of chromosome 9 and 22 (t (9;22)) and this forms a new fusion gene called BCR-ABL [4]. The current standard of care to treat the Philadelphia positive (Ph+ve) ALL is with Tyrosine Kinase Inhibitors (TKIs) plus chemotherapy. These TKIs including imatinib, dasatinib and nilotinib are used in combination with other multidrug chemotherapy regimens such as Hyper-CVAD (chemotherapy regimen which includes fractionated cyclophosphamide, vincristine, Adriamycin, and dexamethasone alternating with high dose methotrexate and high dose Ara-C) to treat Ph+ve ALL 9,10. Hyper-CVAD includes 6-8 cycles of chemotherapy. Hyper-CVAD has been used to treat Philadelphia negative ALL patients [5,6] According to National Cancer Institute (NCI), The treatment of ALL patients is divided into the following four phases: Remission induction, CNS prophylaxis, Postremission (also called consolidation and delayed intensification) and maintenance [7].

ALL patients undergoing intensive chemotherapy or allogeneic HCT are at high risk to develop infections, Invasive Fungal Infection (IFI) is one of the main complications associated with ALL treatment [8]. During

Hyper-CVAD treatment patient will have the low level of neutrophil count (grade IV neutropenia $<500/\text{mm}^3$) and the typical neutropenic nadir is 10-14 days from Hyper-CVAD [9]. Prolonged neutropenia leads to Invasive Fungal Infection (IFI) in patients undergoing intensive chemotherapy [10]. NCCN guidelines recommend Fluconazole or Micafungin as prophylaxis against IFI in ALL patients receiving intensive chemotherapy. Amphotericin B products are listed as an alternative option in NCCN guidelines [11]. Amphotericin B lipid complex is an acceptable alternative as antifungal prophylaxis in ALL patients where Fluconazole cannot be used due to drug interaction with TKIs [12,13]; Patient with Ph+ve ALL are at risk of developing QTc prolongation because of use of TKI and this risk of QTc prolongation is moderately increased when TKIs are combined with Fluconazole because of drug-drug interaction (category C).

The purpose of this study was to Comparing Antifungal Prophylaxis Efficacy between Fluconazole and Amphotericin B lipid complex in adult acute lymphocytic leukaemia and Acute Lymphoblastic Lymphoma (ALL) Patients Receiving Hyper-CVAD based chemotherapy.

3. METHODS

The IRB committee approved our study. This was a retrospective, cohort chart review study conducted on all eligible ALL patients who were treated at the King Abdulaziz Medical City, Jeddah. Patients were eligible if they had ALL and older than 14 years of age, received Hyper-CVAD based chemotherapy regimen and received fluconazole 400 mg IV or PO once daily or amphotericin B lipid complex 2.5 mg/kg three times per week during the neutropenic nadir period as antifungal prophylaxis. We excluded ALL patients who received BFM regimen and other salvage regimens. Our study period was between January 1, 2007, until December 31, 2016. Data was collected using hospital information system (BESTCare, Quadramed, Chem-oRx, Centricity for imaging studies and ARIA Medical Solution). To assess primary endpoint: The incidences of fungal infections were assessed using microbiological studies and CT findings for radiological evidence to assess the primary endpoint. Regarding the secondary endpoints, we looked at the incidence of QTc prolongation in Ph+ve ALL that is associated with fluconazole use in combination with tyrosine kinase inhibitors (imatinib, dasatinib and nilotinib) which was assessed by ECG monitoring, and we determined the cost impact based on the type of antifungal prophylaxis used based on the NGH prices in the oracle system.

4. RESULTS

In this study total of 105 cycles were evaluated during period from January 1, 2007, until December 31, 2016. Baseline characteristics are presented on Table 1. Two third of the patient received fluconazole (67%) and one third of the patient received amphotericin B lipid complex (33%).

The incidence of microbiologically documented fungal infection was 3 out of 70 cycles and radiologically documented fungal infection was found in 1 out of 70 cycles in fluconazole group, while we didn't find any documented fungal infection in amphotericin B lipid complex group (Figure 1).

The three documented fungal infection in microbiological findings in Fluconazole arm were: *Aspergillus flavus*, *Candida albicans* from Mouth and wound culture and Rhizopus.

Regarding the secondary outcomes, the incidences of QTc prolongation were higher with fluconazole group than amphotericin B group; fluconazole (13%) and amphotericin B (9%) (95% CI (0.784 - 2.725); RR= 1.462; P Value = 0.227) which was statistically not significant (Figure 2). Cost impact based on the type of antifungal; the dose was calculated based on the average weight of our population as 70 kg. We found prophylactic ALL patients with fluconazole is cost effective comparing with amphotericin B lipid complex; Cost of 14 days therapy with fluconazole per cycle during neutropenic nadir period is 78 SAR and total cost of fluconazole therapy per 6 cycles of Hyper-CVAD in 59 patients is 27,456 SAR. While cost of amphotericin B lipid complex is 10,956 SAR and total cost of fluconazole therapy per 6 cycles of Hyper-CVAD in 59 patients is 3.9 million SAR (Table 2). Hence, use of fluconazole is 142 times more cost effective than Amphotericin B lipid complex.

Table 1: Baseline characteristics are presented.

Baseline Characteristics of Patient Population (N = 105)		
	Fluconazole group	Amphotericin B group
	(n= 70)	(n=35)
Median (IQR)		
Age (Years)	36.5 (28-46)	35 (30.25-46)
Weight (Kg)	68.7 (56.8-83.2)	65.1 (60.7-84.5)
n (%)		
Males	42 (60)	22 (62.9)
Females	28 (40)	13 (37.1)
ALL	38(54.3)	12 (34.3)
ALL patient with Ph +ve	26 (37.1)	23 (65.7)
Burkitt's lymphoma	6 (8.6)	-

Table 2: Use of fluconazole is 142 times more cost effective than Amphotericin B lipid complex.

Name of Drug	Unit price	Cost per day	Cost per cycle	Cost of 6 cycles of HyperCVAD in 59 patients
			(14 days)	
Fluconazole	150 mg Capsule	5.54 SAR/ 400 mg PO	77.56 SAR	27,456 SAR

	= 2.3 SAR			
	50 mg Capsule			
	= 0.47 SAR			
Amphotericin B Lipid complex	100 mg Vial= 913 SAR	2.5 mg/Kg/3 times per week for 70 Kg patient = 1,826 SAR	10,956 SAR	3.9 million SAR

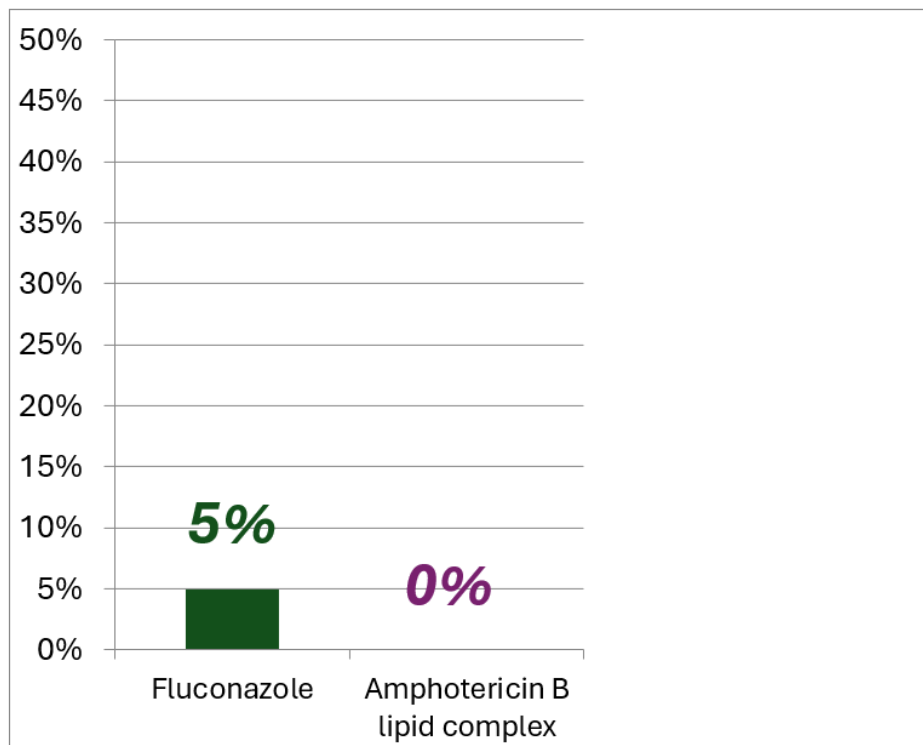


Figure 1: Incidence of Fungal Infection between Fluconazole and Amphotericin B.

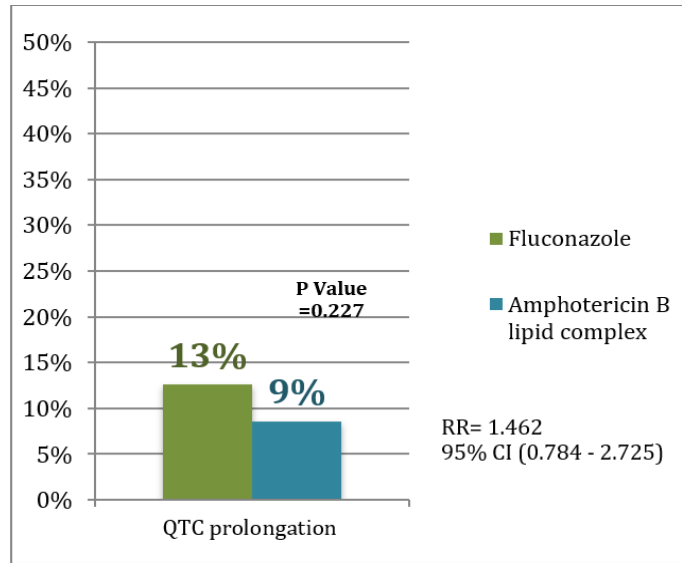
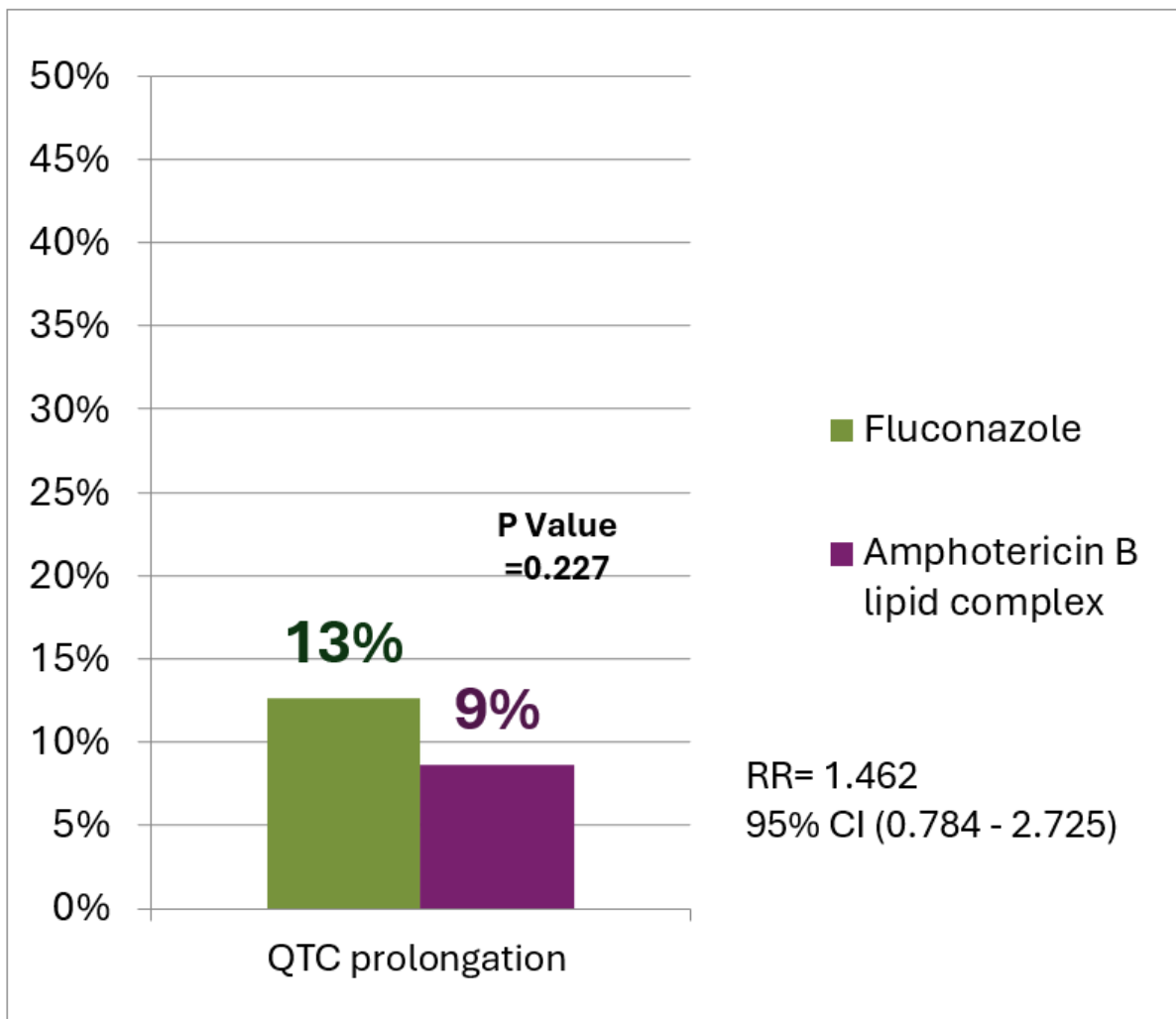


Figure 2: Incidences of QTC Prolongation.



5. DISCUSSION

The Hyper-CVAD based chemotherapy is associated with myelosuppression and grade **IV** neutropenia (Neutrophil count $<500/\text{mm}^3$), the prolonged neutropenia leads to Invasive Fungal Infection (IFI) in patients undergoing intensive chemotherapy. The incidences of documented fungal infections were increased in those patients.

Fluconazole is considered a standard antifungal prophylaxis in ALL patients who receive Hyper-CVAD based chemotherapy.

The NCCN guideline recommends Fluconazole or Micafungin as prophylaxis against IFI in ALL patients receiving intensive chemotherapy. Amphotericin B products are listed as an alternative option in NCCN guidelines. There were no similar head-to-head comparison studies published, which compared between fluconazole and amphotericin B lipid complex as prophylactic therapy against fungal infections in ALL patients who received Hyper-CVAD based chemotherapy.

Our institution adopted using amphotericin B lipid complex in 2007 as an alternative to Fluconazole antifungal prophylaxis in Philadelphia positive ALL patients. We planned to compare the efficacy of two antifungal agents in past 10 years.

There was an outbreak of fungal infection in 2011 which could be a confounding factor in fluconazole arm, however this study demonstrates that there is no significant difference between fluconazole and amphotericin B lipid complex as prophylactic therapy against fungal infections in ALL patients who received Hyper-CVAD based chemotherapy.

Our study showed that patients on fluconazole with TKI were at moderate risk of QTc prolongation in comparison with amphotericin B lipid complex, however this difference was not statistically significant; it could be related to other factors like age and other patient related risk factors (e.g. chronic disease, drug induce etc.). In addition, fluconazole was significantly more cost effective than amphotericin B lipid complex.

- **Limitations in our study:** It is retrospective, single center, unpowered study and we couldn't access laboratory data regarding serum galactomannan as a molecular finding of fungal infection due to changes in the electronic hospital information system.

6. CONCLUSION

Our findings suggest that fluconazole is considered a standard antifungal prophylaxis in ALL patients with acceptable safety profiles and might be comparable to amphotericin B lipid complex. A careful monitoring for QT-prolongation is required for patients in case fluconazole is combined with TKIs. We suggest that fluconazole is a cost-effective first line regimen for prophylaxis for IFI compared to amphotericin B lipid complex.

Further prospective studies are required to compare the efficacy between fluconazole and amphotericin B lipid complex in ALL patients who receive Hyper-CVAD based chemotherapy.

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8. DISCLOSURE

Portions of this work were previously presented at the ASHP midyear in Orlando, 2017.

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